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# **Diagnosis and Therapy of Anal Sphincter Disorders**

**Rachel L. West**

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# **Diagnosis and Therapy of Anal Sphincter Disorders**

## **Diagnostiek en Behandeling van Anale Sfincterafwijkingen**

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To Clive, my dad



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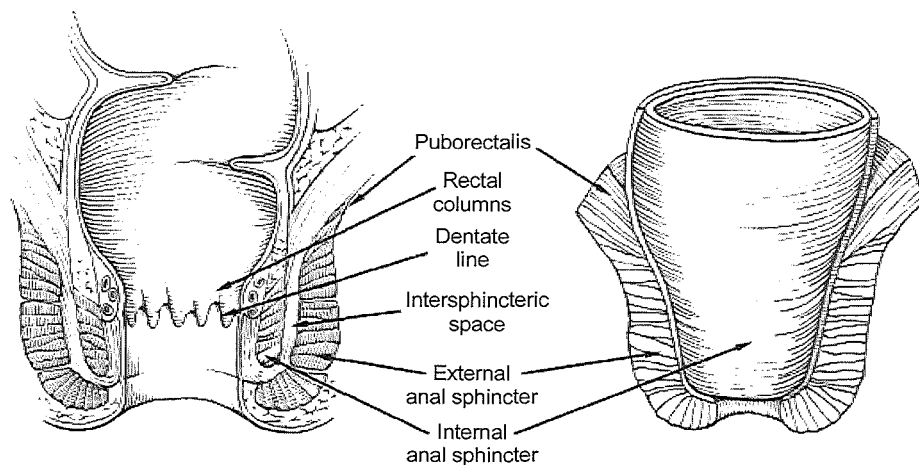
# Chapter 1

## Introduction

### ANATOMY AND PHYSIOLOGY OF THE ANAL CANAL

#### *Anatomy*

The anal canal is the most distal part of the gastrointestinal tract, starting at the anorectal junction and terminating at the anal verge.<sup>1</sup> The lining of the anal canal consists of different types of epithelium at different levels. The dentate line is located at the midpoint of the anal canal, approximately 2 cm from the anal verge. Because the rectum narrows into the anal canal, the tissue above the dentate line has a pleated appearance. These folds are known as the columns of Morgagni, and small crypts are present between these columns. Anal glands exist at the base of these crypts. The mucosa of the upper anal canal is lined with columnar epithelium. Below the dentate line the anal canal is lined with squamous epithelium. The change between these two layers is not abrupt, the 6 to 12 mm segment above the dentate line contains a gradual transition from columnar, to transitional and squamous epithelium.<sup>1</sup> Figure 1 illustrates the anatomy of the anal canal.



**Figure 1.** Anal canal anatomy.

The anal canal comprises two muscular cylinders. The inner cylinder, the internal anal sphincter (IAS), is a 3 cm long thickened continuation of the circular smooth muscle of the rectum. The outer cylinder, the external anal sphincter (EAS), is a 4 cm long downward extension of the striated puborectalis muscle.<sup>1</sup> The puborectalis muscle lies as a sling around the

rectum, pulling it forward and thus creating the anorectal angle. The intersphincteric space is located between the IAS and EAS.

The IAS receives a stimulatory sympathetic innervation and an inhibitory parasympathetic innervation. The pudendal nerve, which arises from the second, third and fourth sacral nerves, innervates the EAS. It is a mixed nerve that provides both sensory and motor function.<sup>1</sup>

### *Physiology*

The anorectum plays an important role in the regulation of defecation and in the maintenance of continence. Several factors such as rectal reservoir function, stool volume and consistency, sphincter reflexes, and anal sensation play a role in this mechanism. Angulation of the anorectal system, owing to the continuous tonic activity of the puborectalis is the most important mechanism for the conservation of gross faecal continence.<sup>1</sup> In addition, the high-pressure zone in the anal canal at rest provides an effective barrier against pressure in the rectum. The IAS and EAS both contribute to the resting tone, but the resting pressure is largely due to the IAS. The haemorrhoidal anal cushions contribute to the finest degree of continence by preventing leakage of liquid stool and mucus.

The stimulus for initiating defecation is distension of the rectum. This induces relaxation of the IAS, which triggers contraction of the EAS. If the decision is made to proceed with defecation, a squatting position will be taken up, by doing this the angulation between rectum and anal canal will be straightened out. The resistance of the EAS is overcome by the Valsalva manoeuvre, the intra-thoracic and intra-abdominal pressure are voluntarily increased. The pelvic floor descends and intrarectal pressure is increased by pressure on the faecal mass in the rectum. The faecal bolus passes due to inhibition of the EAS. After evacuation, the pelvic floor and anal canal muscles regain their resting activity, and the anal canal is closed again.<sup>1</sup>

## **ANORECTAL INVESTIGATIONS**

Different techniques are available to study anorectal structure and function. In this thesis three-dimensional endoanal ultrasonography (3D EUS) and endoanal magnetic resonance imaging (MRI) were used. In addition, anal manometry was used for testing anal function. Other tests for assessing anal function are sphincter electromyography and pudendal nerve terminal motor latency. These tests are not further described here as they are beyond the scope of this thesis.

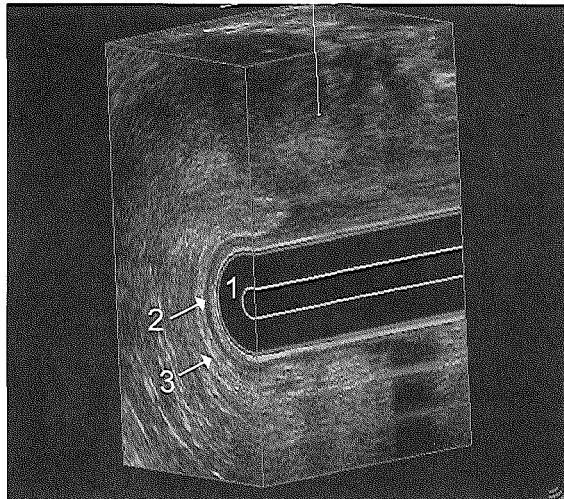
### *Imaging of the anal sphincters*

Endoanal ultrasonography (EUS) is a well-established technique, which is used to evaluate the anal sphincters.<sup>2</sup> A rotating 7 MHz or 10 MHz transducer providing a 360° view is generally used. The low reflective

ring of the IAS is the clearest landmark. The EAS is defined more easily in men because of its low reflectivity, in woman the sphincter is mainly hyperreflective.<sup>3</sup>

EUS provides an ideal tool for assessing the presence of sphincter defects in faecal incontinent patients<sup>4,5</sup> and has also highlighted the role of obstetric trauma in women presenting with incontinence immediately after delivery or at menopause.<sup>6</sup> Furthermore, good correlation with histological<sup>7</sup> and surgical<sup>8,9</sup> findings has been found for sphincter defects. The reproducibility for anal canal measurements using EUS is relatively poor, however not investigator dependent.<sup>10</sup> In addition, good reproducibility has been found for detecting sphincter defects.<sup>10</sup> One of the main indications for EUS is to detect faecal incontinent patients, which have an EAS defect amenable for surgical repair. EUS is also an excellent technique for assessing perianal fistulas, especially when hydrogen peroxide is used as a contrast medium.<sup>11-13</sup>

Not only two-dimensional but also three-dimensional EUS is now available,<sup>14-16</sup> which provides multiplanar imaging of the anal canal. In addition, this technique enables mapping of the location and dimensions of sphincteric components along the length of the anal canal. This yields more information on the anal sphincter complex and makes it easier to perform measurements of the anal sphincters. Figure 2 shows a normal 3D EUS image of the anal sphincters.



**Figure 2.** 3D EUS image of a normal anal sphincter, showing the probe (1), and the internal (2) and external anal sphincters (3).

Magnetic resonance imaging (MRI) is also an accepted technique for assessing anal sphincters.<sup>3</sup> Different techniques for MRI are available.

Initially MRI was performed with a bodycoil, which may give additional information on structures further away from the anal canal, but more detail can be obtained when the receiver coil is placed closer to the structure.<sup>3</sup> With an endoanal coil the depiction of the normal anal sphincter complex on MR images is excellent.<sup>17</sup> This technique correlates well with cross-sectional anatomy.<sup>18</sup> The IAS is seen as a relatively hyperintense structure and the EAS as a hypointense structure.<sup>3</sup>

EUS is superior to MRI for assessing the IAS,<sup>19</sup> both techniques are equivalent in assessing the EAS.<sup>19,20</sup> However, only endoanal MRI has been used to detect EAS atrophy. This has been confirmed with histology of muscle biopsies<sup>21</sup> and has found to be associated with poor clinical outcome of a sphincter repair in incontinent patients.<sup>22</sup>

### *Anal manometry*

Anal manometry is used to assess anal sphincter pressures as well as anorectal sensory response, rectoanal reflexes and rectal compliance.<sup>23</sup> The two major components of the manometric system are the manometry<sup>24</sup> probe and the pressure recording apparatus. Different probes are available.<sup>24</sup> The water-perfused catheter is the most commonly used, and in addition a station pull through technique can be used. The methods used for conducting and analysing anorectal manometry have not been standardised. Measurements should be compared against normal values obtained in age- and gender-matched subjects by the same technique.<sup>24</sup>

For anal sphincter function the resting anal pressure and the maximum squeeze pressure can be determined. The IAS maintains approximately 80% of the resting anal tone. The EAS makes a smaller contribution to the resting pressure and also generates the squeeze response.

## **ANAL SPHINCTER DISORDERS**

Disturbances in the functioning of the anal canal can lead to faecal incontinence or to constipation due to an evacuation disorder. Other anal disorders are haemorrhoids, anal fissures, perianal abscesses, and fistulas. This thesis focuses on anal sphincter disorders. The main disorders studied are faecal incontinence and perianal fistulas.

### *Faecal incontinence*

Faecal incontinence can be defined as the loss of anal sphincter control and the consequent inability to defer the call to defecation to a socially acceptable time and place. The result may be either unawareness of or inability to prevent unwanted release of gas, liquid or solid stool. The prevalence of faecal incontinence increases with age, but the disorder is present in all age groups and both sexes.<sup>25</sup> Nursing home residence is by

far the most prominent association with faecal incontinence, with a prevalence approaching 50%.<sup>25</sup>

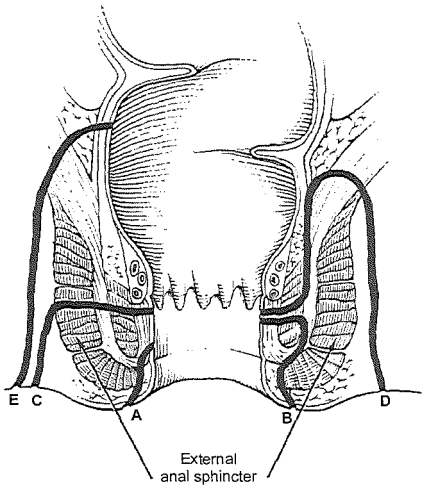
Faecal incontinence occurs when one or more mechanisms that maintain continence are disrupted to an extent that other mechanisms are unable to compensate. Faecal incontinence is often multifactorial.<sup>26</sup> Different causes of faecal incontinence are sphincter trauma, loss of rectal capacity or compliance, congenital anomalies, IAS disease, EAS denervation, reduced stool consistency, and neurological disease.<sup>27</sup> Obstetric trauma is one of the most common factors identified.<sup>27</sup> It used to be believed that most women with faecal incontinence had pelvic floor and sphincter degeneration secondary to pudendal nerve neuropathy from birth trauma. As EUS has allowed accurate imaging of the anal sphincters, this technique has emphasised that tears of the anal sphincter complex are also a main cause of faecal incontinence.<sup>2,4</sup> EAS defects can present at the time of delivery as a third-degree tear, however in many women the sphincter trauma initially is occult.<sup>6</sup> Anorectal surgery is the most common factor identified in men with faecal incontinence.<sup>27</sup>

Depending on the cause of faecal incontinence, different treatment modalities are available. An overlapping sphincter repair is the most common surgical procedure for patients with an EAS defect. Other surgical options are electrically stimulated muscle transfer procedures, the implantation of an artificial sphincter, and sacral nerve stimulation.<sup>28</sup> Conservative treatment can be the use of pads, an anal plug, and biofeedback training.<sup>27</sup> Fibre supplements may be helpful in increasing stool bulk; this may be effective for patients with loose or watery stools. However, when stool consistency is more normal, dietary fibre can be reduced so that a smaller and firmer stool can be produced.<sup>27</sup> Medical treatment such as antidiarrheal agents aims at decreasing intestinal motility and stool frequency resulting in more formed stools.<sup>29</sup>

### *Perianal fistulas*

A fistula tract is a chronic tract of granulation tissue connecting two epithelial lined surfaces. Perianal fistulas probably result from an anal gland abscess that serves as the point of origin for a fistula tract.<sup>30</sup> Anal glands that exist at the base of the anal crypts become infected and penetrate into the intersphincteric space. From the intersphincteric space, a fistula can penetrate through the EAS and track downwards to the skin or upwards in the intersphincteric space, leading to the different types of perianal fistulas commonly seen. The most accurate fistula classification system is that of Parks which uses the EAS as a central point of reference (figure 3).<sup>30</sup>

This classification system describes the primary fistula tract, which links the internal and external opening. Secondary tracts can complicate fistulas. Perianal fistulas can be cryptogenic; these fistulas arise from infected anal glands as described previously.



**Figure 3.** Classification of perianal fistulas according to Parks: a superficial fistula is located below the IAS and EAS (A), an intersphincteric fistula is located between the IAS and EAS (B), a transsphincteric fistula tracks from the intersphincteric space through the EAS (C), a suprasphincteric fistula leaves the intersphincteric space over the top of the puborectalis and penetrates the levator muscle before tracking down to the skin (D), an extrasphincteric fistula is located outside the EAS and penetrates the levator muscle into the rectum (E).

However, perianal fistulas also occur in patients with Crohn's disease. The aetiology of these fistulas is thought to be the same as for cryptoglandular fistulas but penetration of fissures or ulcers in the rectum or anal canal could also play a role.<sup>32</sup> Perianal fistulas in Crohn's disease are often more complex.

Different diagnostic techniques are available for assessing perianal fistulas.<sup>33</sup> Examination under anaesthesia can be performed, and MRI and EUS enable visualisation of fistulas. EUS combined with hydrogen peroxide as a contrast medium improves visualisation. A fistula tract can be seen as bright hyperechogenic on EUS and therefore active fistulas are distinguished from fibrotic tissue.<sup>11-13,34</sup> This makes it easier to identify a fistula tract as well as secondary tracts and the internal opening.

Cryptoglandular fistulas are mainly treated surgically. Different surgical techniques such as fistulotomy, fistulectomy and a transanal advancement flap repair exist, however detailed description of these surgical procedures is beyond the scope of this thesis. There are different treatment options for perianal fistulas in Crohn's disease. For medical treatment antibiotics such as ciprofloxacin and metronidazole can be used. Other options are azathioprine, 6-mercaptopurine and infliximab. Cyclosporine and tacrolimus are only considered for selected patients who do not respond to other treatment.<sup>32</sup> In addition, non-cutting setons can be placed for adequate drainage.<sup>32</sup> The decision for performing surgery should be taken cautiously because these fistulas are often complex and relapse is quite common. Multiple operations might damage the anal sphincters and thus lead to faecal incontinence.

## **AIMS AND OUTLINE OF THE THESIS**

This thesis aims at the diagnosis and treatment of anal sphincter disorders. Its main focus is on the role of 3D EUS in the evaluation of the normal anatomy and disorders of the anal sphincters.

EUS can be used to assess various disorders of the anal sphincters. In Chapter Two an overview is given of all 3D EUS examinations performed in the Erasmus MC between April 2001 and April 2004.

3D EUS enables volume measurements of the anal sphincters. These measurements may provide more insight in anal sphincter morphology and disorders. We therefore studied sphincter volumes, EAS length and thickness in healthy controls and faecal incontinent patients using 3D EUS (Chapter Three).

Endoanal MRI is another well-established technique for evaluation of the anal sphincters. Although both EUS and endoanal MRI are used for assessing the anal sphincters in faecal incontinent patients, only endoanal MRI has been used for detecting EAS atrophy, which condition is associated with poor clinical outcome of a sphincter repair. We aimed to establish whether 3D EUS measurements could be used to detect EAS atrophy. For this purpose 3D EUS measurements were compared to endoanal MRI measurements in patients with faecal incontinence (Chapter Four).

Surgery in the anorectal region may damage the anal sphincters. This is relevant for patients who undergo an ileal pouch-anal anastomosis after proctocolectomy for severe ulcerative colitis or familial adenomatous polyposis. In addition, the colonic pouch-anal anastomosis is a technique that was designed for the treatment of low rectal cancer. Both techniques are used for restorative bowel surgery while preserving the anal sphincters. Pouch surgery is associated with reduced postoperative anorectal function. Many studies have reported on this but studies on sphincter damage are scarce. We assessed whether pouch-anal anastomosis surgery damages the anal sphincters using 3D EUS. For this purpose, the aspect of the anal sphincters as well as sphincter volume, length and thickness were determined prior to and after surgery using 3D EUS (Chapter Five).

Accurate preoperative assessment of perianal fistulas is necessary for optimal surgical treatment. EUS and endoanal MRI can both be used for this purpose. Several studies have compared these two techniques. However, the results differed as different techniques for EUS and MRI were used. Furthermore, administration of hydrogen peroxide into the external opening of the fistula tract, a technique which significantly improves the visualisation of these tracts on EUS, was not used in any of these studies. We therefore studied the agreement between 3D hydrogen peroxide-enhanced EUS (HPUS) and endoanal MRI for the preoperative evaluation of perianal fistulas and compared these results to the surgical findings (Chapter Six). In a second study, with a larger number of patients and a

shorter time interval between the two investigations, only 3D HPUS and endoanal MRI were compared for their performance in the evaluation of perianal fistulas. In addition, patient discomfort and preference for either investigation were taken into account (Chapter Seven).

Treatment of perianal fistulas in Crohn's disease is complex. Ciprofloxacin is moderately effective for treating perianal fistulising Crohn's disease but symptoms reoccur after treatment is discontinued. Infliximab is effective but repeated infusions are usually required. Several imaging studies have reported that infliximab therapy may lead to closure of the external opening, but fistula tracts remain visible on MRI and EUS. A double-blind placebo-controlled study was conducted, to evaluate whether a combination of ciprofloxacin and infliximab is more effective than infliximab alone. Clinical and 3D HPUS findings were used for evaluation (Chapter Eight).

The exact mechanism by which ciprofloxacin has an effect on perianal fistulas in Crohn's disease is unclear. Little is known about the flora, which is involved in these fistulas or the effect of antibiotic treatment on this flora. We aimed to establish which microorganisms are found in perianal fistulas in Crohn's disease and to determine whether additional treatment with ciprofloxacin and infliximab affects these microorganisms (Chapter Nine).

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# Chapter 2

## Three year experience of three-dimensional endoanal ultrasonography

### INTRODUCTION

Imaging has become increasingly important in the management of patients with anorectal disease. Endoanal ultrasonography (EUS) has opened a new field of imaging of the anal sphincters. Ultrasound images are very detailed, and it is tempting to assume that they show an exact histological representation. However, the image is purely based on acoustic reflections and different structures can be distinguished because of tissue dependent reflection. The anal sphincters are best visualised with an endoprobe for optimal penetration depths and circular presentation of the sphincters.

EUS originates in the field of urology, where the technique was used for transrectal imaging and puncturing of the prostate.<sup>1</sup> It was also found to be a reliable technique for staging and follow-up of rectal tumours.<sup>1</sup> Law et al.<sup>2</sup> were the first to report on its use for examining the anal sphincters. EUS is easy to perform and causes no more discomfort than digital examination. In addition, the anal sphincters can be clearly imaged and clear distinction is possible between the internal (IAS) and external (EAS) anal sphincter. The use of EUS for evaluating the anal sphincters has shown that sphincter defects are an important cause of faecal incontinence.<sup>3</sup> In addition, EUS is also a well-established technique for evaluating perianal fistulas,<sup>4</sup> especially when this technique is combined with the use of hydrogen peroxide.<sup>5,6</sup>

With the availability of three-dimensional EUS (3D EUS) it is now possible to reconstruct transversal images of the anal canal in the coronal and sagittal planes. This makes it easier to map the location and dimensions of the sphincters along the anal canal. This yields more information on the anal sphincter complex and its disorders. Another benefit of 3D EUS is that it produces a digital volume that can be reviewed in its entirety and it therefore enables reviewing of paired examinations. Since April 2001 we have used 3D EUS in our centre for evaluation of patients with anal sphincter disorders. In this chapter an overview is given of these patients and the anal disorders seen between April 2001 and April 2004.

## PATIENTS AND METHODS

All EUS examinations performed in our centre between April 2001 and April 2004 are described in this chapter. The main indications for performing EUS were faecal incontinence, perianal fistulas, perianal Crohn's disease and rectal tumours. Others reasons were constipation, perianal pain, anal fissures, and the evaluation of anal sphincters prior to surgery.

In our centre EUS is performed using a 3D diagnostic ultrasound system (Hawk type 2102, B-K Medical) with a 7 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) producing a 360° view. The endoprobe is covered with a hard sonolucent cone (diameter 1.7 cm) filled with degassed water for acoustic coupling and is covered with a lubricated condom. No specific bowel preparation is required. Patients are positioned in the left lateral position. The endoprobe is introduced into the rectum and serial radial images are made of the distal part of the rectum, the puborectalis muscle, and the EAS and IAS.

Three-dimensional images are reconstructed by a 2D setup connected to a frame-grabbing computer. Using a pullback device, it takes 30 seconds to withdraw the probe slowly during frame grabbing at a velocity of 2 mm/sec. The data volume is viewed in a software program used for three-dimensional reconstruction (Life Imaging System 2000, L3Di version 3.5.5). This technique enables axial images of the anal canal to be reconstructed in the coronal and sagittal planes.

The smooth muscle of the IAS is clearly identifiable as a homogenous hypoechoic circular band. The striated muscle of the EAS has a mixed echogenic aspect. Proximal to the EAS the puborectalis muscle (PR) can be easily visualised and is often used for orientation in the anal canal. It has a V-shaped configuration as well as an echogenic aspect. The submucosa can also be seen on EUS and has a mixed echogenic aspect. It is partly collapsed by pressure of the endoprobe. The longitudinal muscle is often neglected. It forms a conjunction between the IAS and EAS and fuses proximally into the longitudinal muscle layer of the rectal wall. It appears as an echogenic band between the IAS and EAS but is not visible in all patients.

Fistula tracts are visualised as tube like hypoechoic lesions on EUS. After conventional EUS we introduce hydrogen peroxide (3%) into the fistula tract with a flexible intravenous cannula (Venflon®, Ohmeda, Helsingborg, Sweden) and repeat EUS. The infusion of hydrogen peroxide generates the formation of small airbubbles and the appearance of a fistula tract on EUS changes from hypoechoic to bright hyperechoic. By comparing the images obtained with and without hydrogen peroxide, the fistula tract and its extensions can be identified and discriminated from previous scars. This makes it possible to distinguish active fistulas from fibrotic tissue in previously operated patients. The internal opening is seen as an echogenic breach at the level of the submucosa. A fluid collection is

defined as the presence of a hyperechoic cavity localised in the peri-anorectal structures distinguishable from the primary fistula tract.

The rectal wall has a typical five-layer appearance on EUS. These layers are a bright interface reflection from the mucosal surface, low reflective layer of the deep mucosal layer, bright reflective layer of submucosa, low reflective layer of muscularis mucosae, bright interface reflection from the outer border of the muscle layer and adventitial fat. Rectal cancers are generally of low reflectivity and can therefore be distinguished from more reflective layers such as the submucosa and the perirectal fat. The EUS criteria for T staging of rectal tumours are presented in table 1.

**Table 1.** EUS criteria for T staging of rectal tumours.

T stage	Criteria
T1	Submucosal penetration with deepest part still intact
T2	Muscularis propria penetrated but outer aspect intact
T3	Disruption of outer border of the muscularis propria with tumour budding or mass extension into perirectal fat
T4	Invasion of adjacent structure or peritoneum

## RESULTS

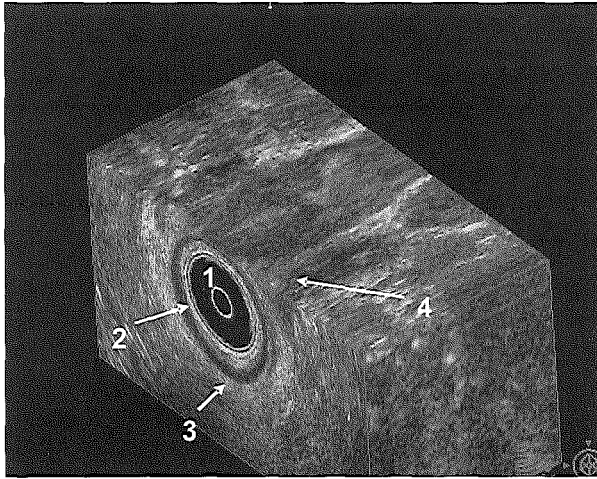
Between April 2001 and April 2004 a total of 1054 EUS examinations were performed in 943 patients (M/F 385/558, median age 49 years, range 14-89) in our centre. The main indications were faecal incontinence (338), perianal fistulas (260), perianal Crohn's disease (114), rectal tumours (48), and other disorders (183).

### *Faecal incontinence*

Of the 338 patients who underwent EUS for symptoms of faecal incontinence, 271 (80%) were female (median age 58 years, range 18-89), of whom 247 (91%) had given birth. The median number of vaginal deliveries was 2 (range 0-8) and 184 females had experienced obstetric trauma; 75 a tear, 73 an episiotomy and 36 both. In this group IAS defects were seen in 0.5% (1/184) of patients, EAS defects in 35% (65/184), combined IAS and EAS defects in 38% (69/184) and no sphincter defects in 27% (49/184). In the females who had not experienced any obstetric trauma IAS defects were found in 3% (2/63), EAS defects in 17% (11/63), combined IAS and EAS defects in 29% (18/63) and no defects in 51% (32/63). Previous anal surgery had been performed on 8 of the nulliparous females; IAS defects were seen in two, EAS defects in one, combined IAS and EAS defects in three and in two no sphincter defects. In the other 16

nulliparous females IAS defects were seen in two, EAS defects in two, combined IAS and EAS defects in one and no defects in 11.

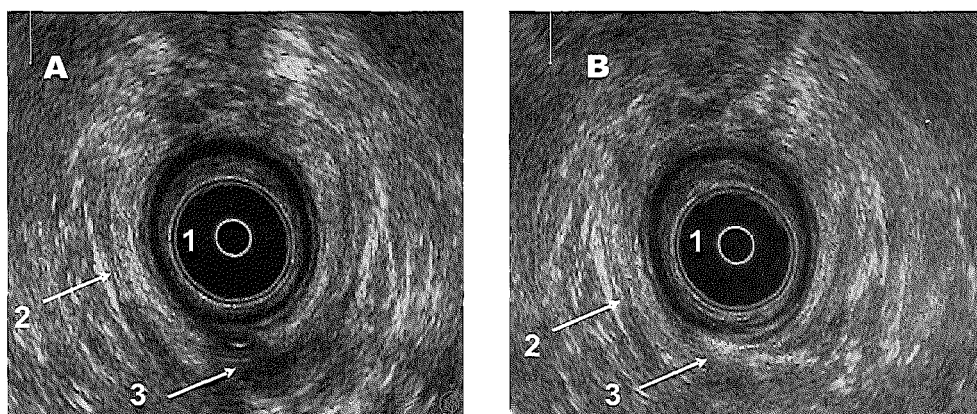
In total 67 males (median age 58 years, range 15-84) underwent 3D EUS for symptoms of faecal incontinence. Anal surgery had been performed in 35 of these patients; six had an IAS defect, four had an EAS defect, 14 had a combined IAS and EAS defect and 11 had no sphincter defects. In the other 32 males who had not undergone previous anal surgery, IAS defects were seen in three, EAS defects in five, combined IAS and EAS defects in two and no defects in 26. Figure 1 shows a 3D EUS image of an EAS defect.



