Surgical treatment of perianal and rectal fistula
van Koperen, P.J.

Citation for published version (APA):
van Koperen, P. J. (2010). Surgical treatment of perianal and rectal fistula s.l

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
UITNODIGING

Voor het bijwonen van de openbare verdediging van het proefschrift

SURGICAL TREATMENT OF PERIANAL AND RECTAL FISTULA

van
P.J. van Koperen

op donderdag 29 april 2010 om 14.00

in de Agnietenkapel
Oudezijds Voorburgwal 231
1102 EZ Amsterdam

Receptie na afloop van de promotie

Paranimfen
Arjan van der Vegt
+31-6-22467806
ajvandervegt@hotmail.com

Jan Wind
+31-6-49784744
janwind79@hotmail.com

P.J. van Koperen
Obrechtstraat 25bis
3572 EB Utrecht
+31-6-24939661
pvankoperen@hotmail.com

Surgical Treatment of Perianal and Rectal Fistula

P.J. van Koperen
Surgical Treatment of Perianal and Rectal Fistula

P.J. van Koperen
The printing of this thesis was financially supported by: Academic Medical Center, J.E. Juriaanse Stichting, Nederlandse vereniging voor Gastroenterologie, B-Braun Medical B.V., Johnson & Johnson Medical B.V., Centocor B.V., Covidien Nederland B.V., KCI Medical B.V., Pentax Nederland B.V., Stöpler, Abbott B.V., Ferring B.V., Gelre Ziekenhuizen, Eurotec B.V., Cook Medical B.V., Schering-Plough, Nycomed B.V., Crohn- en Colitis Ulcerosa Vereniging Nederland (CCUVN), Integraal Kankercentrum Amsterdam (IKA) / Comprehensive Cancer Center Amsterdam (CCCA).

The CCCA is one of eight Comprehensive Cancer Centers in the Netherlands. Its area is the north-western part of the Netherlands and involves 2,800,000 inhabitants, 16 general hospitals, two university hospitals and the Netherlands Cancer Institute. The comprehensive cancer centres (CCCs) in the Netherlands have been founded to provide comprehensive and high-quality cancer care close to home for all cancer patients. The CCCA provides and coordinates a collaboration of all health care professionals and institutions involved in cancer and palliative care. The CCCA functions as a centre of knowledge and quality care that helps to improve cancer treatment, patient care and clinical research as well as prevention of cancer and decrease of cancer mortality.

Colofon
Surgical Treatment of Perianal and Rectal Fistula, Thesis, University of Amsterdam, the Netherlands
Copyright© 2010 P.J. van Koperen, the Netherlands
No part of this thesis may be reproduced, stored or transmitted in any form or by any means without prior permission of the author
Lay-out: P.J. van Koperen, Utrecht & D. de Klerk, Zwolle
Printed by: Ipskamp, Enschede, the Netherlands
ISBN: 978-90-9025226-1
SURGICAL TREATMENT OF PERIANAL AND RECTAL FISTULA

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 29 april 2010, te 14.00 uur

door

Paul Jochem van Koperen

geboren te ’s-Gravenhage
Promotiecommissie

Promotor
Prof. dr. W.A. Bemelman

Co-promotor
Dr. J.F.M. Slors

Overige leden
Prof. dr. C.G.M.I. Baeten
Prof. dr. M.A. Cuesta
Prof. dr. R.J. de Haan
Prof. dr. M.A.G. Sprangers
Dr. P.C.F. Stokkers

Faculteit der Geneeskunde
Fistelpot is een middel uit de 19e eeuw dat gebruikt werd om fistels te genezen. Klaas Ursem (1802-1883) kreeg het recept rond 1825 van een koopman die bij hem overnachtte. De man werd ziek maar wist zichzelf te genezen dankzij zijn kruidenkennis. Hij behandelde vervolgens een familieled van Klaas die last had van een fistel aan zijn been. Als beloning voor de gastvrijheid kreeg Klaas het recept voor het geneesmiddel: de Fistelpot. Het middel wordt nog steeds geproduceerd door de familie Ursem in Nibbixwoud. Het recept van de fistelpot is geheim, maar de Vereniging tegen de Kwakzalverij destilleerde rond 1920 de volgende ingrediënten: - 30 gram karwijzaad - 10 gram wierook - 10 gram lavas - 30 gram sevenboomkruid - 10 gram hertshoorn - 5 gram kruidnagelen - 5 gram witte peper - 5 gram nootmuskaat - 5 gram hondsdraf - 10 gram jeneverbessen - 2 eierdoeiers - 1 kilo verse boter. Het bruine stinkende middel is voor inwendig gebruik. Tijdens de kuur mag de patiënt geen koemelk, varkensvlees of sterke drank nuttigen.
# TABLE OF CONTENTS

*Introduction and outline of thesis*  

**PART I Surgical treatment of perianal fistulas**

Chapter 1  *Perianal fistulas: developments in the classification and diagnostic techniques, and a new treatment strategy*  

Chapter 2  *Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of cryptoglandular origin*  

Chapter 3  *Outcomes of surgical treatment for perianal fistulas in Crohn’s disease*  

Chapter 4  *Fibrin glue and transanal rectal advancement flap for high transsphincteric perianal fistulas; is there any advantage?*  

Chapter 5  *Histological identification of epithelium in perianal fistulas; a prospective study*  

**PART II Novel techniques in fistula surgery**

Chapter 6  *The anal fistula plug for closure of difficult anorectal fistula, a prospective study*  

Chapter 7  *The anal fistula plug versus the mucosal advancement flap for the treatment of Anorectal Fistula (PLUG trial)*  

Chapter 8  *The anal fistula plug treatment compared to the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistulas: A double blinded multicenter randomized trial*
PART III  Presacral pathology and anastomotic leakage

Chapter 9  The persisting presacral sinus following anastomotic leakage after anterior resection: incidence and outcome  119

Chapter 10  Endo-sponge treatment of anastomotic leakage after ileoanal pouch anastomosis  129

Chapter 11  The Dutch multicenter experience of endo-sponge treatment for anastomotic leakage after colorectal surgery  137

Chapter 12  Presacral masses in children and adults: presentation, etiology and risk of malignancy  149

Appendices  Summary  163

Nederlandse samenvatting  171

Dankwoord  179

Curriculum vitae  183
Introduction and outline of thesis

Perianal fistulas

A fistula is an abnormal passage from one surface with epithelium to another. A perianal fistula is a connection between the perianal skin and the anus or the rectum. It is one of the most frequently encountered anorectal diseases in today’s surgical practice. The incidence in females is 5.6 out of 100,000 and 12.3 out of 100,000 in males. Perianal fistulas are predominantly found in patients aged between 30 and 50 years. Patients often complain of perianal pain, discharge of blood, mucous, and pus.

Etiology

The origin of the majority of the fistulas is cryptoglandular (approximately 90%). These fistulas originate from infection and abscess development in the intersphincteric anal glands. There are several other causes, including Crohn’s disease, Human Immunodeficiency Virus (HIV), malignancy, and tuberculosis. The etiology is important because the treatment differs for the different underlying causes. Crohn’s disease interferes with wound healing and fistula closure. As a result, management of these fistulas is directed towards limiting the amount of collateral surgical damage to prevent recurrent fistulas, anal fibrosis, and incontinence.

Classification

Several classification systems have been proposed in the published literature. In 1976 the Parks’ classification of perianal fistulas was introduced. It is an anatomical classification of perianal fistulas based on the relation of the fistula tract and the
external sphincter muscle (Figure 1). Due to developments in the surgical treatment of perianal fistulas it is currently advised to classify perianal fistula into low and high perianal fistulas. This provides insight into the relation between the primary fistula tract and the sphincter muscle. Studies have shown that division of more than 30% of the external sphincter muscle is associated with significantly more incontinence. In low perianal fistulas the fistula tract is submucosal, intersphincteric, or located in the lower third of the external anal sphincter. In high perianal fistulas the fistula tract is located in the upper two-thirds of the external sphincter (Figure 1).

治疗

Hippocrates described the treatment of perianal fistulas and the importance of early drainage of perianal abscesses in 460 BC. He also described the use of the fistulotomy and seton using a strip of linen. In the Middle Ages, John of Arderne, an English surgeon, extensively described the fistulotomy. Later in the 17th century King Louis XIV suffered from a perianal fistula. As his first royal surgeon, Charles-François Félix de Tassy performed a fistulotomy in 1686 and the King recovered successfully. This was after he perfected the technique by operating other patients from different hospitals in Paris before treating the King himself. He was generously awarded for his work with an estate, a title and a significant honorarium. The aim of today’s surgical treatment is to eradicate the fistula without endangering
Introduction and outline of the thesis

continence. When patients experience minor complaints surgical treatment should not be undertaken and a wait and see policy can be chosen. A fistulotomy is performed by laying the fistula tract open from the internal to the external opening. In low perianal fistulas, without significant interference of anal sphincter muscle, it leads to favorable success rates and relatively little impact on fecal continence. The recurrence rates of these fistulas are low, ranging from 2 to 9%. When sphincter muscle is divided in high perianal fistulas this can result in incontinence.

The surgical treatment options that are available and currently widely used for high perianal fistulas include the mucosal advancement flap, fibrin glue, and seton drainage. Currently, the mucosal advancement flap is the treatment of choice for high transsphincteric fistulas. Contra-indications are active proctitis in case of Crohn’s disease, undrained perianal abscesses, anorectal fibrosis or stenosis. By advancing tissue over the internal opening, no fecal material can be forced into the fistula tract during defecation. The internal opening is closed after advancing and suturing the flap over the internal opening. Possible complications of the mucosal flap advancement are flap retraction, hematoma, and necrosis of the flap. The advancement flap is effective in approximately 50-70%. Fibrin glue is an alternative option and can be injected into the fistula tract. By doing this the internal opening is temporary closed. Success rates of the different studies reporting on fibrin glue differ and range from zero to 100%.

A seton can be used as cutting or non-cutting (loose) seton. The loose seton is lead through the fistula tract and is tied on the outside. The seton nowadays serves as a bridge to a definitive procedure. A cutting seton is designed to cut through the sphincter and leads to division of the muscle. It is comparable to the fistulotomy, but the seton migrates slowly through the sphincter. The rationale is that the muscle is divided very slowly and has time to heal. The loose seton is nowadays primarily used for the temporary or long term drainage of the perianal fistula tract.

Over the years several new methods to treat high perianal fistulas have been developed. Recently the anal fistula plug was developed to treat these complex high fistulas. The plug is a bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa. The material has inherent resistance to infection. The fistula tract is closed by installing the plug which achieves closures of the fistulas by tissue remod-
elling. The material is fashioned into a conical plug and secured into the primary opening of the fistula tract. The internal end of the plug is sutured in place with at least two sutures. The external opening is left open to allow for drainage of the tract. An advantage of the plug is the minimally invasive character of the plug. The procedure is repeatable and possibly there is less damage to the sphincter resulting in less incontinence and postoperative pain. In a series of 46 patients a success rate of 83% was found at a follow-up duration of 12 months.\textsuperscript{20}

**Presacral pathology and anastomotic leakage**

**Anastomotic leakage**

In recent decades there are several developments in colorectal surgery. Surgical technique advances through specialized surgery and improvement of anastomotic stapling. Despite these advances anastomotic leakage remains a feared complication following colorectal surgery and an important cause for morbidity and mortality. Morbidity includes abdominal sepsis, intensive care stay, and abdominal wall complications resulting from reinterventions and wound infections. Furthermore, the risk of permanent ostomy is considerable. Ultimately anastomotic leakage is the main cause of postoperative mortality.\textsuperscript{21} In the literature anastomotic leakage is reported for low colorectal surgery up to 24%. Reported risk factors for anastomotic leakage include a difficult surgical procedure, low tumour location, adjuvant radiochemotherapy, and poor preoperative patient condition.\textsuperscript{22} Anastomotic dehiscence can lead to a presacral abscess or chronic para-anastomotic sinus. This presacral abscess cavity results in continuous drainage of debris and considerable patient discomfort. Prolonged pelvic sepsis and fibrosis is held responsible for impaired long term neorectum function after ileostomy closure in many of those patients. To treat these para-anastomotic sinuses transanal, radiological, or endoscopic placement of drains in the abscess cavity are options. Vacuum sponges are used for closure of several types of wounds.\textsuperscript{23} The endo-sponge was developed for the resolution of presacral abscess cavities as a result of anastomotic leakages following colorectal surgery.\textsuperscript{24} The sponge is installed transanally after examination and rinsing of the sinus. It facilitates closure by the application of negative pressure ensuring continuous drainage and thereby infection control. An important part of
the mechanism is that suction provides expansion of the neorectum or pouch to occlude the cavity.

Presacral tumours

The presacral space between the rectum and the sacrum derives from embryological fusion of different layers. Tumours in the presacral region are rare with an incidence 1.4 to 6.3 patients per year in a major referral center. Types of tumours that may arise are both congenital and acquired. The majority of these tumours in both adults and children are congenital. The presentation and origin is different for pediatric and adult patients. In children presacral masses reported are mostly sacrococcygeal teratomas (Altman types III and IV) and tumours seen as part of the Currarino syndrome, a rare syndrome which comprises the presence of a typical bony sacral defect, often in combination with a presacral mass or an anorectal malformation. Presacral tumours presenting in adults are more often developmental cysts. In reported series and reviews benign lesions are more common than malignant lesions.

OUTLINE OF THE THESIS

In this thesis, several aspects of anorectal surgery are highlighted. The aim of this thesis is to evaluate the surgical treatment options and strategies of perianal fistulas (part I), to critically appraise the anal fistula plug as a novel method for the definitive closure of perianal fistulas (part II), and to evaluate the presacral pathology and the treatment of presacral abscesses after anastomotic leakage resulting from rectal surgery (part III).

PART I: Surgical treatment of perianal fistulas

In Chapter 1 the various treatment options and changes in fistula classification for the surgical treatment of perianal fistulas and the available diagnostic options are reviewed. Furthermore a surgical treatment strategy is presented. In Chapter 2 the long-term functional outcome and possible risk factors for the development of recurrent or persistent fistulas are assessed for patients surgically treated by fistu-
lotomy or rectal advancement flap according to a standardized treatment protocol. As the recurrence rate and the continence are the most important factors in the treatment of perianal fistulas, these measures are specifically studied. Chapter 3 assesses the recurrence rates and long term functional outcome after surgical treatment of anal fistulas in Crohn’s disease. Only in selected patients without proctitis or active Crohn’s disease definitive closure by surgical intervention was attempted. Patients were treated by fistulotomy in case of low perianal fistulas. Patients where the fistula tract was located in the upper two-third of the sphincter complex were treated by mucosal advancement flap.

In recent decades, fibrin glue has appeared as an alternative treatment for high perianal fistulas. Early results were promising, with high success rates being reported. However, with increasing follow-up, the enthusiasm was tempered because of disappointing results. The aim of the study presented in Chapter 4 is to assess the additional value of fibrin glue in combination with mucosal advancement flap, compared to advancement flap alone, for the treatment of high transsphincteric fistulas of cryptoglandular origin.

In the process in finding reasons for recurrent or persistent fistulas attention is also directed towards epithelialization of the fistula tract. Epithelialization of the fistula tract might prevent closure. A procedure often performed following fistulotomy and advancement flap is curettage of the fistula tract after fistulotomy or after closing the internal opening. In Chapter 5 the incidence and origin of epithelialization of the fistula tract in patients with perianal fistulas undergoing fistulotomy are described.

PART II: Novel techniques in fistula surgery

In Chapter 6 the results of the use of the anal fistula plug in patients with complex high perianal fistulas are described in this prospective, two-center, clinical study. In Chapter 7 a randomized controlled multi-center trial is proposed to determine whether the anal fistula plug or the mucosal advancement flap is preferred for the treatment of high transsphincteric fistulas of cryptoglandular origin. The results of this trial proposal are described in Chapter 8. In total sixty patients are included in a trial comparing the anal fistula plug with the mucosal advancement flap. Postoperative pain, quality of life, and continence before and after surgery are assessed.
PART III: Presacral pathology and anastomotic leakage

The objective of Chapter 9 is to assess the incidence, the natural course and outcome of persisting presacral sinuses after anterior resection for rectal malignancy or restorative proctocolectomy for ulcerative colitis or poliposis. Recently, application of local vacuum sponge treatment has shown to be effective to treat contained anastomotic leakage after low anterior anastomosis in rectal cancer patients. In Chapter 10 the use of the endo-sponge method and the outcome of two patients with presacral abscesses after restorative proctocolectomy for ulcerative colitis is described. In Chapter 11 a series of patients is described in the Netherlands that underwent endo-sponge treatment. The sponge is used in patients following anastomotic leakage after low anterior resections for malignant disease or after restorative proctocolectomy with ileoanal pouch anastomosis for ulcerative colitis.

The presacral space is a potential area surrounding the rectum in which masses can develop. There is also the risk of development of malignant tumours. In Chapter 12, the aim is to survey the spectrum of presacral masses in children and adults with special attention to the type of presentation, the origin and type of the tumour and the risk of development of malignant tumours. Over a 22-year period of January 1987 to 2009 a series of patients was included. Inclusion criterion was the presence of a congenital presacral mass that was surgically treated.

REFERENCES


Introduction and outline of the thesis


PART I

Surgical treatment of perianal fistulas
Chapter 1

Perianal fistulas: developments in the classification and diagnostic techniques, and a new treatment strategy

P.J. van Koperen, K. Horsthuis, W.A. Bemelman, J. Stoker, J.F.M. Slors

Translated from Nederlands Tijdschrift voor Geneeskunde, 2009
ABSTRACT

The aim of surgical treatment of perianal fistulas is to eradicate the perianal fistula, with low recurrence rates and risk of incontinence. In recent years there were developments regarding imaging and diagnostics of perianal fistulas. Magnetic resonance is the most appropriate diagnostic tool. In the hands of an experienced operator anal endosonography is a suitable, less expensive and readily-available technique.

As a result of developments in fistula surgery it is now recommended to divide perianal fistulas into low or high fistulas, as this has implications for the surgical treatment. Low perianal fistulas are defined as fistulas located in the lower third of the external anal sphincter. High fistulas are fistulas in which the fistula tract is located in the upper two-thirds of the external sphincter muscle. Low perianal fistulas can be treated safely by fistulotomy. Presently, the mucosal advancement flap is the gold standard for the surgical treatment of high transsphincteric perianal fistulas. The anal fistula plug might be an alternative for the treatment of high transsphincteric perianal fistulas.
INTRODUCTION

A perianal fistula is one of the most frequently encountered anorectal disease in today’s surgical practice. The incidence in females is 5.6 out of 100,000 and 12.3 out of 100,000 in males. The incidence is highest between 30 and 50 years of age. When patients experience minor complaints surgical treatment is not necessary and a wait and see policy can be chosen. The aim of surgical treatment of perianal fistulas is to eradicate the fistula with a surgical treatment that leads to the lowest possible recurrence percentage, without endangering continence.

Historically, all perianal fistulas were treated by fistulotomy or by radical fistulectomy. This resulted in high success percentages, however incontinence was frequently encountered. In 2001, Schouten et al. described the classification and the imaging options for perianal fistulas. In the present article the changes in fistula classification, imaging and surgical treatment options are reviewed. Furthermore, a surgical treatment strategy will be presented.

ETIOLOGY

The majority of the fistulas are of cryptoglandular origin (approximately 90%). These non-specific fistulas originate from infection and abscess development in the intersphincteric anal glands. Alternative causes are for instance Crohn’s disease and HIV. In the present article only perianal fistulas of cryptoglandular origin will be reviewed.

CLASSIFICATION

In 1976 the Parks’ classification of perianal fistulas was introduced. It is an anatomical classification of perianal fistulas based on the relation of the fistula tract and the external sphincter muscle. As a result of developments in the surgical treatment of perianal fistulas it is currently advised to divide perianal fistula into low and high perianal fistulas (Figure 1.1). Division of more than 30% of the external sphincter muscle is associated with significantly more incontinence. In low perianal fistulas the fistula tract is submucosal, intersphincteric, or located in the lower third of the...
external anal sphincter. In high perianal fistulas the fistula tract is located in the upper two-thirds of the external sphincter.

![Diagram of anal sphincter muscles](image)

**Figure 1.1** – Low perianal fistulas are fistulas where the fistula tract transverses the lower 1/3 of the external sphincter complex. High fistulas transverse the upper 2/3 of the external sphincter complex.

### DIAGNOSTICS AND IMAGING

It is important to obtain information on the exact location of the internal opening, the route of the fistula tract, the relation of the fistula and anal sphincter muscles, and the presence of abscesses and multiple fistula tracts.

**Fistulography en Computerized Tomography (CT)**

Fistulography is considered obsolete as no information is obtained on the route of the fistula tract in relation to the external sphincter muscle. Secondary fistula tracts are often not filled with contrast, which leads to inaccurate information of the fistula complex. There is currently no role for the CT as result of low contrast resolution. It is also difficult to differentiate between scar tissue and active perianal fistulas. In a prospective study anal endosonography was superior compared to the CT.
Anal endosonography

Anal endosonography is cheap, quick and easily accessible compared to other kinds of imaging. The initial results were promising, however in later studies in which the endosonography was compared to the Magnetic Resonance (MR) scan the results were less promising. This discrepancy in the results may be explained by the experience of the radiologist performing the examination.

For the identification of the internal opening the anal endosonography is suitable as the internal opening is located close to the transducer. From earlier studies it became clear that the endosonography is capable to successfully locate the internal opening in around 70%. In a more recent study involving 151 patients in 93% the localization of the internal opening corresponded with the examination under anesthesia. Furthermore, by injecting hydrogen peroxide into the fistula tract the accuracy was increased in some studies. Three-dimensional images can be produced, however the value in fistula imaging should be studied. With anal endosonography it is possible to assess pre- and postoperatively the presence and the extent of damage to the anal sphincters. A drawback from anal endosonography is the inadequate penetration of the transducer in the perianal fossa and the suprallevatoric area. Secondary extensions of the fistula can be missed for this reason. Furthermore, it is difficult to differentiate between fibrosis and active infection. Hydrogen peroxide can be helpful to differentiate between these two. This makes the anal endosonography less suitable for patients with a history of fistula surgery.

Magnetic Resonance Imaging (MR)

The diagnostic value of the MR became clear in the nineties. Advantages were the correct visualization of secondary fistula tracts, presence of abscesses, and the ability to differentiate between fibrosis and an active fistula. There are two ways to visualize perianal fistulas by MR. The first option is to use an endoanal coil (an internal MR coil) (Figure 1.2b) or by using a body coil (Figure 1.2a). With an endoanal coil it is possible to achieve higher spatial resolution at the level of the anal sphincter compared to the body coil. This results in an anatomically superior image (Figure 1.2b). The internal fistula opening and small secondary fistula tracts should theoretically be better visible compared to the body coil. There are
however no comparable studies available. Due to the limitation in the field of view, high and/or very extensive fistulas are not always easy to visualise. The MR body coil has no limitations in the field of view in the anorectal area. Furthermore the body coil is less invasive for patients and the technique is readily available.

Figure 1.2 – a) MR image (coronal plane) of a female patient using a body coil shows a high transsphincteric fistula b) MR image (sagittal plane) of a male patient using an endoanal coil shows a low intersphincteric fistula with an internal opening.

With the MR it is possible to differentiate between an active infection and scar tissue based on the intensity on the T2-weighted images. Active fistula and abscesses are hyperintense, while scar tissue is hypointense. T1-weighted images enhanced by gadolinium further differentiates between inflammatory tissue (hyperintense) and fluid (hypointens). The clinical value of the MR (with a body coil) for perianal...
Developments in the classification and diagnostic techniques

Fistulas is confirmed by two studies. In a study reporting on 104 patients with the MR lead to the correct diagnosis in 90%. This was significantly higher than examination under anesthesia (61%) and also better than anal endosonography (81%).

The diagnosis was related to a reference standard built up from examination under anesthesia, MR and outcome. In the second study of 71 patients with recurrent perianal fistulas the result of the pre-operative MR scan was used to guide the surgical treatment. This reduced the postoperative recurrent fistulas with 75%.

TREATMENT

Low fistula

Submucosal, intersphincteric, and low transsphincteric fistulas, located in the lower one-third of the external sphincter complex can be treated by fistulotomy, with favorable success rates and relatively little impact on fecal continence (Figure 1.3). The recurrence rates of these fistulas are low, ranging from 2-9%. In a recently published study reporting on 109 patients with cryptoglandular fistulas treated by fistulotomy a recurrence rate of 7% at a follow-up duration of 76 months was found. In 40% of these patients soiling was reported. In the literature the reported incontinence following fistulotomy ranges from 0-70%. In a retrospective series consisting of 624 patients, the factors female sex and a ventral fistula location were associated with incontinence. This is probably the result from obstetric damage of the sphincter-complex. Only in selected patients in this group a fistulotomy should be performed.

High fistula

This group consists of patients with perianal fistulas where the fistula tract is located in the upper two-thirds of the external sphincter. The surgical treatment options are the mucosal advancement flap, fibrin glue, seton drainage, and the anal fistula plug.

Mucosal advancement flap

The mucosal advancement flap is currently the gold standard for high transsphincteric fistulas (Figure 1.4). The rationale behind the advancement flap is that the open internal opening is the cause of the persisting fistula tract. By advancing tis-
sue over the internal opening, it is impossible for fecal material to be forced into the fistula tract during defecation. The advancement flap is done according to the following technique. The internal opening is excised followed by mobilization of the mucosa, submucosa, and a small amount of muscular fibers from the internal sphincter complex. A rectal flap with a two to three centimeters broad base is mobilized. The rectal flap is mobilized sufficiently to cover the internal opening with overlap. Hemostasis is performed to prevent a hematoma under the flap. The fistula tract is curetted and the internal opening is closed after advancing the flap over the internal opening. Finally, the flap is sutured in the distal anal canal with interrupted Vicryl 2-0 sutures (Ethicon Endo-Surgery, Cincinnati, OH). Possible complications of the mucosal flap advancement are retraction, hematoma and necrosis of the flap. In case of acute sepsis, patients can be treated with three months of seton drainage before performing the advancement flap. The recurrence rates for the mucosal advancement flap reported in literature vary and are reported ranging from 0-69%. Van Koperen et al. reported a series of 70 patients with high transsphincteric fistulas with a recurrence rate of 21%. Soiling was reported in 43% of the patients. In the literature problems with continence are reported between zero and 40%.

**Fibrin glue**

By injecting the fibrin glue the fistula tract and the internal opening are temporary closed. When the glue resolves after a few weeks, fibroblasts activated by the fibrin glue matrix, achieve closure of the fistula tract. Although the first results were
Developments in the classification and diagnostic techniques

Figure 1.4 – Mucosal advancement flap; a) seton in situ; b) the internal opening is excised; c) sutures are fixed to the mucosal advancement flap.

good, later studies were disappointing. In a recent systematic review, the success percentages of the 19 included studies varied from 0-100%.\textsuperscript{35} This large variety is possibly the result of different etiologies, operation technique and perioperative policy.

\textit{Seton drainage}

The seton can be used as cutting or non-cutting (loose) seton. The loose seton is lead through the fistula tract. The seton can serve as a bridge for the definitive procedure. The cutting seton is designed to cut through the sphincter and leads to muscle division. It is comparable to the fistulotomy, but the seton migrates slowly through the sphincter. The rationale is that the muscle is divided very slowly and has the time to heal. The seton is nowadays primarily used for the temporary or long term drainage of the perianal fistula tracts.

\textit{Anal fistula plug}

Recently there are reports on the anal fistula plug, a bioabsorbable xenograft made of lyophilized porcine intestinal submucosa which resolves in time (Surgisis, Cook Surgical). Through tissue remodelling the plug closes the fistula tract. The material is fashioned into a conical plug and secured into the primary opening of the fistula tract. The internal end of the plug is sutured in place with two sutures. The external opening is left open to allow for drainage of the tract. In a series of 46 patients a success percentage of 83\% was found at a follow-up duration of 12 months.\textsuperscript{36} A
comparable result was found in a series of 18 patients with a follow-up duration of six months. Recently, the results of a small series of 17 patients with therapy resistant complex high transsphincteric fistulas was published. A recurrence rate of 41% was found (follow-up 15 weeks). An advantage of the plug is the minimally invasive character of the plug. The procedure is repeatable and possibly there is less incontinence and anal scarring.

Figure 1.5 – Treatment strategy perianal fistulas.

Conclusion

Due to the impact on the chosen treatment it is advisable to divide patients with perianal fistulas in low (lower 1/3) and high (upper 2/3) fistulas. The MR is the treatment of choice for imaging of perianal fistulas. The anal endosonography is a cheap, easy and suitable alternative readily available. The anal endosonography is less useful in patients that have a history of fistula surgery. Low perianal fistulas, situated in the lower 1/3 of the external sphincter muscle can be treated with low recurrence rates by fistulotomy. The mucosal advancement flap is the treatment of choice for high perianal fistulas (Figure 1.5). The anal fistula plug is a potential alternative for high perianal fistulas.
REFERENCES


Chapter 2

*Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of cryptoglandular origin*

P.J. van Koperen, J. Wind, W.A. Bemelman, R. Bakx, J.B. Reitsma, J.F.M. Slors

*Diseases of the Colon & Rectum, 2008*
ABSTRACT

Background
This study assessed long-term functional outcome and explored risk factors for fistula recurrence in patients surgically treated for cryptoglandular fistulas.

