LAPAROSCOPIC ANTIREFLUX SURGERY AND HIATAL HERNIA REPAIR: TECHNIQUES AND OUTCOME

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LAPAROSCOPIC ANTIREFLUX SURGERY AND HIATAL HERNIA REPAIR: TECHNIQUES AND OUTCOME

Laparoscopische antireflux chirurgie en correctie van hiatus hernia: technieken en uitkomsten

(met een samenvatting in het Nederlands)

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Promotor:	Prof. dr. M.R. Vriens
Copromotor:	Dr. E.J. Hazebroek

Foar pake

Contents

Chapter 1

General introduction and outline of thesis

Gastroesophageal reflux disease

Physiology and pathophysiology of the gastroesophageal junction

The gastroesophageal junction prevents gastric content from entering the esophagus, and consists of an intrinsic and extrinsic sphincter.[1] The intrinsic sphincter is formed by the lower esophageal sphincter (LES) and the extrinsic sphincter by the crural diaphragm. The antireflux barrier is further formed by the phreno-esophageal ligaments, which secure the LES at the esophageal hiatus, and the angle of His, responsible for a flap-valve effect.[2, 3] Passage of an esophageal food bolus through the gastroesophageal junction is achieved by swallow-induced LES relaxations. Additionally, venting of air from the stomach to the mouth, also called belching, is achieved by transient LES relaxations (TLESR's).[4] Gastro-esophageal reflux, in which there is retrograde flow of gastric content into the esophagus, is a physiological phenomenon, which has been demonstrated in healthy volunteers not experiencing reflux symptoms. However, in patients suffering from gastroesophageal reflux disease (GERD), these reflux episodes cause troublesome complaints, including the typical symptoms heartburn and regurgitation, or result in mucosal damage such as esophagitis or Barretts' esophagus.[5]

Regarding the pathophysiological mechanisms leading to GERD, three mechanisms can be distinguished. First, a low LES pressure (hypotensive LES) may cause a retrograde flow of gastric content, either provoked by an increase in intra-abdominal pressure, or when the LES itself is hypotensive compared to the intra-abdominal pressure (LOS<intra-abdominal pressure).[5-7] A second important pathophysiological mechanism includes a pathologically high number of TLESR's. This may be the result of stimulation through gastric distention, fat, stress, and subthreshold stimulation of the pharynx.[8, 9] The third mechanism involves migration of the gastro-esophageal junction into the thorax (hiatal hernia), in which the overlap between the intrinsic LES and the extrinsic crural diaphragm is disturbed, causing an insufficient antireflux barrier.[10, 11]

Gastroesophageal reflux disease is the most common benign disorder of the upper gastrointestinal tract, with 10-20 percent of the Western population reporting to experience heartburn or regurgitation on a weekly basis.[12] Next to the typical reflux symptoms of heartburn and regurgitation, GERD may also cause a variety of atypical symptoms, including nausea, dysphagia or chronic cough (gastric asthma). Gastroesophageal reflux disease has been demonstrated to severely impair quality of life in patients suffering from this condition compared to healthy control populations, as well as compared to patients with other chronic conditions.[13, 14]

Diagnosis

The diagnosis of GERD is based on the combination of typical reflux symptoms, objectified by either upper gastrointestinal endoscopy, demonstrating unequivocal signs of reflux disease (esophagitis or Barretts'esophagus) with or without the presence of a hiatal

hernia, and/or conventional 24-hour pH monitoring, demonstrating pathological esophageal acid exposure (pH<4 for ≥4% of the time). Conventional esophageal 24-hour pH-monitroing has always been considered the gold standard for diagnosing GERD by detecting acidic reflux episodes with a pH<4, with assessment of the association between reported symptoms and the presence of reflux episodes.[15] However, not all reflux episodes are acidic (pH<4). Non-acidic or weakly-acidic reflux episodes, with a pH ranging between 4 and 7, have been demonstrated to elicit typical reflux symptoms which cannot be detected by conventional 24-hour pH-monitoring and do not adequately respond to acid-suppressing medication.[16, 17] Combined pH-impedance monitoring is a technique which enables visualization of movements of gas and liquids through the esophagus, by measuring differences in resistance encountered by an alternating electric current generated between pairs of electrodes on a non-conductive esophageal catheter.[18] When fluids, characterized by a high conductivity, pass by the electrodes, the impedance level decreases. With the passage of air, characterized by a low conductivity, the impedance level increases. Not merely the movements of gas and liquids, but also the direction and velocity of movements of these substances can be analyzed using this important technique. Using combined pH-impedance monitoring, we are able to analyze the presence of acidic and weakly-acidic reflux, and subsequently determine the effect of surgery on reflux and belching patterns.

Treatment

Lifestyle modifications and pharmacological management, through either antacids, H2-antagonists and/or proton pump inhibitors (PPI's), are considered the initial therapy for patients diagnosed with GERD.[19] However, for patients who suffer from PPI-refractory GERD, severe regurgitation, or for those who are unwilling to take lifelong medication, antireflux surgery is the treatment of choice.

In 1937, dr. Rudolph Nissen (1896-1981), who should be considered a pioneer in the field of (antireflux) surgery, performed a distal esophagectomy in a patient suffering from a bleeding ulcer. In order to protect the anastomosis, Nissen wrapped the fundus of the stomach around the distal esophagus. Several years later, the patient reported to be completely asymptomatic with regards to his severe preoperative reflux complaints. It was not until 1956 that dr. Nissen published the first results of his 'fundoplication' performed on two patients suffering from reflux disease, in which a 360 degree total fundoplication was performed.[20] Since its introduction, the Nissen fundoplication has been modified several times, including the Nissen-Rosetti fundoplication for extremely obese patients, in which only the anterior wall of the stomach was wrapped around the distal esophagus, including dissection of the short gastric vessels.[21] Currently, the Nissen fundoplication, or 360 degree total fundoplication, is the most frequently performed type of fundoplication worldwide, and entails mobilization of the distal esophagus, division of the short gastric vessels, posterior repair of the crural diaphragm, and 360 degree wrapping of the fundus

posteriorly around the distal esophagus.

As occurred with other abdominal surgical procedures after the introduction of laparoscopy, the conventional Nissen fundoplication was rapidly replaced by its laparoscopic counterpart, based on superior morbidity rates and time till recovery.[22, 23] Therefore, laparoscopic fundoplication is currently considered the surgical treatment of choice for patients diagnosed with objectified GERD.

Although providing excellent long-term reflux control, 360 degree total or Nissen fundoplication carries the risk of the development of troublesome side effects, of which dysphagia and postfundoplication symptoms, including gas bloat and inability to belch, are the most important.[24-26] The risk of developing (severe) postoperative dysphagia was already known in the early days of the Nissen fundoplication, which caused Jacques Dor and Andre Toupet to develop a partial wrap in the 1960's, in which the fundus of the stomach is wrapped partially, anteriorly and posteriorly respectively, around the distal esophagus.[27-29]

It was not until the introduction of laparoscopic antireflux surgery that these early partial fundplications were accepted, further developed and implemented in dailly practice.[29] Several RCTs have compared Nissen fundoplication with partial fundoplications, of which the 270 degree posterior (or Toupet fundoplication) and 180 degree anterior partial fundoplication are the most frequently performed.[30-36] Recent meta-analyses of these trials have provided level 1a evidence for equal reflux control, but a significantly lower risk of dysphagia and postfundoplication symptoms after partial fundoplications compared to Nissen fundoplication.[25, 26] This has led to an increasing popularity of these partial fundoplications, which are now being considered the prefered procedures in The Netherlands. Superiority of either one of these two partial fundoplications with regards to reflux control, dysphagia or incidence of gas-related symptoms has not been demonstrated.

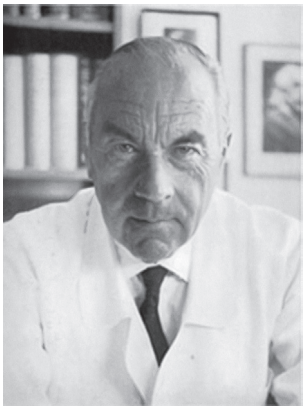

FIGURE 1. Dr. Rudolph Nissen (1896-1981), original image courtesy of Universität Basel

Hiatal hernia

Being one of the most important causes of GERD, hiatal hernia is characterised by the protrusion of an abdominal structure other than the esophagus into the thoracic cavity through a widening of the hiatus.[37] Hiatus hernia can be categorized into four types: the sliding-type (type I), the 'true' paraesophageal type (type II), a mixed type (type III), and the type IV hiatal hernia, with the presence of an upside-down-stomach and possibly omentum and/or intestinal interposition.[37] Hiatal hernia may cause a variety of symptoms, including obstruction, dysphagia, chest pain and heartburn, and may lead to life-threatening complications such as strangulation or perforation. Hiatal hernia is more frequent among elderly patients, with an increasing incidence associated with increasing age. Furthermore, with improved outcome and survival following esophageal cancer, more long-term follow-up of this specific (vulnerable) group of patients is becoming available, including data regarding the incidence of post-esophagectomy hiatal herniation and outcome of subsequent surgical treatment of this postoperative complication.

The first report on elective primary hiatal hernia repair dates back to 1919, in which Angelo Soresi describes an abdominal approach to the hiatus, followed by reduction of the hernia and closure of the crural diaphragm.[29, 38] In his paper, Soresi makes a plea for more awareness among surgeons for diaphragmatic herniation and the need for surgical repair. Following the report of Soresi, interest in this condition grew, and surgical techniques for hiatal hernia repair have been further developed by numerous important names in the world of antireflux surgery, including Nissen, Allisson, Barrett, Belsey, Collis and Hill.[29] Interestingly enough, it was not until the second half of the 20th century that the presence of a hiatal hernia was linked to the development of GERD, in which Philip Allison and Norman Barrett played an important role. It was during this developmental period that surgery for hiatal hernia evolved from anatomic repair to physiological restoration.[29]

With the introduction of minimally invasive surgery, mortality and morbidity rates associated with hiatal hernia repair were further decreased, and over the last decade, laparoscopic repair of symptomatic hiatal hernias has rapidly increased.[24] The basic principles of laparoscopic hiatal hernia repair include complete reduction of the hernial sac, stomach and associated herniated structures with extensive dissection to optimize esophageal mobility, followed by primary closure of the crura using non-absorbable sutures, and performing a fundoplication to reduce the risk of postoperative GERD.[39-42]

Due to the repetitive stress exerted on the diaphragm during respiratory (breathing, coughing) and non-respiratory functions (vomiting), dehiscence and subsequent recurrent hiatal hernia is an important problem following primary repair. Their appears to be a discrepancy in reported incidence of symptomatic recurrent hernias versus radiological recurrences.[43] Based on the succesful implementation of mesh in ventral and inguinal hernia repair, multiple authors have reported on the use of both absorbable and non-absorbable mesh for crural reinforcement in elective hiatal hernia repair.[44-47] Although

short-term outcome appeared to be promising in favour of mesh, midterm results failed to demonstrate superiority of mesh compared to repair using sutures alone with regards to recurrence rate. Additionally, there are reports of mesh-related complications, with erosion being the one most feared.[48] Although the incidence of these complications appears to be low, the true incidence is unknown, and long-term follow-up of patients in whom these synthetics have been used is desperately needed to determine the safety of mesh augmentation in hiatal hernia repair.

Aim of the thesis

In this thesis, we aimed to study the short- and long-term outcome of different surgical techniques for the treatment of gastroesophageal reflux disease and hiatal hernia, using both symptomatic and objective outcome measures.

Outline

Chapter 2 describes 17-year outcome of a randomized clinical trial comparing laparoscopic and conventional Nissen fundoplication. Additionally, long-term outcome of laparoscopic fundoplication is analyzed from the perspective of the patient and referring physician, with special emphasis on the use of acid-suppressing medication and need for surgical reintervention during long-term follow-up.

Chapter 3 describes the pooled 2-year outcome of two multicenter randomized clinical trials comparing laparoscopic 270 degree posterior, or Toupet fundoplication, and 180 degree anterior partial fundoplication for the treatment of gastroesophageal reflux disease.

Chapter 4 analyzes the influence of laparoscopic 270 degree posterior, or Toupet fundoplication, and 180 degree anterior partial fundoplication on reflux-characteristics and belching patterns, using 24-hour combined pH-impedance monitoring. The effect of both procedures on acidic and weakly-acidic reflux episodes, number of air swallows, and gastric- and supragastric belches is reported.

Chapter 5 presents 5-year outcome for patients in whom routine 24-hour pH-monitoring demonstrated pathological esophageal acid exposure following laparoscopic fundoplication. Differences in heartburn, use of acid-suppressing medication and the need for surgical reintervention are compared between patients with physiological and pathological postoperative esophageal acid exposure.

Chapter 6 compares the outcome for patients undergoing laparoscopic hiatal hernia repair using non-absorbable sutures versus sutures reinforced with a non-absorbable mesh, with special emphasis on differences in patient reported outcome measures (PROM's), objective outcome measures and the incidence of mesh-related complications.

Chapter 7 describes one-year outcome of a double-blind multicenter randomized clinical trial comparing laparoscopic hiatal hernia repair using non-absorbable sutures versus sutures reinforced with a non-absorbable mesh.

Chapter 8 analyzes the safety of laparoscopic hiatal hernia repair in elderly patients. Data of two tertiary hospitals are combined and mortality and morbidity rates associated with hiatal hernia repair are compared between patients aged under and over 70 years.

Chapter 9 describes a novel technique for the surgical treatment of giant hiatal hernia, using a simultaneous thoraco-laparoscopic approach.

Chapter 10 reports on the incidence of hiatal hernia following open versus minimally invasive esophagectomy, including the outcome of subsequent hiatal hernia repair in this specific group of patients.

Chapter 11 provides a general discussion and proposes future research concepts.

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-Part I-

Laparoscopic antireflux surgery

Chapter 2

17-year outcome of a randomized clinical trial comparing laparoscopic and conventional fundoplication: a plea for patient counseling and clarification

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Abstract

Objective: To analyze long-term outcome of a randomized clinical trial comparing laparoscopic (LNF) and conventional Nissen fundoplication (CNF) for the treatment of gastroesophageal reflux disease (GERD).

Summary Background Data: LNF has replaced CNF, based on positive short- and midterm outcome. Studies with a follow-up of over 15 years are scarce, but desperately needed for patient counselling.

Methods: Between 1997 and 1999, 177 patients with proton pump inhibitor (PPI)-refractory GERD were randomized to CNF or LNF. Data regarding the presence of reflux symptoms, dysphagia, general health, PPI use and need for surgical reintervention at 17 years are reported.

Results: A total of 111 patients (60 LNF, 51 CNF) were included. Seventeen years after LNF and CNF, 90% and 95% of the patients reported symptom relief, with no differences in GERD symptoms or dysphagia. Forty-three and 49% of the patients used PPI's (NS). Both groups demonstrated significant improvement in general health (77% *vs*. 71%, NS) and quality of life (75.3 *vs*. 74.7, NS). Surgical reinterventions were more frequent after CNF (18% *vs*. 45%, *P*=0.002), mainly due to incisional hernia corrections (3% *vs*. 14%, *P*=0.047).

Conclusions: The effects of LNF and CNF on symptomatic outcome and general state of health remain for up to 17 years after surgery, with no differences between the two procedures. CNF carries a higher risk of surgical reintervention, mainly due to incisional hernia corrections. Patients should be informed that 17 years after Nissen fundoplication, 60% of the patients are off PPI's, and 16% require reoperation for recurrent GERD and/or dysphagia.

Introduction

Fundoplication is considered the standard surgical procedure for patients diagnosed with objectified proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD). Since its introduction in 1991,[1] laparoscopic 360° total (Nissen) fundoplication (LNF) demonstrated excellent short-term results, with a significant reduction in perioperative morbidity and recovery time compared to conventional Nissen fundoplication (CNF).[2] However, since the introduction of Nissen fundoplication for the surgical treatment of GERD, concerns have been raised about long-term sustainability of the beneficial effect, both in terms of subjective and objective outcome. This has induced reluctance to refer patients for surgery by general practitioners, internists and gastroenterologists.[3, 4]

Previously, our group reported the three-months,[5] five-[6] and 10-year[7] subjective and objective outcome of a multicenter randomized clinical trial (RCT) performed between 1997 and 1999 in the Netherlands. In this clinical trial, 177 patients were included and randomized to either laparoscopic (LNF) or conventional Nissen fundoplication (CNF). At five years, no significant differences in subjective and objective outcome after LNF and CNF were found, and 15% and 12% of the patients respectively underwent surgical reintervention.[6] At 10-years, twice as many patients underwent reoperation after CNF than after LNF (15% versus 35%, *P*=0.006), with no differences in reoperation for recurrent GERD and/or dysphagia, and comparable outcome in terms of GERD symptoms, PPI use, quality of life and objective reflux control.[7] These findings have been confirmed by Salminen et al, who published the 11-year outcome of their RCT comparing LNF and CNF (n=110), with no differences in subjective outcome between the two groups, despite a higher incidence of incisional hernia and endoscopically diagnosed insufficient wraps after CNF compared to LNF.[8] Recently, Salminen et al. published the results of 15-year follow-up of this RCT (n=86), which were in line with the outcome at 11 years.[9] The present study is the largest RCT comparing LNF and CNF and provides the longest follow-up duration, with special emphasis on control of reflux symptoms, general health, need for medical treatment and reoperation rate at 17 years.

Methods

Study design and participants

Between 1997 and 1999, 177 patients were included in a multicenter RCT and underwent either LNF or CNF for PPI-refractory GERD in one of the participating tertiary centers (n=98, LNF; n=79, CNF).[5] After three months follow-up was available in 103 patients (n=57, LNF; n=46, CNF), an interim analysis demonstrated a significantly higher incidence of dysphagia requiring endoscopic dilatation or surgical reintervention after LNF compared to CNF, and the trial was therefore prematurely terminated.[5] In the period between the interim analysis and the termination of the trial, another 64 patients had been randomized and were subsequently operated, bringing the total number of included patients to 167 (n=93, LNF; n=74, CNF). All 167 patients underwent symptomatic and objective evaluation, including esophageal manometry and 24-hr pH-monitoring, at three-months follow-up.

At five years, 151 patients were eligible for evaluation of symptomatic outcome using validated questionnaires, and esophageal manometry and 24-hr pH-monitoring (n=8 lost to follow-up, n=4 died, n=4 emigrated).[6] Of these 151 eligible patients, three refused further follow-up. Therefore, at five years, clinical outcome was available in 148 patients (n=79, LNF; n=69, CNF). At 10 years, two patients had died within the CNF-group, consequently clinical 10-year outcome was available for 146 patients (n=79, LNF; n=67, CNF).[7] All patients were identified 17 years after surgery and have been included in the present study. The CONSORT analysis of five- and 10-year follow-up and 17-year follow-up are described in detail in Figure 1A and 1B respectively. All patients were contacted by mail and asked to complete questionnaires on reflux symptoms, general state of health, quality of life (QoL), patient satisfaction, use of acid suppressing drugs, and the need for surgical reintervention.

Surgical procedure

All primary fundoplications were performed between January 1997 and August 1999 in the participating tertiary centers.[5] After division of the short gastric vessels, full esophageal mobilization, and posterior crural repair using non-absorbable sutures, a floppy 360° total fundoplication of 2.5 to 3.0 cm was constructed in both the LNF- and CNF-group. Open surgery was performed using a standard upper midline incision.

Clinical outcome

Clinical outcome, including the use of acid suppressing drugs, the need for surgical reintervention, the interval between primary fundoplication and reintervention, the indication for and type of reintervention, and the Visick scores, were registered at 17 years of follow-up. To enable direct comparison of subjective outcomes at the different follow-up periods, the same questionnaires were used preoperatively, at three months, five years, 10 years and 17 years after surgery. The Visick score was used for analyzing the subjec-

tive effect of surgery, since it has been demonstrated to correlate well with a validated questionnaire for reflux symptoms and provides valuable insight in the overall appreciation of antireflux surgery by patients.[10-12] Patients were asked to rate the effect of surgery on reflux symptoms using the modified Visick grading as follows: complete resolution (Visick I), improvement (Visick II), no effect of surgery (Visick III), and deterioration (Visick IV) compared to their preoperative symptoms. Using a combined frequency and severity grading system, resulting in grades ranging from 0 (no symptom) to 3 (frequent and severe), the presence of heartburn, regurgitation and dysphagia was assessed.[13] Furthermore, the presence and frequency of nausea, vomiting and increased flatulence were monitored. A visual analogue scale (VAS) validated for the QoL assessment following esophageal surgery,[14] was used to assess the impact of surgery on the QoL. The scale ranged from 0 to 100, with 0 representing worst possible health and 100 representing perfect health.[15] The effect of surgery on selfrated change in general health was measured using a 3-point scale ranging from "improved" to "worsened". Finally, patients were asked if they would opt for surgery again in retrospect.

Statistics

All data were entered in a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). All data were analyzed based on the intention-to-treat principle. Per-protocol analysis was also performed in order to examine possible changes between the two groups based upon the surgical procedure patients had undergone. Data were expressed as mean ± standard deviation (SD) or total number of patients (%), unless stated otherwise. The Chi square test was used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. Kaplan-Meier analysis was used to evaluate the surgical reintervention rate during the 17-year follow-up period. Statistical significance was defined as $P<0.05$.

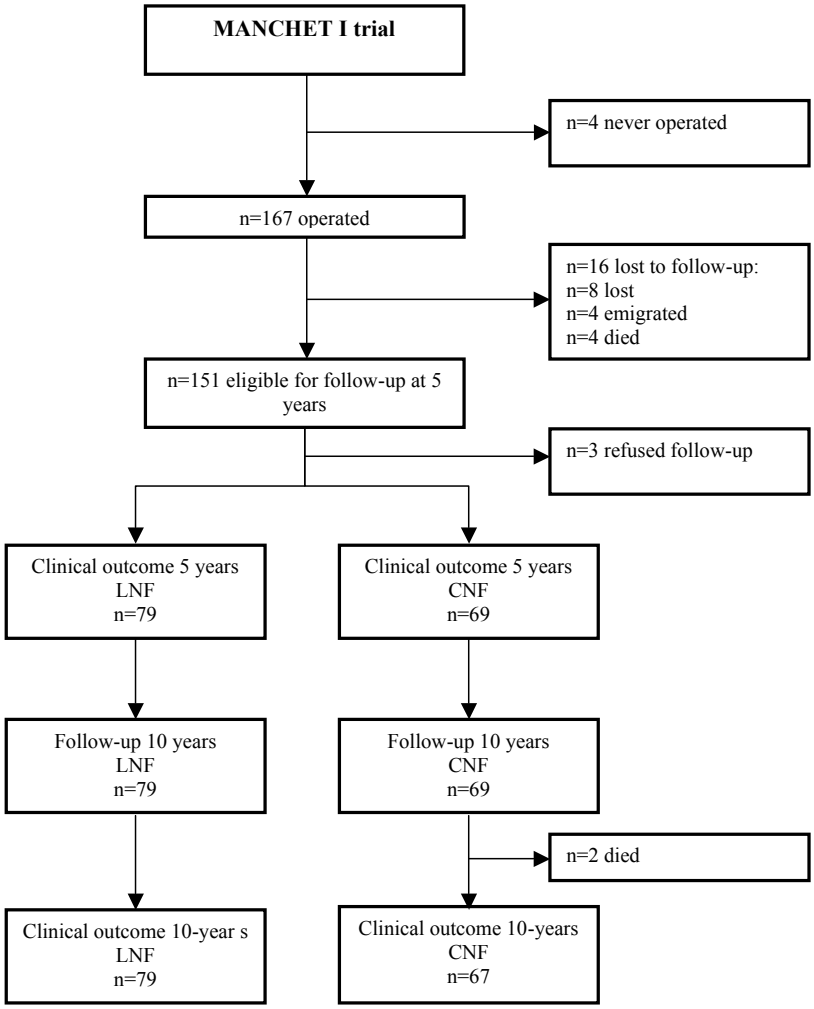


FIGURE 1A. Study profile: CONSORT analysis 5- and 10-year follow-up.

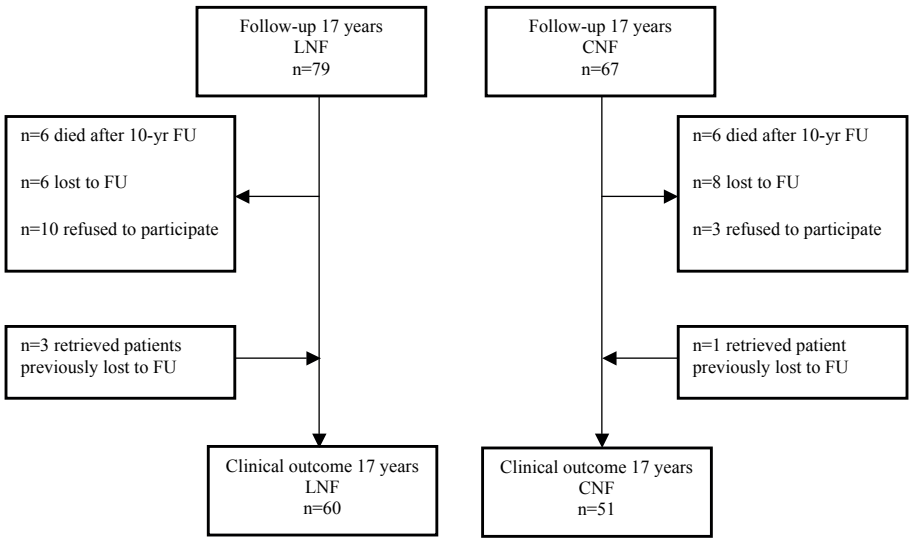


FIGURE 1B. Study profile: CONSORT analysis 17-year follow-up.