**Figure 1.** EAS defect. 3D EUS image showing the endoprobe (1), the IAS (2), the EAS (3) with an anterior defect (4).

### *Perianal fistulas*

In total 260 patients (M/F 178/82, median age 42 years, range 15-78) were seen for symptoms of cryptoglandular perianal fistulas. Of these patients, 110 had undergone previous fistula surgery and 92 had undergone drainage of a perianal abscess. Hydrogen peroxide could be introduced in 177 (68%) patients but in 83 it was not possible to introduce hydrogen peroxide due to the absence of a visible external opening. An abscess only was seen in 7 patients in whom hydrogen peroxide could be introduced and in two in whom no hydrogen peroxide could be introduced. The fistula characteristics are presented in table 2. In the patients in whom hydrogen peroxide could be introduced it was possible to identify a perianal fistula in 99% (168/170) and an internal opening in 97% (165/170). However, in the group in whom no peroxide could be introduced this was only possible in 33% (20/61) for the primary fistula tract and in 5% (4/81) for the internal opening. Secondary tracts were found in the hydrogen peroxide group (43%, 73/170) but no secondary tracts were found in the patients in whom no hydrogen peroxide could be



**Figure 2.** Cryptoglandular fistula. EUS images without (A) and with (B) hydrogen peroxide showing the endoprobe (1), the puborectal muscle (2) and the fistula (3).

**Table 2.** Cryptoglandular fistula characteristics identified on 3D EUS.

	Peroxide (n=170)	No peroxide (n=81)
<i>Classification of the primary fistula tract</i>		
<i>Parks classification</i>		
Intersphincteric	5	0
Transsphincteric	148	14
Suprasphincteric	3	0
Extrasphincteric	2	0
Rectovaginal	10	6
Not classified	2	61
<i>Location of an internal opening</i>		
Identified	165	4
Not identified	5	76
<i>Secondary tracts</i>		
Identified	73	0
None seen	97	80
<i>Fluid collections</i>		
Present	10	2
Not present	160	78

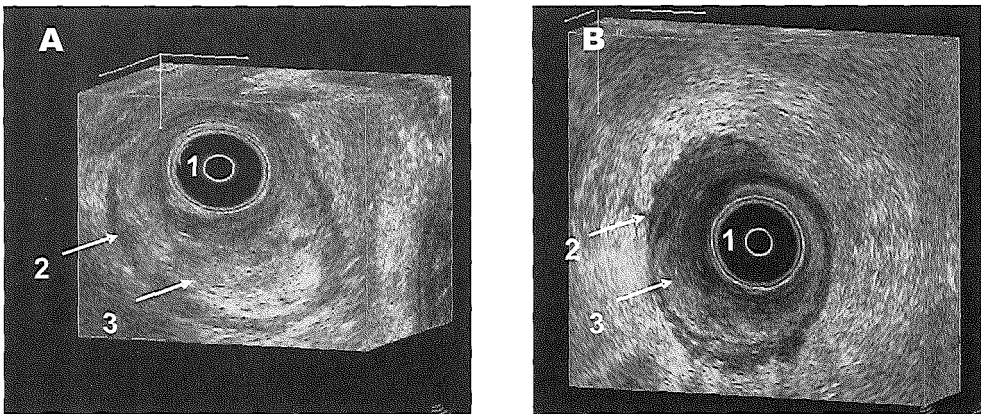
introduced. Figure 2 shows a 3D EUS image of a perianal fistula before and after introduction of hydrogen peroxide.

### *Crohn's disease*

EUS was performed in 114 patients (M/F 43/71, median age 36 years, range 14-71) with Crohn's disease. In 61 (54%) patients a perianal fistula was seen, in 12 (11%) a rectovaginal fistula, in 14 (12%) an abscess and in 27 (23%) no abnormalities could be seen on EUS. Of the 61 patients with a perianal fistula, two had an intersphincteric fistula, 53 a transsphincteric fistula, one a suprasphincteric and five an extrasphincteric fistula. Complex perianal fistulas were seen in 70% (43/61) of these patients. Complex fistulas are fistulas with secondary tracts as well as suprasphincteric and extrasphincteric fistulas.

### *Rectal tumours*

In total 48 patients (M/F 32/16, median age 61 years, range 40-87) underwent 3D EUS for a tumour. Rectal tumours were seen in 30 patients (T1: 10, T2: 4, T3: 12, T4: 4) and anal carcinomas were seen in two patients (T1: 1 and T4: 1). In one patient recurrence of a rectal tumour was suspected. However, this could not be confirmed on 3D EUS because it was not possible to distinguish fibrotic tissue from tumour recurrence. In addition, a prostate tumour was found in one patient, a GIST (gastro intestinal stroma cell tumour) in another and in 12 patients it was not possible to visualise any kind of tumour on 3D EUS. Figure 3 shows a T1 and T3 rectal tumour.



**Figure 3.** Rectal tumours. 3D EUS images showing the endoprobe (1), the muscularis propria (2), a rectal tumour (3): T1 (A) and T3 (B). Note that the muscularis propria is disrupted in image B.



### *Other disorders*

The reasons for performing 3D EUS in this group were constipation (68), perianal pain (22), preoperative assessment of the anal sphincters (41) and miscellaneous symptoms (52). Of the patients with constipation (M/F 9/59, median age 50 years, range 17-78) a thick aspect of the IAS was found in three, however no IAS myopathy was diagnosed. In the patients with perianal pain (M/F 10/12, median age 54 years, range 26-82) an abscess was seen in two and in the others no abnormalities explaining the pain symptoms could be found.

### **CONCLUSIONS**

3D EUS is able to visualise different disorders of the anal sphincters and rectum. Sphincter defects can be detected in faecal incontinent patients. The majority of patients with faecal incontinence are females who have undergone a vaginal delivery. Most of these females had experienced obstetric trauma and a sphincter defect was seen on 3D EUS. However, sphincter defects were also seen in 50% of females who had not experienced any obvious obstetric trauma. Anal surgery was the main cause of a sphincter defect in males.

Perianal fistulas, cryptoglandular as well as in Crohn's disease can be assessed using 3D EUS. The use of hydrogen peroxide makes it possible to distinguish scar tissue from active perianal fistulas and therefore the results of EUS for detecting the primary fistula tract as well as the internal opening improve.

We only have a limited experience with 3D EUS for assessing rectal tumours. It is possible to detect these tumours using 3D EUS. However, the role of 3D EUS for assessing tumour recurrence is uncertain. It is not always possible to obtain an optimal image. In addition, it can be hard to distinguish fibrotic tissue from tumour recurrence.

The value of 3D EUS in constipation is very limited as it shows very little pathology in this group of patients.

We think that 3D EUS is an excellent technique for evaluating anal sphincter disorders and we have performed several studies using this technique for evaluating anal sphincter disorders.

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# Chapter 3

## Volume measurements of the anal sphincter complex in healthy controls and faecal incontinent patients using a three-dimensional reconstruction of endoanal ultrasonography images

### ABSTRACT

#### **Purpose:**

To determine sphincter volumes, length and external anal sphincter (EAS) thickness in healthy controls and faecal incontinent patients using a three-dimensional reconstruction of endoanal ultrasonography (EUS) images.

#### **Methods:**

44 controls (15 M, 15 F, and 14 parous F) and 28 incontinent parous females (with and without a sphincter defect) were studied. Internal anal sphincter (IAS), EAS and puborectalis (PR) volume, sphincter length and EAS thickness were measured. Intraobserver and interobserver variability were assessed. Anal pressure profile was also determined.

#### **Results:**

IAS and EAS volumes were larger in males than in females ( $p=0.001$  and  $p=0.04$ ), EAS volume was smaller in parous females but this was not significant ( $p=0.084$ ). Anterior sphincter length was longer in males ( $p=0.004$ ) and shorter in parous females ( $p=0.060$ ). Males had a larger anterior EAS thickness ( $p=0.018$ ), parity made no difference. Sphincter volumes were not smaller in incontinent females. Incontinent females with a sphincter defect had a shorter anterior sphincter length compared to continent ( $p=0.001$ ) and incontinent females without a sphincter defect ( $p<0.001$ ). Anterior EAS thickness was smaller in incontinent females with a sphincter defect ( $p=0.006$ ), posterior and right EAS thickness were smaller in incontinent females without a sphincter defect ( $p=0.02$  and  $p=0.03$ ). Intraobserver variability was seen for IAS volume and sphincter length, but there was no interobserver variability. Correlation between anal pressures and EUS measurements was poor.

#### **Conclusions:**

Differences in anal sphincter volumes are seen for sex but not for parity. Faecal incontinence is not associated with loss of sphincter volume. However, anterior sphincter length and EAS thickness are smaller.

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Dis Colon Rectum 2004; in press

## INTRODUCTION

Faecal incontinence is a relative common disorder with significant impact on daily life. The majority of the affected individuals are females and incontinence is often related to a previous complicated vaginal delivery.<sup>1</sup> A recent meta-analysis suggested that the incidence of anal sphincter disruption during a vaginal delivery is 27% in primiparous females with an additional 8.5% risk for new sphincter defects in multiparous females.<sup>2</sup> The probability of faecal incontinence associated with a sphincter defect was 77%-83%.

Evaluation of faecal incontinence therefore requires visualisation of the anal sphincters. Endoanal ultrasonography (EUS) is a well-established technique which is used for this purpose.<sup>3-5</sup> In assessing sphincter defects, EUS correlates well with histological<sup>6</sup> and surgical findings.<sup>7,8</sup> The main indication for EUS in patients with faecal incontinence is to detect patients, which have an external anal sphincter (EAS) defect amenable for surgical repair. There is often good correlation between the clinical effect of a sphincter repair and changes seen with EUS and anal manometry, and postoperative persistent incontinence is associated with remaining sphincter defects visible on EUS.<sup>9</sup> Poor clinical outcome of surgical repair is associated with EAS atrophy detected on magnetic resonance imaging (MRI).<sup>10</sup> Studies on the role of EUS in assessing sphincter atrophy are scarce. A thin IAS and/or poorly defined EAS on EUS have been suggested as potential EUS markers for EAS atrophy.<sup>11</sup>

Three-dimensional EUS (3D EUS) has enabled transversal images of the anal canal to be reconstructed in the coronal and sagittal planes. Using this technique it is possible to map the location and dimensions of sphincteric components along the length of the anal canal. This yields more information on the anal sphincter complex as well as sphincter defects in faecal incontinent patients.<sup>12-14</sup>

As 3D EUS makes it possible to study the length of the anal canal, volume measurements of the anal sphincters can also be performed. Volumes are calculated by measuring the area of the anal sphincters in successive images and then multiplying the resulting two-dimensional data by the distances between the images. The distance between the images is kept constant by uniform speed of the movement of the ultrasound probe. Volume measurements could provide more insight in anal sphincter morphology and disorders and therefore also play a role in detecting sphincter atrophy and selecting patients suitable for surgical repair.

The aim of this study was to determine the normal values of volume measurements, sphincter length and EAS thickness in healthy controls and faecal incontinent patients using a 3D reconstruction of EUS images. The effect of sex and parity was also studied, as well as intraobserver and interobserver variability. The 3D EUS results were compared with anal pressure measurements.

## PATIENTS AND METHODS

Our medical ethical board approved the protocol and all participants signed informed consent. Forty-four healthy controls with no history of anal surgery or incontinence were recruited via an advertisement in the hospital. The group consisted of 15 males (mean age 28 years, range 16-64), 15 nulliparous (mean age 31 years, range 20-62), and 14 parous females (mean age 44 years, range 27-57). The median number of vaginal deliveries for the females who had given birth was two (range 1-3); 13 had experienced obstetric trauma (eight a tear, five an episiotomy).

In addition, 28 consecutive parous female patients (mean age 60 years, range 35-78) with symptoms of faecal incontinence (16 with a sphincter defect and 12 without a sphincter defect) were invited to take part in the study. The median number of vaginal deliveries in this group was two (range 1-4); eight had experienced a tear during childbirth and 16 had undergone an episiotomy.

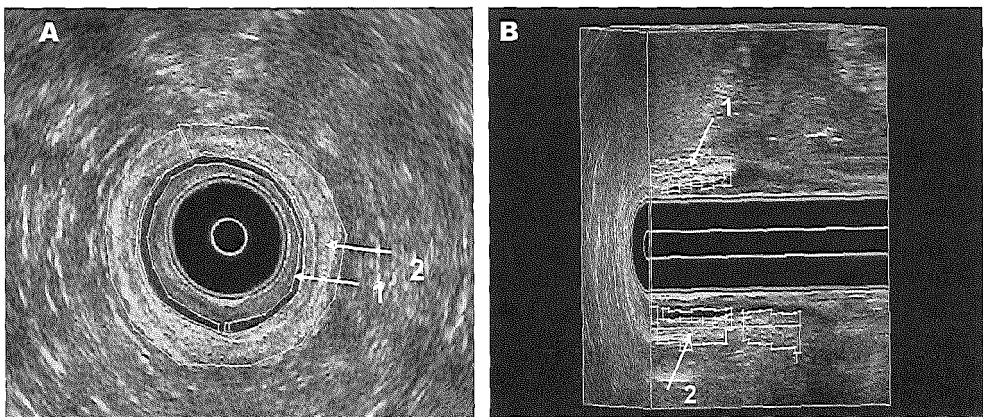
At baseline, a continence score according to Vaizey was obtained.<sup>15</sup> The Vaizey continence questionnaire assesses the presence and frequency of incontinence to solid, as well as liquid stools or flatus and assesses the presence of faecal urgency (score 0-24, 0=total continence and 24=complete incontinence to solid stool on a daily basis).<sup>15</sup> All healthy subjects had a Vaizey score of zero and all incontinent patients had a Vaizey score  $\geq 12$ . Manometry was performed using a pull-through technique (2 mm per second) with a four channel water-perfused (0.5 ml/min) catheter (MMS system, Enschede, The Netherlands). Each channel had a side hole, and the side holes were arranged around the circumference of the catheter, 90° to each other. Zero pressure calibration was done at the anal orifice level before introducing the catheter. After introduction and stabilisation in the rectum, the catheter was withdrawn. The high-pressure zone was registered. The starting point was defined as the point at which the pressure increased to more than 5 mmHg higher than rectal pressure, and the endpoint as where the pressure dropped to zero. Resting anal pressure was averaged across the four channels by using the maximum plateau phase of all channels. Sphincter length was determined by using the mean length of the high-pressure zones of the four channels. After introducing the catheter a second time, the patient was asked to squeeze at 0.5 cm intervals. The maximum squeeze pressure was calculated by averaging the highest squeeze pressures recorded by each channel.

For 3D EUS a Diagnostic Ultrasound System (type 3535, B-K Medical, Herlev, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a water filled hard sonolucent cone (diameter 1.7 cm), producing a 360° view was used. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were taken of the distal part of the rectum, the puborectalis muscle (PR), the EAS and internal (IAS) anal sphincter. Three-dimensional images were reconstructed by a 2D set-up connected to a frame-grabbing computer.

For this purpose, the probe was slowly withdrawn from the rectum in 30 seconds by means of a pullback device at a fixed speed of 2 mm/sec. The data volume was viewed in a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark).

Volume measurements were performed by determining the sum of the area of the IAS, EAS and PR measured at 0.25 mm intervals. Only muscle without scarring was included in these measurements. The most proximal point of the IAS was defined as the first level at which the IAS is seen as a clear hypoechoic ring and the most distal point as the level where the IAS is last seen as a complete ring. For the most proximal point of the EAS the distal verge of the PR was used, and for the most distal point of the EAS the termination of the subcutaneous EAS was used. The most proximal PR point was defined as the level where the PR sling is first seen as a clear sling and the most distal point as the level where the PR sling is last seen.

The anterior and posterior sphincter lengths as well as the EAS thickness were also determined. For the anterior sphincter length the distance between the lower and upper border of the EAS was measured and for the posterior sphincter length the distance between the lower border of the EAS and the upper border of the PR. The EAS thickness was measured at the 3 (left), 6 (posterior), 9 (right) and 12 o'clock (anterior) positions at the anatomical midpoint of the sphincter. Using these measurements the average EAS thickness could be determined (Figure 1).



**Figure 1.** EUS measurements in the axial and lateral plain

**A.** Axial EUS image in which the area of the IAS (1) and EAS (2) have been determined. **B.** Lateral EUS image showing the anterior (1) and posterior (2) sphincter length.

For intraobserver variability of EUS measurements of the anal sphincters, measurements were performed on two separate occasions by one of the authors (RLW) on 30 healthy controls and for interobserver variation, measurements were also performed by a second author (RJFF-B) on 10 healthy controls.

### *Statistical analysis*

Differences in normal values between males, nulliparous and parous females and differences between healthy controls and patients with faecal incontinence were compared using the Kruskal-Wallis Test (median, P value) and for correlation the Spearman's correlation coefficient was used. Volume measurement results are shown in boxplots, the upper and lower limits of the boxes indicate the 75th and the 25th percentiles, the middle line across the boxes indicates the median (50th percentile). The length of the box therefore represents the interquartile range; the box indicates 50% of the data. The upper and lower horizontal bars indicate the 90th and 10th percentiles.

The Wilcoxon Signed Ranks test and the 'limits of agreement' method according to Bland and Altman<sup>16</sup> were used to assess intraobserver and interobserver variability for volume measurements. For the latter test differences were calculated for every individual measurement and plotted against their mean. The limits of agreement are expressed as  $\pm$  two standard deviations of the mean difference and they define the range of values that will encompass the 'true' value on 95% of occasions. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

### *Healthy controls*

There were no significant differences in resting anal pressure between the male, nulliparous female and parous female healthy subjects. Males did have a significantly higher maximum squeeze pressure than nulliparous females ( $p=0.003$ ) but there was no difference between nulliparous and parous females. Mean sphincter length measured during manometry was also significantly longer in males compared to nulliparous females ( $p=0.001$ ) but again parity made no difference in females (Table 1).

No sphincter defects were found in the male and nulliparous female healthy subjects, five of the parous females however had evidence of an EAS defect.

No differences were seen with respect to PR volume. In contrast, EAS and IAS volume were significantly larger in males than in nulliparous females ( $p=0.001$  and  $p=0.04$ ). EAS volume was also larger in nulliparous females compared to parous females, however this difference was not significant ( $p=0.084$ ), there was no difference for IAS volume (Figure 2).

**Table 1.** Anal manometry results in healthy subjects and faecal incontinent parous females (median, range). The Kruskal Wallis test was used for comparison.

	Males	Nulliparous females	Parous females	Incontinent parous females	
				With SD	Without SD
Resting pressure (mmHg)	100 (55-149)	87 (53-150)	89 (62-124)	39 (21-77) <b>▷</b>	46 (20-64) <b>◆</b>
Maximum squeeze pressure (mmHg)	256 (126-378)	164 (105-255) <b>*</b>	144 (72-223)	84 (44-172) <b>†</b>	80 (43-169) <b>✱</b>
Sphincter length (cm)	3.7 (2.1-4.3)	2.6 (1.9-3.5) <b>▲</b>	2.7 (2.2-4.4)	3.3 (1.7-3.9)	2.6 (2.2-3.7) <b>❖</b>

SD sphincter defect

**\*** Males vs. nulliparous females (p=0.003)

**▲** Males vs. nulliparous females (p=0.001)

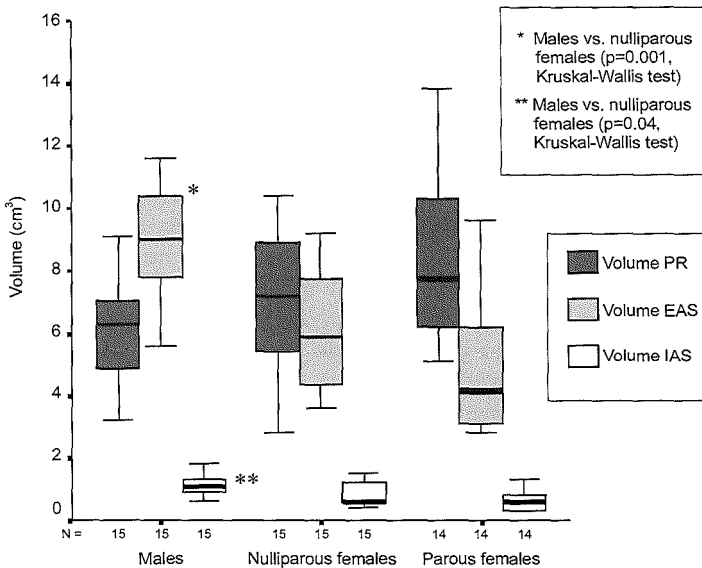
**▷** Continent parous females vs. incontinent parous females with a sphincter defect (p<0.001)

**◆** Continent parous females vs. incontinent parous females without a sphincter defect (p<0.001)

**†** Continent parous females vs. incontinent parous females with a sphincter defect (p=0.003)

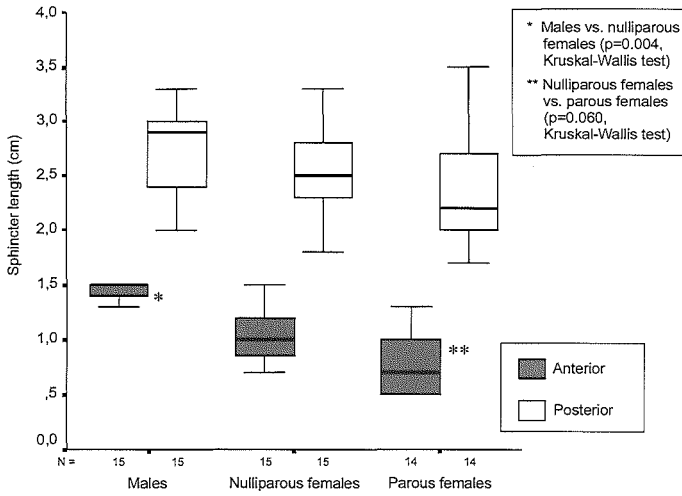
**✱** Continent parous females vs. incontinent parous females without a sphincter defect (p=0.02)

**❖** Incontinent parous females with a sphincter defect vs. incontinent parous females without a sphincter defect (p =0.04)



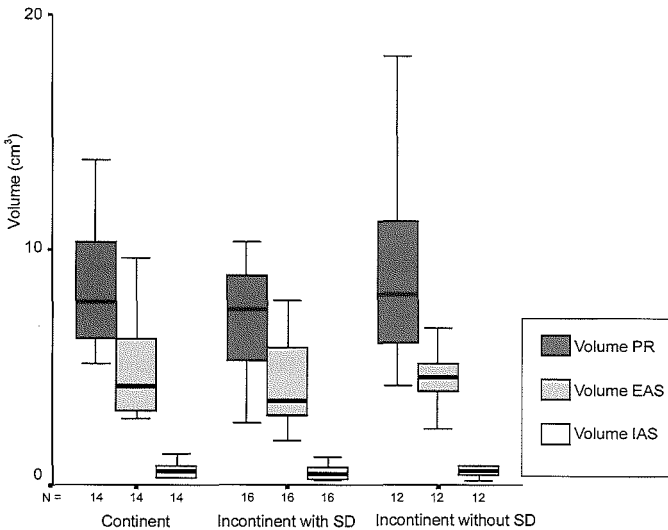
**Figure 2.** Volume measurements of the anal sphincters in healthy controls.





**Figure 3.** Anterior and posterior sphincter length in healthy controls.

Anterior sphincter length was significantly longer in males compared to nulliparous females ( $p=0.004$ ) and significantly shorter in parous females compared to nulliparous females ( $p=0.060$ ) (figure 3). Males also had a significant larger anterior EAS thickness compared to nulliparous females ( $p=0.018$ ) but there was no significant difference between nulliparous and parous females (Table 2).



**Figure 4.** Volume measurements of the anal sphincters in continent and incontinent parous females with and without a sphincter defect (SD).

### Continent and incontinent parous females

Continent parous females had a significantly higher resting anal pressure and maximum squeeze pressure than incontinent parous females with ( $p < 0.001$  and  $p = 0.003$ ) and without ( $p < 0.001$  and  $p = 0.02$ ) a sphincter defect, a sphincter defect in incontinent females made no difference. There were no significant differences between continent and incontinent parous females for sphincter length measured during manometry. However, incontinent females without a sphincter defect had a significant shorter sphincter compared to incontinent females with a sphincter defect ( $p = 0.04$ ) (Table 1).

**Table 2.** Median EAS thickness in healthy subjects and faecal incontinent parous females (cm, range). The Kruskal Wallis test was used for comparison.

	Males	Nulliparous females	Parous females	Incontinent parous females	
				With SD	Without SD
Average	0.6 (0.5-0.7)	0.5 (0.5-0.7)	0.6 (0.4-0.8)	0.5 (0.4-0.6) ▲	0.5 (0.4-0.6) ▸
Anterior	0.5 (0.4-0.7) *	0.4 (0.2-0.6)	0.4 (0.1-0.6) ◆	0.0 (0.0-0.5)	0.4 (0.2-0.5) †
Left	0.6 (0.4-0.8)	0.6 (0.5-0.8)	0.7 (0.4-0.9)	0.6 (0.3-0.9)	0.6 (0.4-0.7)
Posterior	0.5 (0.4-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.9) ✖	0.6 (0.4-0.7) ✚	0.5 (0.4-0.6)
Right	0.6 (0.5-0.8)	0.6 (0.4-0.7)	0.6 (0.4-0.9) ■	0.6 (0.4-0.9)	0.5 (0.4-0.6)

SD sphincter defect

\* Males vs. nulliparous females ( $p = 0.018$ )

▲ Continent parous females vs. incontinent parous females with a sphincter defect ( $p = 0.03$ )

▸ Continent parous females vs. incontinent parous females without a sphincter defect ( $p = 0.03$ )

◆ Continent parous females vs. incontinent parous females with a sphincter defect ( $p = 0.006$ )

† Incontinent parous females without a sphincter defect vs. incontinent parous females with a sphincter defect ( $p = 0.028$ )

✖ Continent parous females vs. incontinent parous females without a sphincter defect ( $p = 0.02$ )

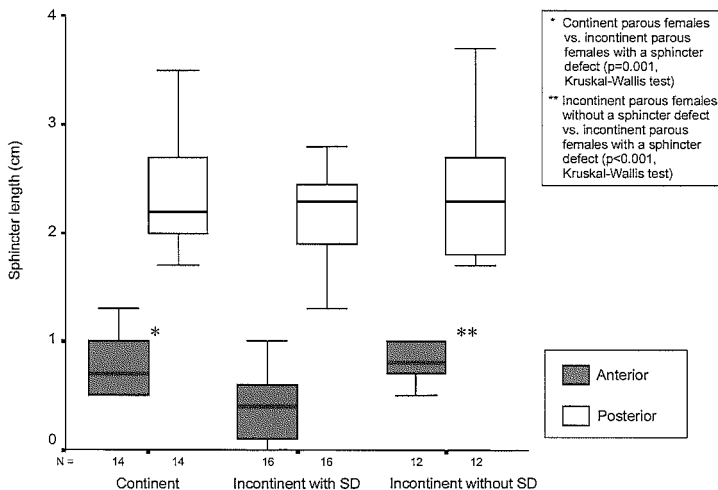
✚ Incontinent parous females with a sphincter defect vs. incontinent parous females without a sphincter defect ( $p = 0.05$ )

■ Continent parous females vs. incontinent parous females without a sphincter defect ( $p = 0.03$ )

Of the 16 faecal incontinent patients with a sphincter defect one had an IAS defect, six an EAS defect, and nine a combined defect.

PR, EAS or IAS volumes did not differ between continent and incontinent parous females with and without a sphincter defect (Figure 4). However, incontinent parous females with a sphincter defect had a significant shorter anterior sphincter length compared to continent parous females ( $p=0.001$ ) and incontinent parous females without a sphincter defect ( $p<0.001$ ) (Figure 5).

Average EAS thickness was significantly smaller in incontinent parous females with and without a sphincter defect (both  $p=0.03$ ) compared to continent parous females. Incontinent parous females with a sphincter defect had a significantly smaller anterior EAS thickness compared to continent parous females ( $p=0.006$ ) and incontinent parous females without a sphincter defect ( $p=0.028$ ). In addition, incontinent parous females without a sphincter defect had a smaller right ( $p=0.03$ ) and posterior ( $p=0.02$ ) EAS thickness compared to continent parous females (Table 2). The latter was also smaller compared to incontinent parous females with a sphincter defect ( $p=0.043$ ).



**Figure 5.** Anterior and posterior sphincter length in continent and incontinent parous females with and without a sphincter defect (SD).

### *Intraobserver and interobserver variability*

Intraobserver variability was seen for IAS volume ( $p=0.002$ ), anterior and posterior sphincter length ( $p=0.026$  and  $p=0.001$ ) using The Wilcoxon Signed Ranks test. The Bland-Altman plot regression line (difference versus mean) compared to the regression line  $y=0$  also showed intraobserver variability for IAS volume, anterior and posterior sphincter length. The mean difference for the IAS volume was 0.14, the limits of agreement ranged from -0.32 to 0.60 and mean percentage measurement

error was 13.4%. Larger IAS volume measurements tended to be more inaccurate than smaller ones. For the anterior sphincter length the mean difference was 0.083 and the limits of agreement -0.34 to 0.50 and for the posterior sphincter length the mean difference was 0.16 and the limits of agreement -0.24 to 0.55, for both mean percentage measurement error was 5.7%. Larger anterior sphincter length measurements were more inaccurate than smaller ones and the second posterior sphincter length measurement was consistently lower than the first. No significant differences were found for interobserver variability using The Wilcoxon Signed Ranks test or the "limits of agreement" method according to Bland and Altman.

