
**Identification of factors affecting the
outcome of transanal advancement flap
repair for high transsphincteric fistulas**

Identification of factors affecting the outcome of transanal advancement flap repair for high transsphincteric fistulas

Identificatie van factoren die de uitkomst van de transanale mucosaverschuivingsplastiek beïnvloeden

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
prof. dr. H.G. Schmidt
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 11 november 2009 om 11.30 uur

door

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geboren te Rotterdam



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Voor mijn lieve familie

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Chapter one

Introduction and outline of the thesis

Introduction

A fistula is defined as an abnormal communication between two epithelium lined surfaces. Perianal fistulas are abnormal communications between the anal canal and the perianal skin. Perianal fistulas have been treated since ancient times. Probably the first to describe the diagnosis and treatment of anal fistula was Sushruta around 600 BC. Around 430 BC, Hippocrates (460-370 BC) described perianal fistulas in more detail ¹. It is remarkable that some of his guidelines carry worldwide popularity up to today. The estimated incidence of perianal fistulas varies between 0.86 and 2.32 per 10,000/year ^{2, 3}. There is a male predominance with a reported male-to-female-ratio varying from 2:1 to 5:1 ^{2, 4-6}. The maximum incidence is between the third and fifth decades of life ². Perianal fistulas account for a substantial discomfort and morbidity to the patient and although many fistulas are easily recognized and treated, others can be complex and difficult to treat.

Aetiology and pathogenesis

The majority of perianal fistulas are of cryptoglandular origin. The cryptoglandular hypothesis states that perianal fistulas arise from anal canal glands, located at the level of the dentate line⁷. The ducts of these glands flow into the crypts of Morgagni and drain into the anal canal. If these glands become blocked, stasis occurs and infection develops. Because a substantial number of these glands branch out into the intersphincteric plane, the infection can pass the internal anal sphincter that serves as a barrier against bacterial contamination. From the intersphincteric plane the infection may progress and extend in various ways. Patients usually present with an abscess. In about half of these patients a fistula persists after drainage of the abscess. Among more specific causes for perianal fistulas Crohn's disease is a major one. Iatrogenic and obstetric trauma may also result in a perianal fistula. Perianal fistulas in specific conditions, such as tuberculosis, HIV or malignant diseases are rarely seen.

Anatomy

A thorough knowledge of the anatomy of the anal canal, rectum, anal sphincters and the pelvic floor is essential for a correct classification of perianal fistulas and their treatment. The anal canal extends from the rectal ampulla to the anal verge and is 2-5 centimeters in length. The upper part is lined with columnar epithelium. The dentate line is situated in the distal part of the anal canal and is defined by the columns of Morgagni (Figure 1.1). At this level the ducts of the anal glands flow into the anal crypts. At the dentate line the epithelium becomes

transitional and is referred to as the anal transition zone. Distal from this zone the anal canal is lined with stratified squamous epithelium. The anal canal is surrounded by the internal and external sphincter muscle.

Although fecal continence depends on many factors, the function of the anal sphincters is considered the most important one. The internal anal sphincter consists of smooth muscle and is innervated by the autonomic nervous system while the external anal sphincter consists of striated skeletal muscle and has somatic innervation. The external anal sphincter is unique compared to other striated muscles regarding its continuous tonic activity. At the upper level the external anal sphincter becomes continuous with the puborectal muscle, which forms a sling behind the anal canal and is attached to the pubic bone. The puborectal muscle is part of the levator ani muscle, a broad thin muscle that forms the pelvic floor. Both the high-pressure zone in the anal canal and the angulation between the rectum and anal canal, which is a result of the tonic contraction of the puborectal muscle, contribute to fecal continence. Both anal sphincters are responsible for the anal high-pressure zone at rest, however the internal anal sphincter supplies the largest contribution to this anal resting pressure.

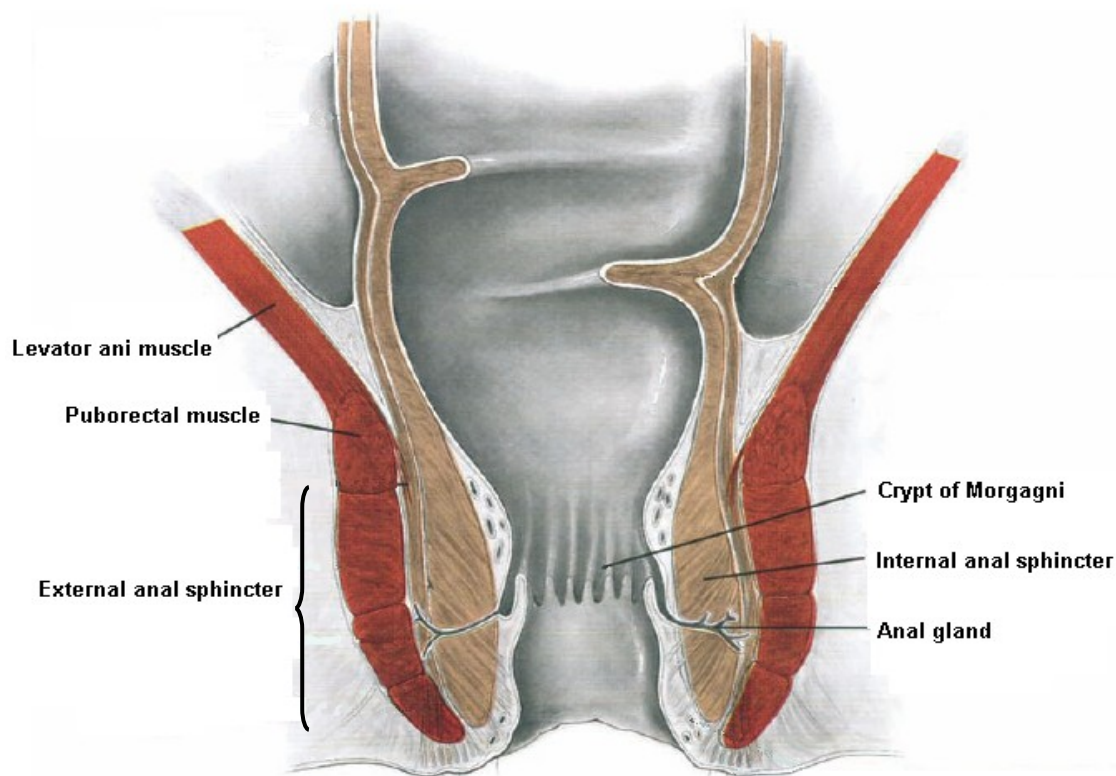


Figure 1.1 Anatomy of the anal canal

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Classification

In 1976 Parks combined anatomical features with the cryptoglandular hypothesis to develop a classification of perianal fistulas, which is now generally used ⁸. Parks classified perianal fistulas by their location in relation to the anal sphincter muscles and defined four types of fistulas (Figure 1.2).

1. Intersphincteric fistula. The fistulous tract traverses the internal sphincter and extends in the intersphincteric space to the perianal skin.

2. Transsphincteric fistula. The tract traverses both the internal and external sphincter muscles.

3. Suprasphincteric fistula. The tract passes the internal anal sphincter, turns upward in the intersphincteric space to a point above the puborectal muscle, crosses this muscle, then extends downward between the puborectal and levator ani muscle to the external opening.

4. Extrasphincteric fistula. The tract begins at the rectum or sigmoid colon and extends downward and passes through the levator ani muscle to the external opening.

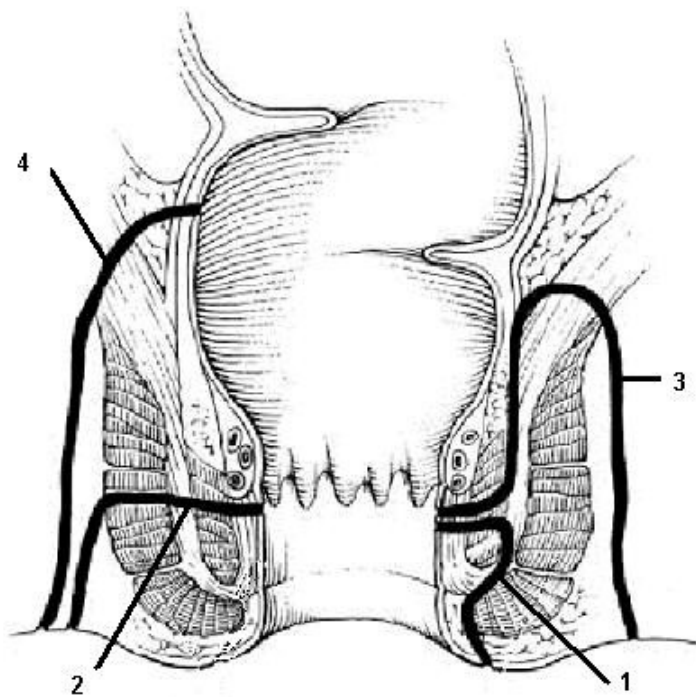


Figure 1.2 Classification of perianal fistulas

Transsphincteric fistulas are subdivided into high and low transsphincteric fistulas, based on the level at which they traverse the external anal sphincter. Fistulas passing through the distal third of the external anal sphincter are classified as low, whereas fistulas passing through the middle or proximal third of the external anal sphincter are referred to as high. This distinction is important because of the surgical implications. Low transsphincteric fistulas can be treated with either fistulotomy (lay-open) or fistulectomy (excision). This will result in division of only a small portion of the external anal sphincter and with only minimal continence disturbances as a result. However, in case of a high transsphincteric fistula the portion of the external sphincter that needs to be divided is too large and continence disturbances are inevitable. This type of fistula requires a more vigilant treatment option, such as the transanal advancement flap repair.

Clinical manifestation

Signs and symptoms

Perianal fistulas are associated with pain and discharge of purulent material or blood⁹. The history of patients with a perianal fistula frequently reveals cyclic periods in which the external opening of the fistula temporarily closes. This may result in an increase of pain and swelling.

Physical examination

Physical examination remains the mainstay of diagnosis. One should inspect the entire perineum, looking for external openings. Spontaneous discharge through the external opening or discharge expressible upon palpation or digital rectal examination may be noted. Sometimes an elevation of granulation tissue marks the external opening. The location of the external opening provides information about the location of the internal opening and the course of the fistulous tract. The relation between the internal and external opening and the course of the fistulous tract was described in 1900 by Goodsall¹⁰. His guidelines have been almost universally accepted and are commonly known as Goodsall's rule. According to this rule, fistulas with an external opening posterior to a plane transverse through the centre of the anus are likely to have their internal opening posterior in the midline and extend in a curved way to the external opening, whereas fistulas with their external opening in the anterior part of the anal canal are likely to originate from the nearest crypt and from there on

run directly to the external opening. It is questionable whether digital rectal examination might reveal the internal opening. A tender palpable mass might indicate an underlying abscess. In some cases it is possible to probe a part of the fistulous tract. Probing should be done with a featherlike touch and great care. Not only can it be painful, it may also create false tracts.

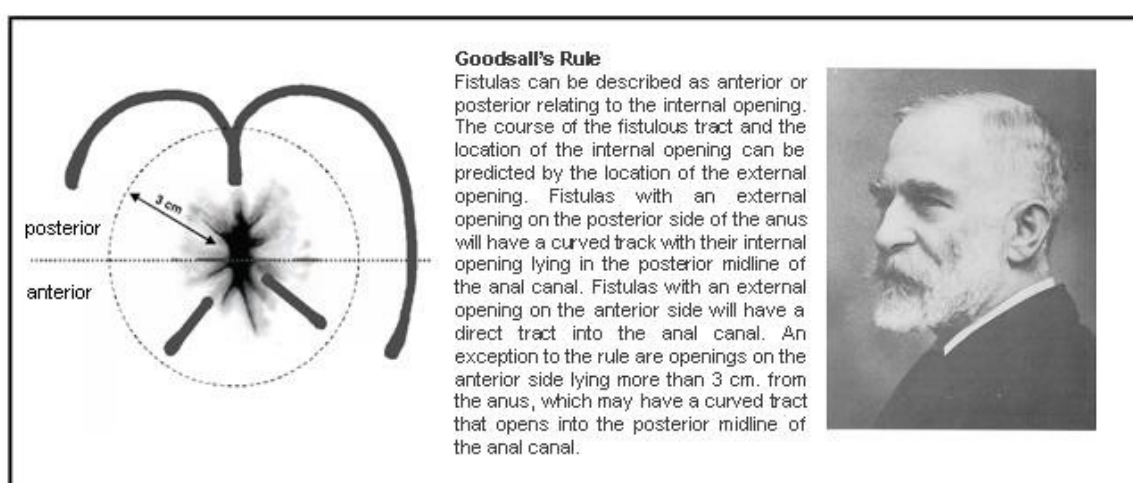


Figure 1.3 Goodsall's rule

Imaging

Fistulography

Fistulography was the first imaging technique used to visualize fistulous tracts. Water-soluble contrast agent is injected gently to define the fistula tract, followed by anteroposterior, lateral and oblique x-ray images to outline the course of the fistula tract. Fistulography has two major drawbacks. First, extensions of the fistulous tract may fail to fill with contrast material if they are plugged with debris or very remote ¹¹. Second, the anal sphincter muscles themselves are not directly imaged, which means that the relationship between the fistulous tract and the anal sphincter muscles cannot be assessed. Furthermore it is difficult to localize the internal opening ¹¹. Based on these aspects fistulographic findings are both difficult to interpret and unreliable ¹². Since the introduction of endoanal ultrasound and MR imaging this technique is seldom used in modern clinical practice.

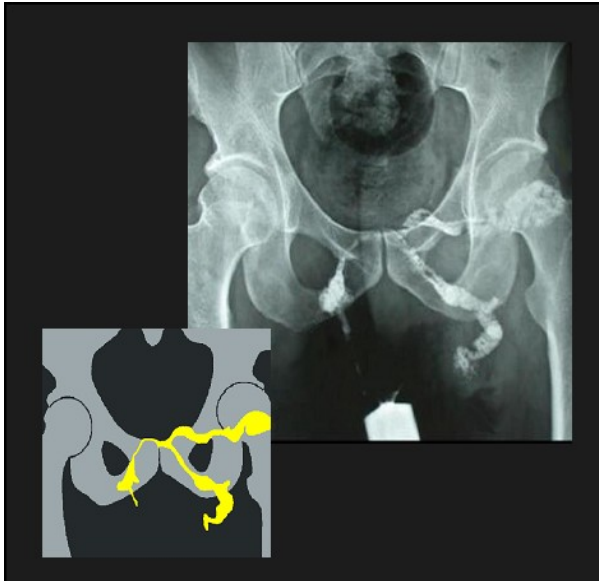


Figure 1.4
Fistulography

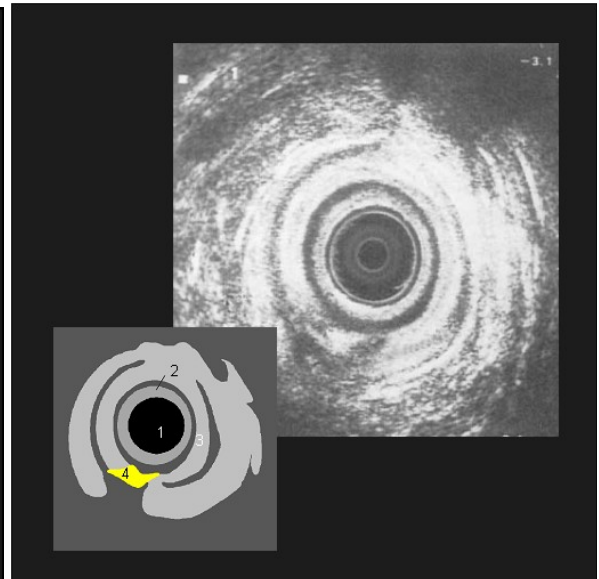


Figure 1.5
Hydrogen enhanced ultrasound
1= endoanal coil
2= internal anal sphincter
3= external anal sphincter
4= fistula

Endoanal ultrasound

Endoanal ultrasound, developed by Clive Bartram, was the first technique to directly depict the anal sphincter complex in detail ¹³. Although endoanal ultrasound is simple, cheap, quick and well tolerated by patients ^{13, 14}, it has also disadvantages. Insufficient penetration of the ultrasound beam beyond the external anal sphincter limits the ability to visualize the region more distant from the anal canal, with the result that extensions from the primary tract may be missed. Moreover, it is difficult to distinguish infection from fibrosis, because both have a hypoechoic appearance ¹⁵. Imaging by endoanal ultrasound can be improved by injecting hydrogen peroxide into the external opening, generating the formation of small air bubbles ¹⁶. This changes the fistulous tract from hypoechoic to hyperechoic, and helps to distinguish the fistulous tract from scar tissue. Since MR imaging is generally available, this imaging technique is increasingly used for the preoperative classification of perianal fistulas.

MR Imaging

In recent years Magnetic Resonance imaging has shown to provide accurate information about the relationship between the fistulous tracts and the anal sphincter muscles. The first reports regarding MR imaging of perianal fistulas date from the early nineties and were conducted using a body coil¹⁷⁻¹⁹. Early studies showed high concordance rates of MR imaging with the findings of examination under anesthesia^{17, 20}. MR imaging was more accurate than clinical assessment in detecting previously missed secondary extensions and in the correct assessment of the level of the fistula with respect to the sphincter muscles. MR imaging has been improved by the introduction of endocoil receivers. They increase the tissue resolution close to the anal canal, providing superior anatomical detail^{21, 22}. The disadvantage of the endoanal coils is the limited ability to visualize areas more distant from the anal canal. It has been suggested that preoperative assessment with MR imaging will alter the surgical treatment in up to ten percent of fistulas treated for the first time²³. Comparing patients with and without preoperative MR imaging Buchanan *et al.* observed postoperatively a persistent fistula in 16 percent and 57 percent of the patients, respectively²⁴. MR imaging has also disadvantages. It is a rather expensive and time-consuming technique. Furthermore, it is not always well tolerated. It is not suitable for patients with claustrophobia. Moreover, patients with metal implants or a pacemaker cannot undergo the investigation. Despite these drawbacks, MR imaging is considered to be the gold standard for assessing and classifying perianal fistulas.