Results

Overall responses and completeness of follow-up

Baseline characteristics of included patients were available and comparable for both groups (Table 1). Six patients (7.6%) required conversion to an open procedure and were maintained in the LNF-group based on the intention-to-treat principle. The mean time to follow-up was 17.8 (0.9) years after LNF and 17.7 (0.9) years after CNF. Of the patients in the LNF group with 10-year clinical outcome (n=79), six patients died and six were lost to follow-up. In the CNF-group (n=69), also six patients died and seven were lost to follow-up (Fig. 1B). Additionally, four patients who had been lost to follow-up at 10 years were contacted at 17 years and included in the present study (n=3, LNF; n=1, CNF). Therefore, a total of 124 patients were available for evaluation 17 years after surgery (n=70, LNF; n=54, CNF). Of these 124 patients, data on clinical outcome could be retrieved for 111 patients (90%; n=60, LNF; n=51, CNF), of whom 105 completed the questionnaires. (n=58, LNF; n=47, CNF). Thirteen patients refused to participate in the present study.

TABLE 1. Baseline characteristics according to treatment allocation.

	LNF	CNF
Patients (n)	60	51
Sex (male / female)	35/25	33/18
Age (yr.)	41.0 (12.6)	41.8 (11.3)
BMI (kg/m2)	26.0 (4.5)	27.1 (3.7)
Conversion rate	6 (7.6%)	-
Follow-up interval (yr.)	17.8 (0.9)	17.7 (0.9)

All data are expressed as mean (SD) or n (%)

Symptomatic outcome

There was no difference in improvement of reflux symptoms after surgery between the two groups, with 57 of 60 patients (95%) reporting their reflux symptoms to be either resolved or improved (Visick I + II resp.) after LNF, and 46 of 51 (90%) patients after CNF (*P*=0.24; Table 2). After LNF, 54 of the 58 patients (93%) who completed the questionnaires reported no or mild symptoms of heartburn, which did not differ between the two groups (39/47 [83%], CNF, *P*=0.41). No or mild regurgitation was reported in 97% after LNF and 90% after CNF (*P*=0.28). There was no difference in the incidence of troublesome dysphagia 17 years after LNF and CNF, with no or mild dysphagia reported in 84% and 85% of the patients respectively (*P*=0.79). The incidence of troublesome nausea,

vomiting and increased flatulence also did not differ between the two groups (17% *vs*. 15%, *P*=0.78; 7% *vs*. 15%, *P*=0.31; and 41% *vs*. 45%, *P*=0.98 respectively). Per-protocol analysis did not change these results.

TABLE 2. Self-rated change in reflux symptoms compared to preoperative state and grades of heartburn, regurgitation, and dysphagia at 17 years.

	LNF (n=60)	CNF (n=51)
Self-rated change in reflux symptoms, n (%)		
Visick I: resolved	30 (50%)	27 (53%)
Visick II: improved	27 (45%)	19 (37%)
Visick III: unchanged	2 (3%)	1 (2%)
Visick IV: worsened	-	4 (8%)
Heartburn, n (%)		
Grade 0	30 (52%)	22 (47)
Grade 1	24 (41%)	18 (38%)
Grade 2	1 (1.7%)	3 (6%)
Grade 3	-	1 (2%)
Regurgitation, n (%)		
Grade 0	43 (74%)	34 (72%)
Grade 1	13 (22%)	9 (19%)
Grade 2	2 (3%)	2 (4%)
Grade 3	-	3 (6%)
Dysphagia, n (%)		
Grade 0	26 (45%)	26 (55%)
Grade 1	23 (40%)	15 (32%)
Grade 2	4 (7%)	4 (8%)
Grade 3	1 (2%)	1 (2%)

No or mild symptoms = grade 0 and 1

Both groups demonstrated a similar general state of health at 17 years, with 77% and 71% of the patients reporting that their general state of health had improved compared to the preoperative state after LNF and CNF respectively, with similar mean QoL VAS scores (Table 3, 75.3 [13] *vs*. 72.4 [20], *P*=0.75). Both LNF and CNF resulted in a

significant increase in QoL at 17 years compared to the preoperative state (both *P*<0.001, Figure 2). Seventeen years after LNF and CNF, 82% and 69% of the patients answered that they would opt for surgery again in retrospect (*P*=0.41), and there was no difference between the two groups in the use of acid suppressing drugs (42% *vs*. 49%, *P*=0.44). In the LNF group, 25 patients (42%) were dependent on daily use of acid suppressing drugs, of whom two reported typical reflux symptoms with no relief compared to the preoperative state (Visick grade III), and 23 reported their reflux symptoms to be either completely resolved or improved (Visick grades I and II). Within the CNF group, 25 patients (49%) were dependent on daily acid suppressing medication, of whom one reported no relief of reflux symptoms compared to the preoperative state (Visick III) and three reported worsening of the symptoms (Visick IV). Despite the fact that in both groups the usage of acid suppressing medication increased at 17 years compared to the use three months after surgery (3 months *vs*. 17 years postoperative *P*<0.001 for both groups), the usage at 17 years was significantly lower compared to the preoperative state (Figure 4, *P*<0.001 and *P*=0.001). Changes in the use of acid suppressing medication during 17-year follow-up are described in Figure 3. Per-protocol analysis did not change these results.

TABLE 3. General state of health, quality of life, and patient satisfaction at 17 years.

	LNF (n=60)	CNF (n=51)
General state of health, n (%)		
Improved	44 (77%)	34 (72%)
Unchanged	6 (11%)	6 (13%)
Worsened	7 (12%)	8 (17%)
General QoL (VAS-score 0-100)*	75.3 (13)	72.4 (20)
Opt for surgery again in retrospect, n (%)		
Yes	49 (85%)	35 (74%)
No	6 (10%)	7 (15%)
Unsure	3 (5%)	5 (11%)
Use of daily acid-suppressing medication, n (%)	25 (42%)[‡]	25 (49%)[§]

* Data are expressed as mean (SD); [†] *P*=0.045; [‡] *P*<0.001 versus preoperative use; [§] *P*=0.001 versus preoperative use

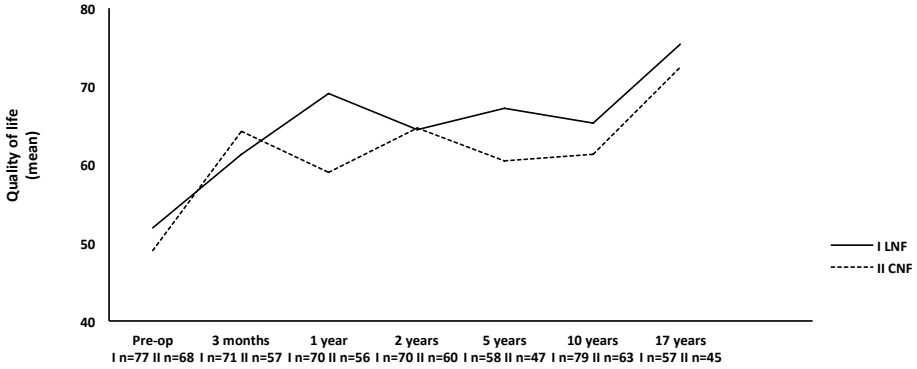


FIGURE 2. Mean quality of life (VAS 0-100) during 17-year follow-up after LNF and CNF.

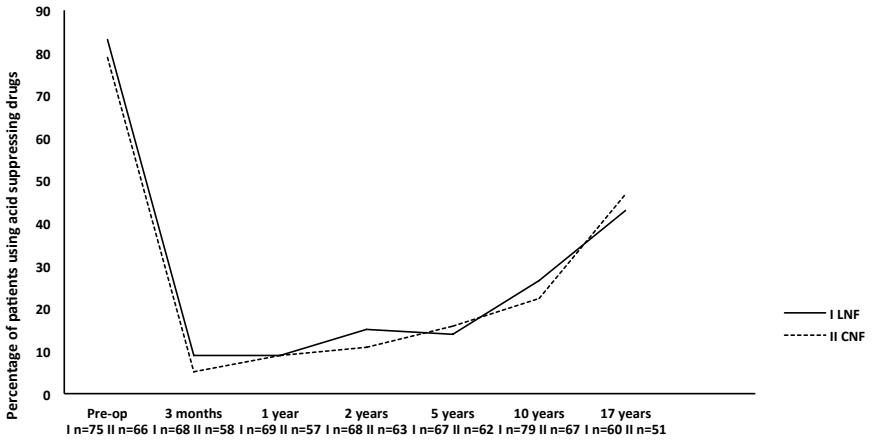


FIGURE 3. Changes in use of acid-suppressing medication (percentage of patients) during 17-year follow-up.

Surgical reintervention

Within the group of patients in whom clinical outcome was available at 17 years, 11 of the 60 patients (18%) and 23 of the 51 patients (45%) had undergone one or more surgical reinterventions after LNF and CNF respectively (*P*=0.002). The specification of surgical reinterventions reported by the included patients at 17 years is provided in table 4. Overall, 18 of the 111 patients (16%) underwent surgical reintervention for recurrent GERD and/or persistent dysphagia, with no significant differences between the groups (7/60 [12%] *vs*. 11/51 [22%], *P*=0.16). Based on the available clinical outcome at 17 years, there was a higher rate of surgical reintervention for incisional hernia after CNF compared to LNF (7/51 [14%] *vs*. 2/60 [3%], *P*=0.047). In the per-protocol analysis, this difference was significant as well (1/54 [2%] *vs*. 8/57 [14%], *P*=0.032).

Table 4. Surgical reinterventions performed during 17-year follow-up.		
	LNF (n=60)	CNF (n=51)
Surgical reintervention, n (%)	11 (19%)	23 (45%)*
Mean time to reintervention (months)	51 (69)	74 (60)
Indication for reintervention (n)		
Recurrent GERD	3	5
Persistent dysphagia	3	2
Recurrent GERD and persistent dysphagia	1	4
Incisional hernia	2	7†
Abdominal pain	1	2
Paraesophageal hernia	0	2
Gastric perforation	1	0
Barrett's esophagus	0	1
Type of reoperation (n)		
Re-Nissen	5	8
Belsey-Mark IV	2	2
Conversion to partial fundoplication	0	1
Correction incisional hernia	2	7†
Adhesiolysis	1	1
Paraesophageal hernia repair	0	2
Esophagectomy	0	1
Other	1	1

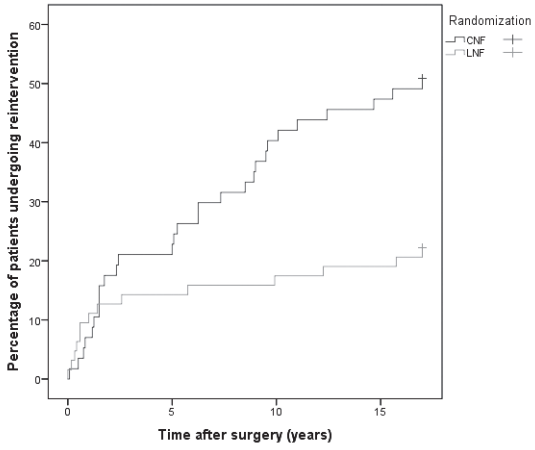
All data are expressed as mean (SD) or n (%); * *P*=0.002 versus LNF; † *P*=0.047 versus LNF

Nine patients (n=3, LNF; n=6, CNF) who had been included in the 10-year study and undergone surgical reintervention within 10 years after surgery, were lost to follow-up (n=7) or had died (n=2) in the period between 10 and 17-year follow-up. Reinterventions and their indications included re-Nissen for recurrent GERD and/or persistent dysphagia (n=1 LNF; n=2 CNF), Belsey-Mark IV for recurrent reflux and/or persistent dysphagia (n=1, LNF; n=1, CNF), and correction of incisional hernia (n=1, LNF; n=3, CNF). When these patients were added to the present analysis, a total of 43 surgical reinterventions had been performed in 120 patients (14/63 [22%], LNF; 29/57 [51%], CNF, *P*=0.001) during the entire 17-year follow-up period, with correction of incisional hernia in 10 patients after

CNF, compared to three after LNF (*P*=0.028; see Figure 4, Supplemental Digital Content 1, demonstrating the percentage of patients undergoing surgical reintervention after LNF and CNF during 17 year follow-up (Kaplan-Meier analysis, one-minus-survival)).

Of the patients who used acid suppressing drugs 17 years after surgery, more had undergone surgical reintervention compared to those not using acid suppressing medication (24/50 [48%] *vs*. 10/51 [20%], *P*<0.001). Surgical reintervention for GERD and/or dysphagia was more frequently performed in this group compared to patients not using acid suppressing drugs (16/50 *vs*. 2/51, *P*=0.013). Per-protocol analysis did not significantly alter these results.

In order to analyze the risk for selection bias, baseline characteristics were compared between patients who responded to the questionnaires and those who did not. Patients who did not respond to the questionnaires were more often male than female (83% *vs*. 17%, *P*=0.024), had a lower mean age (53 [8] *vs*. 60 [12] years, *P*=0.016) and did not undergo more surgical reinterventions up to 10 years of follow-up. These findings suggest that the risk for selection bias in the present study is low.



SUPPLEMENTAL FIGURE 4. Percentage of patients undergoing surgical reintervention after laparoscopic (LNF) and conventional Nissen fundoplication (CNF) during 17-year follow-up (Kaplan-Meier analysis, one-minus-survival).

Discussion

As occurred with other abdominal surgical procedures after the introduction of laparoscopy, the conventional Nissen fundoplication was rapidly replaced by its laparoscopic counterpart. This occurred despite the fact that the previously mentioned interim analysis of this trial demonstrated a higher risk for troublesome dysphagia requiring endoscopic dilatation or surgical reintervention after LNF compared to CNF,[5] and one-year outcome of another RCT comparing LNF and CNF was not yet available.[16] The most important reason for this transition was the reduced short-term morbidity rate associated with laparoscopy and number of days till return to normal activity compared to the conventional approach, which has been confirmed by recent meta-analyses.[17, 18] Currently, laparoscopic Nissen fundoplication is the most frequently performed type of fundoplication worldwide.

In the present study, 17-year symptomatic outcome and the need for surgical reintervention of patients included in the largest RCT comparing LNF and CNF are reported. We demonstrated no differences between the two procedures in improvement of reflux symptoms at 17 years after LNF and CNF, with 90 to 95% of the patients reporting their reflux symptoms to be either completely resolved or significantly improved compared to the preoperative state. Additionally, the symptoms heartburn and regurgitation were either totally absent or only present in a mild form in 83 to 93% and 90 to 97% of the patients respectively, with no differences between the two procedures. In 2012, Salminen et al published the 15-year outcome of their Finnish RCT comparing laparoscopic with conventional Nissen fundoplication, including 86 patients in whom symptomatic outcome was available.[9] Since preoperative symptom-scores were not available in their study, the effect of fundoplication on reflux symptoms could not be determined. Our findings regarding the prevalence and grading of reflux symptoms at 17 years following surgery compare favorably with those reported in their 15-year outcome study, in which approximately 77% of the patients reported to be either asymptomatic or only experiencing mild symptoms of heartburn or regurgitation.

This significant improvement in reflux symptoms 17 years after surgery is supported by the reported decrease in use of acid suppressing drugs after LNF and CNF compared to the preoperative state. However, 17 years after primary fundoplication, 42 to 49% of the patients reported to use acid suppressing drugs. Compared to the use three months after surgery, the number of patients using daily acid suppressing medication at 10 and 17 years after surgery is significantly higher, indicating a progressive increase in use of acid suppressing drugs with extension of follow-up.[5, 7] This is supported by the study of Salminen et al, reporting that 46.5% of the included patients had reinstated PPI use 15 years after surgery.[9] Therefore, if primary indication for Nissen fundoplication is unwillingness of patients to take life-long acid suppressing medication, the success rate is around 60%.

However, these findings should be interpreted with caution, since it is has been demonstrated that only a small portion of the patients using acid suppressing medication after antireflux surgery is diagnosed with abnormal esophageal acid exposure on 24-hr pH-monitoring.[6, 19, 20] Indeed, in the current RCT, 65% of the patients using PPIs on a daily basis had no objectified pathological esophageal acid exposure at 10 years.[7] Possible explanations for the increase in use of acid suppressing drugs include continues use by patients despite absence of typical reflux symptoms, and prescription of acid suppressing drugs to provide gastric protection for concurrent medication, such as nonsteroidal antiinflammatory drugs (NSAIDS) and platelet inhibitors.[21]

Three-month results of the present trial demonstrated a higher incidence of dysphagia requiring endoscopic dilatation or surgical reintervention after LNF,[5] most likely caused by a relative lack of experience with laparoscopic fundoplication by the participating surgeons at the start of this trial. Symptomatic outcome at 5- and 10-years demonstrated no difference in reported dysphagia between LNF and CNF,[6, 7] and our present 17-year findings demonstrate these results are maintained during longterm follow-up, with approximately 85% of the included patients reporting absence or the presence of only mild dysphagia with no differences between the two procedures. The initial higher incidence of dysphagia in the early postoperative period after LNF compared to CNF,[22-24] and the decrease in incidence of dysphagia with extension of follow-up, has also been described by other RCTs comparing outcome of LNF with CNF.[23, 25, 26]

At 17 years, surgical reintervention was more frequently performed after CNF compared to LNF. The main reason for this difference (18% *vs*. 45%) is the higher incidence of symptomatic incisional hernia following CNF. Whilst at five-years follow-up of the present trial no significant difference in the need for surgical reintervention between the two groups was found,[6] significantly more patients required surgery for symptomatic incisional hernia after CNF at 10- and 17-year follow-up.[7] The current study is the first RCT to demonstrate that laparoscopic antireflux surgery reduces the number of incisional hernia corrections compared with upper midline incision in non-obese patients. This is an important finding, again underlining the long-term benefit of laparoscopic surgery compared to the conventional approach.

Eighteen patients (16%) underwent surgical reintervention for recurrent GERD and/or persistent dysphagia, with no significant difference between the two groups at 17 years. This finding indicates that approximately one in eight patients needs a second operation for recurrent GERD and/or dysphagia. This is an important finding that should be addressed when discussing the possibility of Nissen fundoplication for the treatment of GERD. Salminen et al. found lower rates of surgical reintervention in both groups at both 11- and 15-year follow-up.[8, 9] At 15 years, seven (25%) incisional hernias were detected in the CNF-group, which were all asymptomatic and did not require surgical repair, and none after LNF. The overall reoperation rate 15 years after fundoplication was 5.5% (n=3) and 7.3% (n=4) after LNF and CNF respectively (*P*=1.000), which is low compared

to our results.[9] Selection-bias and referral-bias pose an important problem with long-term follow-up studies and could explain differences between trials. Two meta-analyses performed by Catarci et al and Peters et al demonstrated a reoperation rate of 9.6% and 8.2% respectively, with follow-up periods of 2.5 years (mean) and 3.6 years (average) after LNF and CNF.[17, 18] These studies only included reoperation for recurrent GERD, and taking the extended length of follow-up of our trial into account, our findings are largely in line with these two meta-analyses.

The present study is based on the largest RCT comparing LNF with CNF and provides the longest follow-up for both procedures currently available. A possible limitation of this study is the fact that no objective outcome is provided for the patients. This has been performed at five and 10 years after surgery for this cohort of patients however, demonstrating no significant differences in esophageal acid exposure between the two procedures.[6, 7] Since 17-year symptomatic outcome did not demonstrate any differences between the two groups, one may assume objective follow-up will be in line with these results. In the present study, 17-year clinical outcome is provided for 111 (66%) of the initially included and operated 167 patients. Additionally, validated questionnaires were completed by 105 (63%) of the initially included patients, and by using the same questionnaires at all postoperative intervals as those used preoperatively, direct comparison between the preoperative phase and the different follow-up periods could be performed, providing valuable insight in the symptomatic outcome throughout 17 years follow-up. The response rate of 63% in this study was as is to be expected with these type of surveys, especially given the fact that 18 patients died during 17-year follow-up.[27] A potential risk of long-term follow-up studies through questionnaires is selection bias. However, as previously stated, the risk for selection bias in the present study is low.

In summary, this study demonstrates that the previously described effects of both LNF and CNF on symptomatic outcome and general state of health at five and 10 years are sustained for up to 17 years after surgery, with no significant differences between the two procedures. CNF carries a higher risk for surgical reintervention compared to LNF, mainly due to incisional hernia corrections, supporting the use of LNF as the surgical procedure of choice for GERD. Despite the fact that 40% of the patients are back on medical treatment after 15 years and a substantial proportion needs reoperation, when regurgitation is the dominating symptom, surgery is the only option for adequate control of this incapacitating symptom. If a patient is reluctant to take life-long medication, surgery should be proposed, while informing patients that for this indication, their chances of sustained success are approximately 60%, with a 16% chance of needing a second operation for control of recurrent reflux symptoms and/or dysphagia.

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Chapter 3

Two-year outcome of laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication: results from two randomized clinical trials

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Submitted

Abstract

Background: Compared to laparoscopic Nissen fundoplication (LNF), laparoscopic 270 degree posterior, or Toupet (LTF), and 180 degree anterior partial fundoplication (LAF) provide equal reflux control, with a lower risk of postoperative dysphagia and gas-related symptoms. Adequately powered randomized studies comparing short- to mid-term outcomes for these type of partial fundoplication are lacking. The aim of the present study was to analyze two-year outcome from two randomized trials comparing LTF *vs*. LAF for the treatment of gastroesophageal reflux disease (GERD).

Methods: Between 2005 and 2015, 141 patients with proton pump inhibitor (PPI)-refractory GERD were randomized to LTF or LAF in two randomized clinical trials using a common protocol. Data regarding the incidence of dysphagia and gas-related symptoms, presence of reflux symptoms, general health, PPI use and need for surgical reintervention at two years were analyzed.

Results: 141 patients (LTF n=70, LAF n=71) were included. Two years after surgery, there were no differences in GERD symptoms, dysphagia, gas-related symptoms or PPI use. There were also no differences in patient satisfaction with the overall outcome. Endoscopy, esophageal manometry and 24-hour pH-monitoring demonstrated LES resting pressure to be significantly lower after LTF compared to LAF (8.5 [5.8-11.2] *vs.* 18.0 [13.2-22.9], *P*=0.046), with no difference in the prevalence of esophagitis or esophageal acid exposure.

Conclusions: LTF and LAF provide similar reflux control, with no differences in incidence of dysphagia or gas-related symptoms up to two years after surgery. The decision to perform LTF or LAF should be based on the surgeons experience with either of these partial fundoplications.

Introduction

Laparoscopic fundoplication provides excellent reflux control for patients diagnosed with proton pump inhibitor (PPI) refractory gastroesophageal reflux disease (GERD), and for those who are unwilling to take life-long acid suppressing medication.[1, 2] While providing high and stable satisfaction rates, the laparoscopic 360 degree total or Nissen fundoplication (LNF) is associated with a risk of developing undesirable side-effects such as dysphagia and gas-related symptoms.[2-5] Gas-related symptoms, including inability to belch, abdominal bloating and increased flatulence, are caused by a supracompetent valve preventing the stomach from adequately venting ingested air.[6-9]

To reduce the incidence of postoperative dysphagia and gas-related symptoms, partial fundoplications, where the fundus of the stomach is wrapped partially around the distal esophagus, have been developed. Currently, the 270 degree posterior (LTF) and 180 degree anterior partial fundoplication (LAF) are the most frequently performed partial fundoplications. Recently published meta-analyses have indeed demonstrated that both procedures provide equal reflux control when compared to Nissen fundoplication, while significantly reducing the risk of postoperative dysphagia and gas-related symptoms.[3, 4] Furthermore, a recent study by Broeders et al. comparing reflux characteristics and belching between LNF and LTF using combined pH-impedance monitoring, demonstrated that LTF results in significantly more air venting from the stomach, and less gas bloating and flatulence compared to LNF, with similar reflux control at six months after surgery.[10]

In 2015, Daud et al published the results of an Australian randomized clinical trial (RCT) in which patients with GERD were randomized to LTF or LAF.[11] Although being underpowered due to difficulty recruiting patients, this trial demonstrated no significant differences in reflux control or incidence of dysphagia or gas-related symptoms at one year follow-up. Recently, one-year outcome of a sister RCT performed in the Netherlands was published, in which 94 patients were randomized for LTF and LAF.[12] At one year, there were no significant differences in symptomatic nor objective reflux control between the two procedures, with no difference in the incidence of postoperative dysphagia or gas-related symptoms.[12]

These two studies were established using the same protocol and follow-up assessment methods. In the present study, the two trials were combined to improve statistical power. Two-year outcomes for LTF and LAF are reported, with emphasis on the incidence of postoperative dysphagia and gas-related symptoms.

Materials and methods

Study design and participants

Between September 2005 and May 2015, 141 patients were enrolled in two multicenter randomized clinical trials and were randomized to undergo either LTF or LAF.[11, 12] The two trials used the same protocol and methodology, with similar standardized symptom and outcome assessment scores. Both types of partial fundoplication were standardized among the participating tertiary centers.

All included patients were diagnosed with chronic PPI-refractory GERD, which had been objectified through either upper gastrointestinal endoscopy demonstrating unequivocal signs of GERD, or 24-hour pH-monitoring demonstrating pathological esophageal acid exposure, defined as a total percentage of time with pH<4 equal to or more than 4% of the time. Exclusion criteria consisted of esophageal motility disorders, previous antireflux or bariatric surgery, and the presence of a giant hiatal hernia (intrathoracic stomach>50%). All patients gave written informed consent for participation and prospective collection of their medical data.

Forty-seven patients were operated in three tertiary referral centers in Adelaide, South Australia, and Brisbane, Queensland, Australia.[11] Ninety-four patients underwent laparoscopic fundoplication in two tertiary referral centers in Zwolle and Nieuwegein, the Netherlands.[12] Both Dutch surgeons were trained in Australia and used the same surgical technique, clinical outcome scores, and follow-up methodology in the Dutch trial as those used in the Australian trial.[11, 12] All participating surgeons in both the Dutch and Australian trial were well beyond their learning curve for laparoscopic antireflux surgery, with each surgeon performing more than 60 fundoplications per year.[13]

Demographics of the included patients were collected and included sex, age, body mass index (BMI), the presence of comorbidities categorized as diabetes and renal, pulmonary or cardiovascular disease, a history of thoracic and/or abdominal surgery, and the use of acid suppressing drugs. Preoperative symptoms and symptomatic outcome after fundoplication were assessed using structured questionnaires at different postoperative intervals. All patients were scheduled for preoperative upper gastrointestinal endoscopy, esophageal manometry and 24-hr pH-monitoring. Routine three to six month's postoperative upper gastrointestinal endoscopy, esophageal manometry and 24-hour pH-monitoring was performed independently of postoperative symptoms.