### *Correlation between anal manometry and 3D EUS*

The only correlation found was between posterior sphincter length measured on 3D EUS and sphincter length measured during manometry (Spearman's  $\rho=0.48$ ,  $p=0.001$ ) in healthy subjects. Furthermore, a correlation was found between IAS volume and resting anal pressure (Spearman's  $\rho=0.69$ ,  $p<0.001$ ) in incontinent females.

## **DISCUSSION**

EUS has particularly aimed at detecting sphincter defects. However, adequate measurements of sphincter volumes as well as length and thickness would in theory add to the diagnostic yield of EUS. We therefore performed the present study, to evaluate the possibility of determining sphincter volumes, length and thickness using a 3D reconstruction of EUS images in healthy controls and faecal incontinent patients.

Different studies have assessed the role of EUS in evaluating anal sphincters. However, only a few studies<sup>12-14</sup> have used 3D EUS and to our knowledge no studies have looked at anal sphincter volume. There is one study available that has used 3D reconstructed magnetic resonance images (MRI) to evaluate anal sphincter volume.<sup>17</sup> Intrarater reliability for sphincter volume measurements was good, but equivalent to our study, sphincter volumes did not correlate with anal pressures.

In our study, we found that EAS and IAS volumes as well as anterior sphincter length and anterior EAS thickness were larger in males than in nulliparous females and that anterior sphincter length was also longer in nulliparous females compared to parous females. Other studies have reported similar results for sex differences of the anal sphincter complex. EAS thickness has found to be smaller in females than in males.<sup>18-20</sup> However, in a study comparing males, nulliparous and parous females, no differences for IAS and EAS thickness were reported.<sup>21</sup> In accordance with our study anterior sphincter length has found to be longer in males than in females.<sup>12,19</sup>

Although differences in sphincter volume were seen between males and females, surprisingly no differences were seen between continent and incontinent parous females. Under the assumption that faecal

incontinence could be associated with a smaller sphincter volume, these results are in contrast to what we expected. However, anterior sphincter length was shorter and anterior EAS thickness was smaller in incontinent parous females with a sphincter defect and right and posterior EAS thickness were smaller in patients without a sphincter defect. The shorter anterior sphincter measurements in incontinent patients with a sphincter defect can be contributed to the presence of a sphincter defect. In addition, the smaller EAS thickness in patients without a sphincter defect could be because of traumatic denervation and therefore thinning of the EAS.

Our findings that no differences were found for sphincter volumes in incontinent patients, but were found for sphincter length and EAS thickness appear to be inconsistent, as volume depends on the latter two. In this study, volume measurements were determined by measuring the area of the anal sphincters in successive images and then multiplying the resulting two-dimensional data by the distances between the images. The area in successive images was measured by tracing the perimeter of the sphincters. This method could be prone to measurement error due to multiple measurements. It is also possible that the volume measured not only consists of sphincter muscle but also of fatty infiltration, as it is difficult to distinguish between the two on EUS. The sphincter volume could then seem larger than it actually is. Sphincter length and EAS thickness are only single measurements, and they are therefore easier to obtain and might be more reliable.

Although the anal pressures in our study are similar to other studies<sup>22</sup> and confirm that our study group is representative, correlation with EUS measurements was poor. Correlation was seen between IAS volume and resting anal pressure in incontinent females and between posterior sphincter length measured on EUS and sphincter length measured during manometry in healthy subjects. However, in this study the posterior sphincter length measured on 3D EUS represented the length of the EAS and the PR. The contribution of the PR to anal pressure is unclear. In addition, the sphincter length measured on manometry was determined using the length of the high-pressure zone which is attributable to the IAS for 70%, and to the EAS for 15% to 20%. The poor correlation in our study is in accordance to previous studies,<sup>19,21,23,24</sup> however reports are conflicting as other studies have found a good correlation between anal pressures and EUS findings.<sup>4,20,25,26</sup>

Although EUS is a widely used technique, only a few studies have reported on reproducibility of EUS measurements and the results differ.<sup>18,21,27,28</sup> In the present study interobserver variability was good but intraobserver variability was seen for IAS volume, and anterior and posterior sphincter length. Although interobserver variability was better than intraobserver variability in this study, only 10 subjects were used to determine interobserver variability in contrast to 30 for intraobserver variability. The largest intraobserver variability was seen for IAS volume as the mean percentage of the measurement error was 13.4%; this was only 5.7% for anterior as well as posterior sphincter length. Discrepancies in

intraobserver and interobserver variability in EUS measurements are probably related to investigator experience. Better results will be found in studies with investigators more experienced in EUS and a better knowledge of the anal canal anatomy.

Endoanal MRI is also an accepted technique for evaluating the anal sphincters.<sup>29-32</sup> However, interobserver agreement for assessing sphincter integrity is moderate using this technique.<sup>30</sup> EUS is superior to MRI for assessing the IAS,<sup>34</sup> but EUS and MRI have found to be equivalent in assessing the EAS.<sup>34,35</sup> Endoanal MRI has been used to detect EAS atrophy, this has been confirmed with histology of muscle biopsies.<sup>36</sup> In one of the few studies reporting on the role of EUS in evaluating sphincter atrophy, potential EUS markers for EAS atrophy have been suggested.<sup>11</sup> Patients with a thin IAS and/or poorly defined EAS on EUS were more likely to have atrophy. However, 2D EUS, and not 3D EUS was used in this study.

Further investigation is needed to determine whether there is a role for EUS in assessing sphincter atrophy as 3D EUS provides more information on the anal sphincters. In our study, no difference was found in sphincter volumes between continent and incontinent parous females, but anterior sphincter length and EAS thickness were smaller in incontinent patients. As already stated, the latter two parameters might be more reliable in assessing anal sphincters. These parameters can also be measured with 2D EUS. Unlike 2D EUS, 3D EUS produces a digital volume that may be reviewed and used to perform measurements in any plane. This technique provides more reliable measurements. Studies comparing 2D and 3D EUS in performing anal sphincter measurements have still to be carried out. In addition, these results should be compared to MRI findings to determine whether there is a relationship between sphincter atrophy determined on MRI and 3D EUS measurements.

In conclusion, 3D EUS enables determination of anal sphincter volumes. These volumes differ between males and females; however, a vaginal delivery does not influence sphincter volume but does reduce anterior sphincter length. Faecal incontinence is not associated with loss of sphincter volume, but incontinent parous females do have a smaller anterior sphincter length and EAS thickness. With these measurements 3D EUS provides more insight in anal sphincter morphology and disorders. 3D EUS could turn out to be an important tool in the evaluation of sphincter atrophy and in the selection of patients amenable for anal repair.

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# Chapter 4

## Can three-dimensional endoanal ultrasonography detect external anal sphincter atrophy? A comparison with endoanal magnetic resonance imaging

### **ABSTRACT**

#### ***Purpose:***

Anal sphincter atrophy is associated with a poor clinical outcome of sphincter repair in patients with faecal incontinence. Preoperative assessment of the sphincters is therefore relevant. External anal sphincter (EAS) atrophy can be detected by endoanal magnetic resonance imaging (MRI), but not by conventional endoanal ultrasonography (EUS). Three-dimensional EUS allows multiplanar imaging of the anal sphincters and thus enables more reliable anal sphincter measurements. The aim of the present study was to establish whether 3D EUS measurements can be used to detect EAS atrophy. For this purpose 3D EUS measurements were compared to endoanal MRI measurements.

#### ***Methods:***

Patients with symptoms of faecal incontinence underwent 3D EUS and endoanal MRI. Internal anal sphincter (IAS) and EAS defects were assessed on 3D EUS and endoanal MRI. EAS atrophy was determined on endoanal MRI. The following measurements were performed: EAS length, thickness and area. Furthermore, EAS volume was determined on 3D EUS and compared to EAS thickness and area measured on endoanal MRI.

#### ***Results:***

Eighteen parous females (median age 56 years, range 32-80) with symptoms of faecal incontinence were included. Agreement between 3D EUS and endoanal MRI was 61% for IAS defects and 88% for EAS defects. EAS atrophy was seen in all patients on endoanal MRI. Correlation between the two methods for EAS thickness, length and area was poor. In addition, correlation was also poor for EAS volume determined on 3D EUS and EAS thickness and area measured on endoanal MRI.

#### ***Conclusions:***

3D EUS and endoanal MRI are comparable for detecting EAS defects. However, correlation between the two methods for EAS thickness, length and area is poor. This is also the case for EAS volume determined on 3D EUS and EAS thickness and area measured on endoanal MRI. Three-dimensional EUS can be used for detecting EAS defects but 3D EUS measurements are not suitable parameters for assessing EAS atrophy.

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## INTRODUCTION

Sphincter trauma is a common cause of faecal incontinence. Imaging of the anal sphincters allows detection of sphincter defects. Both endoanal ultrasonography (EUS)<sup>1-3</sup> and endoanal magnetic resonance imaging (MRI)<sup>4-7</sup> can be used for this purpose. EUS is superior for evaluating the internal anal sphincter (IAS),<sup>8</sup> both techniques are equivalent for visualisation of the external anal sphincter (EAS).<sup>8,9</sup> In patients with a sphincter defect who are eligible for surgery, sphincter visualisation allows exact delineation of the defect, and also potentially analysis of the condition of the remaining sphincter muscle. Sphincter atrophy has been shown to be associated with poor outcome of a sphincter repair<sup>10</sup> and can thus be used as an important guide for selection of patients who are eligible for surgery. MRI has been used for the detection of sphincter atrophy, and its results correlate with muscle biopsy histology.<sup>11</sup> EUS has found to be less suitable for assessing EAS atrophy as it cannot distinguish fatty infiltration from normal muscle tissue. In addition, the boundaries of the EAS are harder to determine on EUS. However, potential EUS markers for assessing EAS atrophy have been suggested and include a thin IAS and/or poorly defined EAS.<sup>12</sup>

More recently three-dimensional EUS (3D EUS) has become available, which can provide multiplanar imaging of the anal canal. This yields more information on the anal sphincter complex and makes it easier to perform measurements of the anal sphincter complex such as volume measurements.<sup>13</sup> The aim of this study was to establish whether 3D EUS measurements could be used to detect EAS atrophy in faecal incontinent patients. For this purpose 3D EUS measurements were compared to endoanal MRI measurements in patients with faecal incontinence.

## PATIENTS AND METHODS

In our centre 3D EUS and endoanal MRI are standard procedures for assessing patients with faecal incontinence. Female patients with faecal incontinence were eligible for inclusion. Sphincter measurements were performed on 3D EUS and endoanal MRI images by two independent investigators (respectively RLW and SD) who were unaware of each other's results.

### *3D EUS*

3D EUS images were obtained with a Diagnostic Ultrasound System (type 3535, B-K Medical, Herlev, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a water filled hard sonolucent cone (diameter 1.7 cm), producing a 360° view. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were taken of the distal part of the rectum, the puborectalis muscle (PR), and the EAS and IAS.

Three-dimensional images were reconstructed by a 2D set-up connected to a frame-grabbing computer. For this purpose, the probe was slowly withdrawn from the rectum in 30 seconds by means of a pullback device at a fixed speed of 2 mm/sec. The data volume was viewed in a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark). The sphincters were assessed for defects. The following measurements were performed: anterior EAS length, EAS thickness, EAS area, and EAS volume.

For the anterior sphincter length the distance between the lower and upper border of the EAS was measured. The EAS thickness was measured at the 3 (left), 6 (posterior), 9 (right) and 12 o'clock (anterior) positions at the anatomical midpoint of the sphincter. Using these measurements the average EAS thickness could be determined.

The EAS area was determined at the anatomical midpoint of the anal sphincter. In addition, volume measurements were performed by determining the sum of the area of the EAS measured at 0.25 mm intervals. For the most distal point of the EAS the termination of the subcutaneous EAS was used and for the most proximal point, the level where the EAS is last seen as a complete ring.

### *Endoanal MRI*

MRI was performed at 0.5 T (Gyrosan T5-II, Philips Medical Systems, Best, The Netherlands). An endoanal coil with a diameter of 19 mm (Philips Medical Systems, Best, The Netherlands) was used. The endoanal coil was introduced with the patient in the right lateral position. After the introduction of the endoanal coil, the patient was asked to turn onto their back carefully and the position of the endoanal coil was checked. A multi-slice survey was obtained.

In each patient, the following sequences were performed. Axial T2-weighted contrast-enhanced fast field echo (CE-FFE) with acquisition time of 5 minutes 39 seconds, imaging matrix 205x256, number of signal averages (NSA) 2, repetition time (TR) 23 ms, echo time (TE) 14 ms, flip angle 60°, field of view (FOV) 140 mm, slice thickness 2 mm without gaps. Axial T2-weighted fast spin echo (FSE) with fat saturation: acquisition time 2 minutes 23 seconds, imaging matrix 186x256, NSA 3, TR 5086, TE 100 ms, flip angle 90°, FOV 120 mm, slice thickness 4 mm with a gap of 0.4 mm. Coronal and sagittal T2-weighted FSE without fat saturation: acquisition time 2 minutes 34 seconds, imaging matrix 186x256, NSA 4, TR 2454 ms, TE 100 ms, flip angle 90°, FOV 120 mm, slice thickness 4 mm with gaps of 0.4 mm. All MRI images were transported from the local digital media to a viewing station (EasyVision II, Philips Medical Systems) to enable sphincter measurements.

The presence of EAS atrophy was assessed as described previously.<sup>10,11</sup> In brief, atrophy was defined as extreme thinning of the sphincter fibres or generalised fatty infiltration. Sphincter defects were reported and the following measurements were performed on the endoanal MRI images: anterior EAS length, EAS thickness and EAS area.

For the anterior EAS length the distance between the lower and upper border of the EAS was measured. The EAS thickness was measured at the 3 (left), 6 (posterior), 9 (right) and 12 o'clock (anterior) positions at the anatomical midpoint of the sphincter. The EAS area was measured at the anatomical midpoint of the anal sphincter.

### *Statistical analysis*

To assess agreement between 3D EUS and endoanal MRI for detecting IAS and EAS defects, agreement rates and kappa values ( $\kappa \leq 0.20$ , poor;  $\kappa = 0.21-0.40$ , fair;  $\kappa = 0.41-0.60$ , moderate;  $\kappa = 0.61-0.80$ , good;  $\kappa > 0.80$ , very good agreement) were calculated. Spearman's correlation coefficient was used for assessing correlation between 3D EUS and endoanal MRI for the anal sphincter measurements. All P values were calculated with exact methods. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

### *Patient characteristics*

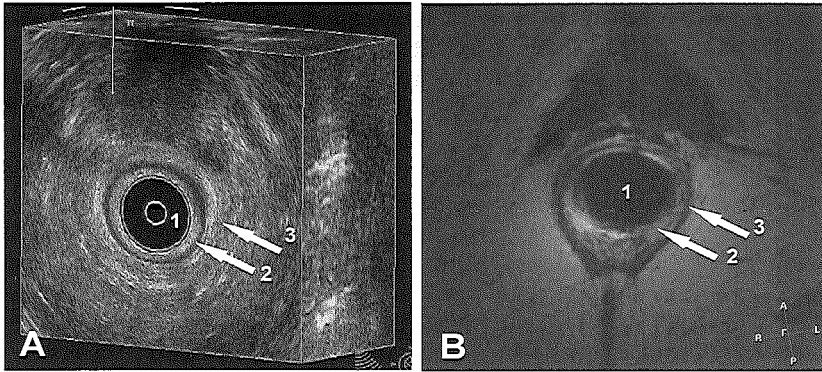
Eighteen parous female patients (median age 56 years, range 32-80) with faecal incontinence were included. All patients were incontinent for liquid and/or solid stool. The median number of vaginal deliveries was 2 (range 1-4); 10 patients had experienced a tear during childbirth and 13 had undergone an episiotomy. None of the patients had undergone previous anal surgery.

### *3D EUS and endoanal MRI findings*

Anal sphincter defects could be demonstrated with both 3D EUS and endoanal MRI. IAS defects were seen in seven patients on 3D EUS and in eight on endoanal MRI. There was agreement in 61% of the patients ( $\kappa = 0.20$ , fair agreement). Three-dimensional EUS showed EAS defects

**Table 1.** Anal sphincter measurements and Spearman's correlation coefficients Measurement (median, range).

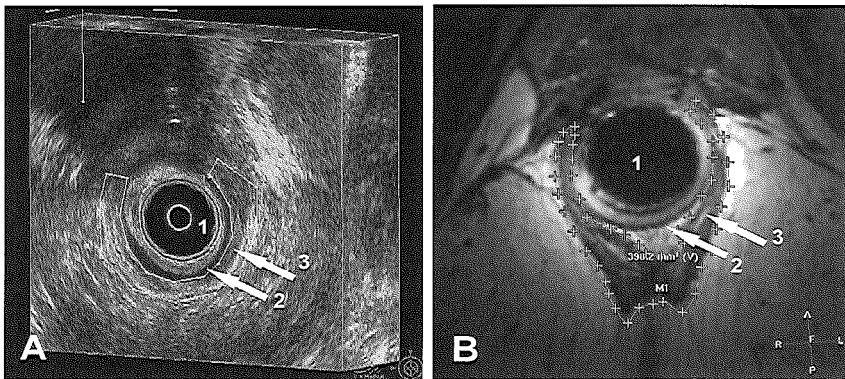
	3D EUS	Endoanal MRI	r value	P value
Anterior EAS thickness (cm)	0.2 (0-0.5)	0 (0-0.2)	-0.064	0.794
Left EAS thickness (cm)	0.6 (0.4-0.8)	0.2 (0.1-0.3)	0.362	0.127
Posterior EAS thickness (cm)	0.5 (0.3-0.7)	0.9 (0.4-1.1)	-0.026	0.917
Right EAS thickness (cm)	0.5 (0.3-0.7)	0.2 (0.1-0.3)	0.321	0.180
Average EAS thickness(cm)	0.4 (0.3-0.6)	0.3 (0.2-0.4)	0.003	0.990
Anterior EAS length (cm)	0.5 (0-0.9)	0.9 (0-4.5)	0.048	0.845
EAS area (cm <sup>2</sup> )	5.3 (4.2-6.4)	3.1 (1.7-4.9)	0.258	0.286



**Figure 1.** EAS atrophy 3D EUS (A) and endoanal MRI (B) image of a patient with EAS atrophy showing the endoprobe (1) and anal coil (1), the IAS (2) and the EAS (3). Atrophy is visualised on the MRI image by extreme thinning of the EAS.

in 14 patients and endoanal MRI in 16 patients, agreement was 88% ( $\kappa=0.61$ , good agreement). All patients had signs of EAS atrophy on endoanal MRI, defined as extreme thinning of the EAS fibres or generalised fatty infiltration. Figure 1 shows the 3D EUS image and endoanal MRI image of a patient with EAS atrophy.

3D EUS measurements were compared to endoanal MRI measurements to assess whether there are 3D EUS parameters that could be used for detecting EAS atrophy. These measurements and correlation results are presented in Table 1.



**Figure 2.** EAS area 3D EUS (A) and endoanal MRI (B) images showing the endoprobe (1) and anal coil (1), the IAS (2) and the EAS area (3) which has been delineated.

Very poor correlation was seen between the two methods for anterior, left, posterior and right EAS thickness. In addition, correlation was also poor for anterior EAS length. Although the correlation between both methods appeared to be better for determination of the EAS area, the kappa score was only 0.26 ( $p=0.29$ ) (Figure 2).

EAS volume was only determined on 3D EUS. Median EAS volume was  $3.6 \text{ cm}^3$  (range 1.9-6.3). To assess whether EAS volume could be used as a parameter for detecting EAS atrophy, these volume measurements were compared to EAS thickness and area measured on endoanal MRI. However, poor correlation was seen between EAS volume determined on 3D EUS and EAS area ( $r=-0.077$ ,  $p=0.76$ ) and average EAS thickness ( $r=-0.083$ ,  $p=0.74$ ) determined on endoanal MRI.

## DISCUSSION

Anal sphincter atrophy is considered to be the end result of denervation. Following denervation, individual muscle fibres either regain nerve supply from the branching of adjacent intact axons, or undergo degeneration and atrophy with fatty replacement. Detecting EAS atrophy in faecal incontinent patients is clinically relevant as it is a predictive factor for the outcome of surgical sphincter repair.<sup>10</sup> In the past, the condition of the EAS and the presence of muscle atrophy could only be assessed by electromyography and pudendal nerve latencies.<sup>14</sup> More recently, endoanal MRI has proved to be an excellent technique for the detection of anal sphincter atrophy.<sup>10,11</sup> Atrophy is characterised by generalised sphincter thinning and fatty replacement. The good results of MRI for the evaluation of atrophy have not been obtained with EUS.<sup>10</sup> This could probably be explained by the fact that EUS is not able to distinguish fatty infiltration from normal muscle tissue.

The introduction of 3D EUS reconstruction facilitates sphincter measurements using EUS.<sup>15</sup> Even though EUS can not detect fatty infiltration, certain sphincter measurements might be able to predict the presence of EAS atrophy. Therefore, the aim of the present study was to find 3D EUS parameters that could be suitable for assessing EAS atrophy. EUS has the advantages of lower costs, wider availability, a quicker technique, and probably lower patient burden. In the present study, we found that 3D EUS and endoanal MRI are comparable for detecting EAS defects. However, we found a very poor correlation between the two techniques for EAS thickness, length and area. Furthermore, no correlation was found between EAS volume measured on 3D EUS and EAS thickness and area determined on endoanal MRI.

Our findings are similar to those of Beets-Tan et al.<sup>16</sup> who compared sphincter measurements performed on 2D EUS and endoanal MRI. They found moderate correlation for IAS measurements but no correlation for EAS measurements. However, in another study<sup>9</sup> excellent correlation as well as interobserver agreement was found between EUS and endoanal



MRI for measuring EAS thickness. In this study 3D EUS with a graphics-overlay technique was used.

In our study, we also found poor correlation for EAS volume measured on 3D EUS and EAS thickness and area measured on endoanal MRI. As 3D EUS enables multiplanar imaging it also allows volume measurements, which could provide EUS parameters for detecting EAS atrophy. However, our results suggest that sphincter volume determined on 3D EUS does not provide extra information on the quality of the EAS in incontinent patients. One reason is that it is hard to distinguish the outer border of the EAS from adjacent ischio-anal fat. This is especially the case in patients with atrophy because the outer interface reflection is lost, as the fat replacement increases and the muscle thins. To determine EAS volume the area of the anal sphincters is measured in successive images. The area is determined by tracing the perimeter of the EAS but if the outer border is not clearly visible measurements of the EAS area on EUS could be unreliable.

A small EAS area measured on endoanal MRI is predictive for the presence of EAS atrophy.<sup>10</sup> Briel et al.<sup>10</sup> found a median EAS area in patients with atrophy of 2.2 cm<sup>2</sup> (range 0.9-3.6). Our results are similar as we found a median EAS area of 3.1 cm<sup>2</sup> (range 1.7-4.9) on endoanal MRI in a group of incontinent patients all with EAS atrophy. However, as discussed earlier the EAS area measured on 3D EUS does not correlate with the EAS area measured on endoanal MRI and can therefore not be used for detecting atrophy.

Measurement errors could have played a role in the poor correlation found between 3D EUS and endoanal MRI measurements. These errors can be caused by the inability of the observer to perform consistent measurements. In this study we did not assess intraobserver or interobserver variability for the EUS and endoanal MRI measurements. However, in a previous study on sphincter volume measurements using 3D EUS we found no intraobserver or interobserver variability for EAS volume or other EAS measurements in healthy subjects.<sup>13</sup>

EUS and endoanal MRI are considered to be comparable for detecting sphincter defects.<sup>17</sup> Several studies have reported on this but the results differ. Some have found that endoanal MRI is superior in detecting EAS and IAS defects<sup>18</sup> and others have found the methods to be comparable for detecting EAS defects but that EUS is better for detecting IAS defects.<sup>8</sup> In the present study, agreement between the two methods was good for detecting EAS defects but it was poor for IAS defects. No conclusion can be drawn from these findings as to which technique is better for assessing IAS defects because the two techniques were not compared to surgery as a gold standard. Previous studies however, have showed that both EUS<sup>19</sup> and endoanal MRI<sup>18</sup> have good agreement with surgery for detecting IAS defects.

In conclusion, we have found that 3D EUS and endoanal MRI are comparable for detecting EAS defects. However, correlation for EAS length, thickness and area is poor. Furthermore, no correlation was found for EAS

volume measured on 3D EUS and EAS thickness and area determined on endoanal MRI. 3D EUS is an optimal technique for detecting EAS defects but has no role in assessing EAS atrophy. For this purpose endoanal MRI should be used.

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# Chapter 5

## Evaluation of the anal sphincters after pouch-anal anastomosis surgery using three-dimensional endoanal ultrasonography measurements: a prospective study

### ABSTRACT

#### **Purpose:**

Postoperative function of colo- and ileo-anal pouches significantly depends on anal sphincter function. Anal surgery may however impair the anatomy and function of the sphincters. The aim of the present study was to assess with 3D endoanal ultrasonography (EUS) whether pouch-anal anastomosis surgery performed with a hand sewn anastomosis and a Scott retractor affects the anal sphincters. For this purpose the aspect of the anal sphincters was studied and sphincter volume, length and thickness were determined prior to and after surgery.

#### **Methods:**

Patients undergoing a colo-anal J-pouch anastomosis (CPAA) or ileo-anal S-pouch anastomosis (IPAA) were included. They were studied before and after surgery using 3D EUS. Internal (IAS) and external (EAS) anal length and volumes were determined. Furthermore, EAS thickness was measured. Anal sphincter resting and maximum squeeze pressure and the rectal inhibitory reflex were assessed using manometry. Continence scores were determined using the Faecal Incontinence Severity Index (FISI).

#### **Results:**

Fifteen patients with a CPAA and 13 patients with an IPAA were included. Six months after the procedure, 3D EUS showed significant alterations of the IAS in 8 patients with a CPAA (53%) and in 8 patients with an IPAA (73%). These alterations were characterised by asymmetry or thinning. No defects were seen in the CPAA group, but in two patients with an IPAA a small defect in the IAS was found. A decrease in IAS volume was only seen in the CPAA group, ( $p=0.009$ ). EAS thickness, length and volume did not change in either group. Six months after the procedure a significant reduction of anal resting pressure was found in both groups (CPAA:  $p<0.001$ , IPAA:  $p=0.001$ ). Maximum anal squeeze pressure was only reduced in the IPAA group ( $p=0.006$ ). The changes in the aspect of the IAS did not correlate with the manometry findings and FISI scores after surgery.

#### **Conclusions:**

After a hand sewn pouch-anal anastomosis performed with a Scott retractor, IAS changes were seen in 62% of patients on 3D EUS. This type of surgery only rarely leads to IAS defects, but is associated with a decrease in IAS volume, in particular after CPAA. The EAS does not seem to change after pouch surgery. In addition, there is no correlation between 3D EUS findings and the functional outcome or the FISI score.

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## INTRODUCTION

Ileal pouch-anal anastomosis (IPAA) is the procedure of choice for patients with ulcerative colitis or familial adenomatous polyposis needing a proctocolectomy.<sup>1</sup> This procedure combined with a total proctocolectomy and mucosectomy not only eliminates the disease but also preserves the anal sphincter. The colonic pouch-anal anastomosis (CPAA)<sup>2-4</sup> also allows restorative surgery with preservation of the anal sphincters in low rectal cancer after an anterior resection.

In the past pouch-anal anastomoses were mainly hand sewn at the dentate line after transanal mucosectomy using a Parks retractor. At present most surgeons prefer a double stapled technique in order to prevent anal stretch and to preserve the transitional zone. This double stapling technique reduces operating time and some reports even indicate better functional results.<sup>5-7</sup> However, the double stapled technique is still controversial because a small rim of rectal mucosa is left in situ, which could lead to disease relapse.<sup>8,9</sup> Therefore, we continue to prefer hand sewn pouch-anal anastomosis. For this procedure, we use a Scott retractor because it appears to cause less postoperative sphincter damage compared to a Parks retractor.<sup>10</sup>

Pouch surgery is associated with reduced anorectal function.<sup>11-16</sup> Postoperative sphincter function is of key relevance for the long-term outcome of pouch surgery. This necessitates a better understanding of the effects of pouch surgery on sphincter anatomy and function. The latter has been repeatedly studied. However, only a few studies have compared preoperative and postoperative endoanal ultrasonography (EUS) examinations to detect sphincter defects and perform sphincter measurements in patients undergoing pouch surgery.<sup>17-21</sup> IAS defects<sup>19,20</sup> and a decrease in IAS thickness after surgery have been reported.<sup>17,18</sup>

Recently, 3D EUS has become available, which can provide multiplanar imaging of the anal canal.<sup>22,23</sup> This yields more information on the anal sphincter complex and makes it easier to perform sphincter measurements such as volume measurements.<sup>24</sup>

The aim of the present study was to assess whether hand sewn pouch-anal anastomosis surgery performed with a Scott retractor affects the anal sphincters using 3D EUS. For this purpose the aspect of the anal sphincters was studied and sphincter volume, length and thickness were determined prior to and after surgery. In addition, anal pressures and a faecal incontinence score were assessed.