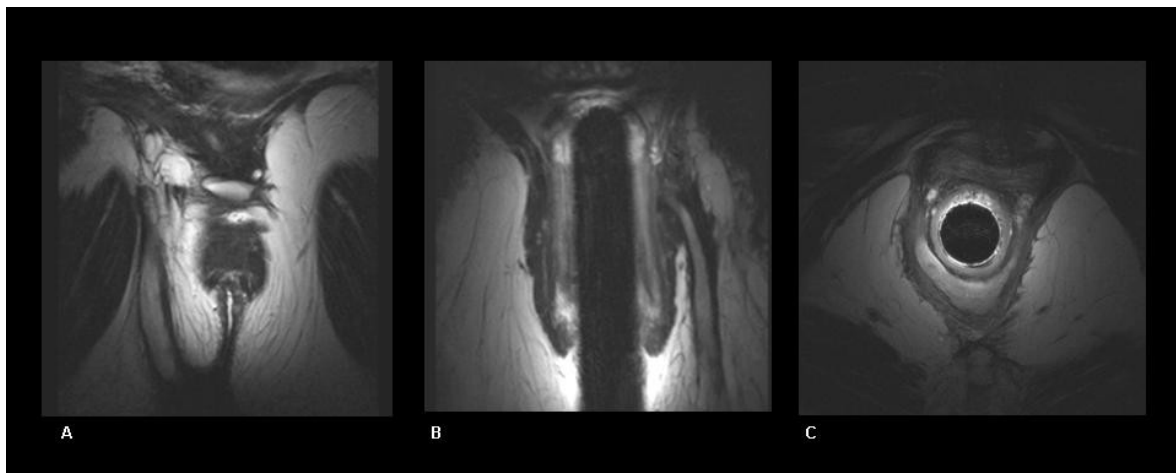


Figure 1.6 MR imaging with an endoanal

- A. Coronal
- B. Sagittal
- C. Axial

Treatment

The principle goal in the treatment of perianal fistulas is fistula healing with minimal or no continence disturbances. Perianal fistulas passing the lower third of the external anal sphincter can be treated with either fistulotomy (lay-open) or fistulectomy (excision). Both procedures are easy to perform, provide excellent healing rates and will result in division of only a small portion of the external anal sphincter^{25, 26}. After these procedures continence disturbances are minimal. In case the fistula passes through the middle or upper third of the external anal sphincter the portion of the sphincter that needs to be divided is too large and continence disturbances are inevitable. Therefore, alternative treatment modalities have been developed, such as transanal advancement flap repair, installation of fibrin glue and the use of anal fistula plugs.

Transanal advancement flap repair

Transanal advancement flap repair (TAFR) enables healing of high transsphincteric fistulas without dividing the anal sphincters muscles. This procedure was developed more than a century ago by Noble for the repair of rectovaginal fistulas. Treatment of transsphincteric fistulas by TAFR became a popular technique only until the eighties. Initially, the reported healing rates were high. However, in recent years, it became clear that the healing rate after transanal advancement flap repair is lower, varying between 60 to 70 percent. Although sphincter division is avoided during flap repair, continence disturbances have been reported in up to 35 percent of the patients²⁷. While creating the flap, fibers of the internal anal sphincter are used to provide strength for the flap. Theoretically, this might affect continence. Zimmerman and co-workers examined the influence of two different anal retractors on fecal continence²⁸. They found that the use of a Parks' retractor had a deteriorating effect on continence, while this effect was not observed after the use of a Scott retractor. Therefore, they advocated the use of a Scott retractor.

Surgical technique

All patients in whom flap repair was performed at the Erasmus Medical Center underwent complete mechanical bowel preparation (polyethylene glycol: Klean-prep® Helsinn Birex Pharmaceuticals, Dublin, Ireland). After induction of general endotracheal anesthesia metronidazole together with cefuroxime was administered intravenously. With the patient in prone jack-knife position, the external opening was enlarged and the fistulous tract was excised as far as possible. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal

sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibers of the internal anal sphincter was raised from the level of the dentate line and mobilized over a distance of four to six cm proximally. The flap was advanced and sutured to the neodentate line with absorbable sutures. Postoperatively, all patients were immobilized for five days. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily.

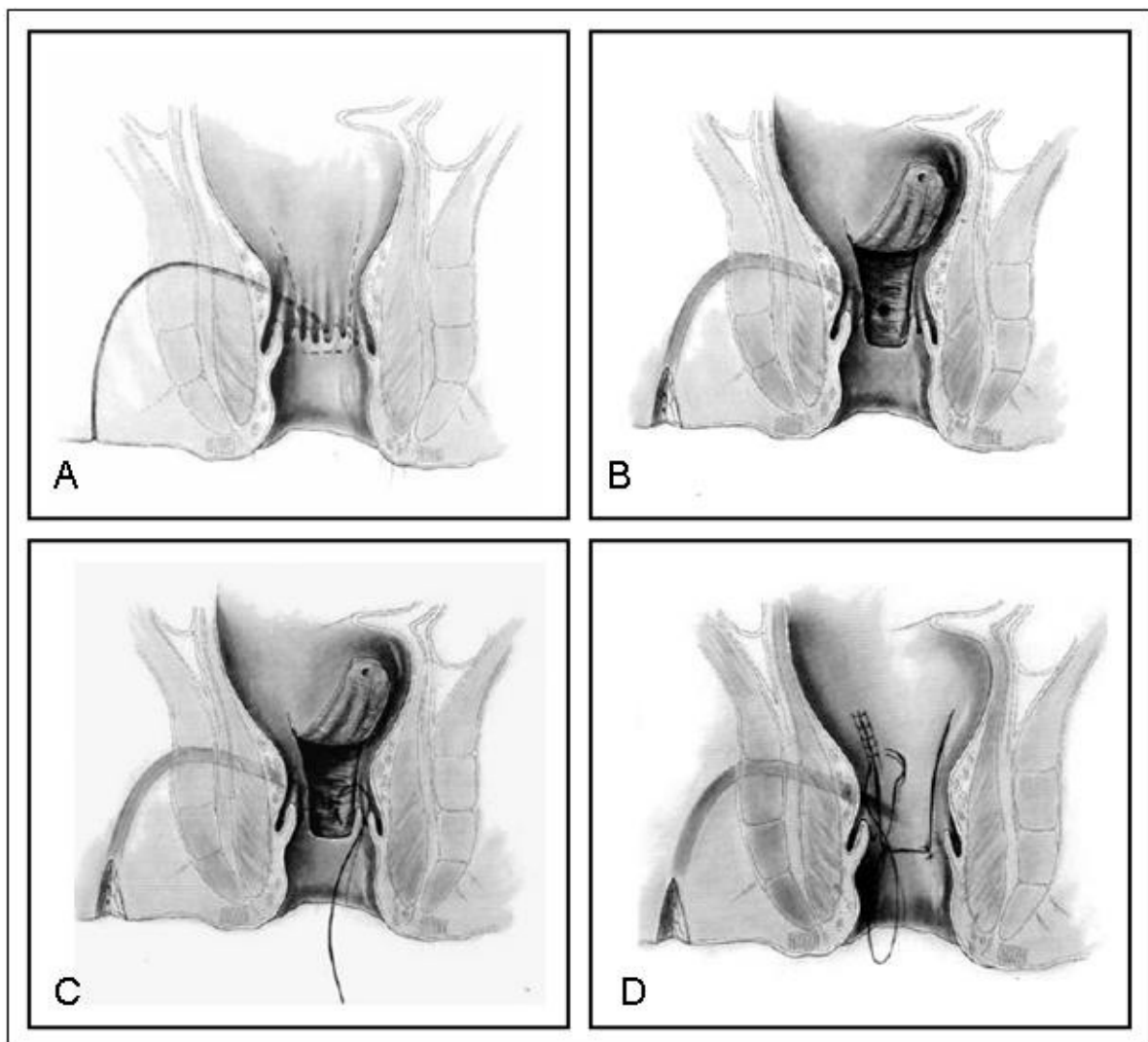


Figure 1.7 Transanal advancement flap repair (reprinted with the permission from P.H. Gordon)

A. Dotted lines outline flap to be raised
B. Fistula is cored out and a flap is elevated

C. Internal opening is closed
D. Flap is drawn down and sutured in place

Author	Year	No.Pts	Healing rate	Follow-up
Oh ²⁹	1983	15	87	NS
Aguilar ³⁰	1985	151	98	range, 8 months- 7 years
Wedell ³¹	1987	27	100	range, 18 months- 4 years
Kodner ³²	1993	31	87	mean, 7 months
Ozuner ³³	1996	19	68	median, 12 months
Miller ³⁴	1998	18	83	mean, 14 months
Schouten ²⁷	1999	44	75	median, 12 months
Ortiz ³⁵	1999	103	93	median, 12 months
Mizrahi ³⁶	2002	41	67	median, 40 months
Sonoda ³⁷	2002	48	77	median, 17 months
Van der Hagen ³⁸	2005	23	78	median, 22 months
Perez ³⁹	2006	27	93	mean, 36 months
Gustafsson ⁴⁰	2006	83	57	12 months
Ellis ⁴¹	2007	29	69	median, 10 months
Toyanege ⁴²	2007	35	94	mean, 12 months
Ortiz ⁴³	2008	91	82	median, 42 months
Van Koperen ⁴⁴	2008	70	79	median, 72 months
Dubsky ⁴⁵	2008	34	65	median, 63 months

Table 1.1
Results of transanal advancement flap repair for high transsphincteric fistulas of cryptoglandular origin

Alternative treatment modalities

Fibrin Glue

Instillation of fibrin glue for the treatment perianal fistulas was first described in 1991 by Hjortup and Kjaergard⁴⁶. The use of fibrin glue is easy and repeatable. Complications such as formation of abscesses and new fistulous tracts are scarce^{47, 48}. Early results were promising, but as the procedure gained wide acceptance, more conflicting data became available including reported healing rates varying between 0 percent⁴⁹ and 74 percent⁵⁰. Moreover, long-term follow-up revealed that healing rates decreased markedly in time^{48, 51, 52}. Continence is not affected after treatment with fibrin glue since there is no trauma to the sphincter muscles.

Some authors have evaluated the additional value of fibrin glue as an adjunct to flap repair^{35, 53-55}. The results of these studies indicate that instillation of a surgical adhesive is not beneficial for patients who undergo a flap repair.

The anal fistula plug

In recent years the Surgisis[®] anal fistula plug (Cook Surgical Inc., Bloomington, IN) has been developed as an alternative to traditional fistula surgery. This plug consists of an extracellular matrix, derived from the submucosa of porcine small intestine. This matrix supports host-tissue remodeling resulting in closure of the fistulous tract and it does not encapsulate when implanted. After irrigating the fistulous tract with hydrogen peroxide, the conical device is placed by drawing it through the fistulous tract. It is then cut to fit and secured in the internal opening using a figure-of-eight suture incorporating it with the mucosa to close the internal opening. According to some authors this minimal invasive technique provides a simple and safe option in the treatment of fistulas. Initially the reported healing rates were high, up to 87 percent^{56, 57}. More recently however, less promising results were reported, with healing rates dropping to 41 percent⁵⁸, 24 percent⁵⁹ and 14 percent⁶⁰. Ellis was the first to compare anal fistula plug closure with transanal advancement flap repair⁶¹. His retrospective analysis revealed that the fistula recurred in 33 percent of the patients after flap repair and in 12 percent of the patients after plug repair. Although this difference seems to be in favor of the anal fistula plug, it did not reach statistical significance. A similar finding has been reported by Chung *et al.*⁶². Recently, two retrospective studies revealed that flap repair provides a significant higher healing rate than the use of an anal fistula plug^{63, 64}. This observation is supported by the outcome of a randomized trial conducted by Ortiz *et al.*⁶⁵. They found fistula recurrence in 80 percent of the patients after plug repair and in 13 percent of the patients after flap repair. Based on the data obtained, flap repair seems to be more favorable than plug repair. More randomized trials are warranted to elucidate the value of flap repair and plug repair in the treatment of high transsphincteric fistulas.

Outline of the thesis

The literature shows that transanal advancement flap repair fails in one of every three patients. This thesis was aimed at identifying factors affecting the outcome of transanal advancement flap repair.

In **Chapter 2** the complexity of high transsphincteric fistulas was assessed with the use of endoanal MR imaging in order to answer the question whether more complex fistulas, such as those with horseshoe extensions and associated abscesses, have a less favorable outcome.

It has been suggested that the healing rate of transanal advancement flap repair diminishes with time. In **Chapter 3** the healing time after transanal advancement flap repair as well as the risk of recurrence after initial fistula healing was assessed in order to determine the required length of follow-up.

In **Chapter 4** the outcome of repeat flap repair, performed in patients in whom the first attempt had failed, is presented. The impact of these second repairs on the overall healing rate is described.

Impaired rectal mucosal blood flow might result in breakdown of the distal part of the flap. In **Chapter 5** the effect of rectal mucosal blood flow on the outcome of transanal advancement flap repair is described.

Some authors advocate the use of a seton prior to flap repair. However, it is still not clear whether this intervention improves the outcome. **Chapter 6** describes a study on the influence of preoperative seton drainage on the outcome of transanal advancement flap repair.

It is generally assumed that the presence of epithelium in the fistulous tract has a detrimental effect on fistula healing. However, there is no evidence for this assumption. **Chapter 7** describes the impact of such epithelium lining on the healing rate of transanal advancement flap repair.

Little is known about the microbiological aspects of perianal fistulas. These aspects were studied with the use of both classical microbiological methods as well as molecular microbiological methods. **Chapter 8** describes the results of this study.

Chapter 9 discusses the data of the experimental studies of this thesis and outlines some future perspectives.

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Is the outcome of transanal advancement flap repair affected by the complexity of high transsphincteric fistulas?

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ABSTRACT

Introduction

Transanal advancement flap repair for the treatment of high transsphincteric fistulas fails in one of every three patients. Until now no definite risk factors for failure have been identified. The question is whether the more complex fistulas, such as those with horseshoe extensions and associated abscesses, have a less favorable outcome. Aim of the present study was to answer this question.

Methods

Between 1995 and 2007 a series of 162 patients underwent endoanal MR imaging prior to transanal advancement flap repair. Two investigators, without prior knowledge of the surgical findings, reviewed all MR images.

Results

Posterior fistulas were identified in 76 percent of the patients. These fistulas had three types of extensions: a direct course (36%), a classic horseshoe extension (23%) or an intersphincteric horseshoe extension (41%). Corresponding healing rates were 37 percent, 81 percent and 74 percent, respectively. Anterior fistulas were observed in 23 percent of the patients. These fistulas had two types of extensions: a direct course (61%) or a classic horseshoe extension (39%). Corresponding healing rates were 60 percent and 52 percent, respectively. The healing rate of fistulas with a direct course was significantly lower than the healing rate of fistulas with a classic or intersphincteric horseshoe extension. Lateral fistulas were identified in one percent of the patients. Associated abscesses were found in 47 percent of the posterior fistulas and five percent of the anterior fistulas. Once adequately drained, these abscesses did not affect the outcome of transanal advancement flap repair.

Conclusion

The complexity of high transsphincteric fistulas does not affect the outcome of transanal advancement flap repair.

INTRODUCTION

Transanal advancement flap repair has been advocated as the treatment of choice for transsphincteric fistulas passing through the upper and middle third of the external anal sphincter. This procedure enables healing of the fistula in two of every three patients without consequent sphincter damage. Several authors have tried to identify factors affecting the outcome of transanal advancement flap repair ^{1, 2, 3, 4}. However, until now no definite predictive factors for failure have been identified. The question is whether the complexity of high transsphincteric fistulas affects the outcome of transanal advancement flap repair. Most of these fistulas have their internal opening at the posterior or anterior midline. From this point they can extend in different ways. Some fistulas have a direct course from the internal to the external opening, whereas others extend in a more complex horseshoe manner. Associated abscesses are not an uncommon finding in patients with a high transsphincteric fistula. It is not known whether high transsphincteric fistulas with an associated abscess and those with a more complex course have a lower tendency to heal.

The classic way in which horseshoe fistulas develop has been described in detail and mainly involves the horseshoe extension of posterior fistulas ⁵⁻¹⁰. When such a fistula penetrates the external anal sphincter it enters the deep postanal space, which is bounded by the levator ani muscle, the anococcygeal ligament, the coccyx and the anal canal. This anatomical space communicates on both sides with the ischioanal spaces. The easiest way to extend from the deep postanal space is to either one or both of these ischioanal spaces, thereby forming a classic horseshoe extension. However, it has been described that the circumferential spread may also occur in the intersphincteric plane, forming an intersphincteric horseshoe extension ¹¹. In 1900 Goodsall described in which way a fistula is most likely to traverse, based on the location of the external opening. His observations have been almost universally accepted and are commonly known as Goodsall's rule. According to this rule, fistulas with an external opening posterior to a plane transverse through the centre of the anus are likely to have their internal opening posterior in the midline and extend in a curved way to the external opening, whereas fistulas with their external opening in the anterior part of the anal canal are likely to originate from the nearest crypt and from there on run directly to the external opening. So, according to Goodsall's rule, the majority of posterior fistulas should form a horseshoe extension, while anterior fistulas should have a direct course ¹⁰. The question is whether this is true. Aim of the present study was to determine the exact prevalence of horseshoe extensions in posterior and anterior high transsphincteric fistulas with the use of endoanal MR Imaging. The present study was also conducted to

answer the question whether the more complex fistulas, such as those with horseshoe extensions and associated abscesses, have a less favorable outcome.

PATIENTS AND METHODS

Between June 1995 and December 2007 a consecutive series of 178 patients with a cryptoglandular, transsphincteric fistula, passing through the upper or middle third of the external anal sphincter underwent transanal advancement flap repair. In 162 of these patients MR imaging was performed prior to this procedure. Patients in whom no MR imaging was performed were excluded. Median age at time of repair was 47 (range 21 -73) years.

Exclusion criteria

Patients with a rectovaginal fistula or a fistula caused by Crohn's disease were excluded from the present series.