Surgical procedures

In both trials, patients were randomized 1:1 to either LTF or LAF. All procedures were commenced laparoscopically. Full esophageal mobilization and posterior crural repair using non-absorbable sutures was performed. Division of the short gastric vessels was performed when deemed necessary. Two-hundred-and-seventy degree posterior fundoplication entailed the creation of a posterior partial fundoplication of the gastric fundus,

which was anchored to the esophagus on the left and right sides, as well as to the right crus posterolaterally, while leaving the anterior esophagus uncovered. When constructing a LAF, the ventral wall of the gastric fundus was sutured to the anterior esophagus and right crus.[14] If the performed fundoplication type was not consistent with the allocated fundoplication type, the patient was not excluded and remained in the allocated group for intention-to-treat analysis.

Clinical outcome

To enable direct comparison of subjective outcomes at the different follow-up periods, the same structured questionnaires were used preoperatively, at one, three, six months and 12 months after surgery, and on a yearly basis thereafter in both trials. The presence or absence of the following symptoms was determined: heartburn, regurgitation, chest pain, epigastric pain, dysphagia for solids and/or liquids, pain during swallowing, postprandial fullness, inability to belch, gas bloating, anorexia, nausea, vomiting, increased flatulence and diarrhea. Additionally, the presence and severity of the symptoms heartburn and dysphagia for solids and liquids was assessed using a 0 to 10 analogue scale (0= no symptom, 10= sever symptom). The presence and severity of dysphagia was further examined using the validated Dakkak dysphagia score, assessing the difficulty of swallowing 9 different types of liquids and solids (0=never; 1=sometimes; 2=always).[15] Overall outcome of surgery was ranked using an analogue satisfaction score (0= dissatisfied, 10= highly satisfied), a modified Visick grading score (1= no symptoms, 5= worse symptoms following surgery), and an overall outcome score (1= perfect; 4= bad outcome).[16] In addition, patients were asked whether or not they considered their original choice to have surgery to be correct (0=no, 1= yes). Changes in the use of proton pump inhibitors and histamine-2 blockers were also recorded.

Statistics and sample size calculation

All data was entered in a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). Data was analyzed based on the intention-to-treat principle. Data were expressed as mean ± 95% confidence interval (95% C.I.) or total number of patients (%), unless stated otherwise. The Chi square test was used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. The effect of surgery on different continues variables in either the LTF or LAF group was analyzed using the Wilcoxon signed rank test (preoperative *vs.* postoperative values). Statistical significance was defined as $P<0.05$.

Sample size calculation has previously been described and was based on an estimated reduction in Dakkak dysphagia score of 50 percent after LAF (Dakkak score 3.5) compared to LTF (Dakkak score 7.0).[12, 17] A two-sample T-test power analysis with a power of 0.8 and α of 0.05 resulted in a sample size of 47 versus 47 (PASS 2008, version 8.0.8.).

Ethics approval and trial registration

The protocols of both trials have been approved by each participating hospital's research ethics committee and consent was obtained from all participants. Both trials have been registered in the Australia and New Zealand Clinical Trials Registry (ACTRN-12605000035628) and the Dutch Trial Register (NTR, RCT number NL39193.100.12).

Results

Overall responses and completeness of follow-up

A total of 141 patients were enrolled in the two randomized clinical trials and underwent LTF (n=70) or LAF (n=71). All but one of the included patients underwent the procedure they were randomized for. One patient from the Australian trial was randomized for LTF, but since a satisfactory posterior fundoplication could not be performed, a 180 degree anterior fundoplication was constructed. Two patients in the Dutch trial who were randomized for LTF underwent conversion to LAF for early dysphagia at five and 14 days after primary surgery respectively and remained in the LTF-group based on intention to treat analysis. Preoperative clinical outcome was available for all patients. Postoperative clinical outcome was available for 129 patients (91.5%) at three and six months, 127 patients (90.1%) at one year, and 125 patients (88.7%) two years after surgery (Fig. 1). Three patients were lost to follow-up and 13 refused to respond to the questionnaires. In the Dutch trial, none of the patients died during the two-year follow-up, and in the Australian trial one patient died 23 months after surgery due to an unknown cause. Preoperative endoscopy, esophageal manometry and pH-monitoring outcomes were available for 132 patients (93.6%), 101 patients (71.6%), and 127 patients (90.1%) respectively. Details of the postoperative follow-up are summarized in Figure 1. There were no significant differences in baseline characteristics between the two groups (Table 1). Additionally, there were no conversions to open surgery in either trial.

TABLE 1. Baseline characteristics according to treatment allocation.

	LTF	LAF
Patients (n)	70	71
Sex (male / female)	29/41	30/41
Age (yr.)	51.5 (48-55)	54.9 (52-58)
BMI (kg/m^2)	28.3 (27-29)	28.0 (27-29)
Previous abdominal surgery	30 (42.9%)	41 (57.7%)
Esophageal acid exposure (% time)	13.8 (10.1-17.6)	14.2 (11.7-16.6)

All data are expressed as mean (95% confidence interval) or n (%)

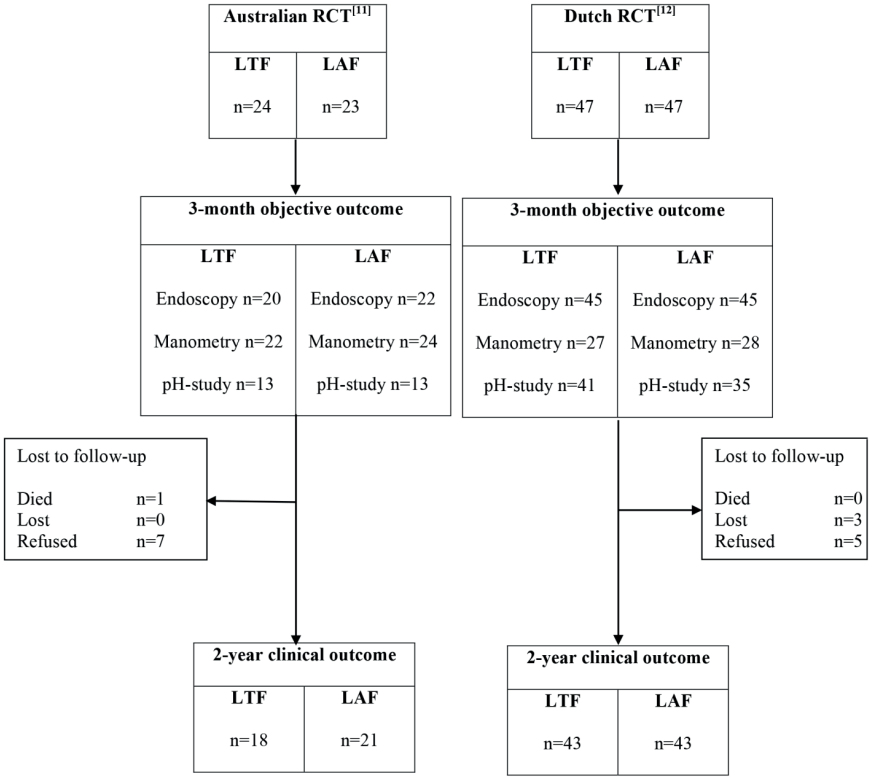

FIGURE 1. Study profile: CONSORT analysis 2-year follow-up.

Symptomatic outcome

There were no differences in preoperative symptoms between the LTF- and LAF-group, with equal prevalence of the symptom heartburn (n=67 [95.7%] *vs.* n=64 [90.1%], *P*=0.197), mean heartburn score (5.7 [5.0-6.4] *vs*. 5.2 [4.5-5.9], *P*=0.383), dysphagia score for liquids (0.8 [0.4-1.2] *vs*. 1.1 [0.5-1.6], *P*=0.727), dysphagia score for solids (2.5 [1.7-3.3] *vs.* 2.0 [1.3-2.6], *P*=0.620) and Dakkak dysphagia score (8.9 [6.5-11.3] *vs.* 8.0 [5.5-10.4], *P*=0.423). Furthermore, there was no difference in the preoperative use of acid suppressing medication (n=68 [97.1%] *vs.* n=66 [93.0%], *P*=0.253).

The presence of symptoms assessed two years after surgery is summarized in Table 2. There were no differences in the prevalence of the symptoms heartburn, dysphagia, or gas-related symptoms, including inability to belch, gas bloating and increased flatulence, after LTF and LAF. In both groups, there was a significant decrease in heartburn score at two years compared to the preoperative state (LTF, 5.7 *vs.* 1.7, *P*<0.001; LAF, 5.2 *vs.* 2.4, *P*<0.001), with equal heartburn scores, dysphagia scores for liquids and solids, and Dakkak dysphagia scores at two years (Table 3). Two years after LTF and LAF, 15 (26.3%) and 16 (25.8%) patients reported the use of acid suppressing medication on a daily basis (*P*=0.950).

TABLE 2. Prevalence of postoperative symptoms after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication at two years.

	LTF (n=70)	LAF (n=71)	*P*-value
Heartburn	14 (23.3%)	15 (22.4%)	0.989
Regurgitation	15 (25.0%)	9 (14.1%)	0.123
Chest pain	14 (23.3%)	15 (23.4%)	0.989
Epigastric pain	17 (28.3%)	22 (34.4%)	0.469
Pain during swallowing	3 (5.0%)	6 (9.4%)	0.493
Postprandial fullness	29 (48.3%)	22 (34.4%)	0.114
Inability to belch	8 (13.3%)	10 (15.6%)	0.717
Gas bloating	14 (23.3%)	12 (18.8%)	0.531
Anorexia	3 (5.0%)	1 (1.6%)	0.353
Nausea	16 (26.7%)	13 (20.3%)	0.404
Vomiting	0 (0.0%)	2 (3.1%)	0.496
Nocturnal coughing	10 (16.7%)	19 (29.7%)	0.087
Increased flatulence	34 (56.7%)	32 (50.0%)	0.457
Diarrhea	10 (16.7%)	9 (14.1%)	0.687

All data are expressed as n (%); LTF= laparoscopic 270 degree posterior fundoplication; LAF= laparoscopic 180 degree anterior fundoplication

TABLE 3. Mean heartburn score, dysphagia score for liquids and solids, Dakkak dysphagia score and usage of acid suppressing medication at two-years.

	LTF (n=70)	LAF (n=71)	*P*-value
Heartburn Controlled	49 (86.0%)	46 (80.7%)	0.451
Heartburn score (VAS 0-10)	1.7 (1.2-2.3)	2.4 (1.7-3.1)	0.337
Dysphagia for liquids (VAS 0-10)	0.7 (0.3-1.1)	1.0 (0.6-1.5)	0.798
Dysphagia for solids (VAS 0-10)	1.6 (1.0-2.1)	3.2 (0.4-5.9)	0.474
Dakkak Dysphagia Score (0-45)	6.4 (4.4-8.5)	7.6 (5.4-9.8)	0.564
Use of daily acid-suppressing medication	15 (26.3%)	16 (25.8%)	0.950

Data are expressed as n (%) or mean (95% C.I.); VAS= visual analogue scale; LTF= laparoscopic 270 degree posterior partial fundoplication; LAF= laparoscopic 180 degree anterior partial fundoplication.

At two years, there was no difference in Visick scores or patient satisfaction (Table 4), with mean satisfaction scores of 8.5 and 8.1 for both groups (*P*=0.337). There was no significant difference in the number of patients considering their choice to undergo surgery to be correct (n=56 [94.9%] *vs.* n=59 [92.2%], *P*=0.601).

TABLE 4. Satisfaction score, Visick score and number of patients reporting they would opt for surgery again after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication at two years.

	LTF (n=70)	LAF (n=71)	*P*-value
Satisfaction score (0-10)	8.5 (7.9-9.0)	8.1 (7.5-8.7)	0.337
Visick score			
I	12 (21.4%)	16 (25.8%)	0.610
II	29 (51.8%)	25 (40.3%)	
III	8 (14.3%)	13 (21.0%)	
IV	7 (12.5%)	8 (12.9%)	
V	0 (0.0%)	0 (0.0%)	
Opt for surgery again			
Yes	56 (94.9%)	59 (92.2%)	0.601
No	3 (5.1%)	4 (6.3%)	
Unsure	0 (0.0%)	1 (1.6%)	

All data are expressed as mean (95% C.I.) or n (%); LTF= laparoscopic 270-degree posterior partial fundoplication; LAF= laparoscopic 180-degree anterior partial fundoplication.

At three months, six months and one year after surgery, there were no differences in mean heartburn score, dysphagia score for liquids and solids and Dakkak score, nor in satisfaction scores or the patients considering their choice of having surgery to be correct. Mean heartburn score and Dakkak score during two year follow-up are summarized for both procedures in Figure 2A and Figure 2B respectively. During two-year follow-up, there was no difference in the prevalence of gas-related symptoms (gas bloat, inability to belch and increased flatulence) at all postoperative intervals (Table 5).

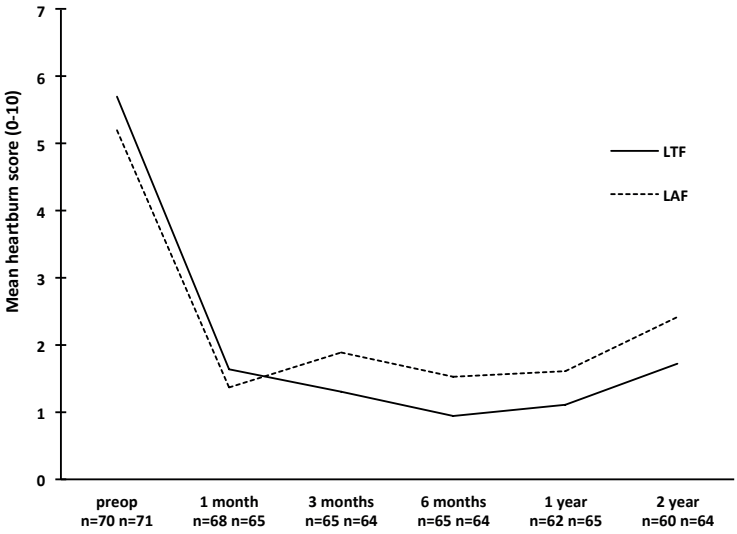

FIGURE 2A. Mean heartburn score (0-10) during two-year follow-up for laparoscopic 270-degree posterior (LTF) and 180-degree anterior (LAF) partial fundoplication groups.

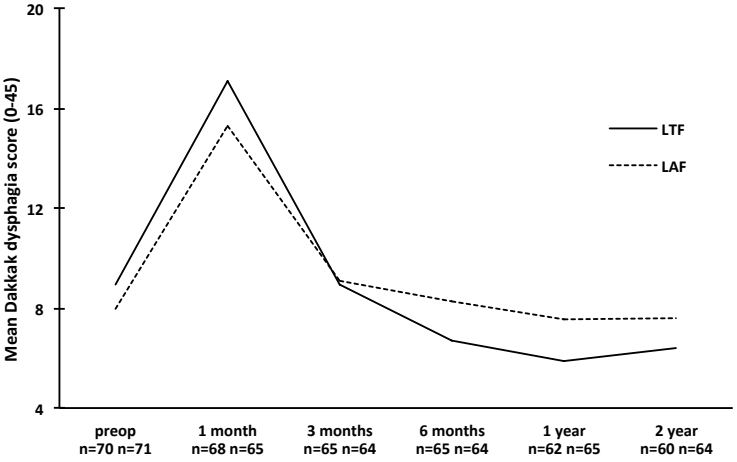

FIGURE 2B. Mean Dakkak dysphagia score (0-45) during two-year follow-up for laparoscopic 270-degree posterior (LTF) and 180-degree anterior (LAF) partial fundoplication groups.

TABLE 5. Prevalence of gas-related symptoms after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication.

	3-months		6-months		1-year		2-years	
	LTF	LAF	LTF	LAF	LTF	LAF	LTF	LAF
Inability to belch	16 (24.6%)	11 (17.2%)	12 (18.5%)	9 (14.1%)	10 (16.1%)	7 (10.8%)	9 (14.8%)	10 (15.6%)
Gas bloating	12 (18.5%)	13 (20.3%)	14 (21.5%)	14 (21.9%)	14 (22.6%)	11 (16.9%)	14 (23%)	12 (18.8%)
Increased flatulence	45 (69.2%)	43 (67.2%)	43 (66.2%)	42 (66.7%)	41 (66.1%)	38 (58.5%)	35 (57.4%)	32 (50.0%)

All data are expressed as n (%); LTF= laparoscopic 270 degree posterior partial fundoplication; LAF= laparoscopic 180 degree anterior partial fundoplication

Objective outcome

The results of pre- and postoperative upper gastrointestinal endoscopy, esophageal manometry and 24-hour pH-monitoring are summarized in Table 6. Preoperative upper gastrointestinal endoscopy did not demonstrate any differences in the presence of hiatal hernia (*P*=0.496), esophagitis (*P*=0.926), or the presence of Barrett's esophagus (*P*=0.782) between the two groups. Postoperatively, there were also no differences in the prevalence of hiatal hernia (*P*=0.526), esophagitis (*P*=0.537) or Barrett's esophagus (*P*=0.770). Twenty patients were diagnosed with Barrett's esophagus preoperatively, of whom 14 underwent postoperative endoscopy, demonstrating regression of Barrett's esophagus in five patients (35.7%). There was no increase in the prevalence of Barrett's esophagus after LTF (*P*=0.10 compared to preoperative state) nor in the LAF group (*P*=0.317). An intact fundoplication was demonstrated in 48 (100%) and 44 (91.7%) patients after LTF and LAF (*P*=0.117).

Preoperative esophageal manometry showed no differences between LTF and LAF in distal esophageal pressure (*P*=0.065), distal amplitude (*P*=0.583), or percentage of primary peristalsis (*P*=0.309), with equal LES resting and residual relaxation pressures (*P*=0.689 and *P*=0.960 respectively). Both LTF and LAF led to a significant increase in LES resting pressure (*P*=0.009 and *P*<0.001 respectively) compared to the preoperative state. The LES resting pressure was significantly lower after LTF compared to LAF (8.5 [5.8-11.2] *vs.* 18.0 [13.2-22.9], *P*=0.046), with no differences in distal resting pressure (*P*=0.054), distal amplitude (*P*=0.778) or percentage of primary peristalsis (*P*=0.361). Compared to LTF, LES residual relaxation pressure was significantly lower after LAF (9.5 [-1.8-20.7] *vs*. 8.2 [5.0-11.5], *P*=0.028).

Preoperative 24-hour pH-monitoring demonstrated no significant differences in upright, supine or total esophageal acid exposure between the two groups (*P*=0.767, *P*=0.374, *P*=0.181 respectively). Both LTF and LAF significantly reduced total esophageal acid exposure compared to the preoperative state (*P*<0.001 and *P*<0.001 respectively).

TABLE 6. Objective outcome before and after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication.

	LTF (n=70)		LAF (n=71)	
	Preoperative	Postoperative	Preoperative	Postoperative
Upper Gastrointestinal Endoscopy				
Fundoplication intact	-	48 (100%)	-	44 (91.7%)
Hiatal hernia present	43 (66.2%)	4 (8.3%)	48 (71.6%)	6 (12.2%)
Esophagitis	30 (46.9%)	12 (25.0%)	31 (47.7%)	15 (30.6%)
Barrett's esophagus	11 (16.9%)	13 (27.1%)	10 (15.2%)	12 (24.5%)
Esophageal Manometry				
Distal resting pressure (mmHg)	-1.7 (-5.4-2.0)	0.6 (-1.8-2.9)	4.2 (-2.8-11.2)	-2.5 (-5.0-0.0)
Distal amplitude (mmHg)	82.3 (47.3-117.3)	75.8 (62.4-89.2)	69.5 (32.5-106.5)	73.8 (59.6-87.9)
Primary peristalsis (%)	82.3 (75.5-89.2)	83.6 (75.8-91.3)	85.5 (78.4-92.7)	80.6 (72.0-89.2)
LES resting pressure (mmHg)	9.4 (6.4-12.5)	12.7 (9.9-15.4)	8.5 (5.8-11.2)	18.0 (13.2-22.9)*
LES residual pressure (mmHg)	2.4 (1.5-3.2)	9.5 (-1.8-20.7)	2.5 (1.4-3.5)	8.2 (5.0-11.5)†
24-Hour pH-Monitoring				
Upright esophageal acid exposure	14.5 (11.2-17.7)	1.7 (0.6-2.8)	13.7 (11.5-16.0)	2.1 (1.0-3.1)
Supine esophageal acid exposure	10.4 (4.9-15.8)	1.5 (0.2-2.8)	14.9 (7.6-22.1)	3.3 (0.5-7.0)
Total esophageal acid exposure	13.8 (10.1-17.6)	1.6 (0.6-2.6)	14.2 (11.7-16.6)	3.2 (1.2-5.2)

All data are expressed as n (%) or mean (95% C.I.); LTF= laparoscopic 270 degrees posterior partial fundoplication; LAF= laparoscopic 180 degrees anterior partial fundoplication; LES= lower esophageal sphincter; * P=0.046 *vs.* LTF; † P=0.028 *vs.* LTF.

Postoperatively, there were no significant differences in upright (*P*=0.655), supine (*P*=0.895) or total esophageal acid exposure (*P*=0.775) between the two groups.

Postoperative reintervention

There were no endoscopic dilatations for persistent or severe dysphagia in either group during two-year follow-up. Three patients underwent early surgical reintervention (within 30 days after primary fundoplication). As stated before, two patients from the Dutch trial who primarily underwent LTF required conversion to LAF (postoperative day 5 and 14 respectively) for severe dysphagia. One patient from the Australian trial required a reoperation on the second postoperative day due to a lost needle, during which the fundoplication was left intact.

Discussion

Recent meta-analyses have demonstrated equal reflux control, with a lower incidence of dysphagia and gas-related symptoms after LTF and 180 degree LAF compared to LNF.[3, 4] These studies provide level 1 evidence to support the use of both types of partial fundoplication in order to avoid the undesirable side-effects associated with LNF. Studies directly comparing the most frequently performed type of partial fundoplications, LTF and 180 degree LAF, were lacking however. This led to the need for directly comparing both partial fundoplications in a randomized fashion. The present study is the first to report two-year outcome of LTF and LAF for the treatment of GERD, based on the original data of two randomized clinical trials directly comparing these partial fundoplication. During the entire two-year follow-up period, there were no differences in subjective nor objective reflux control between LTF and LAF, with no differences in postoperative dysphagia and gas-related symptoms.

The present findings are largely in line with the one-year results of both the Australian and Dutch trial.[11, 12] The Dutch study group also found no significant differences in symptomatic outcome at one year, with only a significant lower LES residual resting pressure after LTF compared to LAF measured three months after surgery.[12] The study of Daud et al. reports a significant higher mean heartburn score one year after LAF compared to LTF, and less ability to belch at three and six months after LTF.[11] After pooling of their data with data of the Dutch trial and extension of follow-up to two years, these findings were no longer present. This could have been due to a type 1 error or a true difference between both fundoplications that fades in time. On the other hand, the Australian trial was underpowered due to difficulty recruiting patients, which could lead to type two errors. By combining the raw data sets of both trials, we have created the largest dataset directly comparing LTF with LAF for the treatment of GERD, and have achieved adequate statistical power. In the present study, the only difference between the two procedures was a significantly lower LES resting pressure after LTF compared to LAF, and a significantly lower LES residual relaxation pressure after LAF. This appears to have no clinical consequences, since there were no differences in postoperative esophageal acid exposure or the prevalence of esophagitis, reflux control or dysphagia between LTF and LAF, indicating that the decrease in LES resting pressure does not increase reflux. Two years after surgery, both types of partial fundoplication established a significant reduction in heartburn score compared to the preoperative state. The mean heartburn scores assessed two years after LTF and LAF, with no significant difference between the two procedures, are in line with previous reports on short- to midterm outcome of LTF and LAF.[17]

Two years after surgery, approximately 26% of the patients included in the present study reported the daily use of acid suppressing medication. This finding should be interpreted with caution, since previous studies have demonstrated that only a minority of the patients who are ´on` PPI's after antireflux surgery have actual gastro-esophageal

reflux confirmed objectively by pH- monitoring or endoscopy.[18, 19] Possible explanations for this finding include the continues use of medication despite absence of typical reflux symptoms, the development of new ´atypical` symptoms, such as gas-related symptoms, or the concomitant use of other medication such as non-steroidal anti-inflammatory drugs requiring acid suppressive medication for gastric protection.

In the present study, LTF was directly compared to 180 degree LAF. Previous studies have suggested that 90 degree anterior partial fundoplication, which involves wrapping of the fundus anteriorly half way across the distal esophagus with a circumference of 90 degrees, results in inferior reflux control but less dysphagia and gas-related symptoms compared to 180 degree anterior partial and Nissen fundoplication.[17, 20] One trial from Sweden compared 120 degree anterior fundoplication with posterior partial fundoplication, and found equal satisfaction with surgery, with better reflux control after posterior partial fundoplication and less troublesome side effects following anterior partial fundoplication.[21]

There were no differences in the incidence or severity of postoperative dysphagia, for either liquids or solids, assessed at all postoperative intervals up to two years after LTF and LAF in the present study. Two patients required early conversion to LAF due to severe dysphagia within the first two weeks after surgery. There were no other revision fundoplications or surgical reinterventions during the follow-up period. Furthermore, there were no endoscopic dilatations for dysphagia in either group during the two-year follow-up period. Previous studies have demonstrated that the development of new gas-related symptoms and severe early dysphagia significantly affects satisfaction with surgery.[22] In the present study, overall satisfaction with surgery remained high up to two years following surgery, with mean satisfaction scores of 8.1 to 8.5, and 92.2% to 94.9% of the patients responding that they considered their choice to undergo surgery to be correct two years after fundoplication.