## PATIENTS AND METHODS

All patients who underwent surgery for a CPAA or an IPAA in our centre between October 2001 and October 2003 were included and studied prospectively. Prior to and six months after surgery patients underwent 3D EUS and anal manometry. In addition, they were asked to fill out a

questionnaire to assess continence. The study was approved by the ethical committee of the Erasmus MC and all patients signed informed consent.

### *Surgical Technique*

All patients were operated on by the same experienced colorectal surgeon (WRS). In order to gain access to the anal canal a Scott retractor was used (Lone Star Retractor System, Lone Star Medical Products, Inc., Houston, Texas). This is a ring retractor with multiple skin hooks on elastic bands, providing an excellent exposure. As no blades are inserted into the anal canal, the amount of stretch on both sphincters is minimised.

The rectum was mobilised until the pelvic floor was reached. Just above the pelvic floor, the rectum was transected between two right-angled bowel clamps. The remaining mucosa was removed from the dentate line to the upper margin of the transected mucosa. The pouch was advanced into the anal canal and sutured to the dentate line. In patients with a tumour in the middle or distal third of the rectum a side-to-end J-pouch-anal anastomosis was performed after total mesorectal excision. All of these patients had received preoperative radiotherapy. In patients with ulcerative colitis or familial adenomatous polyposis an ileal pouch-anal anastomosis was performed. In these patients an "S" reservoir was constructed. After advancement of this pouch an end-to-end anastomosis was sutured to the dentate line.

### *3D EUS*

For 3D EUS a Diagnostic Ultrasound System (type 3535, B-K Medical, Herlev, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a water filled hard sonolucent cone (diameter 1.7 cm), producing a 360° view was used. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were taken of the distal part of the rectum, the puborectalis muscle (PR), EAS and IAS. Three-dimensional images were reconstructed by a 2D set-up connected to a frame-grabbing computer. For this purpose, the probe was slowly withdrawn from the rectum in 30 seconds by means of a pullback device at a fixed speed of 2 mm/sec. The data volume was viewed in a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark).

The anal sphincters were assessed for defects prior to surgery. In addition, the aspect of the IAS was carefully studied and any changes after surgery such as defects, fragmentation, thinning or asymmetry were noted. Volume measurements of the IAS and EAS were performed and, IAS length and EAS length and thickness were determined.

Volume measurements were performed by determining the sum of the area of the IAS and EAS measured at 0.25 mm intervals. Only muscle without scarring was included in these measurements. The most proximal point of the IAS was defined as the first level at which the IAS is seen as a

clear hypoechoic ring and the most distal point as the level where the IAS is last seen as a complete ring. For the most proximal point of the EAS the distal verge of the PR was used, and for the most distal point of the EAS the termination of the subcutaneous EAS was used.

For the anterior and posterior sphincter length the distance between the lower and upper border of the IAS and EAS was measured. The EAS thickness was measured at the 3 (left), 6 (posterior), 9 (right) and 12 o'clock (anterior) positions at the anatomical midpoint of the sphincter. Using these measurements the average EAS thickness could be determined.

### *Anal manometry*

A pull-through technique (2 mm per second) with a four channel water-perfused (0.5 ml/min) catheter (MMS system, Enschede, The Netherlands) was used for manometry. Each channel had a side hole, and the side holes were arranged around the circumference of the catheter, 90° to each other. No specific bowel preparation was used. To perform manometry patients were positioned in the left lateral position. Zero pressure calibration was done at the anal orifice level before introducing the catheter. After introduction and stabilisation in the rectum, the catheter was withdrawn. The high-pressure zone was registered; this was defined as an increase in pressure of more than 5 mmHg. Anal resting pressure was averaged across the four channels by using the maximum plateau phase of all channels. After introducing the catheter a second time, the patient was asked to squeeze at 0.5 cm intervals. The maximum squeeze pressure was calculated by averaging the highest squeeze pressures recorded by each channel. The rectoanal inhibitory reflex was elicited by distending a rectal balloon with different volumes of air. Paradoxical straining was defined as an increase of 10 mmHg combined with a resting pressure of more than 60 mmHg.

### *Faecal incontinence score*

A questionnaire was used to determine the Faecal Incontinence Severity Index (FISI) score prior to and after surgery. This is a validated index based on a type X frequency matrix. The matrix includes four types of leakage commonly found in the faecal incontinent population: gas, mucus, liquid and solid stools and five frequencies: once to three times per month, once per week, twice per week, once per day, and twice per day. Scores range from zero (total continence) to 61 (complete incontinence to solid stool on a daily basis).

### *Statistical analysis*

Differences in 3D EUS measurements, manometry findings and FISI score in both groups prior to and after surgery were compared using the Wilcoxon Signed Ranks test. The Spearman's correlation coefficient was used for correlation between 3D EUS measurements and manometry



findings. The differences prior to and after surgery between the two groups were compared using the Mann Whitney U test. All P values were calculated with exact methods. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## RESULTS

### *CPAA group*

Nineteen consecutive patients with rectal cancer were included in the study. Four patients were excluded; one patient was lost to follow-up, one died during follow-up and in two patients a colo-anal J-pouch anastomosis was not deemed suitable due to metastasis found during surgery, a colostomy was created in these patients.

In total 15 patients (10/5 M/F) with a median age of 58 years (range 40-74) were evaluated. Five female patients had had a vaginal delivery, two had experienced a tear and two had undergone an episiotomy. No patients had undergone previous anal surgery. The median time between surgery and final evaluation was 6.8 months (range 4.7-13.4).

The 3D EUS and manometry results are presented in Tables 1 and 2. Three-dimensional EUS could be performed in all patients prior to and after surgery. Prior to surgery an EAS defect was only seen in one patient who had had four vaginal deliveries and an episiotomy. After surgery no new EAS defects were found. The aspect of the IAS had changed in eight (53%) patients, meaning that the IAS was thinner or asymmetrical (Figure 1). Neither IAS defects nor fragmentation was found in any of these patients. Postoperatively 3D EUS measurements could only be performed in 13 patients because two patients had a stenotic anus so that no reliable measurements could be performed. A significant decrease in IAS volume was observed after surgery ( $p=0.009$ ) but not in IAS length. No significant changes were found in EAS volume, length or average thickness after surgery.

Anal resting pressure decreased significantly after surgery ( $p<0.001$ ). No difference was seen with respect to maximum squeeze pressure. A rectoanal inhibitory reflex was present in all patients prior to surgery and in 10 after surgery (67%; 95% CI: 40%-94%,  $p<0.05$ ). Prior to surgery the median FISI score was 4 (range 0-30), this increased to 13 after surgery (range 0-31) ( $p=0.060$ ).

No correlation was found between the change in IAS volume and anal resting pressure or between IAS volume and anal resting pressure or FISI score.

### *IPAA group*

Sixteen patients with ulcerative colitis and one with familial adenomatous polyposis underwent surgery for an ileo-anal S-pouch. Only 13 patients could be evaluated and four patients were excluded. In one patient surgery was postponed because of a perianal fistula requiring

preoperative treatment, in another patient it was not possible to create a pouch, and two patients were lost to follow-up.

The median age of the 13 patients (M/F 8/5) who could be evaluated was 34 years (range 21-51). Eleven of these patients had undergone a subtotal colectomy with closure of the rectum stump prior to pouch surgery. In the other two a proctocolectomy and IPAA were performed in a single operation. Only one female patient had had a vaginal delivery, which was complicated by an episiotomy, and no patients had undergone previous anal surgery. The median time between surgery and final evaluation was 8.2 months (range 6.0-19.3).

**Table 1.** EUS measurements in the colo-anal J-pouch (CPAA) (n=13) and ileo-anal S-pouch (IPAA) (n=11) group prior to and after surgery.

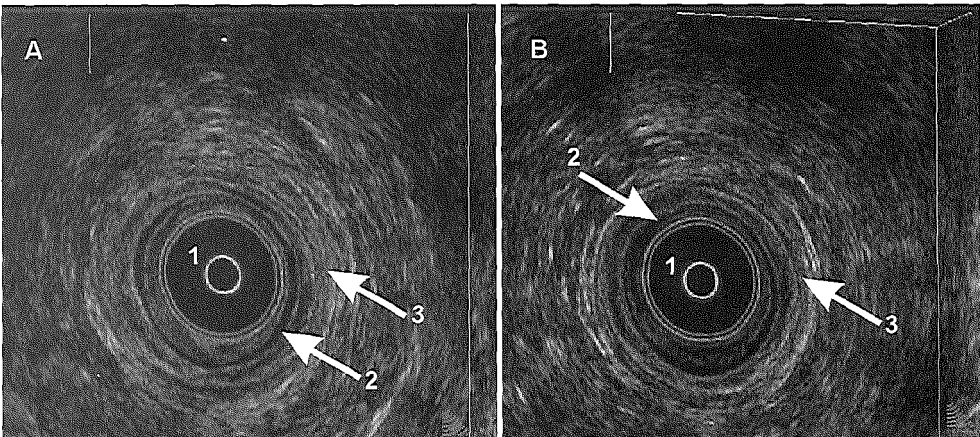
**A.** IAS volume and length (median, range)

	IAS volume (cm <sup>3</sup> )		IAS length (cm)	
	Prior	After	Prior	After
CPAA	0.9 (0.2-1.2)	0.6 (0.1-0.9)*	0.9 (0.3-1.6)	0.8 (0.2-1.5)
IPAA	0.5 (0.4-1.3)	0.5 (0.4-1.0)	1.0 (0.3-1.3)	0.8 (0.3-1.2)

\* p=0.009

**B.** EAS volume, length and average thickness (median, range)

	EAS volume (cm <sup>3</sup> )		EAS length (cm)		Average EAS thickness (cm)	
	Prior	After	Prior	After	Prior	After
CPAA	5.5 (2.2-10.9)	6.1 (2.7-10.8)	1.1 (0.3-1.8)	1.1 (0.3-1.8)	0.5 (0.3-0.6)	0.5 (0.4-0.6)
IPAA	5.6 (3.5-8.5)	5.1 (3.6-8.5)	1.2 (0.4-1.5)	1.0 (0.3-1.5)	0.5 (0.4-0.6)	0.5 (0.4-0.6)

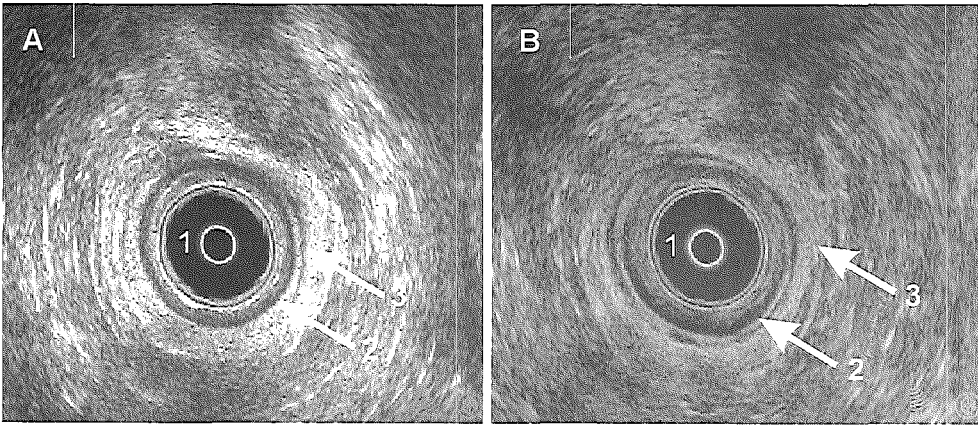


**Figure 1.** IAS asymmetry after CPAA surgery  
3D EUS image prior to (A) and after (B) CPAA surgery showing the endoprobe (1), the IAS (2) and the EAS (3). In the postoperative image (B) asymmetry of the IAS can be seen.

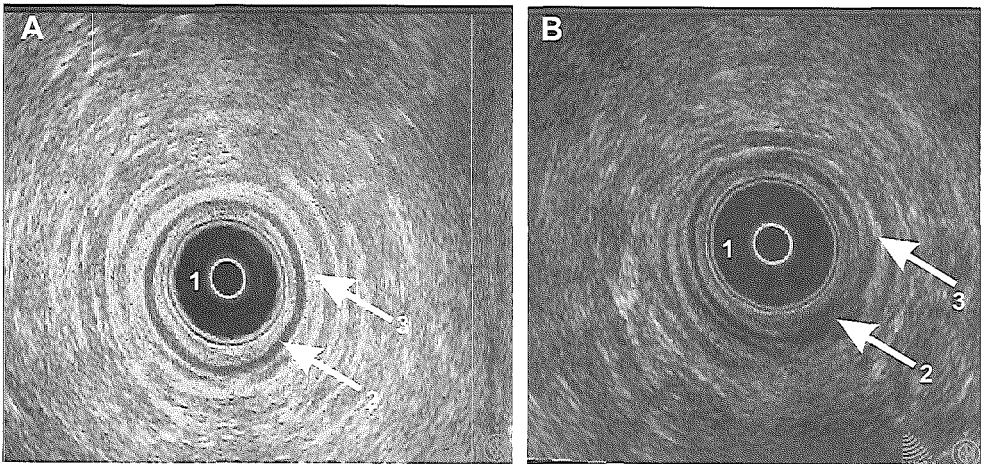
**Table 2.** Manometry results in the colo-anal J-pouch (CPAA) and ileo-anal S-pouch (IPAA) group prior to and after surgery (median, range).

	Maximum squeeze pressure (mmHg)		Maximum anal resting pressure (mmHg)	
	Prior	After	Prior	After
CPAA	83 (32-130)	41 (21-82) *	187 (59-363)	183 (55-307)
IPAA	85 (53-152)	44 (28-98) #	161 (73-450)	132 (70-356) †

\* p<0.001      # p=0.001      † p=0.006



**Figure 2.** Fragmentation of the IAS after IPAA surgery  
3D EUS image prior (A) and after (B) IPAA surgery showing the endoprobe (1), the IAS (2) and the EAS (3). In the postoperative image (B) fragmentation of the IAS can be seen.



**Figure 3.** IAS defect after IPAA surgery  
3D EUS image prior (A) and after (B) IPAA surgery showing the endoprobe (1), the IAS (2) and the EAS (3). In the postoperative image (B) an IAS defect can be seen.

The 3D EUS and manometry results are presented in Tables 1 and 2. Prior to surgery 3D EUS could be performed in all 13 patients. Preoperative 3D EUS showed an EAS defect in the female patient who had an episiotomy. After surgery no new EAS defects were seen. In addition, the aspect of the IAS had changed in eight patients (73%). In six patients the IAS was thinner or asymmetrical, in one IAS fragmentation was seen (Figure 2) and in one an IAS defect (Figure 3).

Three-dimensional EUS measurements of the anal sphincters could only be performed in 11 patients as two patients had a stenotic anus postoperatively. No significant differences were found for IAS and EAS volume and length or EAS thickness after surgery.

A significant decrease was seen in anal resting and maximum squeeze pressure after surgery in this group ( $p=0.001$  and  $p=0.006$ ). Furthermore, a rectoanal inhibitory reflex was present in all patients prior to surgery and in eight after surgery (62%; 95% CI: 31%-92%,  $p<0.05$ ).

The median FISII score was 0 (range 0-19) before surgery but this was not reliable as most of these patients had an ileostomy at the time of preoperative assessment. This score increased to 13 (range 0-31) after surgery.

Comparative to the CPAA group no correlation was found between change in IAS volume and anal resting pressure or between IAS volume and anal resting pressure or FISII score.

#### *CPAA versus IPAA group*

The patients in the CPAA group were significantly older than the patients in the IPAA group ( $p<0.001$ ). Prior to surgery no differences were found in 3D EUS measurements, manometry findings or FISII score. The only significant difference between the two groups after surgery was the change in IAS volume. A larger decrease in IAS volume was seen in the CPAA group compared to the IPAA group ( $p=0.04$ ).

## **DISCUSSION**

The outcome of anal pouch surgery depends to a large extent on postoperative function of the anal sphincters, but reports on anal sphincter conditions after pouch surgery are scarce. Therefore, the aim of the present study was to assess the condition of the anal sphincters after pouch-anal anastomosis surgery. For this purpose, the aspect of the anal sphincters as well as sphincter volume, length and thickness were determined prior to and after surgery by means of 3D EUS and manometry. We found that 3D EUS showed significant alterations of the IAS in most patients after pouch surgery but IAS defects were only seen in two patients with an IPAA. In addition, IAS volume had only decreased in the CPAA group. No changes were seen in the aspect or measurements of the EAS. The changes in the aspect of the IAS did not correlate with the manometry findings and FISII scores after surgery.

Other studies have also used EUS for the evaluation of the anal sphincters after pouch surgery.<sup>17-21</sup> However, most studies have described IAS defects after surgery and have not performed sphincter measurements.<sup>17,19-21</sup> Silvis et al. measured IAS thickness in patients who had undergone an IPAA.<sup>18</sup> They found that the mean IAS thickness was lower in patients with an IPAA than in healthy controls. In addition, they found no correlation between the extent of the reduction in anal resting pressure and IAS thickness. However, no preoperative EUS values were available. In a study comparing CPAA and coloplasty pouch anastomosis surgery IAS thickness was also measured but no change was seen after surgery between the groups or within the groups.<sup>17</sup> In these studies 2D EUS was used and not 3D EUS nor were volume measurements performed on the anal sphincters.

In our study, we did not only report on IAS defects or fragmentation but on all morphological IAS changes, such as thinning and asymmetry. In the CPAA group thinning or asymmetry was observed in eight patients but IAS defects or fragmentation did not occur. In the IPAA group changes of the IAS were seen in eight patients, of whom one had IAS fragmentation and another had an IAS defect. These latter changes are probably due to direct damage to the IAS. In addition, the only change in anal sphincter measurements was a decrease in IAS volume in the CPAA group. Reasons for the changes in IAS morphology are probably denervation of the sphincter or damage during perianal manipulation. It is interesting that we only found changes in the CPAA group for IAS volume and not in the IPAA group as this type of surgery is more aggressive due to transanal mucosectomy. This could be explained by the fact that the patients in the CPAA group were older and an older sphincter might be more prone to atrophy during manipulation.

We did not find any differences in the EAS after surgery. No new defects or change in EAS volume, length or thickness were seen in either the CPAA or IPAA group. Other studies have also reported no change in the EAS after CPAA surgery<sup>17</sup> or a stapled low anterior resection.<sup>20</sup> However, EAS defects have been reported after a stapled colorectal anastomosis.<sup>19</sup> In addition, another study, looking at temporary stool deviation in patients undergoing a CPAA or straight end-to-end anastomosis, found that the EAS does undergo transformation.<sup>25</sup> EAS thickness decreased after creation of a stoma but increased after stoma closure and reconstruction.

In the present study changes were also found in anal sphincter function. Anal resting pressure had decreased in both groups but maximum squeeze pressure had only decreased in the IPAA group. These findings are in agreement with other studies.<sup>11,12,26</sup> The reduced anal resting pressure might be caused by interruption of the autonomic innervation of the sphincter during dissection of the rectum.<sup>27,28</sup> Furthermore, IAS stretching during perianal manipulation probably causes an additional pressure reduction.<sup>29,30</sup> We cannot account for the lower maximum squeeze pressure in patients with an IPAA, especially as

we found no EAS changes on EUS. Others have found similar results in patients undergoing an IPAA.<sup>6</sup> In addition, we found a loss of a rectoanal inhibitory reflex in a significant number of patients. However, a time-dependent recovery after a stapled low anterior resection and stapled IPAA has been reported.<sup>31</sup>

Incontinence scores increased in both groups; however most of the patients in the IPAA group had undergone a proctocolectomy and had an ileostomy before inclusion in this study. This could have affected the preoperative FISI score, making it unreliable in this group of patients. The FISI score ranges from zero (total continence) to 61 (complete incontinence to solid stool on daily basis). In our study the median score only increased to 13 in both groups, which means that continence was not severely impaired after surgery.

In our centre, a hand-sewn pouch-anal anastomosis is preferred to the double-stapled technique. For a CPAA this is the case as the double-stapled technique is associated with a higher risk of anastomotic leakage, especially in patients who have undergone radiotherapy.<sup>32,33</sup> In addition, when an IPAA is performed with the double-stapled technique a small rim of rectal mucosa is left in situ. Patients with familial adenomatous polyposis could develop new adenomatous polyps in this mucosa<sup>34,35</sup> and in patients with ulcerative colitis disease recurrence could occur.<sup>9</sup> Furthermore, we prefer to use a Scott retractor to a Parks retractor for pouch surgery, as we believe that this retractor causes less sphincter damage. In a previous study, comparing the use of the Parks and Scott retractor for perianal fistula surgery, we found a larger deterioration of continence and anal resting pressure in the Parks retractor group than in the Scott retractor group.<sup>10</sup>

In conclusion, after a hand-sewn pouch-anal anastomosis performed with a Scott retractor, thinning and asymmetry of the IAS occurs in most patients. However, a defect or fragmentation was only seen in a small number of patients after an IPAA. A smaller IAS volume was only seen in the CPAA group. In addition, no changes in the aspect of the EAS or EAS length, thickness or volume were found. The IAS changes did not appear to affect functional outcome as no correlation was found with the changes in anal pressure or FISI score. This underlines the good results of pouch surgery performed with this technique and supports its use.

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# Chapter 6

## **Prospective comparison of hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging of perianal fistulas**

### **ABSTRACT**

#### ***Purpose:***

This study was conducted to determine agreement between hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography (3D HPUS) and endoanal magnetic resonance imaging (MRI) in the preoperative assessment of perianal fistulas and to compare these results with the surgical findings.

#### ***Methods:***

Twenty-one patients (aged 26–71 years) with clinical symptoms of a cryptoglandular perianal fistula and a visible external opening underwent preoperative 3D HPUS, endoanal MRI, and surgical exploration. The results were assessed separately by experienced observers blinded to each other's findings. Each fistula was described with notice of the following characteristics: classification of the primary fistula tract according to Parks (intersphincteric, transsphincteric, extrasphincteric, or suprasphincteric), horseshoe, or not classified; presence of secondary tracts (circular or linear); and location of an internal opening.

#### ***Results:***

The median time between 3D HPUS and endoanal MRI was 66 (interquartile range, 21–160) days; the median time between the last study (3D HPUS or endoanal MRI) and surgery was 154 (interquartile range, 95–189) days. Agreement for the classification of the primary fistula tract was 81% for 3D HPUS and surgery, 90% for endoanal MRI and surgery, and 90% for 3D HPUS and endoanal MRI. For secondary tracts, agreement was 67% for 3D HPUS and surgery, 57% for endoanal MRI and surgery, and 71% for 3D HPUS and endoanal MRI in case of circular tracts and 76%, 81%, and 71%, respectively, in case of linear tracts. Agreement for the location of an internal opening was 86% for 3D HPUS and surgery, 86% for endoanal MRI and surgery, and 90% for 3D HPUS and endoanal MRI.

#### ***Conclusions:***

For evaluation of perianal fistulas, 3D HPUS and endoanal MRI have good agreement, especially for classification of the primary fistula tract and the location of an internal opening. These results also show good agreement compared with surgical findings. Therefore, 3D HPUS and endoanal MRI can both be used as reliable methods for preoperative evaluation of perianal fistulas.

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## INTRODUCTION

Different diagnostic methods are available for preoperative evaluation of perianal fistulas. Accurate preoperative assessment of perianal fistulas is necessary for planning the most suitable surgical procedure and enables the surgeon to inform the patient of the type of surgery and its possible complications. Currently, the main techniques used are endoanal ultrasonography (EUS) and magnetic resonance imaging (MRI). EUS is a safe and economical technique that can also be used in patients who cannot undergo MRI because of claustrophobia, obesity, or metallic implants (such as pacemakers). Conventional EUS has limited value in visualising fistula tracts. EUS combined with hydrogen peroxide (HPUS) as a contrast medium improves visualisation and provides an accurate preoperative assessment of fistulas.<sup>1-5</sup> A new technique is three-dimensional (3D) EUS. 3D EUS enables axial images of the anal canal to be reconstructed in the coronal and sagittal planes. The use of 3D images provides more information on the anatomy of anorectal disorders.<sup>6</sup>

Several studies have compared EUS to MRI,<sup>7-11</sup> with some reporting better results with EUS<sup>7,8</sup> and others with MRI.<sup>9,10</sup> In a recent study, Schwartz et al.<sup>11</sup> showed that EUS, MRI, and examination under anaesthesia were all accurate tests for determining fistula anatomy in patients with perianal Crohn's disease.

There are no studies comparing 3D HPUS and endoanal MRI. The purpose of the present study was to assess agreement between 3D HPUS and endoanal MRI for the preoperative classification of perianal fistulas and to compare these results with surgical findings.

## PATIENTS AND METHODS

In total, 39 patients with clinical symptoms of a cryptoglandular perianal fistula who were referred to the colorectal surgeon in our centre (WRS, DDEZ) between April 2000 and April 2002 were invited into a prospective study to undergo 3D HPUS and endoanal MRI before surgery. These techniques are both standard preoperative procedures for patients with perianal fistulas in our centre. Selection of patients was based on a visible external opening so that hydrogen peroxide could be introduced. Exclusion criteria were anovaginal fistulas and perianal fistulas related to Crohn's disease, because these fistulas are not operated on in our center.

Eleven patients were excluded because of no visible external opening. Two patients did not want to undergo 3D HPUS, two patients could not undergo MRI because of intolerance of the endocoil, and no surgical data were available for three patients.

Twenty-one patients (18 males, aged 26–71 years) were included in the study. Five patients had had no previous treatment for a fistula, seven had undergone prior surgical exploration only, three had undergone a fistulectomy, and four had undergone previous transanal advancement

flap repair. Two patients had undergone a previous attempt at repair with fibrin glue treatment.

The endoanal MRI images were interpreted by the radiology department (SD, SMH), 3D HPUS was performed and interpreted by the gastroenterology department (RLW, RJFF-B), and surgery was performed by the colorectal surgeon (WRS). The observers were blinded to each other's results. First, the observers described the course of the fistula tract(s). Next, the following characteristics of the fistula were recorded on a standardised case report form: classification of the primary fistula tract (according to Parks et al.<sup>12</sup> (intersphincteric, transsphincteric, extrasphincteric, or suprasphincteric), horseshoe, or not classified), circular secondary tracts (none, intersphincteric, extrasphincteric, or intramuscular), linear secondary tracts (none, caudal, or cranial), and location of an internal opening (not identified, anterior, posterior, left lateral, or right lateral)(Figures 1 and 2).