MR Imaging

Before transanal advancement flap repair was performed all patients underwent endoanal MR imaging. All MR imaging examinations were performed with the use of an endoanal coil with a 1.5-T MR imager (Gyrosan NT Intera 1.5; Philips Medical Systems, Best, the Netherlands). The endoanal coil (Philips Medical Systems) consisted of a fixed, rectangular, 60-mm-long rigid receiver coil with a width of 16 mm. The coil is contained within an 80-mm-long cylindrical coil holder with a diameter of 19 mm. Before the introduction of the coil into the anal canal, a condom was placed over the coil and US gel was used as a lubricant. The coil was introduced while the patient was lying in the left lateral position. After the coil was introduced, each patient was carefully turned onto his back, and the position of the coil was rechecked. In each patient, the following three sequences were used. Transverse T2-weighted contrast-enhanced fast field-echo imaging was performed (repetition time msec/echo time msec, 23/14; acquisition time, 5 minutes 39 seconds; matrix, 205 x 256; flip angle, 60°; field of view, 140 mm; section thickness, 2 mm with no gaps; and two signals acquired). Contrast-enhanced fast field-echo is a term used by Philips Medical Systems and does not indicate contrast material administration. Transverse T2-weighted fast spin-echo [SE] MR imaging was performed with and without fat saturation (5,086/100; acquisition time, 2 minutes 23 seconds; matrix, 186 x 256; flip angle, 90°; field of view, 120 mm; section

thickness, 4 mm with a 0.4-mm gap; and three signals acquired). Coronal and sagittal T2-weighted SE MR imaging was performed without fat saturation (2,454/100; acquisition time, 2 minutes 34 seconds; matrix, 186 x 256; flip angle, 90°; field of view, 120 mm; section thickness, 4 mm with a 0.4-mm gap; and four signals acquired).

Two investigators, without prior knowledge of the surgical findings, independently reviewed all MR images. Images with disagreement were re-evaluated with both observers working together, and consensus was reached.

Surgical technique

Patients underwent complete mechanical bowel preparation (polyethylene glycol: Klean-prep® Helsinn Birex Pharmaceuticals, Dublin, Ireland). After induction of general endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, the external opening was enlarged and the fistulous tract was excised as far as possible. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibers of the internal anal sphincter, was raised from the level of the dentate line and mobilized over a distance of four to six cm proximally. The flap was advanced and sutured to the neodentate line with absorbable sutures. One surgeon performed all operations (WRS).

Drainage of associated abscesses

All associated abscesses, detected with MR imaging, were drained with a four-winged malecot catheter. A separate elliptical incision was made to gain access to the abscess cavity. Through another small incision the drain was inserted, tunneled subcutaneously and positioned into the abscess cavity. The abscess cavity was irrigated six times daily with saline during ten days.

Postoperative care

All patients were immobilized for five days. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily.

RESULTS

Of the 162 patients who underwent endoanal MR imaging prior to the flap repair the internal opening of the fistula was located posterior in 119 patients, anterior in 38 patients and at the lateral side of the anal canal in five patients. In 36 percent of the patients with an internal opening at the posterior midline endoanal MRI revealed a direct course of the fistula, running from the internal to the external opening in the dorsal quadrant (Figure 2.1). Associated abscesses were found in 55 percent of these patients. The healing rate among patients with this fistula type was 37 percent. In 23 percent of the patients with a posterior fistula a classic horseshoe extension was found. In these patients the fistula passed through the external anal sphincter in the posterior midline, extending from that point in a horseshoe manner to either one or both sides (Figure 2.2). In 35 percent of these patients an associated abscess was detected. The healing rate was 81 percent. In 41 percent of the cases the posterior fistula extended circumferentially in the intersphincteric plane, passing through the external anal sphincter at either one or both lateral sides (Figure 2.3). This fistula type was associated with an abscess in 54 percent of the cases. The healing rate was 74 percent. The healing rate of posterior fistulas with a direct course was significantly lower than the healing rate of fistulas with a classic or intersphincteric horseshoe extension ($P=0.001$). Regarding the healing rate no significant difference was observed between patients with a classic and those with an intersphincteric horseshoe extension.

Endoanal MRI revealed two types of anterior fistulas. The first type are the fistulas with a direct course between the internal opening and the external opening in the anterior quadrant. This fistula type was found in 61 percent of the patients with an internal opening at the anterior midline. The healing rate in these patients was 52 percent. In four percent of these patients an associated abscess was detected. The second type was characterized by a classic horseshoe extension, observed in 39 percent of the patients. The healing rate among these patients was 60 percent. These fistulas were associated with an abscess in six percent of the cases. Anterior fistulas showed no intersphincteric extensions. The healing rate of anterior fistulas did not significantly differ from the healing rate of posterior fistulas.

Endoanal MR imaging revealed associated abscesses in 47 percent of the patients with a posterior fistula and in five percent of the patients with an anterior fistula. These abscesses were classified as intersphincteric (18%), infralevator (13%), intralevator (51%), supralevator (11%) and translevator (7%).

Intersphincteric abscesses are located in the plane between the internal and external anal sphincter. Infralevator abscesses are located below the levator muscle and are commonly known as deep postanal space abscesses. Intralevator abscesses are located in the levator

muscle itself. Abscesses above the pelvic floor are referred to as supralelevator abscesses. Some abscesses are located below the levator muscle and from there on penetrate the pelvic floor to extend above the levator muscle. These hourglass-shaped abscesses are referred to as translevator abscesses.

Associated abscesses were significantly more often present in posterior fistulas than in anterior fistulas. Posterior fistulas with a direct course were significantly less often associated with an abscess than fistulas with either a classic or intersphincteric horseshoe extension (table 2.1). Comparing patients with and without an associated abscess the healing rate was found to be 57 percent and 62 percent respectively. All abscesses were drained as described before. Once adequately drained, abscesses did not affect the outcome of transanal advancement flap repair.

Internal opening	Fistula type	Number (%)	Associated abscesses (%)	Healing rate (%)
	Classic horseshoe	23	35	81
Posterior (76%)	Intersphincteric horseshoe	41	54	73
	Direct course	36	55	37
Total		100	47	61

Table 2.1 Healing rates and prevalence of associated abscesses in high transsphincteric posterior fistulas

Internal opening	Fistula type	Number (%)	Associated abscesses (%)	Healing rate (%)
Anterior (23%)	Classic horseshoe	39	6	60
	Direct course	61	4	52
Total		100	5	55

Table 2.2 Healing rates and prevalence of associated abscesses in high transsphincteric anterior fistulas

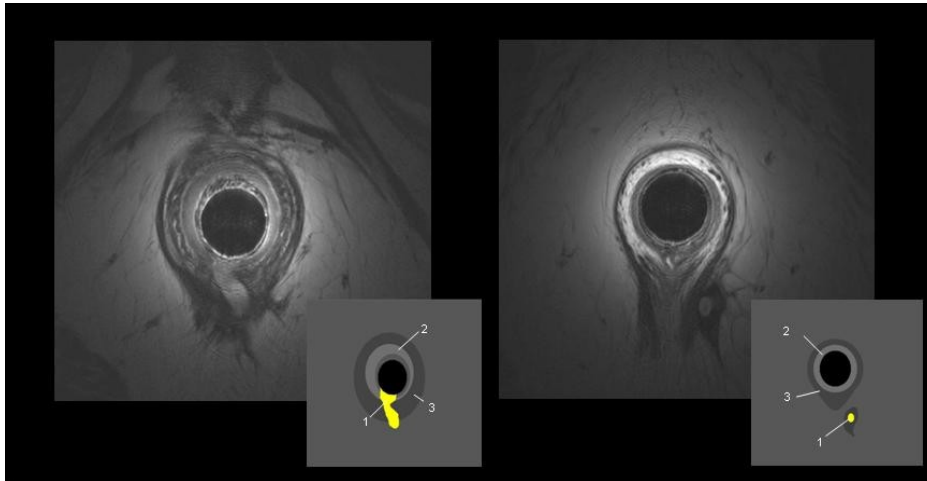


Figure 2.1 Direct fistula

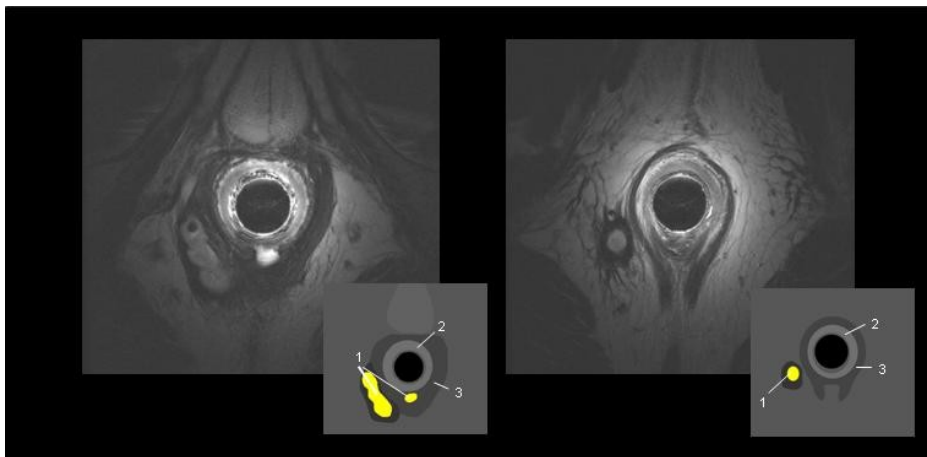


Figure 2.2 Classic horseshoe fistula

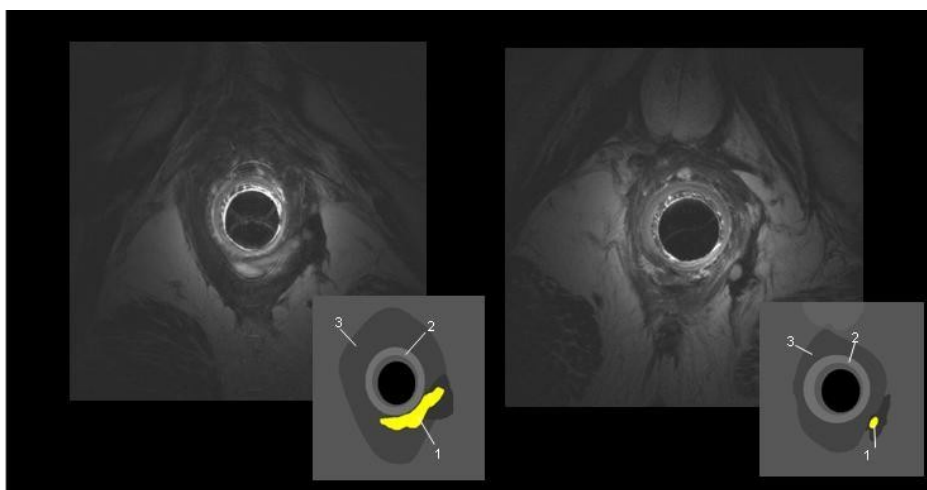


Figure 2.3 Intersphincteric horseshoe

Figure 2.1, 2.2 and 2.3 MR images of fistulas

1= fistula, 2= internal anal sphincter, 3= external anal sphincter

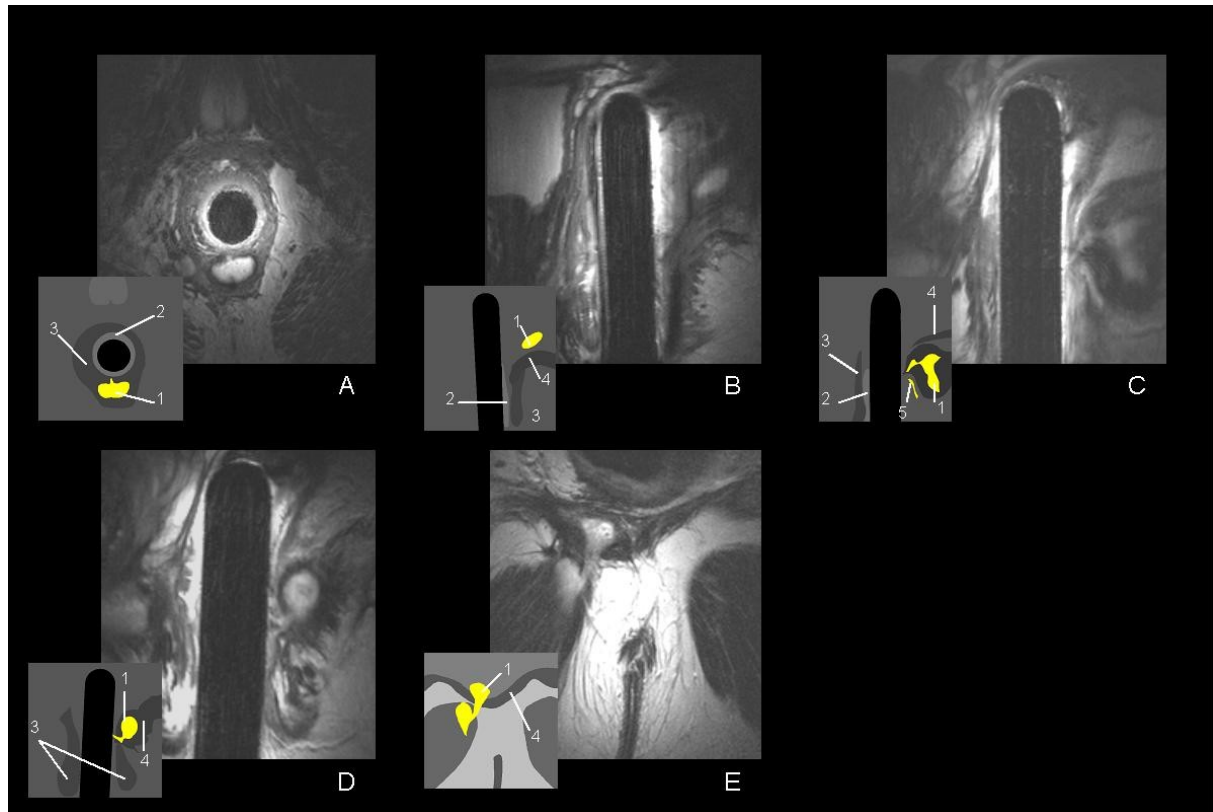


Figure 2.4 Abscesses

A = Intersphincteric abscess

B = Supralelevator abscess

C = Infralelevator abscess

D = Intralevator abscess

E = Translevator abscess

1= abscess, 2= internal anal sphincter, 3= external anal sphincter, 4= levator muscle, 5= fistulous tract

DISCUSSION

The majority of high transsphincteric fistulas, examined in the present study, had their internal opening at the posterior midline. These posterior fistulas showed three different ways of extension: a direct course, a classic horseshoe extension and, the most common one, an intersphincteric horseshoe extension. Anterior fistulas extended in two different ways; a direct course and a classic horseshoe course. The healing rate of fistulas with a direct course was significantly lower than the healing rate of fistulas with a classic or intersphincteric horseshoe extension. Associated abscesses were found in 47 percent of the posterior

fistulas and in five percent of the anterior fistulas. Once adequately drained, these abscesses did not affect the outcome of transanal advancement flap repair.

The most striking finding of the present study is the poor outcome after flap repair in patients with a high transsphincteric fistula, traversing the external anal sphincter in a direct course to the external opening. This finding is difficult to explain and has not been described before. In our opinion it might be possible that both anterior and posterior fistulas with a direct course represent a more aggressive form of perianal fistulous disease.

Another finding of the present study is the high prevalence of associated abscesses, especially in high transsphincteric fistulas with their internal opening at the posterior midline. Most of these abscesses could not be detected by physical examination. Although some of these abscesses presented a rather complex and bizarre course above the pelvic floor, they all could be detected and drained because of preoperative MR imaging. Endoanal MR imaging provides an useful tool for the visualization of these abscesses, enabling adequate drainage. The abscess cavity was deroofed, drained and irrigated during ten days with a malecot catheter. This might explain why these abscesses on itself had no detrimental effect on the outcome. Since the present study was not aimed at comparing flap repair with and without drainage of associated abscesses, it is not known what the outcome would have been in case these abscesses were overlooked and not drained.

In most studies no distinction is made between classic and intersphincteric horseshoe extensions. Furthermore, the exact prevalence of these extensions is not known. MR imaging with an endoanal coil, used in the present study, has revealed that horseshoe extensions of posterior fistulas most frequently occur in the intersphincteric plane. This finding has not been described before. Distinction between the two different types of horseshoe extensions is difficult without preoperative MR imaging. During flap repair, the fistulous tract is excised as far as possible, from the external opening to the exterior of the external anal sphincter. In case of a fistula with classic horseshoe extension a large part of the fistulous tract can be excised without damaging the external anal sphincter. Whilst treating fistulas with an intersphincteric horseshoe extension one should be aware that the fistulous tract penetrates the external anal sphincter closer to the external opening. In such a case only a limited part of the fistulous tract can be removed. Based on these considerations, it seems likely that preoperative imaging decreases the risk on sphincter damage in patients with horseshoe extensions.

High transsphincteric fistulas with horseshoe extensions and associated abscesses are considered as complex fistulas ¹³. The present study shows that the complexity of these fistulas does not affect the healing rate of transanal advancement flap repair. In contrast to

our expectations, the more simple fistulas with a direct course had a worse outcome. A possible explanation for this unexpected finding might be the possibility that the course of the fistula depends on the severity of the fistulous disease. The more fulminant the fistulous disease, the more perpendicular the fistula might traverse the anal sphincter muscles, resulting in a direct course to the external anal opening. Whether or not a fistula develops after incision and drainage of a perianal abscess might also depend on the severity of the fistulous disease. Further research is warranted to investigate this aspect. Since several years it is our policy to offer patients a repeat flap repair in case the first attempt has failed. In all patients who underwent such a second procedure complete healing of the flap was observed, except at the site of the original internal opening¹⁴. This remarkable clinical finding suggests that persistence of fistulas might be caused by ongoing disease within the remaining fistulous tract. Further research is warranted regarding this aspect in order to control this ongoing disease, thereby increasing the healing rate.

CONCLUSION

The complexity of high transsphincteric fistulas characterized by horseshoe extensions and associated abscesses does not affect the outcome of transanal advancement flap repair. Horseshoe extensions occur in two of every three patients with a posterior fistula. Extension in the intersphincteric plane is the most frequent one. In patients with an anterior fistula, only classic extensions are observed, accounting for 20 percent of the cases. Fistulas with a horseshoe extension have a significant better outcome than the more simple fistulas with a direct course.