Methods
Three hundred ten consecutive patients were surgically treated for perianal fistulas. After exclusion of patients with inflammatory bowel disease or human immunodeficiency virus, 179 patients remained. Patients were divided into two groups: those who received fistulotomy for low perianal fistulas and those who received rectal advancement flap for high perianal fistulas. Time to fistula recurrence was the main outcome and Cox proportional hazard models were used to assess the importance of various risk factors. Functional outcome was assessed using the Vaizey and colorectal functional outcome (COREFO) questionnaires.

Results
The median follow-up duration was 76 months (range 7-134). The 3-year recurrence rate for low perianal fistulas treated by fistulotomy (n=109) was 7% (95% confidence interval [CI] 1-13%). In high transsphincteric fistulas treated by rectal advancement flap (n=70) the recurrence rate was 21% (95% CI 9-33%). In both groups soiling was reported by 40% of the patients. None of the seven potential risk factors examined were statistically significant.

Conclusions
Fistula recurrence rate after fistulotomy was low. No clear risk factors were found. Overall functional outcome in terms of continence was good. However, a substantial amount of patients reported soiling.
INTRODUCTION

The aim of fistula surgery is to eradicate the fistula tract by closing the internal opening, without jeopardizing continence. In general, patients with perianal fistulas in the lower one-third of the external sphincter complex are easily treated by fistulotomy with low recurrence rates and relatively little impact on continence.\(^1,2\) For perianal fistulas in the upper two-thirds of the external sphincter complex, the rectal advancement flap is considered the standard surgical treatment. Various treatment options have emerged in recent years for the treatment of high perianal fistulas. During the last decades fibrin glue appeared as an attractive alternative. Reported long-term outcomes vary considerably between the different studies and recurrence rates range from zero to 100%.\(^3\) Inconsistent reports of recurrence rates are likely a result of heterogeneous research designs. Often patients with Crohn’s disease and human immunodeficiency virus (HIV) were included, various classifications of perianal fistulas were used, alternative treatment protocols were used, and sufficient follow-up was lacking.

This study examined long-term functional outcome and assessed possible risk factors for the development of fistula recurrence in patients surgically treated by fistulotomy or rectal advancement flap according to a standardized treatment protocol. As the recurrence rate and the continence are the most important factors in the treatment of perianal fistulas, these outcomes were specifically studied.

METHODS

Patients

Between January 1995 and May 2003, a consecutive series of patients operated for perianal fistulas of cryptoglandular origin were analyzed. Patients in which the internal fistula opening could not be detected and patients with fistulas caused by Crohn’s disease or HIV were excluded, as well as patients aged less than 18 years and patients with rectovaginal fistulas.
Chapter 2

Treatment protocol

Patients were divided into two groups. These groups were operated according to a standardized treatment protocol. The first group comprised of patients in which the fistula tract was submucosal, intersphincteric, or located in the lower third of the external anal sphincter and were treated by fistulotomy (fistulotomy group). The second group comprised patients with perianal fistula in which the fistula tract was located in the upper two-thirds of the external sphincter and were treated by rectal advancement flap (rectal advancement flap group). In case of acute sepsis, patients were treated with three months of seton drainage before definitive surgery. The anal canal was defined on the proximal side by the puborectal sling and the distal side by the lower margin of the external sphincter. On the day of surgery an enema was administered to the patient to clean the proctum. All procedures were performed under general or locoregional anesthesia in the lithotomy position. Broad spectrum antibiotics were administered perioperatively. The rectal advancement flap was done according to a technique described herein. The internal opening was excised followed by mobilization of the mucosa, submucosa, and a small amount of muscular fibers from the internal sphincter complex. A rectal flap with a 2-cm to 3-cm broad base was mobilized. The rectal flap was mobilized sufficiently to cover the internal opening with overlap. Hemostasis was performed to prevent a hematoma under the flap. The fistula tract was curetted. The internal opening was closed after advancing the flap over the internal opening. Finally, the flap was sutured in the distal anal canal with interrupted Vicryl 2-0 sutures (Ethicon Endo-Surgery, Cincinnati, OH). In a consecutive series of patients, fibrin glue was added to the procedure in an attempt to decrease the recurrence rate. No specific postoperative instructions or bowel regimens were given to the patients.

Data collection

Retrospective chart review collected information on demographic data, tertiary referral, previous fistula surgery, smoking, surgical treatment (fistulotomy or rectal advancement flap), complications, and fistula recurrence rate. Previous fistula surgery was defined as surgery aimed to permanently repair the fistula. Drainage of abscesses and seton placement were not considered as previous fistula surgery. All
patients visited the outpatient clinic until closure of the fistula tract was achieved. The fistula was considered closed if the external opening was closed and no discharge or pain were experienced. Otherwise, the fistula was considered persistent or recurrent. Follow-up was calculated from the clinical notes when the patient did not respond to the postal survey and to multiple attempts to contact the patient by telephone. In the questionnaire there was specific attention for complaints indicating a recurrent fistula. Patients were asked if they had been operated on elsewhere after their visits to our clinic.

**Functional outcome**

To assess functional outcome of treatment, a postal survey was undertaken. Patients who did not respond were contacted by telephone. If they had moved, the general practitioner was contacted for their address and telephone number.

Continence was evaluated using the Vaizey scale and the COREFO questionnaire.\(^4^,\(^5\)

The validated Vaizey scale consists of items on the type and frequency of incontinence. Also, changes in lifestyle were assessed. Patients were asked on their use of pads or plugs, constipation medication, and the lack of ability to postpone defecation for 15 minutes. The total score on the Vaizey scale ranges from zero (complete continence) to 24 (complete incontinence). The COREFO questionnaire is a validated questionnaire with 27 questions to assess colorectal functional outcome. Patients were asked to consider the two weeks period prior before filling out the questionnaire. Five categories were assessed; namely, incontinence, social impact, defecation frequency, stool-related aspects (questions on pain during bowel movements, blood loss, and local skin problems), and use of medication. Scores ranged from zero to 100. A total score was calculated from these categories, also ranging from zero to 100. A higher score represents an increased level of continence disturbance. In the same survey patients were asked questions on smoking habits and whether they had fistula surgery in another hospital after discharge.

**Statistical analysis**

Data are presented as median values with ranges unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups
Chapter 2

were tested using Mann-Whitney U test for continuous data. Chi-squared test was used to test for differences between groups in cases of categorical data. Fistula recurrence-free survival was estimated using the Kaplan-Meier method. Cox proportional hazard models were used to examine the association between potential risk factors and the time until fistula recurrence. Hazard ratios (HR) with 95% confidence intervals were used to quantify the strength of these associations. The following potential risk factors were examined: gender, age, tertiary referral, prior fistula surgery, and smoking. For the rectal advancement group, the factors seton drainage and the use of fibrin glue were also examined. Natural cubic splines (4 knots) graphical analysis were used to examine the functional form of continuous variables in relation to the outcome. Based on these graphic analysis, an appropriate transformation or categorization was chosen if the relationship was clearly nonlinear. A p-value of 5% or less was considered as statistically significant. Statistical analysis was done using the SPSS v.12.0 package (SPSS, Chicago, IL).

RESULTS

Patient characteristics

Between January 1995 and May 2003, 310 consecutive patients with perianal fistulas were operated on in the study period. Patients were excluded (n=131) for the following reasons: no internal opening found during surgery (n=8), HIV (n=23), rectovaginal fistulas (n=22), or inflammatory bowel disease (n=78) (Figure 2.1). Of the remaining 179 patients, 109 had low fistulas and were treated by fistulotomy. The remaining 70 patients had high perianal fistulas and were treated by rectal advancement flap. Patient characteristics of both groups are shown in Table 2.1. The majority of patients had outpatient surgery. The minimum observed follow-up for all patients after surgery was 7 months with a median of 76 months (range 7-134 months). Seventy-nine of 179 patients could not be contacted by mail or telephone because they had moved without informing their general practitioner or because they were deceased. These patients were censored at their date of last clinical contact at which they had no sign of recurrence. The response rate for 100 patients successfully contacted by mail or telephone was 95%.
Surgical treatment of perianal fistulas of cryptoglandular origin

Total patients operated for perianal fistulas (n=310)
123 Excluded because of:
- 78 Crohn’s Disease
- 23 HIV
- 22 Rectovaginal fistula

Patients operated for fistulas of cryptoglandular origin (n=187)
8 Excluded because of:
- 8 No internal opening found during surgery

Patients eligible for analysis (n=179)

Low perianal fistulas (n=109)
High perianal fistulas (n=70)

Fistulotomy
Mucosal Advancement flap

Fibrin glue (n=16)
No fibrin glue (n=54)

Figure 2.1 – Patient flow chart.

Fistulotomy group

The median age was 39 years (range 19-69). Seventy-one patients were male (65%). Prior fistula surgery was performed in 22 patients (20%). Fourteen patients (13%) were referred from other hospitals mainly because of complex and/or recurrent fistulas. The median number of previous surgical procedures was one (range 0-5). Patients had fistula-related complaints for a median of 6 months (range 0-240). Preoperative continence was impaired in three patients and varied from incontinence of flatus to soiling, determined by medical history on the initial visit to the outpatient clinic. At the time of surgery, 32% of the patients smoked. A postoperative complication was encountered by two patients: minor bleeding (n=1) and urinary tract infection (n=1). The 3-year recurrence rate was 7% (n=8, 95% CI 1-13%, Figure 2.2) The data on the continence questionnaires completed by 63 patients are
presented in Table 2.2. The median follow-up duration of patients with completed questionnaires was 74 (range 7-134) months. The mean total Vaizey score was 6.5 (±3.5) and 18 of 63 (29%) had a perfect continence (Vaizey score=0). The mean total score for the COREFO questionnaire was 9.8 (±12.4). The mean incontinence scale was 9.2 (±12.8). Soiling was reported in 26 out of the 63 (41%) patients. Only three patients reported having lost solid stool unintentionally. None of the potential risk factors reached statistical significance in the univariate or in the multivariate analysis (Table 2.3). In male patients that smoked and were referred to a tertiary center, the estimated risk for fistula recurrence was more than doubled, but the associated confidence intervals were wide.

### Table 2.1 – Characteristics of patients with low and high perianal fistulas.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fistulotomy (n=109)*</th>
<th>Advancement (n=70)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>71:38</td>
<td>47:23</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>39 (19-69)</td>
<td>42 (21-67)</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>14 (13%)</td>
<td>27 (39%)</td>
</tr>
<tr>
<td>Previous fistula surgery (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>87 (80%)</td>
<td>37 (53%)</td>
</tr>
<tr>
<td>1</td>
<td>13 (12%)</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>5 (5%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>4 (4%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>32%</td>
<td>43%</td>
</tr>
<tr>
<td>Preop incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Soiling</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fibrin glue addition</td>
<td>16 (23%)</td>
<td>37 (39%)</td>
</tr>
<tr>
<td>Seton drainage</td>
<td>-</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>8 (7%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Follow-up (months, range)</td>
<td>77 (7-134)</td>
<td>70 (22-127)</td>
</tr>
</tbody>
</table>

*Low perianal fistulas, †high perianal fistulas

### Rectal advancement flap group

The median age at the time of surgery was 42 (range 21-67) years. Forty-seven patients were male (67%). Twenty-nine patients (41%) had undergone prior fistula surgery (Table 2.1). Twenty-seven patients (39%) were referred from other hospitals because of complex and/or recurrent fistulas. The median number of previous surgical procedures was two (range 0-8). Patients had fistula-related complaints for a median of 12 months (range 1-144). Preoperative continence was disturbed
Surgical treatment of perianal fistulas of cryptoglandular origin

Recurrence

0 12 24 36 48 60

0

20

40

60

80

100

Fistulotomy

Rectal advancement

Follow-Up (months)

Recurrence-Free Survival

Figure 2.2 – Fistula recurrence-free survival after fistulotomy (n=109 patients) and rectal advancement flap (n=70).

Table 2.2 – Vaizey scale and colorectal functional outcome (COREFO) for patients treated by fistulotomy or rectal advancement

<table>
<thead>
<tr>
<th>Scale, mean (SD)</th>
<th>Patients without complaints*</th>
<th>Fistulotomy (n=63)†</th>
<th>Rectal advancement flap (n=37)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaizey §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>1.9 (±3.4)</td>
<td>2.0 (±2.5)</td>
<td>2.3 (±2.8)</td>
</tr>
<tr>
<td>Social impact</td>
<td>9.5 (±3.5)</td>
<td>4.5 (±1.7)</td>
<td>3.9 (±2.5)</td>
</tr>
<tr>
<td>Total</td>
<td>5.6 (±2.8)</td>
<td>6.5 (±3.5)</td>
<td>6.2 (±4.0)</td>
</tr>
<tr>
<td>COREFO ¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence range</td>
<td>5.6 (±7.5)</td>
<td>9.2 (±12.8)</td>
<td>11.8 (±13.6)</td>
</tr>
<tr>
<td>Social impact</td>
<td>9.2 (±11.0)</td>
<td>9.7 (±13.9)</td>
<td>12.3 (±12.3)</td>
</tr>
<tr>
<td>Frequency</td>
<td>6.2 (±8.8)</td>
<td>7.7 (±12.9)</td>
<td>6.4 (±6.4)</td>
</tr>
<tr>
<td>Stool-related aspects</td>
<td>7.7 (±12.9)</td>
<td>14.4 (±19.9)</td>
<td>12.6 (±12.6)</td>
</tr>
<tr>
<td>Medication</td>
<td>6.1 (±15.6)</td>
<td>8.2 (±18.0)</td>
<td>5.9 (±14.9)</td>
</tr>
<tr>
<td>Total</td>
<td>7.7 (±12.9)</td>
<td>9.8 (±12.4)</td>
<td>10.8 (±11.2)</td>
</tr>
</tbody>
</table>

*Group of control patients after right-sided hemicolectomy or laparoscopic cholecystectomy †Low perianal fistulas (amount returned questionnaires), ‡High perianal fistulas (amount returned questionnaires). §Mean score ranging from 0-24 (complete continence-complete incontinence) for the total score. Both subscale scores range from 0-12. ¶Mean score per category after linear transformation to a score from 0-100, higher score represents an increased level of continence disturbance. As the total score, all subscales range from 0-100.

in seven patients. Four of these patients were incontinent for flatus and the three others had soiling. At the time of surgery 43% of the patients smoked. Before performing the rectal advancement flap procedure, 37 patients (39%) were treated by seton drainage. In 16 patients, fibrin glue was added to the procedure. In two patients a postoperative complication was encountered: minor bleeding (n=1) and
Table 2.3 – Fistulotomy group: possible risk factors for fistula recurrence. Values in parentheses are 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>Simple model HR (95% CI)</th>
<th>P-value</th>
<th>Multivariate HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3.748 (0.461-30.471)</td>
<td>0.217</td>
<td>3.833 (0.456-32.296)</td>
<td>0.216</td>
</tr>
<tr>
<td>Age (per 10 years increase)</td>
<td>0.730 (0.333-1.583)</td>
<td>0.424</td>
<td>0.825 (0.385-1.757)</td>
<td>0.610</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>3.846 (0.918-16.117)</td>
<td>0.065</td>
<td>2.810 (0.514-15.346)</td>
<td>0.233</td>
</tr>
<tr>
<td>Prior fistula surgery</td>
<td>1.538 (0.367-6.436)</td>
<td>0.556</td>
<td>1.398 (0.316-6.182)</td>
<td>0.658</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.199 (0.525-9.211)</td>
<td>0.281</td>
<td>1.674 (0.306-9.152)</td>
<td>0.552</td>
</tr>
</tbody>
</table>

HR= Hazard Ratio, CI=confidence interval

Table 2.4 – Rectal advancement flap group: possible risk factors for fistula recurrence. Values in parentheses are 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>Simple model HR (95% CI)</th>
<th>P-value</th>
<th>Multivariate HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.157 (0.395-3.388)</td>
<td>0.590</td>
<td>1.347 (0.440-4.119)</td>
<td>0.602</td>
</tr>
<tr>
<td>Age (per 10 years increase)</td>
<td>0.700 (0.385-1.280)</td>
<td>0.245</td>
<td>0.672 (0.353-1.268)</td>
<td>0.159</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>1.658 (0.601-4.576)</td>
<td>0.329</td>
<td>1.601 (0.501-5.114)</td>
<td>0.390</td>
</tr>
<tr>
<td>Prior fistula surgery</td>
<td>1.163 (0.413-3.276)</td>
<td>0.775</td>
<td>1.384 (0.381-5.030)</td>
<td>0.872</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.516 (0.539-4.261)</td>
<td>0.430</td>
<td>1.157 (0.389-3.437)</td>
<td>0.690</td>
</tr>
<tr>
<td>Seton drainage</td>
<td>1.540 (0.526-4.512)</td>
<td>0.431</td>
<td>1.577 (0.521-4.775)</td>
<td>0.420</td>
</tr>
<tr>
<td>Fibrin glue</td>
<td>1.548 (0.549-4.361)</td>
<td>0.409</td>
<td>1.348 (0.422-4.309)</td>
<td>0.614</td>
</tr>
</tbody>
</table>

HR= Hazard Ratio, CI=confidence interval

bradycardia for which the patient was observed overnight (n=1, patient with cardiac history). The recurrence rate for fistulas treated by rectal advancement flap was 21% (n=15, 95% CI 9-33%, Figure 2.2). The outcome of patients with seton drainage did not significantly differ from the patients without. In the patients that underwent seton drainage, the recurrence rate (24%) was similar to patients without seton drainage (18%, P=0.53). In the group of patients that underwent advancement combined with fibrin glue, the recurrence rate was 31% similar to 17% in the advancement group alone (p=0.31). A median of two operations was necessary in these patients to close the persistent fistulas (range 2-4). In 37 of 39 successfully contacted patients, the continence questionnaires were complete (Table 2.2). The median follow-up duration of patients with completed questionnaires was 64 months (range 22-126). The mean total Vaizey score was 6.2 (±4.0). From the 37 patients, two (5%) had a perfect continence (Vaizey score=0). The mean total score for the COREFO questionnaire was 10.8 (±11.2). Sixteen of 37 (43%) patients reported soiling. Only two patients reported problems with losing solid stool unintentionally.
DISCUSSION

This retrospective study assessed the long-term results of surgical treatment of a large consecutive series of patients with low or high perianal fistulas of cryptoglandular origin treated according to a standardized treatment protocol. In the present series of patients treated by fistulotomy or rectal advancement flap the observed recurrence rate was 7% and 21% respectively at a median follow-up of 76 months. The overall functional outcome measured by the COREFO and the Vaizey scale was not significantly different from normal patients. However, around 40% of the patients in both groups were found to have problems with soiling, which is considerable. No significant risk factors for the development of a recurrent perianal fistula were found in either the fistulotomy or the rectal advancement group with either the univariate or multivariate analysis.

The recurrence rate found in the present study conforms with recurrence rates reported in the literature, which range from 0-39%. This wide range is a result of the heterogeneous population selected for fistulotomy in the different studies, which makes it difficult to compare the different outcomes. In a recent series from Van de Hagen et al., 62 patients with a fistula tract originating from the lower third of the anal sphincter or lower were treated by simple fistulotomy. At a median follow-up of 75 months a cumulative recurrence of 39% was found. In the series, patients with Crohn’s disease also were included. These nine patients had a cumulative recurrence rate of 60% at a follow-up of 48 months. Patients with perianal fistulas caused by Crohn’s disease should therefore be assessed separately because of the origin of the disease and because outcome depends on the presence of proctitis.

The recurrence rate found in the present study for the rectal advancement flap is relatively favorable to the literature, in which success rates are reported between 40 and 90%. These results account for a select patient group since patients with HIV, Crohn’s disease, and inability to find the internal opening were excluded. These recurrence rates however remain relatively high. In our study one in five
patients needed multiple operations to successfully treat high fistulas. In this series of patients treated with fibrin glue in addition to the rectal advancement flap, no significant difference in procedure success rate were observed. However, several other authors found the addition to be deleterious for the closure of the fistula in combination with the advancement flap.\textsuperscript{15,16}

Unfortunately, from a substantial number of patients, no questionnaires were received. To maximize the response rate all patients that failed to return the questionnaires were contacted by telephone. Furthermore, if the patients had moved, their general practitioner was contacted for their address and telephone number. This effort resulted in only five patients that refused to respond by telephone. Since our response rate was only 53\% and no detailed preoperative data on continence was available, there is a potential error in the outcome and conclusions drawn.

Disruption of the sphincter complex leads to incontinence.\textsuperscript{17} The COREFO questionnaire and the Vaizey scale were used in this study for the continence assessment. In both groups, overall continence outcome was not significantly different from normal. The scores found were comparable to the scores reported by Bakx et al. for a group of control patients without complaints after right-sided hemicolectomy or laparoscopic cholecystectomy.\textsuperscript{5} In the subscales, stool aspects and incontinence, our sample had slightly worse scores than in the control group. The subscale, stool aspects, contains questions on blood loss during bowel movement and having irritated perianal skin. Around 25\% of the patients in both groups reported problems in stool aspects. The subscale, incontinence, implies patients having problems ranging from having to use pads to protect underwear to unintentionally passing stools. When looking in detail at soiling, a considerable amount of patients had problems after surgery. This finding was surprising given the fact rectal advancement flap is considered a sphincter-saving procedure. These data indicate that soiling is a considerable problem after surgery for fistula, although it is not clear whether this was solely the result of surgery since no preoperative data on soiling were available for comparison. Furthermore, the number of prior surgical procedures was high in the rectal advancement group.

The question arises as to what extent this relatively young population will develop continence problems in the future. In the literature, many different criteria are used to report incontinence and as a consequence the continence outcome varies a lot
between different publications. Further prospective research is needed to assess long-term outcome of continence after different treatments for perianal fistulas using validated questionnaires before and after surgery. In the risk factor analysis, tertiary referral in the fistulotomy group showed a trend towards significance (p=0.065) and displayed a clinically significant absolute effect size (HR=3.74). However, the confidence interval is large, possibly because of a small sample size, which limits the interpretation of these results. An explanation for this large effect size may be that most patients requiring simple fistulotomy are not referred to tertiary centers. Possibly these patients had complex fistula which were expected by their physician to lead to recurrence. Unfortunately, as a result of the retrospective nature of this study, further data were not available.

Garcia-aguilar et al. described risk factors for recurrence in a series of patients with anorectal fistulas of cryptoglandular origin with the use of a mailed questionnaire. Prior fistula surgery was not found to be significantly associated with recurrence, however a clear trend was described. In a retrospective study of 106 advancement flap procedures by Mizrahi et al., prior attempts at repair of the fistula were not associated with recurrence. However, Crohn’s disease appeared to be correlated to fistula recurrence.

Smoking is well known to influence wound healing in various patient groups. In the literature smoking was assessed as a possible risk factor and discrepancies exist as to whether smoking has an effect on the outcome of surgical treatment for anorectal fistulas. Zimmermann et al. described smoking to be associated with a high risk of fistula recurrence in 105 patients with perianal fistulas of cryptoglandular origin treated with a rectal advancement flap. A reduced blood flow in the flap was noted as a possible contributing factor. Recently, Gustafsson et al. did not find any relationship between smoking and a lower healing rate in their randomized trial of 83 patients surgically treated by rectal advancement flap for high anorectal fistulas. In the present study, no significant relation could be found between smoking and fistula recurrence as well.

This study assessed long-term outcome of two distinctive groups of patients with perianal fistulas of cryptoglandular origin. The recurrence rate was low in the group treated by fistulotomy. In patients treated with rectal advancement flap procedure for high perianal fistulas, a considerable number of recurrences occurred. No clear
risk factors for the development of a recurrent perianal fistula were found in the fistulotomy nor in the rectal advancement group. Overall, continence disturbances were infrequent and similar in both groups. However, a reasonable amount of patients in both groups reported soiling. Further research is warranted to develop new techniques to deal with high perianal fistulas of cryptoglandular origin and to solve the probable high incidence of soiling.

REFERENCES


Chapter 3

Outcomes of surgical treatment for perianal fistulas in Crohn’s disease

P.J. van Koperen, F. Safiruddin, W.A. Bemelman, J.F.M. Slors

British Journal of Surgery, 2009
ABSTRACT

Background
The aim of this study was to assess recurrence rates and long term functional outcome after surgical treatment of anal fistulas in Crohn’s disease.

Methods
Between 1995 and 2006, a consecutive series of patients were treated for perianal fistulas as a result of Crohn’s disease. Only patients without proctitis or active sepsis underwent fistulotomy or advancement. The following risk factors for recurrence were examined: gender, seton usage, use of infliximab, prior fistula surgery, history of segmental resection, and smoking. Continence was assessed by Vaizey and COREFO (colorectal functional outcome) questionnaires. Results were compared with institutional data for cryptoglandular fistulas.

Results
Sixty-one patients were included. Follow-up duration was 79 months (range 13-140). Patients were treated with a seton (n=24), fistulotomy (n=28) or mucosal advancement (n=9). For low fistulas the fistulotomy was used more frequently compared to the seton. This was the other way around in higher more complex fistulas where seton drainage was used in the majority of the cases. Recurrence occurred following fistulotomy and advancement in 5/28 and 5/9 respectively. Half of the patients treated by seton reported soiling compared to two thirds and three quarters of those treated by fistulotomy and mucosal advancement respectively. Functional outcomes were worse for all patient groups compared to patients with simple cryptoglandular fistula disease. No potential risk factor reached significance in the regression analysis.

Conclusions
The outcome of surgical treatment of complex and high fistulas in Crohn’s disease remains disappointing and recurrence is unpredictable.
INTRODUCTION

Crohn’s disease is complicated by the development of anal fistulas in approximately one third of patients. The goal of fistula surgery for patients with Crohn’s disease is to relieve symptoms and to achieve closure in selected cases. Surgical treatment for fistulas in Crohn’s disease consists of abscess drainage, loose-setons, fistulotomy, and mucosal advancement. The success rate after fistulotomy is around 80% compared to a success rate of about 55% for high fistulas treated by advancement flap. These fistulas are often refractory to surgery and associated with recurrent sepsis, discomfort, and impaired quality of life. In most papers no distinction is made between cryptoglandular fistulas and fistulas in Crohn’s disease confusing true outcome data for surgically treated Crohn’s fistula. Furthermore, continence is rarely assessed using validated questionnaires. The aim of this study was to assess the recurrence rates and long term functional outcome after surgical treatment of anal fistulas in Crohn’s disease.

METHODS

Patients

Between May 1995 and January 2006, a consecutive series of patients operated for anal fistulas in Crohn’s disease were retrospectively analyzed. Patients with cryptoglandular fistulas, human immunodeficiency virus, pouch fistulas, rectovaginal fistulas, as well as patients aged under 18 were excluded.

Treatment protocol

Patients were primarily treated by surgical drainage through incision and drainage of abscesses and seton drainage in case of insufficiently drained fistulas. Subsequently, optimization by medical therapy was pursued. Only in selected patients without proctitis or active Crohn’s disease definitive closure by surgical intervention was attempted. For the definitive surgical treatment these patients were divided into two groups. The first group comprised of patients in which the fistula tract was submucosal, intersphincteric or located in the lower third of the anal sphincter.
Chapter 3

This group was treated by fistulotomy. The second group treated by advancement flap consisted of patients with high fistulas in which the fistula tract was located in the upper two-third of the sphincter complex. The advancement flap was done according to a technique described herein. All procedures were performed under general or locoregional anesthesia in the lithotomy position.

Follow-up

All patients visited the outpatient’s clinics following surgery. The fistula was considered closed if the external opening was closed and no discharge or pain were experienced. Patients were contacted by telephone using a standard questionnaire to assess fistula recurrence, abscess development, and use of infliximab. Furthermore, patients, including the patients with loose setons, were sent a postal survey to assess functional outcome. Functional outcome was evaluated using the Vaizey scale and the COREFO questionnaire. The validated Vaizey scale consists of items on the type and frequency of incontinence and change in lifestyle. The total score on the Vaizey scale ranges from zero (complete continence) to 24 (complete incontinence). The COREFO questionnaire is a validated questionnaire with 27 questions to assess colorectal functional outcome. Five categories and a calculated total score were assessed and these scores ranged from zero to 100. A higher score represents an increased level of continence disturbance. Follow-up was calculated from the clinical notes when the patient could not be contacted successfully by phone.

Statistical analysis

Differences between groups were tested using Mann-Whitney U test for continuous data. Chi-squared test was used to test for differences between groups in case of categorical data. Cox proportional hazard models were used to examine the association between potential risk factors and the time until fistula recurrence. The following risk factors were examined: gender, seton usage, use of infliximab, prior fistula surgery, history of segmental resection, and smoking. Statistical analysis was performed using the SPSS version 15.0.1. for Windows (SPSS, Chicago, Illinois, USA).
RESULTS

A total of 61 patients with anal fistulas were included. Anal fistulas due to HIV, ulcerative colitis, and rectovaginal and cryptoglandular fistulas were excluded (n=301 patients) (Figure 3.1). Patient characteristics are shown in Table 3.1. The median follow-up duration was 79 months (range 13-140).