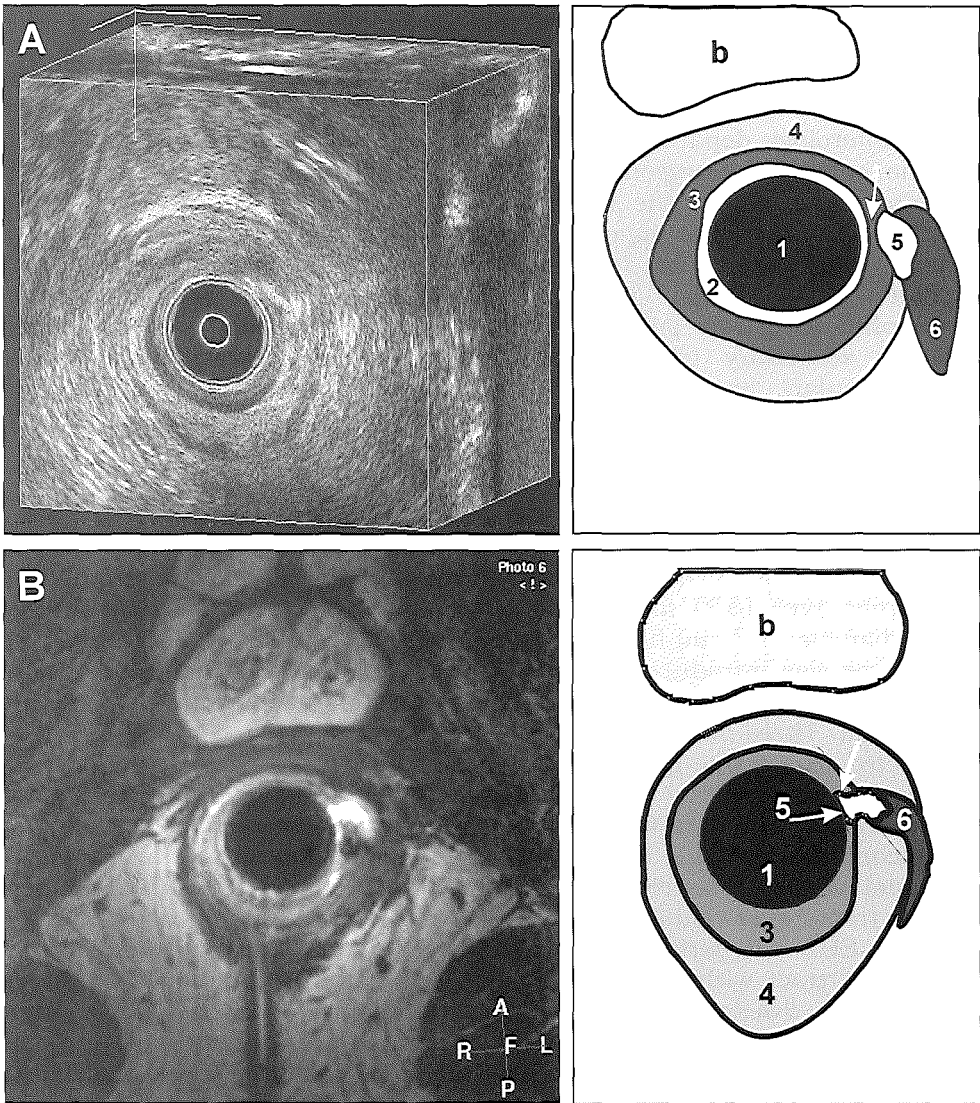
### *3D HPUS*

EUS was performed with a 3D diagnostic ultrasound system (Hawk type 2102, B-K Medical, Herlev, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2–4.5 cm) covered by a hard sonolucent cone (diameter 1.7 cm) filled with water, which produced a 360° view. The endoprobe was introduced into the rectum, and serial radial images were made of the distal part of the rectum, the puborectalis muscle, and the anal canal. Three-dimensional images were reconstructed by a 2D set-up connected to a frame-grabbing computer. With a pullback device, it took 30 seconds to withdraw the probe slowly during frame grabbing at a speed of 2 mm/ sec. The data volume was viewed in a software program used for 3D reconstruction (B-K Medical). This technique enabled axial images of the anal canal to be reconstructed in the coronal and sagittal planes. Fistula tracts were visualised as tubelike hypoechoic lesions.

After EUS was performed, hydrogen peroxide (3%) was introduced into the fistula tract with a flexible intravenous cannula (Venflon®, Ohmeda, Helsingborg, Sweden), and EUS was repeated as described above. After infusion of hydrogen peroxide, which generates the formation of small air bubbles, the ultrasonographic appearance of a fistula tract changed from hypoechoic to bright hyperechoic. By comparing the images obtained with and without hydrogen peroxide, the fistula tract and its extensions could be identified and discriminated from previous scars. This made it possible to make a distinction between active fistulas and fibrotic tissue in patients who had undergone previous surgery. An internal opening was defined as an echogenic (HPUS) breach at the level of the submucosa.

### *Endoanal MRI*

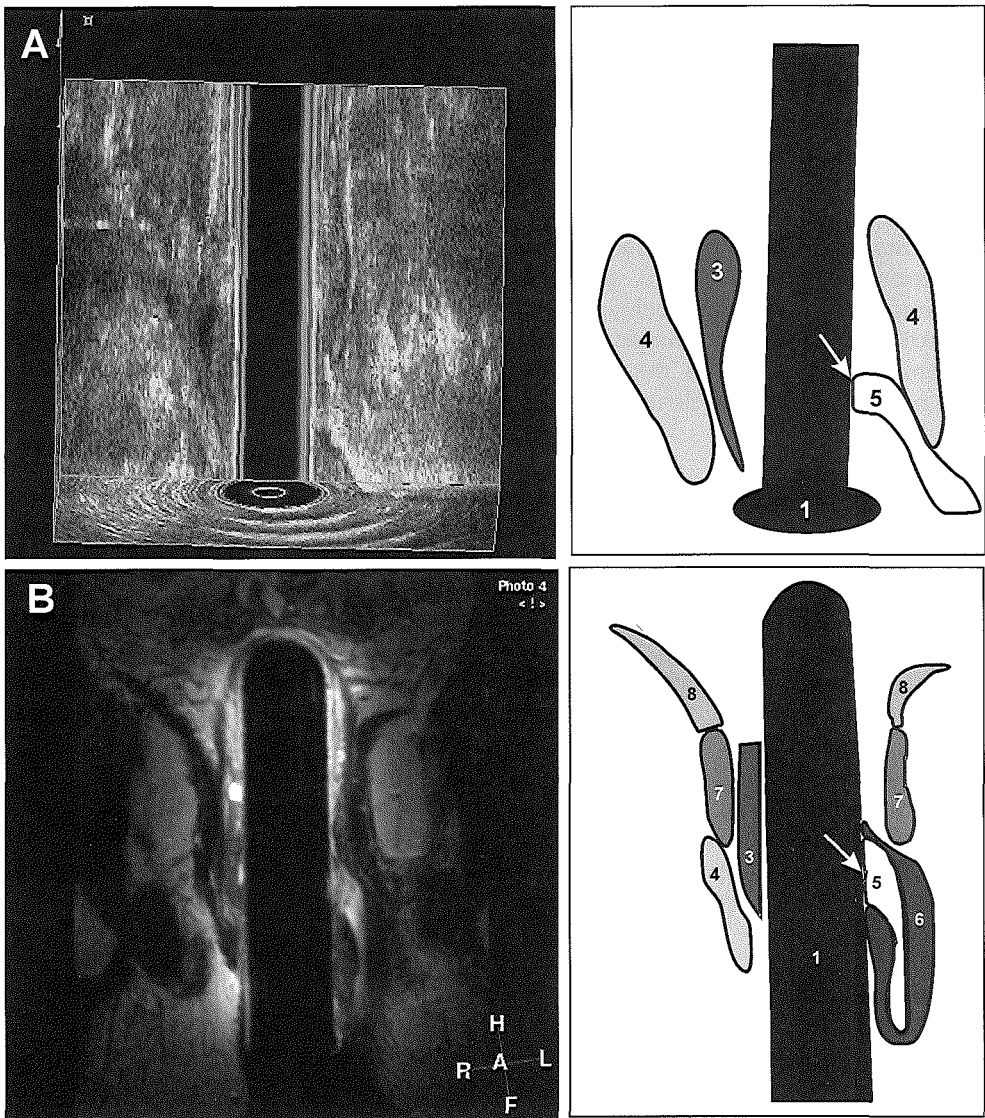
MRI was performed at 1.5 T (Philips Medical Systems, Best, the Netherlands). The endoanal coil consisted of a fixed, rectangular, 60 mm



**Figure 1.** Transsphincteric fistula and the internal opening.

Axial 3D HPUS image (A) and axial endoanal MRI (T2-weighted, gradient echo) image (B) showing the endoprobe (1) and anal coil (1), submucosa (2), the IAS (3), the EAS (4), the fistula and the internal opening (5; black arrow), fibrosis (6), and the bulbocavernous muscle (b). A = anterior; R = right; F = feet; L = left; and P = posterior.

long rigid receive coil with a width of 16 mm. The coil is contained within an 80 mm long cylindrical coil holder with a diameter of 19 mm. Before introduction of the coil into the anal canal, a condom was placed over the



**Figure 2.** Coronal image of a transsphincteric fistula.

3D HPUS image (A) and endoanal MRI (T2-weighted, fast spin echo) (B) showing the endoprobe (1) and anal coil (1), the IAS (3), the EAS (4), the fistula and the internal opening (5; arrow), fibrosis (6), puborectal muscle (7), and levator ani muscle (8). H = head; A = anterior; L = left; R = right; and F = feet.

coil, and ultrasound gel was used as a lubricant. The coil was introduced while the patient was lying in the left lateral position. After introduction of the coil, the patient carefully turned to a supine position, and the position of the coil was rechecked.

The following sequences were performed in each patient: axial T2-weighted contrast-enhanced fast field echo with acquisition time of 5 minutes 39 seconds, imaging matrix 205x256, number of signal averages 2, repetition time 23 ms, echo time 14 ms, flip angle 60°, field of view 140 mm, and slice thickness 2 mm without gaps; axial T2-weighted fast spin echo with fat saturation, acquisition time 2 minutes 23 seconds, imaging matrix 186x256, number of signal averages 3, repetition time 5086 ms, echo time 100 ms, flip angle 90°, field of view 120 mm, and slice thickness 4 mm with a gap of 0.4 mm; and coronal and sagittal T2-weighted fast spin echo without fat saturation, acquisition time 2 minutes 34 seconds, imaging matrix 186x256, number of signal averages 4, repetition time 2454 ms, echo time 100 ms, flip angle 90°, field of view 120 mm, and slice thickness 4 mm with gaps of 0.4 mm.

### *Surgery*

All patients underwent complete mechanical bowel preparation (polyethylene glycol). After introduction of general endotracheal anesthesia, metronidazole (500 mg) and cefuroxime (1500 mg) were administered intravenously. With the patient in the prone jackknife position, the internal opening of the fistula was exposed with an anal retractor, and the fistula tract was explored.

After surgical exploration, the 3D HPUS and endoanal MRI case report forms were reviewed, and on the basis of these results and the surgical results, the most appropriate surgical treatment was performed. Intersphincteric and transsphincteric fistulas that traversed the lower third of the external anal sphincter were then laid open in the traditional manner. Transsphincteric fistulas that traversed the upper two-thirds of the external anal sphincter were treated by performance of a transanal advancement flap repair as described previously.<sup>13,14</sup>

### *Statistical analysis*

3D HPUS, endoanal MRI, and surgical findings were compared to assess agreement between the three methods. Agreement rates and kappa values ( $\kappa \leq 0.20$ , poor agreement;  $\kappa = 0.21-0.40$ , fair;  $\kappa = 0.41-0.60$ , moderate;  $\kappa = 0.61-0.80$ , good; and  $\kappa > 0.80$ , very good agreement) were calculated. Percentages of positive findings were compared with the McNemar test. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

The median time between 3D HPUS and endoanal MRI was 71 (interquartile range, 21–150) days, and the median time between the last study (3D HPUS or endoanal MRI) and surgery was 154 (interquartile range, 95–189) days. No complications occurred that were related to 3D



HPUS or endoanal MRI. Patients did not receive any treatment in the period between 3D HPUS, endoanal MRI, and surgery except for one patient who underwent drainage of a perianal abscess in the period between endoanal MRI and 3D HPUS. Results of the assessment of the perianal fistulas are given in Tables 1 and 2.

### *Primary fistula tract*

Classification of the primary tract was possible in 100% (21) of the patients with 3D HPUS, in 95% (20/21) with endoanal MRI, and in 90% (19/21) during surgery. These differences were not statistically significant. The agreement between 3D HPUS and surgery was 81% (17/21). No kappa value could be calculated because of the high prevalence of transsphincteric fistulas. The agreement between endoanal MRI and surgery was 90% (19/21,  $\kappa=0.47$ ). For 3D HPUS and endoanal MRI, the agreement was 90% (19/21); no kappa value could be calculated. Although classification of a primary tract was not possible in two patients during surgery, 3D HPUS and endoanal MRI showed a transsphincteric fistula in one patient, and in the other, 3D HPUS showed a transsphincteric fistula and endoanal MRI was not able to classify the fistula. However, this is the same patient who underwent drainage of an abscess after endoanal MRI had been performed and before 3D HPUS had been performed, so that a fistula may not have been identified on endoanal MRI. In one patient, 3D HPUS classified a fistula as intersphincteric, and surgery and endoanal MRI classified this fistula as transsphincteric. In another patient, 3D HPUS and endoanal MRI found a transsphincteric fistula, and during surgery, an intersphincteric fistula was found.

### *Secondary tracts*

Circular secondary tracts were found in five patients during 3D HPUS, in nine patients during endoanal MRI, and in two patients during surgery. The difference between endoanal MRI and surgery was statistically significant ( $p=0.039$ ). The agreement between 3D HPUS and surgery was 67% (14/21); no kappa value could be calculated. For endoanal MRI and surgery, the agreement was 57% (12/21,  $\kappa=0.07$ ), and for 3D HPUS and endoanal MRI, the agreement was 71% (15/21,  $\kappa=0.45$ ).

In total, four linear secondary tracts were found during surgery, one with 3D HPUS, and none with endoanal MRI. These differences were not statistically significant. The agreement was 76% (16/21) between 3D HPUS and surgery, 81% (17/21) between endoanal MRI and surgery, and 95% (20/21) between 3D HPUS and endoanal MRI. No kappa values could be calculated for the linear secondary tracts. Of the four patients who had a cranial linear secondary tract during surgery, one patient had an intersphincteric circular secondary tract on endoanal MRI. Three-dimensional HPUS showed a caudal linear secondary tract in one patient, whereas endoanal MRI showed an intersphincteric circular secondary tract in this patient.

The median time between 3D HPUS and endoanal MRI was 66 (interquartile range, 21–160) days; median time between the last study (3D HPUS or endoanal MRI) and surgery was 154 (interquartile range, 95–189) days. In the period between 3D HPUS and endoanal MRI and between 3D HPUS or endoanal MRI and surgery, the perianal fistula could have changed; healing or deterioration could have occurred. The main difference we found between 3D HPUS, endoanal MRI, and surgery was the identification of circular secondary tracts. Endoanal MRI was able to identify more circular secondary tracts than 3D HPUS and surgery, and the difference between endoanal MRI and surgery was statistically significant ( $p=0.039$ ). These results could be because of the time interval between the different studies, because some of these patients could have improved clinically, but it may also be that endoanal MRI is more effective in detecting secondary tracts.

Another limitation of the present study is the high prevalence of transsphincteric fistulas in the classification of the primary fistula tract and the lack of extrasphincteric and suprasphincteric fistulas in this group of patients. Previous studies have shown that extrasphincteric and suprasphincteric fistulas have a lower prevalence, occurring mainly in patients with recurrent fistulas and patients with Crohn's disease.<sup>4,15</sup> Because perianal fistulas caused by Crohn's disease are not operated on in our centre, they were excluded from the present study.

Several studies have compared the results of endoanal ultrasonography and MRI for assessing perianal fistulas.<sup>7–11</sup> Two studies<sup>9,10</sup> found MRI to be more accurate than EUS. Lunniss et al.<sup>9</sup> used body coil MRI, and Hussain et al.<sup>10</sup> used endoanal coil MRI. In both studies, a 7 MHz radial endoanal probe was used for EUS. Orsoni et al.<sup>7</sup> found EUS performed with a 7 MHz rigid linear endoanal probe to be a more sensitive modality for imaging perianal Crohn's disease than pelvic MRI in a prospective study with 22 patients. When using a 10 MHz rotating ultrasound probe complemented with probing, Gustafsson et al.<sup>8</sup> found results comparable to those of body coil MRI in 23 patients with a perianal fistula. In a recent study, Schwartz et al.<sup>11</sup> concluded that EUS, MRI, and examination under anaesthesia were all accurate tests for determining fistula anatomy in patients with perianal Crohn's disease. They suggested that the optimal approach may be to combine any two of the three methods. EUS was performed with a 7.5 MHz biplane probe, and a phased-array coil was used for pelvic MRI. A consensus of the three methods was used as a gold standard, unlike in most studies in which only surgery is used as a gold standard.

In most of the studies mentioned above, surgery was also used as a gold standard,<sup>7–9</sup> although EUS and MRI are both well-established techniques for assessing fistulas. The use of surgery as a gold standard has been questioned. Poen et al.<sup>2</sup> demonstrated two secondary tracts with HPUS that were not found during surgery; these patients developed a recurrent fistula, which suggests that these branches were actually present at the time of HPUS. In a follow-up study with 37 patients, body coil MRI was shown to make better predictions regarding patient outcome

than surgical findings.<sup>16</sup> Another study<sup>8</sup> with 23 patients found that in 2 patients who did not heal after surgery, EUS showed an extension or abscess that was not identified at the time of operation. For body coil MRI, the corresponding figure was three. In the same study, no internal opening was found during surgery in three patients. EUS identified an opening in one case, and body coil MRI identified an opening in two cases. Therefore, we found it justified in the present study to determine the agreement of the results of 3D HPUS and endoanal MRI in evaluating perianal fistulas and to compare these results with surgical findings instead of using surgery as a gold standard. In the present study, surgical treatment failed in one of the patients for whom the surgical outcome is known. Three-dimensional HPUS and endoanal MRI found a circular secondary tract in this patient that was not found during surgery. However, the reason the advancement flap repair was not successful could also be because this patient had been operated on before<sup>13,17</sup> or because he was a heavy smoker.<sup>14</sup>

The results in the studies mentioned above differ,<sup>7-11</sup> and different techniques for MRI and EUS were used. One of the reasons for the different results found could be the use of different probes for EUS. Better results were found when a linear probe or biplane probe was used.<sup>7,11</sup> More information can be obtained with these probes. A linear probe has the ability to follow the echo rich bubbles that move along the fistula tract. Gustafsson et al.<sup>8</sup> used a 10 MHz probe and found a higher sensitivity for identifying the internal opening than other studies. This is probably because of the higher resolution with a 10 MHz probe, although its lesser depth penetration can be a disadvantage in identifying deeper extensions and abscesses. In the present study, we used 3D EUS, which offers extra visualisation of the anal canal and enables axial images of the anal canal to be reconstructed in the coronal and sagittal planes. It is also possible to map the location and dimensions of sphincteric components along the length of the anal canal. More information on the course of the fistula tract and its secondary tracts in relation to the sphincters can be obtained, and the internal opening can be identified.<sup>6</sup>

In the present study, MRI was performed with an endoanal coil. Most of the studies mentioned earlier used a body coil.<sup>7-9</sup> Body coil MRI may give additional information on structures farther away from the anal canal, but it can be difficult to make a distinction between fistula tracts and vessels.<sup>8</sup> With an endoanal coil, the depiction of the normal anal sphincter complex on magnetic resonance images is excellent.<sup>18</sup> DeSouza et al.<sup>19</sup> found that the use of an endoanal coil allows high resolution of images of anal musculature and perianal fat to be obtained so that detailed evaluation of these areas is possible, and a high accuracy for detecting fistula tracts and abscesses can be achieved. In a comparative study of ten patients with an anal fistula, use of the endoanal coil appeared to be superior to use of a surface coil.<sup>20</sup> Hussain et al.<sup>10</sup> found that classification of fistulas was possible in 25 (89%) of 28 patients with endoanal MRI, although concordance with surgery was moderate (64%,  $\kappa=0.43$ ). Halligan and Bartram<sup>21</sup> found a lower surgical concordance for endoanal imaging (68%)

than with body coil imaging (96%), especially for secondary extensions. deSouza et al.<sup>22</sup> showed in a study with 20 patients that the concordance between MRI and surgery for identifying the presence and site of the collection, the primary tract, and the internal opening in both simple and complex cases was superior with the endoanal coil compared with the phased array. However, for supralelevator/ subcutaneous extensions, concordance was superior with the phased array compared with the endoanal coil. A combination of both techniques would offer the best results for preoperative evaluation of perianal fistulas.

An important issue is that hydrogen peroxide was not used in any of the studies mentioned above. This could be a reason for some of the disappointing results found with EUS. Excellent results have been reported for the assessment of perianal fistulas when hydrogen peroxide is used as a contrast medium.<sup>1-5</sup> Poen et al.<sup>2</sup> found that the accuracy for determining the Parks classification rose by 30%. A problem encountered by conventional EUS is that it is difficult to distinguish between scar tissue and active fistulas. When hydrogen peroxide is introduced into the external opening, a fistula tract appears as hyperechoic. This way, it is easier to identify a fistula tract and the internal opening or any secondary tracts. The use of hydrogen peroxide has proved to be a safe method. In our centre, no complications have occurred related to the introduction of hydrogen peroxide, nor are any documented in the studies mentioned above.<sup>1-5</sup> Although this method provides good results and is safe, an external opening must be visible to introduce hydrogen peroxide.

In the present study, 3D HPUS and endoanal MRI proved to have comparable results for evaluating perianal fistulas. These results are also comparable to the results found during surgical exploration. Therefore, we can conclude that both 3D HPUS and endoanal MRI can be used for reliable preoperative evaluation. 3D EUS combined with hydrogen peroxide offers extra visualisation of perianal fistulas and therefore provides more information than conventional EUS. 3D HPUS is more economic and can be used for patients who cannot undergo MRI. The choice of technique should depend on the expertise and availability of imaging techniques in a centre.

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# Chapter 7

## Hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography and endoanal magnetic resonance imaging in evaluating perianal fistulas: agreement and patient preference

### Abstract

#### **Purpose:**

To determine agreement between hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography (3D HPUS) and endoanal magnetic resonance imaging (MRI) in preoperative assessment of perianal fistulas and to assess patient discomfort and preference with regard to these techniques.

#### **Methods:**

Forty patients (31 M, aged 21-70 years) with symptoms of a perianal fistula and a visible external opening underwent preoperative 3D HPUS and endoanal MRI. The results were assessed separately by experienced observers. Fistulas were described according to the following characteristics: classification of the primary fistula tract according to Parks, location of the internal opening, presence of secondary tracts and fluid collections. Patients were asked to score the amount of discomfort experienced during both procedures and express their preference for either method.

#### **Results:**

The median time interval between 3D HPUS and endoanal MRI was 14 days (range: 0-91). The methods agreed in 88% (35/40,  $\kappa=0.45$ ) for the primary fistula tract, in 90% (36/40,  $\kappa=0.83$ ) for the location of the internal opening, in 78% (31/40,  $\kappa=0.62$ ) for secondary tracts, and in 88% (35/40,  $\kappa=0.63$ ) for fluid collections. Both methods were associated with similar discomfort, and there was no patient preference for one procedure over the other.

#### **Conclusions:**

3D HPUS and endoanal MRI are equally adequate for the evaluation of perianal fistulas. Both methods are associated with similar discomfort and patients have no preference for either procedure.

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## INTRODUCTION

Preoperative assessment of perianal fistulas is necessary for optimal surgical treatment. This assessment should ideally be performed with high adequacy, low patient burden and costs. The main techniques for this purpose are endoanal ultrasonography (EUS) and magnetic resonance imaging (MRI).

Several studies have compared these techniques,<sup>1-6</sup> often using examination under anaesthesia as a gold standard.<sup>1,4</sup> Some studies favoured EUS<sup>3,4</sup> and others MRI.<sup>1,2</sup> Experience and variations in technique, such as the use of hydrogen peroxide during EUS and an endocoil during MRI can partly explain these differences. In addition, the use of surgery as a gold standard has been questioned as studies have proved that EUS<sup>6,7</sup> and MRI<sup>4,8,9</sup> are both able to detect fistula tracts that are not seen during examination under anaesthesia.

The latest development in EUS is the combined use of three-dimensional EUS and hydrogen peroxide. Until recently no studies had been done comparing hydrogen peroxide-enhanced three-dimensional endoanal ultrasonography (3D HPUS) and endoanal MRI in evaluating cryptoglandular fistulas. In a previous study<sup>6</sup> with 21 patients both techniques showed good agreement with surgical findings. Although excellent agreement was found for the primary fistula tract and location of the internal opening, less agreement was seen for secondary tracts, these were mainly seen on endoanal MRI. However, limitations of this study were the small number of patients and the considerable time interval between 3D HPUS, endoanal MRI and surgery. These limitations may well explain some of the differences found. In addition, no previous study has looked into patient preference for one technique over the other.

Therefore, a new study was performed with a shorter time interval between the two investigations and based on earlier studies surgery was not used as a gold standard. The aim of the present study was to determine agreement between 3D HPUS and endoanal MRI for preoperative evaluation of perianal fistulas and to assess patient discomfort and preference.

## PATIENTS AND METHODS

In a retrospective study, 40 patients (31 M, aged 21-70 years), including seven who were included in a previous study<sup>6</sup> with symptoms of a cryptoglandular perianal fistula were studied between January 2002 and January 2003. A previous attempt at surgical repair had been performed in 19 patients. All patients underwent 3D HPUS and endoanal MRI. Patients were excluded if there was no visible external opening as this prevented the use of hydrogen peroxide during 3D HPUS and if the time interval between 3D HPUS and endoanal MRI exceeded three months. The amount of discomfort experienced during 3D HPUS and endoanal MRI and



preference with regard to the two procedures was assessed in all patients by means of a questionnaire.

The endoanal MRI images were interpreted by the Radiology Department (SD, SH), and 3D HPUS was performed and interpreted by the Gastroenterology Department (RW, RF). The observers were blinded to one another's results. The following characteristics were recorded: classification of the primary fistula tract (according to Parks et al.:<sup>10</sup> intersphincteric, transsphincteric, extrasphincteric, suprasphincteric or not classified), secondary tracts (none, intersphincteric, transsphincteric, supralevator, extrasphincteric) and location of the internal opening (not identified, anterior, posterior, left lateral, right lateral) and fluid collections.

EUS was performed using a 3D diagnostic ultrasound system (Hawk type 2102, B-K Medical, Herlev, Denmark) with a 7 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a hard sonolucent cone (diameter 1.7 cm) filled with water, producing a 360° view. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were made of the distal part of the rectum and the anal canal using a pullback device at a speed of 2mm/sec. Three-dimensional images were obtained using a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark). Fistula tracts were visualised as tube like hypoechoic lesions.

Hydrogen peroxide (3%) was introduced into the fistula tract with a flexible intravenous cannula (Venflon®, Ohmeda, Helsingborg, Sweden) and EUS was repeated as described earlier. After infusion of hydrogen peroxide, which generates the formation of small air-bubbles within the fistula tract, the ultrasonographic appearance of such tracts changes from hypoechoic to bright hyperechoic. By comparing the images obtained with and without hydrogen peroxide, the fistula tract and its extensions can be identified and discriminated from previous scars. This makes it possible to distinguish between active fistulas and fibrotic tissue in patients who had previously undergone surgery. An internal opening was defined as an echogenic (HPUS) breach at the level of the submucosa. A fluid collection was defined as the presence of a hyperechoic cavity localised in the peri-anorectal structures distinguishable from the primary fistula tract.

Endoanal MRI was performed at 1.5 T (Philips Medical Systems, Best, The Netherlands). The endoanal coil consisted of a fixed, rectangular, 60 mm long rigid receive coil with a width of 16 mm and was contained within an 80 mm long cylindrical coil holder with a 19 mm diameter. The coil was introduced with the patient in the left lateral position and after introduction the patient was carefully turned to a supine position. A MRI protocol as described before was used.<sup>6</sup>

A questionnaire consisting of three multiple-choice and two open questions was sent to patients included in the study. Patients were asked to score the amount of discomfort they had experienced during 3D HPUS and endoanal MRI on a five-point scale ranging from one (no discomfort at

all) to five (severe discomfort). They were also asked which procedure (3D HPUS or endoanal MRI) they would prefer to undergo should this be necessary in future. In addition, patients were asked to state any positive or negative points in their experience of 3D HPUS and endoanal MRI.

### *Statistical analysis*

To assess agreement between the two methods the 3D HPUS and endoanal MRI results were compared. Agreement rates and kappa values ( $\kappa \leq 0.20$ , poor;  $\kappa = 0.21-0.40$ , fair;  $\kappa = 0.41-0.60$ , moderate;  $\kappa = 0.61-0.80$ , good;  $\kappa > 0.80$ , very good agreement) were calculated. The paired Wilcoxon test was used in comparing the amount of discomfort experienced during 3D HPUS and endoanal MRI. The Mann-Whitney test was used for comparison of the amount of discomfort experienced between groups. Correlation coefficients given are Spearman's. For patient preference 95% confidence intervals were calculated. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

Successful 3D HPUS and endoanal MRI examinations were conducted in all 40 patients. In one patient, hydrogen peroxide was inadvertently introduced subcutaneously without further problems. No complications occurred following endoanal MRI. The median time interval between 3D HPUS and endoanal MRI was 14 days (range: 0-91), in 14 patients 3D HPUS was performed first, in 25 endoanal MRI and in one patient both examinations were performed on the same day. A questionnaire was sent to 39 of the 40 patients, one patient had died during follow-up of a condition unrelated to the perianal fistula. A total of 37 (95%) patients responded and two patients could not be traced. The median time interval between 3D HPUS and completing the questionnaire was 240 days (range 79-463) and between endoanal MRI and completing the questionnaire was 260 days (range 85-477). Results of the assessment of the perianal fistulas are given in table 1.