Due to the randomized design, the use of identical study protocols, and pooling of original raw datasets, the present study provides the largest randomized clinical trial comparing outcome for LTF *vs*. LAF. Clinical outcome data was available for approximately 88% of the originally included patients, which compares favorably to what is to be expected with this type of study.[23] A possible weakness of our study is the fact that it combines data from a trial performed in Australia with data from a Dutch trial. However, the design of both trials was deliberately identical, with the same pre- and postoperative symptomatic and objective evaluation in both countries. Additionally, all operations in the Dutch trial were performed by two surgeons who had previously worked with the Australian research group and learnt and applied identical surgical techniques. Another potential limitation is the fact that patients did not undergo additional objective investigations at two years. In both trials upper gastrointestinal endoscopy, esophageal manometry and 24-hour pH-monitoring was performed three to six months after surgery, demonstrating only a significantly lower LES resting pressure after LTF, with no differences in symptomatic

outcome at three months and two years after surgery. Therefore, one may assume that objective evaluation at two years would be in line with the short-term results.

In conclusion, the present study demonstrates that both LTF and LAF provide subjective and objective reflux control, with no differences in the incidence or severity of dysphagia or gas-related symptoms up to two years after surgery. The decision to perform a LTF or LAF should be based on the individual surgeon's experience with either of these two partial fundoplications. Long-term follow-up of both trials is needed to confirm equivalence of both types of partial fundoplication with regards to reflux control, dysphagia, or the incidence of gas-related symptoms.

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Chapter 4

Reflux and belching after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication

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Abstract

Objective: To determine differences in effect of laparoscopic 270 degree posterior or Toupet fundoplication (LTF) and 180 degree anterior (LAF) partial fundoplication on reflux characteristics and belching patterns.

Summary of Background Data: LTF and LAF ensure equal reflux control and reduce the risk of gas-related symptoms compared to 360 degree (Nissen) fundoplication. It is unclear which type of partial fundoplication is superior in preventing gas-related side-effects.

Methods: Upper gastrointestinal endoscopy, esophageal manometry, and 24-hour combined pH-impedance monitoring were performed before and 6 months after fundoplication (n=10, LTF *vs.* n=10, LTF). Observed changes after surgery (Δ) were compared between the two procedures.

Results: Symptomatic reflux control, as well as reduction in acid (Δ -58.5 *vs.* -66.5), liquid (Δ -17.0 *vs.* -43.5) and mixed liquid-gas reflux episodes (Δ -38.0 *vs* -40.0) was comparable following LTF and LAF. There were no differences in the total number of weakly acidic reflux episodes after LTF and LAF (1.0 [0.8 – 4] *vs.* 1.0 [0 – 3], *P*=0.436). The reduction in proximal, mid-esophageal and distal reflux episodes was similar. Both procedures equally reduced the number of gastric belches and supragastric belches, with no significant reduction in the number of air swallows after either procedure.

Conclusions: LTF and LAF provide similar reflux control, with a comparable effect on acidic, liquid and gas reflux. Both procedures equally reduced the number of belches and supragastric belches. This study provides the physiological evidence for the published randomized trials reporting similar symptomatic outcome after both types of partial fundoplication.

Introduction

Laparoscopic fundoplication is an effective and definitive treatment for patients suffering from proton pump inhibitor (PPI) refractory gastroesophageal reflux disease (GERD), or for those who are unwilling to take life-long medication. Until recently, laparoscopic 360 degree total (Nissen) fundoplication (LNF) has been the surgical treatment of choice, providing excellent reflux control with high and stable satisfaction rates.[1-3] However, an important problem associated with total fundoplication is the development of postfundoplication symptoms, including dysphagia and gas-related symptoms, such as gas bloat and increased flatulence, caused by a supracompetent antireflux barrier.[4, 5] The development of postoperative dysphagia and/or gas-related symptoms has a significant impact on patient-perceived success of surgery, with lower satisfaction scores after surgery.[4-7]

To reduce the risk of postoperative dysphagia and gas-related symptoms, partial fundoplications have been developed. The two most frequently performed types of partial fundoplication include the laparoscopic 270 degree posterior or Toupet fundoplication (LTF) and the 180 degree anterior fundoplication (LAF).[4, 8] Both are created by wrapping the fundus of the stomach partially around the distal esophagus, either posteriorly or anteriorly. Recent meta-analyses have demonstrated that both types of partial fundoplication, LTF and LAF, offer durable and comparable control of reflux symptoms, with a lower incidence of 'post-fundoplication symptoms' compared with LNF.[4, 8] Recently, our study group published the results of a multicenter randomized clinical trial comparing LTF and LAF for the treatment of GERD.[9] At one year, there were no differences in the presence and/or severity of heartburn, nor in the incidence or severity of dysphagia for liquids or solids between the two groups. Additionally, routine upper gastrointestinal endoscopy, conventional 24-hour pH-monitoring and esophageal manometry performed three months after surgery did not demonstrate any differences in the presence of esophagitis, total esophageal acid exposure, or lower esophageal resting pressure after both procedures.[9]

The exact physiological effects of both types of partial fundoplication and the relationship with the development of gas-related symptoms are scarcely described. To clarify the latter, combined pH-impedance monitoring is the esophageal function test of choice. This technique enables visualization of movements of gas and liquids through the esophagus.[10, 11] This provides valuable information regarding the effect on acid and weakly acidic reflux, air swallows, gastric belches and supragastric belches. These are important factors when evaluating the outcome of antireflux surgery. Weakly acidic reflux has been demonstrated to elicit typical reflux symptoms which cannot be detected by conventional 24-hour pH-monitoring and do not respond to acid-suppressing medication.[12, 13] Gastric belching is a physiologic mechanism during which the stomach vents ingested air. It is hypothesized that gas-related symptoms are largely caused by an inability to belch.[14, 15] A previous study of our group used combined pH-impedance monitoring to compare reflux characteristics and belching patterns between LTF and LNF, and demonstrated that

LTF reduces reflux to a similar extend compared with LNF, but with less reduction in gas reflux and gastric belches, resulting in a lower incidence of gas bloating and flatulence following LTF.[16]

The present study is the first to use combined pH-impedance monitoring to compare LTF and LAF, and determine differences in effects of both partial fundoplications on reflux characteristics and belching.

Methods

Study design and data collection

Between January 2009 and March 2016, 20 patients diagnosed with GERD with pathological esophageal acid exposure and who were on the waiting list for primary LTF or LAF were prospectively included. Patients who had undergone previous antireflux surgery, hiatal hernia repair or bariatric surgery were excluded. All patients were asked to complete structured questionnaires preoperatively and six months postoperatively, and were scheduled for routine pre- and postoperative esophageal manometry and 24-hour combined pH-impedance monitoring. Baseline characteristics, including age, body mass index and the presence of comorbidities, and pre- and postoperative symptomatic and objective outcome were prospectively entered into a digitalized database.

Symptomatic outcome

All included patients were asked to complete structured questionnaires preoperatively and six months postoperatively by mail. The structured questionnaire focused on the presence and severity of typical GERD symptoms, dysphagia, and gas-related symptoms (the presence of bloating, inability to belch and increased flatulence). The presence and intensity of reflux symptoms was assessed using the validated GERD Health-Related Quality of Life score (GERD-HRQoL).[17, 18] The presence of and changes in dysphagia were analyzed using the validated European Organization for Research and Treatment of Cancer QLQ-OES 18 questionnaire.[19] The validated Short-Form 36 (SF-36) was used to assess the possible changes in health-related Quality of Life (QoL).[20] The presence of bloating, inability to belch and increased flatulence were assessed using a binary scale (absent/present).

Endoscopy

Upper gastrointestinal endoscopy was not routinely performed, but based upon the preoperative presence of or clinical suspicion for esophagitis, Barrett's esophagus or stenosis. Endoscopy was performed after eight hours of fasting. During endoscopy, postsurgical anatomy, healing of esophagitis, and/or the presence of any esophageal obstruction or hiatal hernia was assessed and scored according to the Los Angeles Classification.[21]

Esophageal manometry

All patients were scheduled for pre- and postoperative esophageal manometry. Three days after cessation of medication that could possibly affect esophageal motility, manometry was performed using a multi-lumen water-perfused catheter with incorporated sleeve sensor (Dentsleeve International Ltd, Mississauga, Canada) and a low-compliance perfusion system. Following transnasal introduction, the position of the proximal part of the lower esophageal sphincter (LES) was determined by slowly withdrawing the catheter, and intra-luminal esophageal pressures were registered at 5, 10, 15, 20 and 25 cm above

the proximal border of the LES. Next, the manometric response to 10 standardized wet swallows (5-mL water bolus) was recorded. The gastric baseline pressure was registered 2cm below the distal margin of the sleeve sensor and used as the zero reference point.

Ambulatory 24-hour combined pH-impedance monitoring

Ambulatory 24-hour combined pH-impedance monitoring was performed after cessation of acid-suppressing medication or medication which could influence esophageal motility, with PPIs being ceased for seven days and H2-recepetor antagonists for three days before monitoring. Using transnasal introduction, the antimony pH electrode was placed 5 cm from the upper border of the manometrically determined proximal border of the LES, whereas the recording segments of the impedance catheter (VersaFlex, Alpine Biomed, Fountain Valley, CA, USA) were placed 2-4, 4-6, 6-8, 8-10-, 14-16 and 16-18 cm from the proximal border of the LES. The 24-hour pH- and impedance signals were recorded using a digital data recorder (Medical Measurements Systems, Enschede, The Netherlands) with a sampling frequency of 1 Hz and 50 Hz respectively.[22] The presence of symptomatic episodes was assessed by asking patients to press a button on the digital data recorder. Furthermore, the patient registered the occurrence of all symptoms, the associated body position and the relation with food and drink intake in a diary. If symptoms were recorded during a 24-hour measurement, the symptom-index (SI) and symptom association probability index (SAP) were calculated for all reflux episodes, gastric belches, and supra gastric belches, with an SI of more than 50% and SAP of more than 95% regarded as being positive.[23, 24]

Surgical procedure

All fundoplications were performed by a single experienced gastrointestinal surgeon specialized in antireflux surgery, who was well beyond his learning curve.[25] In all patients, a standardized fundoplication was performed that aimed to create a loose valve in order to minimize the development of post-fundoplication symptoms. The distal esophagus was fully mobilized and short gastric vessels were ligated and divided if considered necessary. The surgeon verified that the gastroesophageal junction was placed in a tension-free position in the abdomen and the fundoplication was tension-free as well. Posterior crural repair was performed using non-absorbable sutures and without the use of a bougie, after which a floppy fundoplication of 2.5 to 3.0 cm was constructed. In case of LTF, the fundus was wrapped 270 degree behind the distal esophagus and attached to the esophagus on the right and left sides and to the hiatus on the right side, leaving the anterior esophagus uncovered. Constructing a LAF, the fundus was wrapped for 180 degrees around the anterior distal esophagus and sutured to the front of the esophagus and the diaphragmatic hiatus.[26]

Data analysis

The classification of reflux characteristics, and gastric and supragastric belches has been described in detail in two previous studies from our research group examining the physiological effects of 360 degree LNF.[27, 28] This also accounts for the used classification of air-containing swallows, gas, liquid, mixed, acid and weakly acidic reflux episodes.[28] One single observer (JEO) manually analyzed all pre- and postoperative 24-hour pH-impedance recordings of the included patients using a software program (MMS, Enschede, The Netherlands). In case of any uncertainty, two expert observers (JO and AJB) could be consulted, who were blinded for patient characteristics and pre- and postoperative status to minimize the risk of observer bias. The upper limit of the normal number of total, acid and weakly acidic reflux episodes were 75, 50 and 33 episodes per 24-hours respectively.[29] The proximal extent in centimeters above the LES was determined for each reflux episode. The extent of liquid component of liquid-containing reflux episodes (pure liquid and mixed reflux) was classified as proximal (≥15cm above LES), mid-esophageal (5-15cm above LES) or distal reflux (≤5cm above LES).[27] For liquid-containing reflux episodes, the total esophageal reflux distance (TERD), defined as the sum of the proximal extent above the LES of all reflux episodes in centimeters, and the mean proximal extent were calculated.[27]

Gastric belches included gas components of pure gas and mixed liquid gas reflux episodes that reached the most proximal channel.[30] Supragastric belches were identified using the criteria previously described by Bredenoord et al., defining supragastric belches as rapid increases in impedance (≥1000 Ω) moving in an abnormal direction and followed by a return to baseline moving from distal to proximal.[31] This was considered to indicate a pattern reflecting the expulsion air following rapid esophageal air ingestion. When a supragastric belch occurred prior (<1 sec) to the onset of a reflux episode or during a reflux episode, with the onset within 10 seconds after the start of the episode, it was considered to be a reflux related supragastric belch.[32]

The number of air swallows, gastric and supragastric belches, as well as all reflux episodes were normalized to a 24-hour period for adequate comparison, with exclusion of periods of meal consumption, based on the diary from the included patients.

Statistical analysis

Statistical analysis was performed using the statistical software package SPSS, version 20.0 (SPSS, Inc., Chicago, IL, USA). All continuous variables are presented as median ± interquartile range (IQR). Absolute differences (Δ) between pre- and postoperative values were used to express the effect of surgery on continuous variables. The Mann-Whitney *U*-test was used to compare the absolute differences between the LTF group and the LAF group. In order to determine whether the effect of surgery was significant in either the LTF group or the LAF group, the Wilcoxon signed rank test was used. The χ^2 test was used to compare groups for nominal variables. A p-value<0.05 was considered to be statistically significant.

Results

Included patients

Between January 2009 and March 2016, 20 patients who were on the waiting list for a primary LTF or LAF were included. Patients who underwent LTF were matched to patients who underwent LAF based on total esophageal acid exposure time on 24-hour pH-impedance monitoring performed preoperatively (ratio 1:1). There were no differences in baseline characteristics between the patients who underwent LTF and LAF (Table 1).

TABLE 1. Baseline characteristics of included patients according to fundoplication type.

	LTF	LAF
Patients (n)	10	10
Male / female	5 / 5	5 / 5
Age (years)	41.5 [24 - 62]	42.0 [37 - 51]
Body mass index (kg/ m^2)	29.0 [24 - 33]	26.7 [24 - 30]
Total esophageal acid exposure (%)*	11.1 [10 - 19]	9.0 [7 - 13]

Values are given as number of patients or median (interquartile range); LTF= laparoscopic 270 degree posterior partial fundoplication; LAF= laparoscopic 180 degree anterior partial fundoplication;
* preoperative total esophageal acid exposure measured using 24-hour combined pH-impedance monitoring

Upper gastrointestinal endoscopy and esophageal manometry

Eighteen patients (90%) had undergone preoperative gastrointestinal endoscopy. Of these patients, six (33%) were diagnosed with esophagitis, and 18 (69%) with a sliding hiatal hernia. There were no differences between the two groups in the prevalence of esophagitis or hiatal hernia before or after surgery.

Preoperative esophageal manometry was performed in all patients, with no differences in preoperative mean LES resting pressure between the two groups. Postoperative manometry was performed in all but one patient (95%). Neither LTF nor LAF caused a significant increase in LES resting pressure compared to the preoperative state (LTF Δ +0.5 [-0.2 – 1.1] kPa, *P*=0.240; LAF +0.4 [0.0 – 1.8] kPa, *P*=0.137). LES relaxation pressure significantly increased after LTF, but the increase did not reach statistical significance after 180 degree LAF (LTF Δ +0.3 [0.1–0.8] kPa, *P*=0.020; LAF +0.3 [0.0–0.6] kPa, *P*=0.093). The distal contraction amplitude was not significantly altered by LTF (Δ +1.7 [-0.9–2.8], *P*=0.721) nor LAF (-1.2 [-2.3–4.0] kPa, *P*=0.441).

Effect on acid and weakly acidic reflux

All 20 patients underwent pre- and postoperative 24-hour pH-impedance monitoring (Table 2 and 3). Both LTF and LAF led to a significant reduction in total esophageal acid exposure time, with no significant difference in absolute reduction between the two procedures (Δ -10.8 [-16.1 – -10.8] *vs*. -7.9 [-11.9 – -6.2], *P*=0.497). Both procedures significantly reduced the number of reflux episodes (*P*=0.005 compared to preoperative state), with no difference in absolute reduction between the two groups (Δ -65.0 [-87 – -47] *vs*. -100.5 [-105 – - 50], *P*=0.218), and an equal and significant reduction in acid reflux episodes (Δ -58.5 [-83 – -40] *vs.* -66.5 [-80 – -45], *P*=0.912). Preoperatively, there was a trend towards a higher number of weakly acidic reflux episodes in the LAF-group (6.0 [3.3 – 12.5] *vs.* 12.5 [5.0 – 36.3], *P*=0.105). Therefore, the total number of weakly acidic reflux episodes was reduced to a greater extend by LAF (Δ-12.0 [-32.0 – -4.8]) compared to LTF (Δ -4.0 [-9.3 – -1.3], *P*=0.023), with no significant difference in the total number of postoperative weakly acidic reflux episodes (1.0 [0.8 – 4.0] *vs.* 1.0 [0.0 – 2.5], *P*=0.436). Both liquid and mixed reflux episodes were significantly reduced by LTF and LAF respectively, with no significant differences in absolute reduction (Table 2). Furthermore, there were no significant differences in the reduction of acid and weakly acidic liquid or mixed gas-liquid reflux episodes. The total number of gas reflux episodes was significantly reduced in both groups, but to a greater extend by LAF (Δ -3.0 [-11.5 – 1.5] *vs.* -15.0 [-29.5 - -12.5], *P*=0.010, Figure 1). This was most likely caused by a significantly higher number of preoperative gas reflux episodes in the LAF-group compared to the LTF group (7.0 [4.0 – 14.5] *vs*. (18.0 [13.3 – 36.5], *P*=0.011).

Both LTF and LAF led to an equal reduction in proximal (Δ -36.0 [-64.0 – -16.3] *vs.* -38.0 [-49.0 – -19.5, *P*=1.000), mid (Δ -19.5 [-26.8 – 0.8] *vs.* -28.0 [-74 – -20], *P*=0.063) and distal reflux (Δ -1.0 [-5.0 – 0.0] *vs.* -2.0 [-8.8 – -1.0], *P*=0.315). Both procedures significantly reduced TERD, with no difference in absolute reduction between the two groups (Δ -1026.5 (-1268.8 – -675.0] *vs.* -1427.5 [-1658.8 – -665.0], *P*=0.247).

TABLE 2. Number of acid and weakly acidic and liquid and mixed reflux episodes during 24-hour monitoring after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication.

	LTF			LAF		
	Preoperative	Postoperative	Δ	Preoperative	Postoperative	Δ
Total reflux episodes	76.0 (47–93)	1.0 (0.8–17)	-65.0 (-87—47)	101.0 (59–115)	1.0 (0–5)	-101 (-105—50)
Acid reflux	63.0 (40–89)	0.0 (0–6)	-58.5 (-83—40)	66.5 (51–91)	0.0 (0–4)	-66.5 (-80—45)
Weakly acidic reflux	6.0 (3–13)	1.0 (0.8–4)	-4.0 (-9—1)	12.5 (5–36)	1.0 (0–3)	-12.0 (-32—5)*
Liquid reflux	28.5 (16–43)	1.0 (0–13)	-17.0 (-42—13)	44.5 (22–69)	0.5 (0–4)	-43.5 (-57—22)
Acid reflux	21.5 (12–37)	0.0 (0–5)	-19.0 (-33—9)	33.0 (20–45)	0.0 (0–2)	-30 (-40—20)
Weakly acidic reflux	4.0 (0–6)	1.0 (0–3)	-2.0 (-5–0.3)	7.0 (2–18)	0.0 (0–2)	-6.5 (-17—2)
Mixed reflux	42.0 (34–57)	0.0 (0–3)	-38.0 (-56—34)	48.5 (32–53)	0.0 (0–1)	-40.0 (-52—20)
Acid reflux	39.0 (30–52)	0.0 (0–1)	-35.0 (-52—30)	37.5 (22–47)	0.0 (0–0.3)	-37.5 (-47—22)
Weakly acidic	4.0 (1–5)	0.0 (0–0.3)	-4.0 (-4—1)	5.5 (4–15)	0.0 (0–1)	-5.5 (-15—3)

All data are expressed as median (interquartile range); LTF= laparoscopic 270 degree posterior partial fundoplication; LAF= laparoscopic 180 degree anterior partial fundoplication; * P=0.023 *vs.* LTF

TABLE 3. Number of air swallows and gastric- and supragastric belches during 24-hour monitoring before and after laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication.

	LTF			LAF		
	Preoperative	Postoperative	Δ	Preoperative	Postoperative	Δ
Air swallows	213 (149–363)	266 (185–360)	46.0 (23–68)	382 (338–488)	332 (261–432)	-31.0 (-156–81)
Gastric belches	66.0 (50–86)	19.0 (10–30)	-41.0 (-64–-26)	117 (70–130)	37.0 (20–61)	-76.0 (-103–-35)
SGBs without reflux	0.0 (0.0–1.)	0.5 (0–25)	0.5 (0–23)	0.5 (0–12)	7.5 (0–26)	4.0 (0–12)
SGBs with reflux	0.0 (0–3)	0.0 (0–9)	0.0 (0–5)	0.0 (0–27)	0.0 (0–2)	0.0 (-19–1)
SGB before reflux	0.0 (0–1)	0.0 (0–7)	0.0 (0–6)	0.0 (0–13)	0.0 (0–1)	0.0 (-8–0)
SGB during reflux	0.0 (0–1)	0.0 (0–0.3)	0.0 (-0.3–0)	0.0 (0–6)	0.0 (0–0.3)	0.0 (-5–0)

All data are expressed as median (interquartile range); LTF= laparoscopic 270 degree posterior partial fundoplication; LAF= laparoscopic 180 degree anterior partial fundoplication; SGBs: supragastric belches

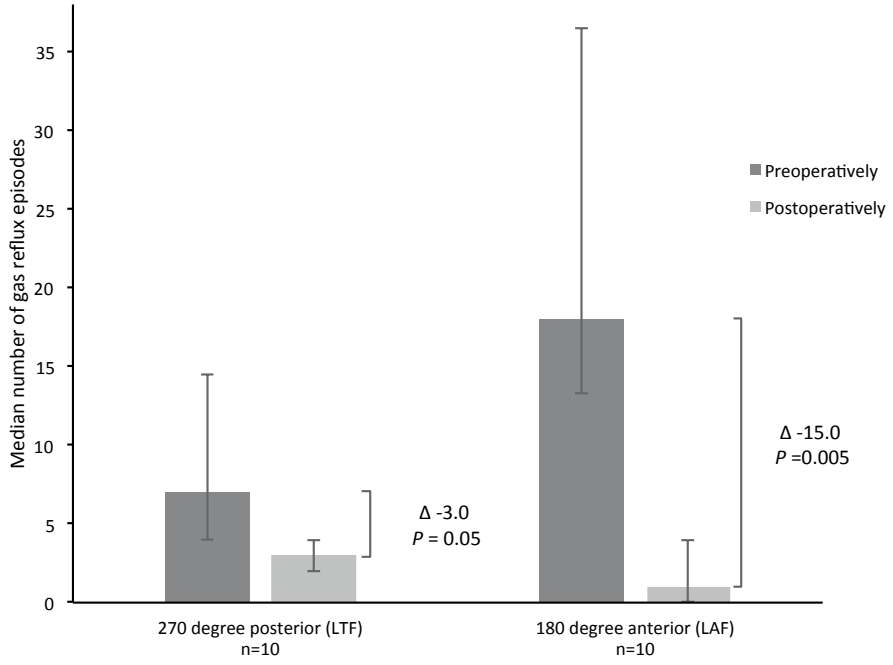

FIGURE 1. Median number of gas reflux episodes during 24-hour monitoring after 270 degree posterior and 180 degree anterior partial fundoplication.

Effect on belching

There was no difference in the effect of LTF compared to LAF on the number of air swallows during 24-hour monitoring (Δ +46.0 [23 – 86] *vs.* -31.0 [-156 – 81], *P*=0.278), with both procedures not significantly altering the number of air swallows (Table 3). Gastric belches were present in all patients both pre- and postoperatively. Both LTF and LAF significantly decreased the number of gastric belches (*P*=0.008 and *P*=0.007 respectively) compared to the preoperative state, with no difference in absolute reduction between the two procedures (*P*=0.278; Figure 2).

Supragastric belching, either associated with reflux or not, was present preoperatively in nine patients (45%), with no difference in prevalence between the two groups (Table 3). Twelve patients (60%) demonstrated supragastric belches during the postoperative measurements, of whom three did not demonstrate supragastric belches before surgery. Both LTF and LAF led to a significant and equal increase in supragastric belches not associated with reflux. There was no significant difference in the effect of LTF on the prevalence of supragastric belches associated with reflux, either prior to or during reflux, compared to LAF (*P*=0.123, *P*=0.075 and *P*=0.684 respectively).

Symptomatic outcome

Both procedures significantly reduced reflux symptoms, assessed using the GERD-HRQoL-score, with the absolute reduction not differing between the two procedures (Δ -20.0 [-29.0 – -12.0] *vs.* -17.5 [-23.3 – -12.3], *P*=0.536). The presence and severity of postoperative dysphagia, assessed using the QLQ-OES 18 questionnaire, did not differ between the two groups (23.5 [21.5 – 25.8] *vs.* 22.0 [21.0 – 25.5], *P*=0.579), with both groups demonstrating a significant and comparable reduction compared to the preoperative state (*P*=0.018 and *P*=0.008 respectively). The prevalence of inability to belch, gas bloating and increased flatulence did not differ after LTF or LAF (*P*=0.242, *P*=0.367, and *P*=0.304 respectively). Compared to the preoperative state, the health-related QoL significantly increased after both LTF (Δ +17.5 [12.2 – 29.0], *P*=0.018) and LAF (Δ +21.1 [3.4 – 38.9], *P*=0.022), with no significant differences between the two procedures (*P*=0.792).