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Required length of follow-up after transanal advancement flap
repair of high transsphincteric fistulas

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Colorectal Dis. 2009 Sep;11(7):726-8

ABSTRACT

Introduction

Repair of high perianal fistulas present a major challenge to many surgeons. Transanal advancement flap repair provides a useful tool in the treatment of these fistulas. Initially, promising results have been reported. More recent studies indicate that transanal advancement flap repair fails in one of every three patients. Aim of the present study was to determine the appropriate length of follow-up needed to assess the healing rate after transanal advancement flap repair of high transsphincteric fistulas.

Methods

Between 1992 and 2000 a consecutive series of 80 patients with a high transsphincteric fistula of cryptoglandular origin underwent transanal advancement flap repair. Medical records of all patients were studied. The initial healing rate and the median healing time were assessed. The initial outcome was successful in 54 patients. The medical records revealed that only one of these patients presented with a recurrent fistula after 28 months. The other 53 patients were sent a questionnaire in 2006. Aim of this questionnaire was to determine whether they had any complaints or signs of a recurrent fistula.

Results

The initial healing rate was 68 percent. The median healing time was 3.6 months.

The completed questionnaire was returned by 48 patients. None of these patients reported any complaints or signs of a recurrent fistula. Median duration of follow-up in these patients was 92 months.

Conclusion

At a median time interval of 3.6 months fistula healing was observed in 54 patients (68%). Only one patient (2%) encountered a recurrence. The length of follow-up can be restricted to the healing time.

INTRODUCTION

Perianal fistulas passing through the upper or middle third of the external anal sphincter present a major challenge to many surgeons. Despite new treatment modalities such as closure of the fistulous tract with fibrin glue or a bioprosthesis plug, transanal advancement flap repair (TAFR) is still considered an attractive option for the treatment of these high transsphincteric fistulas. Initially, the reported healing rates varied between 84 and 100 percent¹⁻⁴. More recent studies, however, revealed lower healing rates, varying between 45% and 77%⁵⁻¹¹. In none of these studies reported so far a distinction was made between persistence rate and actual recurrence rate. Therefore, it is not known to which extent these rates contribute to the ultimate failure rate. Furthermore, the length of follow-up required to assess the healing rate of TAFR has not been established yet. According to Golub and co-workers most failures were observed within the first weeks after flap repair¹². It seems obvious that they described persistent fistulas rather than recurrent fistulas, because the actual recurrence rate after initial healing of the fistula was found to be only 3.28% at a mean follow-up of 71 months. A recent study conducted by Ortiz *et al.* among 91 patients revealed that no recurrences occurred after 12 months¹³. In contrast to these findings, Van der Hagen *et al.*⁸ reported that recurrences still occur many years after initial healing and the success rate of TAFR decreases with time. Similar findings have been described by Ozuner and co-workers¹⁴. In order to determine the required length of follow-up after TAFR the present study was conducted aimed at evaluating the healing time after TAFR as well as the risk on recurrence after initial fistula healing.

METHODS

In the time period between 1992 and 2000, a consecutive series of 80 patients with a transsphincteric fistula of cryptoglandular origin, passing through the middle or upper third of the external anal sphincter, underwent transanal advancement flap repair. The present series comprised 57 men and 23 women. Median age at the time of repair was 48 (range 23-73) years. The first postoperative visit to the outpatient clinic occurred in six to eight weeks. Thereafter all patients were seen at a two monthly interval until the fistula had healed. Six months later the patients were re-examined. Healing of the fistula was defined as complete wound healing and closure of all external openings in combination with absence of symptoms. A persistent fistula was defined as a fistula without any tendency to heal after flap

repair. A recurrent fistula was defined as a fistula occurring after initial healing. The initial healing rate and the median healing time were assessed. All patients, in whom the fistula healed, were sent a questionnaire in 2006, except for one patient who encountered a recurrent fistula after 28 months after the procedure. Aim of this questionnaire was to determine whether they had any complaints or signs of a recurrent fistula.

Inclusion and exclusion

Only patients with a high transsphincteric fistula of cryptoglandular origin were included. Patients with a superficial transsphincteric fistula, passing through the lower third of the external anal sphincter and those with a rectovaginal fistula or a fistula caused by Crohn's disease were excluded.

Surgical technique

Patients underwent complete mechanical bowel preparation (polyethylene glycol). After induction of general endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, all external openings were enlarged and all fistulous tract were cored out. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening, as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibers of the internal anal sphincter, was raised from the level of the dentate line and mobilized over a distance of four to six cm proximally. The base of the flap was about twice the width of its apex. The flap was advanced and sutured to the neodentate line with absorbable sutures. A single surgeon performed all operations (WRS).

Postoperative care

All patients were immobilized for five days. During these five days a Foley catheter was given to obtain complete bed rest. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily. Average duration of hospital stay was seven days.

RESULTS

At a median time interval of 3.6 months fistula healing was achieved in 54 patients (68%). Study of medical records revealed only one recurrent fistula (2%). In this subject endoanal MR imaging was performed to confirm the presence and course of the recurrent fistulous tract, which was found to be exactly the same as the original one. The other 53 patients were sent a questionnaire. The completed questionnaire was returned by 48 of the 53 patients. One patient died from unrelated cause and four patients were lost-to-follow-up caused by missing address data. None of the responding patients reported any complaints or signs of a recurrent fistula. Median duration of follow-up in these patients was 92 months (range 52-161).

DISCUSSION

Transanal advancement flap repair is considered an attractive treatment option for perianal fistulas passing through the upper or middle third of the external anal sphincter. Initially, healing rates between 84 and 100 percent were reported¹⁻⁴. During the last decade several studies have revealed considerably lower healing rates⁵⁻¹¹. The duration of follow-up in these studies is highly variable⁵⁻¹⁰ whereas the length of follow-up required to assess the healing rate of flap repair is not clearly established.

Recently, Van der Hagen *et al.*⁸ reported that recurrences still occur many years after initial healing, indicating that the outcome of TAFR decreases with time. Among a consecutive series of 41 patients who underwent TAFR, they observed a healing rate of 78% at 12 months. The overall healing rate dropped to 56% and 37% after 24 and 48 months, respectively. Ozuner *et al.* have reported similar data¹⁴. In contrast to these findings, Ortiz *et al.* found no recurrences after 12 months¹³. This is in concordance with the findings reported by Golub and co-workers¹². In their series of 164 patients undergoing TAFR a initial healing rate of 94% was observed. Average healing time was six weeks. Only 60 of the 164 patients were available for long-term follow-up. Two of these 60 patients (3%) encountered with a recurrent fistula after 33 and 47 months, respectively. These fistulas developed on a site remote from the index fistula and may thus actually represent new fistulas rather than recurrent fistulas.

In our present study the median healing time after TAFR was found to be 3.6 months. After initial healing the recurrence rate was very low (2%). The failure rate in the present

consecutive series was mainly due to persistence of the fistulas. These observations are in concordance with those reported by Golub and Ortiz. The rather conflicting results as reported by Van der Hagen and Ozuner are difficult to explain. The inclusion of patients with a fistula caused by Crohn's disease might provide a possible explanation. In the study conducted by Van der Hagen *et al.* nearly one third of the patients had a perianal fistula caused by Crohn's disease. After 24 months the healing rate among these subjects was 67%, whereas the healing rate of 52% was observed in patients with a cryptoglandular fistula. Examining the recurrence rate at 48 and 72 months the authors did not differentiate between patients with or without Crohn's disease. In our opinion it is therefore not justified to draw any conclusions concerning the recurrence rate of cryptoglandular fistulas after the first two years. It might be possible that the late recurrences after 48 months are mainly due to underlying Crohn's disease. It is known that TAFR is more likely to fail in these patients because of the recurrent character of the disease^{7, 11}. In our present series, as well as those studied by Ortiz and Golub patients with Crohn's disease were excluded. The data obtained from these studies indicate that the recurrence rate after initial healing following TAFR is very low and the failure rate is mainly influenced by persistence of the fistula. In our opinion the length of follow-up after TAFR in patients with a high transsphincteric cryptoglandular fistula can therefore be restricted to the healing time.

CONCLUSION

At a median time interval of 3.6 months fistula healing was observed in 54 patients (68%). Only one patient (2%) encountered a recurrence. In our opinion follow-up can therefore be restricted to the point of time on which complete healing of the fistula is observed.

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Repeat transanal advancement flap repair: impact on the
overall healing rate of high transsphincteric fistulas and on
fecal continence

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Dis Colon Rectum. 2007; 50:1508-11

ABSTRACT

Introduction

Transanal advancement flap repair has been advocated as the treatment of choice for transsphincteric fistulas passing through the upper or middle third of the external anal sphincter. It is not clear whether prior attempts at repair adversely affect the outcome of transanal advancement flap repair. The purpose of the present study was to evaluate the success rate of a repeat transanal advancement flap repair and to assess the impact of such a second procedure on the overall healing rate of high transsphincteric fistulas and on fecal continence.

Methods

Between January 2001 and January 2005 a consecutive series of 87 patients (M: F= 62: 25, median age: 49 (range 27-73) underwent a transanal advancement flap repair. Median follow-up was 15 (range 2-50) months. Patients in whom the initial operation failed were offered two further treatment options: a second flap repair or a long-term indwelling seton drainage. Twenty-six patients (male/female-ratio 5: 2, median age 51 (range 31-72) years) preferred a repeat repair. Continence status was evaluated before and after the procedures using the Rockwood Fecal Incontinence Severity Index.

Results

The healing rate after the first transanal advancement flap repair was 67 percent. Of the 29 patients in whom the initial procedure failed, 26 underwent a repeat transanal advancement flap repair. The healing rate after this second procedure was 69 percent, resulting in an overall success rate of 90 percent. Both before and after the first attempt of transanal advancement flap repair the median Rockwood Fecal Incontinence Severity Index was seven (range 0-34). In patients who underwent a second transanal advancement flap repair the median Rockwood Fecal Incontinence Severity Index before and after this procedure was nine (range 0-34) and eight (range 0-34), respectively. None of these changes were statistically significant.

Conclusion

Repeat transanal advancement flap repair increases the overall healing rate of high transsphincteric fistulas from 67 percent after one attempt to 90 percent after two attempts without a deteriorating effect on fecal continence.

INTRODUCTION

Transanal advancement flap repair has been advocated as the treatment of choice for transsphincteric perianal fistulas passing through the upper or middle third of the external anal sphincter. Initially, the reported healing rates varied between 84 and 100 percent¹⁻⁴. In a recent study among 105 patients, conducted in two tertiary referral centers, a healing rate of 69 percent was found⁵. Similar results were reported by other authors⁶⁻⁹. It is still unclear whether the outcome after transanal advancement flap repair is influenced by prior attempts at repair. According to some authors, prior procedures, such as fistulotomy, fistulectomy and the use of fibrin glue adversely affect the healing rate after transanal advancement flap repair^{6, 10}. However, these findings could not be confirmed by others^{7, 11}. Until now data regarding the healing rate after repeat flap repair and the impact on fecal continence are scarce. It has been suggested that one single transanal advancement flap repair may result in incontinence. The reported incidence of this side effect varies between eight and 35 percent^{2, 6, 7, 10-12}. According to some authors inclusion of internal anal sphincter fibers, which is necessary to strengthen the flap, contributes to the impairment of continence. Based on this assumption it is possible that a second flap repair further deteriorates fecal incontinence. Aim of the present study was to investigate the healing rate after a repeat flap repair and to assess the impact of such a second procedure on the overall healing rate of high transsphincteric fistulas. In addition fecal continence was assessed before and after the first and second flap repair, using the Rockwood Fecal Incontinence Severity Index¹³.

PATIENTS AND METHODS

Between January 2001 and January 2005, a consecutive series of 87 patients with a transsphincteric fistula of cryptoglandular origin, passing through the middle or upper third of the external anal sphincter, underwent transanal advancement flap repair. The present series comprised 25 women and 62 men. Median age at the time of repair was 49 (range 27-73) years. Prior to the procedure all patients underwent endoanal MR imaging in order to confirm the transsphincteric course of the fistulous track. This imaging technique was also performed to identify the location of the internal opening and to detect the presence of any horseshoe extensions. This first attempt at repair failed in 29 patients (33%). These subjects were offered two further treatment options: a second flap repair or a long-term indwelling

seton drainage. Twenty-six patients (male/female-ratio 5: 2, median age 51 (range 31-72) years) preferred a repeat repair. Three patients were treated by the loose-seton technique. This loose-fitting seton is left in situ for at least three to four years. In our experience, the seton slowly migrates through the external sphincter. When it reaches the subcutaneous level it is removed and the remnant of the fistulous tract is excised.

Surgical technique

Patients underwent complete mechanical bowel preparation (polyethylene glycol). After induction of general endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, the internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening, as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibers of the internal anal sphincter, was raised from the level of the dentate line and mobilized over a distance of four to six cm proximally. The base of the flap was about twice the width of its apex. The flap was advanced and sutured to the neodentate line with absorbable sutures. A single surgeon performed all operations (WRS). Exactly the same surgical technique was used in both the first and the second repair.

Postoperative care

All patients were immobilized for five days. During these five days, a Foley catheter was given to obtain complete bed rest. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily. Average duration of hospital stay was seven days.

Assessment of fecal continence

Impairment of continence was evaluated both before and after the first and second attempt, using the Rockwood Fecal Incontinence Severity Index (RFISI). This is a validated index based on a type X frequency matrix. The matrix includes four types of leakage commonly found in the fecal incontinent population: gas, mucus, liquid and solid stools and five frequencies: once to three times a month, once per week, twice per week, once per day, and twice per day. For the specification of the weighting scores patient input was used. Scores range from zero (total continence) to 61 (complete incontinence to solid stool on daily bases).

Statistical analysis

For statistical analysis the Fisher's exact test was used. A p-value <0.05 was considered to be statistically significant.

RESULTS

Median duration of follow-up was 15 months (range 2-50). Fistula healing was observed in 58 of the 87 patients (67 percent). Of the 29 patients in whom the initial procedure failed 26 underwent a repeat transanal advancement flap repair. The healing rate after this second procedure was 69 percent, resulting in an overall success rate of 90 percent. Prior to the first attempt at transanal advancement flap repair the median Rockwood Fecal Incontinence Severity Index was seven (range 0-34). The median score did not change after the first procedure. In three of these patients the RFISI improved and in three patients it worsened. In all other patients Rockwood Fecal Incontinence Severity Index did not change after the first procedure. Before and after the second repair the median Rockwood Fecal Incontinence Severity Index was nine (range 0-34) and eight (range 0-34), respectively. This change was not statistically significant. In one of these patients the Rockwood Fecal Incontinence Severity Index improved, in one it worsened and in 24 patients the Rockwood Fecal Incontinence Severity Index did not change after the second procedure. Of the eight patients in whom the second flap repair failed, one patient was successfully treated with anocutaneous advancement flap repair. The other seven patients were treated with long-term indwelling seton drainage.

	No.Pts	Median follow-up (in months)	Healing rate	Median RFISI before	Median RFISI after
First repair	87	15	67%	7	7
Second repair	26	15	69%	9	8
After two repairs	87	15	90%	8	8

Table 4.1. Results of repeat TAFR

DISCUSSION

Transanal advancement flap repair has been advocated as the treatment of choice for transsphincteric perianal fistulas passing through the upper or middle third of the external anal sphincter. Initially, healing rates between 84 and 100 percent were reported¹⁻⁴. During the last decade several studies have revealed considerably higher recurrence rates^{5-8, 10, 14}. In a Dutch study among 105 patients, conducted in two tertiary referral centers, a recurrence rate of 31 percent was observed⁵. Similar results have been reported by other investigators^{6-8, 10, 14}. There is some evidence that prior attempts at repair are a negative predictor of outcome. A previous study, conducted at our own institution revealed a less favorable outcome in patients who had undergone two or more previous attempts at repair, such as fistulotomy or fistulectomy¹⁰. In 44 patients, who underwent a flap repair, we found that the healing rate was 87 percent in patients who had undergone no, or only one previous attempt at repair. This healing rate dropped to 50 percent in patients who had undergone two or more prior attempts at repair. A similar finding was observed by Ozuner and coworkers⁶. According to others, however, the number of previous repair, does not affect the outcome of transanal advancement flap repair^{7, 8, 11}.

Until now data regarding the healing rate after repeat flap repair and the impact on fecal continence are scarce. According to Lindsey *et al.* the efficacy of a repeat transanal advancement flap repair is limited since “the scarring associated with a failed advancement flap compromises the changes of success with subsequent flaps”¹⁵. In a study conducted by Kodner *et al.*⁴, nine patients in whom the initial flap repair failed, underwent a second operation, which was successful in all patients. In a study conducted by Mizrahi *et al.*⁷ 12 patients underwent repeat surgery because of initial failure, of whom eight healed (67%). These two small series indicate that a repeat flap repair might be worthwhile. However, in none of these two studies the impact on fecal continence was assessed. The data obtained from our present study are in accordance with those reported by Kodner and Mizrahi. The healing rate of the second procedure was 69 percent. This successful outcome resulted in an overall healing rate of 90 percent. We do not know which factors are predictors of outcome and why flaps that initially failed did succeed on the second repair. We choose to report this data after a median follow-up of 15 months. Although this time period might seem relatively short, there are indicators that more than 80 percent of the recurrences occur within the first 12 months⁶. In a study conducted by Athanasiadis *et al.* 90 percent recurrent fistulas developed within the first year after treatment¹⁶.

The reported incidence of disturbed continence following transanal advancement flap repair varies between eight and 35 percent ^{2, 4, 5, 7, 10, 11}. It has been postulated that the inclusion of internal anal sphincter fibers, which is necessary to strengthen the flap, contributes to the impairment of continence ¹⁷. A second flap also requires inclusion of internal anal sphincter fibers, which might result in further impairment of fecal continence. In a previous study we were able to demonstrate that the use of a Parks retractor has a deteriorating effect on fecal continence. This side effect was not observed after flap repair with the use of a Lonestar retractor ¹⁸. In the present study this ring retractor, with multiple skin hooks on elastic bands, was also used in order to gain access to the anal canal. Although internal anal sphincter fibers were included to strengthen the second flap no deterioration of continence was observed after the repeat flap repair. Therefore it seems unlikely that inclusion of internal anal sphincter fibers contributes to the impairment of fecal continence after transanal advancement flap repair. In our opinion avoidance of anal stretch during the procedure is far more important in reducing the risk of postoperative continence disturbances. The median postoperative Rockwood Fecal Incontinence Severity Index score, observed in our patients, was eight. It seems likely that this minor deterioration of continence did not affect the quality of life of our patients, because it has been reported that only a score of over 30 has a detrimental effect on quality of life ¹⁹.