### *Primary fistula tract*

Classification of the primary tract was possible in 39 of the 40 patients using 3D HPUS; this was also the case for endoanal MRI. The agreement between 3D HPUS and endoanal MRI was 88% (35/40,  $\kappa = 0.45$ , indicating moderate agreement). In the patient in whom 3D HPUS could not identify a fistula, endoanal MRI showed a transsphincteric fistula, and in the patient in whom endoanal MRI could not detect a fistula, 3D HPUS showed an intersphincteric fistula. In two other patients 3D HPUS identified a transsphincteric fistula and endoanal MRI identified an intersphincteric fistula in both patients. In addition, 3D HPUS found a suprasphincteric fistula in one patient that was identified as a transsphincteric fistula on endoanal MRI.

**Table 1.** Results of the assessment of perianal fistulas using 3D HPUS and endoanal MRI.

	3D HPUS	Endoanal MRI
<i>Classification of the primary fistula tract ♦</i>		
Parks classification		
Intersphincteric	2	3
Transsphincteric	35	35
Suprasphincteric	2	1
Extrasphincteric	0	0
Not classified	1	1
<i>Location of an internal opening ✖</i>		
Not identified	2	1
Anterior	10	9
Posterior	23	25
Left lateral	4	4
Right lateral	1	1
<i>Secondary tracts ●</i>		
None	23	21
Intersphincteric	2	4
Transsphincteric	1	4
Supraleatory	14	11
Extrasphincteric	0	0
<i>Fluid collections ▲</i>		
Present	7	10
Not present	33	30

♦: agreement 88% (35/40),  $\kappa=0.45$

✖: agreement 90% (36/40),  $\kappa=0.83$

●: agreement 78% (31/40),  $\kappa=0.62$

▲: agreement 88% (35/40),  $\kappa=0.63$

### *Location of an internal opening*

The location of an internal opening could be identified in 38 patients (95%) with 3D HPUS and in 39 (98%) patients with endoanal MRI, agreement was 90% (36/40,  $\kappa=0.83$ , indicating very good agreement). In two patients in whom 3D HPUS could not identify an internal opening, endoanal MRI was successful. In one of these patients the primary fistula tract could not be detected with 3D HPUS. In one patient, an anterior internal opening was seen during 3D HPUS, however, a posterior internal opening was found during endoanal MRI. After revision of 3D HPUS, the internal opening was found to be located posteriorly.

### *Secondary tracts*

Three-dimensional HPUS was able to detect secondary tracts in 17 patients and endoanal MRI in 19 patients, agreement was 78% (31/40,  $\kappa=0.62$ , indicating good agreement). In 18 patients, no secondary tracts were seen with either method. Secondary tracts were seen in five patients with endoanal MRI that were not seen with 3D HPUS and three were seen with 3D HPUS and not with endoanal MRI. In one patient, 3D HPUS found a supraleatory secondary tract and endoanal MRI found a transsphincteric secondary tract.

### *Fluid collections*

Fluid collections were found in seven patients with 3D HPUS and in 10 with endoanal MRI, agreement was 88% (35/40,  $\kappa=0.63$ , indicating good agreement). A fluid collection was seen in one patient with 3D HPUS that was not seen with endoanal MRI. In four patients a fluid collection was seen with endoanal MRI that was not seen with 3D HPUS, however, the latter found a secondary tract in three of these patients.

### *Patient preference*

Thirteen patients experienced more discomfort during 3D HPUS, 14 during endoanal MRI and in 10 patients the rating was the same. This difference was not significant (Wilcoxon:  $p=0.99$ ). Younger patients experienced more discomfort than older patients did ( $r=-0.37$ ,  $p=0.024$  for 3D HPUS and  $r=-0.34$ ,  $p=0.042$  for endoanal MRI). There was no difference between males and females (Mann-Whitney:  $p=0.120$  for 3D HPUS and  $p=0.622$  for endoanal MRI) nor did the order in which the two procedures were performed affect the amount of discomfort experienced ( $p=0.107$  for 3D HPUS and  $p=0.256$  for endoanal MRI). Ten patients (27%; 95% CI: 14%-44%) preferred 3D HPUS, 15 (41%; 95% CI: 25%-58%) endoanal MRI, and 12 (32%; 95% CI: 18%-50%) had no preference.

The main negative points put forward by patients were: the use of peroxide during 3D HPUS (11), discomfort because of the probe used for endoanal MRI (7) and position or noise in the MRI (10).

## **DISCUSSION**

Our results show a very good agreement between 3D HPUS and endoanal MRI in evaluating perianal fistulas and that patients experience no difference in discomfort and have no preference for either procedure. Thus, both 3D HPUS and endoanal MRI can be considered to be reliable preoperative assessment procedures. Although good agreement was found in the classification of the primary fistula tract, the kappa value showed only moderate agreement. This may be explained by the high prevalence of transsphincteric fistulas in this group of patients.

Studies comparing EUS and endoanal MRI for evaluating perianal fistulas have reported conflicting results. Some studies found better

results with EUS<sup>3,4</sup> and others with MRI.<sup>1,2</sup> The good agreement found in our study is probably due to the use of hydrogen peroxide as a contrast medium combined with 3D EUS. EUS combined with hydrogen peroxide has improved the visualisation of perianal fistulas compared to conventional EUS,<sup>7,11-15</sup> and allows a better distinction between scar tissue and active fistulas. In one study<sup>7</sup> secondary tracts were found with HPUS that were not found during surgery. These patients developed a recurrent fistula, suggesting that these branches were actually present at the time of HPUS. The use of hydrogen peroxide is safe and no complications have been documented in the studies cited.<sup>7,11-15</sup>

In addition, 3D EUS can reconstruct axial images in the coronal and sagittal planes, which makes it possible to map the location and dimensions of the different components of the anal sphincter along the length of the anal canal.<sup>16-18</sup> More information on the course of the fistula tract and its secondary tracts in relation to the sphincters can be obtained and the internal opening identified.

Even though we found good agreement between 3D HPUS and endoanal MRI for evaluating perianal fistulas our study has some limitations. One limitation is the time interval between the two procedures. Although we aimed for a shorter time interval between the two investigations compared to our previous study,<sup>6</sup> a median interval of 14 days with a range up to three months could be the reason for some of the differences found. The main difference found was for secondary tracts. In the period between 3D HPUS and endoanal MRI the perianal fistula could have changed; healing or deterioration could have occurred. However, no significant differences were found in median time interval between the patients with agreement and without agreement with regard to 3D HPUS and endoanal MRI findings. This indicates that the time interval had no major effect on these results.

Another limitation of this study was the high prevalence of transsphincteric fistulas and the low prevalence of suprasphincteric and extrasphincteric fistulas. Therefore, no conclusions can be drawn as to how adequate the two methods are in detecting these types of fistulas. However, the prevalence of these types of fistulas is low<sup>13,19</sup> and transsphincteric fistulas are the main type of fistulas seen. In addition, our centre is a referral centre and we often see patients with fistulas that have been operated on numerous times. These fistulas are often complex. The results of this study show that 3D HPUS and endoanal MRI are both good techniques for evaluating these fistulas.

In the present study we found it justified to compare 3D HPUS and endoanal MRI in evaluating perianal fistulas and not to use surgery as a gold standard. Several studies suggest that MRI is superior to examination under anaesthesia for fistula classification because this technique can identify fistulas and secondary tracts that are not found during examination under anaesthesia.<sup>1,4,8,9,20</sup> MRI has also been found to have an important impact on surgical outcome.<sup>21-23</sup> Beets-Tan et al.<sup>21</sup> concluded that high spatial resolution MRI provided additional information in

patients with complex fistulas leading to changes in operative approach. In a study with 71 patients with a recurrent fistula, surgery guided by MRI reduced further recurrence of perianal fistulas by 75%.<sup>22</sup> The same group also found that MRI has a therapeutic impact of 10% for primary perianal fistulas, precipitating surgery that is likely to reduce recurrence.<sup>23</sup> EUS studies have also reported that EUS is able to identify tracts not seen during surgery.<sup>4,7</sup> Furthermore, in a previous study we found that 3D HPUS and endoanal MRI both compare well to surgical findings and that tracts were identified on both 3D HPUS and endoanal MRI that were not found during surgery.<sup>6</sup> Another study<sup>5</sup> reported that examination under anaesthesia, EUS and MRI could all accurately determine fistula anatomy and that therefore the optimal approach might be a combination of two of the three methods.

As well as comparing 3D HPUS and endoanal MRI in evaluating perianal fistulas, we also assessed patient preference, which to our knowledge has not been taken into account in previous studies. We found that patients did not experience any difference in the amount of discomfort with either procedure. This result did not differ for males and females nor was it related to the order in which patients underwent the procedures. However, there was a significant difference for age, younger patients experienced more discomfort than older patients did. Furthermore, patients expressed no preference for one technique over the other. However, a limitation of these findings is that the questionnaires were sent to the patients after they had undergone the examinations. The median time interval between 3D HPUS and the questionnaire was 240 days and between endoanal MRI and the questionnaire was 260 days. Since these intervals are relatively long, recall bias may have occurred. However, as this is the case for both procedures, this bias has probably not affected the results.

In conclusion, 3D HPUS and endoanal MRI show good agreement for evaluating perianal fistulas and can both be used for reliable preoperative assessment. Furthermore, no differences in patient discomfort or preference were found. The choice of technique should depend on the expertise and availability of imaging techniques in a centre.

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# Chapter 8

## **Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulas in Crohn's disease with infliximab: a double-blind placebo-controlled study**

### **Abstract**

#### **Purpose:**

Ciprofloxacin is moderately effective for treating perianal fistulizing Crohn's disease but symptoms usually reoccur when treatment is discontinued. Infliximab is effective but often requires maintenance therapy. We aimed to evaluate whether a combination of ciprofloxacin and infliximab is more effective than infliximab alone.

#### **Methods:**

We performed a double blind placebo-controlled study in patients with perianal fistulizing Crohn's disease. Patients were randomly assigned to receive 500 mg ciprofloxacin twice daily or a placebo for 12 weeks. All patients received 5 mg/kg infliximab in week 6, 8 and 12 and were followed for 18 weeks. Primary endpoint was clinical response, defined as a 50% or greater reduction from baseline in the number of draining fistulas. Secondary endpoints were the change in Perianal Disease Activity Index (PDAI) and hydrogen peroxide-enhanced 3D endoanal ultrasonography (3D HPUS) findings between baseline and week 18. Analysis was by intention-to-treat.

#### **Results:**

Twenty-four patients were included, two discontinued treatment and 22 completed the study. After six weeks, clinical response was 9% (1/11) in the ciprofloxacin group and 15% (2/13) in the placebo group ( $p=1.0$ ). At week 8 and 12 this increased to 91% (10/11) in the ciprofloxacin group and 62% (8/13) in the placebo group ( $p=0.17$ ). At week 18, response was 73% (8/11) in the ciprofloxacin group and 39% (5/13) in the placebo group ( $p=0.12$ ). Logistic regression analysis showed a tendency for patients treated with ciprofloxacin to respond better (OR= 2.37, CI: 0.94-5.98,  $p=0.07$ ). PDAI scores had improved ( $p=0.008$ ) in the ciprofloxacin group but not in the placebo group. On 3D HPUS, improvement was seen in three patients with a clinical response.

#### **Conclusions:**

A combination of ciprofloxacin and infliximab is more effective than infliximab alone in the treatment of perianal fistulas in Crohn's disease. Despite clinical response, persistent fistula tracts remain visible on 3D HPUS.

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## INTRODUCTION

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract that can be complicated by perianal fistulas. These fistulas develop either as a result of a deep penetrating ulcer in the anus or rectum, or secondary to an anal gland abscess.<sup>1,2</sup> Patients with colonic disease have a higher incidence of perianal fistulas, in particular when the rectum is involved, but a perianal fistula can also be the initial presentation of Crohn's disease when other signs are still absent. The prevalence of perianal fistulas in patients with Crohn's disease ranges from 20% to 50%.<sup>1</sup>

Fistulas rarely heal spontaneously; medical or surgical treatment is often required.<sup>2</sup> The main medical therapies include antibiotics, azathioprine or 6-mercaptopurine, and infliximab. Other drugs that are sometimes used include tacrolimus and cyclosporine.<sup>1,2</sup>

The efficacy of antibiotics for the treatment of Crohn's fistulas has only been tested in uncontrolled studies, which have suggested a short-term benefit of both ciprofloxacin and metronidazole either alone or in combination.<sup>3-8</sup> However, drug discontinuation or dose reduction often led to disease relapse. Ciprofloxacin is often preferred to metronidazole because it is associated with fewer side effects.<sup>3-8</sup>

Infliximab, a chimeric anti-TNF alpha monoclonal antibody has more consistently been shown to be effective in healing perianal fistulas in Crohn's disease.<sup>9,10</sup> The median duration of fistula closure following induction treatment is three months, and repeated infusions are often required. Rapid closure of the external opening may be associated with abscess formation and fistula recurrence because of delayed healing of the underlying fistula. Furthermore, several imaging studies have reported that infliximab therapy may lead to closure of the external opening, but fistula tracts remain visible on magnetic resonance imaging (MRI)<sup>11,12</sup> or endoanal ultrasonography (EUS).<sup>13,14</sup>

As ciprofloxacin and infliximab both have an effect on perianal fistulas in Crohn's disease, the aim of the present study was to evaluate whether a combination of the two is more effective than infliximab alone. We therefore conducted a double-blind placebo-controlled study using clinical and endosonographic findings.

## PATIENTS AND METHODS

### *Patients*

The study was conducted in the Erasmus MC from January 2002 to January 2004. Patients were eligible for inclusion if they had previously been diagnosed with Crohn's disease based on endoscopy and histology and if the disease was complicated by single or multiple draining perianal fistulas.

All patients in the reproductive phase had to use adequate birth control measures throughout the study. Concomitant therapy could be used at a stable dose, aminosalicylates for at least four weeks and oral corticosteroids for at least three weeks. Immunosuppressive therapy could also be used, azathioprine for the last three months at a stable dose and methotrexate for at least three months at a dosage that had been stable for more than four weeks. Patients who were included from January 2003 onwards received hydrocortisone intravenously immediately prior to the infliximab infusions if they were not on concomitant immunosuppressive therapy.

Patients using concomitant treatment with cyclosporine were excluded. Other exclusion criteria were complications of Crohn's disease such as current strictures or abscesses or extraintestinal manifestations of Crohn's disease. Patients were excluded in case of serious infections or any currently known malignancy or premalignant lesion or any history of malignancy in the last five years. Patients could neither have been treated with ciprofloxacin in the last three months or with infliximab in the last six months, or have undergone previous anal surgery, with exception of drainage of an abscess.

All patients signed informed consent; the ethical committee of the Erasmus MC approved the study protocol.

### *Protocol*

After inclusion, patients were randomly assigned to receive 500 mg ciprofloxacin twice daily or a placebo for 12 weeks. Randomisation was stratified according to concomitant therapy with azathioprine and methotrexate. Patients and physicians were blinded to therapy. At week 6, 8 and 12 all patients additionally received 5 mg/kg infliximab intravenously.

Baseline evaluation of patients consisted of a medical history, physical examination, routine blood tests, and a urine pregnancy test in women. A tuberculin skin test and chest X-ray were performed on all patients to exclude active tuberculosis. The Perianal Disease Activity Index (PDAI) was determined to assess perianal disease. Hydrogen peroxide enhanced three-dimensional endoanal ultrasonography (3D HPUS) was performed to classify perianal fistulas and exclude abscess formation. Photographs were taken to document perianal disease.

### *PDAI*

The PDAI score is a simple five-point index that is able to detect important change in perianal status. Scores range from 0 to 20 and higher scores indicate more severe disease activity. The five elements are the presence or absence of discharge, pain or restriction of daily living activities, restriction of sexual activity, the type of perianal disease, and the degree of induration.<sup>15</sup>

### 3D HPUS

EUS was performed using a 3D diagnostic ultrasound system (Hawk type 2102, B-K Medical, Herlev, Denmark) with a 7.5 MHz rotating endoprobe (type 1850, focal range 2 to 4.5 cm) covered by a hard sonolucent cone (diameter 1.7 cm) filled with water, producing a 360° view. In patients with a stenotic anus, a smaller endoprobe (7 MHz, type 6004, focal range 0.5 to 3 cm) and cone (diameter 0.9 cm) were used. The endoprobe was introduced into the rectum with the patient in the left lateral position. Serial radial images were made of the distal part of the rectum and the anal canal using a pullback device at a speed of 2mm/sec. Three-dimensional images were obtained using a software program used for 3D reconstruction (Life Imaging System 2000, L3Di version 3.5.5, B-K Medical, Herlev, Denmark).

Fistula tracts were visualised as hypoechogenic tube like lesions. Hydrogen peroxide (3%) was used as a contrast medium and fistula tracts were seen as bright hyperechogenic. By comparing the images obtained with and without hydrogen peroxide, fistula tracts and previous scars could be distinguished.

The following characteristics of the fistula were recorded: classification of the primary fistula tract (according to Parks et al.:<sup>16</sup> intersphincteric, transsphincteric, extrasphincteric, suprasphincteric), secondary tracts, location of the internal opening, and fluid collections. Baseline images were compared to the images at week 18. Improvement was defined as a change in the number and size of active fistulas and secondary tracts, and the number of collections. Images with and without hydrogen peroxide were used for this purpose.

### Follow-up

Patients were evaluated by means of a medical history and physical exam at week 6 (before the first infliximab infusion), 8 (before the second infliximab infusion), 12 (before the last infliximab infusion) and 18 (six weeks after the last infliximab infusion). Final evaluation at week 18 also included blood tests equivalent to baseline. Furthermore, the PDAI score was determined and 3D HPUS was repeated. Adverse events were scored during all visits.

### Outcome measures

Clinical response, PDAI and 3D HPUS were used to evaluate treatment. The primary endpoint was a clinical response defined as a 50% or greater reduction from baseline in the number of draining fistulas determined at week 6, 8, 12 and 18. Closure of a perianal fistula was defined as no drainage despite firm finger compression. Secondary endpoints were the change in PDAI score and 3D HPUS findings between baseline and week 18.

### *Statistical analysis*

When this study protocol was set up, only two small studies<sup>6,7</sup> (eight and five patients) evaluating the effect of ciprofloxacin in the treatment of perianal fistulas in Crohn's disease were available. No randomised studies had been done. Therefore, it was not possible to predict what the difference would be between the two groups after treatment. Thus no accurate sample size could be determined. A randomised trial was performed so that there was no bias in the selection of patients for the different treatments. The enrolment period was two years.

Analysis was performed according to the intention-to-treat principle and included all patients who were screened and randomly assigned to treatment. In case of a missing endpoint a patient was classified as a non-responder. The effect of treatment with ciprofloxacin and placebo on the clinical outcome was compared with a Fisher exact test. Furthermore, a logistic regression including a random effect, which controls for four measurements in each patient, was done.

The difference in PDAI score between the two treatment groups was compared using the Mann Whitney U test. To determine changes in PDAI score between baseline and week 18 over time the Wilcoxon Signed Ranks Test was used. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

### *Patient characteristics*

Forty-one patients were invited to participate in the study. Twenty-four were enrolled and randomised. Seventeen patients were excluded, eight patients did not want to participate in the study, and nine were not eligible either because they did not have an active perianal fistula ( $n = 8$ ) at the time of randomisation, or because they had received previous treatment with ciprofloxacin in the last three months ( $n = 1$ ).

Patient characteristics of the 24 randomised patients are shown in Table 1. Eleven patients received ciprofloxacin and 13 placebo. Three patients were assigned to receive intravenous hydrocortisone prior to infliximab treatment. Two patients, one in either treatment group discontinued treatment. The patient in the ciprofloxacin group experienced an adverse event after the first infliximab infusion (arthralgias), and the patient in the placebo group had an exacerbation of Crohn's colitis leading to a change in concomitant medication prior to the first infliximab infusion. Twenty-two patients completed the study.

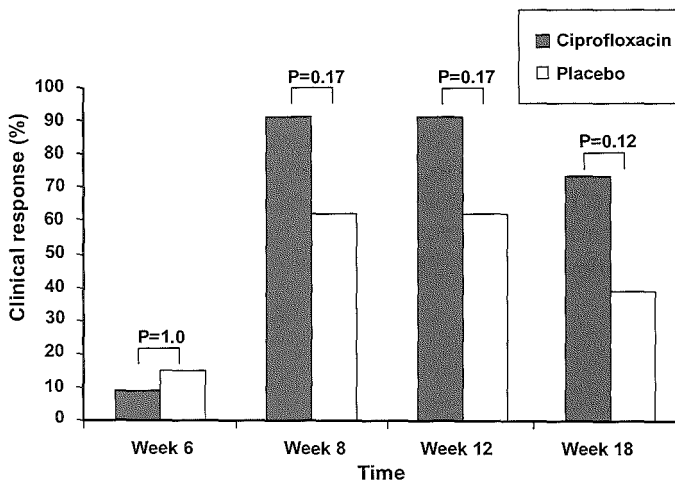
**Table 1.** Patient characteristics.

	Patients (n=24)
Sex (M/F)	12/12
Age (years)*	34 (18-61)
Age Crohn's disease was diagnosed (years)*	23 (11-34)
Time between diagnosis of Crohn's disease and onset of a perianal fistula (years)*	6 (0-27)
<b>Concomitant therapy:</b>	
Azathioprine	13
Methotrexate	2
Corticosteroids	4
Previous infliximab treatment	2
Ileostomy	3
Previous drainage of a perianal abscess	3

\* Values are expressed in median and range

### Clinical response

The clinical response results for week 6, 8, 12 and 18 are shown in Figure 1. After six weeks of treatment with ciprofloxacin or placebo, only one (9%) patient in the ciprofloxacin group and two (15%) in the placebo group ( $p=1.0$ ) had a clinical response defined as a 50% or greater reduction from baseline in the number of draining fistulas. At week 8,



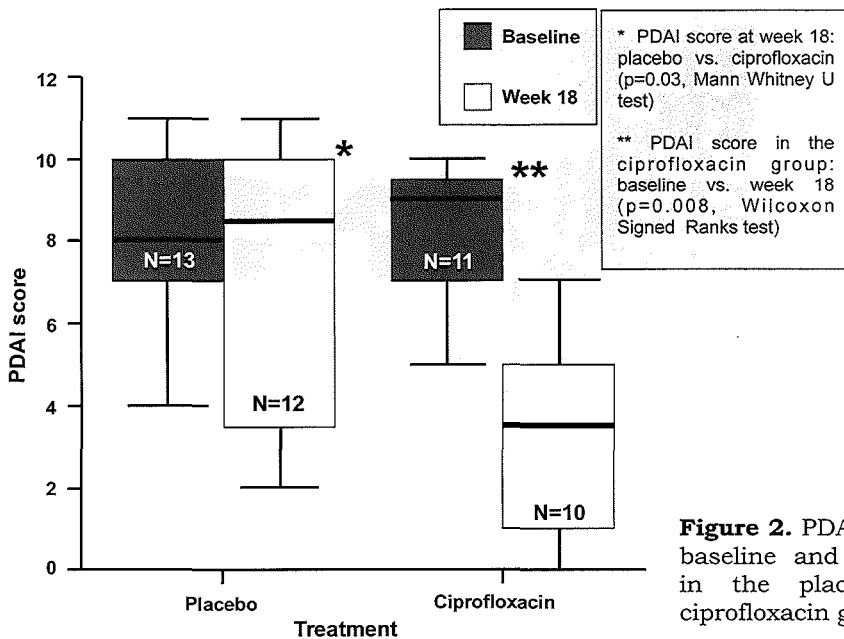
**Figure 1.** Clinical response at week 6, 8, 12 and 18 in the ciprofloxacin and placebo group.

At week 8, after one infusion of infliximab, a higher response rate was seen in the ciprofloxacin group (91%, 10/11) compared to the placebo group (62%, 8/13), but this difference was not statistically significant ( $p=0.17$ ). Similar results were found at week 12. At week 18, six weeks after discontinuation of treatment, the clinical response had decreased but was still higher in the ciprofloxacin group (73%, 8/11) compared to the placebo group (39%, 5/13) but again this difference was not statistically significant ( $p=0.12$ ).

Logistic regression analysis showed that there was a tendency towards better clinical response with ciprofloxacin than with a placebo (OR= 2.37, CI: 0.94-5.98,  $p=0.07$ ).

### PDAI score

At baseline there was no significant difference in median PDAI score between the ciprofloxacin group and the placebo group (9, range 5-10 vs. 8, range 4-11,  $p=0.77$ ). However, at week 18 the PDAI score was significantly lower in the ciprofloxacin group compared to the placebo group (3.5, range 0-7 vs. 8.5, range 2-11,  $p=0.03$ ). There was also a significant difference between baseline and week 18 in the ciprofloxacin group ( $p=0.008$ ) but not in the placebo group ( $p=0.47$ ) (Figure 2).

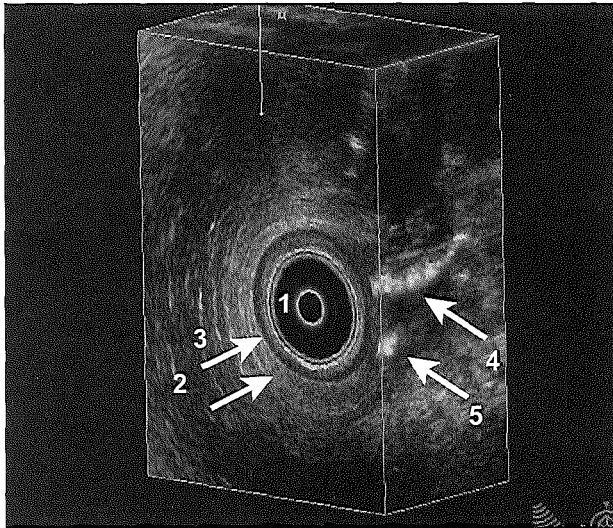


### 3D HPUS findings

At baseline 3D HPUS was performed in all 24 patients. In one patient with a known anal stenosis, a smaller endoprobe had to be used. The types of fistulas seen on 3D HPUS at baseline were: intersphincteric (1)

transsphincteric (6), complex transsphincteric with secondary tracts (16) and extrasphincteric (3). In two female patients with a complex transsphincteric fistula an anovaginal fistula was also seen. Figure 3 shows a 3D HPUS image of a complex fistula.

At week 18, 3D HPUS was performed in 21 patients, two patients had discontinued treatment and in one patient with a clinical response 3D HPUS was not possible due to technical problems with the smaller probe. In nine patients without a clinical response (two treated with ciprofloxacin and seven with a placebo) no change was seen in 3D HPUS findings compared to baseline. In the 12 patients with a clinical response (seven treated with ciprofloxacin and five with placebo), hydrogen peroxide could only be introduced in five patients, in three no change was seen but in two the fistula was only partially visible on 3D HPUS. Hydrogen peroxide could not be introduced in the other seven patients with a clinical response. In six patients hypoechogenic lesions were still visible, but in one an improvement was seen on 3D EUS.



**Figure 3.** 3D HPUS image of a complex perianal fistula in Crohn's disease. Axial and lateral HPUS image showing the endoprobe (1), the IAS (2), the EAS (3), and a transsphincteric fistula located anteriorly (4) and a transsphincteric fistula located posteriorly (5). In a more proximal view the two fistulas join together, this is not visualised on this image.

In the two patients with an anovaginal fistula, the aspect of these anovaginal fistulas remained unchanged on 3D HPUS. In one of these patients a clinical response as well as improvement on 3D HPUS was seen for the perianal fistula, the other patient showed no clinical or ultrasonographic improvement.



This means that only three of the 13 patients with a clinical response at week 18 also showed improvement on 3D HPUS.

### *Adverse events*

After two weeks of treatment one patient in the placebo group had an exacerbation of Crohn's colitis. This patient had to discontinue treatment because of a change in concomitant medication. At week 6, prior to the first infliximab infusion, three patients on ciprofloxacin and two on placebo reported adverse events. These included nausea, a rash and diarrhoea in the ciprofloxacin group and change of taste in the placebo group. These symptoms were mild and did not require discontinuation of medication in any patient.

During the first infliximab infusion, one patient in the placebo group who was on azathioprine and had not received prior treatment with infliximab experienced an infusion reaction, which was treated successfully with clemastine intravenously. Two other patients, one in the ciprofloxacin group and one in the placebo group, reported symptoms of arthralgias after the first infliximab infusion. The patient in the ciprofloxacin group was not on any concomitant immunosuppressive therapy and did not receive intravenous hydrocortisone prior to every infliximab infusion as inclusion took place before January 2003. This patient had been treated with infliximab 12 months previously without any problems. Treatment was discontinued in this patient, as symptoms were severe. In the other patient, who had never been treated with infliximab before but was on azathioprine, treatment could be continued as symptoms disappeared.