Fourteen of the twenty patients reported symptoms during postoperative 24-hour pH-impedance monitoring, of whom none had a positive SI or SAP for acid or weakly acidic reflux. Only four of the 49 reported symptoms (8.2%) were preceded by weakly acidic reflux episodes.

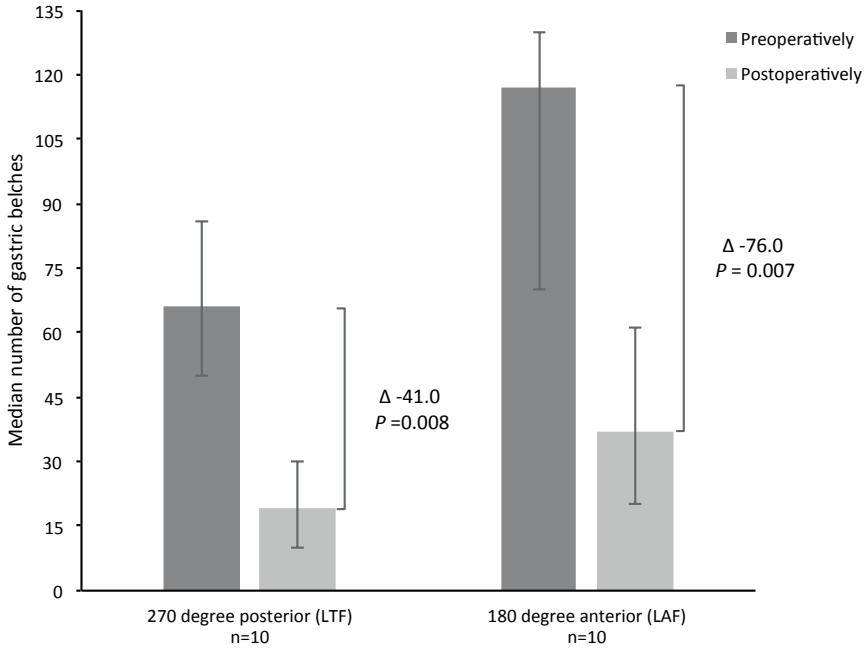

FIGURE 2. Median number of gastric belches during 24-hour monitoring after 270 degree posterior and 180 degree anterior partial fundoplication.

Discussion

Laparoscopic fundoplication yields excellent results with regards to reflux control.[33] However, troublesome side-effects, of which dysphagia and gas-related symptoms are the most important, pose a significant challenge to both the clinician and patient, since they significantly reduce patient satisfaction.[7] This study demonstrates that LTF and LAF significantly reduce esophageal acid exposure and the total number of acidic and weakly acidic reflux episodes, with no difference in reduction between the two procedures. This is the first study to use combined pH-impedance monitoring to evaluate differences in reflux control and belching patterns after LTF and LAF. While the absolute reduction in the number of weakly acidic reflux episodes and gas reflux episodes is greater after LAF compared to LTF, there was no difference in the total number of postoperative weakly acidic and gas reflux episodes between the two procedures. Additionally, there was no difference in symptomatic reflux control between LTF and LAF

The reduction in gastric belches following fundoplication results in reduced air venting from the stomach, and is therefore held responsible for the development of postoperative gas-related symptoms.[31] The number of belches was significantly reduced by both types of fundoplication, with no difference in absolute reduction. Additionally, there was no difference in the prevalence of postoperative bloating or inability to belch between the two procedures. Previous studies have used combined pH-impedance monitoring to compare the influence of LTF and LNF on gastric belching, with contradictory results. Two studies provoked belching by insufflating gas into the stomach, with one study reporting a superior reduction in gastric belches after partial fundoplication,[34] and the other reporting similar numbers of gastric belches after posterior partial and total fundoplication.[35] Broeders et al. were the first to compare belching patterns after LTF and LNF using combined pH-impedance monitoring during an entire 24-hour period and without insufflation of gas.[16] As stated before, that study reported an equal reduction in both acid and weakly acidic reflux episodes, with a significantly lower reduction in gas reflux and gastric belches after LTF compared to LNF, thereby providing the physiological explanation for the reduced incidence of gas-related symptoms after LTF.[4]

Recently, our group published the results of a randomized clinical trial comparing LTF and LAF, in which 94 patients were included and underwent routine pre- and postoperative upper gastrointestinal endoscopy, esophageal manometry and conventional 24-hour pH-monitoring.[9] One year after surgery, there were no significant differences between the two procedures in terms of subjective and objective reflux control, postoperative dysphagia or incidence of gas-related symptoms. By using combined pH-impedance monitoring, the present study confirms our previous findings from the randomized clinical trial and demonstrates that LTF and LAF not only have a comparable short-term effect on acidic reflux, but also on the total amount of acidic and weakly acidic reflux and belching, providing physiological support for the equal symptomatic outcome after both types of

partial fundoplication. Both types of partial fundoplication did not completely eliminate reflux, but significantly reduced the number of reflux episodes, thereby rendering patients asymptomatic during the described follow-up period. As is the case with every type of antireflux procedure, long-term follow-up of both physiological studies and randomized clinical trials needs to determine whether this effect is sustained.

The present study has several limitations. First, patients were not randomized to either LTF or LAF. However, a randomized design is less critical in physiological studies compared to studies analyzing clinical or subjective endpoints. The first group of 10 patients were allocated to LTF and the second group of 10 patients were allocated to LAF by the same surgeon, hence there was no selection whether a patient was treated with a posterior or anterior partial fundoplication. Additionally, preoperative characteristics did not determine whether a patient underwent LTF or LAF, which is supported by the fact that baseline characteristics of patients undergoing LTF and LAF were identical. Furthermore, we also compared clinical outcome of LTF and LAF in a randomized fashion, of which the results are in line with the outcome of the present physiological study.[9] Since all fundoplications were performed by a single surgeon, with experience in performing both types of partial fundoplication, the risk of bias based on experience is low. Another possible limitation is the fact that the physiological effects of both type of partial fundoplications were not directly compared to those of LNF. However, this has been performed previously by Broeders et al, directly comparing outcome of 24-hour combined pH-impedance monitoring after LTF and LNF,[16] and two recent meta-analyses comparing outcome of LTF with LNF,[4] and LAF with LNF.[8] Due to the superior outcome of LTF and LAF compared to LNF with regards to the postoperative incidence of dysphagia and gas-related symptoms and equivalent reflux control demonstrated by these level Ia studies, LNF is no longer being regarded the procedure of choice for primary antireflux surgery in the Netherlands.

In conclusion, this study demonstrates that LTF and LAF provide equal reflux control, with a comparable effect on reflux episodes and belching. Both procedures equally reduced the number of belches and supragastric belches. The present study provides the physiological evidence for the previously published randomized trials reporting equal symptomatic outcome after both types of partial fundoplication.[9, 36] The choice for performing LTF or LAF should be based on the surgeons experience with either procedure. Long-term follow-up of both randomized clinical trials as well as physiological studies comparing LTF and LAF need to confirm equivalence of both partial fundoplications at the long term.

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Chapter 5

Outcome for patients with pathological esophageal acid exposure after laparoscopic fundoplication

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Abstract

Objective: The aim of the present study was to assess symptomatic outcome and need for surgical reintervention for patients identified with pathological esophageal acid exposure by routine postoperative 24-hour pH-monitoring.

Summary Background Data: Although laparoscopic fundoplication is associated with excellent short- and midterm results, recurrent symptoms pose an important challenge. Postoperative pH-monitoring is considered the "gold standard" for diagnosing recurrent GERD and frequently used for routine postoperative follow-up.

Methods: Analysis of prospectively collected data from patients who underwent laparoscopic fundoplication between April 1994 and June 2015 and underwent routine postoperative 24-hr pH-monitoring was performed. Symptomatic outcome and need for surgical reintervention up to five years was compared between patients with pathological and physiological postoperative esophageal acid exposure. Primary endpoints were heartburn score and need for surgical reintervention for recurrent reflux.

Results: 309 patients in whom routine postoperative 24-hr pH-monitoring was performed were included. Pathological acid exposure was present in 33 patients (11%) compared to 276 patients (89%) with physiological acid exposure. During five-year follow-up, there were no differences in heartburn, dysphagia, or satisfaction scores. Eighteen percent of all patients with abnormal postoperative pH-studies underwent redo fundoplication during five-year follow-up.

Conclusions: Pathological acid exposure demonstrated by routine postoperative pH-monitoring was not associated with worse symptomatic outcome in terms of reflux control and satisfaction. A possible explanation for this finding is that laparoscopic fundoplication reduces the patients' ability to perceive reflux. This underlines the importance of assessing the association between symptomatic outcome and esophageal function tests in determining outcome of antireflux surgery.

Introduction

Gastroesophageal reflux disease (GERD) is an important benign disorder of the gastrointestinal tract, affecting up to 20% of the Western population.[1] Laparoscopic fundoplication is considered the standard surgical procedure for patients diagnosed with objectified proton pump inhibitor (PPI)-refractory GERD. The 360° total (Nissen) fundoplication is the most frequently performed type of fundoplication worldwide, providing excellent long-term reflux control.[2-4] In order to reduce the incidence of side-effects associated with total fundoplication, including dysphagia and bloating, partial fundoplications have been developed. Depending on the type of partial fundoplication, the fundus is wrapped partially, either in an anterior or posterior fashion, around the distal esophagus. Recent meta-analyses have demonstrated a lower incidence of these side-effects after partial fundoplications.[5, 6]

Recurrent reflux symptoms are an important problem with a significant impact on patient's quality of life and satisfaction with surgery.[7] Twenty-four-hour pH-monitoring is considered the "gold standard" for the diagnosis of recurrent GERD, by categorizing between pathological and physiological esophageal acid exposure. It is frequently used for routine postoperative follow-up and determining outcome of fundoplication. The results of routine studies should be interpreted with caution however, since a pH-study demonstrating pathological esophageal acid exposure, does not have to be associated with symptoms. Furthermore, symptoms interpreted as recurrent reflux appear to demonstrate a weak correlation with esophageal acid exposure.[8]

So far, no data have been published regarding the outcome of patients identified with pathological esophageal acid exposure by routine postoperative pH-monitoring. In the present study, we compare five-year symptomatic outcome and need for surgical reintervention between patients with pathological and physiological esophageal acid exposure.

Methods

Study designs and participants

Prospectively collected data from patients who underwent primary laparoscopic total or partial fundoplication were analyzed. Patients had been included in one of six randomized clinical trials comparing laparoscopic Nissen fundoplication with versus without division of short gastric vessels [9], Nissen versus 180° anterior partial fundoplication [10], Nissen with anterior versus posterior hiatal repair [11], Nissen versus 90° anterior partial fundoplication [12], Nissen versus 270° posterior partial versus 180° anterior partial fundoplication [13], and 270° posterior versus 180° anterior partial fundoplication [14], of which the outcomes have been described. All patients gave written informed consent for inclusion in a prospective database. The diagnosis chronic PPI-refractory GERD was objectified through upper gastrointestinal endoscopy demonstrating unequivocal signs of GERD or 24-hour pH-monitoring demonstrating pathological esophageal acid exposure. Exclusion criteria included esophageal motility disorders, previous antireflux surgery, and the presence of a giant hiatal hernia (intrathoracic stomach>50%).

Demographics included sex, age, body mass index (BMI), comorbidities categorized as diabetes and renal, pulmonary or cardiovascular disease, and a history of thoracic and/or abdominal surgery. Pre- and postoperative symptoms were assessed using structured questionnaires at different intervals. All patients were scheduled for preoperative upper gastrointestinal endoscopy and esophageal manometry. Preoperative 24-hour pH-monitoring was only performed on patients with no unequivocal reflux disease demonstrated by endoscopy and manometry. Due to trial-participation, routine three to six month's postoperative upper gastrointestinal endoscopy, esophageal manometry and 24-hour pH-monitoring was performed in all patients, independently of symptoms.

All patients who had undergone routine 24-hour pH-monitoring within 12 months after surgery were identified. Symptomatic outcome was assessed at six months, one, two, three and five years after surgery. Differences in symptomatic outcome and need for reoperation were analyzed for patients identified with pathological and physiological esophageal acid exposure. Patients in whom it was likely that abnormal esophageal acid exposure was caused by migration of the pH-probe were excluded.

Surgical procedures

All primary fundoplications were performed between April 1994 and May 2015 in the participating tertiary centers in The Netherlands and Australia by experienced laparoscopic surgeons. Division of short gastric vessels was performed depending on the type of procedure and/or trial a patient was enrolled in.[9] Following full esophageal mobilization, posterior and/or anterior crural repair using non-absorbable sutures was performed, and a floppy 360° total, 270° posterior, or a 90° or 180° anterior partial fundoplication was constructed.[15, 16]

Subjective outcome

Subjective outcome was assessed using a structured questionnaire completed preoperatively, six months postoperatively, and on a yearly basis thereafter. For the present study, only changes in heartburn and dysphagia scores were compared between patients with pathological and physiological acid exposure up to five years after surgery. The presence and severity of heartburn was scored using a visual analogue scale (0= no heartburn; 10= severe heartburn). The presence and severity of dysphagia was assessed for liquids and solids using a visual analogue scale (0= no dysphagia; 10= severe dysphagia). Additionally, a validated dysphagia score (Dakkak score 0= no dysphagia; 45= severe dysphagia) integrating dysphagia for various types of liquids and solids was applied.[17] The effect of surgery was ranked using the Visick grading system: complete resolution of symptoms (Visick I), mild symptoms easily controlled by simple care (grade II), moderate symptoms not interfering with social life/work (grade III), symptoms interfering with social life/work (grade IV), and symptoms worse than before surgery (grade V).[18] Overall satisfaction was scored by a visual analogue scale (0= dissatisfied; 10= satisfied). The use of acid suppressing drugs was assessed, including PPIs, histamine H2-recepter antagonists (H2-blockers), antacids and prokinetics, and patients were asked if they would opt for surgery again in retrospect. Symptomatic outcome for patients who had undergone surgical reintervention during six-months to five-year follow-up was excluded beyond the date of reoperation.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed preoperatively and three to six months postoperatively to assess postsurgical anatomy, healing of esophagitis, and the presence of any esophageal obstruction. The presence of reflux esophagitis was scored using the Savary-Miller classification.[19] Endoscopic findings were categorized as: no esophagitis, presence of esophagitis (grades 1-3), stricture (grade 4), or Barrett's esophagus (grade 5). A fundoplication was determined to be sufficient if the following criteria were met: 1) the fundoplication snuggly encircled the retroflexed endoscope at the gastroesophageal junction; 2) when the stomach was insufflated with air, the fundoplication remained competent at endoscopy (no venting or belching of air); 3) the fundoplication was in an anatomically correct position and a hiatus hernia was not visualized.

Stationary esophageal manometry

Through transnasal introduction, a motility catheter was introduced into the esophagus and positioned with a sleeve sensor straddled across the lower esophageal sphincter (LES). After the proximal and distal border of the LES were determined using the pull-through technique, intraluminal esophageal pressures were recorded at 5, 10 and 15 cm above the proximal border. Mean resting pressure (mmHg), amplitude of contractions (mmHg) and the percentage of primary peristalsis of the distal esophagus were included, as well

as the LES mean resting pressure (mmHg). A LES mean resting pressure ≥10 mmHg and propagation of at least 80% primary peristalsis during 10 swallows of 5-ml water boluses were defined as normal.

Ambulatory 24-hour pH-monitoring

Acid suppressing medication was ceased five days before the pH-study. A pH probe was introduced through the nose into the esophagus and positioned 5 cm proximal to the manometrically determined proximal border of the LES, after which it was connected to an ambulatory pH-recorder for 24 hours. Results of 24-hour monitoring were analyzed for the percentage of time during which the esophageal pH was less than 4 and the correlation between reported symptoms and recorded reflux episodes. A reflux episode was defined as pH<4 for at least 5 seconds. Categorization as pathological and physiological esophageal acid exposure was based on the percentage of time with pH<4, with pathological acid exposure defined as an acid exposure time of at least 4% of the total time.

Statistics

All data were transferred into a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). Data were expressed as mean (95% confidence interval) or number of patients (%). The Chi square test, or Fisher's exact test where necessary, were used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. Statistical significance was defined as $P<0.05$.

Results

Available symptomatic and objective outcome

Between April 1994 and May 2015, 309 patients underwent primary fundoplication and completed routine 24-hour pH-monitoring. Nissen fundoplication was performed in 153 patients (49%) and partial fundoplication in 156 patients (51%), including 270° posterior (n=48, 16%), 180° anterior (n=69, 22%), and 90° anterior partial fundoplication (n=39, 13%). Preoperative symptomatic outcome was available for 284 (92%) patients and postoperative outcome for 270 patients (87%) at six months, 283 (92%) at one year, and 254 (82%) at two years. Seventy patients from the Dutch trial had not yet reached three and five-year follow-up, and were therefore excluded beyond two years.[14] Eight patients died during three- to five-year follow-up due to causes unrelated to fundoplication. Of the remaining 234 patients, 184 (79%) and 195 patients (84%) completed three and five-year follow-up respectively. This was after excluding patients who had undergone a reoperation during five-year follow-up.

Baseline characteristics and objective outcome

Thirty-three patients (11%) were identified with pathological acid exposure and 276 (89%) with physiological acid exposure. There were no differences in age, BMI, presence of comorbidities, or previous abdominal or thoracic surgery between the two groups (Table 1 and 2). There were more patients with ASA score 3 in the group of patients with pathological acid exposure (*P*=0.033). Preoperative heartburn scores (4.2 [3.1–5.3] *vs* 4.9 [4.5–5.3], *P*=0.31), dysphagia scores for liquids (1.3 [0.4–2.2] *vs* 0.8 [0.6–1.1], *P*=0.33) or solids (2.1 [1.1–3.1] *vs* 2.0 [1.6–2.3], *P*=0.86), and Visick scores (Visick score 3-5: 100% *vs*. 95%, *P*=0.32) were similar. A total of 253 patients (92%) were dependent on daily acid suppressing medication preoperatively, with no differences between the two groups.

Preoperative upper gastrointestinal endoscopy demonstrated more patients with Barrett's esophagus in the group with pathological acid exposure (10 [33%] *vs* 37 [16%], *P*=0.017). Preoperative manometry demonstrated similar esophageal peristalsis and LES resting pressures. Twenty-four-hour pH-monitoring revealed a similar preoperative total percentage of time pH<4 (*P*=0.16). Pathological postoperative acid exposure was more frequent after partial compared to Nissen fundoplication (25/156 [16%] *vs* 8/153 [5%], *P*=0.002).

Routine postoperative upper gastrointestinal endoscopy demonstrated a higher prevalence of esophagitis among patients with pathological acid exposure (19% *vs* 6%, *P*=0.029). Patients with pathological acid exposure demonstrated a lower mean contraction amplitude of the distal esophagus (60.3 *vs* 77.6, *P*=0.024), and a lower mean LES pressure (16.4 mmHg *vs* 22.6 mmHg, *P*<0.001). Within the group of patients with pathological postoperative acid exposure, there was no significant decrease in esophageal acid exposure compared to the preoperative state (mean percentage of time pH<4

12.1% preoperative to 10.3% postoperative, *P*=0.38). In 14 of these patients there was an increase in total acid exposure compared to the preoperative state. Symptom analysis did not demonstrate differences in correlation between symptoms and reflux events identified at pH-monitoring between the two groups (*P*=0.07; table 2).

TABLE 1. Baseline characteristics of patients with available routine postoperative 24-hour pH-monitoring.

	Pathological acid exposure n=33	Physiological acid exposure n=276
Sex (male)	17 (52%)	135 (49%)
Age (yrs.)	50.1 (46.0–54.1)	59.5 (47.2–71.8)
Body mass index (kg/m^2)	27.5 (24.5–30.5)	28.7 (28.1–29.4)
Presence of comorbidities		
Diabetes	0 (0%	6 (2.4%)
Pulmonary	8 (25%)	53 (22%)
Renal	0 (0%)	8 (3%)
Cardiovascular	7 (21%)	49 (18%)
ASA-classification		
I	9 (31%)	89 (40%)
II	15 (52%)	120 (54%)
III	4 (14%)*	11 (5%)
IV	1 (3%)	0 (0%)
Previous abdominal or thoracic surgery	16 (50%)	130 (50%)
Preoperative endoscopy		
Studied	31 (94%)	238 (86%)
Esophagitis	12 (40%)	109 (46%)
Stricture	2 (7%)	6 (3%)
Barrett's	10 (33%)†	37 (16%)
Hernia	18 (60%)	130 (58%)
Preoperative 24-hour pH-monitoring		
Studied, n (%)	26 (79%)	204 (74%)
Pathologic total acid exposure	22 (88%)	180 (88%)
Total percentage time pH<4	12.1 (9.1–15.1)	11.0 (9.8–12.3)

TABLE 1. Continued

	Pathological acid exposure n=33	Physiological acid exposure n=276
Preoperative esophageal manometry		
Studied, n (%)	25 (76%)	240 (87%)
Resting pressure distal esophagus (mmHg)	0.1 (-1.6–1.7)	0.3 (-043–1.0)
Amplitude distal esophagus (mmHg)	60.9 (37.5–84.2)	63.9 (57.0–70.9)
Primary peristalsis distal esophagus (%)	81.4 (68.8–94.1)	88.2 (85.2–91.3)
LES resting pressure, mmHg	6.6 (2.2–10.9)	8.2 (7.2–9.2)
Type of fundoplication		
360° total	8 (24%)	145 (53%)
270° posterior partial	8 (24%)	40 (15%)
90° anterior partial	5 (15%)	34 (12%)
180° anterior partial	12 (36%)‡	57 (21%)

All data are expressed as n (%) or mean (95% confidence interval); LES= lower esophageal sphincter; * *P*=0.020 pathological *vs* physiological acid exposure; † *P*=0.017 *vs* pathological acid exposure; ‡ *P*=0.047 *vs* physiological acid exposure

TABLE 2. Objective outcome of patients with postoperative pathological and physiological esophageal acid exposure.

	Pathological acid exposure n=33	Physiological acid exposure n=276
Postoperative endoscopy		
Studied	22 (67%)	188 (68%)
Interval, months	3.7 (2.8–4.6)	3.8 (3.5–4.2)
No esophagitis	10 (48%)	149 (81%)
Esophagitis	4 (19%)*	11 (6%)
Stricture	0 (0%)	1 (1%)
Barrett's	7 (33%)	23 (13%)
Hernia	0 (0%)	7 (4%)
Insufficient fundoplication	1 (7%)	0 (0%)
Postoperative 24-hour pH-monitoring		
Interval, months	4.4 (3.8–5.1)	3.8 (3.7–4.0)
Total percentage time pH<4	10.3 (8.0–12.5)†	0.6 (0.5–0.7)
pH<4 between 4 to 7%	13 (19%)	-
pH<4 more than 7%	20 (61%)	-
SI≥50%, no (%)	3 (13%)	11 (4%)
Postoperative esophageal manometry		
Studied	21 (64%)	236 (86%)
Interval, months	3.9 (2.9–4.9)	3.7 (3.4.–3.9)
Resting pressure distal esophagus mmHg	0.3 (-2.2–2.8)	-1.0 (-1.6–-0.4)
Amplitude distal esophagus, mmHg	60.3 (29.1–91.5)‡	77.6 (71.0–84.3)
Primary peristalsis distal esophagus	74.7 (43.5–106.0)	86.4 (82.6–90.2)
LES resting pressure, mmHg	16.4 (7.8–25.1)§	22.6 (20.5–24.8)

All data are expressed as n (%) or mean (SD) or n (%); SI= % of reflux associated symptom episodes; LES= lower esophageal sphincter; * P=0.029 *vs* physiological acid exposure; † P<0.001 *vs* physiological acid exposure; ‡ P=0.024 *vs* physiological acid exposure; § P<0.001 *vs* physiological acid exposure; Sufficient fundoplication: n=57 data missing

Symptomatic outcome

Postoperative symptomatic outcome is summarized in tables 3 and 4. Due to surgical reintervention during follow-up, 11 and six patients with pathological and physiological acid exposure respectively were excluded from further follow-up. Six months after surgery, there was a significant decrease in heartburn score among patients with pathological acid exposure (4.4 preoperative to 1.1 postoperative, $P<0.001$), with 21 patients (67%) reporting complete absence of heartburn. Of the 14 patients demonstrating an increase in total acid exposure, only one (7%) reported an increase in heartburn score at six months compared to the preoperative state, with 9 patients (65%) reporting a decrease in heartburn score. At all postoperative intervals, there were no differences in heartburn scores between the two groups (figure 1). At one year, more patients with physiological acid exposure were categorized with none or mild heartburn (VAS 0-6) compared to those with pathological acid exposure ($P=0.03$). This difference was not sustained at two, three and five years. There were no differences in dysphagia at all postoperative intervals. Although significantly more patients with Barrett's esophagus were diagnosed with pathological esophageal acid exposure, there were no differences in pre- or postoperative heartburn scores between patients with *vs*. without Barrett's esophagus.

Satisfaction scores were similar for both groups. Only at one year, more patients with pathological acid exposure were categorized as having a 'fair and poor' outcome (25.9% *vs* 13.5%, $P=0.04$). Visick scores were similar and there was no difference in the number of patients indicating that they considered their original decision to have surgery to be correct, with approximately 91% of the patients reporting they would again opt for surgery.

Recategorizing pathological and physiological acid exposure based on pH<4 for ≥7% (n=20) and less than 7% (n=289) of the total time respectively, did not significantly alter the previously described results, with no differences in heartburn and dysphagia scores between the two groups, apart from a significantly higher dysphagia (0-45) score for physiological acid exposure at three years (mean score 1.3 *vs* 8.5, $P=0.029$). Furthermore, satisfaction scores, Visick scores or the number of patients indicating they who would still opt for surgery in retrospect as well were similar.

There were no differences in use of acid suppressing drugs. At five years, 17% and 19% of the patients reported to use acid suppressing medication on a daily basis, which was a significant reduction compared to the preoperative state for both groups ($P=0.013$ and $P<0.001$ respectively, figure 2).