Figure 3.1 – Flow chart of patients with anal fistula in Crohn’s disease.

Surgical treatment

Figure 3.1 demonstrates how patients were treated surgically. Twenty-four patients (39%) were treated with loose seton drainage. In 37 of the 61 patients definite closure was attempted. In the low fistula group six patients were treated by seton drainage before fistulotomy. In the group with the high fistulas three patients underwent
Table 3.1 – Characteristics of 61 patients low and high fistulas in Crohn’s disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low fistulas (n=39)</th>
<th>High fistulas (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>24:15</td>
<td>9:13</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>33 (19-70)</td>
<td>36 (21-70)</td>
</tr>
<tr>
<td>Previous fistula surgery</td>
<td>11 (28%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Duration of Crohn’s disease (years)</td>
<td>7 (0-37)</td>
<td>8 (3-25)</td>
</tr>
<tr>
<td>Segmental resection*</td>
<td>17 (44%)</td>
<td>8 (36%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (23%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Fibrin glue addition</td>
<td>-</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>5/28 (18%)</td>
<td>5/9 (56%)</td>
</tr>
<tr>
<td>Follow-up (months, range)</td>
<td>79 (13-140)</td>
<td>82 (17-132)</td>
</tr>
</tbody>
</table>

*Patients that underwent segmental bowel resection prior to the fistula surgery.

seton drainage before performing the advancement. Recurrence rates in patients that were treated by fistulotomy and advancement were 18% and 56% respectively. In all patients with a fecal diversion that were operated the ostomy was still present during the assessment of closure.

None of the potential risk factors reached significance in low or high fistulas. None of the factors were analyzed in the multivariate model as result of the low amount of patients in the subgroups. There were no postoperative complications in either group.

Follow-up

Fifty patients were contacted successfully (82%). The patients in the different groups are presented in Table 3.2. From the 11 patients that could not be contacted, two had deceased, four underwent a complete proctectomy, and the five remaining were lost to follow-up. In the group that was contacted four patients had undergone surgery for an anal abscess in the low anal fistulas group compared to four in the high group. Two patients in the group with high fistulas underwent a proctectomy because of recurrent anal fistulas and anal stenosis.

Functional outcome

The results of the continence questionnaires were presented in Table 2.2. There were no statistically significant differences between the seton drainage, fistulotomy, and the advancement group in either the COREFO (p=0.714) or the Vaizey score
Surgical treatment of perianal fistulas in Crohn’s disease

Table 3.2 – Vaizey scale and colorectal functional outcome (COREFO) for patients treated by fistulotomy or rectal advancement.

<table>
<thead>
<tr>
<th>Scale, mean (SD)</th>
<th>Fistulotomy (crypto)* (n=63)</th>
<th>Advancement Seton drainage (crypto)* (n=37)</th>
<th>Fistulotomy (n=23)†</th>
<th>Advancement flap (n=8)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaizey§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>2.0 (±2.5)</td>
<td>2.3 (±2.8)</td>
<td>2.0 (±1.9)</td>
<td>3.8 (±3.5)</td>
</tr>
<tr>
<td>Social impact</td>
<td>4.5 (±1.7)</td>
<td>3.9 (±2.5)</td>
<td>5.5 (±1.6)</td>
<td>4.9 (±1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>6.5 (±3.5)</td>
<td>6.2 (±4.0)</td>
<td>7.4 (±2.5)</td>
<td>8.7 (±4.4)</td>
</tr>
<tr>
<td>COREFO¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence range</td>
<td>9.2 (±12.8)</td>
<td>11.8 (±13.6)</td>
<td>25.9 (±7.5)</td>
<td>30.2 (±21.6)</td>
</tr>
<tr>
<td>Social impact</td>
<td>9.7 (±13.9)</td>
<td>12.3 (±12.3)</td>
<td>31.3 (±11.0)</td>
<td>24.5 (±21.1)</td>
</tr>
<tr>
<td>Frequency</td>
<td>7.7 (±12.9)</td>
<td>6.4 (±6.4)</td>
<td>16.7 (±8.8)</td>
<td>26.1 (±24.7)</td>
</tr>
<tr>
<td>Stool-related aspects</td>
<td>14.4 (±9.9)</td>
<td>12.6 (±12.6)</td>
<td>28.5 (±12.9)</td>
<td>16.7 (±15.4)</td>
</tr>
<tr>
<td>Medication</td>
<td>8.2 (±18.0)</td>
<td>5.9 (±14.9)</td>
<td>24.3 (±15.6)</td>
<td>15.2 (±21.2)</td>
</tr>
<tr>
<td>Total</td>
<td>9.8 (±12.4)</td>
<td>10.8 (±11.2)</td>
<td>27.2 (±7.0)</td>
<td>24.6 (±15.4)</td>
</tr>
</tbody>
</table>

*Perianal fistulas of cryptoglandular origin treated by fistulotomy and mucosal advancement flap in the same institution. †Low perianal fistulas (amount returned questionnaires), ‡High perianal fistulas (amount returned questionnaires). §Mean score ranging from 0-24 (complete continence-complete incontinence) for the total score. Both subscale scores range from 0-12. ¶Mean score per category after linear transformation to a score from 0-100, higher score represents an increased level of continence disturbance. As the total score, all subscales range from 0-100.

(p=0.451). In the seton group 54% of the patients reported soiling compared to 61% and 75% in the fistulotomy and the mucosal advancement group respectively. In Table 3.2 results from an institutional series of cryptoglandular fistulas were included. The recurrence rates in these series were 7% and 21% for cryptoglandular fistulas treated by fistulotomy and mucosal advancement flap respectively. Soiling was seen in 40% of the patients in both groups.

DISCUSSION

In the present series, surgically treated patients with anal fistulas in Crohn’s disease were described. Surgical treatment options were chronic seton drainage, fistulotomy, and advancement flaps. Attempted definitive closure by surgical intervention was only done in a selected group excluding those with active Crohn’s disease or proctitis. In the group in which definitive closure was attempted, low and high fistulas were treated by fistulotomy and advancement flap respectively which resulted in 18% and 56% recurrence rates. There were no significant continence differences between the groups treated by loose seton drainage, fistulotomy and advancement flap.
Active Crohn’s disease, especially proctitis, interferes with wound healing and fistula closure. The aim of the treatment protocol was to limit the amount of inflicted surgical damage in terms of anal scarring, incontinence, and recurrent fistulas. Despite patient selection, patients in the current series treated surgically for Crohn’s anal fistula did worse both in terms of recurrence rates and incontinence compared to patients operated for cryptoglandular disease treated in our institute. The recurrence rates found for fistulotomy were worse compared to recurrence rates of cryptoglandular fistulas treated by fistulotomy (18% vs. 7%). The recurrence rates following advancement flap were also worse (56% vs. 21%). Possibly, as the flap is constructed with rectal mucosa affected by Crohn’s disease wound healing might be compromised. A recurrent Crohn’s anal fistula could be a true recurrence or a newly developed fistula. This could not be discriminated in the present study.

The continence results were significantly worse compared to data from a series of patients operated in the same hospital for cryptoglandular fistulas. In the different groups of the cryptoglandular fistulas the reported soiling was around 40%. In the present series between 54% and 75% of the patients reported soiling. Incontinence following fistula surgery in Crohn’s disease in literature ranges from low to very high. Often a mixed group of patients consisting of both cryptoglandular and Crohn’s disease fistulas were reported. It could only be speculated whether surgery has contributed to the incontinence, since preoperative data were lacking. Probably the incontinence has multiple causes. It could result from previous sphincter damage, scarring, diarrhea and impaired rectal reservoir function resulting from long standing proctitis.

Disappointing results in closure of anal fistulas in Crohn’s disease lead to much interest for novel techniques. Nowadays, infliximab has an important role in the treatment of anal fistula due to Crohn’s disease. It is effective in closing the fistula but the fistula often recurs after stopping the medication. Currently, the anal fistula plug has been used extensively in various studies. The anal fistula plug, a bioabsorbable xenograft made of porcine intestinal submucosa, is placed in the fistula tract. The plug is replaced by own tissue within several weeks. The anal fistula plug has been used in a series of 20 patients with Crohn’s disease leading to 80% closure. These results are not confirmed yet by other groups.

An interesting technology is the use of stem cells to treat fistulas in Crohn’s disease.
Surgical treatment of perianal fistulas in Crohn’s disease

Mesenchymal adipose stem cells are harvested by liposuction and used to stimulate fistula closure. García-Olmo et al. performed a randomized clinical trial comparing adipose derived stem cells and fibrin glue with only fibrin glue in the treatment of anal fistulas. Cryptoglandular (n=35) and Crohn’s disease (n=14) fistulas were included in the study. The stem cells were isolated by liposuction and after preparation of the material the cells were injected into the rectal mucosa. The fistula closed in 71% in the stem cell group compared to 16% in the fibrin glue group. Currently a multinational trial is being conducted in Europe assessing the value of stem cell therapy.

In conclusion, only in selected patients with Crohn’s disease treatment aiming for fistula closure was possible. The majority were treated with loose setons. Recurrence rates in patients with Crohn’s fistula were higher compared to similarly treated patients with cryptoglandular fistulas after fistulotomy and particularly advancement flaps respectively. Functional outcome in terms of continence was worse compared to cryptoglandular fistulas.

REFERENCES

Chapter 4

Fibrin glue and transanal rectal advancement flap for high transsphincteric perianal fistulas; is there any advantage?

P.J. van Koperen, J. Wind, W.A. Bemelman, J.F.M. Slors

International Journal of Colorectal Disease, 2008
ABSTRACT

Background
In recent decades, fibrin glue has appeared as an alternative treatment for high perianal fistulas. Early results seemed promising, with high success rates being reported. However, with increasing follow-up, the enthusiasm was tempered because of disappointing results. The aim of this retrospective study was to assess the additional value of fibrin glue in combination with transanal advancement flap, compared to advancement flap alone, for the treatment of high transsphincteric fistulas of cryptoglandular origin.

Methods
Between January 1995 and January 2006, 127 patients were operated for high perianal fistulas with an advancement flap. After exclusion of patients with inflammatory bowel disease or human immunodeficiency virus, 80 patients remained. Patients were matched for prior fistula surgery, and the advancement was performed identically in all patients. A consecutive series of 26 patients had an advancement flap combined with obliteration of the fistula tract with fibrin glue. In the fibrin glue group, glue was installed retrogradely in the fistula tract after the advancement was completed and the fistula tract had been curetted.

Results
Follow-up after surgery was a median of 67 months (range 13-127). The overall recurrence rate was 26% (n=21). Recurrence rates for advancement flap alone vs. the combination with glue were 13% vs. 56% (p=0.01) in the group without previous fistula surgery, and 23% vs. 41% (p=0.216) in the group with previous fistula surgery.

Conclusions
Obliterating the fistula tract with fibrin glue was associated with worse outcome after rectal advancement flap for high perianal fistulas.
INTRODUCTION

Perianal fistulas of cryptoglandular origin cause considerable discomfort and arise from infections in anal glands lying in the intersphincteric space.\(^1\) To delineate the fistula tract, magnetic resonance (MR) and anal endosonography are nowadays readily available and are increasingly used for fistula imaging.\(^2\) The essence of surgical treatment of perianal fistulas is to eradicate the fistula tract and at the same time preserve continence. Low fistulas, where the fistula tract is submucosal, intersphincteric or located in the lower third of the external anal sphincter can be treated by fistulotomy with low recurrence rates and relatively little impact on continence.\(^3\) In patients with high perianal fistulas, the fistula tract is located in the upper two-third of the external sphincter. Fistulotomy performed on high fistulas results in loss of sphincter function in a considerable number of patients due to the interference of the external sphincter complex.\(^4,5\) There are various alternative surgical options for high fistulas, namely rectal advancement flap, fibrin glue, and seton drainage.

In 2006, Johnson et al. reported a new biologic anal fistula plug to treat high transsphincteric perianal fistulas.\(^6\) The anal fistula plug is biologic absorbable and consists of lyophilized porcine intestinal submucosa. In their series of 46 patients treated with the anal fistula plug, a success rate of 83% was achieved at a median follow-up of 12 months.\(^7\) Following this publication, several authors have reported their experience with the anal fistula plug, resulting in success rates ranging from 41-88%.\(^8-10\)

Currently, the transanal rectal advancement flap (AF) remains the "gold standard" in the treatment of high transspmhincteric perianal fistulas of cryptoglandular origin. The rationale behind the advancement flap is that the open internal opening is the cause of the persisting fistula tract. By advancing tissue over the internal opening, it would be impossible for fecal material to be forced into the fistula tract during defecation. However, recurrence rates of the advancement flap found in literature vary considerably and extend up to 63%.\(^11-15\) Roughly, one out of every four patients requires multiple surgical interventions in order to close the fistula tract successfully. In recent decades, fibrin glue has appeared as an alternative treatment for high perianal fistulas. As the result of the obliteration of the fistula tract and the closure of the internal opening the fistula might heal. Early results seemed promising, with high success rates being reported. However with increasing follow-up the enthu-
siasm was tempered, because of disappointing results. \textsuperscript{16–20} Recently, Zmora \textit{et al.} conducted a retrospective study including 37 patients with high perianal fistulas.\textsuperscript{21} In a subset of 13 patients with fistulas of various etiologies, the advancement flap was used in addition to the fibrin glue installation. The results showed a recurrence rate of 46%.

The aim of this study was to assess the additional value of fibrin glue to the transanal rectal advancement flap in a well defined group of patients with high transsphincteric fistulas of cryptoglandular origin. Patients with previous fistula surgery are a surgically more challenging group as the result of scar tissue, and sometimes anal stenosis. Therefore patients were matched for the presence of a history of fistula surgery.

**METHODS**

**Patient characteristics**

Between January 1995 and January 2006, a consecutive series of patients were treated by advancement. Only patients with high transsphincteric perianal fistulas of cryptoglandular origin were analyzed. High perianal fistulas were defined as patients with fistulas running through the upper 2/3 of the external sphincter complex, which is confined by the puborectal sling and the end of the anal canal. Patients in whom the internal fistula opening was not detectable and patients with perianal fistulas as a result of Crohn’s disease, HIV and other causes were excluded. Patients over 18 years of age were included. A consecutive series of patients were operated on with fibrin glue (Tissucol Duo, Baxter International Inc.) in addition to the advancement in an attempt to decrease the recurrence rate of the advancement flap. This series of patients were treated on between February 2003 and January 2006. Patients were matched for previous surgery and divided into two groups; one group with previous fistula surgery and the other without. Preoperatively, no routine imaging was performed. Only in selected cases when the fistula was complex and/or recurrent, MR or anal endosonography was used to outline the fistula tract. In the Netherlands and Belgium, non-experimental clinical case series of patients treated with a CE approved device, do not require approval of the local Medical Ethics Commission. A subset of patients from this series were also included in
a study where the aim was to assess the long term functional outcome and identify risk factors for the development of recurrence in patients surgically treated for cryptoglandular fistulas.\(^22\)

**Surgical technique**

On the day of surgery an enema was administered to the patient to clean the proc-tum. All procedures were performed under general or locoregional anesthesia in the lithotomy position and broad spectrum antibiotics were administered periop-eratively. Subsequently, the internal opening was located by probing the external opening. During surgery the amount of sphincter involved was judged by palpation of the puborectal sling and the inferior edge of the external sphincter complex. In cases where the internal opening was not found by probing, hydrogen peroxide was injected to locate the internal opening. In case of active sepsis, a seton was placed for a period of at least three months insuring adequate drainage. In the group which was operated with the advancement, the internal opening was excised followed by mobilization of the mucosa, submucosa and a small amount of muscular fibers from the internal sphincter complex. The rectal flap was mobilized to sufficiently cover the internal opening with overlap. Hemostasis was performed to prevent a hematoma under the flap. The base of the advancement flap was kept wide enough to ensure adequate circulation in the flap. The internal opening was not closed before advanc-ing the flap over the internal opening. This was followed by suturing the flap in the distal anal canal with Vicryl 2/0, after the fistula tract had been curetted. In the group in which the advancement flap was combined with the fibrin glue (AF+G) the identical procedure was carried out. In addition to the advancement procedure, fibrin glue was installed retrogradely in the fistula tract after the advancement was completed and the fistula tract had been curetted. Installation of the fibrin glue was performed *via* the external opening, under direct vision of the advancement flap to prevent flap dislocation and subsequent failure. No specific postoperative instructions were given to the patients.
Data collection

Chart review was performed on age, gender, tertiary referral, previous fistula surgery, smoking habits, complications and fistula recurrence. All patients visited the outpatient’s clinics on a regular basis (every 2-4 weeks) until full closure of the fistula tract was achieved. The fistula was considered closed if the external opening was closed and no discharge or pain were experienced and otherwise it was considered as a persistent or recurrent fistula. No routine postoperative imaging or proctoscopy was performed to confirm the closure of the fistula tract. The data was collected retrospectively and the outcome was compared between groups.

Statistical analysis

Data are presented as median values with ranges, unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Mann-Whitney U test for continuous data. Chi-squared test or Fisher’s exact test were used when appropriate, to compare groups in case of categorical or dichotomous variables. All reported p-values are two-sided. A p-value of 5% or less was considered as statistical significant. Statistical analysis was done using the SPSS v.12.0 package (SPSS, Chicago, Illinois, USA).

RESULTS

In the study period, a total of 127 patients were operated for high perianal fistulas. In 47 patients the reasons of exclusion were inflammatory bowel disease (n=30), HIV (n=12) or no internal opening found during surgery (n=5). In total, 80 patients were analyzed in this comparative study. Of these, 54 patients were treated with the advancement flap and 26 patients underwent advancement flap combined with the installation of fibrin glue. Patient characteristics for both groups are shown in Table 4.1 and 4.2. The groups were comparable for patients’ characteristics as sex, age, smoking, seton drainage and number of tertiary referrals.
**Table 4.1** – Characteristics of patients with high anorectal fistula without previous fistula surgery.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AF (n=32)†</th>
<th>AF+G (n=9)‡</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>18:14</td>
<td>6:3</td>
<td>0.711</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>42 (21-67)</td>
<td>41 (29-55)</td>
<td>0.653</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>26 (81%)</td>
<td>7 (78%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoking</td>
<td>43%</td>
<td>71%</td>
<td>0.232</td>
</tr>
<tr>
<td>Seton drainage</td>
<td>18 (56%)</td>
<td>6 (67%)</td>
<td>0.711</td>
</tr>
</tbody>
</table>

† Rectal advancement group, ‡ Rectal advancement group with the addition of fibrin glue

**Table 4.2** – Characteristics of patients with high anorectal fistula with previous fistula surgery.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AF (n=22)†</th>
<th>AF+G (n=17)‡</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>18:4</td>
<td>11:6</td>
<td>0.282</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>43 (22-62)</td>
<td>47 (35-72)</td>
<td>0.136</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>15 (68%)</td>
<td>8 (47%)</td>
<td>0.209</td>
</tr>
<tr>
<td>Smoking</td>
<td>53%</td>
<td>50%</td>
<td>1.000</td>
</tr>
<tr>
<td>Seton drainage</td>
<td>10 (46%)</td>
<td>12 (71%)</td>
<td>0.193</td>
</tr>
</tbody>
</table>

† Rectal advancement group, ‡ Rectal advancement group with the addition of fibrin glue

**Clinical outcome**

All patients were operated in day case setting. There were no intraoperative complications. In two patients out of the AF group, a postoperative complication was encountered, consisting of a minor bleeding (n=1) and a bradycardia for which the patient was observed overnight (n=1, patient with cardial history). In the AF+G group there were no postoperative complications recorded. The minimal follow-up after surgery was 13 months with a median of 67 months (range 13-127). There were no patients lost to follow-up. The overall recurrence rate was 26% (n=21) (Table 4.3). In 17% of the patients the fistula persisted in the AF group compared to 46% in the AF+G group (p=0.05). In the matched group without previous fistula surgery the result was significantly worse for the AF+G group compare to the AF group (p=0.014). The recurrence rates were 56% (n=5) and 13% (n=4) respectively. In the group with a history of fistula surgery the recurrence rate was 23% (n=5) compared to 41% (n=7) in the AF and the AF+G group respectively (p=0.216).
Table 4.3 – Recurrence rates for the matched group analysis.

<table>
<thead>
<tr>
<th>Group</th>
<th>AF†</th>
<th>AF+G‡</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=80)</td>
<td>9/54 (17%)</td>
<td>12/26 (46%)</td>
<td>0.050</td>
</tr>
<tr>
<td>No previous fistula surgery (n=41)</td>
<td>4/32 (13%)</td>
<td>5/9 (56%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Previous fistula surgery (n=39)</td>
<td>5/22 (23%)</td>
<td>7/17 (41%)</td>
<td>0.216</td>
</tr>
</tbody>
</table>

†Rectal advancement group, ‡Rectal advancement group with the addition of fibrin glue

DISCUSSION

High perianal fistulas remain a surgical challenge. There are various treatment options for treating high transsphincteric fistulas, e.g. the rectal and anodermal advancement flap, loose and cutting seton, fibrin glue, and potentially the newly developed anal fistula plug. However, the results from these therapies vary. Transanal rectal advancement flap is nowadays the treatment of choice because of its sphincter saving approach. The recurrence rate after advancement flap is 30%. This leaves a lot of room for improvement. Fibrin glue was developed to obliterate the fistula tract by stimulating fibroblasts which leads to permanent closure of the fistula tract. Unfortunately, the long term results were not as good as expected. In the present series, an attempt was made to decrease the recurrence rate of the surgical treatment of high transsphincteric perianal fistulas of cryptoglandular origin by combining the two methods, i.e. fibrin glue and the rectal advancement flap in a consecutive series of patients. Overall, although not significant, a clear trend was found consisting of a worse outcome for patients from the AF+G group. The recurrence rate was 46% compared to 17% in the AF+G and AF group respectively. In the group without a history of fistula surgery, patients in the AF+G group did significantly worse than the AF group. In the group with a history of fistula surgery no significantly different recurrence rates were found. In 2003, Zmora et al. described a small retrospective series of 13 patients with perianal fistulas of different origins treated with fibrin glue in combination with the AF. In their series, a recurrence rate of 46% was found after a mean follow-up of 12.1 months. The group contained patients with fistulas of cryptoglandular origin and fistulas associated with Crohn’s disease or surgical trauma. Also, two patients with rectovaginal fistulas were included. More recently, Ellis et al. reported on a series of 58 patients randomized into advancement flap repair alone or advancement flap repair combined with fibrin glue. Selected were patients with perianal fistulas where the fistula tract comprised more than 30 to
50% of the sphincter complex. Furthermore, patients were included when the fistula was located anteriorly in women or when the patient had a history of incontinence. In 2/3 of the patients, the mucosal advancement flap was used and the remaining patients were treated by anodermal advancement flap. The recurrence rate was significantly higher in the group where fibrin glue was combined with the advancement flap compared to the group treated only by advancement (46% vs. 20%). Two techniques, i.e. mucosal advancement flap and anodermal advancement flap were used. Furthermore, no information was provided on the distribution of causes of the fistulas in both groups making the results difficult to interpret.

The effectiveness of the AF is the result of the closure of the internal opening. The reason why addition of fibrin glue fails to decrease the recurrence rate and even seems to worsen the result is still unclear. An explanation might be that after AF, the fistula tract acts as a drainage canal for any remaining sepsis, with the external opening left open. With the installation of the fibrin glue, a temporarily closure of the fistula tract is theoretically achieved. After a few weeks, when the clot resolves, the fibroblasts activated by the matrix should provide collagen syntheses for a definitive closure of the tract. A possible explanation to why the AF+G group does worse, is that the closure of the fistula tract with the fibrin glue leads to a situation where insufficient drainage from the primary and eventual secondary fistula tracts occurs.

Sentovich et al. reported on a prospective series of 48 patients (75% of cryptoglandular origin) treated with fibrin glue. In their technique of using the fibrin glue, the procedure was combined with closure of the internal opening with only a figure eight suture without an advancement flap. After a median follow-up of 22 months a recurrence rate of 31% was found. Surprisingly, the patients with longer fistula tracts did significantly worse than those with short fistula tracts. Loungnarath et al. reported on 39 patients with perianal fistulas treated with fibrin glue. The overall recurrence rate was 69%. In six of the 39 patients the internal opening was closed using a figure eight suture to avoid clot extrusion because of high pressure from the anal canal during defecation. Four of these patients had a recurrence (67%). This retrospective study, in contrast to earlier studies, assessed the additional value of fibrin glue to the transanal rectal advancement flap of only patients with high transsphincteric fistulas of cryptoglandular origin with a long follow-up. The
rectal advancement flap combined with fibrin glue installation was associated with a significantly higher recurrence rate, compared to the advancement flap treatment alone, in patients without previous fistula surgery. This observation must be interpreted with caution because of the small sample size of the group that combined the advancement and the fibrin glue. Since the costs of the fibrin glue are considerable and the therapeutic effect very doubtful, it cannot be recommended routinely in the adjunct of transanal rectal advancement flap treating high perianal fistulas. The rectal advancement flap remains the treatment of choice for high transsphincteric perianal fistulas of cryptoglandular origin until novel methods like the anal fistula plug are studied sufficiently in randomized trials.

REFERENCES

Fibrin glue and rectal advancement flap for high perianal fistulas


Chapter 5

Histological identification of epithelium in perianal fistulas; a prospective study

P.J. van Koperen, F.J.W. ten Kate, W.A. Bemelman, J.F.M. Slors

Colorectal Disease, 2009
ABSTRACT

Background
A procedure often performed following fistulotomy and advancement flap is curettage of the fistula tract after fistulotomy or after closing the internal opening. Epithelialization of the fistula tract might prevent closure of the fistula tract. The aim of this study was to assess the incidence and origin of epithelialization of the fistula tract in patients with perianal fistulas undergoing fistulotomy.

Methods
Only patients with low perianal fistulas that were surgically treated by fistulotomy were included. Surgical biopsies were taken from the fistula tract from three different locations; on the proximal side at the internal opening, in the middle of the fistula tract and near the distal end close to the external opening.

Results
In the study period, 18 patients with low perianal fistulas were included. In 15 of the 18 patients, squamous epithelium was found at least in one of the biopsies taken from the fistula tract. Epithelium was predominantly found near the internal opening. There was no relation between the duration of fistula complaints and the presence of epithelialization (p=0.301). The amount of epithelium was not related to the presence of a history of fistula surgery (p=1.000).

Conclusions
The study demonstrated epithelialization in the fistula tract in the majority of the patients surgically treated by fistulotomy for low perianal fistulas. Curettage of perianal fistulas must therefore be considered an essential step in the surgical treatment of perianal fistulas.
INTRODUCTION

The aim of fistula surgery is eradication of the fistula tract by closing or removing the internal opening without endangering continence. Although there are many different treatment options, perianal fistulas remain difficult to treat. In patients with low perianal fistulas, located in the lower third of the external sphincter, fistulotomy results in low recurrence rates and relatively little impact on continence. The recurrence rates of fistulotomy vary and range from approximately 2-9%.\textsuperscript{1–3} A division of the anal sphincter of more than 30-50% leads to significant continence disorders.

The treatment of choice for high perianal fistulas of cryptoglandular origin currently is the mucosal advancement flap. The success percentages reported in the literature have an average of about 60%.\textsuperscript{4} A procedure often performed following fistulotomy and advancement flap is curettage of the fistula tract after division or after closing the internal opening respectively. The rationale is that epithelialization prevents complete closure of the fistula tract. In a series of 18 patients published in 1995 by Lunniss \textit{et al.}, biopsies were taken to assess the amount of epithelium present in the fistula tract.\textsuperscript{5} They found that in 13 of the 18 patients epithelialization was present.

The aim of this study was to assess the incidence and origin of epithelialization of the fistula tract in patients with low perianal fistulas undergoing fistulotomy.

METHODS

Between April 2007 and September 2008, a consecutive series of patients were prospectively enrolled in the study. Only patients with low perianal fistulas that were surgically treated by fistulotomy were included. Low perianal fistulas were defined as fistulas in which the fistula tract was submucosal, intersphincteric, or located in the lower third of the external anal sphincter muscle and a fistulotomy could be performed without endangering continence.