Based on the data obtained from the present study it is recommended to offer all patients a repeat transanal advancement flap repair after a failed first flap repair.

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Does rectal mucosal blood flow affect the outcome of transanal advancement flap repair?

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ABSTRACT

Introduction

Transanal advancement flap repair provides a useful tool in the treatment of high transsphincteric fistulas. Recent studies indicate that transanal advancement flap repair fails in one of every three patients. Until now, no definite risk factors for failure have been identified. A previous pilot study, conducted in our own institution, revealed a significant decrease in rectal mucosal blood flow after creation of the advancement flap. We postulated that impaired blood flow might result in breakdown of the distal part of the flap. This study was designed to evaluate the effect of rectal mucosal blood flow on the outcome of transanal advancement flap repair.

Methods

Between August 2004 and June 2007 a series of 54 patients with a high transsphincteric fistula underwent transanal advancement flap repair. The present series comprised 34 men and 20 women. Median age at the time of repair was 45 (range 25-68) years. Rectal mucosal blood flow was determined by laser Doppler flowmetry before and after creation of the flap. The flow was expressed in arbitrary units.

Results

Transanal advancement flap repair was successful in 34 patients (63 percent). Median healing time was 2.2 months. Median mucosal blood flow before and after transanal advancement flap repair was 145 arbitrary units and 94 arbitrary units respectively. This decrease was statistically significant. Comparing patients with and without a successful repair no differences were found regarding mucosal blood flow before and after creation of the flap (146 vs. 138 arbitrary units, 83 vs. 104 arbitrary units).

Conclusion

Rectal mucosal blood flow does not affect the outcome of transanal advancement flap repair.

INTRODUCTION

Transanal advancement flap repair is considered an attractive treatment option for transsphincteric perianal fistulas passing through the upper or middle third of the external anal sphincter. It enables healing of the fistula without sphincter damage and consequent continence disturbances. Initially, healing rates between 84 and 100 percent were reported¹⁻⁴. During the last decade, however, it became clear that transanal advancement flap repair fails in one of every three patients⁵⁻¹¹. Potential risk factors for failure, such as gender, age, BMI, prior attempts at repair or the previous use of a seton have been analyzed. So far, no definite risk factors have been identified. A previous pilot-study, conducted in our own institution, revealed a significant decrease in rectal mucosal blood flow after creation of the advancement flap¹². We postulated that impaired rectal mucosal perfusion might result into breakdown of the distal part of the flap, thereby affecting the outcome of transanal advancement flap repair. This study was designed to evaluate the effect of rectal mucosal blood flow on the outcome of transanal advancement flap repair.

PATIENTS AND METHODS

In 61 patients who underwent transanal advancement flap repair between 2004 and 2007 rectal mucosal blood flow (MBF) was determined by laser Doppler flowmetry before and after creation of the flap. In seven of these patients BioGlue® was installed as an adjunct to their flap repair. Because an unexpected, detrimental effect of BioGlue® was observed, these patients were excluded. Eventually, the present series comprised 54 patients, of whom 34 were men and 20 were women. Median age at the time of repair was 45 (range 25-68) years.

Exclusion criteria

Women with a rectovaginal fistula, patients with a perianal fistula caused by Crohn's disease, and patients who underwent concomitant instillation of BioGlue® were excluded from the present series.

Endoanal Magnetic Resonance Imaging

Prior to the procedure all patients underwent endoanal MR imaging in order to confirm the transsphincteric course of the fistulous track. This imaging technique was also performed to

identify the location of the internal opening and to detect the presence of any horseshoe extensions.

Laser Doppler Flowmetry

Rectal mucosal blood flow was measured using the O2C® (Lea Medizin Technik, Giesen, Germany). This device combines two optical techniques, namely laser Doppler flowmetry and reflectance spectrophotometry (RS), in one optic fiber. There is no interference between the two techniques because they operate at different light wave ranges. In the present study a flat probe was used, with a measurement depth of four to six mm. Using laser Doppler flowmetry, rectal mucosal blood flow is determined by analysis of the power spectra from moving blood cells, generated by Doppler frequencies of backscattered laser light (820 nm). The mucosal blood flow value is defined mathematically as the first moment of the Doppler power spectra, so it relates to the velocity of the erythrocytes multiplied by the number of moving erythrocytes, and it is described in arbitrary units (AU). Before creation of the flap, mucosal blood flow was measured just above the dentate line. All measurements were performed by the same investigator. During each measurement (two minutes), the probe was held by hand. To prevent occlusion of the underlying microvessels, pressure to the mucosa was avoided. Measurement artefacts were identified by a drop in signal in the laser Doppler flowmetry and RS curve and a change in configuration of the RS signal. Directly after placing the probe on the mucosa, we observed changes in signal. However, after about one minute, the signal stabilized. From that moment, we started recording. During subsequent recording, no noteworthy changes in signal were observed. After advancing and suturing the flap to the neodentate line, the probe was applied to the apex of the flap and the recording was repeated.

Surgical Technique

Patients underwent complete mechanical bowel preparation (polyethylene glycol). After induction of general endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, the external opening was enlarged and the fistulous tract was excised as far as possible. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa, and some of the most superficial fibers of the internal anal sphincter, was raised from the level of the dentate

line and mobilized over a distance of four to six cm proximally. The flap was advanced and sutured to the neodentate line with absorbable sutures. One surgeon performed all operations (WRS).

Postoperative Care

All patients were immobilized for five days. During these five days a Foley catheter was given to obtain complete bed rest. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily.

Statistical Analysis

The sample size calculation of the present study was based on results from an earlier pilot-study. In this previous study we found a significant difference in blood flow between smoking and nonsmoking patients in a relatively small group of patients. The difference in blood flow found in this previous study was more than 50 percent. Our assumption was that this diminished blood flow would contribute to failure. To detect a blood flow of 40 percent less in the failure group, using a significance level of five percent, at least 40 patients were required to achieve a power of 80 percent. All measurements were analyzed using Graphpad Prism (version 3.0; Graphpad Software, San Diego, CA, USA). Median value of each measurement was determined. Changes within groups were evaluated using Wilcoxon's signed-rank test. Comparison of the changes between groups was conducted using the Mann-Whitney U test. $P \leq 0.05$ was considered to be statistically significant.

RESULTS

Transanal advancement flap repair was successful in 34 patients (63 percent). Median healing time was 2.2 months. Median rectal mucosal blood flow before transanal advancement flap repair was 145 (range 29-411) AU. After creation of the flap the flow dropped to 94 (range 4-529) AU. This decrease was statistically significant ($P = 0.03$; Wilcoxon). In patients in whom flap repair was successful, the preoperative rectal mucosal blood flow varied between 29 and 364 AU, with a median value of 146 AU. In the group of patients in whom flap repair failed, the median rectal mucosal blood flow before transanal advancement flap repair was 138 (range 37-411) AU. This slight difference in preoperative rectal mucosal blood flow between patients with a successful outcome and patients with a failure was not statistically significant, neither in the univariate nor in the multivariate

analysis. In patients with a successful outcome, the rectal mucosal blood flow, measured shortly after creation of the flap, varied between four and 529 AU, with a median value of 83 AU. In the patients who encountered a failure the median postoperative rectal mucosal blood flow was 104 (range 9-280) AU. This difference in postoperative rectal mucosal blood flow between patients with a successful outcome and patients with a failure was not statistically significant, neither in the univariate nor in the multivariate analysis. Among the present series were 22 patients who smoked cigarettes. No difference in healing rate between smoking and non-smoking patients was observed (64 percent vs. 63 percent, respectively). Although the median rectal mucosal blood flow before and shortly after transanal advancement flap repair was lower in smoking patients than in non-smoking patients (126 vs. 162 AU, 75 vs. 122 AU, respectively), these differences were not statistically significant. Patients in whom transanal advancement flap repair was not successful were offered two further treatment options; repeat transanal advancement flap repair or a long-term indwelling seton. One patient did not want further treatment. Eleven patients underwent repeat transanal advancement flap repair, whereas a seton was placed in the remaining eight patients. During both procedures, careful examination of the primary advancement flap was performed. In all patients the flap was completely healed, except at the site of the original internal opening.

Potential risk factors for failure			
	OR	95% CI	<i>P</i> -value
Flowreduction	1.00	0.99-1.01	0.82
Gender	1.83	0.49-6.90	0.37
Age	0.70	0.95-1.06	0.83
BMI	1.07	0.91-1.25	0.43
Prior attempts at repair	1.44	0.41-5.05	0.57
Smoking	0.70	0.99-1.00	0.61
Location of internal opening	3.03	0.78-11.81	0.11

OR = Odds Ratio; CI = Confidence Interval

Table 5.1 Multivariate regression analysis for possible risk factor for failure

	Overall	Success	Failure
Before TAFR	145	146	138
After TAFR	94	83	104

Table 5.2. Median MBF expressed in AU in patients with and without a successful outcome

	Non-smokers	Smokers
Before TAFR	62	122
After TAFR	126	75

Table 5.3. Median MBF expressed in AU in smoking and non-smoking patients

DISCUSSION

Despite new treatment modalities such as closure of the fistulous tract with fibrin glue or with a bioprosthesis plug, transanal advancement flap repair still provides a useful tool in the treatment of high transsphincteric fistulas. Initially, the reported healing rates after transanal advancement flap repair varied between 84 and 100 percent ¹⁻⁴. In recent years it has become clear that flap repair fails in one of every three patients ⁵⁻¹¹. Until now, no definite factor predisposing to failure has been identified ¹³.

In a previous pilot-study, designed to assess rectal mucosal blood flow before and after flap repair in smoking and non-smoking patients, we observed a significant decrease in rectal mucosal blood flow after creation of the flap ¹². Furthermore, rectal mucosal blood flow was found to be significantly lower in smoking patients, both before and after transanal advancement flap repair. Based on these findings, we postulated that impaired rectal mucosal blood flow might contribute to failure of the advancement flap. A remarkable finding in the present study was the wide interindividual variability in rectal mucosal blood flow. This wide variability is difficult to explain. This calls into question the reliability of the measurements. Although laser Doppler flowmetry is a well-established technique, it has of course also its drawbacks. One of the major limitations is the influence of motion artifacts ¹⁴.

However, in the present study, artifacts could easily be identified by a drop in signal in the laser Doppler flowmetry and RS curves and a change in configuration of the RS signal. Directly after placing the probe on the mucosa, we observed great changes in signal. However, the signal stabilized after a short period. From that moment on, we started recording. During subsequent recording, no noteworthy changes in signal were observed. In our previous pilot study, we also observed a substantial variability in rectal mucosal blood flow between individuals. Moreover, a similar variability in rectal mucosal blood flow was observed by other authors^{12, 14-17}.

In the present study we did not find any correlation between blood flow and the outcome of transanal advancement flap repair. This observation indicates that a diminished rectal mucosal blood flow does not have a detrimental effect on transanal advancement flap repair. If impaired rectal mucosal blood flow were a risk factor, one would expect a complete breakdown of the flap caused by local necrosis in case of a failure. However, in all our patients with a persistent fistula, we observed complete healing of the flap except at the site of the original internal opening. This remarkable clinical observation supports the finding of the present study that impaired rectal mucosal blood flow is not a major risk factor. In contrast to the finding of our previous study the difference in blood flow between smoking and non-smoking patients did not reach statistical significance. Several studies have been conducted to assess the effect of smoking on blood flow. However, the results of these studies are rather conflicting. Emmanuel and Kamm observed a detrimental effect of smoking on rectal mucosal bloodflow¹³. This effect lasted for only 30 minutes. Monfrecola and colleagues recorded cutaneous blood flow on the tip of the third finger¹⁸. According to these authors the flow decreased during and after smoking a cigarette, returning to baseline values within two to five minutes. Similar findings have been reported by others^{16, 19}. Although Mavrouopoulos *et al.* also observed a decrease in cutaneous blood flow of the thumb, they observed an opposite response in forehead skin and gingiva²⁰. This latter finding has been confirmed by Meekin and colleagues²⁰. These results, although conflicting, provide some evidence that smoking has a short lasting effect on blood flow. In our present series none of the patients smoked for at least eight hours prior to flap repair. Therefore, it seems unlikely that the short-term effect of cigarette smoke did affect the blood flow in our study population. However, it is generally accepted that the use of tobacco is also notorious for its chronic, detrimental effect on the microcirculation. Comparing smoking and non-smoking subjects, Petschke *et al.* and Van Adrichem and coworkers observed lower baseline values of blood flow, recorded at the tip of the finger or thumb, in smoking subjects^{16, 19}. This difference, however, lacked significance. In the present study we also observed lower baseline values of rectal mucosal blood flow in smoking patients. This difference also lacked

significance. In contrast to these findings, other authors did not observe any difference in baseline values in smoking patients^{18, 21-23}.

Although our smoking patients had lower rectal mucosal blood flow, both before and after creation of the flap, this non-significant difference did not result in a lower healing rate among smoking patients. This finding is inconsistent with our earlier observations and those reported by Ellis and co-workers²⁴. However, two recent studies, conducted by Gustafsson *et al.* and Van Koperen and colleagues did not reveal any relation between smoking and impaired healing^{25, 26}. Our earlier observations revealed that the healing rate after flap repair was significantly lower only in those patients who smoked ten or more cigarettes per day. Based on this observation we encouraged our patients to quit or at least reduce smoking several weeks before and after the operation. Although we never analyzed the outcome of this intervention, this might have affected the healing rate among smoking patients in a positive way. In the present series only five patients smoked ten or more cigarettes per day. Our advice to quit or reduce smoking prior to the procedure and the small number of heavy smokers in the present series might explain the difference between our previous study and the present one.

CONCLUSION

In contrast to our expectations, the present, prospective study reveals that rectal mucosal blood flow does not affect the outcome of transanal advancement flap repair. This is in accordance with the clinical observation that all our patients with a failure showed complete healing of the flap except at the site of the original internal opening. The lack of factors contributing to failure and the findings of the present study suggest that failure after flap repair is caused by ongoing disease within the remaining fistulous tract.

ACKNOWLEDGEMENT

The authors thank J.C. Hop of the department of Biostatistics for the statistical analysis, D.A.M.P.J. Gommers of the department of Anesthesiology for his collaboration regarding the use of the O2C®, and J.J. van Wijk for his efforts in conducting the laser Doppler flowmetry measurements.

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Seton drainage prior to transanal advancement flap repair:
useful or not?

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ABSTRACT

Introduction

Transanal advancement flap repair provides a useful tool in the treatment of high transsphincteric fistulas. Recent studies indicate that transanal advancement flap repair fails in one of every three patients. Until now, no definite predictive factor for failure has been identified. Although some authors have reported that preoperative seton drainage might improve the outcome of transanal advancement flap repair, this could not be confirmed by others. We conducted the present study to assess the influence of preoperative seton drainage on the outcome of transanal advancement flap repair in a relatively large series.

Methods

Between December 1992 and June 2008 a consecutive series of 278 patients (M: F=179: 99, median age 46 (range 19–73) years) with a cryptoglandular, transsphincteric fistula, passing through the upper or middle third of the external anal sphincter underwent transanal advancement flap repair. Patients were recruited from the colorectal units of two university hospitals (Erasmus Medical Center, Rotterdam: n=211, Leiden University Medical Center, Leiden: n=67). Baseline characteristics did not differ between the two clinics. Sixty-eight of these patients underwent preoperative seton drainage for at least two months and until the day of the flap repair.

Results

Median healing time was 2.2 months. In patients without preoperative seton drainage the healing rate was 63 percent, whereas the healing rate was 67 percent in patients who underwent preoperative seton drainage. This difference was not statistically significant. No differences in healing rates were found between the series from Leiden and Rotterdam

Conclusion

Preoperative seton drainage does not improve the outcome of transanal advancement flap repair.

INTRODUCTION

Perianal fistulas passing through the upper or middle third of the external anal sphincter present a challenge to many surgeons. Despite new treatment modalities such as closure of the fistulous tract with fibrin glue or a bioprosthetic plug, transanal advancement flap repair still provides a useful tool in the treatment of these fistulas. It enables healing of the fistula without damage of the external sphincter and consequent fecal incontinence. Initially the reported healing rates varied between 84 and 100 percent¹⁻⁴. However, during the last decade it has become clear that transanal advancement flap repair fails in one of every three patients⁵⁻¹¹. Until now no definite risk factor for failure has been identified. Recently we examined the outcome of repeat flap repair in 26 patients, who encountered a failure after the initial procedure¹². In all these patients we noticed complete healing of the advancement flap, except at the site of the original internal opening. This remarkable clinical finding and the lack of predictive factors for failure suggest that persistence of the fistula might be caused by ongoing disease within the remaining fistulous tract. Obliteration of this tract with a surgical adhesive, such as fibrin glue and Bio Glue®, as an adjunct to flap repair has not only failed to improve the healing rate, but even had a detrimental effect on the outcome¹³⁻¹⁵. Some authors advocate preoperative seton drainage, since it allows drainage of the fistulous tract, thereby reducing the inflammatory activity within the tract and resolving secondary tracts^{9, 16, 17}. Although two reports^{7, 9} indicate that preoperative seton drainage improves the healing after transanal advancement flap repair, this beneficial effect could not be confirmed by others^{10, 14}. However, the reported series were rather small and study populations were often of heterogeneous consistency, including patients with a rectovaginal fistula and patients with fistulas caused by Crohn's Disease. The aim of the present study was to assess the effect of preoperative seton drainage on the outcome of transanal advancement flap repair in a relatively large series of patients with a high transsphincteric fistula of cryptoglandular origin.