After the second infliximab infusion, one patient in the placebo group who was on azathioprine reported symptoms of a headache and nausea. Treatment was not stopped, as these symptoms were mild. No further symptoms occurred in this patient during treatment.

During the third infliximab infusion one patient in the ciprofloxacin group experienced an infusion reaction which was treated with intravenous clemastine. Several days later the same patient had severe symptoms of arthralgias, which were successfully treated with pain medication. This patient was not using any concomitant immunosuppressive therapy and had not received intravenous hydrocortisone prior to every infliximab infusion nor had this patient previously been treated with infliximab.

Four patients, one patient on ciprofloxacin and three on placebo developed a perianal abscess after the third infliximab infusion. All four patients had complete closure of the fistula before the third infusion. Two patients underwent incision and drainage of the abscess and in the other two the abscess drained spontaneously.

## DISCUSSION

To our knowledge this is the first controlled study evaluating the effect of ciprofloxacin in the treatment of perianal fistulas in Crohn's disease. We found that treatment with a combination of ciprofloxacin and infliximab in perianal fistulas in Crohn's disease was more effective than treatment with infliximab alone. Although this difference was not significant, logistic regression analysis showed a tendency towards a better clinical response with ciprofloxacin than with placebo. Furthermore, the PDAI score showed a significant improvement. However, despite this improvement, persistent fistula tracts remained visible on 3D HPUS in most patients.

Initial studies found that both ciprofloxacin and metronidazole had a beneficial effect on perianal fistulas in Crohn's disease.<sup>3-7</sup> However, after treatment discontinuation symptoms often reoccurred. These studies were uncontrolled and only included small numbers of patients. More recently, an open-label study with 52 patients reported that 50% of patients responded to treatment with ciprofloxacin and/or metronidazole.<sup>17</sup> Patients receiving additional treatment with azathioprine were more likely to achieve response than patients without immunosuppression.

Although efficacy between ciprofloxacin and metronidazole might not differ, the latter is associated with more frequent and potentially more severe side effects such as paresthesias. In our study, ciprofloxacin treatment was only associated with infrequent mild to moderate side effects, which did not necessitate discontinuation of therapy.

Both controlled<sup>9</sup> and uncontrolled trials<sup>18-20</sup> have found infliximab to be effective in the treatment of perianal fistulas in Crohn's disease. Although infliximab was effective and the vast majority of fistulas closed before the third infliximab infusion, the median duration of response was only three months. Therefore, a large long-term study evaluating infliximab maintenance therapy every eight weeks was conducted.<sup>10</sup> Maintenance infliximab therapy was effective in patients who responded to induction therapy and the median time to loss of response was more than 40 weeks.

Side effects associated with infliximab are infusion reactions, delayed hypersensitivity reactions and formation of anti-double-stranded DNA. Furthermore, the formation of antibodies to infliximab can lead to allergic reactions and a reduced response in the long term.<sup>1</sup> The use of concomitant immunosuppressive therapy with azathioprine, 6-mercaptopurine or methotrexate is recommended because it may reduce the frequency of such adverse events.<sup>21</sup> In the present study side effects due to infliximab were seen in five of 23 patients who received this drug, three were on azathioprine and two were not on any concomitant immunosuppressive therapy. One patient had to discontinue treatment after the first infliximab infusion.

Another side effect of infliximab treatment in patients with fistulising Crohn's disease is abscess formation, which occurs after rapid closure of the fistula's external opening. Infliximab in combination with either the placement of non-cutting setons or antibiotics could decrease the rate of

new abscess formation by controlling the rate of fistula closure and by treating local bacterial infection.<sup>20,21</sup> In the present study, four patients with fistula closure after the second infliximab infusion developed an abscess after the third infliximab infusion. One of these patients was being treated with ciprofloxacin, the other three with placebo. These numbers do not allow any definite conclusions. The hypothesis is that ciprofloxacin plays a role in controlling bacterial infection and thus may prevent abscess formation in patients with a good initial response to infliximab.

In most of our patients, the fistula tracts remained visible and unchanged on 3D HPUS during follow-up irrespective of their clinical response. These results are in agreement with the literature, in which several studies have reported on radiological findings after induction treatment with infliximab.<sup>11-14</sup> Even though clinical improvement was seen after short term infliximab treatment, most fistulas still persisted on either MRI<sup>11,12</sup> or EUS.<sup>13,14</sup> We prefer to perform EUS in combination with hydrogen peroxide so that an active fistula can be distinguished from fibrotic tissue.<sup>22</sup> However, some of the patients in our study had a rapid closure of the external opening, thus not allowing hydrogen peroxide to be introduced during follow-up. Persistent hypoechoic lesions were still visible in most of these patients. In such cases, the question remains whether persistent lesions result from an active fistula or fibrotic tissue, and whether further treatment is necessary. Other studies<sup>11-14</sup> have reported that these persistent lesions may lead to relapse of symptoms or abscess formation. Furthermore, two long-term studies showed a significant radiological improvement in patients who responded to maintenance infliximab therapy.<sup>11,14</sup> Thus if defects are still visible on EUS after initial treatment, further treatment could be required even to a point that radiological improvement is seen so that symptom relapse and abscess formation can be prohibited.

Our study in a limited number of patients suggests that the combination of ciprofloxacin and infliximab is more effective in the treatment of perianal fistulas in Crohn's disease than infliximab alone. These findings necessitate further studies into the additive effect of antibiotics to infliximab, and allow a power analysis to determine how many patients are needed to perform these future studies. These future studies should also focus on long-term follow-up to assess whether this drug combination gives a better long-term response than treatment with infliximab alone.

The PDAI score did improve significantly in the ciprofloxacin group. This score is used for the assessment of perianal disease and has also been used as a secondary endpoint in other studies for this purpose.<sup>9,17</sup> However, the minimum clinically significant difference in PDAI score and the cut-off value indicating remission remain to be determined.<sup>23</sup>

In conclusion, the addition of ciprofloxacin to infliximab treatment for perianal Crohn's disease has a significant effect on improvement of perianal disease activity scores, but has no effect on ultrasonographic findings. Ciprofloxacin may play a role in the prevention of abscess

formation in patients treated with infliximab. These findings necessitate further studies.

### **ACKNOWLEDGEMENT**

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# Chapter 9

## Perianal fistulas in Crohn's disease are predominantly colonised by skin flora: implications for antibiotic treatment?

### ABSTRACT

#### **Purpose:**

Perianal fistulas can complicate Crohn's disease. Little is known about the microflora present in Crohn's fistulas nor is there much insight in the effect of antibiotics on these microorganisms. We aimed to determine which microorganisms are found in perianal fistulas in Crohn's disease and whether treatment with ciprofloxacin affects these microorganisms.

#### **Methods:**

Thirteen patients (M/F 7/6, median age 34 yrs, range 18-61) with perianal fistulising Crohn's disease were treated with infliximab 5 mg/kg intravenously at week 6, 8 and 12. Patients were randomised to double blind treatment with ciprofloxacin 500 mg bd (n=6) or placebo (n=7) for 12 weeks. Samples from perianal fistulas were taken at baseline and after 6 and 18 weeks.

#### **Results:**

In the ciprofloxacin group 10 different genera of microorganisms were identified, while 13 genera could be identified in the placebo group. In contrast to what is generally assumed gram-negative enteric flora was present in a small minority. The predominant genera found in the ciprofloxacin group were *Corynebacteria* spp., coagulase-negative staphylococci and *Arcanobacterium* spp. at baseline, *Corynebacteria* spp. and coagulase-negative staphylococci at week 6 and *Corynebacteria* spp. and streptococci at week 18. In the placebo group this was *Corynebacteria* spp., streptococci and *Escherichia coli* at baseline, *Corynebacteria* spp. and coagulase-negative staphylococci at week 6 and *Corynebacteria* spp. and coagulase-negative staphylococci at week 18. No significant differences in types of bacteria were found over time in the separate groups or between the groups.

#### **Conclusions:**

Gram-positive microorganisms predominantly colonise perianal fistulas in Crohn's disease. Therefore, antimicrobial treatment should be directed towards these microorganisms.

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## INTRODUCTION

Perianal fistulas are a frequent complication of Crohn's disease and can result in substantial morbidity. A fistula develops locally, either as a result of a deep penetrating ulcer in the anus or rectum, or secondary to an anal gland abscess.<sup>1,2</sup> The lifetime risk for the development of perianal fistulas in Crohn's disease ranges from 20% to 50%.<sup>1</sup> Symptoms associated with a fistula are the presence of local pain, drainage and abscess formation.

Treatment of patients with fistulising Crohn's disease is complex. Apart from surgery and treatment with immunosuppressive drugs and infliximab, empirical treatment with antibiotics is often started.<sup>1,2</sup> Metronidazole<sup>3-5</sup> is a preferred drug for this purpose, based on the hypothesis that fistula tracts are predominantly colonised with anaerobic bacteria. Treatment with metronidazole is moderately effective, but is associated with marked side effects. Ciprofloxacin, a quinolone antibiotic with a broad-spectrum coverage including gram-negative aerobic microorganisms, is a good alternative with fewer side effects.<sup>6,7</sup> However, discontinuation or dose reduction of either antibiotic may rapidly lead to disease relapse.<sup>8</sup>

The exact mechanisms by which metronidazole and ciprofloxacin have an effect on perianal Crohn's disease are not clear, and thus it remains to be resolved why withdrawal of treatment usually leads to a rapid disease relapse. In addition, little is known about the microbial flora involved in Crohn's fistulas or the effect of antibiotic treatment. The aim of this study was to establish which microorganisms are present in perianal fistulas in Crohn's disease and to determine the effect of antimicrobial treatment with ciprofloxacin on the microbial colonisation of these fistulas.

## PATIENTS AND METHODS

Thirteen patients (M/F 7/6, median age 34 yrs, range 18-61) with Crohn's disease and perianal fistulas were randomised to receive double-blind treatment with either ciprofloxacin 500 mg bd. (n=6) or placebo (n=7) for 12 weeks. In addition, they all received infliximab 5 mg/kg intravenously at weeks 6, 8 and 12. Samples from perianal fistulas were taken at baseline and after six and 18 weeks.

Patients who had been treated with ciprofloxacin in the last three months or infliximab in the last six months preceding the study were excluded. Only one patient had been treated with infliximab 12 months before inclusion, seven patients were on azathioprine, and one on corticosteroids. All patients signed informed consent; the ethical committee of the Erasmus MC approved the study protocol.

Samples were taken from one single fistula in every patient using a sterile flexible intravenous cannula (Venflon®, Ohmeda, Helsingborg, Sweden) attached to a syringe. The cannula was introduced into the fistula as far as possible through the external opening and material was



aspirated. No samples were taken from patients in whom the external opening was closed. After collection samples were directly taken for culture. Routine microbiological methods were used for the isolation and identification of microorganisms.

### *Statistical analysis*

The Mann Whitney U test was used for determining differences in the total number of genera found between the two groups at baseline, week 6 and 18 as well as for each genus separately at baseline, week 6 and week 18. The Wilcoxon Signed Ranks Test was used for assessing the change in the number of genera between baseline and week 6 and between baseline and week 18 in the two separate groups. In addition, the McNemar test was used to assess a change in the presence of each genus separately between baseline and week 6 and, between baseline and week 18 in the two separate groups. All P values were calculated with exact methods. Two-sided P values less than 0.05 were considered to indicate statistically significant differences.

## **RESULTS**

At baseline samples from all patients were available for analysis. At week 6 samples were available for four of the six patients in the ciprofloxacin group and for five of the seven patients in the placebo group. No material was obtained from one patient in the ciprofloxacin group because of treatment discontinuation and from three patients (1 ciprofloxacin, 2 placebo) because of inadequate samples. At week 18, samples were available from four of six patients in the ciprofloxacin group, one had discontinued treatment and in the other the external opening of the fistula had closed. In the placebo group samples were obtained from five of the seven patients, in two patients the external opening had closed.

In the ciprofloxacin group, microorganisms belonging to 10 different genera were identified, and in the placebo group microorganisms belonging to 13 different genera were identified. An overview of the genera identified in each group at baseline, week 6 and 18 is given in Table 1. The predominant genera found in the ciprofloxacin group were *Corynebacteria* spp. (isolated from 4 of the 6 patients), coagulase-negative staphylococci (2/6), and *Arcanobacterium* spp. (2/6) at baseline, *Corynebacteria* spp. (3/6) and coagulase-negative staphylococci (2/6) at week 6, and *Corynebacteria* spp. (3/6) and streptococci (3/6) at week 18. In the placebo group we found *Corynebacteria* spp. (6/7), streptococci (3/7), and *Escherichia coli* (3/7) at baseline, *Corynebacteria* spp. (3/7) and coagulase-negative staphylococci (2/7) at week 6 and *Corynebacteria* spp. (3/7) and coagulase-negative staphylococci (3/7) at week 18. There were no significant differences between the ciprofloxacin and placebo group for the total number of genera found at baseline ( $p=0.23$ ),

**Table 1.** Summary of predominant genera found in the ciprofloxacin group (n=6) and placebo group (n=7).

Genus	Baseline		Week 6		Week 18	
	Ciprofloxacin n (%)	Placebo n (%)	Ciprofloxacin n (%)	Placebo n (%)	Ciprofloxacin n (%)	Placebo n (%)
<i>Corynebacteria</i> spp.	4 (67)	6 (86)	3 (50)	3 (43)	3 (50)	3 (43)
<i>Dermabacter</i> spp.	-	-	1 (17)	-	-	1 (14)
<i>Escherichia coli</i>	-	3 (43)	-	1 (14)	1 (17)	-
CNS*	2 (33)	2 (29)	2 (33)	2 (29)	1 (17)	3 (29)
streptococci	-	3 (43)	-	-	3 (50)	-
<i>Listeria</i> spp.	1 (17)	-	-	-	1 (17)	1 (14)
<i>Arcanobacterium</i> spp.	2 (33)	-	-	-	-	-
<i>Micrococcus</i> spp.	-	-	1 (17)	-	-	-
<i>Acinetobacter</i> spp.	-	-	1 (17)	-	-	-
<i>Neisseria</i> spp.	-	1 (14)	-	-	-	-
<i>Klebsiella</i> spp.	-	-	-	-	-	1 (14)
<i>Brevibacterium</i> spp.	-	-	-	1 (14)	-	-
<i>Aeromonas</i> spp.	-	-	-	-	-	1 (14)
<i>Pasteurella</i> spp.	-	-	-	-	-	1 (14)
<i>Pseudomonas</i> spp.	-	-	-	1 (14)	-	-
<i>Gardnerella</i> spp.	-	1 (14)	-	-	-	-
<i>Candida albicans</i>	-	-	-	-	1 (17)	-

\*Coagulase-negative staphylococci

week 6 (p=1.0) or 18 (p=0.70). In addition, no differences were found for each genus separately between the two groups at baseline (all P values >0.08), week 6 (all P values >0.43) or week 18 (all P values >0.70).

Between baseline and week 6, and between baseline and week 18 no significant differences were seen in the number of genera involved in the ciprofloxacin (p=0.50 and p=0.50) or in the placebo group (p=0.81 and p=1.0). Furthermore, no significant difference was seen in either the ciprofloxacin or placebo group between baseline and week 6 for each genus separately (all P values 1.0) or between baseline and week 18 (all P values 1.0).

## DISCUSSION

Perianal fistulas are a common and complex problem in Crohn's disease. They often require multimodality treatment including empirical therapy with antibiotics. Treatment with antibiotics like ciprofloxacin and metronidazole is effective but after discontinuation of treatment symptoms usually reoccur. Why antibiotics are effective still remains unclear. It could be that bacteria play a role in the pathogenesis of fistulas but there is not much evidence supporting this assumption. We studied which microorganisms can be isolated from perianal fistulas in Crohn's disease and the effect that treatment with ciprofloxacin has on these microorganisms. Opposite to general beliefs and our expectations, gram-positive microorganisms predominated over gram-negative enteric flora. Treatment with ciprofloxacin did not influence this bacterial colonisation.

Studies on the role of bacteria in the pathogenesis of perianal fistulising Crohn's disease are scarce. One study described the microbiology of cryptoglandular fistulas.<sup>9</sup> During surgery samples of granulation tissue were obtained from the fistula tracts in 18 patients. The predominant organisms found were *Escherichia coli*, *Enterococcus* spp. and *Bacteroides fragilis*. The investigators concluded that either excessive numbers of organisms or organisms of an unusual type do not maintain chronic inflammation in cryptoglandular fistulas. The bacterial species nevertheless differed from those in our study. Although samples were taken during surgery, this is unlikely to have lead to different results compared to our study. We predominantly found gram-positive bacteria while they found a mixed population of gram-positive and gram-negative enteric microorganisms. It is also possible that different microorganisms play a role in cryptoglandular fistulas than in fistulas in Crohn's disease.

We observed that the predominant microorganisms that colonise perianal fistulas in Crohn's disease are gram-positive microorganisms. It appears that the microbial flora does not change during treatment with ciprofloxacin. Ciprofloxacin is bactericidal against a great variety of gram-negative aerobic microorganisms but is less active against gram-positive microorganisms. In addition, the effect of ciprofloxacin on the healing of perianal fistulas in Crohn's disease might not be related to its antimicrobial activity but to other, yet unknown mechanisms. It has been suggested that ciprofloxacin has some immunosuppressive properties that may influence inflammatory activity.<sup>10</sup> This is also based on the observation that ciprofloxacin is effective in the treatment of active Crohn's disease, irrespective of the presence of specific microorganisms.<sup>10,11</sup> If, however, antibiotics interfere with the activity of Crohn's disease through the antimicrobial activity on the microflora, then the outcome of the present study suggests that future clinical studies should involve treatment options with antibiotics with enhanced activity towards gram-positive bacteria.

We found no change in type of bacteria due to treatment with infliximab. Infliximab is a chimeric anti-TNF alpha monoclonal antibody, which binds to TNF and blocks its interaction with cellular receptors what has proven to be beneficial in the treatment of perianal fistulas in Crohn's disease.<sup>12</sup> The results of the present study suggest that the immune suppressive effect of infliximab treatment has no major effect on bacterial colonisation of perianal fistulas in Crohn's disease.

In conclusion, gram-positive microorganisms predominantly colonise perianal fistulas in Crohn's disease. Therefore, antimicrobial treatment for this condition should be directed towards these microorganisms.

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# Chapter 10

## Summary and discussion

The anal canal is the most distal part of the gastrointestinal tract and plays an important role in the regulation of defecation and maintenance of continence. The anal canal consists of two muscular cylinders: the internal (IAS) and external (EAS) anal sphincter. Endoanal ultrasonography (EUS) was the first technique to directly visualise these sphincters and therefore give insight in defects that may cause faecal incontinence. In addition, it has also made it possible to visualise perianal fistula tracts and locate their internal opening. The use of hydrogen peroxide has optimised this technique by visualising the fistula tract as bright hyperechogenic, making it possible to distinguish a fistula tract from fibrotic tissue. Recently, 3D EUS has become available, a great advantage of this technique is that a digital volume is produced that may be reviewed in any plane. Using this technique it is possible to map the location and dimensions of sphincteric components along the length of the anal canal. This yields more information on the anal sphincter complex and enables measurements of the anal sphincters in any plane.

This thesis aimed at the diagnosis and therapy of anal sphincter disorders. Its main focus was on the role of 3D EUS in the evaluation of the normal anatomy and disorders of the anal sphincters. The aims are presented in **Chapter One**.

In the last three years 3D EUS has been used in the Erasmus MC for evaluating anal sphincter disorders. The main indications for performing 3D EUS were detecting sphincter defects in faecal incontinent patients and assessment of perianal fistulas, cryptoglandular fistulas as well as fistulas in patients with Crohn's disease. In **Chapter Two** an overview is given of the indications and findings of all 3D EUS examinations performed in our centre between April 2001 and April 2004.

### *Volume measurements of the anal sphincters using 3D EUS*

As 3D EUS makes it possible to study the length of the anal canal, volume measurements can be performed. Volumes are calculated by measuring the area of the anal sphincters in successive images and then multiplying the resulting 2D data by the distances between the images. Volume measurements could provide more information on the anal sphincter morphology and therefore play a role in detecting sphincter atrophy which is important for selecting patients amenable for surgical repair. In **Chapter Three** the normal values of anal sphincter volumes, EAS length and thickness were determined in healthy subjects and faecal incontinent parous females. The effect of sex and parity as well as intraobserver and interobserver variability was also studied. The 3D EUS results were compared with anal pressure.

IAS and EAS volume as well as anterior sphincter length and anterior EAS thickness were larger in males compared to females. A tendency for a larger EAS volume was seen in nulliparous females compared to parous females. Furthermore, anterior sphincter length was shorter in parous females compared to nulliparous females. No differences were found in sphincter volume between continent parous females and incontinent parous females with and without a sphincter defect. However, anterior sphincter length was shorter and anterior EAS thickness smaller in incontinent females with a sphincter defect. In addition, right and posterior EAS thickness were smaller in incontinent females without a sphincter defect. Intraobserver variability was seen for IAS volume, and anterior and posterior sphincter length but interobserver variability was minimal. The only correlation found between sphincter function and 3D EUS measurements was between IAS volume and resting pressure in incontinent females and between sphincter length measured on manometry and posterior sphincter length in healthy subjects.

It is remarkable that although differences were found in sphincter volume between males and females, no differences were seen between continent and incontinent parous females. However, a smaller anterior sphincter length and EAS thickness were found in incontinent parous females. The shorter anterior sphincter length and smaller anterior EAS thickness in incontinent parous females with a sphincter defect can be explained by anterior sphincter defects. The smaller right and posterior EAS thickness in incontinent parous females without a sphincter defect are probably due to traumatic denervation and therefore thinning of the EAS.

These findings that no differences were found for sphincter volumes in incontinent females, despite a shorter sphincter length and thinner EAS appears to be inconsistent as volume depends on the latter two. The area in successive images was measured by tracing the perimeter of the sphincters. This method could be prone to measurement error due to multiple measurements. Another reason for these inconsistencies could be that the volume measured not only consisted of muscle tissue but also of fatty infiltration as it is difficult to distinguish between the two on EUS.

EAS atrophy is an important entity as it is associated with poor clinical outcome of a sphincter repair. The better delineation of the EAS at endoanal MRI, especially of its borders and fat content, makes this an excellent method for detecting EAS atrophy. This has been validated both surgically and histologically. Furthermore, a small EAS area measured on endoanal MRI is predictive for the presence of EAS atrophy. EUS has found to be less suitable for detecting atrophy as it cannot distinguish fatty infiltration from normal muscle tissue. However, endoanal MRI is more expensive and time consuming than EUS. In **Chapter Four** we aimed to find 3D EUS measurements that could be used as parameters for assessing EAS atrophy. For this purpose we compared EAS length, thickness and area determined on 3D EUS and endoanal MRI in faecal

incontinent patients. In addition, EAS volume determined on 3D EUS was compared to EAS thickness and area determined on endoanal MRI.

Good agreement was found between the two methods for detecting EAS defects but agreement was poor for IAS defects. Correlation between the two methods for EAS length, thickness and area measurements was poor. Furthermore, correlation was also poor between EAS volume determined on 3D EUS and EAS thickness and area determined on endoanal MRI. These results suggest that sphincter volume determined by 3D EUS does not provide extra information on the quality of the EAS in incontinent patients. As mentioned before, volume measurements are performed by measuring the area of the EAS in successive images. The outer border of the EAS is hard to distinguish from adjacent ischio-anal fat, especially in patients with atrophy because the outer interface reflection is lost due to muscle thinning and fat replacement. Therefore if the outer border of the EAS is not clearly visible, measurements of the EAS area could be unreliable.

#### *Evaluation of the anal sphincters after pouch-anal anastomosis surgery*

Total proctocolectomy with ileal pouch-anal anastomosis and mucosectomy in patients with ulcerative colitis or familial adenomatous polyposis not only eliminates the disease but also preserves the anal sphincters. The colonic pouch-anal anastomosis has also allowed restorative surgery with preservation of the anal sphincters in low rectal cancer after an anterior resection. Postoperative function is of key relevance for the long-term outcome of pouch surgery. This necessitates better understanding of the effect of pouch surgery on sphincter anatomy and function. The latter has been studied repeatedly but studies using EUS for assessing the sphincters after pouch surgery are scarce. In **Chapter Five** a study using 3D EUS was performed to assess whether pouch-anal anastomosis surgery performed with a hand sewn anastomosis and a Scott retractor affects the anal sphincters. For this purpose the aspect of the IAS and EAS were studied and sphincter volume, length and thickness were determined in patients who underwent an ileal pouch-anal anastomosis (IPAA) or a colonic pouch-anal anastomosis (CPAA). In addition, anal function and a faecal incontinence score were assessed.

In most patients undergoing pouch surgery thinning or asymmetry of the IAS occurred. However, fragmentation or a defect of the IAS was only seen in two patients in the IPAA group. IAS volume decreased significantly in the CPAA group but not in the IPAA group. No new EAS defects or changes in EAS measurements were seen in either group. Furthermore, anal resting pressure decreased in both groups but maximum squeeze pressure only decreased in the IPAA group. No correlation was found between 3D EUS findings and anal pressures or faecal incontinence scores.

The IAS defects in the IPAA group are caused by direct damage to the sphincter. However, the question remains whether the decrease in IAS

volume in the CPAA group is due to direct damage to the sphincter or to damage to its nerve supply during rectal mobilisation. It is interesting that we only found a decrease in IAS volume in the CPAA group and not in the IPAA group as this type of surgery is more aggressive due to transanal mucosectomy. However, the patients in the CPAA group were significantly older and therefore sphincter atrophy could have played a role in these patients. We cannot account for the decrease found in maximum squeeze pressure in the IPAA group especially as no changes were seen in the EAS on 3D EUS.

### *Preoperative assessment of perianal fistulas*

Preoperative assessment of perianal fistulas is important for successful surgical treatment. The main techniques used are EUS and MRI. Several studies have compared these techniques for this purpose. However, the results reported differ and different techniques were used. In most studies surgery is used as a gold standard. Furthermore, 2D EUS was used in most studies and not combined with the use of hydrogen peroxide. The use of hydrogen peroxide allows a better distinction between scar tissue and active fistulas. In **Chapter Six** a study was conducted assessing agreement between hydrogen peroxide-enhanced 3D EUS (3D HPUS) and endoanal MRI. In addition, these findings were compared to the surgical findings. We found a good agreement between 3D HPUS and endoanal MRI and both techniques compared well to the surgical findings. Excellent agreement was found between the three methods for the classification of the primary fistula tract and the location of the internal opening. These items are both of great importance to the surgeon for planning and performing the right procedure. Less agreement was found for secondary tracts, these were mainly seen on endoanal MRI.

Limitations of this study were the small number of patients included and the long time interval between the investigations. This long time interval could be the reason for some of the differences found as healing or deterioration could have occurred. Therefore a second study described in **Chapter Seven** was performed with a larger number of patients and a shorter time interval between the two investigations. In addition, patient discomfort and preference for either investigation were also taken into account. Surgery was not used as a gold standard as our first study and other studies have showed that EUS and endoanal MRI are able to detect tracts that were not found during surgery.

In this second study the median time interval between the two investigations was 90 days. Good agreement was found between the two techniques for assessing the primary fistula tract, location of the internal opening, secondary tracts and fluid collections. The time interval between the two investigations could also have played a role in this study. However, no significant differences were found in median time interval between the patients with and without agreement with regard to 3D HPUS and endoanal MRI findings.



Patients did not experience any difference in the amount of discomfort during either procedure. This result did not differ for males or females nor was it related to the order in which the patients underwent the procedures. However, there was a significant difference for age, younger patients experienced more discomfort than older patients did. Furthermore, patients expressed no preference for one technique over the other. A limitation of these findings is that the questionnaires were sent to the patients some time after they had undergone the examinations. Therefore, recall bias could have occurred. However, as there was no difference in time interval between the examination and filling out the questionnaire for both 3D HPUS and endoanal MRI, we assume that recall bias did not affect these results.

### *Perianal fistulas in Crohn's disease*

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract that can be complicated by perianal fistulas. These fistulas rarely heal spontaneously and medical or surgical treatment is often required. Ciprofloxacin is moderately effective but symptoms often reoccur when treatment is discontinued. Infliximab is effective but repeated infusions are often required. Rapid closure of the external opening may be associated with abscess formation and fistula recurrence. Furthermore, several imaging studies have reported that infliximab therapy may lead to closure of the external opening, but that fistula tracts remain visible on EUS or MRI.