The complete procedure was done in day case setting. All patients had an enema on the day of surgery. All procedures were performed under general or locoregional anaesthesia in the lithotomy position. Broad spectrum antibiotics were administered perioperatively. The fistulotomy was done according to the following technique. The internal fistula tract opening was identified by probing the external fistula opening. During surgery the amount of sphincter involved was judged by palpation of the
puborectal sling and the inferior edge of the external sphincter complex. The tissue was divided by laying open the complete fistula tract from the internal to the external opening. After the division of the fistula, surgical biopsies were taken from the fistula tract from three different locations, respectively on the proximal side close to the internal opening, in the middle of the fistula tract and near the distal end close to the external opening. When the fistula tract was too short to take multiple biopsies only one biopsy in the middle of the tract was taken. Care was taken to obtain biopsies from the fistula tract and not from the tissue surrounding it. After taking the biopsies the fistula tract was curetted to remove potentially present epithelial lining. Only patients with low perianal fistulas were included as it is very difficult to obtain biopsies from high perianal fistulas from different locations. Routine H&E staining was performed using a standardized protocol. No additional immunohistochemical staining techniques were used. Multiple sections were made and the evaluation was done by a pathologist unaware of any clinical characteristics of the patients, i.e. duration of the fistula and clinical outcome. The amount and the type of epithelium and granulation present in the fistula tract were assessed. All patients visited the outpatient’s clinics frequently during the follow-up period. Patient’ clinical records were reviewed and data were collected on demographic data, previous fistula surgery, fistula duration, complications and fistula recurrence rate. Previous fistula surgery was defined as surgery aimed to permanently repair the fistula. Duration of the fistula was defined as the time from when the complaints started until the present operation. In case of multiple interventions for the same fistula the time from the latest intervention was taken until the present surgical procedure.

Statistical analysis

Continuous data are presented as median values (range) unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Mann-Whitney U test for continuous data. For the comparison of categorical variables, the Chi-squared or Fisher exact test was used. A p-value of 5% or lower was considered statistically significant. Statistical analysis was done using the SPSS version 15.0.1 for Windows (SPSS, Chicago, Illinois, USA).
RESULTS

In the study period 18 patients with low perianal fistulas were included. Patient characteristics are presented in Table 5.1. The median age was 46 years (range 23-76). Eleven patients were male (61%). The majority of the fistulas were cryptoglandular (16 patients, 89%). There was one patient with a perianal fistula in Crohn’s disease and one with human immunodeficiency virus (HIV). Previous fistula surgery was performed in ten patients (56%). Patients had a fistula for a median of six months (range 1-24). None of the patients underwent seton drainage previous to the fistulotomy. There were no intra- or postoperative complications. The median follow-up duration was nine months (range 1-19). In one out of the 18 patients the fistula persisted (6%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low fistulas (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>11:7</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>46 (23-76)</td>
</tr>
<tr>
<td>Previous fistula surgery (n)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1/18 (6%)</td>
</tr>
<tr>
<td>Follow-up (months, range)</td>
<td>9 (1-19)</td>
</tr>
</tbody>
</table>

Pathological results

In 18 patients biopsies were taken. A median of three biopsies were taken from the fistula tract (range 1-3). In 15 of the 18 patients squamous epithelium was found at least in one of the biopsies taken from the fistula tract (Table 5.2). A picture of epithelialization was presented in Figure 5.1. In none of the patients cylindrical epithelium was found. In the majority of the biopsies a larger part of the surface was denuded. Epithelium was predominantly found near the internal opening. In 9 out of the 12 patients with several biopsies, epithelium was found at the proximal end of the fistula tract. In the middle biopsy this was the case in four patients, compared to only two patients with epithelium found in the distal biopsy. In none of the patients epithelium was found in all three locations. In the majority of the patients (17 of the 18) an active inflammatory response was visible. This ranged from a mild to severe inflammation. No skin appendages were found in either of the
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Fistula duration (months)</th>
<th>Origin</th>
<th>Epithelium present</th>
<th>Proximal</th>
<th>Mid</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>58</td>
<td>6</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>33</td>
<td>9</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>30</td>
<td>3</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>25</td>
<td>4</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>52</td>
<td>5</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>39</td>
<td>4</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>46</td>
<td>1</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>56</td>
<td>12</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>40</td>
<td>9</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>56</td>
<td>1</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>49</td>
<td>8</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>46</td>
<td>4</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>56</td>
<td>3</td>
<td>Crohn</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>76</td>
<td>8</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>27</td>
<td>12</td>
<td>Crypto</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>46</td>
<td>4</td>
<td>Crypto</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Female</td>
<td>23</td>
<td>24</td>
<td>Crypto</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>Male</td>
<td>54</td>
<td>7</td>
<td>HIV</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Crypto = Cryptoglandular fistula, Crohn = Crohn's disease, HIV = Human immunodeficiency virus
Histological identification of epithelium in perianal fistulas.

There was no relation between the duration of fistula complaints and the presence of epithelialization \((p=0.301)\). The amount of epithelium was not related to the presence of a history of fistula surgery \((p=1.000)\).

**Figure 5.1** – Biopsy from a fistula tract with routine haematoxylin-eosine staining (25x). In the smaller picture keratin immunohistochemistry staining (25x) was used to present the keratin in the biopsy.

**DISCUSSION**

The present study assessed the incidence and origin of epithelialization of the fistula tract in a consecutive series of patients undergoing fistulotomy for low perianal fistulas. In these series in 15 out of the 18 patients epithelium was found by the pathologist after obtaining surgical biopsies from the fistula tract after performing the fistulotomy. Epithelium was predominantly located close to the internal opening at the proximal location of the fistula tract. There were only two patients with epithelial lining of the distal part of the fistula tract. None of the biopsies were taken from the anal skin as no skin appendages were found by the pathologist. Epithelialization was not found more often in patients with a previous fistula surgery. Perianal fistulas remain difficult to treat and often a fistula persists after surgical treatment especially in high transsphincteric fistulas. A possible explanation for the
persistent or recurrent fistula is the existence of epithelialization in the fistula tract which prevents the fistula to close. Williams et al. recently stated that the presence of epithelialization may be more important for the persistence of a fistula than the chronic infection.\textsuperscript{4} The question arises whether there is a relation between the recurrent or persistent fistula and the presence of epithelium. Furthermore it is not clear where the epithelium originates from. In a histological study by Parks et al. from 1961, 30 specimens were examined for epithelialization among other things.\textsuperscript{6} Epithelium was found in 13 out of 30 patients. Lunniss et al. described in their series of 18 specimens 13 patients with epithelium originating from the anal canal.\textsuperscript{5} Presumably this was the result of ingrowth of anal epithelium into the internal opening. In the present series a comparable result was found as the majority of the epithelium was seen close to the internal opening. In only two of the patients’ epithelium was found at the distal segment of the fistula tract. When there was epithelium in the middle there was always epithelium in the proximal biopsy taken close to the internal opening. In these two patients no epithelium was found in the biopsy taken from the middle of the fistula tract. It might be that the amount of epithelium in the middle of the fistula tract was low and the biopsy did not contain this epithelium.

Epithelium located near the internal opening in the anal canal could potentially be cylindrical or squamous epithelium depending on the height of the internal opening. Surprisingly however, in the patients reported in the present series no cylindrical epithelium but only squamous epithelium was found at the proximal end close to the internal opening. Metaplastic degeneration of cylindrical epithelium as result of the chronic inflammatory response may explain this.

In this study no information could be provided on the role of the seton in the development of epithelialization of the fistula tract. As all patients had low perianal fistulas and none of them were treated by seton drainage before to ensure optimal drainage. Hypothetically there may be more epithelialization in fistulas which exist longer and are drained by a seton.

There is also the possibility of malignant transformation of the chronically retained epithelium in the fistula tract.\textsuperscript{7} The incidence of a perianal mucinous adenocarcinoma is low and ranges from 3-11% of all anal carcinomas. In literature there are only case reports reporting this phenomenon.\textsuperscript{8} The anal fistula plug appears a promising device for the treatment of high peri-
Histological identification of epithelium in perianal fistulas

anal fistulas. The results reported by Champagne et al. were very good with a success percentage of 83%. Overall the success percentages appear to be around 50-60% in the literature. However, these rates vary a lot in the different studies. Randomized clinical trials can provide information on the true effectiveness of the anal fistula plug. In the product instructions of the plug provided by the manufacturing company the advice is not to perform debridement, curettage of brushing of the tract. At a consensus conference on this subject held in Chicago in 2007, the advise was not to perform any debridement of the tract to prevent increase of the fistula tract diameter. By flushing the tract with hydrogenperoxide all loose debris should be sufficiently removed. The presence of epithelial lining in the fistula tract shown in this study might be an explanation for the less successful outcome of the anal fistula plug in some patients. Removal of any epithelial lining would be of added value to the plug installation. The plug may grow into the tissue more easily which leads to increased closure rates without leading to substantial increase in the fistula diameter. In conclusion, the present study demonstrated a degree of epithelialization in the fistula tract in the majority of the patients surgically treated by fistulotomy for low perianal fistulas. There was no relation with the duration of the fistula. Curettage of perianal fistulas after closure may prevent recurrent and persistent fistulas and should be used in all surgical treatment options, i.e. the anal fistula plug. The question remains whether curettage of the fistula tract is sufficient to remove all epithelial lining.

REFERENCES

Chapter 5

50.


PART II

Novel techniques in fistula surgery
Chapter 6

The anal fistula plug for closure of difficult anorectal fistula, a prospective study


Diseases of the Colon and Rectum, 2007
ABSTRACT

Background
Complex high and recurrent fistulas remain a surgical challenge. Simple division, i.e. fistulotomy, will likely result in fecal incontinence. Various surgical treatment options for these fistulas have shown disappointing results. Recently a biologic anal fistula plug was developed to treat these high transsphincteric fistulas. To assess the results of the anal fistula plug in patients with complex high perianal fistulas, a prospective, two-center, clinical study was undertaken.

Methods
Between April 2006 and October 2006, a consecutive series of patients with difficult therapy-resistant high fistulas were enrolled. During surgery, the internal fistula tract opening was identified. A conical shaped collagen plug was pulled through the fistula tract. Any remaining portion of the plug that was not implanted in the tract was removed. The plug was fixed at the internal opening with a deep 3/0 polydioxanone suture.

Results
Seventeen patients with a median age of 45 years (range 27-75) were included. Of these patients, 71% (12/17) were male. At a median length of follow-up of seven months (range 3-9), seven of 17 fistulas had healed (41%). In ten patients the fistula recurred.

Conclusions
In these small series of 17 patients with difficult high perianal fistulas a success rate of 41% is noted. Larger series preferably in trial setting, must be done to establish the efficacy of the anal fistula plug in perianal fistula.
INTRODUCTION

The main objective in fistula surgery is to eradicate the fistula tract by closing the internal opening while preserving continence. Submucosal, intersphincteric, and low transsphincteric fistulas in the lower third of the external sphincter complex are easy to treat by simple fistulotomy, with a favorable success rate and relatively little impact on fecal continence. High transsphincteric fistulas remain a surgical challenge. Simple division, i.e., fistulotomy will likely result in fecal incontinence. In recent years many options have been explored to successfully treat these difficult perianal fistulas. Surgical procedures suitable for high fistulas include advancement flaps, loose-seton placement, installation of fibrin glue, and diverting ostomy. Unfortunately these techniques have disappointing success rates. Champagne et al. reported a new biologic anal fistula plug to treat these high transsphincteric fistulas. This plug is biologic absorbable and consists of lyophilized porcine intestinal submucosa. In their series of 46 patients treated with the anal fistula plug, a success rate of 83% was achieved at a median follow-up of 12 months. Some patients have complex or recurrent therapy-resistant fistulas. Various treatment options have been tried to eradicate the fistula without success. The anal fistula plug might be an attractive alternative in these patients because it is minimally invasive and can be repeated without major consequences. To assess the results of the anal fistula plug in patients with complex high perianal fistulas this prospective, two-center, clinical study was undertaken.

METHODS

Patients

Between April 2006 and October 2006, a consecutive series of patients with difficult and complex therapy-resistant fistulas were enrolled in the Academic Medical Center of Amsterdam, the Netherlands, and in the University Clinics of Leuven, Belgium, and treated with the anal fistula plug. High perianal fistulas were defined as patients with fistulas running through the upper two-thirds of the external sphincter complex, which is confined by the puborectal sling and the end of the anal canal (Figure 6.1) A history for previous fistula surgery, inflammatory bowel disease, and
HIV was obtained. Inclusion criteria included age 18 years and older and informed consent. Patients with submucosal, intersphincteric, and low transsphincteric fistulas were excluded. If the internal opening of the fistula could not be identified under locoregional or general anesthesia, the patient was not included. During surgery, the amount of sphincter involved was judged by palpation of the puborectal sling and the inferior edge of the external sphincter complex. In the Netherlands and Belgium, non-experimental clinical case series such as this do not require approval of the local Medical Ethics Commission.

Figure 6.1 – Low perianal fistulas are fistulas where the fistula tract transverses the lower 1/3 of the external sphincter complex. High fistulas transverse the upper 2/3 of the external sphincter complex.

Surgical technique

All patients had an enema on the day of surgery. The complete procedure was done in day-case setting. All procedures were performed under general or locoregional anaesthesia in the lithotomy position. Broad spectrum antibiotics were administered perioperatively.

The introduction of the anal fistula plug (Surgisis, Cook Surgical, Inc., Bloomington, IN) was done as described by Champagne et al. During surgery the internal fistula tract opening was identified. No real surgical debridement of the fistula tract was performed. Only cleaning and chemical debridement was obtained by the use of hydrogen peroxide. A suture was attached to the tail of the plug. A probe was inserted into the external opening and via the fistula tract the internal opening was
found. The plug with the suture attached was lead through the fistula tract and pulled in. The suture was drawn into the tract until the plug completely blocked the internal opening. Any remaining portion of the plug that was not implanted in the tract was removed. The plug was fixed at the internal opening with two 3/0 polydioxanone (PDS) sutures. The external side of the plug was fixed to the skin with Vicryl 3/0. The external fistula opening was not completely closed, enabling further drainage from the fistula tract and possible secondary tracts.

**Follow-up**

Patients were advised to perform no strenuous work during the first two weeks. No specific dietary recommendations were given. Patients were followed-up at two, four, and 12 weeks. Each follow-up visit contained an interview and a physical examination. Fistula closure was defined if the external opening was closed and no discharge and pain were experienced. Otherwise it was considered as a persistent fistula.

**Statistical analysis**

Continuous data are presented as median values (range) unless otherwise specified. Categorical data are presented as frequencies or percentages. Analysis was performed with SPSS version 12.0.1 for Windows (SPSS Inc, Chicago, IL).

**RESULTS**

**Patient characteristics**

During the study period, 17 patients with a median age of 45 (range, 27-75) years were included in the prospective study. Patient characteristics are presented in Table 6.1. The study group consisted of one patient with Crohn’s disease, two patients had human immunodeficiency virus (HIV). The patient with Crohn’s disease used azathioprine and mesalamine at the time of surgery. The remaining 14 patients had perianal fistulas of cryptoglandular origin. Twelve patients had a history of perianal fistula surgery. The remaining patients had, among other things, anal stenosis, anal fibrosis, and problems with haemorrhoidal tissue. All patients had a single internal
Chapter 6

and external opening except for one patient that had three external openings. The median number of previous procedures was one (range, 0-6). Various treatment modalities had been tried to close the perianal fistula. Treatment options that were used consisted of seton drainage and subsequent mucosal advancement flap, bioglue installation and performing a colostomy in one patient.

Table 6.1 – Patient characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Etiology</th>
<th>Previous surgery (n)</th>
<th>Result</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>Crypto</td>
<td>3</td>
<td>Closed</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>54</td>
<td>Crypto</td>
<td>4</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>75</td>
<td>Crypto</td>
<td>1</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>53</td>
<td>Crypto</td>
<td>6</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>62</td>
<td>Crypto</td>
<td>2</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>43</td>
<td>HIV</td>
<td>1</td>
<td>Closed</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>59</td>
<td>Crypto</td>
<td>1</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>32</td>
<td>Crypto</td>
<td>3</td>
<td>Recurrence</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>50</td>
<td>Crypto</td>
<td>1</td>
<td>Recurrence</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>51</td>
<td>Crypto</td>
<td>0</td>
<td>Recurrence</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>45</td>
<td>Crypto</td>
<td>4</td>
<td>Closed</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>27</td>
<td>Crohn</td>
<td>1</td>
<td>Closed</td>
<td>7</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>32</td>
<td>Crypto</td>
<td>0</td>
<td>Recurrence</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>37</td>
<td>Crypto</td>
<td>0</td>
<td>Closed</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>36</td>
<td>HIV</td>
<td>2</td>
<td>Closed</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>39</td>
<td>Crypto</td>
<td>0</td>
<td>Recurrence</td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>39</td>
<td>Crypto</td>
<td>0</td>
<td>Closed</td>
<td>3</td>
</tr>
</tbody>
</table>

M=Male, F=Female, Crypto=Cryptoglandular

Clinical outcome

All patients were operated in day-case setting. The median duration of surgery was 25 (range, 10-50) minutes. No complications were encountered during the postoperative course. No readmissions were encountered. At a median length of follow-up of seven (range, 3-9) months, seven of the 17 fistulas had healed (41%). The results in both clinics were comparable in terms of amount of patients and recurrence rate. Ten patients had a persistent fistula. Although a significant improvement of one patient’s symptoms had occurred, it was considered as a persistent fistula. In all three patients with HIV or Crohn’s disease, the fistula had healed. In seven patients, the reason for the recurrence was the falling out of the plug. In two patients this was because of a very wide fistula tract. During primary surgery, only one plug had been
inserted. One patient underwent a reoperation in which two plugs were inserted. No other modifications were performed during surgery to avoid plug fallouts. In 12 patients with a history of fistula surgery, five had closed. In the group without previous fistula surgery, two out of five fistulas had closed.

**DISCUSSION**

A mucosal advancement flap seems to be the standard approach in complex, recurrent high fistulas. This results in an overall healing rate between 60 and 80% for fistulas of cryptoglandular origin and in a healing rate between 50 to 60% for patients with fistulas caused by Crohn’s disease. In recurrent fistulas, after previous surgery, healing rates are reduced. Therefore, the use of an anal fistula plug, a minimally invasive procedure, could be an attractive alternative and avoid more complex surgery in those patients. As a consequence, this prospective, two-center, clinical study was started to assess the fistula closure rate in patients with complex and therapy-resistant high perianal fistulas. In some of these patients, the only remaining treatment option was chronic seton drainage or a diverting ostomy.

Champagne et al. recently reported on 46 patients treated with the anal fistula plug. A conical-shaped, bioprosthetic plug made from porcine small intestinal submucosa was used. Patients with high anorectal fistulas (high transsphincteric or deeper) were included. Excluded were patients with Crohn’s disease or superficial fistulas (low transsphincteric or more superficial). At a median follow-up of 12 (range, 6-24) months, a fistula closure rate of 83% was achieved. The same research group reported on the treatment of 20 patients with Crohn’s disease treated with the anal fistula plug. Patients with superficial fistulas, which could be safely treated by fistulotomy, were excluded. Of the 20 patients 16 had closed (80%). In both series the presence of multiple fistula tracts was significantly associated with failure. Their results seem to be very encouraging; however, the fact that they do not define high and low transsphincteric fistula could be criticized.

In our series of 17 patients, a closure rate of only 41% was found after a median follow-up of seven months. Most of the patients operated on were patients with complex and therapy-resistant perianal fistulas. Of the total of 17 patients in this study, 12 had a history of fistula surgery. In that perspective, these short-term re-
sults can be interpreted as relatively good. Patients with Crohn’s disease and HIV infection showed more favorable results than those observed in patients with fistulas of cryptoglandular origin. In the subset of patients with cryptoglandular fistulas, better results were obtained in patients who had not been previously operated on compared with patients who had undergone multiple surgical procedures. In the majority of persistent fistulas, the reason of recurrence was falling out of the plug. This could be considered as a technical failure. Possibly there is a learning curve to be overcome. It is important to assure adequate fixation of the plug during surgery to prevent plug extrusion.

In the series from Champagne et al., high transsphincteric fistulas were selected for surgery. Unfortunately, no information is presented on the previous surgery undergone before using the anal fistula plug and the exact definition of high transsphincteric fistula. In these series high perianal fistulas were defined as patients with fistulas containing the upper two-thirds of the external sphincter complex, which is confined by the puborectal sling and the end of the anal canal.

Although not objectified by questionnaires, patients treated with the anal fistula plug in our series seemed to report less postoperative pain compared to patients treated with the mucosal advancement flap.

The principal effect of the anal fistula plug as stated by Johnson et al. is to close the internal opening by using the plug-shaped device. This is the same principle that is used when performing the mucosal advancement flap. Theoretically, the fistula tract also can close as the result of incorporation of the plug.

The anal fistula plug is fabricated from porcine collagen, which stimulates tissue remodelling to eventually fully close the fistula tract. Furthermore, the advantage of the plug is that it can be used repeatedly, without risk of damaging the anal sphincter. Another advantage is that installing the plug is minimally invasive with probably less postoperative pain.

The anal fistula plug seems to be a promising alternative for high perianal fistula of various origins. In a group of “last resort” patients, an acceptable healing rate was achieved. However, the present study consists of a small series of patients with a limited follow-up, which makes it difficult to draw firm conclusions. Because most of the failures are caused by plug fallout, which we consider to be a technical failure, the true efficacy is not yet known. To assess the value of the anal fistula plug,
randomized, controlled trials should be awaited before broader implementation.

REFERENCES


Chapter 7

The anal fistula plug versus the mucosal advancement flap for the treatment of anorectal fistula (PLUG trial)


BMC Surgery, 2008
ABSTRACT

Background
Low transsphincteric fistulas less than 1/3 of the sphincter complex are easy to treat by fistulotomy with a high success rate. High transsphincteric fistulas remain a surgical challenge. Various surgical procedures are available, but recurrence rates of these techniques are disappointingly high. The mucosal flap advancement is considered the gold standard for the treatment of high perianal fistula of cryptoglandular origin by most colorectal surgeons. In the literature a recurrence rate between zero and 63% is reported for the mucosal flap advancement. Recently Armstrong et al. reported on a new biologic anal fistula plug, a bioabsorbable xenograft made of lyophilized porcine intestinal submucosa. Their prospective series of 15 patients with high perianal fistula treated with the anal fistula plug showed promising results. The anal fistula plug trial is designed to compare the anal fistula plug with the mucosal flap advancement in the treatment of high perianal fistula in terms of success rate, continence, postoperative pain, and quality of life.

Methods
The PLUG trial is a randomized controlled multicenter trial. Sixty patients with high perianal fistulas of cryptoglandular origin will be randomized to either the fistula plug or the mucosal advancement flap. Study parameters will be anorectal fistula closure-rate, continence, post-operative pain, and quality of life. Patients will be followed-up at two weeks, four weeks, and 16 weeks. At the final follow-up closure rate is determined by clinical examination by a surgeon blinded for the intervention.

Conclusions
Before broadly implementing the anal fistula plug results of randomized trials using the plug should be awaited. This randomized controlled trial comparing the anal fistula plug and the mucosal advancement flap should provide evidence regarding the effectiveness of the anal fistula plug in the treatment of high perianal fistulas.
INTRODUCTION

A perianal fistula is a common condition. It has an incidence of 5.6 per 100,000 in women and 12.3 per 100,000 in men.\textsuperscript{1} The disease occurs predominantly in the third and fourth decade of life.\textsuperscript{2} It is believed that infection of the intersphincteric glands is the initiating event in fistula in ano, in a process known as the \textquote{cryptoglandular hypothesis}.\textsuperscript{3} Parks \textit{et al.}\textsuperscript{4} developed a classification system in which fistula are divided into intersphincteric fistula, transphincteric fistula, supra sphincteric fistula and extraspincteric fistula. However the type of treatment depends not on the location of the fistula tract but of the level of the internal opening in the anal canal. Low transphincteric fistulas comprising less than 1/3 of the external sphincter complex are easy to treat by fistulotomy with a high success rate. High transphincteric fistulas remain a surgical challenge. Surgical procedures include advancement flaps, loose-seton placement, and the installation of fibrin glue. All of these techniques have disappointing success rates. In the literature a recurrence rate between zero and 63\% is reported for the mucosal flap advancement.\textsuperscript{5-7} Recently, Van der Hagen \textit{et al.}\textsuperscript{6} published the result of 41 patients with high transphincteric, supra sphincteric and extraspincteric fistula treated with a mucosal flap advancement. The success rate was 37\% (with a median follow-up of 72 months).

The fibrin glue is an alternative to the mucosal advancement flap, however long-term closure rates are low.\textsuperscript{8-14} The percentages being as low as 16\%. The liquid consistency of fibrin glue is possibly not ideal for the purpose of closing anorectal fistulas, because the glue is easily extruded from the fistula tract by increased pressure.\textsuperscript{15} Armstrong \textit{et al.} reported a new biologic anal fistula plug.\textsuperscript{16} The plug is a FDA and CE approved bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa by Cook Surgical, Inc., Bloomington, IN. The material has inherent resistance to infection, produces no foreign body or giant cell reaction, and becomes repopulated with host cell tissue during a period of three months. The material was fashioned into a conical plug and secured into the primary opening of the fistula tract. Armstrong achieved promising results in a prospective series of 15 patients treated with the anal fistula plug. They compared the results with ten patients using fibrin glue. Patients with high anorectal fistulas (high transphincteric or deeper) were included. Excluded were patients with Crohn’s disease or superficial fistulas.
Chapter 7

(low transsphincteric or more superficial). At a median follow-up of 13.8 weeks they achieved a significant better fistula closure rate of 87% compared to the fibrin glue group ($P < 0.05$).

These results call for a prospective randomized controlled trial. Since mucosal flap advancement is the preferred treatment for high cryptoglandular perianal fistula, the anal fistula plug will be compared with mucosal flap advancement in a randomized setting.

METHODS

Study objective

The objective of this study is to compare, in a prospective randomized way, the anal fistula plug with the mucosal advancement flap in the treatment of high transsphincteric perianal fistula in terms of fistula closure rate, continence, morbidity, postoperative pain, and quality of life.

Study design

The PLUG trial is a prospective double blinded randomized multicenter trial. Patients with high perianal fistulas of cryptoglandular origin will be randomized to either the fistula plug or the mucosal advancement flap. Randomization will be performed during surgery after finding the internal opening. The computer randomization will be done centrally in the Academic Medical Center in Amsterdam, the Netherlands. Stratification is performed for the randomizing centers. Patients will be blinded for the type of intervention i.e. anal fistula plug or mucosal advancement flap. Patients are followed-up at two weeks, four weeks, and 16 weeks. At the final follow-up closure rate is determined by clinical examination. Follow-up is done by a colorectal surgeon, who is blinded for the type of intervention. The fistula will be rated closed if the external and the internal opening are closed and no discharge is experienced. Otherwise it is considered as a persistent fistula.
Study population

The study population consists of patients with high perianal fistulas. Inclusion criteria are; age above 18 years, high anorectal fistula of cryptoglandular origin (transssphincteric, upper 2/3 of the sphinctercomplex which is confined by the puborectal sling and the end of the anal canal), and informed consent. Exclusion criteria are; no internal opening found during surgery, HIV-positive patients, Crohn’s disease, malignant cause, tuberculosis, hydradenitis suppurativa, and pilonidal sinus disease.

Primary and secondary endpoints

The primary endpoints of the PLUG trial are fistula closure rate and continence. Continence will be evaluated pre- and postoperatively using the COREFO, the Wexner and the Vaizey score. The COREFO questionnaire has 27 questions to assess colorectal functional outcome. The Vaizey scale consists of three items about the type (gas, fluid, solid) and frequency of incontinence (all scored from zero to four) and four additional items that address alteration in lifestyle (zero to four), the need to wear a pad or plug (zero or two), the use of constipating medication (zero or two), and the lack of ability to defer defecation for 15 minutes (zero or four). The total score on the Vaizey scale ranges from zero (complete continence) to 24 (complete incontinence).

Secondary endpoints are morbidity, postoperative pain, and quality of life. Postoperatively patients will be asked to grade their pain on a visual analogue scale (VAS: 0, no pain; 10, worst imaginable pain) on different moments during the follow-up. Quality of life will be evaluated using the SF-36 questionnaire. The SF-36 measures eight health attributes: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception. The higher the score, the better the health rating with 100 points as the maximum for each concept. In addition the EQ-5D questionnaire is used.
Participating centers

Six Dutch hospitals, including one academic and five non-academic hospitals, will enrol patients.

Ethics

The study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The protocol has been approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam and the local Ethical Committees of the participating centers. Prior the randomization informed consent will be obtained from all patients.

Study outline

Patients presenting in the outpatient department with high perianal fistulas of cryptoglandular origin will be asked for informed consent when the patient fulfils the in- and exclusion criteria.

Positioning of the anal fistula plug will be done according to the instructions of Cook SIS technology. The plug is fabricated from surgisis material (Cook Surgical, Inc., Bloomington, IN), a bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa. The material has inherent resistance to infection, produces no foreign body or giant cell reaction, and becomes repopulated with host cell tissue during a period of three months. All procedures will be performed under general or locoregional anaesthesia. Prophylactic broad-spectrum antibiotics will be administered before surgery. During surgery the internal fistula tract opening will be identified, followed by cleaning and debriding the fistula tract with hydrogen peroxide. A suture will be attached to the tail of the plug. A probe is inserted into the external opening exiting through the internal opening and the suture attached to the tail of the plug is grasped. Then the plug is pulled into the fistula tract, tail first. The suture is drawn into the tract until the plug securely blocks the internal opening and fits snugly within the tract. Any remaining portion of the plug that is not implanted in the tract is trimmed and discarded. The internal end of the plug is sutured in place with at least two sutures. The internal sutures should close the anal canal opening. In contrast with former instructions, no external fixation suture is placed.
The external opening is left open to allow for drainage of the tract. In case of a wide fistula tract, a second fistula plug can be put in place.