PATIENTS AND METHODS

Between December 1992 and June 2008 a consecutive series of 278 patients with a cryptoglandular, transsphincteric fistula passing through the upper or middle third of the external anal sphincter underwent transanal advancement flap repair. The patients were recruited from the colorectal units of two university hospitals (Erasmus Medical Center,

Rotterdam: n=211, Leiden University Medical Center, Leiden: n=67). Baseline patient characteristics did not differ between the two clinics. Sixty-eight of these patients underwent preoperative seton drainage for at least two months until the day of flap repair. In the Leiden University Medical Center and in the Erasmus Medical Center, transanal advancement flap repair after preoperative seton drainage was performed in 33 and 35 patients, respectively. Clinical charts were studied to analyze the reason for seton placement. The present series comprised 179 men and 99 women. Median age at the time of repair was 46 (range, 19 – 73) years.

Exclusion criteria

Patients with a rectovaginal fistula or a fistula caused by Crohn's disease were excluded from the present series.

Imaging

Prior to flap repair all patients underwent either hydrogen peroxide-enhanced endoanal ultrasonography or endoanal magnetic resonance imaging in order to assess the course of the transsphincteric fistulous tract. These imaging techniques were also performed to identify the location of the internal opening and to detect the presence of any horseshoe extensions and associated abscesses.

Surgical technique

Patients referred to the Erasmus Medical Center underwent complete mechanical bowel preparation (polyethylene glycol). In the Leiden University Medical Center a single phosphate enema was instilled on the day of the operation. After induction of general endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, the seton, if present, was removed. The external opening was enlarged and the fistulous tract was curetted. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibers of the internal anal sphincter, was raised from the level of the dentate line and mobilized over a distance of four to six centimeters proximally. The flap was advanced and sutured to the neodentate line with absorbable sutures.

Postoperative care

Patients who underwent transanal advancement flap repair at the Erasmus Medical Center in Rotterdam were immobilized for five days. Patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily. The patients who underwent transanal advancement flap repair at the Leiden University Medical Center were immobilized for a minimum of 24 hours and did not receive additional antibiotics.

Follow-up

All patients visited the outpatient clinic at six and 18 weeks and 12 months postoperatively. Healing of the fistula was defined as complete wound healing and closure of all external openings in combination with absence of symptoms.

RESULTS

The charts of 278 consecutive patients who had undergone transanal advancement flap repair for cryptoglandular, transsphincteric fistulas, passing through the upper or middle third of the external anal sphincter were analyzed. Median healing time was 2.2 months. In patients without preoperative seton drainage the healing rate was 63 percent, whereas the healing rate was 67 percent in patients who underwent preoperative seton drainage. This difference was not statistically significant. No specific reasons for seton placement were identified. Both university hospitals are tertiary referral centers and most patients were referred from smaller district hospitals. Many surgeons in these hospitals are not confident with the treatment of high, transsphincteric fistulas. To our knowledge most of the referring surgeons performed seton drainage until definite treatment. Baseline fistula and patients characteristics did not differ between the patients with and without preoperative seton drainage (table 6.1). No differences in healing rates were found between the series from Leiden and Rotterdam (table 6.2).

		Seton	No seton
Internal opening	Posterior	63%	70%
	Anterior	29%	26%
	Lateral	7%	4%
Horseshoe extension	Yes	50%	47%
	No	50%	53%
Prior attempts at repair	Yes	59%	56%
	No	41%	44%
Gender Ratio (M : F)		2:1	2:1
Age (range)		43 (21-69)	46 (19-73)
Body Mass Index		24	25
Smoking	Yes	56%	52%
	No	44%	48%

Table 6.1. Comparison of baseline patients and fistula characteristics between patients with and without preoperative seton drainage

	Leiden	Rotterdam	Both centers
Seton drainage	64%	69%	67%
No seton drainage	68%	62%	63%
Overall	66%	63%	64%

Table 6.2. Healing rates in patients with and without preoperative seton drainage.

DISCUSSION

The main goal of the present study was to investigate whether preoperative seton drainage has a beneficial effect on the outcome of transanal advancement flap repair or not. In a large cohort of patients no difference in healing rate between patients with and without preoperative seton drainage was observed.

In the past many factors that might influence the outcome, such as gender, age, body mass index, smoking and the number of prior attempts at repair have been analyzed. So far, no definite risk factor for failure has been identified. The effect of preoperative seton drainage has been analyzed before. However, there is still no consensus whether this intervention has a positive effect or not. The reported series were rather small and study populations were often of heterogeneous consistency, including patients with a rectovaginal fistula and patients with fistulas caused by Crohn's disease. In a retrospective study, Sonoda and co-workers were the first to observe a beneficial effect ⁷. In a relatively large series of 105 patients, 56 patients underwent preoperative seton drainage. Comparing patients with and without preoperative seton drainage, they found a healing rate of 73.2 percent and 51.2 percent, respectively. This difference was statistically significant. However, their study included a large number of patients suffering from a rectovaginal fistula and patients with a fistula caused by Crohn's disease. Only 44 patients presented with a fistula of cryptoglandular origin. Unfortunately, the authors omitted to provide data regarding preoperative seton drainage in this group of patients. Van der Hagen and co-workers described the outcome of transanal advancement flap repair after preoperative seton drainage in 23 patients with a fistula of cryptoglandular origin ⁹. Five of these patients also had a diverting stoma. Although the healing rate was quite high (78%), no comparison was made with patients undergoing transanal advancement flap repair alone. Two other studies, conducted by Zimmerman *et al.* and by Van Koperen and co-workers indicate that preoperative seton drainage does not affect the outcome of transanal advancement flap repair ^{10, 14}.

The present series comprised 278 patients. Sixty-eight of our patients underwent seton drainage prior to transanal advancement flap repair. Since we were not able to show any beneficial effect of preoperative seton drainage in this relatively large series, it seems unlikely that this type of preoperative treatment provides a useful tool to enhance the outcome of transanal advancement flap repair. A limitation of the present study is its retrospective design with inherent risk for selection bias. It might be possible that the complexity of the fistula was a major reason for the referring surgeon to perform preoperative seton drainage. To analyze this aspect, not only patient characteristics, but also fistula

characteristics were assessed. No differences were found in both baseline characteristics between patients with and those without preoperative seton drainage. Patients who underwent seton drainage before admission to one of both university hospitals, did not present with a more complex fistula. Clinical chart review revealed no specific reasons for seton placement. Many surgeons from referring district hospitals are not confident with the treatment of high, transsphincteric fistulas. It is obvious that most of them perform seton drainage to minimize complaints, to prevent acute anal sepsis and to tide over the time until definite treatment. Based on these aspects, the risk for selection bias seems to be minimal. So far, no factors have been identified that affect the outcome of transanal advancement flap repair. Persistence of the fistula seems to be caused by ongoing disease in the remaining fistulous tract. Further research is warranted to assess the impact of this ongoing disease on the outcome of flap repair.

CONCLUSION

Seton drainage prior to transanal advancement flap repair does not improve the outcome.

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The impact of epithelialisation of high transsphincteric fistulas
on the outcome of transanal advancement flap repair

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ABSTRACT

Introduction

Transanal advancement flap repair has been advocated as the treatment of choice for transsphincteric fistulas passing through the upper and middle third of the external anal sphincter. This procedure enables healing of the fistula in two out of three patients without consequent continence disturbances. It is generally assumed that chronic fistulas become lined with epithelium, preventing the fistula to heal. However, actual data supporting this hypothesis are scarce. Aim of the present study was to assess the prevalence of epithelium lining of the high transsphincteric fistulas and to examine the effect of this epithelialisation on the outcome of transanal advancement flap repair (TAFR).

Methods

Thirty-four patients (M: F= 23: 11, median age 46 years (range 21-65)) with a high transsphincteric fistula of cryptoglandular origin were included. All patients underwent TAFR. During this procedure the fistulous tract was excised from the external opening until the border of the external anal sphincter. Histopathological examination of this specimen was performed by a pathologist without prior knowledge of the clinical data.

Results

Epithelium lining of the fistulous tract was found in only seven patients (21%). This epithelialisation was complete in two patients and incomplete in five patients. Median time interval since onset of the fistula in patients with and those without epithelialisation was 13 and 17 months, respectively. No difference in healing rate was found between fistulas with or without epithelium lining.

Conclusion

In contrast to what is generally accepted, most perianal fistulas are not lined with epithelium. Epithelialisation of high transsphincteric fistulas does not affect the outcome of transanal advancement flap repair.

INTRODUCTION

The main goal in the treatment of patients with a transsphincteric fistula, passing through the upper or middle third of the external anal sphincter is healing of the fistula without subsequent damage to the external anal sphincter. Transanal advancement flap repair (TAFR) provides a useful tool to obtain this goal, enabling fistula healing in two out of three patients. Several authors have tried to identify factors affecting the outcome of TAFR. However, until now no definite factor predisposing to failure has been identified. It is generally assumed that chronic fistulas are lined with epithelium, preventing the fistula to heal. However, actual data supporting this theory are absent. So far, there is only one study that analyzed how often fistulous tracts are lined with epithelium. In 1995 Lunniss *et al.* reported the results of a study aimed at evaluating the lining of fistulous tracts. In a rather small series of 18 patients epithelium lining was observed in 13 of these patients ¹. Although the authors did not report any correlation between the presence of epithelium lining and the outcome of surgical treatment, they suggested that epithelialisation of the fistulous tract might prevent the fistula to heal. In many papers and text books this study is cited ²⁻⁵. Aim of the present study was to assess the prevalence of epithelium lining of high transsphincteric fistulous tracts and to examine its effect on the outcome of transanal advancement flap repair.

PATIENTS AND METHODS

Between June and December 2008 a consecutive series of 34 patients with a cryptoglandular, transsphincteric fistula passing through the upper or middle third of the external anal sphincter underwent TAFR. The present series comprised 23 males and 11 females. Median age at time of repair was 46 (range 21-64) years.

Exclusion criteria

Patients with a rectovaginal fistula or a fistula caused by Crohn's disease were excluded from the present series.

Surgical technique

Patients underwent complete mechanical bowel preparation (polyethylene glycol: Klean-prep® Helsinn Birex Pharmaceuticals, Dublin, Ireland). After induction of general

endotracheal anesthesia, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously. With the patient in prone jack-knife position, the external opening was enlarged and the fistulous tract was excised as far as possible. The internal opening of the fistula was exposed using a Lone Star retractor (Lone Star Retractor System, Lone Star Medical Products®, Inc. Houston, TX). The crypt-bearing tissue around the internal opening as well as the overlying anodermis was then excised. The fistulous tract was cored out of the sphincters. The defect in the internal anal sphincter was closed with absorbable sutures. A flap consisting of mucosa, submucosa and some of the most superficial fibres of the internal anal sphincter, was raised from the level of the dentate line and mobilized over a distance of four to six centimetres proximally. The flap was advanced and sutured to the neodentate line with absorbable sutures. One surgeon performed all operations (WRS).

Postoperative care

All patients were immobilized for five days. All patients received a clear liquid diet for five days. During this time period metronidazole and cefuroxime were administered intravenously three times daily.

Histopathological examination

The fistulous tract was excised as far as possible from the external opening up to the outer border of the external anal sphincter. The outmost part of this tract, containing the original external opening with surrounding skin, was removed. After fixation in 10% formalin, the remaining specimen was cut in sections. These sections were stained using the routine hematoxylin and eosin stain method. The sections were examined under the microscope under different magnifications.

Statistical analysis

Comparison of the changes between groups was conducted using the Fisher's exact probability test. The limit of statistical significance was set at $P = 0.05$.

RESULTS

The healing rate after TAFR was 68 percent. Median healing time was 2.3 months. Median follow-up was 11 (range 6-13) months. Median time interval since the onset of the fistula was 17 months (range 5-73). Epithelium lining of the central part of the fistulous tract was found in seven patients (21 percent). In two of these patients the specimen was completely lined with

epithelium (figure 7.1), while in five patients the specimen was only partly lined with epithelium (figure 7.2). In most patients (n= 27, 79 percent) the fistulous tract was lined with granulation tissue (figure 7.3). We found no differences in either the time interval since onset of the fistula or healing rate between fistulas with or without epithelium lining.

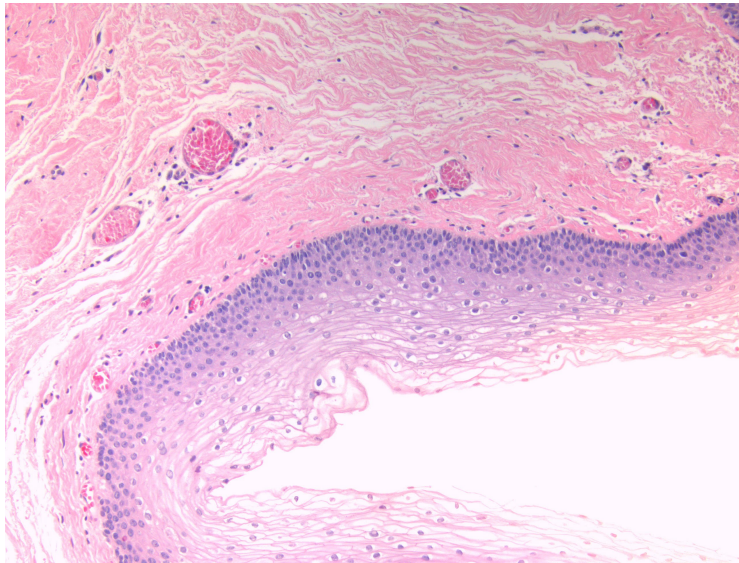


Figure 7.1

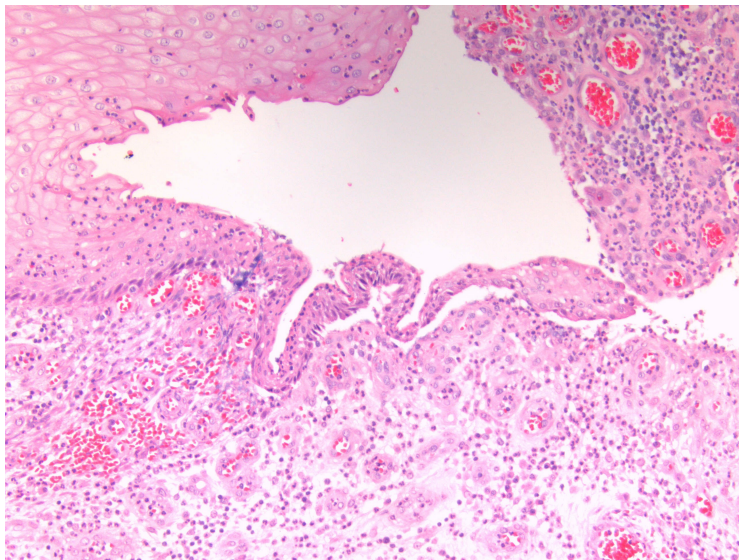


Figure 7.2

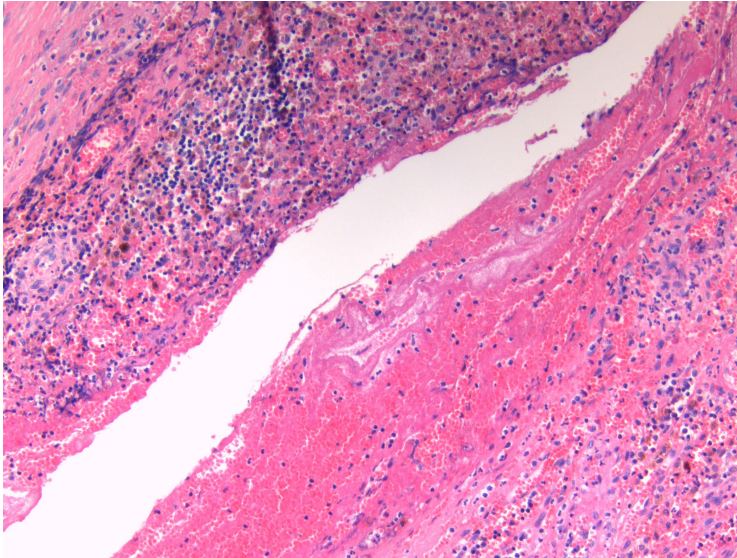


Figure 7.3

DISCUSSION

In the present study epithelialisation of the central part of the fistulous tract was found in seven patients (21%). In only two of them the specimen was completely lined with epithelium, whereas in the other five patients the central part of the fistulous tract was only partly lined with epithelium. In all other patients (79%) the specimen was lined with granulation tissue. Comparing patients with and without epithelialisation of their fistulous tract, no differences were found regarding the time interval since onset of the disease and the healing rate of TAFR.

In 1995 Lunniss and co-workers were the first to describe epithelium lining of perianal fistulas ¹. They observed epithelium lining in 13 out of 18 patients. They did not mention however, whether this epithelium lining was complete or not. Although they did not assess the impact of this epithelialisation on fistula healing, the authors stated that it might be a cause for persistence of the fistula. Although this report from Lunniss *et al.* does not provide any evidence for this hypothesis, it is still generally accepted.

Recently Van Koperen and colleagues performed a study to assess the presence of epithelium in the fistulous tract ⁷. In 18 patients with a low transsphincteric fistula they took biopsies from the fistulous tract from three different locations, respectively on the proximal side at the internal opening, in the middle of the fistulous tract and near the distal end close to the external opening. Epithelium was observed in the majority of patients. However, most epithelium was found in the biopsies taken from the proximal side, close to the internal opening. In our opinion this epithelium does not represent epithelialisation of the fistulous

tract since it is most likely derived from the epithelium lining of the crypts of Morgagni and the anal glands. Epithelium was observed in only four biopsies taken from the central part of the fistulous tract. This observation is similar to the findings obtained from our present study. Despite the fact that complete epithelialisation of the fistulous tract was present in only a small minority of patients, Van Koperen *et al.* state that epithelial lining of the fistulous tract is present in the majority of patients and might contribute to failure. In our opinion this study does not provide evidence for this hypothesis. If epithelialisation of perianal fistulas would be detrimental, one should expect a worse outcome after fistulotomy compared to fistulectomy, since the inner lining of the fistulous tract is not completely removed during fistulotomy.