TABLE 3. Postoperative control of heartburn and presence of dysphagia during five-year follow-up.

	6-month postop		1-year postop	
	Path.	Phys.	Path.	Phys.
Visual analog scale heartburn				
Mean score	1.1	0.5	1.4	0.8
95% C.I.	(0.2–2.0)	(0.4–0.7)	(0.4–2.4)	(0.6–1.0)
Heartburn, categorical				
None or mild heartburn (0-3)	89.7%	94.1%	81.5%	94.1%*
Moderate (4-6)	3.4%	5.0%	11.1%	3.5%
Severe (7-10)	6.9%	0.8%	7.4%	2.4%
Visual analog scale dysphagia				
Liquids				
Mean score	0.7	0.7	0.5	0.9
95% C.I.	(0.2–1.2)	(0.5–0.9)	(0.1–0.9)	(0.6–1.1)
Solids				
Mean score	1.9	1.6	1.1	1.8
95% C.I.	(0.9–2.9)	(1.3–1.9)	(0.3–2.0)	(1.5–2.0)
Dakkak dysphagia score (0-45)				
Mean	8.1	6.1	5.8	8.0
95% C.I.	(4.1–12.0)	(5.0–7.1)	(2.3–9.2)	(6.8–9.2)
Use of acid suppressing drugs	25.9%	13.4%	19.2%	16.0%

All data are expressed as mean (95% confidence interval) or n (% of patients who responded to questionnaire); Path.= pathological esophageal acid exposure; Phys.= physiological esophageal acid exposure; * P=0.015 *vs* pathological acid exposure

2-year postop		3-year postop		5-year postop	
Path.	Phys.	Path.	Phys.	Path.	Phys.
1.7	1.5	1.7	1.4	0.9	1.5
(0.7–2.6)	(1.2–1.8)	(-0.1–3.5)	(1.1–1.8)	(0.2–1.6)	(1.2–1.9)
77.3%	82.6%	91.7%	83.8%	100.0%	82.8%
18.2%	11.7%	0.0%	10.8%	0.0%	13.3%
4.5%	5.7%	8.3%	5.4%	0.0%	3.9%
0.6	1.1	0.7	1.0	1.2	1.2
(-0.5–1.1)	(0.8–1.4)	(-0.3–1.6)	(0.7–1.3)	(-0.3–2.6)	(0.8–1.5)
1.6	2.1	1.0	2.2	1.4	2.3
(0.6–2.5)	(1.8–2.4)	(-0.5–2.5)	(1.8–2.6)	(0.0–2.8)	(1.9–2.7)
6.3	9.2	5.0	8.5	7.6	8.9
(2.7–9.8)	(7.9–10.5)	(1.3–8.7)	(7.1–10.0)	(2.7–12.4)	(7.5–10.2)
30.0%	18.6%	25.0%	15.7%	16.7%	19.0%

TABLE 4. Satisfaction score, Visick score and overall outcome during five-year follow-up.

	6-month postop		1-year postop	
	Path.	Phys.	Path.	Phys.
Satisfaction score (0-10)				
Mean score	8.2	8.5	8.2	8.6
95% C.I.	(7.1–9.3)	(8.2–8.8)	(7.2–9.2)	(8.3–8.8)
Patient satisfaction, categorical				
Excellent and good (7-10)	84.0%	88.2%	74.1%	86.5%
Fair and poor (0-6)	16.0%	11.8%	25.9%*	13.5%
Visick score				
Visick 1 & 2	78.6%	78.2%	62.5%	80.2%
Visick 3, 4, & 5	21.4%	21.8%	37.5%	19.8%
Opt for surgery again				
Yes	89.7%	94.9%	88.5%	90.0%
No	10.3%	5.1%	11.5%	7.6%
Unsure	0.0%	0.0%	0.0%	2.4%

All data are expressed as mean (SD) or n (% of patients who responded to questionnaire);
Path. = pathological esophageal acid exposure; Phys. = physiological esophageal acid exposure;
* *P*=0.04 *vs* physiological acid exposure

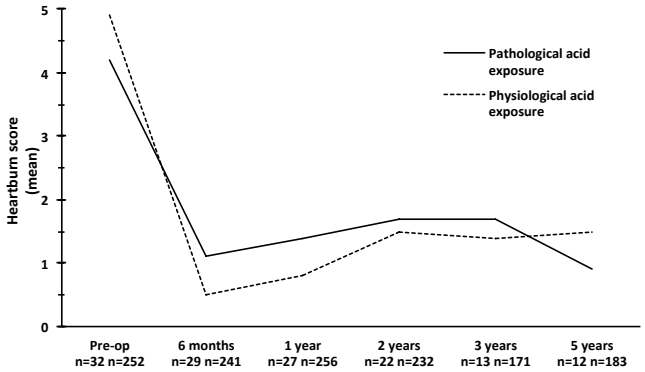

FIGURE 1. Changes in mean heartburn score during five-year follow-up for patients with pathological (pH<4 equal to or more than 4% of the time) and physiological (pH<4 less than 4% of the time) post-operative acid exposure.

2 -year postop		3-year postop		5-year postop	
Path.	Phys.	Path.	Phys.	Path.	Phys.
8.6	8.3	8.9	8.5	8.6	8.4
(7.6–9.6)	(8.0–8.6)	(7.6–10.3)	(8.2–8.9)	(7.3–9.8)	(8.1–8.8)
86.4%	86.1%	91.7%	86.4%	81.8%	87.6%
13.6%	13.9%	8.3%	13.6%	18.2%	12.4%
84.6%	66.3%	66.7%	76.8%	72.7%	81.1%
15.4%	33.7%	33.3%	23.2%	27.3%	18.9%
100%	91%	91.7%	89.3%	91.7%	91.2%
0.0%	6.1%	8.3%	7.1%	8.3%	7.2%
0.0%	3.0%	0.0%	3.6%	0.0%	1.7%

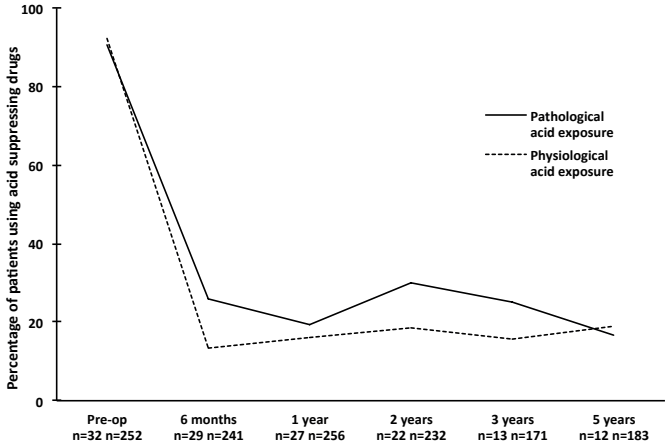

FIGURE 2. Changes in the use of acid-suppressing drugs for patients with pathological (pH<4 equal to or more than 4% of the time) and physiological (pH<4 less than 4% of the time) postoperative esophageal acid exposure during five-year follow-up.

Surgical reintervention

Seventeen patients (6%) underwent surgical reintervention for recurrent reflux, persistent dysphagia or hiatal hernia, with a mean interval between primary fundoplication and reoperation of 25 months (table 4). There were more reoperations in the group of patients with pathological acid exposure (n=6 [18%] *vs*. n=11 [4%], *P*=0.001), based on a higher number of reoperations for recurrent GERD (n=6 [100%] *vs* n=3 [27%], *P*=0.009). Patients who underwent reoperation for recurrent GERD reported higher heartburn scores at all postoperative intervals, compared to those who did not undergo surgical reintervention (*P*=0.002, *P*=0.013, *P*=0.016, *P*=0.005, *P*=0.024). Within the group of patients with pathological acid exposure, reoperation was performed at 4, 7, 17, 31, 33 and 53 months after primary fundoplication. Of the 14 patients who demonstrated an increase in postoperative esophageal acid exposure, five underwent redo fundoplication for recurrent GERD.

TABLE 5. Surgical reinterventions performed during five-year follow-up.

	Pathological esophageal acid exposure n=33	Physiological esophageal acid exposure n=276
Surgical reintervention, n (%)	6 (18%)*	11 (4%)
Mean time to reintervention (months)	24.2 (4.8–43.6)	25.1 (13.3–36.9)
Indication for reintervention (n)		
Recurrent GERD	5 (83%)†	3 (27%)
Dysphagia	0 (0%)	6 (55%)‡
Recurrent GERD and persistent dysphagia	1 (17%)	0 (0%)
Hiatal hernia	0 (0%)	2 (18%)
Type of reoperation (n)		
Redo fundoplication	4 (67%)§	1 (9%)
Redo fundoplication with HH repair	2 (33%)	4 (40%)
HH repair with redo fundoplication	0 (0%)	3 (30%)
Release hiatus / widening hiatus	0 (0%)	2 (20%)
Adhesiolysis	0 (0%)	1 (9%)

All data are expressed as mean (95% confidence interval) or n (%); GERD= gastroesophageal reflux disease; * *P*=0.001 *vs* physiological acid exposure; † *P*=0.009 *vs* physiological reflux; ‡ *P*=0.043 *vs* pathological reflux; § *P*=0.028 *vs* physiological reflux

Discussion

The definition of "surgical failure" plays an important role in the discrepancy in reported failure rates after laparoscopic fundoplication.[20, 21] Using symptoms suggestive of recurrent reflux as a marker of surgical outcome causes a potential overestimation of the true "failure rate", since it has been demonstrated that abnormal pH-studies are found in only 23-39% of these patients.[8,22-24] Therefore, postoperative 24-hour pH-monitoring is considered to be the "gold standard" for objectifying recurrent symptoms.

We identified 33 patients (11%) with pathological acid exposure through routine postoperative 24-hr pH-monitoring due to participation in a randomized trial, and who could therefore be considered to be objectified "failures". Compared to patients with physiological acid exposure, there was no difference in symptomatic outcome or satisfaction during five-year follow-up, indicating that routine postoperative pH-monitoring should not be used as a sole marker for outcome of fundoplication.

In 2000, Eubanks et al published the results of routine postoperative pH-monitoring performed in 228 patients 12 weeks after laparoscopic fundoplication.[21] Forty-seven patients (21%) were identified with pathological acid exposure, of whom 38 (17% of total) had symptoms less than once a week, and were regarded as having false negative pH-studies. Mid- to long-term follow-up of these patients was not provided. Our findings are in line with these results. As addressed by Eubanks et al, a possible explanation for these apparently "false positive" pH-studies is that the postoperative reduction in esophageal acid exposure has been enough to stop, or at least significantly reduce the patients' perception of reflux.[21] Esophageal acid exposure is still present, as demonstrated by pH-monitoring, but the patient is not perceiving it as such. If this is the case, our study indicates that this positive effect of fundoplication could be maintained for up to five years, with only 18% requiring surgical reintervention for recurrent GERD.

Another explanation for the lack of symptoms in patients with pathological acid exposure could be a "placebo-effect" of antireflux surgery. This is supported by the results of a randomized trial comparing an injectable esophageal prosthesis with a sham procedure for the endoscopic treatment of GERD.[25] The trial was prematurely terminated due to a lack of efficacy and the occurrence of complications after prosthesis placement. Interestingly, patients who received the sham procedure demonstrated significant improvement in regurgitation symptoms and quality-of-life at six-months, indicating a significant "placebo effect". However, one would expect this effect to resolve over time, which is not the case in our cohort of patients.

Routine postoperative upper gastrointestinal endoscopy demonstrated esophagitis to be more prevalent among patients with pathological acid exposure, indicating ongoing esophageal acid exposure. This is further supported by the lower mean contraction amplitude and LES resting pressure in patients with pathological acid exposure. These findings indicate that despite the lack of accompanying reflux symptoms, there is ongoing abnor-

mal esophageal acid exposure. Only two of the patients who had not previously been diagnosed with Barrett's esophagus and who demonstrated pathological postoperative esophageal acid exposure had undergone additional postoperative upper gastrointestinal endoscopy (2.5 and 3 years respectively), and this failed to demonstrate Barrett's esophagus on both occasions. The majority of patients did not undergo additional endoscopic follow-up beyond the routine 3-6 months follow-up as it was not clinically indicated.

Patients with pathological acid exposure underwent more redo fundoplications for recurrent GERD compared to patients with physiological acid exposure. However, only six of the 33 patients (18%) with an abnormal pH-study underwent redo surgery, indicating that one in every five patients identified with abnormal postoperative acid exposure indeed has an indication for redo surgery and/or is willing to undergo reoperation due to the severity of recurrent symptoms. This is supported by the fact that postoperative endoscopy did not reveal a higher rate of insufficient wraps compared to patients with physiological acid exposure. Hunter et al. reported outcome of routine postoperative pH-monitoring performed six to 12 weeks after laparoscopic fundoplication.[26] Seven of the 55 patients (13%) were found to have an abnormal pH-study, of whom nil reported symptoms and only one required reoperation (not specified).

Our findings indicate that merely the presence of an abnormal routine postoperative pH-study should not be considered to be an independent marker for "wrap failure", and these results should not be used in isolation as an indication for surgical revision. We have only performed routine postoperative pH-monitoring when patients participated in a randomized clinical trial. When patients present with recurrent symptoms in clinical practice, however, full workup should include pH monitoring and a careful history taking, with assessment of typical reflux symptoms, including heartburn and regurgitation. Analysis of the association between symptoms and reflux episodes at pH-monitoring, as well as barium swallow radiology to determine the position of the wrap, upper-gastrointestinal endoscopy to assess the presence of esophagitis and wrap insufficiency, and esophageal manometry to exclude possible esophageal motility disorders should all be undertaken, and the results considered carefully and in context before deciding to revise the fundoplication.

Pathological acid exposure was more frequent after partial compared to total fundoplication. Two previous randomized trials have demonstrated 90° anterior partial fundoplication to be associated with few adverse side effects, like bloating and inability to belch, but less effective long-term reflux control compared to total fundoplication. Indeed, in the present study more patients who had undergone laparoscopic 90° anterior partial fundoplication underwent recurrent surgery compared to patients who underwent Nissen fundoplication, 270° posterior or 180° anterior partial fundoplication (5/39 [13%] *vs* 12/270 [4%], P=0.032).

For the present analysis, pathological acid exposure was defined as pH<4 for ≥4% of the total time. One could argue that a cut-off value of ≥7% would be more appropriate, since pH<4 between 4-7% of the time is sometimes considered to be equivocal reflux. Hence, we performed a further analysis following re-categorization based on pH<4 for ≥7% (n=20) *vs*. less than 7% (n=289). However, this did not significantly alter the previously described results or conclusions, with no differences in mean heartburn and dysphagia score, nor in satisfaction with surgery.

A possible limitation of this study is the fact that symptomatic follow-up was not available in all patients. However, we included 309 patients with available routine postoperative 24-hour pH-monitoring and report up to five-year follow-up using structured questionnaires for 83% of the patients, which compares favorably to what is to be expected with these type of surveys.[27] Since symptomatic outcome was available preoperatively and at all postoperative intervals, detailed insight in outcome of patients identified with abnormal acid exposure is provided. Another limitation is the fact that data regarding symptom association probability (SAP) of routine pH-studies was not available and could not be included.

In conclusion, postoperative pathological acid exposure demonstrated by routine pH-monitoring is not necessarily associated with worse symptomatic outcome in terms of reflux control, dysphagia or satisfaction with surgery. A possible explanation for this finding includes the effect of fundoplication on reducing the patients' ability to perceive reflux. This underlines the importance of assessing the association between symptomatic outcome and results of objective esophageal function tests in determining the outcome of antireflux surgery.

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-Part II-

Laparoscopic hiatal hernia repair

Chapter 6

Equal patient satisfaction, quality of life and objective recurrence rate after laparoscopic hiatal hernia repair with and without mesh

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Abstract

Introduction: Laparoscopic hiatal hernia repair has become standard practice for most surgeons performing antireflux surgery. Hiatal hernia repair consists of cruroplasty with sutures only or additional reinforcement using mesh. Use of mesh was initiated to reduce recurrence rates. Recent analyses show that use of mesh may influence radiologic recurrence rates, but it does not seem to prevent symptomatic recurrences and the need for reoperation. This study compares clinical and radiologic outcomes of primary cruroplasty and cruroplasty with non-absorbable mesh after laparoscopic hiatal hernia repair.

Methods: Retrospective analysis of prospectively followed cohort of patients undergoing laparoscopic correction of hiatal hernia type II–IV in two tertiary referral centers was carried out. Radiologic recurrence, symptomatic recurrence, and reoperation rate, complications and patient-reported outcome measures were analyzed for all patients.

Results: A total of 189 patients were analyzed after laparoscopic hiatal hernia correction with an additional fundoplication (127 [67.2%] primary correction, 62 [32.8%] with mesh reinforcement). After a mean follow-up of 39.3 months, the overall radiologic recurrence rate was 24.3%, which was equal in both groups (25.8% [mesh] *vs* 23.6% [no mesh], $P = 0.331$). Symptomatic recurrence rate was 13.2% (16.1 *vs* 11.8%, $P = 0.495$) and reoperation rate 7.4% (9.7 *vs* 6.3%), which was comparable between the two groups. Complication rates were equal, and no serious mesh-related complications were reported. Health-related quality of life improved after surgery, dysphagia decreased and patient satisfaction was high for both groups, without significant differences.

Conclusion: Radiologic recurrences, symptomatic recurrences and reoperation rates are equal after laparoscopic hiatal hernia repair with or without non-absorbable mesh reinforcement, irrespective of hernia size and type. Quality of life, dysphagia and patient satisfaction were comparable. No serious mesh-related complications occurred. The results of this study do not support the routine use of mesh in hiatal hernia repair.

Introduction

Laparoscopic repair of large hiatal hernias has become standard therapy for patients with symptomatic hiatal hernia, and covered around 50% of laparoscopic antireflux procedures in the last decade.[1] Hiatal hernia is associated with impaired quality of life, caused by symptoms including dysphagia, chest pain, reflux, regurgitation and airway symptoms like cough and dyspnea. It is more common in the elderly patient, with a higher incidence with increasing age.[2, 3] Surgery consists of dissection of the hernial sac from the mediastinum into the abdomen, followed by cruroplasty with sutures and fundoplication.[4] This procedure has demonstrated acceptable morbidity and low symptomatic recurrence rates.[5-7] More recent studies providing radiologic follow-up with barium-swallow X-rays, report high numbers of radiologic, asymptomatic recurrent hiatal hernia, with rates up to 30-42%, although only 5% of these patients had symptomatic recurrence.[8, 9] An asymptomatic recurrence may become symptomatic over time and can lead to severe complications like strangulation.[9, 10]

In an attempt to reduce recurrence rates, several surgeons were looking for firmer crural repair using mesh, demonstrating promising results in the first clinical trials.[11-15] However, the use of mesh was associated with certain rare, but serious complications such as stenosis and erosion that could result in partial or total gastrectomy or even esophagectomy.[16-19] For that reason, several randomized clinical trials have compared primary suturing versus prosthetic, non-absorbable and absorbable mesh, not just for comparing recurrence rates, but also to analyze the incidence of mesh-related complications.[12-14, 20] Two recent meta-analyses demonstrated that all procedures provide comparable results, with a possible favorable outcome of mesh regarding the asymptomatic recurrence rate, but not for reoperation rate.[21, 22] Patient satisfaction and quality of life was equal after primary cruroplasty, use of biologic absorbable mesh, and prosthetic non-absorbable mesh in a recent randomized controlled trial.[23]

The present study describes the symptomatic and objective outcome of a large cohort of patients who underwent laparoscopic repair for a symptomatic type II-IV hiatal hernia. Data were prospectively collected and retrospectively analyzed. In contrast to many studies, we used patient reported outcome measures (PROM's) to evaluate patient satisfaction and quality of life after surgery.

We hypothesized that clinical outcome following primary cruroplasty and cruroplasty reinforced with a non-absorbable mesh would be similar. Therefore, the aim was to analyze radiologic and symptomatic recurrences, and compare reoperations, complications, and PROM's to find which factors could be associated with symptomatic recurrence and reoperation rate.

Materials and methods

Patient selection

Patients who underwent laparoscopic hiatal hernia repair of a type II, III or IV hiatal hernia with a minimal follow-up of six months were included in this study. All patients were operated in two tertiary referral centers for antireflux surgery (both centers >80 cases per year). Patients who were mentally incapable, younger than 18 years old at the time of surgery, unable to speak the Dutch language or patients who were diagnosed with a different disease during preoperative investigations or during surgery were excluded. Also, patients with previous antireflux surgery were excluded.

Preoperative workup

The majority of patients were referred by gastroenterologists. Preoperative upper gastrointestinal endoscopy, barium-swallow X-ray, and/or computed tomography (CT) were performed preoperatively to confirm the diagnosis of hiatal hernia. Esophageal manometry and 24-hours pH-monitoring was only performed on clinical indication. Hiatal hernia was categorized according to the guidelines for the management of hiatal hernia by the Society of American Gastrointestinal and Endoscopic Surgeons.[24]

Data collection

Data was prospectively collected using standardized questionnaires. Comorbidity was categorized as the presence of cardiovascular disease (including hypertension, cardiac arrhythmias, coronary artery disease, peripheral vascular disease, cerebrovascular disease); presence of diabetes mellitus (including type I and II); presence of chronic obstructive pulmonary disease (COPD); and a history of previous abdominal surgery (either laparoscopic or open surgery). Primary symptoms were categorized into dysphagia, airway symptoms (coughing and dyspnea), reflux, chest pain and anemia.

Surgical technique

All procedures were performed laparoscopically, with no conversions to laparotomy. First step in the procedure was reduction of the stomach, and if present other abdominal organs, followed by dissection of the hernia sac. Following complete mobilization of the esophagus, posterior crural repair, and anterior repair if deemed necessary, was performed using non-absorbable sutures. When there was insufficient or weak crural tissue, a U-shaped, non-absorbable mesh was used for posterior crural reinforcement (TiMESH®, pfm medical titanium gmbh, Nürnberg, Germany). The mesh was fixed using non-absorbable sutures or absorbable tackers, while carefully avoiding direct contact to the esophagus. In addition, a fundoplication was performed to avoid recurrent reflux. According to the preference of the surgeon this was either a 180° anterior partial fundoplication (180°LAF),[25, 26] a 270° posterior partial Toupet fundoplication (LTF)[27] or a 360° total Nissen fundoplication (LNF).[28]

Follow-up

Barium-swallow X-rays were performed three to six months postoperatively. Postoperative endoscopy, CT scanning, 24-hour pH-monitoring, and/or esophageal manometry were only performed on indication given the invasive character of these investigations.

One hospital prospectively followed patients using validated questionnaires, including the validated Gastro-Esophageal Reflux Disease health related Quality of Life (GERD-hr-QoL) for GERD-related quality of life,[29-32] and the validated QLQ-OES-24 for analyzing the presence and severity of dysphagia.[33, 34] Furthermore, symptoms were scored on a 10-point Visual Analogue Scale,[35] and satisfaction regarding preoperative information, quality of care (outpatient, surgical department, ward, etc.), waiting time for the operation, and postoperative care were assessed using a 10-point Visual Analogue Scales. Finally, patients were asked in retrospect if they would undergo the same operation again, should have undergone this operation earlier and if they would recommend this operation to a close relative or good friend with equal symptoms. Patients were asked to complete these questionnaires preoperatively, and at three months and one year postoperatively and then yearly up until five years after surgery. Data collection was either on paper or online.

Statistics

Parametrically distributed data were analyzed using the Student t test. Non-parametric data were analyzed using the Mann-Whitney U test. Categorical data were analyzed using the Chi-square tests or Fisher´s exact test when necessary. Univariate logistic regression analyses were performed to predict risk factors. Multivariate logistic regressions were performed with factors that showed significant univariate regression ($P<0.05$). Statistical analyses were performed using IBM´s Statistical Package for Social Sciences (SPSS), version 22 for Apple Macintosh OS (IBM corp., Armonk, New York, USA). A *p*-value of less than 0.05 was considered to be statistically significant.

Ethical approval

Patients gave informed consent and were informed about the purposes of the completed questionnaires and securely saved data. The Institutional Review Board of the hospitals has evaluated our study protocol and approved it without further obligations.

Results

Patient characteristics

Between July 2009 and December 2015, a total of 189 patients with a mean age of 66.0 ± 11.2 years underwent laparoscopic hiatal hernia repair with additional fundoplication. Mean follow-up was 39.3 months ± 17.2. Patients were equally distributed over both hospitals (109 patients (57.7%) in hospital 1 versus 80 patients (42.3%) in hospital 2). 145 patients (76.7%) were female, 44 were male (23.3%), and mean body mass index (BMI) was 28.8 ± 4.3. Mean age, gender, and mean BMI did not differ between the two groups. The proportion of ASA II patients was higher in the non-mesh group, with a higher percentage of patients with ASA I and III in the mesh group (P=0.038). The prevalence of cardiovascular disease was higher in the non-mesh group (P=0.008).

Indications for surgery for the overall group were dysphagia in 29.3% of patients, chest pain in 28.3%, reflux and regurgitation complaints in 20.1%, airway complaints including dyspnea or coughing in 17.4%, and anemia or bleeding in 4.9% of patients. Indications for surgery were equal in the non-mesh and the mesh group. Hiatal hernia type and percentage of the stomach in the thoracic cavity were equal for both groups. The majority of patients had a type III hiatal hernia (67.2%) and more than 50% of the stomach displaced (77.1%).

A non-absorbable mesh was used in 62 patients (32.8%). Baseline characteristics are described in table 1.

TABLE 1. Patient characteristics.