The rectal advancement flap is done according to the following technique. The internal opening is excised followed by mobilization of the mucosa, submucosa, and a small amount of muscular fibers from the internal sphincter complex. A rectal flap with a 2 to 3 cm broad base is mobilized. The rectal flap is mobilized sufficiently to cover the internal opening with overlap. Hemostasis is performed to prevent a hematoma under the flap. The fistula tract is curetted. The internal opening is not closed before advancing the flap over the internal opening. Finally the flap is sutured in the distal anal canal.

**Statistical analysis**

*Intention to treat*

The analysis will be performed in accordance with the intention to treat principle.

*Sample size calculation*

A success percentage of 87% was reported by Armstrong et al. for the anal fistula plug.\(^\text{16}\) For the mucosal advancement flap a success percentage of 37% was reported recently by Van der Hagen et al. in a series of 41 patients with a follow-up of 72 months.\(^\text{6}\)

To detect an increase in success percentage from 40% to 80%, using a significance level of 0.05, at least 46 patients have to be randomized to achieve a power of 80%. In total, 60 patients will be randomized.

**Data collection and monitoring**

Data are collected via datasheets on paper, which are sent to the Academic Medical Center by mail. Postoperatively questionnaires on pain are filled in by patients. Sixteen weeks after surgery questionnaires are sent to the patients to assess continence and quality of life. There will be regular contact between the study coordinators and the participating centers. One research fellow will monitor the included data of every patient.
DISCUSSION

The main objective in the treatment of perianal fistula is the healing of the fistula by closing the internal opening while preserving the anal continence. Submucosal, intersphincteric, and low transsphincteric fistulas, in the lower third of the external sphincter complex are easy to treat by simple fistulotomy, with a favorable success rate and relatively little impact on fecal continence.\textsuperscript{19,20} The surgical treatment of high perianal fistulas of cryptoglandular origin in relation to morbidity remains a problem. The anal fistula plug appears to be a promising alternative to the current treatment options for high perianal fistulas.\textsuperscript{20–24} The anal fistula plug is fabricated from porcine collagen which stimulates tissue remodeling leading to full closure of the fistula tract. Furthermore, the advantage of the plug is that it can be used repeatedly, without risk of damaging the anal sphincter. In a recent study describing the results of the surgical treatment of perianal fistulas of cryptoglandular origin soiling was reported following surgery in 40% of the patients. In these series 109 patients were treated by fistulotomy for low perianal fistulas. A rectal advancement flap was performed in 70 patients for high transsphincteric fistulas.\textsuperscript{25} Another advantage is that installing the plug is minimally invasive with possibly less postoperative pain. During mucosal flap advancement, the fistula tract is excised externally to the anal sphincter in order to ensure an optimal drainage. Before broadly implementing the anal fistula plug results of randomized trials using the plug should be awaited. This randomized controlled trial comparing the anal fistula plug and the mucosal advancement flap should provide evidence regarding the effectiveness of the anal fistula plug in the treatment of high perianal fistulas.

REFERENCES

5. Ortiz H, Marzo J. Endorectal flap advancement repair and fistulectomy for high trans-

6. van der Hagen SJ, Baeten CG, Soeters PB, van Gemert WG. Long-term outcome following
mucosal advancement flap for high perianal fistulas and fistulotomy for low perianal fistu-
las: Recurrent perianal fistulas: failure of treatment or recurrent patient disease? Int J
Colorectal Dis 2006; 21(8):784-790.

outcome following loose-seton technique for external sphincter preservation in complex anal


of fibrin sealant in the management of complex anal fistula: a prospective trial. Dis Colon
Rectum 2003; 46(9):1167-1174.

10. Ellis CN, Clark S. Fibrin glue as an adjunct to flap repair of anal fistulas: a randomized,


13. Williams JG, Farrands PA, Williams AB, Taylor BA, Lunniss PJ, Sagar PM et al. The

14. Gisbertz SS, Sosef MN, Festen S, Gerhards MF. Treatment of fistulas in ano with fibrin

15. Hammond TM, Grahm MF, Lunniss PJ. Fibrin glue in the management of anal fistulae.

16. Johnson EK, Gaw JU, Armstrong DN. Efficacy of anal fistula plug vs. fibrin glue in closure

and validation of a colorectal functional outcome questionnaire. Int J Colorectal Dis 2005;

18. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence

72(12):970.


Chapter 8

The anal fistula plug treatment compared to the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistulas: A double blinded multicenter randomized trial

P.J. van Koperen, W.A. Bemelman, M.F. Gerhards, L.W.M. Janssen, W.F. van Tets, A.D. van Dalsen, J.F.M. Slors

Submitted, 2010
ABSTRACT

Background
The anal fistula plug was developed as alternative treatment for perianal fistulas. The aim was to compare the plug with the mucosal advancement flap for the treatment of high transsphincteric fistulas.

Methods
In a double blinded multicenter randomized trial sixty patients with perianal fistulas were randomized to anal fistula plug or mucosal advancement flap and were blinded for the type of treatment. Outcome parameters were closure rate, postoperative pain (VAS), continence (COREFO, Vaizey, and Wexner score) and quality of life (SF-36 and EQ-5D). Closure was determined by clinical examination by a surgeon blinded for the intervention.

Results
At a follow-up of 11 months the recurrence rates were 71% (n=22) in the anal fistula plug group and 52% (n=15) in the mucosal advancement group, which was not significantly different. There were no significant differences in postoperative pain, in pre- and postoperative incontinence scores, soiling, and quality of life.

Conclusions
The results of the anal fistula plug and advancement flap are disappointing in multicenter setting. There were no significant differences in recurrence, functional outcome and quality of life between de plug and advancement flap. As the plug is simple to apply and minimally invasive it can be considered as initial treatment option for high transsphincteric fistulas.
INTRODUCTION

Perianal fistulas are frequently encountered in today’s surgical practice. Surgical treatment of high transsphincteric perianal fistulas results in low success rates compared to treatment of low perianal fistulas.¹ Several new treatment options have been developed over time, however none of these resulted in success percentages above 80%.² The mucosal advancement flap is currently the best available treatment option resulting in a success percentage of around 60%.³⁴ The anal fistula plug was developed to treat perianal fistulas. The plug is a FDA and CE approved bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa by Cook Surgical, Inc., Bloomington, IN. The material has inherent resistance to infection. Furthermore, it does not produce a foreign body reaction, and becomes repopulated by own tissue in a period of about three months. The plug is easy to use and could provide a solution for perianal fistulas. Moreover, the anal fistula plug may reduce the recurrence rate, postoperative pain and incontinence. Johnson et al. reported 15 patients treated with the anal fistula plug in a prospective study. They compared the results with ten patients using fibrin glue. Patients with high perianal fistulas were included. At a median follow-up of 13.8 weeks they achieved a significant better fistula closure rate of 87% compared to 40% in the fibrin glue group (P < 0.05).⁵ Later publications reported less favorable closure rates (24-71%).⁶⁻¹¹ The aim of this randomized prospective multicenter trial was to compare the anal fistula plug with the mucosal advancement flap for the surgical treatment of cryptoglandular high transsphincteric perianal fistulas with respect to fistula recurrence rate and functional outcome.

METHODS

Study design

The study design was a multicenter double blinded randomized trial comparing the anal fistula plug with the mucosal advancement flap in the treatment of high transsphincteric perianal fistula.
Study population

The study population consisted of patients with perianal fistulas eligible for surgical repair. Inclusion criteria were; age above 18 years, high perianal fistulas of cryptoglandular origin as established during surgery (transspincteric, upper 2/3 of the sphincter complex which was confined by the puborectal sling and the end of the anal canal), and informed consent. Exclusion criteria were; no internal opening found during surgery, HIV-positive patients, Crohn’s disease, malignancy or other causes. Patients presenting in the outpatients department with high perianal fistulas of cryptoglandular origin were asked for informed consent when the patient fulfilled the in- and exclusion criteria. Six hospitals participated in this study, including one academic and five non-academic hospitals.

Study outline

Patients were randomized during surgery to either the anal fistula plug or the mucosal advancement flap. During examination under anaesthesia the in- and exclusion criteria were carefully reviewed before randomization. The computer randomization was done centrally in the Academic Medical Center in Amsterdam, the Netherlands. Block randomization with random block sizes (four and six) was used. Stratification was performed for the randomizing centers.

All the participating surgeons were instructed to obtain uniformity in the use of the plug and the construction of the mucosal flap. Whenever appropriate, surgeons were proctored in the use of the plug by one of the surgeons. Anal fistula plug treatment was done according to the recommendations provided by the consensus panel during the conference held in Chicago in 2007. The plug was purchased from Surgisis (Cook Surgical, Inc., Bloomington, IN). Only in selected cases when the fistula was complex and/or recurrent, MR or anal endosonography was used to outline the fistula tract. All procedures were performed under general or locoregional anaesthesia. Prophylactic broad-spectrum antibiotics were administered only before surgery. During surgery the internal fistula tract opening was identified, followed by cleaning and debriding the fistula tract with hydrogen peroxide. No further curettage was done to minimize trauma to the fistula tract. A suture was attached to the tail of the plug. A probe was inserted into the external opening exiting through the
Comparison of the anal fistula plug and the advancement flap

internal opening and the suture attached to the tail of the plug was grasped. Then the plug was pulled into the fistula tract, tail first. The suture was drawn into the tract until the plug securely blocked the internal opening and fitted snugly within the tract. Any remaining portion of the plug that was not implanted in the tract was trimmed and discarded. The internal end of the plug was sutured in place with at least two Vicryl 3-0 sutures (Ethicon, Amersfoort, the Netherlands). In contrast with former instructions, no external fixation suture was placed. The external opening was left open to allow for drainage of the tract. In case of a wide fistula tract, a second fistula plug was inserted. The mucosal advancement flap was done according to the following technique. The internal opening was excised followed by mobilization of the mucosa, submucosa, and a small amount of muscular fibers from the internal sphincter complex. A rectal flap with a 2 to 3 cm broad base was mobilized. The rectal flap was mobilized sufficiently to cover the internal opening with overlap. Hemostasis was performed to prevent a hematoma under the flap. The fistula tract was curetted. The mucosal flap was sutured in the distal anal canal with Vicryl 3-0 (Ethicon, Amersfoort, the Netherlands). Finally, the fistula tract was excised externally to the anal sphincter in order to ensure an optimal drainage. Patients were blinded for the type of intervention i.e. the anal fistula plug or mucosal advancement flap. Postoperatively there was no bowel regimen. Patients in both groups were advised to refrain from physical labour, cycling and sports for two weeks. Patients visited the outpatient department at two weeks, four weeks, and 16 weeks after surgery. Follow-up ended when fistula closure was achieved. At the final follow-up closure rate was determined by clinical examination in the outpatients clinic by a surgeon blinded for the intervention. The fistula was rated closed if the external and the internal opening were closed and no discharge and pain were experienced. Otherwise it was considered as a persistent fistula. No standard endoanal ultrasound or MR was performed at final follow-up.

Primary and secondary endpoints

The primary endpoints of the study were fistula closure rate and continence. Continence was evaluated pre- and postoperatively using the COREFO, the Wexner and the Vaizey score. The COREFO questionnaire has 27 questions to assess colorectal functional outcome. The Vaizey scale consists of three items about the type
(gas, fluid, solid) and frequency of incontinence (all scored from zero to four) and four additional items that address alteration in lifestyle (zero to four), the need to wear a pad or plug (zero or two), the use of constipating medication (zero or two), and the lack of ability to defer defecation for 15 minutes (zero or four). The total score on the Vaizey scale ranges from zero (complete continence) to 24 (complete incontinence).\textsuperscript{14}

Secondary endpoints were morbidity, postoperative pain, and quality of life. Postoperatively patients were asked to fill out visual analogue scales (VAS) for pain measurement. Quality of life was evaluated using the SF-36 questionnaire.\textsuperscript{15} The SF-36 measures eight health attributes: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, pain, vitality and general health perception. The higher the score, the better the health rating with 100 points as the maximum for each concept.

Health related quality of life was assessed pre- and postoperatively by EQ-5D. This is a simple, self-administered questionnaire in which a patient had to score a one, two or three, reflecting 'no problems', 'moderate problems' and 'extreme problems', respectively. This was scored on five dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. These scores were generated in a tariff reflecting the preference value associated with a given health state. The utility by Dolan \textit{et al.}\textsuperscript{16} was used to calculate the overall health status (= EQ-5D tariff). In which a tariff of -0.6 represented the worst quality of life and 1.0 the best quality of life. Both had to be filled out at postoperative day one till seven and at day 14.

\textbf{Data collection and monitoring}

Data were collected \textit{via} datasheets on paper. Postoperatively questionnaires on pain were filled in by patients. Four months after surgery questionnaires were sent to the patients to assess continence and quality of life.

\textbf{Ethics}

The study was conducted in accordance with the principles of the Declaration of Helsinki and ‘good clinical practice’ guidelines. The protocol was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam and the...
local ethical committees of the participating centers. Prior the randomization informed consent was obtained from all patients. The article was drafted according to the Consort Statement.¹⁷

**Statistical analysis**

Data are presented as median values with ranges unless otherwise specified. Categorical data are presented as frequencies or percentages. Differences between groups were tested using Mann-Whitney U test for continuous data. Chi-squared test was used to test for differences between groups in cases of categorical data. \( P < 0.05 \) was considered as statistically significant. Statistical analysis was done using the SPSS v.15.0.1 package (SPSS, Chicago, IL). The analysis was performed in accordance with the intention to treat principle.

A success percentage of 87% was reported by Armstrong *et al.* for the anal fistula plug.⁵ For the mucosal advancement flap a success percentage of 37% was reported recently by Van der Hagen *et al.* in a series of 41 patients with a follow-up of 72 months.⁴

To detect an increase in success percentage from 40% to 80%, using a significance level of 0.05, at least 46 patients had to be randomized to achieve a power of 80%. In total, 60 patients were randomized.

**RESULTS**

**Patient characteristics**

Between October 2006 and 2008, 104 patients were eligible for this study. Sixty patients were randomized during surgery after fulfilling the inclusion criteria. The flow diagram and the patient characteristics at baseline are presented in Figure 8.1 and Table 8.1 respectively. There were no differences between the two groups with respect to sex, age, BMI, previous fistula surgery, smoking, preoperative seton drainage. Thirty-one patients were randomized to the anal fistula plug, and 29 to the mucosal advancement flap. Seton drainage was done in 17 of the 60 patients for a median duration of four months before final surgery (range 1-36).

Drainage of perianal abscesses during surgery was not necessary in any of the pa-
Chapter 8

Patients. There were no peroperative complications. Three patients had postoperative complications, one in the plug group and two in the advancement group. In the anal fistula plug group one patient was reoperated because of a perianal abscess occurring one day after surgery at the site of the installed fistula plug. The plug was removed and the abscess drained. One patient was readmitted four days after performing an advancement flap with abdominal pain. Retroperitoneal air was seen in the pelvis on CT scan. The patient was admitted for observation and was discharged after one week without a reintervention. The other patient had a postoperative bleeding 10 days after flap repair requiring reoperation. The postoperative pain was assessed by using the visual analogue scale (VAS).

Figure 8.1 - Trial flow diagram.

The mean VAS was 3 (+3) at day one compared to 4 (+2.5) in the advancement group (Figure 8.2). Overall there were no differences between both groups (p=0.143). Four of the 31 patients (13%) reported that plug had fallen out, all within 10 days after surgery.

At a median follow-up of 11 months (range 5-27), the recurrence rate was 71% (n=22) in the anal fistula plug group. In the advancement flap repair group the fistula recurred in 52% (n=15) which was not significant different from the anal fistula plug group. All patients with a recurrent fistula were symptomatic. Con-
tinence was assessed by COREFO, Vaizey and the Wexner score. The outcome of these questionnaires is presented in Table 8.2. The continence was not significantly different pre- and postoperatively in the COREFO (p=0.373), Vaizey (p=0.618) and Wexner (p=0.947) questionnaires. The same results were found when soiling was assessed. Soiling was reported preoperatively in the fistula plug group and the advancement group in 33% and 36% respectively (p=0.852). Postoperatively soiling was reported in the plug group and the advancement group in 29% and 48% respectively (p=0.143). The amount of soiling pre- and postoperatively was not statistically significant different in either group. The Wexner score in the plug group was 5.50 (range 0-16) before surgery and was 5.50 (range 0-14) after surgery. In the advancement group the Wexner score was 7.00 (range 0-12) before surgery and 6.50 (range 0-16) after surgery. These results were not significantly different before (p=0.859) or after surgery (p=0.947) between the anal fistula plug group and the advancement group.

Quality of life was assessed by SF-36 and EQ-5D before surgery and after 16 weeks. In the SF-36 in none of the subscales there were statistically significant differences. The results were equal pre- and postoperative in both groups. The EQ-5D tariff in the plug group was 0.796 (range 0.62-1.00) before surgery compared to 0.830 (range 0.52-1.00) after surgery. The analysis of the EQ-5D the results were also not significantly different pre- and postoperatively.

### Table 8.1 – Patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plug (n=31)</th>
<th>Adv (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>23:8</td>
<td>19:10</td>
<td>0.464</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>45 (24-79)</td>
<td>42 (24-61)</td>
<td>0.211</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (17-35)</td>
<td>27 (21-36)</td>
<td>0.429</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>11</td>
<td>8</td>
<td>0.616</td>
</tr>
<tr>
<td>Previous fistula surgery (n)</td>
<td>23</td>
<td>20</td>
<td>0.882</td>
</tr>
<tr>
<td>Amount of previous surgery</td>
<td>2 (1-6)</td>
<td>2 (1-5)</td>
<td>0.494</td>
</tr>
<tr>
<td>Smoking</td>
<td>14</td>
<td>9</td>
<td>0.469</td>
</tr>
<tr>
<td>Preoperative seton drainage</td>
<td>8</td>
<td>9</td>
<td>0.647</td>
</tr>
<tr>
<td>Day case surgery</td>
<td>22</td>
<td>22</td>
<td>0.668</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>25 (13-36)</td>
<td>28 (17-50)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

* Anal fistula plug, † Advancement flap
Table 8.2 – Vaizey scale and colorectal functional outcome (COREFO) for patients treated by anal fistula plug or rectal advancement before and after surgery.

<table>
<thead>
<tr>
<th>Scale, mean (SD)</th>
<th>Fistula plug (pre)</th>
<th>Fistula plug (post)</th>
<th>Advancement (pre)</th>
<th>Advancement (post)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaizey</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>1.3 (±1.8)</td>
<td>1.8 (±2.0)</td>
<td>1.4 (±2.3)</td>
<td>2.0 (±2.3)</td>
</tr>
<tr>
<td>Social impact</td>
<td>5.4 (±2.4)</td>
<td>5.4 (±2.3)</td>
<td>5.6 (±2.0)</td>
<td>5.7 (±1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>6.7 (±3.3)</td>
<td>7.2 (±3.7)</td>
<td>7.0 (±3.9)</td>
<td>7.7 (±3.2)</td>
</tr>
<tr>
<td><strong>COREFO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence range</td>
<td>14.8 (±13.1)</td>
<td>19.2 (±17.2)</td>
<td>16.8 (±15.6)</td>
<td>13.9 (±13.7)</td>
</tr>
<tr>
<td>Social impact</td>
<td>18.8 (±21.7)</td>
<td>22.4 (±21.9)</td>
<td>13.8 (±19.7)</td>
<td>17.7 (±21.0)</td>
</tr>
<tr>
<td>Frequency</td>
<td>10.0 (±15.7)</td>
<td>8.5 (±10.0)</td>
<td>6.0 (±6.4)</td>
<td>9.5 (±7.8)</td>
</tr>
<tr>
<td>Stool-related aspects</td>
<td>22.3 (±23.2)</td>
<td>20.3 (±22.0)</td>
<td>27.8 (±23.5)</td>
<td>19.8 (±16.3)</td>
</tr>
<tr>
<td>Medication</td>
<td>12.0 (±14.5)</td>
<td>11.3 (±22.4)</td>
<td>7.1 (±17.4)</td>
<td>7.5 (±17.4)</td>
</tr>
<tr>
<td>Total</td>
<td>16.3 (±14.5)</td>
<td>18.7 (±16.0)</td>
<td>15.1 (±13.5)</td>
<td>14.8 (±12.7)</td>
</tr>
</tbody>
</table>

1Mean score ranging from 0-24 (complete continence-complete incontinence) for the total score. Both subscale scores range from 0-12. 4Mean score per category after linear transformation to a score from 0-100, higher score represents an increased level of continence disturbance. As the total score, all subscales range from 0-100.

Figure 8.2 – Postoperative pain was assessed by using the visual analogue scale (VAS). Adv=Advancement flap group
DISCUSSION

The present randomized multicenter trial was conducted to assess the value of the anal fistula plug for the treatment of high perianal fistulas in comparison to the mucosal advancement flap. At a median follow-up of 11 months the recurrence rates in both groups were not significantly different. In the plug group the recurrence rate was 71% compared to 52% in the group treated by the mucosal advancement. There were no differences in terms of postoperative pain scores and quality of life after surgery. The continence was not significantly different pre- and postoperatively for COREFO, Vaizey, or the Wexner score in both groups.

The main objective in the treatment of perianal fistula is healing of the fistula by closing the internal opening while preserving anal continence. The treatment currently most often used is the mucosal advancement flap. However, this technique does not result invariably in high success rates.\textsuperscript{1} The anal fistula plug appears to be a promising alternative to the current treatment options for high perianal fistulas.

The initial results indicated potential advantages with respect to recurrence rate, postoperative pain and continence. Furthermore the plug is minimally invasive as it is technically easy to install in the fistula tract. In this series, the results of the anal fistula plug placement were disappointing. The recurrence rates found in literature for the anal fistula plug vary and range from 12% to 86%.\textsuperscript{7,18–21} Ortiz \textit{et al.} conducted a randomized clinical trial that was discontinued due to a high amount of early recurrences in the fistula plug group.\textsuperscript{11} In a series of 31 patients with high transsphincteric fistulas the fistula recurred in 12 of 15 patients (80%) treated with anal fistula plug. It is believed that inadequate fixation and early fall out of the plug is responsible for the failures.\textsuperscript{10} In the current study this occurred only in four patients, all within the first 10 days. All plugs were fixed according to the guidelines as presented after the consensus meeting.\textsuperscript{12} One of the features of plug placement was the expected reduction of postoperative pain compared to the advancement flap. Part of the pain and discomfort after mucosal flap advancement is caused by the excision of the fistula tract externally to the anal sphincter in order to ensure optimal drainage. Surprisingly no differences were found. A subanalysis was done assessing the pain in the first days following surgery. Also in these groups no differences were found.

Continence was assessed by COREFO, Vaizey, and Wexner questionnaires pre-
and postoperatively. There were no differences between the groups before or after surgery. In both groups soiling was reported in a significant amount of patients, however this was not significantly different from the situation before surgery. In a recent study describing the results of the surgical treatment of perianal fistulas of cryptoglandular origin soiling was reported following surgery in 40% of the patients. However, in these series 109 patients were treated with fistulotomy for low perianal fistulas and a rectal advancement flap was performed in 70 patients for high transsphincteric fistulas. In a series of 61 patients with perianal fistulas as result of Crohn’s disease between 54% and 75% of the patients reported soiling.

In neither of these two studies the preoperative amount of soiling was known. In the current study the quality of life was assessed by SF-36 and EQ-5D questionnaires. The results were comparable in both groups. A possible drawback from the quality of life assessment in patients with perianal fistulas is the small impact of the anal disease in overall quality of life. None of the used questionnaires is directed towards perianal disease. Currently there is no data in the literature on quality of life in perianal fistulas.

The sample size calculation was based on the first study available on the anal fistula plug in which the success rate was 87%. Looking at the current available literature probably if the trial would be conducted at this moment the sample size would be larger which could result in significant results.

Another important aspect of the plug is the cost of the device. Besides the plug itself, the materials used for the installation of the plug are identical to the advancement flap. When the plug is compared to the conventional treatment option it is considerably more expensive. The price of the anal fistula plug is 690 euro. As a result, the cost of the placement of the plug is 690 euro more than the mucosal advancement flap.

In conclusion, both the results of the anal fistula plug and mucosal advancement flap are disappointing in multicenter setting in a group of patients with only high transsphincteric fistulas. There were no significant differences in recurrence, functional outcome and quality of life between de plug and advancement. As the plug is technically simple to install and minimally invasive, it can be considered to use as an initial treatment option for high transsphincteric fistulas despite of the high costs.
REFERENCES


PART III

Presacral pathology and anastomotic leakage
Chapter 9

The persisting presacral sinus following anastomotic leakage after anterior resection: incidence and outcome

P.J. van Koperen, E.S. van der Zaag, J.M.T. Omloo, J.F.M. Slors, W.A. Bemelman

Submitted, 2010
ABSTRACT

Background
Despite improvements of anastomotic techniques and specialised surgery, anastomotic leakage is still frequently encountered following anterior resection. Anastomotic leakage of a low anterior resection can eventually evolve into a presacral sinus. This study assesses the incidence, the natural course and outcome of the persisting presacral sinuses resulting from anastomotic leakages.

Methods
In a two center retrospective study, all consecutive patients who underwent anterior resection for cancer or restorative proctocolectomy for ulcerative colitis or familial poliposis were eligible. Patients with an anastomotic leakage or presacral abscess were included in this study. Primary outcome parameters were the incidence of persistent presacral sinuses, the closure rate of these sinuses, the average time to closure and the rate of successful closure of the ostomy.

Results
Between 1997 and 2007, 25 patients (M:F=14:11) had an anastomotic leakage complicated by a presacral sinus after low anterior resection (n=20) or a restorative proctocolectomy (n=5). Definitive resolution of the sinus occurred in 12 out of 25 patients (52%). This was achieved in a median of 340 days (range 23-731). In the malignant group in 10 patients (56%) the treatment was successful compared to three out of five patients (60%) in the benign group (p=1.000). At final follow-up, nine of the 23 patients had permanent fecal diversion due to recurrent abscesses or a persistent sinus, seven after low anterior resection and two after restorative proctocolectomy.

Conclusions
A significant part of patients with anastomotic leakage after low anterior resection or restorative proctocolectomy develop a chronic sinus of which only half heal over time. The persisting sinuses are the main cause of a permanent ostomy in these patients. Since treatment of the persistent sinus is difficult, all effort should be directed to the prevention of the development of the sinus once the anastomotic leakage has been established.
INTRODUCTION

Despite improvements of anastomotic techniques and specialised surgery, anastomotic leakage is still frequently encountered following anterior resection. Considerable morbidity and even mortality can result from anastomotic leakage.\(^1\)\(^-\)\(^4\) Mostly a surgical reintervention is required demanding dismantling of the anastomosis or defunctioning by performing a loop ileostomy to treat imminent abdominal sepsis. Presacral abscesses might develop as result of a sealed leakage, in the presence of a defunctioning ileostomy with preserved anastomosis or as a result of an infected hematoma perforated through the low anastomosis. Surgical or non-surgical drainage is mostly required and is characterised by long term drainage and increased hospital stay.\(^2\) When the acute sinus does not heal, a chronic sinus will develop which delays or even precludes ostomy closure. When the sinuses eventually resolves and ostomy closure is possible, the function of the neorectum is often jeopardized by the fibrosis due to the chronic inflammation.\(^5\)

It is unknown what the incidence is of these chronic presacral sinuses as a late complication of anastomotic failure, and it is unknown how many of these sinuses resolve over time.

The object of the present study is to assess the incidence, the natural course and outcome of the persisting presacral sinuses after anterior resection for rectal malignancy and after restorative proctocolectomy for ulcerative colitis or familial poliposis.

METHODS

Patients

In a two center retrospective study, all consecutive patients who underwent anterior resection for cancer or restorative proctocolectomy for ulcerative colitis or familial poliposis were eligible. Patients with an anastomotic leakage and presacral abscess were included in this study. Anastomotic leakage was generally detected by CT scan which was done on clinical suspicion of anastomotic leakage. Patients with generalised peritonitis were managed by relaparotomy. Anastomotic dehiscence of the low colorectal, coloanal or pouch anal anastomosis was defunctioned by a loop ileostomy and the abdominal cavity was lavaged. Dismantling of the low anastomosis
was generally not done, because the height of the anastomosis precluded future restoration of the continuity. In the absence of peritonitis and a sealed presacral abscess, the abscess was drained transanastomotically or percutaneously. Primary outcome parameters were the incidence of persistent presacral sinuses, the closure rate of these sinuses, the average time to closure and the rate of successful closure of the ostomy. Closure of the abscess cavity was assessed by endoscopy, CT scan or by double contrast study of the colon.

Data collection

Retrospectively, patients’ charts were reviewed and data was extracted on demographic data, Body Mass Index (BMI), pre-operative chemo and/or radiotherapy, type and indication of surgery (possible diverting ileostomy/colostomy), level of anastomosis, time till closure abscess cavity, 30-day morbidity and mortality, post-operative hospital stay, readmissions, and amount of reoperations.