Kiehne and co-workers assessed the role of epithelium-derived antimicrobial peptides in the inner lining of perianal fistulas ⁶. Based on the expression of these peptides the authors concluded that epithelialisation occurs frequently in chronic fistulas as a late event and that the epithelium is derived from the perianal skin growing into the fistula tract. However, they did not describe the exact prevalence of epithelialisation. The finding of the present study that epithelialisation of fistulous tracts occurs in only a minority of the patients is supported by the report of Buchanan *et al.* from 2006 ². They used a porcine model of fistula-in-ano. Eight pigs underwent surgical creation of three fistulas. In all these fistulas a seton was placed. After 26 days, the setons were removed. Two of the pigs underwent anorectal excision under terminal anesthesia to obtain histology. In none of these fistulas epithelium was present. The lumen of all fistulas was surrounded by granulation tissue, as observed in the majority of our patients. It is questionable whether epithelialisation of the fistulous tract would have occurred after a longer period of time.

In the present study epithelialisation was observed in only one out five high transsphincteric fistulas. Most of the fistulas were lined with granulation tissue. As already stated above, it has been suggested that epithelium lining develops in time. Therefore, epithelium would only be present in longstanding fistulas. However, in the present study the median time interval since onset of the fistula did not differ between patients with and without epithelium lining of their fistula. The presence of granulation tissue in the fistulous tracts of most of our patients might represent ongoing inflammatory disease, characterized by pain and discharge of purulent liquid. If complete epithelialisation of the fistulous tract would occur, it seems more likely that these symptoms would disappear and the patients' only complaint would be the existence of an connection between the anus and the perianal skin. However, this seldom happens. In recent years it has become clear that there are no predisposing factors for failure. Recently we examined the outcome of repeat flap repair in 26 patients, who encountered a failure after the initial procedure ⁸. In all these patients we noticed complete healing of the advancement flap, except at the site of the original internal opening. This

remarkable clinical finding and the lack of predictive factors for failure suggest that persistence of the fistula might be due to ongoing disease within the remaining fistulous tract. Further studies are warranted to assess the pathologic, microbiologic or immunologic characteristics of this inflammatory process.

CONCLUSION

In contrast to what is generally accepted, most perianal fistulas are not lined with epithelium. Moreover, the presence this epithelium lining does not affect the outcome of TAFR.

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Are high transsphincteric fistulas colonized by pathogenic bacteria? A microbiological study using 16S ribosomal RNA gene sequencing

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ABSTRACT

Introduction

Transanal advancement flap repair (TAFR) provides a useful tool in the treatment of high transsphincteric fistulas. This procedure fails in one of every three patients. There is some evidence that persistence of the fistula after flap repair might be the result of ongoing disease in the remaining fistulous tract. Infection seems to be an integral part of the pathogenesis of perianal fistulas. Conventional microbiological studies, conducted so far, did not reveal pathogenic bacteria as the primary cause of chronic inflammation in fistulous tracts. The present pilot study was aimed to assess the presence of pathogenic bacteria in the fistulous tract by means of 16S ribosomal RNA (rRNA) gene sequencing.

Methods

Between February and March 2008 a consecutive series of ten patients (M: F =8: 2, median age 48 (range, 28-56) years) with a high transsphincteric fistula of cryptoglandular origin underwent TAFR. The fistulous tract was excised from the external opening as far as possible. Granulation tissue obtained from the central part of this tract was examined by means of conventional culture technique as well as molecular microbiological techniques.

Results

In one patient the culture was negative (10%). Aerobic or facultative organisms only were isolated in three patients (30%), anaerobic bacteria only in three patients (30%) and mixed aerobic and anaerobic flora in three patients (30%). No mycobacterium species were grown. 16S rDNA gene sequencing failed to identify bacteria in all but one patient, most likely as a result of low numbers of organisms.

Conclusion

High transsphincteric fistulas are not colonized by monocultures of pathogenic bacteria. Based on the paucity of organisms in the fistulous tract, as demonstrated by 16S rRNA gene sequencing, it seems unlikely that infection by a single bacterial species plays a role in maintaining the fistulous disease.

INTRODUCTION

Transsphincteric fistulas passing through the lower third of the external sphincter can be easily treated by either classic laying open (fistulotomy) or by excision (fistulectomy). These procedures provide excellent healing rates and a minimal risk on postoperative incontinence^{1, 2}. However, transsphincteric fistulas, passing through the upper or middle third of the external anal sphincter are a notorious condition. Fistulotomy or fistulectomy will result in unacceptable continence disturbances in these cases. Therefore, sphincter saving techniques have been developed. Despite new treatment modalities such as application of fibrin glue or the use of an anal fistula plug, transanal advancement flap repair (TAFR) remains the treatment of choice for patients with high transsphincteric fistulas³. This procedure is successful in two of every three patients.⁴ Until now no definite factor predisposing to failure has been identified. A previous study, conducted in patients with a persistent fistula after TAFR, revealed complete healing of the flap, except at the site of the original internal opening⁵. This observation and the lack of factors predisposing to failure suggest that persistence of the fistula is caused by ongoing disease in the remaining fistulous tract. Infection seems to be an important part of the pathogenesis of perianal fistulas. A recent study, conducted in our hospital, revealed that most perianal fistulas are lined with granulation tissue. The presence of granulation tissue in the fistulous tract seems to indicate an inflammatory process. Some authors studied the bacteriology of perianal fistulas of cryptoglandular origin⁶⁻⁹. Their reports failed to demonstrate pathogenic bacteria. Moreover, only small numbers of organisms were found, suggesting that permanent infection is not a major contributing factor to the persistence of perianal fistulas. However, these data were obtained with the use of conventional culture techniques. These cultures require viability of the strains for which accurate handling of the clinical material is essential. It might be that bacteria died due to inadequate sample processing. Furthermore, conventional culture techniques are largely dependent on the type and range of media used. Modern molecular techniques that use bacterial 16S rRNA provide alternative and more sensitive means for the study of bacterial flora¹⁰⁻¹². For this technique, viability of strains is not required and even bacteria that have died can still be identified. The present study was aimed to assess the presence of pathogenic bacteria in the fistulous tract by means of 16S rRNA gene sequencing.

PATIENTS AND METHODS

Between February and March 2008 a consecutive series of ten patients with a cryptoglandular, transsphincteric fistula, passing through the upper or middle third of the external anal sphincter underwent TAFR. The present series comprised eight males and two females. Median age at time of repair was 48 years (range 28-56).

Exclusion criteria

Patients with a rectovaginal fistula or a fistula caused by Crohn's disease were excluded from the present series.

Excision of the specimen

With the patient in prone jack-knife position, the external opening was enlarged and the fistulous tract was excised as far as possible towards the outer border of the external anal sphincter. The outmost part of this tract, containing the original external opening with surrounding skin, was removed. The remaining specimen, containing the central part of the fistulous tract, was immediately stored in an anaerobic container and processed within two hours. After excision of the fistulous tract, metronidazole (500 mg) together with cefuroxime (1500 mg) was administered intravenously and a transanal advancement flap repair was performed according to the previously described technique. A single surgeon performed all procedures (WRS).

Conventional microbiology

The surgical materials were immersed in liquid growth media (including aerobic and anaerobic blood culture bottles) and were subjected to standard aerobic and anaerobic culture using various culture media including blood, McConkey and Sauboroud agar plates. After incubation, the media were examined by an experienced clinical microbiologist and pure cultures were identified. In case of such pure cultures the strains involved were stored for future use. In case of mixed cultures, the biomaterial was collected from the plate and stored in glycerol containing media for later usage. After presumptive identification, pure cultures were analysed for precise species nature using Vitek technology.

Molecular testing

DNA extraction from the surgical material was piloted using a variety of methods. Employing small aliquots of an initial specimen the optimal procedure was defined on the basis of DNA yield. Once a protocol was established all specimens were treated similarly. DNA extracted from biopsies was amplified using general primers for the bacterial 16S rRNA genes. This involved broad-spectrum amplification of DNA from all bacterial species known and generated a mixture of PCR products.

RESULTS

Patient characteristics and the organisms cultured are shown in table 8.1. In one patient the culture was negative (10%). Aerobic or facultative organisms only were isolated in three patients (30%), anaerobic bacteria only in three patients (30%) and mixed aerobic and anaerobic flora in three patients (30%). The organisms, cultured from granulation tissue in the fistulous tract were bowel-derived, skin-derived or a combination of both. No mycobacterium species were grown from any of the ten patients.

The molecular technique, used in the present study, failed to identify bacteria in all but one patient. In this patient *Escherichia coli* was identified. Failure to detect bacteria in the other nine patients was most likely caused by low numbers of organisms. Therefore, the culture-positive results were considered to be clinically insignificant.

DISCUSSION

The present study demonstrates that high transsphincteric fistulas are not colonized or infected with pathogenic bacteria. The organisms, cultured from granulation tissue, obtained from the fistulous tract represented bowel-derived, skin-derived or a combination of both flora types. It seems unlikely that permanent infection with these bacteria contributes to the chronicity of perianal fistulas, since they were present in such small numbers that 16S rRNA sequencing could not detect them.

It is generally accepted that perianal fistulas are secondary to perianal abscesses. After incision and drainage of such an abscess a fistula remains in about half of the patients^{13,14}. It is not clear which factors contribute to the development of a chronic and persistent fistula. The microbiology of perianal abscesses has been well described^{13,15-17}. The bacteria

Patient	Gender	Age	Aerobic	Anaerobic	mycobacteria	16S rRNA gene sequencing
1	M	54	neg	<i>E.coli</i>	neg	<i>E. coli</i>
2	M	43	Skinflora	neg	neg	neg
3	M	56	Mixed flora	Mixed flora	neg	neg
4	F	31	<i>Pantoea</i> spp	neg	neg	neg
5	M	28	neg	neg	neg	neg
6	M	55	Hemolytic streptococcus gr C	Mixed flora	neg	neg
7	M	45	CNS gr 1	Mixed flora	neg	neg
8	F	52	neg	Mixed flora	neg	neg
9	M	47	<i>S.aureus</i> gr 1/ skinflora	neg	neg	neg
10	M	49	neg	<i>Peptostreptococcus</i> <i>Asaccharolyticus</i> gr 1	neg	neg

Table 8.1. Patient characteristics and organisms isolated

cultured from perianal abscesses include bowel-derived organisms, skin-derived-organisms or a combination of both. According to some authors bowel-derived organisms are associated with subsequent occurrence of a fistula ^{13, 15, 16}. However, this finding could not be confirmed by others ¹⁸. Three studies have been conducted to assess the microbiology of cryptoglandular, perianal fistulas ⁶⁻⁸. Seow-Choen *et al.* were the first to show that the microflora in perianal fistulas is similar to the microflora of perianal abscesses ⁸. However, cultures of granulation tissue, obtained from perianal fistulas, yielded much smaller numbers of organisms in comparison with pus obtained from perianal abscesses. Furthermore, they were not able to detect pathogenic bacteria. Similar findings have been reported by others ^{6, 7}. The conventional culture techniques, used in these studies, have several drawbacks. First, they require viable strains. Therefore, accurate handling of the material is essential to prevent organisms from dying. Second, conventional culture techniques are largely dependent on the type and range of media used. In the present study, conventional culture techniques as well as 16S rRNA gene sequencing were used. Molecular diagnostic techniques, such as polymerase chain reaction (PCR), have been developed to aid in the diagnosis of bacterial infection by detecting bacterial genetic material ^{11, 19}. Unlike culture, most molecular assays are designed specifically for one organism. This provides high sensitivity and specificity. However, multiple assays may be required to screen for multiple organisms. Broad-range assays, based on ribosomal genes (rDNA), are designed to

overcome this limitation. Bacterial rRNA consists of highly conserved nucleotide sequences that are shared by all bacterial species, interspersed with variable regions that are genus- or species-specific. The DNA sequences of the variable regions form the basis of phylogenetic classification of microbes²⁰. By using PCR primers that are targeted at conserved regions of rDNA, it is possible to design broad-range PCRs capable of detecting DNA from almost any bacterial species. Bacterial identification can be revealed by nucleotide sequencing of the PCR product followed by comparison of this sequence with known sequences located in GenBank or other databases^{21,22}. In the present study 16S rRNA gene sequencing failed to identify bacteria in all but one patient. This was most likely caused by a very low number of organisms. Therefore, it seems unlikely that the bacteria, cultured from granulation tissue, obtained from perianal fistulas contribute to the chronicity of these fistulas.

Flap repair of high transsphincteric fistulas fails in one of every three patients^{3,4}. Several factors that might influence the healing rate of TAFR have been analyzed. However, until now no definite factor predisposing to failure has been identified and reasons for fistula persistence are still not understood. Recently we examined the outcome of repeat flap repair in patients, who encountered a failure after the initial procedure⁵. In all patients complete healing of the advancement flap was observed, except at the site of the original internal opening. This remarkable clinical finding and the lack of predictive factors for failure suggest that persistence of the fistula might be due to ongoing disease within the remaining fistulous tract. The present study does not provide any evidence for the hypothesis that bacteria are responsible for this ongoing disease, which is in concordance with the three earlier studies, using conventional culture techniques. The question is whether the anal glands, which are considered to be the origin of cryptoglandular perianal fistulas, contribute to the chronicity and persistence of perianal fistulas. The ducts of the anal glands flow into the crypts of Morgagni and drain into the anal canal. If these glands become blocked, stasis occurs and infection develops. Because a number of these glands branch out into the intersphincteric plane, the infection can pass the internal anal sphincter that serves as a barrier against bacterial contamination. From the intersphincteric plane the infection may progress and extend in various ways. Recently, ligation of the intersphincteric fistulous tract (LIFT-procedure) has gained attention²³⁻²⁷. During this procedure, the fistulous tract in the intersphincteric plane is identified and ligated close to the internal anal sphincter. The intersphincteric part of the fistulous tract, including infected cryptoglandular tissue, is removed. Subsequently, the defects in the internal and external anal sphincter are closed. The preliminary results of this procedure are promising and indicate that the intersphincteric part of the fistulous tract might be the origin of the chronicity and persistence of perianal fistulas. Further studies are warranted to elucidate the exact role of ongoing cryptoglandular

disease in failure of flap repair.

CONCLUSION

The present study demonstrates a paucity of organisms in the fistulous tract. Therefore, it seems unlikely that bacterial infection plays a role in maintaining the fistulous disease.

ACKNOWLEDGEMENT

The authors thank J. van Kampen of the department of Medical Microbiology and Infectious diseases for his help in data interpretation.

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Summary and discussion

The principle goal in the treatment of perianal fistulas is healing of the fistula, while the function of the anal sphincter remains intact. In low transsphincteric fistulas, passing through the lower third of the external anal sphincter, this goal can easily be achieved by either fistulotomy (lay-open) or fistulectomy (excision). This will result in division of only a small portion of the external anal sphincter and therefore continence disturbances are generally minimal. However, in case the fistula passes the middle or upper third of the external anal sphincter, the portion of the sphincter that needs to be divided is too large to maintain its function and continence disturbances are inevitable. This type of fistula requires a more vigilant treatment. Despite new treatment modalities such as closure of the fistulous tract with fibrin glue or with a bioprosthesis plug, transanal advancement flap repair remains the treatment of choice for these fistulas. Early reports revealed high healing rates after the transanal advancement flap. In recent years, however, it became clear that the procedure fails in one of every three patients. This thesis was aimed at identifying factors that affect the outcome of the transanal advancement flap repair.

Chapter 1 provides a general introduction to this thesis. Pathogenesis, anatomy of the anal canal, clinical manifestation, classification, imaging techniques and treatment options are briefly discussed. In addition the outline of the thesis is presented.

The course of high, transsphincteric fistulas is highly variable. Some have a direct course from the internal to the external opening, whereas others extend in a more complex horseshoe manner. In addition, associated abscesses are not uncommon in patients with a high transsphincteric fistula. **Chapter 2** deals with the question whether the complexity of high transsphincteric fistulas affects the outcome of transanal advancement flap repair. The complexity of the fistulous tract and the presence of abscesses were assessed with endoanal MR imaging. Prolonged drainage of all associated abscesses was performed. The complexity of high transsphincteric fistulas did not affect the outcome of transanal advancement flap. Associated abscesses, once adequately drained, neither affected the outcome. The most striking finding of the present study was the fact that the most simple fistulas with a direct course had a significant worse outcome. A possible explanation for this unexpected finding might be that the course of the fistula depends on the severity of the fistulous disease. The more fulminant the fistulous disease, the more straightforward the fistula might traverse the anal sphincter muscles, resulting in a direct course to the external anal opening.

In **Chapter 3** the appropriate length of follow-up needed to assess the healing rate after transanal advancement flap repair and the risk of recurrence after initial fistula healing were studied. Healing of the fistula was defined as complete wound healing and closure of all external openings in combination with absence of symptoms. Fistula healing was observed in 54 patients (68%). Median time interval until healing was 3.6 months. Only one patient (2%) encountered a recurrence. Median duration of follow-up was 92 months. In our opinion follow-up can therefore be restricted to the point of time of complete healing of the fistula.

In **Chapter 4** the success rate of repeat transanal advancement flap repair was evaluated and the impact of such a second procedure on the overall healing rate of high transsphincteric fistulas and on fecal continence was assessed. Healing rate of the second repair was equal to the first attempt, which resulted in a substantial increase of the overall healing rate of high transsphincteric fistulas. Fecal continence was not affected by such a second procedure. During repeat transanal advancement flap repair we observed complete healing of the flap except at the site of the original internal opening. This suggests that persistence of fistulas might be caused by ongoing disease within the remaining fistulous tract.

Chapter 5 describes a study on the effect of rectal mucosal blood flow on the outcome of transanal advancement flap repair. In this study laser Doppler flowmetry was used to assess rectal mucosal blood flow before and after creation of the advancement flap. No correlation was found between blood flow and the outcome of transanal advancement flap repair. This indicates that a diminished rectal mucosal blood flow does not have a detrimental effect on transanal advancement flap. If impaired rectal mucosal blood flow were a risk factor, one would expect a breakdown of the flap caused by local necrosis in case of a failure. However, in all our patients with a persistent fistula, we observed complete healing of the flap except at the site of the original internal opening. This clinical observation supports the finding that impaired rectal mucosal blood flow is not a major risk factor.

Seton drainage has been advocated since it allows drainage of the fistulous tract and is thereby supposed to reduce the inflammatory activity within the tract and to resolve secondary tracts. This might have a beneficial effect on the healing rate after transanal advancement flap repair. In **Chapter 6** the effect of preoperative seton drainage on the outcome of transanal advancement flap repair was evaluated. We did not find differences in healing rate between patients with and without preoperative seton drainage.