	Mesh (n=62)	No Mesh (n=127)	*P*-value
Age[a]	64.1 ±12.8	66.9 ±10.3	0.140
Gender[b]			
Male	15 (24.2%)	29 (22.8%)	0.856
Female	47 (75.8%)	98 (77.2%)	
BMI[a]	28.9 ± 4.7	28.7 ± 4.2	0.873
ASA[b]			
I	9 (14.5%)	10 (7.9%)	0.038
II	38 (61.3%)	100 (78.7%)	
III	15 (24.2%)	17 (13.4%)	
Comorbidity[b]			
Cardiovascular	21 (33.9%)	70 (55.1%)	0.008
Diabetes Mellitus	4 (6.5%)	10 (7.9%)	1.000
Abdominal surgery	27 (43.5%)	65 (51.6%)	0.353
COPD	10 (16.1%)	19 (15.0%)	0.832
Primary symptom[b]			
Dysphagia	16 (27.1%)	38 (30.4%)	0.929
Airway	12 (20.3%)	20 (16.0%)	
Reflux	12 (20.3%)	25 (20.0%)	
Chest pain	17 (28.8%)	35 (28.0%)	
Anemia	2 (3.4%)	7 (5.6%)	
Hernia type[b]			
II	6 (9.7%)	13 (10.2%)	0.483
III	45 (72.6%)	82 (64.6%)	
IV	11 (17.7%)	32 (25.2%)	
Percentage intrathoracic stomach[b]			
0-24%	1 (1.6%)	7 (5.6%)	0.113
25-74%	26 (42.6%)	68 (72.3%)	
75-100%	34 (55.7%)	51 (40.5%)	

BMI = Body Mass Index; ASA = American Society of Anesthesiologists physical status score; COPD = Chronic Obstructive Pulmonary Disease; Data presented as either [a]:mean ± standard deviation, or [b]:number (percentage).

Perioperative outcome

Table 2 demonstrates perioperative outcome of the included patients. The majority of patients underwent a 180° anterior fundoplication (67.9%), which was most frequently conducted in the non-mesh group (89.7% versus 23.0%). A Toupet fundoplication was performed in 30.5% of the patients and more common in the mesh group (77.0% versus 7.9% in the non-mesh group; $P<0.001$). Laparoscopic Nissen fundoplication was performed in three cases of severe Barrett's esophagus (2.4%). Intra-operative complications occurred in 9.8% of the patients without any major complications, and with no differences between the two groups. Minor intra-operative complications consisted of asymptomatic pleural tear (3.2%, n=6); bleeding (1.6%, n=3); atrial fibrillation de novo (1.6%, n=3); small lesion of the spleen (1.1%, n=2); perforation of the esophagus (0.5%; n=1); and gastric perforation (0.5%; n=1). Complications were recognized and repaired if deemed necessary. Median hospital stay was two days (IQR 2.0), and median duration of surgery was 100 minutes (IQR 42.5). Operation times were longer in the mesh-group (110 minutes versus 95 minutes; $P=0.045$). Postoperative complications were present in 11.6% of patients (n=22), with no differences between the two groups. Postoperative complications consisted of urinary tract infection (2.6%; n= 5); pneumonia (1.6%; n=3); asymptomatic atelectasis (1.1%; n=2); pulmonary edema (1.1%; n=2); dysphagia requiring reoperation in one case (1.1%; n=2); mediastinal bleeding requiring reoperation (0.5%; n=1); and distal esophageal stenosis requiring esophageal stenting (0.5%; n=1); recurrent hiatal hernia causing pain requiring reoperation (0.5%; n=1); and five other rare complications (e.g. pulmonary embolus, gastro-enteritis, esophageal edema, atrial fibrillation de novo, and constipation). There were no mesh-related complications during short- or long-term follow-up.

TABLE 2. Perioperative characteristics and outcome.

	Mesh (n=62)	No Mesh (n=127)	*P*-value
Fundoplication type[a]			
180°LAF	14 (23.0%)	113 (89.7%)	
LTF	47 (77.0%)	10 (7.9%)	<0.001
LNF	0	3 (2.4%)	
Minor intra-operative complications[a]	5.0 (8.1%)	12 (9.4%)	1.000
Time of surgery[b]	110 (30)	95 (50)	0.045
Hospital days[b]	2.0 (2.0)	2.0 (2.0)	0.273
Postoperative complications[a]	8 (12.9%)	14 (11.0%)	0.810
Radiologic recurrence[a]	16 (25.8%)	30 (23.6%)	0.331
Symptomatic recurrence[a]	10 (16.1%)	15 (11.8%)	0.495
Reoperation[a]	6 (9.7%)	8 (6.3%)	0.393
Satisfaction after surgery (n=88)[b]	8.5 (3.0)	9.0 (2.0)	0.946
Follow-up after surgery[a]	49.2 (16.2)	34.5 (15.6)	<0.001

180°LAF = 180° anterior fundoplication, LTF = Toupet (270° posterior) fundoplicion, LNF = Nissen (360°) fundoplication, Data presented as either [a]: number (percentage), or [b]: median (interquartile range).

Symptomatic and objective outcome

109 patients were invited for follow-up using PROM's (57.7%). Response rate was 80.7% (n=88) and mean follow-up was 33.3 months ± 13.6. Median satisfaction with surgery was 9.0 (IQR 2.0) and equal for both groups. Postoperative GERD-hr-QoL improved significantly (*P*<0.001, n=77) from median 7.0 (IQR 15.0) preoperative, to 2.0 (IQR 2.0) postoperative. This improvement was equal for both groups (figure 1). The QLQ-OES-24 also showed significant improvement after surgery (*P*<0.001, n=74) from 49 (IQR 15.0) to 34 (IQR 12.0). No differences were seen between the groups with crural repair with sutures only and the group with crural reinforcement using mesh (figure 2).

A total of 153 patients (81.0%) underwent postoperative radiological investigations. Radiologic recurrence was present in 46 patients (24.3%) and comparable between the two groups (25.8%, n=16 in mesh versus 23.6%, n=30 in sutures; *P*=0.749). Symptomatic recurrence rate was 13.2% and equal for both groups as well (*P*=1.000). The reoperation rate was 7.4% (n=14) and comparable for both groups. 13 reoperations were categorized as 'late' (after > 4 weeks), and mean time between primary operation and reoperation was 19.4 months ± 13.8, which was equal between the mesh- and sutures-group (*P*=0.902). Only one reoperation was performed 'early' after primary surgery (five days). This was for acute recurrence of hiatal hernia with obstruction.

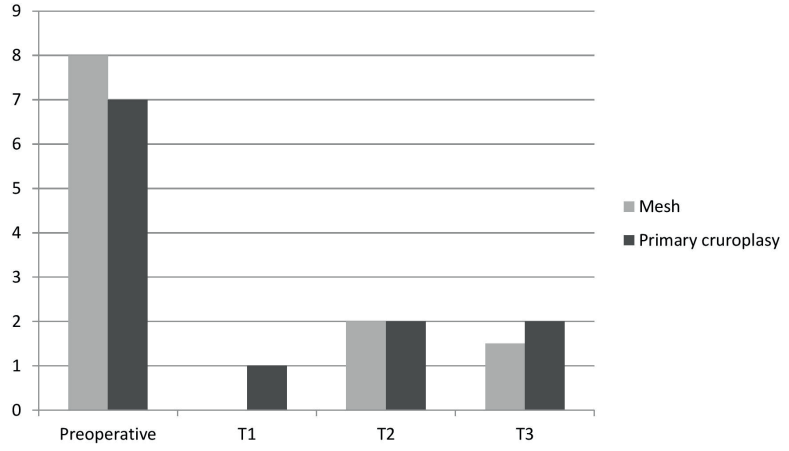

FIGURE 1. GERD-hr-QoL improvement after laparoscopic hiatal hernia repair.

T1 = 3 months postoperative (n = 69). T2 = 12 months postoperative (n = 55). T3 = 24 months postoperative (n = 32). GERD-hr-QoL = gastroesophageal reflux disease health-related quality of life questionnaire. All postoperative scores show significant improvement compared to preoperative (P<0.001; preop *vs* T2 P=0.001). No difference in postoperative scores. No difference between mesh and primary cruroplasty

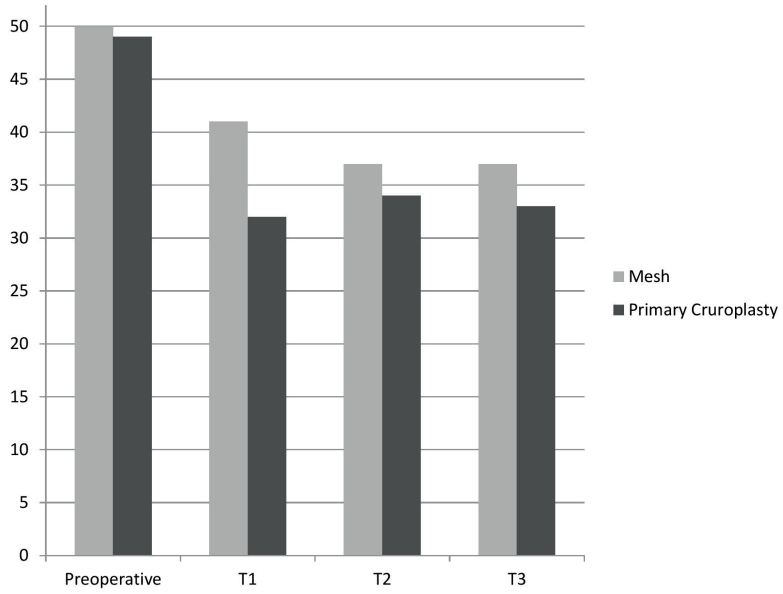

FIGURE 2. QLQ-OES-24 scores after laparoscopic hiatal hernia repair.

T1 = 3 months postoperative (n = 69). T2 = 12 months postoperative (n = 55). T3 = 24 months postoperative (n = 32). QLQ-OES- 24 = quality of life questionnaire scoring dysphagia after surgery. All postoperative scores show significant improvement compared to preoperative (P<0.001). No difference in postoperative scores. No difference between mesh and primary cruroplasty.

TABLE 3. Univariate analyses.

	Radiologic recurrence		Symptomatic recurrence		Reoperation	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR 95% CI	*p*-value
Age	0.985 (0.954-1.017)	0.348	0.971 (0.936-1.007)	0.108	0.954 (0.912-0.998)	0.042
Sex	0.734 (0.334-1.611)	0.441	0.586 (0.233-1.469)	0.254	0.370 (0.121-1.131)	0.081
BMI	0.923 (0.848-1.005	0.065	0.942 (0.850-1.044)	0.256	0.869 (0.756-0.999)	0.049
ASA	1.106 (0.525-2.329	0.791	1.276 (0.563-2.894)	0.559	0.754 (0.260-2.186)	0.603
Cardiovascular comorbidity	1.019 (0.510-2.034)	0.958	1.440 (0.617-3.362)	0.399	0.794 (0.265-2.384)	0.681
Abdominal surgery history	0.727 (0.363-1.458)	0.369	0.453 (0.185-1.110)	0.083	0.260 (0.070-0.966)	0.044
Hernia type	0.766 (0.408-1.437)	0.406	0.989 (0.465-2.104)	0.977	0.825 (0.310-2.191)	0.699
Percentage intrathoracic stomach	1.018 (0.778-1.331)	0.898	0.851 (0.610-1.186)	0.341	0.810 (0.526-1.247)	0.338
Fundo	1.637 (0.824-3.251)	0.159	1.291 (0.582-2.862)	0.529	1.433 (0.525-3.911)	0.483
Intra-operative complications	1.064 (0.348-3.257)	0.913	2.183 (0.651-7.323)	0.206	3.136 (0.782-12.573)	0.107
Mesh	1.505 (0.715-3.167)	0.282	1.410 (0.594-3.351)	0.436	1.594 (0.528-4.812)	0.408
Postoperative complications	0.542 (0.171-1.719)	0.298	1.026 (0.280-3.757)	0.969	1.292 (0.269-6.194)	0.749

BMI = Body Mass Index; ASA = American Society of Anesthesiologists physical status score; OR = Odds ratio; CI = confidence interval

Risk factor analyses

Univariate analyses demonstrated that age, BMI and previous abdominal surgery might be predictive factors for reoperation (table 3). Specific predictive factors for radiologic recurrence and symptomatic recurrence were not found. Use of mesh is not found to be a risk factor for radiologic recurrence, symptomatic recurrence or reoperation. Multivariate analyses showed comparable results and did not alter the influence of these predictive factors.

Large hiatal hernias

Table 4 shows a subanalysis of 85 patients suffering from a large hiatal hernia, categorized as more than 75% of intrathoracic stomach. Intraoperative and postoperative complication rates were comparable with the overall group, with no differences in complication rate between reinforcement with mesh and primary cruroplasty. Radiologic recurrence, symptomatic recurrence and reoperation rates were all equal in both groups, comparable with the analyses in the total cohort of patients.

TABLE 4. Subanalysis for large hiatal hernia (>75% intrathoracic stomach); perioperative characteristics and outcome.

	Mesh (n=34)	No Mesh (n=51)	*P*-value
Minor intra-operative complications[a]	3 (8.8%)	5 (9.8%)	1.000
Time of surgery[b]	120 (43.3)	104 (45)	0.232
Hospital days[b]	2.0 (2.8)	2.0 (2.0)	0.949
Postoperative complications[a]	5 (14.7%)	5 (9.8%)	0.512
Radiologic recurrence[a]	8 (23.5%)	13 (25.4%)	0.749
Symptomatic recurrence[a]	4 (11.8%)	5 (9.8%)	1.000
Reoperation[a]	2 (5.9%)	4 (7.8%)	1.000

Data presented as either [a]: number (percentage), or [b]: median (interquartile range)

Discussion

This study describes the results of a large cohort of patients suffering from a symptomatic hiatal hernia. After laparoscopic correction of these large hiatal hernias, radiologic recurrence rate was 24.3%, symptomatic recurrence rate was 13.2%, and only 7.4% of the patients needed reoperation due to hiatal hernia recurrence. This was equal for patients who underwent primary cruroplasty and for those who underwent cruroplasty with the use of prosthetic mesh. Univariate and multivariate analyses could not reveal a reduction of a symptomatic recurrence or reoperation rate with the use of mesh. Age, previous abdominal surgery and body mass index were associated with a higher rate of symptomatic recurrence and reoperation. This is explained by difficulties during surgery in patients after previous abdominal surgery, a higher BMI being associated with higher complication rates after surgery, and weakening of muscular and fascia tissue with increasing age. However, a recent study demonstrated laparoscopic correction of large hiatal hernias to be safe in the elderly patient, when carefully selected.[36] The incidence of minor perioperative (9.8%) and postoperative complications (11.2%) was comparable for both groups and no major mesh-related complications occurred, which is in line with the results of the previously mentioned trials. Only the total operation time was significantly different between the groups. Prolonged operation time in the mesh-group was expected, as the reinforcement with mesh carries an extra step in the procedure. This was also described in the study of Frantzides et al,[12] but not in other studies nor in pooled data in meta-analyses.[7, 13, 21, 22]

A subanalyis of the large hiatal hernias in this cohort showed comparable results, except for operation time, which was prolonged for both procedures, but not significantly longer for repair with mesh when compared to primary cruroplasty. Patient reported satisfaction was high in both groups. Health related quality of life on both the reflux-scores (GERD-hr-QoL) and the dysphagia-scores showed significant improvement following surgery. All scores were comparable between primary cruroplasty and reinforcement with mesh.

This study demonstrates no differences in objective and symptomatic recurrence after laparoscopic hiatal hernia repair with primary cruroplasty versus non-absorbable mesh. This is in contrast to most previously published trials and meta-analyses. Granderath et al[13] and Frantzides et al[12] found lower recurrence rates with use of prosthesis compared to primary cruroplasty. Frantzides even found a 0% recurrence rate using a "keyhole" polytetrafluorethylene (PTFE) mesh that surrounded the whole esophagus. Since no long-term follow-up was reported, it is unclear whether mesh related complications occurred on later term or recurrence rates altered in time. Comparable reduction in recurrence rate has not been published yet. Two meta-analyses described higher recurrence rates after use of sutures only. Antoniou et al. found a 24.3% recurrence rate following primary cruroplasty after six months, compared to 5.8% after use of mesh.[37] Furnee et al described

comparable results with a recurrence rate of 26.3% following primary crural correction and 14.6% with use of mesh.[38] Oelschlager et al reported promising results after six months using an absorbable mesh, with a 9% recurrence rate in the mesh-reinforced group and 24% in the primary cruroplasty group.[14] However, the five-year results that were published in 2011 revealed different numbers: 54% recurrences in the group that underwent reinforcement using mesh, and 59% recurrences in the group after primary correction.[15] The need for redo surgery for recurrences was low: only 3.5% in the group after primary cruroplasty. Watson et al published their 12 month-results of a three-armed trial using primary correction, absorbable mesh and non-absorbable mesh, demonstrating comparable results with our study. They found no difference in recurrence rate, neither radiological nor symptomatic.[7] Meta-analyses of Memon et al and Tam et al confirmed these findings.[21, 22]

A possible weakness of this study is that the groups are not randomized for the different treatments. It was the surgeon's decision to perform primary cruroplasty or reinforce the cruroplasty with mesh. However, we did analyze both groups and did not find major differences in patient characteristics and perioperative characteristics. Primary symptoms, hiatal hernia size and the percentage of intrathoracic stomach were equal for both groups. It is therefore likely to assume that both groups are comparable. The total duration of follow-up is not equal for both groups. Follow-up is shorter in the group without mesh, which can be explained by the difference in total group-size, causing the more recent patients to have undergone surgery without mesh.

The majority of studies that describe outcome of laparoscopic hiatal hernia repair focus on clinical and objective outcome. However, patient-reported outcome measures (PROM's) like quality of life and satisfaction scores are important as a reflection of outcome that is more relevant to the individual patient.[39] Only a few studies describe quality of life using the Short-Form 36.[15, 23] However, this might not be an adequate measure for symptom and quality of life alteration after laparoscopic antireflux surgery.[32] Health-related quality of life measures like the GERD-hr-QoL and the Gastrointestinal Quality of Life Index (GIQLI) and symptom scores using Visual Analog Scores are more reliable for outcome measurement. In our prospective data collection we use PROM's to evaluate outcome. This study describes significant improvement of health-related quality of life and high patient satisfaction, using validated questionnaires.

In conclusion, our study demonstrates comparable radiologic (objective) and symptomatic recurrence rates after primary cruroplasty and mesh reinforced cruroplasty. Additionally, the need for reoperation is also equal. Patient reported outcome measures reflecting patient satisfaction with surgery and quality of life are equal for both groups as well. The data in this study do not support the routine use of mesh. Randomized clinical trials comparing mesh and primary crural repair, using health-related quality of life measures and symptom scores, as well as radiologic versus symptomatic recurrence rates and reoperation rates have been undertaken. Long-term results of these randomized

trials should be awaited before drawing definite conclusions regarding the routine use of mesh in hiatal hernia repair.

Disclosures

Drs. Koetje, Oor, Roks, Van Westreenen, Hazebroek and Nieuwenhuijs have no conflicts of interest or financial ties to disclose.

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Chapter 7

Randomized clinical trial comparing laparoscopic hiatal hernia repair using sutures versus sutures reinforced with non-absorbable mesh

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Submitted

Abstract

Background: To analyze one-year outcome from a randomized clinical trial comparing laparoscopic repair of hiatal hernia using sutures versus sutures reinforced with non-absorbable mesh.

Methods: Between 2013 and 2016, 72 patients with an objectified hiatal hernia were randomized for primary repair using non-absorbable sutures and sutures reinforced with non-absorbable mesh. Data regarding the incidence of recurrent hiatal hernia, need for endoscopic dilatation or surgical reintervention, postoperative dysphagia and/or reflux symptoms, general health and use of acid suppressing medication were analyzed.

Results: 72 patients (n=36 *vs.* n=36) were included. One year after primary repair and repair using non-absorbable mesh, there were no differences in the number of recurrent hiatal hernia's demonstrated by barium swallow radiology (n=4 [11.4%] vs. n=6 [19.4%], P=0.370) or upper gastro-intestinal endoscopy (n=5 [14.4%] vs. n=5 [17.2%], P=0.746), the number of surgical reinterventions (n=2 [5.6%] vs. n=1 [2.8%], P=1.000), nor in chest pain and heartburn scores, with comparable dysphagia and satisfaction scores. Compared to the preoperative state, both groups demonstrated a comparable and significant reduction in chest pain score and Dakkak dysphagia score.

Conclusions: Use of non-absorbable mesh to reinforce primary hiatal hernia repair results in equal hiatal hernia recurrence and symptomatic outcome compared to repair using sutures alone. During one-year follow-up, there were no mesh-related complications. Follow-up beyond one year needs to demonstrate whether these findings are sustained.

Introduction

Hiatal hernia is characterized by the protrusion of an abdominal structure other than the esophagus into the thoracic cavity through a widening of the hiatus, which can be categorized into the sliding-type (type I), the 'true' para-esophageal type (type II), a mixed type (type III), and the type IV hiatal hernia, with the presence of an upside-down-stomach and possibly omentum and/or intestinal interposition.[1] Hiatal hernia may cause a variety of invalidating symptoms, including obstruction, dysphagia and chest pain, and in rare occasions, may lead to life-threatening complications such as strangulation or perforation. Over the last decade, laparoscopic repair of hiatal hernia has rapidly increased, with low reported mortality and morbidity rates, and good clinical outcome.[2]

Due to the repetitive stress exerted on the diaphragm during both respiratory and non-respiratory functions, dehiscence and the subsequent development of a recurrent hiatal hernia is an important problem following primary hiatal hernia repair.[3] There appears to be a discrepancy between the reported incidence of radiological recurrences (30-42%) and true symptomatic recurrences (5%) following primary repair.[4] By providing a tension-free repair, the use of mesh in inguinal and ventral hernia repair has resulted in lower recurrence rates.[5, 6] Therefore, it is suggested that routine crural reinforcement will reduce the rate of recurrent hiatal hernia. Currently, three randomized clinical trials compared the outcome of repair of large hiatal hernias using sutures alone versus sutures reinforced with different types of mesh.[7-10] In 2002, Frantzides et al. published the results of a randomized clinical trial in which patients with a hiatal hernia were randomized for repair using non-absorbable sutures versus sutures reinforced with a polytetrafluoroethylene (PTFE) mesh, demonstrating a significant lower incidence of recurrent hernia 2.5 years after PTFE (0%) compared to primary suturing (22%).[7] In 2006, Oelschlager et al. randomized 108 patients for either sutures alone or sutures reinforced with an absorbable mesh.[8] At six months, there was a significantly lower incidence of recurrent hernia after sutures reinforced with absorbable mesh (9%) compared to sutures only (24%). However, after five years this difference was no longer present (59% *vs*. 54%, *P*=0.7).[9] Recently, Watson et al randomized 126 patients with a large hiatal hernia (>50% intrathoracic stomach) for primary repair using non-absorbable sutures versus sutures reinforced with absorbable mesh versus sutures reinforced with a non-absorbable mesh.[10] At one-year, a recurrent hiatal hernia was seen in 23.1%, 30.8%, and 12.8% of the patients respectively (*P*=0.161), with no clinically relevant differences in symptomatic outcome.[10]

In 2015, Furnee et al. published the results of a survey among European gastrointestinal surgeons regarding the use of mesh in large hiatal hernia repair, with 14.5% of the respondents reporting the routine use of mesh and 77.6% in selected cases only.[11] The majority of the respondents (52.6%) reported to use polypropylene mesh, despite the fact that esophageal erosions were encountered by 20% of all respondents. This survey demonstrates the diversity among European gastrointestinal surgeons regarding mesh

type, configuration and fixation in hiatal hernia repair, and the lack of evidence still causing controversy regarding these isues.[11]

Since primary repair and non-absorbable mesh appear to result in a lower incidence of recurrent hiatal hernia compared to absorbable mesh, we aimed to validate the previously reported results in a European study population using a well-designed randomized clinical trial. In the present trial, one-year symptomatic and objective outcome of hiatal hernia repair using sutures versus sutures reinforced with non-absorbable mesh are compared.

Methods

Study design and participants

Between April 2013 and March 2016, patients were enrolled in a multicenter double-blind randomized clinical trial and were randomized to undergo either primary repair using non-absorbable sutures or non-absorbable sutures reinforced with a non-absorbable mesh.

All included patients were diagnosed with a large hiatal hernia, defined as a diaphragmatic defect with ≥25% of intrathoracic stomach, which had been objectified by either barium swallow radiology, upper gastro-intestinal endoscopy, or thoracic and/or abdominal computed tomography (CT) scanning. Patients diagnosed with a large hiatal hernia were considered eligible irrespective of their age, previous thoracic or abdominal surgery, or presence of comorbidities.[12] Exclusion criteria consisted of esophageal motility disorders, previous antireflux surgery or hiatal hernia repair. All patients gave written informed consent for participation and prospective collection of their medical data.

Demographics of the included patients were collected and included sex, age, body mass index (BMI), the presence of comorbidities categorized as diabetes and renal, pulmonary or cardiovascular disease, a history of thoracic and/or abdominal surgery, and the use of acid suppressing medication. Preoperative symptoms and quality of life (QoL), as well as symptomatic outcome after surgery were assessed using structured questionnaires at three months, six months, and one year after surgery. All patients were scheduled for routine six months postoperative barium swallow radiology and upper gastrointestinal endoscopy, performed irrespective of postoperative symptoms.

Primary outcome was the incidence of a recurrent hiatal hernia, demonstrated by barium swallow radiology and/or upper gastrointestinal endoscopy. Secondary endpoints included operating time, development of perioperative morbidity, need for surgical reintervention, incidence of postoperative dysphagia, gas-related symptoms (inability to belch, gas bloating, and increased flatulence), postoperative reflux disease and satisfaction with surgery.

Randomization and blinding

After informed consent, 1:1 randomization to primary repair using non-absorbable sutures or non-absorbable sutures augmented with non-absorbable mesh was performed using web-based randomization. Patients were not informed regarding the type of procedure that was performed throughout the entire 12 months follow-up. Objective follow-up investigations were carried out by an observer blinded to the type of surgical procedure performed. Barium swallow radiology was analyzed by an experienced radiologist, and upper gastrointestinal endoscopy performed by a gastroenterologist, with experience in determining postsurgical anatomy.