Statistical analysis

Continuous data are presented as median values (range) unless otherwise specified. Categorical data are presented as frequencies or percentages. For the comparison of categorical variables, the Chi-squared or Fisher exact test was used. A p-value of 5% or lower was considered statistically significant. Statistical analysis was done using the SPSS version 15.0.1 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Between January 1997 and 2007, 834 patients underwent a low anterior resection (LAR) for malignant disease and 229 patients had a restorative proctocolectomy for ulcerative colitis or familial poliposis with ileoanal pouch anastomosis. From this group, 69 (7%) patients had an anastomotic leakage which required a reintervention, 46/834 after LAR and 23/229 after restorative proctocolectomy (Figure 9.1). In 25 of these 69 patients (36%) a presacral sinus was found at a median of 10 days after surgery (range 3-79). In the pouch group, five out of the 23 (22%) patients with anastomotic leakage developed a presacral abscess. Twenty of the 46 (43%) patients
with anastomotic leakage after LAR presented with a presacral abscess (Table 9.1). In the majority of the cases (n=20), a contrast CT scan was used to diagnose the anastomotic leakage. In one patient the leakage was discovered by flexible endoscopy. In two patients a double contrast study of the colon established the diagnosis. In two patients a reoperation was performed based on clinical judgment. In all patients a diverting ostomy was constructed after discovery of the leakage if this had not been done during the initial surgery. In two patients (LAR group) the anastomosis was dismantled and an end colostomy was fashioned and these patients were excluded from the analysis.

**Figure 9.1** – Flow chart. TME=Total Mesorectal excision, IPAA=Ileal Pouch-Anal Anastomosis

Percutaneous drainage, ultrasound or CT guided, was done in four patients in the
Table 9.1 - Characteristics of patients with a presacral abscess.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>14:11</td>
</tr>
<tr>
<td>Age (median in years)</td>
<td>58 (23-68)</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
</tr>
<tr>
<td>Malignancy</td>
<td>20</td>
</tr>
<tr>
<td>BMI (kg/m², median, range)</td>
<td>26 (19-31)</td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>12</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>1</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>22</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>3</td>
</tr>
<tr>
<td>Anastomosis level (cm, mean, range)</td>
<td>4 (2-8)</td>
</tr>
<tr>
<td>ostomy created before or during initial surgery</td>
<td>14</td>
</tr>
<tr>
<td>Hospital stay (median, days, range)</td>
<td>22 (3-249)</td>
</tr>
<tr>
<td>Readmittance (n=12) (median, days, range)</td>
<td>20 (3-122)</td>
</tr>
<tr>
<td>Closure of abscess cavity (n)</td>
<td>12 (52%)</td>
</tr>
<tr>
<td>Time till closure (days, median, range)</td>
<td>340 (23-731)</td>
</tr>
<tr>
<td>Follow-up (months, range)</td>
<td>30 (9-61)</td>
</tr>
</tbody>
</table>

BMI=Body Mass Index, cm=centimeters

course of treatment. In eight patients the presacral abscesses were drained transanastomotically. A combined treatment of relaparotomy and drainage transanastomotically was done in eight patients. Five patients underwent a relaparotomy and the abscess was drained transabdominally.

Definitive resolution of the sinus occurred in 12 out of 23 patients (52%). This was achieved in a median of 340 days (range 23-731). In the malignant group in 10 patients (56%) the treatment was successful compared to three out of five patients (60%) in the benign group (p=1.000). A persistent sinus was present in 8/18 (44%) after LAR and 2/5 (40%) after restorative proctocolectomy. Twelve patients received preoperative radiotherapy out of the group of 18 patients that underwent colorectal resection for malignant disease. The sinus closed in half of the patients that underwent radiotherapy. In the group without radiotherapy the sinus closed in four of the six patients (p=0.638). Overall, in twelve of the thirteen patients with a closed abscess cavity the ostomy could be closed. In one patient with a closed sinus the ostomy was considered definitive because of patient preference. In three patients with a small, not completely closed sinus the ostomy was closed without further complications in two patients. As result of recurrent abscesses the third
Persisting presacral sinus following anastomotic leakage

A patient needed a reoperation and an end colostomy was fashioned. In another three patients the anastomosis was dismantled later in the course of treatment and an end-colostomy was constructed. At final follow-up, nine of the 23 patients had permanent fecal diversion due to recurrent abscesses or a persistent sinus, seven after LAR and two after restorative proctocolectomy.

**DISCUSSION**

In the present study course and outcome of conventionally treated presacral sinuses resulting from anastomotic leakage after rectal surgery were assessed. Anastomotic leaks were associated with the development of chronic presacral sinus in 36% of the patients. One year postoperatively half of the presacral sinuses were closed spontaneously.

After colorectal surgery, one of the most feared complications is anastomotic leakage. The reported incidence of anastomotic leakage after low anterior resection for colorectal cancer is significant and ranges between 1-24%.\(^6\) Reported risk factors for anastomotic leakage include difficult surgical procedure, low tumour location, adjuvant radiochemotherapy, and poor preoperative patient condition.\(^7\) Early discovery of anastomotic leakage is crucial for prevention of serious adverse events which result from the septic source in the pelvis. The anastomotic disruption can lead to a presacral abscess and/or chronic para-anastomotic sinus. Often a wait and see strategy is used after the construction of an ileostomy. When the cavity is large the sinus is surgically or transanally drained by placement of a flexible drain. Radiological interventions are possible by positioning drains (percutaneously) in the abscess cavity. Flexible endoscopy can be performed to diagnose or to lavage the sinus.

One of the major problems for patients is the continuous drainage of debris from the sinus resulting in considerable patient discomfort. The continuous foul smell can result in patient isolation. In the long term recurrent pelvic sepsis can result in reinterventions, ongoing sepsis and neorectal insufficiency due to reduced neorectal capacity. Nesbakken et al. reported on eleven patients with anastomotic leakage following total mesorectal excision (TME).\(^8\) The neorectal capacity was significantly lower in the group treated for anastomotic leakage compared to the non-leakage group, 120 vs. 180 ml (p=0.04) respectively. Hallbook et al. compared two groups of
patients with and without anastomotic leakage after TME. Patients were matched according to sex, age, height of the anastomosis and follow-up duration. In the group with the anastomotic leakage the neorectal function was clearly reduced. More recently a consecutive series of 86 patients was described by Arumainayagam et al. Of the patients that underwent TME with protecting ileostomy, in eight patients a presacral sinus developed. The sinus closed in three out of the eight patients with an average healing time of six months. In two patients, tumour recurrence was found in the presacral sinus (six and 19 years after surgery). This might be due to chronic inflammation. Several options are available to treat a persisting presacral sinus. Options are permanent fecal diversion, pouch-excision or excision of the neorectum, and omentoplasty of the cavity. Another option described by Whitlow et al. in six patients is the so-called deroofing of the anastomosis. This is performed by dividing the wall between the presacral sinus and the adjacent bowel lumen under direct vision through a rigid proctoscope. By dividing the wall, the lumen of the bowel and the sinus are connected avoiding retention in the presacral sinus. Patients were treated a median of 3.5 months after diagnosis of the sinus. The sinus resolved in five patients within one month and in another patient after twelve months. Besides one anastomotic stricture there were no complications reported. An alternative is closure of the opening in the anastomosis to the sinus with fibrin glue. Swain et al. applied this technique in the treatment of seven patients with sinus tracts following restorative proctocolectomy or low rectal anastomosis. The sinus was cleaned and filled with fibrin glue. After one week healing of the sinus was observed in all patients and after 11 months no recurrences were reported. Fibrin glue closure is probably only possible if the sinus tract is rather small, while deroofing is indicated when a large presacral sinus drains via a small gap in the anastomosis. According to the literature the treatment of a para-anastomotic sinus is difficult and results in a variable success rates. Furthermore, treatment often does not prevent the formation of a chronic sinus. The abscess cavity remains present next to the neorectum. In several studies it was shown that due to the chronic inflammation and fibrosis of the sinus the neorectal capacity is at risk. Since the treatment of the persistent presacral sinus is difficult, prevention of the development of a chronic sinus seems to be essential. Weidenhagen et al. introduced the endo-sponge. The low vacuum sponge ensures optimal drainage and the pre-
Persisting presacral sinus following anastomotic leakage

The closure percentages from the endo-sponge range from 56-100%.[14-17] In a series of 29 patients presented by Weidenhagen et al. the mean total hospital stay was 31 days.[13] An advantage of the endo-sponge treatment is that patients can be treated as outpatients returning every 3-4 days for endo-sponge exchange. Endo-sponge treatment is probably only successful if started early after the discovery of the anastomotic leak when the neorectum is still compliant.

In conclusion, a significant part (36%) of patients with anastomotic leakage after LAR or restorative proctocolectomy develop a chronic sinus of which only half heal over time. The persisting sinuses are the main cause of a permanent ostomy in these patients. Since treatment of the persistent sinus is difficult, all effort should be directed to the prevention of the development of the sinus once the anastomotic leakage has been established. Endo-sponge treatment might play an important role in achieving this.

REFERENCES


Chapter 10

Endo-sponge treatment of anastomotic leakage after ileoanal pouch anastomosis

P.J. van Koperen, M.I. van Berge Henegouwen, J.F.M. Slors, W.A. Bemelman

Colorectal Disease, 2008
Chapter 10

ABSTRACT

Background
Anastomotic leakage is a feared complication following colorectal surgery. It is associated with considerable morbidity and mortality. Recently, application of local vacuum sponge treatment has shown to be effective to treat contained anastomotic leakage after low anterior anastomosis in rectal cancer patients. The negative pressure of the endo-sponge results in constant drainage and potentially infection control, reduction of the size of the cavity, increased blood flow and therefore the stimulation of granulation tissue.

Results
Two patients (1 male, 18 years; 1 female, 40 years) who underwent proctocolectomy because of ulcerative colitis with ileo-anal J-pouch reconstruction developed a localized anastomotic leakage without general peritonitis. This was endoscopically managed by transanal placement of an endo-sponge (B. Braun Medical B.V., Melsungen, Germany) after a diverting ileostomy was performed. The sponge was frequently replaced until resolution of the sinus was obtained in respectively 35 and 56 days.

Conclusions
Endo-sponge placement can be helpful in treatment of anastomotic leakage after ileo-anal pouch surgery.
INTRODUCTION

Anastomotic leakage is a feared complication following colorectal surgery. It is associated with considerable morbidity and mortality including pelvic sepsis, prolonged ICU stay and even death. After pouch surgery, anastomotic leakage is a serious complication which is known to be an important cause of long term pouch failure.\(^1\) Prolonged pelvic sepsis before resolution or persistent presacral sinus are responsible for this.

Recently, the application of local vacuum sponge treatment has shown to be effective to treat locally contained anastomotic leakage after low anterior anastomosis in rectal cancer patients.\(^2\) In this study, four patients were described achieving rapid closure of the presacral cavity. The vacuum sponge was installed in the cavity endoscopically. The time until closure was considerably lower compared to a group treated with conservative treatment in a previous 5-year period.

The negative pressure of the endo-sponge results in constant drainage and potentially infection control, reduction of the size of the cavity, increased blood flow and therefore the stimulation of granulation tissue.\(^3\) Since rapid resolution of the pelvic sepsis and closure of the presacral sinus is considered to be an important factor in long term pouch function, an aggressive approach treating this condition is justified.

Two cases with anastomotic leakage after restorative proctocolectomy are described.

METHODS

**Endo sponge material**

The material used for the sponge was an open-pored polyurethane sponge (Figure 10.1, B. Braun Medical B.V., Melsungen, Germany). The sponge was installed transanally after examination and rinsing (saline 0.9%) of the abscess cavity using a small calibre flexible gastroscope (GIF-100 Video Gastroscope, Olympus, 9.8 mm in diameter). The length and size of the abscess cavity was estimated and the size of the endo-sponge was cut accordingly. A plastic tube positioned over the gastroscope was installed into the deepest point of the cavity. After the gastroscope was withdrawn with the plastic tube in place, the endo-sponge was inserted through the tube by using a pushing probe after which the plastic tube was retracted. Next,
the sponge was connected to a low vacuum suction bottle (Redyron TRANS PLUS suction device), creating a constant negative pressure in the sponge. No fixation of the sponge was necessary, because low pressure suction fixed the sponge in the abscess cavity. The endo-sponge was changed every 3-4 days to prevent the tissue from growing into the sponge causing painful sponge exchanges.

![Figure 10.1 - 1/2/3 Installation of the endo-sponge in the abscess cavity (altered with the permission of B. Braun Medical B.V.) *abscess cavity, †mucosa bridge, ‡pouch. a) Endoscopic view of abscess cavity before endo-sponge treatment. b) After two weeks of endo-sponge treatment. c) End result after 5 weeks of endo-sponge treatment.](image)

### RESULTS

#### Case 1

An 18-year-old male underwent an open restorative proctocolectomy with ileoanal J-pouch reconstruction for therapy-resistant ulcerative colitis diagnosed four years earlier. The pouch was constructed using a 100mm linear stapler (Proximate linear cutter 100 mm, Ethicon) and an ileo-anal anastomosis was made using the double stapled technique (Proximate ILS Circular Stapler CDH29, Ethicon). As the patient was on high dose of steroids a protecting loop-ileostomy was performed. There were no intra-operative complications. With the exception of an episode of urinary reten-
tion, the postoperative course was uneventful and the patient was discharged on day seven after surgery. Three days later the patient was readmitted with abdominal pain and anal blood loss. A CT scan with transanal contrast showed an anastomotic leakage with abscess formation. A relaparotomy was performed changing the diverting ileostomy into an end-ileostomy due to insufficient defunctioning. In the same procedure the size of the anastomotic leakage and abscess cavity were assessed endoscopically. A two third circumferential anastomotic dehiscence was present (Figure 10.1a). The large cavity was extensively cleansed and two endo-sponges were installed. During the following weeks multiple replacements of the endo-sponge were performed under a light sedative (5 mg Midazolam). This was partially done in the endoscopy suite of the outpatient’s clinic. After 35 days the cavity had resolved and vacuum treatment was stopped (Figure 10.1b,c). The ileostomy was closed ten weeks after resolution.

Case 2

A 40-year-old female underwent a subtotal colectomy with a diverting ileostomy two years earlier for therapy-resistant ulcerative colitis. Recently, an open completion proctocolectomy with ileoanal J-pouch reconstruction was done without a defunctioning ileostomy. The pouch was constructed as described in Case 1. There were no intra-operative complications. Postoperatively anticoagulant therapy (Fenprocoumon) was restarted for a known protein S deficiency. Unfortunately, due to high international normalized ratio (INR) a bleeding occurred resulting in the development of a large presacral hematoma. A relaparotomy was performed on the ninth postoperative day because of an anastomotic leakage diagnosed with a rectal contrast-enhanced CT. The presacral hematoma was evacuated and a diverting ileostomy was constructed. The patient recovered slowly and two weeks later the endo-sponge was inserted after endoscopic examination and washing out of the cavity. A three fourth anastomotic dehiscence was seen at this first postoperative endoscopy. The patient was discharged from the hospital 7 1/2 weeks after the primary surgery. The sponge was frequently replaced under a light sedative until complete resolution of the sinus was obtained after 56 days. Only a very small sinus remained after treatment on endoscopic examination. Ileostomy closure has not been scheduled yet because of patients’ preference.
DISCUSSION

Restorative proctocolectomy is the preferred surgical option to treat patients with ulcerative colitis and familial adenomatous polyposis coli. It leads to a good functional outcome and good long-term quality of life. Historically the anastomosis was performed hand-sewn. At present, most surgeons use the double stapled technique. Anastomotic leakage is a feared complication which is one of the most important determinants of long term pouch failure. For this reason, most surgeons routinely fashion a covering ileostomy reducing the clinical significance of anastomotic leakage when occurring. This diverting ileostomy is usually closed six to 12 weeks after radiological assessment of the anastomosis and pouch. If a leak is discovered, the resolution of this leak is generally assessed using gastrografin enemas. Most of the small leaks will eventually heal, but some of them cause a persistent presacral sinus precluding ileostomy closure. The prolonged pelvic sepsis and fibrosis is held responsible for impaired long term pouch function after ileostomy closure in many of those patients. Aggressive treatment of the presacral abscess enforcing quick resolution of the pelvic sepsis might be important for long term outcome.

Small presacral sinuses are generally defunctioned and a wait and see policy is applied with sometimes successful outcome. Occasionally a redo-procedure is needed. Large sinuses can be treated with a transanally inserted double lumen Foley catheter enabling irrigation. The difficulty treating these presacral sinuses is essentially an inadequate drainage of the sinuses.

Vacuum-assisted closure therapy is nowadays extensively used for different appliances, ranging from diabetic ulcers to postoperative wound dehiscences. In the treatment of the open abdomen the vacuum-assisted wound management is also used increasingly. However it is not yet clear whether overall vacuum assisted therapy is superior to alternative options. Further research is in this field is warranted. Weidenhagen et al. recently presented their first experience with a vacuum assisted closure of presacral sinuses after anastomotic leakages of low anterior resection. A series of seven patients with a large anastomotic leak were treated with the endo-sponge. Time until closure was between 21 and 42 days. Nagell et al. reported on a small group of four patients successfully treated with a vacuum-assisted device for anastomotic leakage after rectal resection. All patients had a protective ileostomy and sponges were replaced every 2-3 days. Sponge changing was stopped...
Endo-sponge treatment of anastomotic leakage after pouch surgery

when the cavity was smaller than the sponge and enough granulation tissue was present. Three out of four patients were followed (one patient died from cerebral hemorrhage) and healing times were 43, 51 and 195 days.

In the present study, two cases of large presacral abscesses after a semicircular anastomotic dehiscence after restorative proctocolectomy were closed effectively using the endo-sponge technique. Although the treatment is quite intensive as changing the sponge is necessary every 3-4 days, most of the replacements could be done in an outpatient setting. Resolution of the large cavities in these two cases was achieved in 35 and 56 days. A persistent presacral sinus was thereby avoided. Although these results are promising, long term pouch function after ileostomy closure has to be awaited.

In conclusion, use of the endo-sponge in the treatment of anastomotic leakage after ileoanal pouch anastomosis resulted in quick resolution of the presacral abscess cavity and finally healing of the anastomosis. Endo-sponge treatment can be considered a promising method avoiding prolonged pelvic sepsis and fibrosis in patients with leakage of low ileoanal pouches. This treatment might improve ostomy closure rate and long term functional outcome after restorative proctocolectomy complicated by anastomotic dehiscence.

REFERENCES


Chapter 11

The Dutch multicenter experience of endo-sponge treatment for anastomotic leakage after colorectal surgery

P.J. van Koperen, M.I. van Berge Henegouwen, C. Rosman, C.M. Bakker, P. Heres, J.F.M. Slors, W.A. Bemelman

Surgical Endoscopy, 2008
ABSTRACT

Background
Anastomotic leakage is a feared complication following colorectal surgery and is associated with early and long-term morbidity and mortality. The presacral cavity as the result of anastomotic leakage can be treated with an endo-sponge (B-Braun Medical). The aim was to assess the effectiveness of endo-sponge treatment of the presacral cavity as result of anastomotic leakage in the Netherlands.

Methods
Between July 2006 and April 2008, 16 patients (M/F = 9:7) with a median age of 64 years, (range 19-78 years) who underwent surgery for rectal cancer (n=13), or ulcerative colitis (n=3) were treated with the endo-sponge treatment after anastomotic leakage.

Results
Of the 16 patients, eight patients started with the endo-sponge treatment within six weeks after the initial surgery. In these patients the endo-sponge was placed after a median of 24 days (range 13-39) following surgery. In the remaining eight patients the endo-sponge treatment was started later than six weeks after the initial surgery. In this group there was a median of 74 days (range 43-1602) between surgery and the start of the endo-sponge placement. There was closure in six out of eight patients (75%) in the group that started with the endo-sponge treatment within six weeks of surgery compared to three out of eight patients (38%) in the group that started later (p=0.315). Closure was achieved in a median of 40 (range 28-90) days with a median amount of 13 sponge replacements (range 8-17).

Conclusions
Endo-sponge placement can be helpful in the treatment for anastomotic leakage after colorectal surgery and might prevent a chronic presacral sinus. However, it is not yet clear if this new treatment modality results in quicker healing.
INTRODUCTION

Anastomotic leakage is a serious and feared complication following colorectal surgery, which is associated with early and long-term morbidity and mortality.\(^1\)\(^-\)\(^4\) Particularly, (low) anterior resections are associated with a high leakage rate ranging from 1-24%.\(^5\)\(^-\)\(^6\) For this reason many surgeons prefer defunctioning the colorectal or coloanal anastomosis using a loop ileostomy. Anastomotic leakage of a functioning anastomosis mostly requires surgical reintervention to fashion a loop ileostomy and to drain the pelvic cavity in order to prevent severe septic complications.

Defunctioning of a low anastomosis by loop ileostomy does not prevent the leakage to occur, but diminishes the septic sequelae. Mostly, a presacral cavity originates from the site of the leakage. The cavity probably heals spontaneously when it is small. When it is large, it might delay the closure of the ileostomy and probably results in a devastating future function of the neorectum.\(^7\)\(^-\)\(^8\) Closure of the loop ileostomy in the presence of a chronic presacral sinus is considered hazardous since septic complications or bad function can be expected in some cases.

In the treatment of various wounds the vacuum-assisted therapy is often used to achieve wound closure.\(^9\) Recently, the application of local vacuum sponge treatment has shown to be effective to treat locally contained anastomotic leakage after low anterior anastomosis in rectal cancer patients. In a recent publication by Weidenhagen et al., a series of 29 patients with anastomotic leakage following rectal resection for malignant disease were treated with the endo-sponge.\(^10\) The endo-sponge facilitates closure of the presacral space by negative pressure of the endo-sponge ensuring a continuous drainage and thereby infection control, increased blood flow and therefore the stimulation of granulation tissue and reduction of the size of the cavity. In 28 out of the 29 patients described there was complete closure of the cavity. The aim of this study was to assess the effectiveness of endo-sponge (B-Braun Medical B.V., Melsungen, Germany) treatment of presacral cavities associated with anastomotic leakage.

METHODS

Between July 2006 and April 2008, a series of patients with a presacral cavity after anastomotic leakage were treated using the endo-sponge. All hospitals that had used
the endo-sponge were contacted to collect the data of the experience with the endo-
spoon; the endo-sponge had been used in patients following anastomotic leakage
after low anterior resections for malignant disease or after restorative proctocele-
tomy with ileoanal pouch anastomosis for ulcerative colitis.

After surgery, when anastomotic leakage was suspected a CT scan was performed in
the majority of the cases. Using flexible endoscopy, the presence of an abscess cav-
ity was confirmed. Subsequently a diverting ostomy was routinely constructed when
this had not been done during the primary operation. Primary outcome parameters
were closure of the cavity and the ability to close the ileostomy. Factors associated
with successful closure were analyzed e.g., time of initiation of endo-sponge treat-
ment after surgery, and experience with endo-sponge treatment (number of cases
-treated). Approval of the Medical Ethics Committees was not necessary, since in
the Netherlands for nonexperimental clinical case series such as this approval is not
required.

Endo-sponge treatment

The endo-sponge is an open-pored polyurethane sponge (B. Braun Medical B.V.,
Melsungen, Germany). A photograph of the introduction set is presented in Figure
11.1. The sponge is installed transanally after examination and rinsing (saline 0.9%)
of the abscess cavity using a small calibre flexible gastroscope (GIF-100 Video Gas-
troscope, Olympus, 9.8mm in diameter). The length and size of the abscess cavity
is estimated and the size of the endo-sponge is cut accordingly.

When the cavity is too large for one sponge, multiple sponges are placed. After
introduction of a small calibre gastroscope into the deepest point of the cavity, a
plastic tube, positioned over the gastroscope, is advanced into the deepest point of
the cavity. After withdrawal of the gastroscope, the endo-sponge is inserted through
the lubricated tube by using a pushing probe, while retracting the plastic tube.
Next, the sponge is connected to a low vacuum suction bottle (Redyron TRANS
PLUS suction device), creating a constant negative pressure in the sponge. The
correct positioning of the sponge is endoscopically checked. Fixation of the sponge
is not necessary, because low pressure suction fixes the sponge in the abscess cavity.
The endo-sponge is changed every 3-4 days to prevent the tissue from growing into
the sponge causing painful sponge exchanges. Saline (0.9%) is introduced into the
sponge just before removal to facilitate the painless extraction. Some hospitals use lidocaine instead of saline for this matter. During every endo-sponge exchange the size of the endo-sponge is reduced. Closure of the sinus is confirmed by flexible endoscopy and watersoluble contrast enema.

Data collection

Patients’ charts were reviewed and data was extracted on demographic data, Body Mass Index (BMI), preoperative chemo and/or radiotherapy, type and indication of surgery (possible ileostomy/colostomy), level of anastomosis, morbidity, mortality, time between surgery and start treatment, duration of endo-sponge treatment, amount of sponge exchanges, sponge related complications, follow-up, and short-term outcome.

Statistical analysis

Continuous data are presented as median values (range) unless otherwise specified. Categorical data are presented as frequencies or percentages. For the comparison of categorical variables, the Chi-squared or Fisher exact test was used. A p-value of 5%
or lower was considered statistically significant. Statistical analysis was performed using the SPSS version 14.0.2 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Patient characteristics

In total 16 patients (M/F = 9:7) with a median age of 64 years (range 19-78) were included. (Table 11.1) Thirteen patients had undergone surgery for rectal cancer and three for therapy-resistant ulcerative colitis. Nine patients of the 13 who underwent colorectal resection for malignant disease received preoperative radiotherapy. Two patients had chemoradiation preoperatively. In four patients the procedure was performed laparoscopically and in twelve patients an open procedure was performed. The anastomosis was constructed at a median height of five cm (range 2-8 cm) from the anal verge. During the initial operation a defunctioning ileostomy was created in eight patients. In seven patients the diverting ostomy was created after the discovery of the anastomotic leakage. In one patient a previously present diverting loop-ileostomy was changed into an end-ileostomy.

Table 11.1 – Characteristics of patients with an presacral abscess.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>9:7</td>
</tr>
<tr>
<td>Age (yrs, median, range)</td>
<td>64 (19-78)</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>3</td>
</tr>
<tr>
<td>Malignancy</td>
<td>13</td>
</tr>
<tr>
<td>BMI (kg/m², median, range)</td>
<td>26 (23-31)</td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>9</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>2</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>12</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>4</td>
</tr>
<tr>
<td>Anastomosis level (cm, mean, range)</td>
<td>5 (2-8)</td>
</tr>
<tr>
<td>ostomy created before or during initial surgery</td>
<td>8</td>
</tr>
</tbody>
</table>

BMI=Body Mass Index, cm=centimeters
Outcome

Postoperatively, anastomotic leakage was diagnosed by CT scan in 15 patients. In one patient the leakage was discovered by flexible endoscopy. None of the patients had generalized peritonitis during the use of the endo-sponge. After endoscopic confirmation of the abscess cavity the endo-sponge was placed. The median duration between the initial surgery and the discovery of the leakage was 11 days (range 3-150). From the 16 patients, eight patients started with the endo-sponge treatment within six weeks after the initial surgery. In these patients the endo-sponge was placed after a median of 24 days (range 13-39) following surgery (Table 11.2). In the remaining eight patients the endo-sponge treatment was started later than six weeks after the initial surgery. In this group there was a median of 74 days (range 43-1602) between surgery and the start of the endo-sponge placement. The experience in the different hospitals ranged from one to five patients in the study period. The median number of sponges initially placed ranged from one to three. In six patients the endo-sponge was placed under general anaesthesia. In three patients replacements were performed under a light sedative (5 mg Midazolam). The remaining seven patients underwent sponge placement without any anaesthesia. Definitive resolution of the sinus was achieved in the total group in nine out of 16 patients (56%). Closure was achieved in a median of 40 (range 28-90) days with a median amount of 13 sponge replacements (range 8-17). There was closure in six out of eight patients (75%) in the group that started with the endo-sponge treatment within six weeks of surgery compared to three out of eight patients (38%) in the group that started later (p=0.315). In the malignant group in 6 patients (46%) the endo-sponge treatment was successful compared to three out of three patients in the benign group (p=0.213).

In one patient the sponge exchange was complicated by a bleeding in abscess cavity (500 cc blood loss). The endo-sponge treatment was stopped in one patient after thirteen exchanges because the vacuum therapy was very painful. A possible explanation for this was that the abscess cavity was close to the hypogastric plexus. In a third patient, with a nearly complete dehiscent anastomosis, the sponge treatment was stopped after eight exchanges because there was insufficient progress in the closure of the cavity. Finally an end colostomy was constructed. In two patients due to recurrent abscesses an intersphincteric proctectomy was performed.
The median follow-up after closure of the abscess cavity was four months (range 2-16).

Out of nine patients with a closed abscess cavity the ostomy has been closed in five patients. One of these patients underwent a relaparotomy after ostomy closure as a result of anastomotic leakage of the short bowel anastomosis. A diverting ileostomy was constructed. Two patients are currently on the waiting list to close the ostomy. In the remaining two patients the ostomy is considered definitive because of patient preference or metastatic disease.