It is generally believed that chronic fistulas become lined with epithelium, preventing the fistula to heal. However, data supporting this theory are scarce. In **Chapter 7** the presence of an epithelium lining of the fistulous tract was assessed and the effect of such an epithelium layer on the outcome of transanal advancement flap repair was examined. This revealed that only a small part of the fistulas was lined with epithelium. Moreover, the presence this epithelium lining did not affect the outcome of transanal advancement flap repair.

There is some evidence that persistence of the fistula after flap repair might be the result of ongoing disease in the remaining fistulous tract. Infection seems to be an integral part of the pathogenesis of perianal fistulas. Conventional microbiological studies, conducted so far, did not reveal pathogenic bacteria as the primary cause of chronic inflammation in fistulous tracts. In **Chapter 8** the presence of pathogenic bacteria in the fistulous tract was assessed by means of 16S ribosomal RNA (rRNA) gene sequencing. This pilot study revealed that high transsphincteric fistulas are not colonized by monocultures of pathogenic bacteria. Based on the paucity of organisms in the fistulous tract, as demonstrated by 16S rRNA gene sequencing, it seems unlikely that infection by a single bacterial species plays a role in maintaining the fistulous disease.

Conclusions

- The complexity of high transsphincteric fistulas does not affect the outcome of transanal advancement flap repair.
- Recurrence after initial healing of the fistula is rare. The length of follow-up after transanal advancement flap repair can therefore be restricted to the healing time.
- Repeat transanal advancement flap repair results in a substantial increase of the overall healing rate of high transsphincteric fistulas without deteriorating effect on fecal continence.
- A diminished rectal mucosal blood flow does not have a detrimental effect on transanal advancement flap repair.
- Seton drainage prior to transanal advancement flap repair does not seem to improve the outcome.

- Most perianal fistulas are not lined with epithelium. The presence of this epithelium lining does not affect the outcome of transanal advancement flap repair.
- High transsphincteric fistulas are not colonized by monocultures of pathogenic bacteria. Based on the paucity of organisms in the fistulous tract, it seems unlikely that infection by a single bacterial species plays a role in maintaining the fistulous disease.

Despite the fact that perianal fistulas are treated since early history, high transsphincteric fistulas remain a frustrating and challenging pathology. Failure after transanal advancement flap repair seems more and more to be caused primarily by ongoing inflammation in the remaining fistulous tract. Therefore, we performed a pilot-study on the occurrence of pathogenic bacteria in the remaining fistulous tracts. This study suggested that high transsphincteric fistulas are not colonized by pathogenic bacteria. This does not exclude, however, that non-pathogenic bacteria or their products elicit or sustain the inflammation. We therefore propose that future studies should be devoted to the nature of the inflammatory process and the underlying factors.

Samenvatting en discussie

Het doel bij de behandeling van perianale fistels is het genezen van de fistel, zonder de functie van de externe anale sfincter in gevaar te brengen. Bij laag transsfincterische fistels, die door het onderste eenderde deel van de externe anale sfincter verlopen, kan dit eenvoudig bereikt worden door het verrichten van een fistulotomie (klieven van de fistel) of fistulectomie (excideren van de fistel). Op deze manier wordt slechts een klein deel van de externe anale sfincter gekliefd en is de verstoring van de continentie minimaal. In het geval de fistel echter door het bovenste of middelste eenderde deel van de externe anale sfincter loopt, zal op deze wijze een dusdanig groot deel van de sfincter gekliefd worden dat verstoring van de continentie onvermijdelijk is. Dit type fistel vraagt dus om een meer voorzichtige aanpak. Ondanks nieuwe behandelmogelijkheden, zoals het opspuiten van de fistel met fibrine lijm of het inbrengen van een bioprothetische plug, blijft de transanale mucosaverschuivingsplastiek de voorkeursbehandeling bij deze fistels. De eerste publicaties ten aanzien van de transanale mucosaverschuivingsplastiek rapporteerden zeer hoge slagingspercentages van deze ingreep. De afgelopen jaren is echter duidelijk geworden dat de ingreep bij een op de drie patiënten faalt. Het doel van dit proefschrift was het identificeren van factoren die het resultaat van de transanale mucosaverschuivingsplastiek beïnvloeden.

Hoofdstuk 1 geeft een algemene inleiding op dit proefschrift. De pathogenese, anatomie van het anale kanaal, het klinische beeld, de classificatie, beeldvormende technieken en behandelmogelijkheden worden kort besproken. Daarnaast beschrijft dit hoofdstuk de doelstellingen van dit proefschrift.

Het verloop van transsfincterische fistels kan sterk variëren. Sommige fistels hebben een direct verloop van de inwendige opening naar de uitwendige opening, terwijl andere op een meer complexe hoefijzervormige wijze verlopen. Daarnaast zijn geassocieerde abcessen een veel voorkomende bevinding bij patiënten met een hoge transsfincterische fistel. **Hoofdstuk 2** beschrijft in hoeverre de complexiteit van hoge transsfincterische fistels de uitkomst van de transanale mucosaverschuivingsplastiek beïnvloedt. De complexiteit van de fistel en de aanwezigheid van abcessen werden geanalyseerd met behulp van endoanale MRI beelden. De complexiteit van de fistels bleek geen invloed te hebben op de uitkomst van de transanale mucosaverschuivingsplastiek. Ook abcessen, eenmaal adequaat gedraineerd, hadden geen negatieve invloed op de genezing. De meest opmerkelijke bevinding was dat simpele, directe fistels een significant slechtere uitkomst hadden. Een mogelijke verklaring hiervoor zou kunnen zijn dat het verloop van de fistel afhangt van de agressiviteit van de ziekte. Hoe fulminanter de ziekte is, des te agressiever de fistel de anale sfincter penetreert, wat resulteert in een direct verloop naar de externe anale opening.

In **Hoofdstuk 3** wordt beschreven hoe lang de duur van de follow-up moet bedragen om vast te stellen wat het genezingspercentage is, en hoe groot de kans op een recidief is na genezing van de fistel. Genezing van de fistel werd gedefinieerd als complete wondgenezing en het volledig sluiten van alle openingen gecombineerd met de afwezigheid van symptomen passend bij een fistel. Genezing van de fistel trad op in 68 procent van de patiënten. De mediane duur tussen de operatie en complete genezing van de fistel was 3.6 maanden. Bij slechts een patiënt (2%) trad een recidiverende fistel op. De mediane follow-up was 92 maanden. Op basis van deze gegevens zijn wij van mening dat de follow-up beperkt kan worden tot het moment waarop de fistel genezen is.

In **Hoofdstuk 4** wordt het genezingspercentage van een tweede transanale mucosaverschuivingsplastiek geëvalueerd en wordt vastgesteld wat de invloed van een dergelijke tweede ingreep is op het totale genezingspercentage van hoge transsfincterische fistels en op de continentie. Het genezingspercentage van een tweede transanale mucosaverschuivingsplastiek was gelijk aan dat van de eerste. Dit resulteerde in een aanzienlijke toename van het totale percentage genezen patiënten. Een dergelijke tweede procedure had geen negatieve invloed op de fecale continentie. Tijdens de tweede ingreep stelden wij vast dat na de eerste ingreep de flap overal was ingegroeid, behalve op de plaats van de oorspronkelijke inwendige opening. Deze opmerkelijke klinische bevinding suggereert dat het persisteren van de fistel na de transanale mucosaverschuivingsplastiek veroorzaakt zou kunnen worden door het voortduren van het ziekteproces in het resterende fistelkanaal.

Een eerdere pilot-studie, uitgevoerd in ons ziekenhuis, liet een significante afname in de doorbloeding van het rectummucosa zien na het creëren van de flap. In **Hoofdstuk 5** wordt de invloed van de mate van doorbloeding van het rectummucosa op de uitkomst van de transanale mucosaverschuivingsplastiek beschreven. Met behulp van laser Doppler flowmetrie werd de doorbloeding van het rectummucosa gemeten voor en na het creëren van de flap. Wij vonden geen verband tussen de mate van doorbloeding en het slagen van de ingreep. Het lijkt er dus op dat een afname in de doorbloeding geen negatief effect heeft op de transanale mucosaverschuivingsplastiek. Als een verminderde doorbloeding tot het falen van de ingreep zou leiden, zou men loslating van de flap verwachten als gevolg van locale necrose. In alle patiënten bij wie de fistel persisteerde, zagen wij echter dat de flap volledig ingegroeid was, behalve op de plaats van de oorspronkelijke inwendige opening. Deze opmerkelijke klinische waarneming steunt de bevinding dat een afgenomen doorbloeding niet direct een risicofactor voor falen van de uitgevoerde operatie is.

Door sommige auteurs wordt een setondrainage voorafgaande aan de transanale mucosaverschuivingsplastiek aangeraden, omdat dit drainage van het fistelkanaal mogelijk maakt en het op die wijze de inflammatoire activiteit in het kanaal zou kunnen verminderen, en secundaire fistelgangen zou laten opdrogen. Dit zou een gunstig effect hebben op de uitkomst van de transanale mucosaverschuivingsplastiek. In **Hoofdstuk 6** wordt het effect van preoperatieve seton drainage op de uitkomst van de transanale mucosaverschuivingsplastiek geëvalueerd. Wij vonden geen verschil in slagingspercentage tussen patiënten met en zonder preoperatieve seton drainage. Seton drainage voorafgaande aan de transanale mucosaverschuivingsplastiek lijkt de uitkomst dus niet te kunnen verbeteren.

Algemeen wordt aangenomen dat langer bestaande fistels bekleed zijn met epitheel. Er is echter weinig bewijs voor deze aanname. In **Hoofdstuk 7** wordt de aanwezigheid van eventuele epitheliale bekleding van het fistelkanaal onderzocht en wordt beschreven wat de invloed is van een dergelijke epitheliale bekleding op de uitkomst van de transanale mucosaverschuivingsplastiek. Slechts een klein deel van de fistels bleek bekleed te zijn met epitheel. De aanwezigheid van deze epitheliale bekleding bleek geen invloed te hebben op het slagingspercentage van de transanale mucosaverschuivingsplastiek.

Hoewel de behandeling van fistels al sinds de oudheid geschiedt, blijven hoogverlopende transsfincterische fistels een frustrerend chirurgisch probleem. Het falen van de transanale mucosaverschuivingsplastiek lijkt steeds meer veroorzaakt te worden door het voortduren van de inflammatie in het resterende fistelkanaal. Daarom hebben we in **Hoofdstuk 8** een pilot-studie uitgevoerd om het vóórkomen van pathogenen in dit resterende fistelkanaal te onderzoeken. Uit deze studie bleek dat hoogverlopende transsfincterische fistels niet gekoloniseerd zijn door pathogenen. Dit sluit echter niet uit dat niet-pathogene bacteriën of hun producten de ontsteking in stand houden. Wij stellen daarom voor dat toekomstige studies zich richten op de aard van dit ontstekingsproces en de onderliggende factoren.

Conclusies

- De complexiteit van hoge, transsfincterische fistels heeft geen invloed op de uitkomst van de transanale mucosaverschuivingsplastiek.
- Recidieven na genezing van de fistel komen zelden voor. De duur van de follow-up

na transanale mucosaverschuivingsplastiek kan derhalve beperkt worden tot het tijdstip waarop de fistel volledig genezen is.

- Een tweede transanale mucosaverschuivingsplastiek heeft een slagingspercentage dat gelijk is aan een eerste ingreep. Een tweede transanale mucosaverschuivingsplastiek leidt derhalve tot een aanzienlijke verbetering van het totale succespercentage van deze ingreep zonder verslechtering van de fecale continentie.
- Een afname van de doorbloeding van het rectale mucosa heeft geen negatieve invloed op het slagingspercentage van de transanale mucosaverschuivingsplastiek.
- Seton drainage voorafgaande aan de transanale mucosaverschuivingsplastiek heeft geen gunstig effect op de uitkomst.
- De meeste hoge transsfincterische fistels zijn niet bekleed met epitheel. Wanneer dit wel het geval is, heeft de aanwezigheid van dit epitheel geen negatief effect op het slagingspercentage van de transanale mucosaverschuivingsplastiek.
- Hoge transsfincterische fistels zijn niet gekoloniseerd door monoculturen van pathogene bacteriën. Aangezien er slechts weinig bacteriën aanwezig zijn in het fistelkanaal, lijkt het onwaarschijnlijk dat een infectie, veroorzaakt door een bepaalde bacterie, een rol speelt in het onderhouden van de fistel.

Dankwoord

Bij de totstandkoming van dit proefschrift zijn vele mensen betrokken geweest. Ik wil hen bedanken voor hun hulp en steun. Enkelen van hen wil ik graag in het bijzonder noemen.

Mijn co-promotor, dr. W.R. Schouten. Uw bevoegen en innovatieve gedachtegoed inspireren mijn telkens weer. Het werken binnen uw colorectale onderzoeksgroep heb ik ervaren als een ontzettend leerzame en verrijkende periode. Ik ben er trots op dat ik de kans heb gekregen om onder uw kundige begeleiding te leren en te werken. Uw kritische benadering en scherpe blik hebben eens te meer een groter begrip en een verbeterd inzicht bij mij tot stand gebracht. Heel veel dank hiervoor.

Prof. dr. R. Benner, mijn promotor, hartelijk dank voor de geweldige kans die u mij geboden heeft. Het vertrouwen dat u mij aldoor heeft gegeven en de prettige wijze waarop u mij begeleidt heb ik als enorm stimulerend ervaren. Ik hoop dat onze samenwerking in de toekomst tot nieuwe inzichten zal leiden.

Prof. dr. Tilanus, mijn promotor. Ik ben u veel dank verschuldigd voor het in mij gestelde vertrouwen. Ik waardeer het zeer dat u de tijd en de moeite heeft willen nemen om bij mijn promotie betrokken te zijn.

De leden van de kleine commissie, prof. dr. J.J.B. van Lanschot, prof. dr. W.A. Bemelman, prof.dr. A. van Belkum. Ik wil u allen hartelijk bedanken voor de vlotte en kritische beoordeling van het manuscript.

De leden van de grote commissie ben ik erkentelijk voor de bereidheid zitting te nemen in de promotiecommissie.

Dr. D.D E. Zimmerman. Beste David, mijn promotietraject begon waar het jouwe eindigde, jouw boekje heeft de basis gelegd voor het mijne. Bedankt voor al jouw hulp, adviezen en je aanstekelijke enthousiasme. Ik vind het heel erg leuk dat je nu ook het begin van mijn klinische carrière van dichtbij meemaakt. Ik hoop nog veel van je te leren.

Dr. M.P. Gosselink. Beste Martijn, jij bent vanaf het begin van mijn onderzoekstijd altijd nauw betrokken geweest bij alles wat ik deed. Bedankt voor de steun, de gezelligheid en de schop onder mijn kont die ik af en toe even nodig had. Ik waardeer het ten zeerste dat je ondanks je drukke baan altijd voor me klaar staat.

Daniëlla Oom. Lieve Daan, bedank voor je steun, je kritische blik en bovenal de ontzettend gezellige tijd samen op het functielab. Onze promoties, zo kort na elkaar zijn een geweldige afsluiting van een intensieve en leuke periode. Ik bewonder jouw gedrevenheid en weet zeker dat er een fantastische carrière binnen de gynaecologie voor je in het verschiet ligt.

Alle mede-onderzoekers en co-auteurs wil ik van harte bedanken voor hun inzet, wetenschappelijke inbreng en prettige samenwerking.

Anneke van der Meulen en Geertje de Korte. Ik wil jullie heel erg bedanken voor jullie inzet en efficiëntie die een geweldige ondersteuning zijn geweest bij het tot stand komen van dit proefschrift.

Alle medewerkers op de OK van het Havenziekenhuis wil ik van harte bedanken voor hun oprechte interesse in mijn onderzoek, de soepele samenwerking en de gezelligheid.

De maatschap Chirurgie en mijn collega arts-assistenten van het Reinier de Graaf Ziekenhuis in Delft wil ik bedanken voor de prettige werksfeer waarin ik mijn eerste klinische ervaringen heb kunnen opdoen.

Mijn paranimf en goede vriendin, Jorinde van Laanen. Lieve Jopie, ik ben ontzettend blij dat jij mij bij wilt staan als paranimf. Ik vind het fantastisch hoe jij en Alger altijd voor mij klaar staan. Bedankt voor alle steun en de talloze gezellige (en lange) avonden, ik hoop dat er nog vele zullen volgen.

Mijn lieve zus en paranimf, Katinka. Lieve Toontje, jij bent niet alleen mijn zus je bent ook mijn beste vriendin. Wij zijn twee handen op een buik en hebben aan een half woord genoeg. Ik wil je ontzettend bedanken voor je steun en gezelligheid. Ik kan me niet voorstellen dat er ooit een einde komt aan onze wekelijkse logeerpartijtjes. En natuurlijk bedankt voor je taalkundige hulp. Jij bent, denk ik, de enige zonder medische achtergrond die mijn boekje van voor tot achter heeft gelezen. Lieve Daniel, bedankt voor de vele gezellige avonden bij jullie thuis in Amsterdam, waarbij ik alle promotieperikelen even los kon laten.

Georgios en Anjo. Lieve Jor, ik bof ontzettend met een grote broer als jij. Ik wil jou en An bedanken voor alle steun en gezelligheid. Lieve Elia en Jiska, met jullie is het altijd een feest. Nu mijn boekje af is heb ik weer meer tijd; komen jullie weer snel logeren?

Lieve papa en mama, heel erg bedankt voor alle steun die ik altijd van jullie krijg. Jullie interesse, zorgzaamheid en waardering is hartverwarmend.

Curriculum Vitae

Curriculum Vitae

Evangelia (Litza) Mitalas werd geboren op 26 december 1975 te Rotterdam. Na het eindexamen VWO, aan het Krimpenerwaard College te Krimpen aan den IJssel, studeerde zij geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens haar studie deed zij haar eerste ervaring op binnen de colorectale onderzoeksgroep van de afdeling Heelkunde onder leiding van dr. W.R. Schouten. In januari 2008 behaalde zij haar artsexamen, waarna een aanstelling als arts-onderzoeker volgde op de afdeling Immunologie (prof. dr. R. Benner). Sinds september 2009 is zij werkzaam als ANIOS Heelkunde in het Reinier de Graaf Gasthuis te Delft (dr. M. van der Elst).