In **Chapter Eight** the results are presented of a study evaluating whether a combination of ciprofloxacin and infliximab is more effective than infliximab alone. A double-blind placebo-controlled study was conducted. Primary endpoint was a clinical response defined as a 50% or greater reduction from baseline in the number of draining fistulas. Secondary endpoints were the change in Perianal Disease Activity Index (PDAI) score and HPUS findings between baseline and final evaluation.

Treatment with ciprofloxacin and infliximab seemed to be more effective than treatment with infliximab alone. Logistic regression analysis showed a tendency towards a better clinical response with ciprofloxacin than with a placebo. In addition, the PDAI score improved significantly. However, despite clinical improvement, persistent fistula tracts remained visible on 3D HPUS.

To our knowledge this is the first controlled study evaluating the effect of ciprofloxacin in the treatment of perianal fistulas in Crohn's disease. This study suggests that a combination of ciprofloxacin and infliximab is more effective than infliximab alone, however it has some drawbacks. The number of patients included is limited. Further studies should be conducted with a larger number of patients. Furthermore, a longer follow-up period should be used so that the long-term response of this drug combination can be assessed.

In this small study we also found that more abscesses occurred in the placebo group than in the ciprofloxacin group. This limited number of

patients does not allow any definite conclusions to be drawn but it could be that ciprofloxacin plays a role in controlling bacterial infection and thus may prevent abscess formation in patients with a good initial response to infliximab.

Irrespective of clinical response fistula tracts remained visible and unchanged on 3D EUS in most patients. It was not possible to introduce hydrogen peroxide in all patients because of closure of the external opening. However, persistent hypoechogenic lesions were still visible in most of these patients. In such cases, the question remains whether such lesions result from an active fistula or fibrotic tissue, and whether further treatment is necessary. Other studies have shown that persistent lesions may lead to symptom relapse or abscess formation. Thus if defects are still visible on EUS after initial treatment, further treatment could be required even to a point that radiological improvement is seen so that symptom relapse or abscess formation can be prohibited.

Why ciprofloxacin is effective in the treatment of perianal fistulas in Crohn's disease is unclear. It could be that bacteria play a role in the pathogenesis of fistulas but there is not much evidence supporting this assumption. In **Chapter Nine** we determined which microorganisms are present in perianal fistulas in Crohn's disease and what the effect of treatment with ciprofloxacin is on these microorganisms. Opposite to general beliefs and our expectations, gram-positive microorganisms predominated over gram-negative flora. Treatment with ciprofloxacin did not influence this bacterial colonisation.

Ciprofloxacin is bactericidal against a great variety of gram-negative aerobic microorganisms but is less active against gram-positive microorganisms. In addition, the effect of ciprofloxacin on the healing of perianal fistulas in Crohn's disease might not be related to its antimicrobial activity but to other, yet unknown mechanisms. It has been suggested that ciprofloxacin has some immunosuppressive properties that may influence inflammatory activity. If, however, antibiotics interfere with the activity of Crohn's disease through the antimicrobial activity on the micro flora, then the outcome of the present study suggests that future clinical studies should involve treatment options with antibiotics with enhanced activity towards gram-positive bacteria.

## CONCLUSIONS

The results of the studies described in this thesis are relevant for the diagnosis and therapy of anal sphincter disorders, especially concerning the use of 3D EUS. This technique has an important role in assessing anal sphincter disorders. 3D EUS can be used to detect sphincter defects. In addition, using this technique sphincter measurements, for example volume measurements of the anal sphincters can be performed. However, 3D EUS measurements are not suitable for assessing EAS atrophy.

Pouch surgery performed with a hand sewn anastomosis and a Scott retractor affects the IAS in most patients, but defects are only seen in a

very small number of patients. These IAS changes, however, do not seem to affect sphincter function.

3D HPUS is an excellent technique for evaluating perianal fistulas. The choice of technique, 3D HPUS or endoanal MRI, should depend on the expertise and availability in a centre.

Ciprofloxacin in combination with infliximab seems to be more effective than treatment with infliximab alone in the treatment of perianal fistulas in Crohn's disease. However, treatment should be evaluated with EUS and continued until lesions are no longer visible on EUS.

Gram-positive microorganisms and not gram-negative microorganisms mainly colonise perianal fistulas in Crohn's disease and ciprofloxacin has no effect on this flora. Treatment of perianal fistulas in Crohn's disease should therefore also be directed towards these bacteria.



## Samenvatting en discussie

Het anale kanaal vormt het meest distale deel van de tractus gastrointestinalis en speelt een belangrijke rol bij de regulatie van defaecatie en continentie. Het anale kanaal bestaat uit twee cilindervormige spieren: de interne (IAS) en externe (EAS) anale sfincter. Endoanale echografie is de eerste techniek die het mogelijk heeft gemaakt deze sfincters direct te visualiseren en inzicht te geven in defecten die faecale incontinentie kunnen veroorzaken. Daarnaast is het mogelijk geworden om perianale fistelkanalen te vervolgen en de interne fistelopeningen te lokaliseren. De toevoeging van waterstofperoxide heeft de interpretatie van endoanale echografie verbeterd door de fistelkanalen als heldere hyperechogene structuren weer te geven, waardoor het mogelijk is geworden om fistelkanalen te onderscheiden van fibrotisch weefsel. Recentelijk is de drie dimensionale endoanale echografie geïntroduceerd met als voordeel dat een digitaal volume wordt weergegeven dat in elk vlak kan worden bekeken. Met behulp van deze techniek is het mogelijk om de lokatie en dimensies van de verschillende sfincterstructuren over de gehele lengte van het anale kanaal in kaart te brengen. Dit levert meer informatie op over het anale sfinctercomplex en maakt metingen van de anale sfincters in elk vlak mogelijk.

In dit proefschrift worden de diagnostiek en behandeling van anale sfincterafwijkingen beschreven. Het belangrijkste doel was de rol van 3D endoanale echografie in de beoordeling van de normale en afwijkende anatomie van de anale sfincters te bepalen. Het doel van dit proefschrift wordt beschreven in **Hoofdstuk 1**.

De afgelopen drie jaar is in het Erasmus MC de 3D endoanale echografie gebruikt om anale sfincterafwijkingen te diagnostiseren. De belangrijkste indicaties voor het verrichten van 3D endoanale echografie waren het aantonen van sfincterdefecten bij patiënten met faecale incontinentie en het in kaart brengen van perianale fistelkanalen, zowel cryptoglandulaire fistels als fistels bij patiënten met de ziekte van Crohn. In **Hoofdstuk 2** wordt een overzicht gegeven van de indicaties en bevindingen van alle 3D endoanale echografieverrichtingen die in ons centrum tussen april 2001 en april 2004 werden uitgevoerd.

### *Anale sfincter volumemetingen met 3D endoanale echografie*

Omdat 3D endoanale echografie het mogelijk maakt de lengte van het anale kanaal te bestuderen, kunnen volumemetingen worden verricht. Volumina worden berekend door de gemeten oppervlakten van de anale sfincters in de opeenvolgende 2D afbeeldingen te vermenigvuldigen met de afstanden tussen de gemaakte afbeeldingen. Volumemetingen zouden meer informatie kunnen verschaffen over de anale sfinctermorfologie, waardoor deze een rol zouden kunnen spelen in het aantonen van sfincterdefecten wat belangrijk is om te bepalen welke patiënten geschikt zijn voor chirurgisch herstel. In **Hoofdstuk 3** werden de normaalwaarden bepaald van anale sfinctervolumina en EAS lengte en dikte van gezonde vrijwilligers en vrouwen met faecale incontinentie ten gevolge van een vaginale

bevalling. Daarnaast werden de effecten van geslacht en pariteit evenals de intra- en interwaarnemer variabiliteit bestudeerd. De 3D endoanale echografieresultaten werden vergeleken met anale drukmetingen.

Zowel IAS en EAS volume als anterieure sfincterlengte en anterieure EAS dikte waren groter bij mannen dan bij vrouwen. Er was een trend voor een groter EAS volume bij nullipara vergeleken met vrouwen na één of meerdere vaginale bevallingen. Daarnaast was de anterieure sfincterlengte kleiner bij vrouwen na één of meerdere vaginale bevallingen dan bij nullipara. Er kon geen verschil worden aangetoond tussen het sfinctervolume van continente en incontinente vrouwen na één of meerdere vaginale bevallingen. Echter, anterieure sfincterlengte en EAS dikte waren respectievelijk korter en kleiner bij incontinente vrouwen met een sfincterdefect. Daarnaast waren rechtzijdig en posterieure AAS dikte kleiner bij incontinente vrouwen zonder een sfincterdefect. Intrawaarnemer variabiliteit werd gevonden voor IAS volume en voor anterieure en posterieure sfincterlengte, maar interwaarnemer variabiliteit was minimaal voor alle metingen. De enige correlatie tussen sfincterfunctie en 3D endoanale echografietingen werd gevonden tussen IAS volume en anale rustdruk bij incontinente vrouwen en tussen sfincterlengte bepaald met manometrie en posterieure sfincterlengte bij gezonde vrijwilligers.

Het is opmerkelijk dat, ofschoon verschillen werden aangetoond tussen sfinctervolumina van mannen en vrouwen, geen verschillen werden gezien tussen continente en incontinente vrouwen na één of meerdere vaginale bevallingen. Echter, een kleinere anterieure sfincterlengte en EAS dikte werden gevonden bij incontinente vrouwen na één of meerdere vaginale bevallingen. Deze laatste bevindingen bij deze vrouwen kunnen worden verklaard door defecten in de anterieure sfincter. De kleinere rechtszijdige en posterieure EAS dikte bij incontinente vrouwen na één of meerdere vaginale bevallingen zonder een sfincterdefect zijn waarschijnlijk het gevolg van traumatische denervatie van de EAS resulterend in een EAS afname.

De bevinding dat geen verschillen konden worden aangetoond tussen sfinctervolumina bij incontinente vrouwen, ondanks een kortere sfincterlengte en dunnere EAS, lijkt inconsistent omdat het volume hiervan afhankelijk is. De oppervlakten van de opeenvolgende afbeeldingen werden gemeten door de omtrek van de sfincters te bepalen. Deze methode zou gevoelig kunnen zijn voor meetfouten omdat multi-pele metingen verricht worden. Een andere reden voor de eerdergenoemde inconsistentie zou kunnen zijn dat het gemeten sfinctervolume niet alleen uit spierweefsel bestond maar ook uit vette infiltratie ten gevolge van atrofie. Het is namelijk zeer moeilijk spier en vet van elkaar te onderscheiden door middel van endoanale echografie.

Het is belangrijk om EAS atrofie aan te kunnen tonen omdat het geassocieerd is met een slecht operatieresultaat na chirurgisch sfincterherstel. De betere onderscheiding van met name de begrenzing en het vetgehalte van de EAS door middel van endoanale MRI maakt dit een uitstekend onderzoek om EAS atrofie aan te tonen. Dit is zowel chirurgisch als histologisch bevestigd. Daarnaast is een kleinere EAS oppervlakte

gemeten met de endoanale MRI voorspellend voor de aanwezigheid van EAS atrofie. Van endoanale echografie is aangetoond dat het een minder geschikte techniek is om atrofie te detecteren, omdat het niet goed vette infiltratie kan onderscheiden van normaal spierweefsel. Echter, het verrichten van een endoanale MRI scan kost meer tijd en is duurder dan endoanale echografie. In de studie beschreven in **Hoofdstuk 4** hebben we geprobeerd 3D endoanale echografiemetingen te vinden die gebruikt zouden kunnen worden om EAS atrofie aan te tonen. Daarom hebben we EAS lengte, dikte en oppervlakte gemeten met zowel 3D endoanale echografie als endoanale MRI bij patiënten met faecale incontinentie en met elkaar vergeleken. Daarnaast werd het met 3D endoanale echografie verkregen EAS volume vergeleken met de door middel van endoanale MRI gemeten EAS dikte en oppervlakte.

Er werd een goede overeenstemming gevonden tussen beide methoden voor het aantonen van EAS defecten, maar er bestond een slechte overeenstemming voor IAS defecten. De correlatie tussen beide methoden voor het bepalen van EAS lengte, dikte en oppervlakte bleek slecht te zijn. Verder bestond er ook een slechte correlatie tussen EAS volume gemeten met 3D endoanale echografie en EAS dikte en oppervlakte bepaald met endoanale MRI. Deze resultaten suggereren dat sfinctervolume gemeten met 3D endoanale echografie geen extra informatie verschaft over de kwaliteit van de EAS bij incontinentie patiënten. Zoals eerder gezegd worden volumemetingen verricht door de EAS oppervlakten van opeenvolgende afbeeldingen te meten. De EAS begrenzing is moeilijk van het naastliggende ischioanale vet te onderscheiden, met name bij patiënten met atrofie, omdat de reflexie van het buitenste grensvlak verloren gaat door vette infiltratie en afname van de EAS. Omdat de buitenrand van de EAS niet duidelijk zichtbaar is, kunnen EAS oppervlaktemetingen onbetrouwbaar zijn.

### *Evaluatie van de anale sfincters na ileo- en colo-anale pouch chirurgie*

Totale proctocolectomie gevolgd door een ileo-anale anastomose met pouch (IPAA) en mucosectomie bij patiënten met colitis ulcerosa of familiale adenomateuze polyposis neemt niet alleen de ziekte weg maar spaart ook de anale sfincters. Daarnaast heeft de colo-anale anastomose met pouch (CPAA) het mogelijk gemaakt de darmcontinuïteit te herstellen en de anale sfincters te sparen bij een anterieure resectie vanwege een rectum carcinoom. Daarom is een beter begrip noodzakelijk van de effecten van pouch chirurgie op de anale sfincter解剖学 en functie. Dit laatste is reeds meerdere malen onderzocht, echter er zijn zeer weinig studies die gebruik hebben gemaakt van endoanale echografie om de anale sfincters te bestuderen na pouch chirurgie. In **Hoofdstuk 5** wordt een studie beschreven waarin werd onderzocht of anale pouch chirurgie uitgevoerd met een handgelegde anastomose en een Scott retractor de anale sfincters negatief beïnvloedt. Daarom werd zowel pre- als postoperatief de morfologie van de IAS en EAS bestudeerd en werden sfinctervolume, lengte en dikte bepaald bij patiënten die een IPAA of CPAA ondergingen. Daarnaast werd

de anale functie gemeten en werd een faecale incontinentiescore afgenomen.

Bij de meeste patiënten werd een afname of asymmetrie van de IAS na pouch chirurgie vastgesteld. Echter, fragmentatie of een defect van de IAS werd slechts gezien bij twee patiënten van de IPAA groep. IAS volume nam significant af in de CPAA groep maar niet in de IPAA groep. In beide groepen werden geen nieuwe EAS defecten of veranderingen in EAS metingen waargenomen. Verder nam de anale rustdruk af in beide groepen, maar de maximale knijpdruk verminderde slechts in de IPAA groep. Er werd geen correlatie gevonden tussen de 3D endoanale echografiebevindingen en de anale drukmetingen en faecale incontinentiescores.

De IAS defecten in de IPAA groep worden veroorzaakt door directe sfincterschade. Echter, de vraag blijft bestaan of de afname in IAS volume in de IPAA groep het gevolg is van directe sfincterschade of van innervatieschade door het mobiliseren van het rectum tijdens de ingreep. Het is interessant dat we alleen een afname in IAS volume vonden in de CPAA groep en niet in de IPAA groep omdat dit type chirurgie agressiever is door de transanale mucosectomie. Echter, de patiënten in de CPAA groep waren significant ouder en daarom zou sfincteratrofie een versturende rol kunnen hebben gespeeld bij deze patiënten. We hebben geen duidelijke verklaring voor de gevonden afname in maximale knijpdruk in de IPAA groep, vooral omdat met 3D endoanale echografie geen veranderingen werden gezien in de EAS.

### *Preoperatieve beoordeling van perianale fistels*

Preoperatieve beoordeling van perianale fistels is belangrijk voor een succesvolle chirurgische behandeling. De meest gebruikte technieken hiervoor zijn endoanale echografie en MRI. Verscheidene studies hebben deze technieken voor dit doel vergeleken. Echter, de gerapporteerde resultaten spreken elkaar tegen en verschillende technieken werden gebruikt. In de meeste studies werd chirurgie gebruikt als gouden standaard. Daarnaast werd in de meeste studies 2D endoanale echografie gebruikt zonder de toevoeging van waterstofperoxide. Het gebruik van waterstofperoxide zorgt voor een beter onderscheidend vermogen tussen littekenweefsel en actieve fistels. In **Hoofdstuk 6** wordt een studie gepresenteerd die de overeenstemming onderzocht tussen 3D endoanale echografie met waterstofperoxide en endoanale MRI. Daarnaast werden de resultaten vergeleken met de chirurgische bevindingen. We vonden een goede overeenstemming tussen 3D endoanale echografie met waterstofperoxide en endoanale MRI en de resultaten van beide technieken waren vergelijkbaar met de chirurgische bevindingen. Een uitstekende overeenstemming werd gevonden tussen de drie methoden voor de classificatie van het primaire fistelkanaal en de locatie van de interne opening. Juiste informatie hierover is voor de chirurg van groot belang bij het plannen en uitvoeren van de meest geschikte operatietechniek. Een



mindere overeenstemming werd gevonden voor secundaire fistelkanalen; deze werden met name met behulp van endoanale MRI vastgesteld.

Beperkingen van deze studie waren het kleine aantal geïncludeerde patiënten en het lange tijdsinterval tussen de onderzoeken. Dit lange tijdsinterval zou de reden kunnen zijn voor sommige van de gevonden verschillen tussen de methoden, omdat in de tussentijd spontane genezing of verslechtering kan hebben plaatsgevonden. Daarom werd een tweede studie uitgevoerd, beschreven in **Hoofdstuk 7**, met een groter aantal patiënten en een korter tijdsinterval tussen de twee onderzoeken. Daarnaast werden tevens patiëntongemak en onderzoeksvoorkeur in beschouwing genomen. Chirurgie werd niet als gouden standaard gebruikt omdat onze eerste studie en anderen reeds hebben aangetoond dat endoanale echografie en endoanale MRI fistelkanalen kunnen aantonen die met chirurgie worden gemist.

In deze tweede studie was het mediane tijdsinterval tussen de twee onderzoeken 90 dagen. Goede overeenstemming werd gevonden tussen de twee technieken voor het vaststellen van een primair fistelkanaal, locatie van de interne opening, secundaire fistelkanalen en vochtcollecties. Het tijdsinterval tussen de twee meetmethoden zou ook in deze studie een rol kunnen hebben gespeeld. Echter, geen significante verschillen konden worden gevonden in het mediane tijdsinterval tussen de patiënten met en zonder overeenstemming tussen de 3D endoanale echografie met waterstofperoxide en MRI bevindingen.

De patiënten gaven geen verschil aan in ongemak tijdens beide onderzoeksmethoden. Er was geen verschil tussen mannen en vrouwen en er bestond geen relatie met de volgorde waarin de patiënten het onderzoek hadden ondergaan. Er werd echter wel een significant verschil voor leeftijd gevonden: jongere patiënten ervoeren meer ongemak dan oudere. Verder rapporteerden de patiënten geen voorkeur voor één onderzoeksmethode boven de andere. Een beperking van deze studie is dat de vragenlijsten pas enige tijd nadat de patiënten de onderzoeken hadden ondergaan werden verzonden. Daarom zou een vertekening door herinnering kunnen hebben plaatsgevonden. Echter, omdat er geen verschil in tijdsinterval bestond tussen het ondergaan van het onderzoek en het invullen van de vragenlijst voor zowel de 3D endoanale echografie met waterstofperoxide als de endoanale MRI, nemen we aan dat de resultaten niet zijn beïnvloed door herinnering.

### *Perianale fistels bij de ziekte van Crohn*

De ziekte van Crohn is een chronische inflammatoire aandoening van de tractus gastrointestinalis die kan worden gecompliceerd door perianale fistels. Deze fistels genezen zelden spontaan en behoeven meestal medicamenteuze of chirurgische therapie. Ciprofloxacin is effectief, maar symptomen recidiveren meestal wanneer hiermee wordt gestopt. Infliximab is tevens effectief, maar vaak zijn meerdere intraveneuze giften nodig. Snelle sluiting van de externe opening kan gepaard gaan met abscesvorming en een recidief van de fistel. Verder hebben verscheidene

studies gemeld dat behandeling met infliximab kan leiden tot sluiting van de externe opening, maar dat fistelkanalen zichtbaar blijven op endoanale echografie of MRI.

In **Hoofdstuk 8** worden de resultaten gepresenteerd van een studie waarin de effectiviteit van ciprofloxacin met infliximab werd vergeleken met die van alleen infliximab. Er werd een dubbel blind placebo gecontroleerde studie verricht met als primair eindpunt een klinische respons met een minimale afname van 50% van het aantal drainerende fistels ten opzichte van het begin van de studie. Secundaire eindpunten werden gedefinieerd als een verandering in de "Perianal Disease Activity Index" (PDAI) score en in de bevindingen van 3D endoanale echografie met waterstofperoxide aan het begin en einde van de studie.

Gecombineerde behandeling met ciprofloxacin en infliximab leek effectiever dan behandeling met alleen infliximab. Een logistische regressie analyse liet een trend zien voor een betere respons op ciprofloxacin dan op een placebo. Daarnaast verbeterde de PDAI score significant ten opzichte van het begin van de studie. Echter, ondanks een klinische verbetering bleven fistelkanalen zichtbaar met 3D endoanale echografie met waterstofperoxide.

Voor zover bij ons bekend is dit de eerste gecontroleerde studie die het effect van ciprofloxacin voor de behandeling van perianale fistels bij de ziekte van Crohn heeft bestudeerd. Deze studie liet zien dat een behandeling met ciprofloxacin en infliximab meer effectief lijkt te zijn dan met alleen infliximab. Er is echter een aantal tekortkomingen: het aantal geïncludeerde patiënten was beperkt en de vervolgperiode was relatief kort. Daarom zouden in de toekomst studies moeten worden verricht met een groter aantal patiënten die voor een langere periode worden vervolgd, zodat de langetermijnsresultaten van deze gecombineerde behandeling kunnen worden vastgesteld.

In onze relatief kleine studie werd tevens duidelijk dat er meer abscessen voorkwamen in de placebogroep dan in de ciprofloxacinegroep. Door het beperkt aantal patiënten kunnen geen definitieve conclusies worden getrokken, maar mogelijk speelt ciprofloxacin een rol in het controleren van een bacteriële infectie en zou daarom abscesvorming kunnen voorkomen bij patiënten die initieel goed reageren op infliximab.

Onafhankelijk van de klinische respons bleven bij de meeste patiënten fistelkanalen zichtbaar met 3D endoanale echografie met waterstofperoxide. Het bleek niet mogelijk om bij alle patiënten waterstofperoxide in het fistelkanaal te spuiten, omdat soms de externe opening reeds was gesloten. Echter, in het merendeel van deze patiënten bleven hypoëchogene laesies zichtbaar. In deze gevallen rijst de vraag of zulke laesies het gevolg zijn van een actieve fistel dan wel littekenweefsel en of verdere behandeling noodzakelijk is. Andere studies hebben aangetoond dat persisterende laesies kunnen leiden tot recidivering van symptomen en abscesvorming. Dus wanneer defecten nog steeds aantoonbaar zijn met endoanale echografie na initiële behandeling, zou deze misschien dienen te worden voortgezet tot een punt waarop

radiologische verbetering wordt gezien, zodat recidivering van symptomen of abscessen kan worden voorkomen.

Waarom ciprofloxacin effectief is voor de behandeling van perianale fistels bij de ziekte van Crohn blijft onduidelijk. Mogelijk spelen bacteriën een rol in de pathogenese van fistels, echter er bestaat niet veel bewijs voor deze aanname. In **Hoofdstuk 9** onderzochten we welke microorganismen aantoonbaar zijn in perianale fistels bij de ziekte van Crohn en wat het effect van ciprofloxacin hierop is. In tegenstelling tot wat algemeen wordt aangenomen en onze verwachtingen werden meer grampositieve dan gramnegatieve bacteriën gevonden. Behandeling met ciprofloxacin had geen enkele invloed op deze kolonisatie.

Ciprofloxacin is een bactericide antibioticum tegen een groot aantal gramnegatieve microorganismen maar is minder werkzaam tegen grampositieve bacteriën. Daarnaast kan de genezende werking van ciprofloxacin op perianale fistels bij de ziekte van Crohn mogelijk meer verklaard worden door tot op heden onbekende werkingsmechanismen dan door de bactericide eigenschappen. Er is gesuggereerd dat ciprofloxacin immunosuppressieve eigenschappen heeft die de inflammatoire activiteit zouden kunnen beïnvloeden. Als echter antibiotica de activiteit van de ziekte van Crohn verminderen door hun antimicrobiële werking op de microflora, dan impliceren de resultaten van deze studie dat toekomstig onderzoek het effect van antibiotica met specifieke werkzaamheid tegen grampositieve bacteriën zou moeten evalueren.

## CONCLUSIES

De resultaten van de in dit proefschrift beschreven studies zijn relevant voor de diagnostiek en behandeling van anale sfincterafwijkingen door middel van 3D endoanale echografie. Deze techniek speelt een belangrijke rol in de beoordeling van anale sfincterafwijkingen. 3D endoanale echografie kan worden gebruikt voor het aantonen van sfincterdefecten. Daarnaast kunnen met deze techniek metingen aan het sfinctercomplex worden verricht zoals bijvoorbeeld volumemetingen. Echter, 3D endoanale echografie is niet geschikt voor het aantonen van EAS atrofie.

Anale pouch chirurgie met een handgelegde anastomose en een Scott retractor beïnvloedt de IAS morfologie bij de meeste patiënten, maar defecten worden slechts bij een klein deel gezien. Deze IAS veranderingen lijken echter de sfincterfunctie niet aan te tasten.

3D endoanale echografie met waterstofperoxide is een uitstekende techniek om perianale fistels te beoordelen. De keuze tussen 3D endoanale echografie met waterstofperoxide en endoanale MRI zou moeten afhangen van de expertise en beschikbaarheid in een centrum.

Ciprofloxacin samen met infliximab lijkt een effectievere behandeling voor perianale fistels bij de ziekte van Crohn dan alleen infliximab. Echter, het effect van de behandeling zou moeten worden beoordeeld met endoanale echografie en zou moeten worden gecontinueerd tot de afwijkingen hiermee niet meer aantoonbaar zijn.

Grampositieve in tegenstelling tot gramnegatieve bacteriën koloniseren voornamelijk perianale fistels bij de ziekte van Crohn en ciprofloxacine heeft geen enkel effect op deze kolonisatie. Behandeling van perianale fistels bij de ziekte van Crohn zou daarom gericht moeten zijn op grampositieve microorganismen.

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## **Curriculum vitae**

Rachel West was born in Canberra (Australia) on 31 October 1973. After three years in Nigeria, she moved to the Netherlands at the age of six years.

In 1992, she completed her gymnasium secondary education at the rijksscholengemeenschap 'Het Wagenings Lyceum'. In the same year she started her medical studies at the University of Groningen. During this time, she carried out a research project in 1996 on respiratory syncytial virus in young infants at the Department of Paediatrics of Flinders University of South Australia in Adelaide under the supervision of Professor Dr K. Forsyth. In addition, she participated in clinical work in 1997 in the Department of Gastroenterology and Hepatology of Trinity College Dublin (Republic of Ireland) at St James' Hospital under the supervision of Professor Dr D.G. Weir and Dr N. Mahmud.

During the clinical phase of her medical study, she was attached in 1999 to the Department of Gastroenterology and Hepatology of the Academic Medical Centre Amsterdam under Drs J.F.W.M. Bartelsman. Here she also carried out research on the long-term outcome of pneumatic dilation in patients with achalasia under the supervision of Dr G.E.E. Boeckxstaens. In 1999, she graduated in medicine from the University of Groningen with distinction (cum laude).

She then took up a position in the Department of Internal Medicine of the Leyenburg Hospital in The Hague (Head of Department: Dr J.C.M. van der Vijver). In February 2001 she commenced work in the Department of Gastroenterology and Hepatology of the Erasmus Medical Centre Rotterdam where, in April 2001, she started the research described in this thesis under the supervision of Dr R.J.F. Felt-Bersma, Dr C.J. van der Woude and Professor Dr E.J. Kuipers.

In May 2004, she began the initial part of her specialist training in gastroenterology at the Department of Internal Medicine of the Sint Franciscus Hospital in Rotterdam (Head of Department: Dr H.S.L.M. Tjen). Rachel will return to the Department of Gastroenterology and Hepatology of the Erasmus Medical Centre Rotterdam in May 2006 to complete her specialist training in gastroenterology under Professor Dr E.J. Kuipers.