Table 11.2 – Results of the use of the endo-sponge.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start amount of sponges</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Time between surgery and start sponge treatment (days, median, range)</td>
<td>41 (13-1602)</td>
</tr>
<tr>
<td>≤6 weeks (n=8, days)</td>
<td>24 (13-39)</td>
</tr>
<tr>
<td>&gt;6 weeks (n=8, days)</td>
<td>74 (43-1602)</td>
</tr>
<tr>
<td>Time till closure (days, median, range)</td>
<td>40 (28-90)</td>
</tr>
<tr>
<td>Amount of spons exchanges (median, range)</td>
<td>13 (8-17)</td>
</tr>
<tr>
<td>Closure of abscess cavity (n)</td>
<td>9 (56%)</td>
</tr>
</tbody>
</table>

BMI=Body Mass Index, cm=centimeters

DISCUSSION

The present study shows that the endo-sponge is a promising device and could potentially be helpful in the treatment of anastomotic leakage after colorectal surgery. Furthermore, it might prevent the development of a chronic presacral sinus.

Anastomotic leakage after surgery is a complication that has major consequences for the patient, resulting in major morbidity and even mortality. Small anastomotic leakages after surgery in the pelvic area can potentially be treated by wait-and-see policy. This is not the case when the leakage involves a significant part of the circumference. This frequently leads to a large presacral sinus which often requires additional surgical procedures and long-term drainage of the abscess cavity. Furthermore, the purulent discharge and the often accompanying foul odour have an inevitable influence on the patient’s quality of life. The prolonged pelvic sepsis and fibrosis is held responsible for impaired long term neorectum function after ileostomy closure in many of those patients. Aggressive treatment of the presacral abscess...
enforcing quick resolution of the pelvic sepsis might be important for long term outcome. Following the application of vacuum sponges for the closure of abdominal wounds\(^3\), the endo-sponge was developed for the resolution of presacral abscess cavities as a result of anastomotic leakages following colorectal surgery. In the literature a small group of patients (n=4) with a significant anastomotic leakage after rectal resection that were treated in 2004 with a transanal VAC has been reported by Nagell \textit{et al.}\(^{14}\) All patients had a protective ileostomy before the start of the vacuum treatment. The median healing time of these patients was 51 (range 43-195) days. Weidenhagen \textit{et al.} described a series of 29 patients treated with the endo-sponge.\(^{10}\) The majority of these patients underwent surgery for malignant disease and nine patients received preoperative chemoradiation. Definitive closure was achieved in 28 of the 29 patients (97%). The mean total duration of the treatment was 34 days (range 4-79) and the number of sponge exchanges was 11 (range 1-27). Twenty-two out of the 25 patients with a protecting ostomy the ostomy could be closed after the abscess cavity was obliterated. Mees \textit{et al.} described a small series of five patients with a presacral abscess following anastomotic leakage after low anterior resection and restorative proctocolectomy.\(^{15}\) The median time to closure was 45 days (range 32-68).

In the present series closure of the abscess cavity after low anastomotic leakage after colorectal surgery was achieved in nine of sixteen patients. This is lower than reported by Weidenhagen \textit{et al.} in their series (97%). In our series not in all patients the endo-sponge treatment was started shortly after the initial surgical procedure. Although not significantly, the results were better in the group of patients that started within six weeks after surgery compared to the group that started later than six weeks (75% vs. 56%). A difference in closure rate, between the groups that started early compared to late, can be explained by the development of fibrosis of the neorectum precluding alignment of the bowel with the abscess cavity. As a result, endo-sponge treatment of chronic presacral sinuses probably has an unsatisfactory effect. Up to now five out of nine patients with a closed cavity had their ostomy removed and in two cases ostomy closure is planned.

In these series, all patients had a diverting ostomy after anastomotic leakage. The question is whether it is necessary to divert the fecal stream when an endo-sponge is inserted. If the endo-sponge closes the abscess cavity effectively, it prevents feces
Chapter 11

and debris to be pushed into the sinus. In the series of Weidenhagen et al. four patients were treated without the construction of a diverting ostomy.\textsuperscript{10} With the current endoluminal vacuum therapy patients have to undergo sponge exchanges every 3-4 days. This is done to prevent tissue growing into the sponge causing painful sponge exchanges. In the majority of the patients in these series the early exchanges were done in a clinical setting. After a few sponge exchanges most patients were discharged and treated in an outpatient setting. The patient has to return to the hospital two times a week. This cycle has a considerable impact on the patient and is demanding for the team performing the sponge exchanges in terms of time effort and availability of operating room and/or endoscopy suite space. Furthermore the costs are considerable. A complete set with the vacuum bottle that is used for one sponge exchange costs 195 euros.

Until now, there is insufficient literature whether the endo-sponge treatment is superior to a wait and see policy after fecal deviation. There is enough information on the different aspects of anastomotic leakage, \textit{e.g.} potential risk factors and oncological outcome.\textsuperscript{3−6,11,16} However, there are only few reports on the long-term outcome of anastomotic leakage after colorectal surgery in terms of functional outcome. A series of 19 patients with a median follow-up duration of 30 months was reported by Hallbook \textit{et al.}\textsuperscript{7} It showed that neorectal volume and compliance were significantly reduced in patients with anastomotic leakage. Nesbakken \textit{et al.} reported on the functional outcome after anastomotic leakage following low anterior resection for rectal cancer.\textsuperscript{8} In their series, 11 patients with anastomotic leakage were compared to patients without leakage after surgery. In the group with the leakage the neorectal capacity was significantly lower compared to the group without, 120 vs. 180 ml (p=0.04) respectively. Furthermore, significantly more evacuation problems were reported.

In conclusion, endo-sponge placement can be helpful in treatment of anastomotic leakage after colorectal surgery and might prevent a chronic presacral sinus. Starting early with endo-sponge treatment is probably more effective than late treatment of the presacral sinus. The long-term follow-up and functional outcome of the neorectum must be awaited.
REFERENCES


Chapter 12

Presacral masses in children and adults: presentation, etiology and risk of malignancy


Submitted, 2009
ABSTRACT

Background
Congenital presacral tumours are seen in children and adults. The aim of this study was to survey the spectrum of these masses in both groups focused on the type of presentation, origin of the tumour and the development of malignant tumours.

Methods
This was a retrospective review of 23 patients surgically treated for congenital presacral masses over a 22-year period.

Results
Constipation was the main symptom in 13 out of 16 children, all seven adults presented with pain. Masses were evident on digital examination in 18 patients. In children mature teratomas (n=8) were mostly observed and three malignancies were diagnosed, all in patients over the age of one year. In the adult group mainly developmental cysts (n=5) were observed, one malignancy had developed in a tailgut cyst. Currarino syndrome was diagnosed in 9 children; one HLXB9 gene mutation was found. Bony sacral defects typical for Currarino syndrome were present in one adult patient.

Conclusions
Congenital presacral masses in children and adults differ in type of presentation, origin and therefore risk of malignancy. The risk of malignancy mandates early surgical resection. Tumours as part of the Currarino syndrome were observed only in children and in one adolescent member of an affected family.
INTRODUCTION

The presacral region is the space between the mesorectum and the sacrum, also referred to as the retrorectal region. It is an area of embryologic fusion of the hindgut, proctodeum, neural elements and bone. Therefore it contains numerous types of tissue derived from all three germinal layers which can lead to the development of a variety of neoplasms.\(^1,2\) These tumours are rare, incidence has been estimated at one in 40,000 admissions\(^3-4\) and at 1.4-6.3 patients per year in a major referral center.\(^5\) Presacral tumours generally have been categorised into congenital and acquired tumours. With 50-77% congenital tumours account for the majority, occurring in both children and adults.\(^5,5\) A classification of congenital tumours can be found in Table 12.1. Diagnosis is often difficult and late because of the non-specific symptoms. In children presacral masses reported are mostly sacrococcygeal teratomas (Altman types III and IV) and tumours seen as part of the Currarino syndrome, a rare syndrome which comprises the presence of a typical bony sacral defect, often in combination with a presacral mass or an anorectal malformation.\(^6,7\) It clearly has a familial character and genetic mutations of the HLXB9 homeobox gene on chromosome 7q36 have been identified in different studies.\(^8,9\) Different types of tumours occur in this syndrome; most frequently seen are teratomas, anterior meningoceles, dermoid or duplication cysts or a combination of these.\(^6,10\) Presacral tumours presenting in adults are more often developmental cysts. In reported series and reviews benign lesions are more common than malignant lesions.\(^3,5,11\) The exact risk of malignancy rising in presacral lesions remains unclear and estimates differ for specific types of masses.

The aim of the present study is to survey the spectrum of presacral masses in children and adults with special attention to the type of presentation, the origin and type of the tumour and the risk of development of malignant tumours.

METHODS

Patients

Over the 22-year period from January 1987 to January 2009 a consecutive series of 23 patients was included. Inclusion criterion was the presence of a congenital
Table 12.1 – Classification of congenital presacral tumours.

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature teratoma</td>
<td>Chordoma</td>
</tr>
<tr>
<td>Anterior meningocele</td>
<td>Malignant teratoma</td>
</tr>
<tr>
<td>Developmental cysts</td>
<td>Yolk sac tumour</td>
</tr>
<tr>
<td>-Epidermoid cyst</td>
<td></td>
</tr>
<tr>
<td>-Dermoid cyst (mature cystic teratoma)</td>
<td></td>
</tr>
<tr>
<td>-Tailgut cyst (retrorectal cystic hamartoma)</td>
<td></td>
</tr>
</tbody>
</table>

Table 12.2 – Tumour histology.

<table>
<thead>
<tr>
<th>Benign</th>
<th>N</th>
<th>Malignant</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature teratoma</td>
<td>10</td>
<td>Chordoma</td>
<td>1</td>
</tr>
<tr>
<td>Lipoma</td>
<td>2</td>
<td>Yolk sac tumour</td>
<td>1</td>
</tr>
<tr>
<td>Tailgut cyst</td>
<td>2</td>
<td>Mixed malignant germ cell tumour (yolk sac tumour in malignant teratoma)</td>
<td>1</td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>3</td>
<td>Adenocarcinoma in tailgut cyst</td>
<td>1</td>
</tr>
<tr>
<td>Teratoid tumour</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamartoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>Total</td>
<td>4</td>
</tr>
</tbody>
</table>

Presacral mass that was surgically treated. Up to the age of 18 years at first presentation patients were defined as children, above that age limit they were classified as adults. Medical records were reviewed retrospectively on patient demographics, medical history, symptoms at presentation and physical findings. Radiological reports of X-rays, ultrasound and magnetic resonance imaging of the pelvic region were reviewed for presence of presacral masses and sacral bony defects. The magnetic resonance images of the adult patients were re-evaluated by a pediatric radiologist for the presence of a sacral bony defect typical for Currarino syndrome. Furthermore, surgical and definite histology reports were reviewed. Genetic reports were reviewed for the presence of the HLXB9-mutation. Follow-up was based on outpatient clinical records. Primary outcome measures were symptoms at presentation, histology, survival and surgical outcome. Gastrointestinal, urological and neurological function was assessed. Postoperative bowel motility function was classified into three groups according to the Krickenbeck conference classification: continent with voluntary bowel movement, constipation or soiling. Urological function at outpatient follow-up was classified as continent, intermittently incontinent or continuously incontinent according to the Report from the Standardisation Committee.
of the International Children’s Continence Society. Patients were contacted and interviewed in case of missing data.

### Statistical analysis

Data are presented as median values with ranges, unless otherwise specified. Categorical data are presented as frequencies or percentages. Statistical analysis was done using the SPSS v.15.0.1 package (SPSS, Chicago, Illinois, USA).

### RESULTS

In the study period 23 patients were included. The group treated during childhood includes 16 patients and seven patients were treated at adult age. These groups are described separately.

#### Pediatric patients

Patient characteristics and histological diagnoses are presented in Table 12.2 and 12.4. Of the 16 pediatric patients three were male and thirteen were female. Age ranged from newborn to four years at presentation (median age zero weeks). Three malignant tumours were diagnosed, all in patients over one year of age: a chordeoma, a yolk sac tumour and a mixed malignant germ cell tumour which contained yolk sac tumour and malignant teratoma. The main symptom at presentation was constipation (13 of 16 patients) varying from moderate constipation to a neonatal bowel obstruction based on anal stenosis or anal atresia. In 13 patients the mass or anorectal malformation was evident on rectal digital examination. Nine patients had a sacral defect and one had a lumbar spine defect. Anorectal malformation was present in eight patients of whom seven had anal stenosis, one had anal atresia and a rectoperineal fistula was present in two patients. Three patients had a tethered cord. In four patients genetics were studied for a mutation or deletion on the HLXB9 gene on chromosome 7q36, typical for Currarino syndrome; one patient had an unclassified mutation and in three patients the mutation could not be located. All 16 patients underwent surgery in which the presacral mass was extirpated, explored or debulked. A Posterior Sagittal AnoRectoPlasty (PSARP) procedure with anal di-
latations subsequently was performed in seven patients, two patients also underwent a procedure of untethering of the spinal cord. Several patients underwent more than one procedure. The minimal follow-up after surgery was 44 days with a median of 37 months (range 44 days-18 years).

**Surgical outcome**

One patient died at the age of four years due to a metastasized yolk sac tumour, five months after the last debulking operation. Of the other 16 patients, bowel movements at outpatient follow-up were classified. Five patients were classified as totally continent at present time. Constipation remained in ten of the patients, of whom eight patients had moderate constipation and two patients had severe constipation. Three of the patients with constipation had regular soiling. Urological dysfunction over the age of five was present in two patients, one patient had intermittent incontinence of urine and one had continuous incontinence of urine. Two patients under the age of five had continuous incontinence for which one patient was on clean intermittent catheterization. Neurological symptoms were present in one patient who had a gait disturbance caused by a tethered cord.

**Adult patients**

Patient characteristics and histological diagnoses are presented in Table 12.3 and Table 12.4. Seven patients were treated surgically at adult age: one male and six females. The median age was 23 (range 18-66) years at presentation. One patient was already known to have Currarino syndrome during childhood due to family screening, but she presented with pain at the age of 19. In one patient the tailgut cyst degenerated into a malignant adenocarcinoma. All patients presented with complaints of pain, mainly located at the sacrum. In five patients the tumour was evident at rectal digital examination. Three patients underwent multiple fistula operations before definite diagnosis was made. The adolescent patient known to have Currarino syndrome had a sacral bony defect on X-ray. This defect was not observed in the other patients. None of the adult patients had an anorectal malformation or a tethered cord. In six patients the presacral mass was removed via a posterior sagittal approach, in three of them the coccyx was removed. One patient underwent an abdominoperineal resection with extirpation of the coccyx. Median follow-up after initial surgery was 18 months (range 32 days - 44 months).
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at first presentation</th>
<th>Present mass</th>
<th>Symptons</th>
<th>Clinical features</th>
<th>Genetic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>prenatal</td>
<td>none</td>
<td>none</td>
<td>contraction, sacral pain</td>
<td>not assessed</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>prenatal</td>
<td>none</td>
<td>none</td>
<td>contraction, sacral pain</td>
<td>not assessed</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>0 weeks</td>
<td>lipoma</td>
<td>constipation, anal stenosis</td>
<td>VATER deletion, no 22q11 deletion</td>
<td>not assessed</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>0 weeks</td>
<td>mature teratoma</td>
<td>urological problems, constipation, anal stenosis</td>
<td>7q36 deletion, not located</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>0 weeks</td>
<td>mature teratoma</td>
<td>urological problems, constipation, anal stenosis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>0 weeks</td>
<td>mature teratoma &amp; neonatal bowel obstruction</td>
<td>anal stenosis</td>
<td>mosaic trisomy chromosome 13</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>0 weeks</td>
<td>benign teratoid tumour &amp; anterior meningocele</td>
<td>constipation, anal atresia, RP fistula</td>
<td>familial inversion chromosome 22</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>0 weeks</td>
<td>mature cystic teratoma &amp; intradural teratoma</td>
<td>constipation, anal stenosis</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>0 weeks</td>
<td>ruptured dermoid cyst</td>
<td>constipation, sacral pain</td>
<td>none</td>
<td>not assessed</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>3 weeks</td>
<td>mature teratoma</td>
<td>constipation</td>
<td>none</td>
<td>no HLXB9 mutation</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>8 months</td>
<td>lipoma</td>
<td>constipation, anal stenosis, RP fistula</td>
<td>+ no HLXB9 mutation</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>20 months</td>
<td>yolk sac tumour</td>
<td>constipation, sacral dimple, urinary retention, constipation</td>
<td>unknown variant, unclassified mutation, HLXB9 gene</td>
<td>not assessed</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>21 months</td>
<td>mixed malignant germ cell tumour (yolk sac tumour in malignant teratoma)</td>
<td>abdominal pain, sacral pain, swelling and hematoma, constipation</td>
<td>none</td>
<td>not assessed</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>3 years</td>
<td>mature teratoma</td>
<td>sacral pain, swelling and hematoma, sacral dimple</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>4 years</td>
<td>hamartoma</td>
<td>constipation, anal stenosis</td>
<td>-</td>
<td>unclassified variant, HLXB9 gene</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>4 years</td>
<td>chordoma</td>
<td>constipation, sacral pain, swelling, hematoma</td>
<td>-</td>
<td>not assessed</td>
</tr>
</tbody>
</table>
Table 12.4 – Summary of clinical data, pediatric patients (n=16).

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age first presentation</th>
<th>Presacral mass</th>
<th>Symptoms</th>
<th>Sacral defect</th>
<th>ARM</th>
<th>Tethered cord</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>F</td>
<td>18 yr</td>
<td>tailgut cyst</td>
<td>sacral pain, diarrhea, recurrent fistulas</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>19 yr</td>
<td>mature teratoma &amp; anterior meningocele</td>
<td>constipation, dysmenorrhea, dyspareunia, sacral pain</td>
<td>+</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>21 yr</td>
<td>dermoid cyst</td>
<td>perianal pain, abscess with recurrent fistulas</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>23 yr</td>
<td>dermoid cyst</td>
<td>lower abdominal pain, constipation with diarrhea</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>36 yr</td>
<td>mature teratoma</td>
<td>pain, pyrexia, constipation</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>61 yr</td>
<td>tailgut cyst</td>
<td>perineal &amp; sacral pain</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>66 yr</td>
<td>adenocarcinoma in tailgut cyst</td>
<td>lower abdominal pain, constipation, recurrent fistulas</td>
<td>-</td>
<td>none</td>
<td>-</td>
<td>not assessed</td>
</tr>
</tbody>
</table>

ARM = anorectal malformation, *Patients 15 and 18 are first cousins
Presacral masses in children and adults

Surgical outcome

Bowel movement classification at outpatient follow-up showed two continent patients, two patients mildly constipated, one moderately constipated and two patients with a colostomy, one after an abdominoperineal resection and one because of severe soiling. None of the patients had urological dysfunction. One patient had neuropathic pains of the S2 and S3 dermatome postoperatively, which persisted until present time. No neurological dysfunction was present in any of the adult patients.

DISCUSSION

The current study surveyed the spectrum of congenital presacral masses in children and adults, with special attention to type of presentation, origin of the mass and to the development of malignancies. The vast majority of the group of children presented with constipation. Pain in the sacral region and urological problems were also seen. All adult patients initially presented with complaints of pain, mainly sacral, perianal or lower abdominal pain. These non-specific symptoms are often caused by compression, displacement or invasion of pelvic structures and have been misdiagnosed frequently and have even been surgically treated, e.g. for fistulae in ano or pilonidal cyst.\textsuperscript{11,14} Lesions were evident in rectal digital examination in 78% of the patients. These findings are in accordance with results described in other studies; in a large series of presacral tumours, Jao \textit{et al.} found that the tumours were palpable on rectal examination in 97%.\textsuperscript{3} In both groups there was a female prelominance, consistent with different series of patients with presacral tumours, sacrococcygeal teratoma and Currarino syndrome.\textsuperscript{2,6,14,15} In the pediatric group mature teratoma was the tumour histology most frequently observed. All tumours that were diagnosed in the first year of life were benign at the time of surgery. Three malignancies occurred at the ages of 20 months, 21 months and 4 years. In this study, they represent 50% of the pediatric patients with symptoms starting after the age of one year. In a study in the Netherlands over the period of 1970-2003, Derikx \textit{et al.} showed that in all types of sacrococcygeal teratomas the risk of malignancy increases with age, at birth the risk was 1.5%, but sacrococcygeal teratomas discovered after the age of one year had a risk up to 40% of being malignant.\textsuperscript{16} Mature teratoma is a benign well differentiated tumour with
a minimal risk of malignant degeneration, however some studies suggest that the risk of malignancy rising in a mature teratoma increases with time and thus with age.\textsuperscript{16–18} Although this theory is still matter of discussion, treatment \textit{i.e.} surgical exploration should commence at the earliest convenience. The findings in the pediatric group clearly differ from adult group where mostly developmental cysts were seen. In the latter group malignant degeneration was observed in a tailgut cyst in a 66 year old patient. The exact risk of malignancy rising in cystic lesions of any type in adults remains unclear but is estimated between 10 and 60%. Solid lesions are more likely to be malignant than cystic lesions.\textsuperscript{2,11,14} Malignancy in tumours as part of the Currarino syndrome has so far been reported in three children and four adults.\textsuperscript{8,19–22} Based on clinical and radiological features nine children were diagnosed with a presacral tumour as part of the Currarino syndrome, and a mutation of the \textit{HLXB9} gene on chromosome 7q36 was detected in one out of the four patients tested. Apart from one 19-year old adolescent member of a Currarino family, none of the adult patients showed a bony sacral defect on re-evaluation of magnetic resonance images, so in this series presacral tumours part of the Currarino syndrome were exclusively observed in the pediatric group. Patients with the Currarino syndrome are mostly diagnosed early in life because of functional symptoms. Only few case reports exist in which a presacral tumour as part of Currarino syndrome presents at adult age.\textsuperscript{23} Different theories exist regarding the etiology of the different types of presacral tumours. Currarino \textit{et al.} suggested a model of the ‘split notochord syndrome’, in which persistent abnormal adhesions between the endoderm (future gut) and the neural ectoderm occur before the appearance of the notochord. This causes the notochord to split or to be displaced, preventing anterior fusion of the vertebrae. A fistula may form between the gut and spinal canal, giving possible rise to a meningocele or enteric cyst. The presacral teratoma would be formed by local enteric and neuroectodermal elements combined with mesodermal elements.\textsuperscript{24} More recently, Gegg \textit{et al.} proposed a theory in which the pluripotent caudal eminence, precursor of all caudal embryo tissues, is affected. By errors in secondary neurulation or migration it would incorporate adjacent endoderm, which not only results in a trilaminar teratomatous mass but also affects the caudal spinal cord, anorectal complex, genitourinary tract, and neural crest derivatives, giving rise to the Currarino syndrome.
Presacral masses in children and adults

The occurrence of sacrococcygeal teratomas is widely believed to be the consequence of aberrant patterns of migration from primordial germ cells, the exact oncogenetic mechanisms are still being studied. The precise nature of developmental cysts remains controversial; for tailgut cysts the origin is by some believed to be in remnants of the neuroenteric canal, others believe that the embryological tailgut (the most caudal part of the hindgut) is the source of certain types of congenital cysts.

In conclusion, this series showed that congenital presacral tumours in children and adults differ in type of presentation and origin. The Currarino syndrome is almost exclusively seen in the pediatric patient because of early manifestation of functional symptoms. There is a risk of malignancy in patients older than one year, both in the pediatric as well as the adult patient, which mandates early surgical resection.

REFERENCES


Presacral masses in children and adults


Summary

In the present thesis, several aspects of surgery in the anorectal area are evaluated. The aim of this thesis was to evaluate the surgical treatment options and strategies of perianal fistulas (Part I), to critically appraise the anal fistula plug as a novel method for the definitive closure of complex perianal fistulas (Part II), and to evaluate the treatment of presacral pathology and abscesses after anastomotic leakage resulting from rectal surgery (Part III).

Part I: Surgical treatment of perianal fistulas

A perianal fistula is one of the most frequently encountered anorectal disease in today’s surgical practice. In Chapter 1 the evolution of the classification of perianal fistulas, imaging and surgical treatment options are reviewed. The aim of surgical treatment of perianal fistulas is to cure the perianal fistula with the lowest possible recurrence rate without endangering continence. When patients experience minor complaints surgical treatment is not always necessary and a wait and see policy can be chosen. The Parks’ classification was introduced in 1976 for perianal fistulas. It is an anatomical classification of perianal fistulas based on the relation of the fistula tract and the external sphincter muscle. As a result of developments in the surgical treatment of perianal fistulas it is currently advised to classify perianal fistulas into low and high perianal fistulas as this has implications for the surgical treatment. For imaging of perianal fistulas MR (Magnetic Resonance) is currently the treatment of choice. Anal endosonography is a cheap, easy and suitable alternative readily available. However, the anal endosonography requires expertise and is less useful in patients that have a history of fistula surgery as it is difficult to differentiate between fibrosis and active infection. Hydrogenperoxide can be helpful to differentiate.
between these two. However, this makes the anal endosonography less suitable for patients with a history of fistula surgery. Low perianal fistulas, situated in the lower 1/3 of the external sphincter muscle can be treated with low recurrence rates by fistulotomy. A fistulotomy is performed by dividing the tissue of the complete fistula tract from the internal to the external opening. The mucosal advancement flap is the treatment of choice for high perianal fistulas. The rationale behind the advancement flap is that the internal opening is the cause of the persisting fistula tract. By closing the internal opening, it is not possible anymore that fecal material is forced into the fistula tract during defecation. In the literature the results of surgical treatment of perianal fistulas are very inconsistent. This is partly caused by heterogeneous research designs. Often patients with fistulas of different etiologies are included, various classifications and treatment protocols were used, and sufficient follow-up is lacking. In the study presented in Chapter 2 the long-term functional outcome and possible risk factors for the development of a recurrent fistula in patients surgically treated according to a standardized treatment protocol are assessed. Between 1995 and 2003, 179 patients with low and high perianal fistulas of cryptoglandular origin were treated by fistulotomy or rectal advancement flap respectively. In these series the observed recurrence rates were 7 and 21% for low and high perianal fistulas respectively at a follow-up of 76 months. No significant risk factors for development of recurrent perianal fistulas were found in both univariate and multivariate analysis. Soiling was reported in 40% of the patients. Overall continence was not significantly different from normal reference patients.

The goal of fistula surgery for patients with Crohn’s disease is to relieve symptoms and to achieve closure in selected cases. Surgical treatment for fistulas in Crohn’s disease consists of abscess drainage, loose-setons drainage, fistulotomy, and mucosal advancement. These fistulas are often refractory to surgery and associated with recurrent sepsis, discomfort, and impaired quality of life. Active Crohn’s disease, especially proctitis, interferes with wound healing and fistula closure. Patients with perianal Crohn’s disease are studied in Chapter 3. Between 1995 and 2006, a consecutive series of patients were primarily treated by surgical drainage by incision and drainage of abscesses and seton drainage in case of insufficiently draining fistulas. Subsequently, optimization by medical therapy was pursued. Only in selected
patients without proctitis or active Crohn’s disease definitive closure by surgical intervention was attempted. In the group in which definitive closure is attempted, low and high fistulas were treated by fistulotomy and advancement flap respectively which resulted in 18% and 56% recurrence rates. There was no difference in continence between patients who were treated by loose seton drainage, fistulotomy or advancement flap. Patients treated surgically for Crohn’s perianal fistulas did worse both in terms of recurrence rates and incontinence compared to patients operated for cryptoglandular disease.

Chapter 4 assesses the use of fibrin glue in the treatment of high perianal fistulas. Fibrin glue has appeared as an alternative treatment for high perianal fistulas. The fibrin glue is injected into the fistula tract. When the glue resolves after a few weeks, fibroblasts, activated by the fibrin glue matrix, enhance fistula tract closure. The initial results were promising, with high success rates being reported. However, with increasing follow-up, the enthusiasm was tempered because of disappointing results. In the current study an attempt was made to decrease the recurrence rate of the surgical treatment of high transsphincteric perianal fistulas of cryptoglandular origin by combining mucosal advancement flap and fibrin glue installation. Between 1995 and 2006, 80 patients were operated for high perianal fistulas with an advancement flap. A consecutive series of 26 patients were treated by an advancement flap combined with obliteration of the fistula tract with fibrin glue. The overall recurrence rate was 26%. Recurrence rates for advancement flap alone and the combination with glue were 17 and 46%. Since the costs of the fibrin glue are considerable and the therapeutic effect very doubtful, it can not be recommended routinely in the adjunct of transanal rectal advancement flap treating high perianal fistulas. The rectal advancement flap remains the treatment of choice for high transsphincteric perianal fistulas of cryptoglandular origin.

A procedure often performed following fistulotomy and advancement flap is curettage of the fistula tract after fistulotomy or after closing the internal opening. Epithelialization of the fistula tract might prevent closure of the fistula tract. The aim of the study presented in Chapter 5 is to assess the incidence and origin of epithelialization of the fistula tract in patients with perianal fistulas undergoing fistulotomy. Eighteen patients with low perianal fistulas that were surgically treated by fistulotomy were included. Surgical biopsies were taken from the fistula tract from three
different locations; on the proximal side at the internal opening, in the middle of the fistula tract and near the distal end close to the external opening. In 15 of the 18 patients, squamous epithelium was found at least in one of the biopsies taken from the fistula tract. Epithelium was predominantly found near the internal opening. There was no relation between the duration of fistula complaints and the amount of epithelialization. The study demonstrated epithelialization in the fistula tract in the majority of the patients surgically treated by fistulotomy for low perianal fistulas. Curettage of perianal fistulas must therefore be considered an essential step in the surgical treatment of perianal fistulas.

Part II: Novel techniques in fistula surgery

Complex high and recurrent fistulas remain a surgical challenge. Simple division, i.e. fistulotomy, will likely result in fecal incontinence. Various surgical treatment options for these fistulas have shown disappointing results. The standard treatment for high fistulas is the mucosal advancement flap. However, this technique does not result invariably in high success rates. The anal fistula plug is developed to treat these perianal fistulas. The plug is a bioabsorbable xenograft, made of lyophilized porcine intestinal submucosa. The material has inherent resistance to infection. Furthermore, it does not produce a foreign body reaction, and becomes repopulated by own tissue in a period of about three months. The plug is designed to close the fistula tract from the internal to the external opening. The plug is easy to use and could provide a solution for perianal fistulas. Moreover, the anal fistula plug may reduce the recurrence rate, postoperative pain and incontinence. To assess the results of the anal fistula plug in patients with complex high perianal fistulas, a prospective, two-center, clinical study (PLUG trial) was undertaken which is described in Chapter 6. Between April 2006 and October 2006, a consecutive series of 17 patients with difficult therapy-resistant high fistulas were enrolled. For some of these patients, the only remaining treatment option was chronic seton drainage or a diverting ostomy. At a follow-up of seven months, 41% of the fistulas healed. In seven patients, the reason for the recurrence was the falling out of the plug. In this group of “last resort” patients, an acceptable healing rate was achieved. In Chapter 7 a randomized controlled multicenter trial is proposed. The objective of this study is to compare, in a prospective randomized way, the anal fistula plug with
Summary

the mucosal advancement flap in the treatment of high transsphincteric perianal fistulas in terms of fistula closure rate, continence, morbidity, postoperative pain, and quality of life. Patients with high perianal fistulas of cryptoglandular origin are randomized to either the fistula plug or the mucosal advancement flap. Patients will be blinded for the type of intervention i.e. anal fistula plug or mucosal advancement flap. At the final follow-up closure rate is determined by clinical examination. Follow-up is done by a colorectal surgeon, who is blinded for the type of intervention. Inclusion criteria are: age above 18 years, high anorectal fistula of cryptoglandular origin (transsphincteric, upper 2/3 of the sphinctercomplex which is confined by the puborectal sling and the end of the anal canal), and informed consent. Exclusion criteria are: no internal opening found during surgery, HIV-positive patients and Crohn’s disease. The primary endpoints of the PLUG trial are fistula closure rate and continence. Secondary endpoints are morbidity, postoperative pain, and quality of life.

The results of this double blinded multicenter trial are described in Chapter 8. Between October 2006 and 2008, 104 patients were eligible for this study. Sixty patients were randomized during surgery after fulfilling the in- and exclusion criteria. Thirty-one patients were randomized to the anal fistula plug, and 29 to the mucosal advancement flap. Four of the 31 patients (13%) reported that the plug had fallen out, all within 10 days after surgery. At a follow-up of 11 months the recurrence rates were 71% (n=22) in the anal fistula plug group and 52% (n=15) in the mucosal advancement group, which was not significantly different. The continence was not significantly different pre- and postoperatively. Postoperatively soiling was reported in the plug group and the advancement group in 29% and 48% respectively which was not significantly different. Quality of life was assessed by SF-36 and EQ-5D before surgery and after 16 weeks. The results were equal pre- and postoperative in both groups. The price of the anal fistula plug is 690 euro. As a result, the cost of the placement of the plug is 690 euro more than the mucosal advancement flap. As the plug is technically simple to install and minimally invasive, it can be considered to use as initial treatment option for high transsphincteric fistulas despite of the high costs.
Anastomotic leakage is a feared complication following colorectal surgery. It is associated with considerable morbidity and mortality. Particularly, (low) anterior resections are associated with a high leakage rate ranging from 1-24%. In case of significant anastomotic leakages a presacral abscess can develop in the pelvic area.

In Chapter 9 the incidence, the natural course and outcome of the persisting presacral sinuses resulting from anastomotic leakage were studied. Between 1997 and 2007, 25 patients were identified out of a group of 1063 patients having low anterior resection or a restorative proctocolectomy which was complicated by anastomotic leakage resulting in a chronic presacral sinus. Primary outcome parameters were the incidence of persistent presacral sinuses, the closure rate of these sinuses, the average time to closure and the rate of successful closure of the ostomy. Definitive resolution of the sinus occurred in 12 patients (48%). This was achieved in a median of 340 days (range 23-731). At final follow-up, 9 of the 25 analyzed patients had permanent fecal diversion due to recurrent abscesses or a persistent sinus. The persisting sinuses were the main cause of a permanent ostomy in these patients. Since treatment of the persistent sinus is difficult, all effort should be directed to the prevention of the development of the sinus once the anastomotic leakage has been established. In the treatment of various wounds the vacuum-assisted therapy is often used to achieve wound closure. Recently, the application of local vacuum sponge treatment has shown to be effective to treat locally contained anastomotic leakage after low anterior anastomosis in rectal cancer patients. In Chapter 10, two patients with anastomotic leakage after restorative proctocolectomy are described. The material used for the sponge is an open-pored polyurethane sponge (B. Braun Medical B.V., Melsungen, Germany). The sponge was installed transanally after examination and rinsing (saline 0.9%) of the abscess cavity using a small calibre flexible gastroscope (GIF-100 Video Gastroscope, Olympus, 9.8mm in diameter). Next, the sponge was connected to a low vacuum suction bottle (Redyon TRANS PLUS suction device), creating a constant negative pressure in the sponge. The endo-sponge was changed every 3-4 days to prevent the tissue from growing into the sponge causing painful sponge exchanges. Two patients (1 male, 18 years; 1 female 40 years) who underwent proctocolectomy because of ulcerative colitis with ileo-anal J-pouch (reservoir) reconstruction developed a localized anastomotic leakage.
without general peritonitis. This was endoscopically managed by transanal placement of an endo-sponge after a diverting ileostomy was constructed. The sponge was frequently replaced until resolution of the sinus was obtained in respectively 35 and 56 days. The use of the endo-sponge in the treatment of anastomotic leakage after ileoanal pouch anastomosis resulted in quick resolution of the presacral abscess cavity and finally healing of the anastomosis. In Chapter 11 a series of patients is described with presacral cavities associated with anastomotic leakage in the Netherlands that were treated with the endo-sponge. Between July 2006 and April 2008, 16 patients who underwent surgery for rectal cancer (n=13), or ulcerative colitis (n=3) were treated with the endo-sponge treatment after anastomotic leakage. Of the 16 patients, eight patients started with the endo-sponge treatment within six weeks after the initial surgery. In the remaining eight patients the endo-sponge treatment was started later than six weeks after the initial surgery. The cavity closed in six out of eight patients (75%) in the group that started with the endo-sponge treatment within six weeks of surgery, compared to 3 out of 8 patients (38%) in the group that started later. Closure was achieved in a median of 40 (range 28-90) days with a median amount of 13 sponge replacements (range 8-17). Endo-sponge placement can be helpful in the treatment of anastomotic leakage after colorectal surgery and might prevent a chronic presacral sinus.

Starting early with endo-sponge treatment is probably more effective than late initiation of treatment of the presacral sinus. The long-term follow-up and functional outcome of the neorectum must be awaited.

The presacral region is the space between the mesorectum and the sacrum, also referred to as the retrorectal region. It is an area of embryologic fusion of the hindgut, proctodeum, neural elements and bone. Congenital presacral tumours are seen in children and adults. The exact risk of malignancy rising in presacral lesions remains unclear and estimates differ for specific types of masses. The aim of the study presented in Chapter 12 is to survey the spectrum of these masses in both groups focusing on the type of presentation, origin of the tumour and the development of malignant tumours. The vast majority of children presented with constipation. Pain in the sacral region and urological problems were also seen. All adult patients initially presented with complaints of pain, mainly sacral, perianal or lower abdominal pain. In children mature teratomas (n=8) were mostly observed.
and three malignancies were diagnosed, all in patients over the age of one year. In the adult group mainly developmental cysts (n=5) were observed, one malignancy had developed in a tailgut cyst. The Currarino syndrome was diagnosed in nine children. Bony sacral defects typical for Currarino syndrome were present in one adult patient. This series showed that congenital presacral tumours in children and adults differ in type of presentation and origin. The Currarino syndrome is almost exclusively seen in the pediatric patient because of early manifestation of functional symptoms. There is a risk of malignancy in patients older than one year, both in the pediatric as well as the adult patient, which mandates early surgical resection.
In dit proefschrift worden verschillende aspecten van de chirurgie in de anale regio beschreven. Het doel was om de chirurgische behandelingsopties van perianale fistels te evalueren (Deel I), de anale fistel plug kritisch te beschouwen als een nieuwe methode voor de definitieve behandeling van complexe perianale fistels (Deel II) en de behandeling van presacrale pathologie en abcessen als gevolg van naadlekkage na rectale chirurgie te evalueren.

Deel 1: Chirurgische behandeling van perianale fistels

Een perianale fistel is één van de meest voorkomende aandoeningen van het gebied rond de anus in de tegenwoordige chirurgische praktijk. Het is een verbinding tussen endeldarm en de huid. In Hoofdstuk 1 worden de ontwikkeling van de classificatie, diagnostiek en de mogelijkheden voor chirurgische behandeling beschreven. Het doel van de chirurgische behandeling van perianale fistels is de klachten van de patiënt te verhelpen, waarbij de kans op een recidief en op incontinentie zo laag mogelijk is. Als patiënten weinig klachten ondervinden van de fistel, hoeft er geen operatie plaats te vinden en kan voor een afwachtend beleid gekozen worden. In 1976 werd de Parks classificatie voor perianale fistels geïntroduceerd. Dit is een anatomische classificatie die gebaseerd is op het verloop van de fistelgang ten opzichte van de buitenste kringspier. Door ontwikkelingen in de chirurgische behandeling van fistels is het praktischer een indeling te maken in lage en hoge fistels. Deze indeling heeft consequenties voor het te volgen chirurgische beleid. Voor de beeldvorming van fistels is de MRI het meest geschikte onderzoek voor de diagnostiek. Analeneo-echografie is in ervaren handen een geschikt, goedkoop en gемakkelijk toegankelijk alternatief. Het is echter moeilijk om te differentiëren tussen fibrose en
een actieve ontsteking, aangezien beide hetzelfde beeld geven. Hoewel inspuiting van waterstofperoxide dit probleem deels kan ondervangen, maakt het de endo-echografie minder geschikt voor patiënten die al vaker geopereerd zijn.

Oppervlakkige perianale fistels, die in het onderste derde deel van de externe sfincter gelegen zijn, kunnen veilig worden behandeld door middel van een fistulotomie. Een fistulotomie is het klieven van het gehele fisteltraject van de binnenste tot aan de buitenste fistelopening. Op dit moment is de slijmvliesverschuivingsplastiek de operatieve behandeling van eerste keus bij dieper gelegen fistels (hoge fistels) met een transsfincterisch verloop. Hierbij wordt een vrijgeprepareerd stuk slijmvlies over de inwendige opening in de endeldarm heen gehecht. Men veronderstelt namelijk dat deze inwendige fistelopening de oorzaak is van het persisteren van de fistel. Immers, bij elke defecatie ontstaat er een hogedrukzone in het anale kanaal en worden kleine hoeveelheden ontlasting via de inwendige opening het fisteltraject ingeperst, wat de fistel in stand houdt. De recidiefpercentages van de slijmvliesverschuivingsplastiek in de literatuur lopen sterk uiteen. Dit is waarschijnlijk het gevolg van sterk heterogene studies. Vaak worden patiënten met fistels van verschillende oorzaken geïncludeerd.

Daarnaast worden verschillende classificaties en behandelingen gebruikt en is de follow-up kort. In Hoofdstuk 2 worden de lange termijn functionele uitkomsten en mogelijke risicofactoren van het ontwikkelen van een recidiverende fistel onderzocht. In de periode van 1995 tot 2003 werden 179 patiënten met lage en hoge perianale fistels van cryptoglandulaire oorsprong geopereerd. Deze patiënten werden behandeld volgens een standaard behandelingsprotocol. Lage fistels werden gekliefd (fistulotomie) en bij hoge fistels werd een slijmvliesverschuivingsplastiek verricht. Het percentage recidieven was 7% voor de lage fistels en 21% voor de hoge fistels bij een follow-up duur van meer dan 6 jaar. Er werden geen statistisch significante risicofactoren gevonden in univariate of de multivariate analyse. De continentie was ook niet statistisch significant verschillend vergeleken met een referentiegroep patiënten.

Het doel van fistelchirurgie bij patiënten met de ziekte van Crohn is de bestrijding van de symptomen en bij geselecteerde patiënten de fistel te sluiten. Chirurgische behandeling van Crohnse fistels omvat abces drainage, (langdurige) seton behandeling, fistulotomie en slijmvliesverschuivingsplastiek. Deze fistels zijn moeilijk te behandelen en leiden regelmatig tot recidiverende ontstekingen en abcessen, ongemak en mindere kwaliteit van leven.
Actieve ziekte van Crohn, voornamelijk proctitis, hindert de wondgenezing en sluiting van de fistel. In Hoofdstuk 3 worden patiënten met de ziekte van Crohn en perianale fisteling bestudeerd. In de periode van 1995 tot 2006, werd een opeenvolgende serie van patiënten met Crohns fistels behandeld. Patiënten werden primair behandeld met chirurgische drainage door middel van incisie en drainage van eventuele abcessen en seton drainage in het geval van niet voldoende drainerende fistels. Daarbij werd de medicatie geoptimaliseerd. Alleen bij geselecteerde patiënten zonder proctitis of actieve Crohn werd een poging gedaan tot definitieve sluiting van de fistel. Bij deze patiënten werden lage fistels met een fistulotomie en hoge fistels met een slijmvliesverschuivingsplastiek behandeld. Dit resulteerde in respectievelijk 18 en 56% in een persisteerd fistel. Er was geen verschil in continentie tussen patiënten met de ziekte van Crohn die op verschillende manieren werden geopereerd of behandeld. Patiënten die chirurgisch behandeld werden vanwege Crohns fistels deden het slechter dan patiënten die geopereerd werden in verband met cryptoglandulaire fistels wat betreft het aantal recidieven en continentie.

De eerste resultaten zoals in de literatuur beschreven van het gebruik van fibrine lijm voor de behandeling van diepegelegen (hoge) fistels waren veelbelovend. Echter na verloop van tijd werd het enthousiasme getemperd door teleurstellende resultaten. Fibrinelijn wordt in de fistelgang geïnjecteerd en na een aantal weken lost de lijm op en worden geactiveerde fibroblasten aangezet tot sluiting van de fistelgang. In Hoofdstuk 4 wordt een poging gedaan om het aantal recidieven na de chirurgische behandeling van hoge transsfincterische fistels te verminderen door het combineren van de slijmvliesverschuivingsplastiek en de fibrine lijm. In de periode van 1995 tot 2006, werden 80 patiënten geïncludeerd en met een slijmvliesverschuivingsplastiek behandeld. Een opeenvolgende serie van 26 patiënten uit deze groep werden behandeld met een slijmvliesverschuivingsplastiek gecombineerd met sluiting van de fistelgang met fibrine lijm. Het recidief percentage van de gehele groep was 26%. Recidiefpercentages van de slijmvliesverschuivingsplastiek alleen versus de combinatie met fibrine lijm was 17 en 46% respectievelijk. De kosten van de fibrine lijm zijn aanzienlijk en het effect is twijfelachtig, derhalve is het niet aan te raden routinematig fibrinelijn te gebruiken in combinatie met de slijmvliesverschuivingsplastiek voor de behandeling van hoge transsfincterische fistels. De slijmvliesverschuivingsplastiek blijft de operatieve behandeling van eerste keus bij hoge perianale fistels.
met een hoog transsfincterisch verloop. Curettage van de fistelgang na een fistulotomie en slijmvliesverschuivingsplastiek wordt vaak gedaan. Het idee is om eventueel aanwezige epitheel te verwijderen. Deze epithelialisatie hindert mogelijk de sluiting van de fistelgang. Het doel van de studie in Hoofdstuk 5 is om de incidentie en de oorsprong van epitheel van de fistelgang te bepalen bij patiënten met perianale fistels die een fistulotomie ondergingen. Achtien patiënten met lage perianale fistels werden behandeld met een fistulotomie. Er werd een biopsie verricht van de fistelgang van drie verschillende locaties: aan de proximale zijde bij de inwendige opening, in het middel van de fistelgang en distaal dicht bij de uitwendige opening. In 15 van de 18 patiënten werd plaveiselepithel gevonden in ten minste een van de biopsiën. Epitheel werd voornamelijk gevonden dicht bij de inwendige opening. Er was geen relatie tussen de duur van de klachten en de aanwezigheid van epitheel. Deze studie toonde aan dat er epithelialisatie is in de fistelgang in het grootste gedeelte van de patiënten welke behandeld werden met een fistulotomie voor lage perianale fistels. Curettage van perianale fistels moet daarom gezien worden als een belangrijke stap in de chirurgische behandeling van perianale fistels.

Deel II: Nieuwe technieken in fistel chirurgie

De chirurgische behandeling van complexe hoge fistels blijft een uitdaging. Een fistulotomie verrichten bij deze hoge fistels leidt tot sluiting van de fistel. De patiënt zal echter continentieklachten ontwikkelen omdat een gedeelte van de sfincter wordt doorgenomen. In de afgelopen tientallen jaren zijn er verscheidene methoden onderzocht wat meestal teleurstellende resultaten liet zien. De standaard behandeling voor hoge fistels is de slijmvliesverschuivingsplastiek. Deze techniek resulteert echter niet in onvoorwaardelijk hoge succespercentages. De nieuw ontwikkelde anale fistel plug is bedoeld voor deze hoge fistels. Het is een oplosbare plug die is gemaakt van bewerkte varkensdarm (Surgisis, Cook Surgical Inc., Bloomington, VS). De plug sluit de fistelgang af en zorgt voor weefsel ingroei. De plug is ontwikkeld om de fistelgang te sluiten van de inwendige tot aan de uitwendige fistelopening en is gemakkelijk te gebruiken. Mogelijk is het een alternatief voor de slijmvliesverschuivingsplastiek en leidt het tot lagere recidiefpercentages, minder postoperatieve pijn en incontinentie. Om de resultaten te bepalen van de anale fistel plug bij patiënten met complexe
hoge perianale fistels is een prospectieve klinische studie beschreven in **Hoofdstuk 6**. In de periode van april 2006 tot oktober 2006 werd een opeenvolgende serie van 17 patiënten met therapie-resistente hoge fistels onderzocht. Voor sommige van deze patiënten waren de enige overgebleven opties nog chronische seton drainage of het aanleggen van een stoma. Bij een follow-up van zeven maanden, waren 41% van de fistels genezen. In zeven patiënten was de oorzaak van het voortbestaan van de fistel het uitvallen van de fistel plug. Bij deze groep van last resort“ patiënten werd een acceptabele uitkomst behaald.

In **Hoofdstuk 7** is een voorstel gedaan voor een gerandomiseerde studie. Het doel van deze studie is om prospectief de anale fistel plug en de slijmvliesverschuivingsplastiek te vergelijken voor de behandeling van hoge transsfincterische fistels. De uitkomstmaten zijn fistel sluiting, continentie, morbiditeit, postoperatieve pijn en kwaliteit van leven. Na randomisatie via de computer worden patiënten verdeeld in de groep waarin de anale fistel plug of de slijmvliesverschuivingsplastiek werd gebruikt. Patiënten worden geblindeerd voor het type behandeling en aan het einde van de follow-up wordt de sluiting bepaald door klinisch onderzoek. De follow-up wordt gedaan door een chirurg die geblindeerd is voor de uitslag van de randomisatie. Inclusie criteria zijn; leeftijd boven 18 jaar, hoge perianale fistels (transsfincterisch) en informed consent. Exclusie criteria zijn; geen inwendige opening gevonden peroperatief, HIV-positieve patiënten en patiënten met de ziekte van Crohn. De primaire uitkomstmaten zijn sluiting van de fistel encontinentie. Secundaire uitkomstmaten zijn morbiditeit, postoperatieve pijn en kwaliteit van leven. De resultaten van dit dubbel geblindeerde onderzoek zijn beschreven in **Hoofdstuk 8**. In de periode van oktober 2006 tot 2008 werden 104 patiënten geschikt bevonden voor deze studie. Zestig patiënten werden gerandomiseerd tijdens chirurgie nadat aan de in- en exclusie criteria werd voldaan. Eenendertig patiënten werden gerandomiseerd voor de anale fistel plug en 29 voor de slijmvliesverschuivingsplastiek. Vier van de 31 patiënten (13%) rapporteerden dat de plug uitgevallen was. Alle vier vielen uit binnen 10 dagen na de operatie. Bij een follow-up van 11 maanden waren de recidiefpercentages 71% (n=22) in de anale fistel plug groep en 52% (n=15) in de slijmvliesverschuivingsplastiek groep, wat niet significant verschillend was. De post-operatieve pijnscores waren niet significant verschillend. De continentie was niet significant verschillend pre- en postoperatief gemeten met behulp van de COREFO,
Vaizey en Wexner vragenlijst. Postoperatief werd soiling gemeld in de plug groep en in de slijmvliesverschuivingsplastiek groep in respectievelijk 29 en 48%. Deze soiling was echter niet significant verschillend pre- en postoperatief in beide groepen. De resultaten waren gelijk pre- en postoperatief in beide groepen. De prijs voor de anale fistel plug is 690 euro. Als gevolg hiervan zijn de kosten van de plug 690 euro meer dan de slijmvliesverschuivingsplastiek. Aangezien de plug technisch gemakkelijk is te installeren en minimaal invasief, kan het gebruikt worden als eerste behandeloptie voor hoge transssfincterische fistels ondanks de hoge kosten.

Deel III: Presacrale pathologie en naadlekkages

Een naadlekkage is een ernstige complicatie na colorectale chirurgie en leidt tot aanzienlijke morbiditeit en mortaliteit. In de literatuur worden naadlekkages na lage anterieure resecties beschreven variërend van 1-24%. Bij een significante naadlekkage kan een presacraal abces ontstaan. In Hoofdstuk 9 is de incidentie, het natuurlijk beloop en de uitkomsten van de behandeling van de persisterende presacrale sinus na een naadlekkage bestudeerd. In de periode van 1997 tot 2007, werden 25 patiënten geïdentificeerd uit een groep van 1063 patiënten die een anterieure resectie of een totale proctocolectomie hebben ondergaan. Uitkomstmaten waren de incidentie, sluiting van de sinus en hoe lang dit duurde. Daarnaast werd gekeken naar mogelijkheid tot sluiting van het stoma. Definitieve sluiting van de sinus werd bereikt in 12 patiënten (48%). De sluiting van de sinus duurde 340 dagen (range 23-731). Uiteindelijk hadden negen van de 25 geanalyseerde patiënten een permanent stoma vanwege recidiverende abcessen of een persisterende sinus. Aangezien de behandeling van de presacrale sinus na een naadlekkage moeilijk is, zou alle aandacht gericht moeten worden op het voorkomen van een sinus.

In de behandeling van wonden wordt de vacuüm therapie frequent gebruikt om de wond sneller dicht te krijgen. Recent onderzoek liet zien dat het gebruik van een vacuüm spons geschikt is om een presacrale abcesholte na een naadlekkage te behandelen. In Hoofdstuk 10 zijn twee patiënten beschreven met een naadlekkage na een totale proctocolectomie. De spons (B. Braun Medical B.V., Melsungen, Duitsland) werd via de anus geplaatst na inspectie en spoelen (NaCl 0,9%) van de abces holte gebruik makend van een kleine gastroscopy (GIF-100 Video Gastroscope, Olympus, 9.8mm diameter). Aansluitend werd de spons aangesloten op een laag vacuüm
Nederlandse samenvatting

zuigsysteem (Redyron TRANS PLUS), wat een constante negatieve druk creëert in de spons. De Endo-spons werd elke 3-4 dagen vervangen om ingroei van de spons in de omliggende weefsels te voorkomen aangezien anders de sponswissels erg pijnlijk zijn. Twee patiënten (1 man, 18 jaar; 1 vrouw, 40 jaar) die een totale proctectomie ondergingen wegens colitis ulcerosa ontwikkelden een gelokaliseerde naadlekkage met een presacraal abces. Dit werd endoscopisch behandeld door plaatsing van een endo-spons nadat een stoma werd aangelegd. De spons werd frequent gewisseld totdat sluiting werd bereikt in respectievelijk 35 en 56 dagen. Het gebruik van de endo-spons voor presacrale abcessen leidt tot snelle sluiting van de holte en herstel van de naad.

In Hoofdstuk 11 is een serie patiënten beschreven met een presacrale holte na een naadlekkage in Nederland. In de periode van juli 2006 tot april 2008 werden 16 patiënten beschreven die geopereerd werden vanwege een rectumcarcinoom (n=13), of colitis ulcerosa (n=3) en behandeld met de endo-spons na een naadlekkage. Van de 16 patiënten, begon de helft met de endo-spons behandeling binnen zes weken na de ingreep. De andere helft begon later dan zes weken na de eerste operatie. De abces holte was gesloten in zes van de acht patiënten (75%) in de groep die binnen zes weken startte met de endo-spons behandeling vergeleken met drie van de acht patiënten (38%) in de groep die later is gestart. Sluiting werd bereikt in een mediane duur van 40 (range 28-90) dagen met 13 spons wisselingen (range 8-17). Endo-spons plaatsing kan mogelijk een chronische sinus voorkomen door snelle sluiting van de holte. Vroeg beginnen met de endo-spons behandeling is waarschijnlijk effectiever dan laat starten met de behandeling van de presacrale sinus. De lange termijn follow-up en de functie van het neorectum moeten afgewacht worden.

De presacrale ruimte is de ruimte tussen het mesorectum en het sacrum. Het is een ruimte waarin verschillende fusies van embryologische structuren heeft plaatsgevonden. Congenitale presacrale tumoren worden gezien bij kinderen en volwassenen. Het exacte risico op maligne ontvouwing in presacrale afwijkingen blijft onduidelijk en verschilt tussen de verschillende types tumoren. Het doel van de studie die is beschreven in Hoofdstuk 12 was om het spectrum van deze afwijkingen te beschrijven en de aandacht te richten op de presentatie, oorsprong van de tumor en de het voorkomen van maligniteiten. Het grootste gedeelte van de kinderen met presacrale tumoren presenteert zich met obstipatie klachten. Daarnaast werden ook
regelmatig sacrale pijn en urologische problemen gezien. Alle volwassen patiënten
presenteerden zich met pijnklachten, meestal sacraal, perianaal of laag abdominaal.
Bij kinderen werden teratomen het meest gezien (n=8) en drie maal een diagnose
maligniteit gesteld. In de volwassen groep werden voornamelijk ontwikkelingscys-
ten (n=5) gezien. In één geval werd een maligniteit ontdekt in een tailgut cyste.
De diagnose Currarino syndroom werd gesteld bij negen kinderen. Het Currarino
syndroom is zeldzaam en bevat een ossale afwijking van het sacrum, vaak in com-
binatie met een presacrale massa en een anorectale malformatie. Het benige sacrale
defect typisch voor het Currarino syndroom was aanwezig in één volwassen patiënt.
Deze studie liet zien dat congenitale presacratal tumoren in kinderen en volwassenen
verschillen in presentatie en oorsprong. Het Currarino syndroom werd zo goed als
alleen gezien bij kinderen aangezien de functionele symptomen zich vroeg presen-
teren. Er is een risico op maligne onttaarding van deze presacratal afwijkingen in
patiënten ouder dan een jaar waardoor chirurgische excisie noodzakelijk is bij zowel
jonge als oudere patiënten.
Curriculum Vitae

Paul Jochem van Koperen was born on March 30th 1978 in The Hague, the Netherlands. After graduating in 1996 from the Vrijzinnig-Christelijk Lyceum in The Hague, he started medical school at the Catholic University of Leuven, Belgium. One year later he continued medical school at the University of Utrecht, the Netherlands and received his medical degree in 2004. The following year he worked as a surgical resident at the Tergooi Hospitals in Hilversum. In March 2006, he started his research fellowship at the surgical department in the Academic Medical Center in Amsterdam (Prof. Dr. W.A. Bemelman and Dr. J.F.M. Slors). The current thesis is the result from this work in the area where the sun does not shine. In January 2009 he became a surgical resident at the surgery department of the Gelre Hospitals in Apeldoorn (Dr. W.H. Bouma). The last part of his residency before he will become a general surgeon will be fulfilled in the Academic Medical Center in Amsterdam (Dr. O.R.C. Busch).