Surgical procedures

All included patients were operated by three experienced gastrointestinal surgeons specialized in laparoscopic hiatal hernia repair and who were well beyond their learning curve for laparoscopic hiatal hernia repair (>30 hiatal hernia repairs per year).[13] Before the trial commenced, tutoring and a convention meeting between the three surgeons ensured similar techniques in both tertiary hospitals.

All procedures were commenced laparoscopically. First, the content of the hernial sac was reduced into the abdominal cavity, followed by complete dissection of the sac from the mediastinum, while carefully avoiding vagal nerve or pleural injury.[14, 15] After complete esophageal mobilization, the crural defect was repaired using posterior non-absorbable sutures irrespective of the type of procedure a patient was randomized for, with addition of anterior sutures if deemed necessary. Mesh repair involved a sutured posterior hiatal repair followed by placement of a U-shaped piece of non-absorbable mesh (Timesh®, PFM Medical, Köln, Germany) over the sutures and the hiatal pillars, but not circumferential. The mesh was anchored with sutures or absorbable tackers to reinforce the repair. Because of the risk of de novo esophageal acid exposure, all patients underwent an additional fundoplication consisting of either a 270 degree posterior or 180 degree anterior partial fundoplication, based upon the surgeon's preference.[16] Division of the short gastric vessels was performed when necessary to ensure a floppy fundoplication.

Intra-abdominal findings and the difficulty of each procedure were scored by the surgeon using a 0 to 10 analogue scale (10 representing the most difficult procedure). If the performed procedure was not consistent with the allocated repair type, the patient was not excluded and remained in the allocated group for intention-to-treat analysis.

Postoperative admission to the intensive care unit (ICU) was only performed if clinically necessary. Patients were allowed oral fluids directly, and soft solid food the next day.

Clinical outcome

Structured questionnaires were used preoperatively and three, six and 12 months after surgery. All questionnaires were send by regular mail. The presence or absence of the following symptoms was determined: heartburn, chest pain, epigastric pain, regurgitation, dysphagia for solids and/or liquids, pain during swallowing, postprandial fullness, inability to belch, gas bloating, anorexia, nausea, vomiting, nocturnal coughing, increased flatulence and diarrhea. Additionally, the severity and frequency of the symptoms chest pain, heartburn and dysphagia for solids and liquids was assessed using a 0 to 10 analogue scale (0= no complaints, 10= very severe complaints). The presence and severity of dysphagia was further examined using the validated Dakkak dysphagia score, assessing the difficulty of swallowing 9 different types of liquids and solids (0=never; 1=sometimes; 2=always).[17] Overall outcome of surgery was ranked using an analogue satisfaction score (0= dissatisfied, 10= highly satisfied), a modified Visick grading score (1= no symptoms, 5= worse symptoms following surgery), and an overall outcome score (1= perfect; 4= bad

outcome).[18] In addition, patients were asked whether or not they considered their original choice to have surgery to be correct (0=no, 1= yes). Changes in the use of proton pump inhibitors and histamine-2 blockers were also recorded.

Statistics and sample size calculation

All data was entered in a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). Data was analyzed based on the intention-to-treat principle. Data was expressed as mean ± 95% confidence interval (95% C.I.) or total number of patients (%). The Chi square test was used for comparing binary variables between groups, and the Mann-Whitney U test for continuous variables. The effect of surgery on different continuous variables in both groups was analyzed using the Wilcoxon signed rank test (preoperative *vs.* postoperative values). Statistical significance was defined as $P<0.05$.

Sample size calculation using a two-sample T-test power analysis, with a power of 0.8 and α of 0.05, resulted in a required sample size of 72 (36 *vs*. 36) to demonstrate a 25% difference in incidence of radiological recurrent hiatal hernia (30% *vs.* 5%). This difference was based on several studies examining outcome of hiatal hernia repair, including the randomized clinical trial of Frantzides et al.[7]

Ethics approval and trial registration

The protocol of the present trial has been approved by each participating hospital's research ethics committee and consent was obtained from all participants. This trial has been registered in the Dutch Trial Register (NTR, RCT number NL42495.100.12).

Results

Overall responses and completeness of follow-up

A total of 72 patients were included and consequently underwent primary repair using non-absorbable sutures (n=36) or sutures augmented with non-absorbable mesh (n=36; Figure 1). All included patients underwent the procedure they were randomized for. Preoperative symptomatic outcome scores were available for all patients. Postoperative symptomatic outcome scores were available for 69 patients (94.5%) at three and six months, and for 68 (94.4%) patients at one year (Figure 1). Two patients in the mesh-group died during one-year follow-up. One patient died three months after surgery due to cardiac decompensation with a history of severe heart failure. The second patient died 11 months after surgery due to extensive intestinal ischemia following a caecal volvulus (not related to hiatal hernia repair).

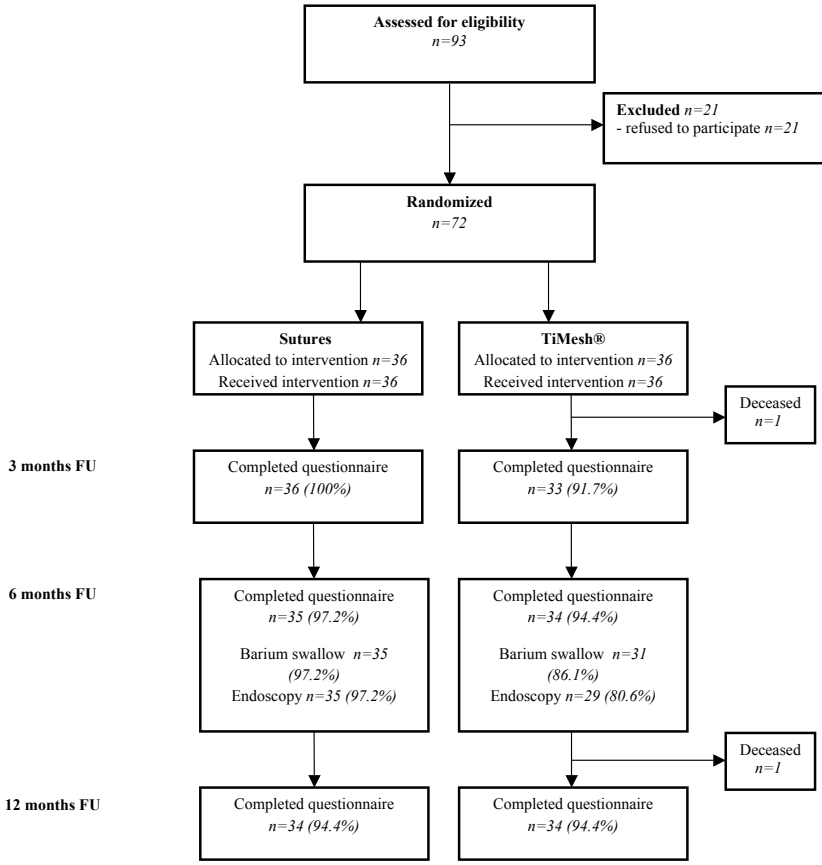

FIGURE 1. CONSORT flow chart of enrolment and follow-up of patients.

Routine six months postoperative barium swallow radiology and upper gastrointestinal endoscopy was available for 66 (91.7%) and 64 (88.9%) of the patients respectively, causing objective follow-up to be available in 68 patients (94.4%). There were no significant differences in baseline characteristics between the two groups (Table 1). Furthermore, there were no conversions to open surgery in either group.

TABLE 1. Baseline characteristics according to treatment allocation.

	Sutures	TiMesh®
Patients (n)	36	36
Sex (male / female)	9/27	14/22
Age (yrs.)	64.3 (61.0-67.5)	62.3 (58.4-66.2)
BMI (kg/m^2)	29.4 (27.9-30.8)	29.0 (27.3-30.8)
Previous thoracic /abdominal surgery	20 (55.6%)	22 (61.1%)
ASA-classification*		
I+II	32 (91.4%)	29 (80.6%)
III+IV	3 (8.6%)	7 (9.4%)
Primary indication surgery		
Obstruction	10 (27.8%)	16 (44.8%)
Reflux	9 (25.0)	7 (19.4%)
Obstruction + reflux	3 (8.3%)	1 (2.8%)
Regurgitation	3 (8.3%)	3 (8.3%)
Chest pain	2 (5.6%)	-
Dyspnoea	3 (8.3%)	3 (8.3%)
Other	3 (8.3%)	4 (11.1%)

All data are expressed as n (%) or mean (95% confidence interval);
ASA: American Society of Anesthesiologists physical status classification

Perioperative outcome

Perioperative details are summarized in table 2. There was no significant difference in intraoperatively diagnosed hernia size nor in the total operating time between patients who underwent suturing alone versus sutures reinforced with mesh (61.3 min [54.7 – 67.9] vs. 69.3 min [58.2 – 80.4], P=0.528). Furthermore, there was no difference in the difficulty of the procedure reported by the participating surgeons (3.0 [2.2-3.8] vs. 3.0 [2.1-3.8], P=0.716). Compared to the suture-group, significantly more posterior hiatal

sutures were placed (2.5 [2.3 – 2.7] *vs.* 2.8 [2.5 – 3.1], *P*=0.038) in the mesh-group, and more patients underwent a 270 degree posterior partial fundoplication (6 [16.7%] *vs.* 30 [83.3%], *P*<0.001). There were no differences in total blood loss or the incidence of intraoperative complications between the two groups (Table 2). Total hospital stay (days) did not differ between the two groups (2.1 [1.1 – 3.1] *vs.* 2.0 [1.1 – 2.8], *P*=0.994), nor the incidence of postoperative complications (3 [8.3%] *vs.* 5 [14.3%], *P*=0.478).

TABLE 2. Intraoperative details.

	Sutures	TiMesh®
Intrathoracic stomach		
25-49%	17 (47.3%)	14 (30.0%)
50-74%	3 (8.3%)	6 (17.1%)
75-99%	10 (27.8%)	9 (25.7%)
100%	6 (16.7%)	6 (17.1%)
Operating time (min)	61.3 (54.7-67.9)	69.3 (58.2-80.4)
Blood loss (cc)	26.0 (1.7-50.3)	18.9 (5.4-32.5)
Hiatal repair		
Anterior	-	-
Posterior	1 (2.8%)	2 (5.6%)
Anterior + posterior	35 (97.2%)	34 (94.4%)
Number of hiatal sutures		
Anterior	1.4 (1.1-1.7)	1.4 (1.2-1.7)
Posterior	2.5 (2.3-2.7)	2.8 (2.5-3.1)*
Fundoplication type		
180° anterior partial	30 (83.3%)	6 (16.7%)
270° posterior partial	6 (16.7%)	30 (83.3%)†
Difficulty procedure (0-10)	3.0 (2.2-3.8)	3.0 (2.1-3.8)
Intraoperative complication		
Bleeding	3 (8.3%)	2 (5.6%)
Perforation	-	-
Total hospital stay (days)	2.1 (1.1 – 3.1)	2.0 (1.1 – 2.8)
Postoperative complication		
Cardiac	-	2 (5.6%)
Pulmonary	3 (8.3%)	1 (2.8%)
Postoperative vomiting	-	1 (2.8%)
Urinary	-	1 (2.8%)

All data are expressed as n (%) or mean (95% confidence interval);
ASA: American Society of Anaesthesiologists physical status classification;
* *P*<0.038 *vs.* sutures-group; † *P*<0.001 *vs.* sutures-group;

Objective outcome

Outcome of routine six months postoperative barium swallow and upper gastrointestinal endoscopy are summarized in Table 3. Routine six-months postoperative barium swallow radiology demonstrated a recurrent hiatal hernia in 10 patients, with no significant differences between two groups (4 [11.4%] *vs.* 6 [19.4%], *P*=0.370).

Routine upper gastrointestinal endoscopy demonstrated a recurrent hiatal hernia of any size in five patients (14.3%) in the sutures-group and in five patients (17.2%) in the mesh-group (0.746). When only hiatal hernias of two or more cm's were regarded as a true recurrence, there was still no significant difference in incidence between the two groups (5 [14.3%] *vs.* 4 [17.2%], *P*=1.000).

Seven (19.4%) and 8 patients (25%) of the 36 and 32 patients who underwent either a routine postoperative barium swallow and/or upper gastrointestinal endoscopy after suture-repair versus mesh-repair demonstrated a recurrent hiatal hernia of any size on at least one postoperative study (*P*=0.581). Patients with a recurrent hernia diagnosed through either barium swallow or endoscopy demonstrated a significant higher heartburn score at six months (2.1 [0.5 – 3.7] *vs.* 0.2 [0.0-0.3], *P*<0.001), with no differences in the use of acid suppressing medication and comparable chest pain scores (*P*=0.180) and dysphagia scores (*P*=0.515).

Subanalysis of patients intraoperatively diagnosed with a large hernia (>50% intrathoracic stomach, n=40) did not significantly alter the previously described results, with three patients in both groups diagnosed with a recurrent hernia using barium swallow radiology (3 [15.8%] vs. 3 [16.7%], P=0.942), and three patients in both groups with an endoscopically diagnosed recurrence (16.7% vs. 17.6%, P=0.939).

Preoperatively, 12 patients (17.9%) demonstrated signs of esophagitis and 8 (11.9%) were diagnosed with Barrett's esophagus, with no differences between the two groups (*P*=0.954 and *P*=0.709 respectively). Six months after surgery, there was no significant difference in the prevalence or severity of esophagitis or Barrett's esophagus between the two groups (*P*=0.476 and *P*=0.377). Of the 12 patients with preoperatively diagnosed esophagitis, 10 (83.3%) demonstrated complete resolution after surgery.

Symptomatic outcome

There were no differences in prevalence of preoperative symptoms between the sutures- and mesh-group (Table 4), with comparable preoperative heartburn scores (1.5 *vs*. 1.7, *P*=0.435), chest pain scores (2.9 *vs.* 3.8, *P*=0.211), dysphagia scores for liquids (1.2 *vs.* 1.3, *P*=0.720) and solids (2.7 *vs.* 3.1, *P*=0.405), or Dakkak-score (13.7 *vs.* 21.6, *P*=0.276).

TABLE 3. Objective outcome 6 months following hiatal hernia repair using sutures and TiMesh®.

	Sutures (n=36)	TiMesh® (n=36)	*P*-value
Barium swallow			
Studied	35 (97.2%)	31 (86.1%)	0.199
Recurrent hernia	4 (11.4%)	6 (19.4%)	0.370
Upper gastrointestinal Endoscopy			
Studied	35 (97.2%)	29 (80.6%)	0.055
Recurrent hernia	5 (14.3%)	5 (17.2%)	0.746
Recurrent hernia ≥2 cm	5 (14.3%)	4 (14.3%)	1.000
Esophagitis*	7 (19.4%)	8 (27.9%)	0.476
Grade A	2 (5.7%)	3 (10.3%)	
Grade B	5 (15.6%)	2 (6.9%)	
Grade C	-	3 (10.3%)	
Grade D	-	-	
Barretts'esophagus	7 (20.0%)	3 (11.5%)	0.377
Either barium or endoscopy performed	36 (100%)	32 (88.9%)	0.115
Recurrent hernia on either barium or endoscopy	7 (19.4%)	8 (25.0%)	0.581

All data are expressed as n (%);
*Based on the Los Angeles Classification of Gastroesophageal Reflux Disease

During one-year follow-up, there were more patients reporting postprandial fullness and inability to belch six months after suture repair (60.0% and 25.7% respectively) compared to mesh-repair (35.3% and 5.9%; *P*=0.040 and *P*=0.024 respectively). At one year, more patients reported inability to belch after suturing (26.5%) compared to mesh-repair (5.9%, *P*=5.9%; Table 4). At all postoperative intervals, there were no differences in heartburn or chest pain, with similar heartburn (1.3 *vs.* 0.7, *P*=0.192) and chest pain scores (1.5 *vs.* 1.3, *P*=0.945; Figure 2) one year after hernia repair. Additionally, there was no difference in the usage of acid suppressing medication between the groups, with 13 (41.9%) and 10 (30.3%) patients reporting the daily use of acid suppressing medication (*P*=0.332). There was no difference in dysphagia at all postoperative intervals, with equal Dakkak scores at one year (4.2 *vs.* 5.8, *P*=0.239; Table 5 and Figure 3). Furthermore, there were no differences in satisfaction score, Visick scores or the number of patients reporting they considered their choice of having surgery to be correct (Table 6), with 87.9% and 93.9% (*P*=0.672) of the patients reporting they would opt for surgery again. One year after suture-repair and mesh-repair, a mean satisfaction score of 8.0 (7.0-8.9) and 8.4 (7.6-9.3; *P*=0.401) respectively was reported.

Surgical reintervention

Three patients (4.2%) underwent recurrent surgery 9 months (n=1) and 11 months (n=2) after primary hernia repair (n=2) and sutures reinforced with mesh (n=1), with no difference between the groups (2 [5.6%] *vs.* 1 [2.8%], *P*=1.000). In the two patients who were primarily treated with sutures alone, recurrent surgery entailed a redo hiatoplasty with augmentation using a non-absorbable mesh, and conversion of the 180 degree anterior fundoplication into a 360 degree total fundoplication in one of the patients. In the patient who primarily underwent hiatal hernia repair with mesh augmentation, relaparoscopy demonstrated a recurrent lateroanterior hiatal hernia with an intact mesh, which was left in place, followed by a redo cruroplasty both posteriorly and anteriorly, and conversion of the 180 degree anterior fundoplication into a 360 degree total fundoplication. The three patients who underwent recurrent surgery demonstrated a significantly higher heartburn score at six months compared to those who did not require a redo operation (4.7 [-5.4 – 14.7] vs. 0.3 [0.1 – 0.6], P=0.019), with no differences in chest pain or dysphagia at six months.

TABLE 4. Pre- and postoperative presence of symptoms during one-year follow-up.

	Preoperative		3-months postoperative		6-months postoperative		1-year postoperative	
	Sutures	TiMesh®	Sutures	TiMesh®	Sutures	TiMesh®	Sutures	TiMesh®
Heartburn	44.4%	38.9%	8.3%	6.1%	8.6%	8.8%	14.7%	11.8%
Chest pain	63.9%	69.4%	22.2%	15.2%	20.0%	17.6%	17.6%	23.5%
Epigastric pain	38.9%	58.3%	27.87%	24.2%	25.7%	8.8%	14.7%	14.7%
Regurgitation	61.6%	44.4%	19.4%	12.1%	14.3%	26.5%	11.8%	11.8%
Dysphagia	50.0%	52.8%	25.0%	12.1%	25.7%	20.6%	14.7%	23.5%
Pain during swallowing	11.1%	16.7%	5.6%	3.0%	2.9%	2.9%	2.9%	0.0%
Postprandial fullness	36.1%	38.9%	44.4%	54.5%	60.0%*	35.3%	41.2%	32.4%
Inability to belch	-	-	22.2%	18.2%	25.7%†	5.9%	26.5%‡	5.9%
Gas bloating	-	-	33.3%	24.2%	31.4%	20.6%	14.7%	26.5%
Anorexia	25%	22%	2.8%	0.0%	0.0%	0.0%	2.9%	2.9%
Nausea	47.2%	27.8%	11.1%	18.2%	22.9%	14.7%	11.8%	14.7%
Vomiting	44.4%	30.6%	13.9%	3.0%	8.6%	5.9%	8.8%	0.0%
Nocturnal cough	16.7%	16.7%	5.6%	15.2%	2.9%	11.8%	11.8%	8.8%
Increased flatulence	-	-	52.8%	57.6%	40.0%	45.5%	38.2%	52.9%
Diarrhea	-	-	11.1%	21.2%	11.4%	18.2%	11.8%	26.5%

All data are expressed as percentage of patients who responded to questionnaire with 'Yes');
* P=0.040 versus TiMesh-group; † P=0.024 versus TiMesh-group; ‡ P=0.021 *vs.* Mesh-group;

TABLE 5. Pre- and postoperative presence and severity of dysphagia.

	Preoperative		3-mo postoperative		6-mo postoperative		1-year postoperative	
	Sutures	TiMesh®	Sutures	TiMesh®	Sutures	TiMesh®	Sutures	TiMesh®
Visual analog scale dysphagia								
Liquids								
Mean score	1.2	1.3	1.3	0.8	1.0	0.9	0.6	0.9
95% C.I.	(0.5 – 1.9)	(0.6 – 2.0)	(0.5 – 2.1)	(0.1 – 1.4)	(0.3 – 1.7)	(0.3 – 1.6)	(0.0 – 1.2)	(0.2 – 1.5)
Solids								
Mean score	2.7	3.1	2.1	1.5	1.6	1.4	1.1	1.4
95% C.I.	(1.8 – 3.6)	(2.2 – 4.1)	(1.0 – 3.1)	(0.8 – 2.2)	(0.7 – 2.5)	(0.5 – 2.2)	(0.2 – 1.9)	(0.7 – 2.2)
Dakkak dysphagia score (0-45)								
Mean	13.7	21.6	14.7	6.1	6.4	5.3	4.2	5.8
95% C.I.	(9.2 – 18.2)	(11.5 – 31.7)	(-1.7 – 31.4)	(3.5 – 8.7)	(3.5 – 9.4)	(2.7 – 8.0)	(1.2 – 7.2)	(3.0 – 8.6)

All data are expressed as mean (95% confidence interval) or n (% of patients who responded to questionnaire);

TABLE 6. Pre- and postoperative Visick-score, satisfaction score and number of patients considering their choice to undergo surgery to be correct.

	Preoperative		3-mo postoperative	
	Sutures	TiMesh®	Sutures	TiMesh®
Visick-score				
I	-	-	9 (29.0%)	12 (38.7%)
II	5 (15.6%)	1 (3.0%)	10 (32.3%)	9 (29.0%)
III	7 (21.9%)	11 (33.3%)	3 (9.7%)	4 (12.9%)
IV	20 (62.5%)	21 (63.6%)	9 (29.0%)	6 (19.4%)
Satisfaction score				
Mean score	-	-	8.0	8.4
95% C.I.	-	-	(7.1 - 8.9)	(7.6 - 9.1)
Patients opting for surgery again	-	-	31 (88.6%)	32 (32 (97%)

All data are expressed as mean (95% confidence interval) or n (% of patients who responded to questionnaire)

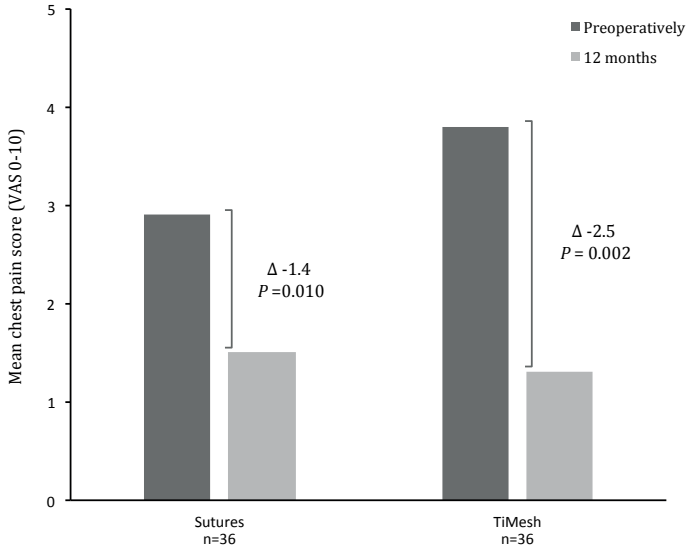

FIGURE 2. Mean chest pain score (VAS 0-10) preoperatively and 12 months after sutures versus TiMesh®.

	6-mo postoperative		1-year postoperative	
	Sutures	TiMesh®	Sutures	TiMesh®
	10 (31.3%)	11 (34.4%)	10 (31.3%)	14 (48.3%)
	10 (31.3%)	14 (43.8%)	14 (43.8%)	11 (37.9%)
	4 (12.5%)	5 (15.6%)	3 (9.4%)	2 (6.9%)
	8 (25.0%)	2 (6.3%)	5 (15.6%)	2 (6.9%)
	7.6	8.7	8.0	8.4
	(6.5 - 8.7)	(8.2 - 9.2)	(7.0 - 8.9)	(7.6 - 9.3)
	28 (80.0%)	(31 (96.9%)	29 (87.9%)	31 (93.9%)

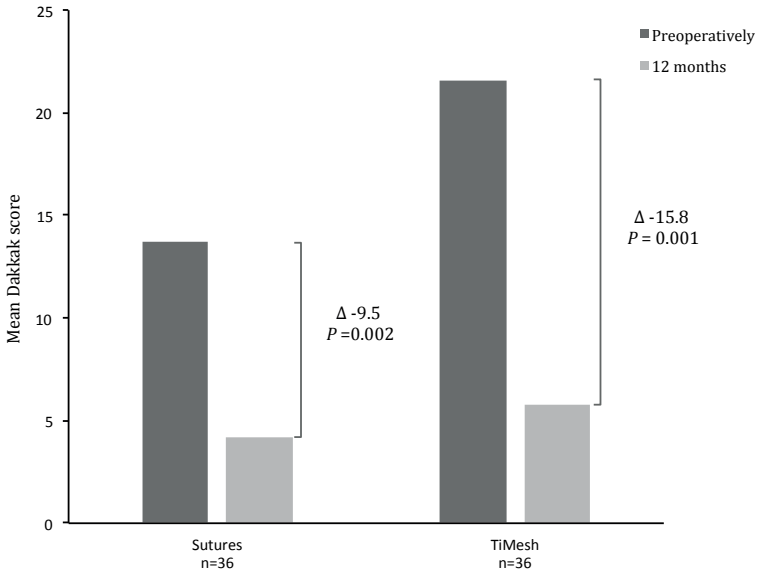

FIGURE 3. Mean Dakkak dysphagia score (0-45) preoperatively and 12 months after sutures versus TiMesh®.

Discussion

In the present study, routine augmentation of primary hiatal hernia repair using a non-absorbable mesh did not result in improved recurrence rates or superior symptomatic outcome up to one year after surgery compared to repair using non-absorbable sutures alone. Furthermore, there were no significant differences in satisfaction with both types of procedure.

Our results are largely in line with the findings of Watson et al, reporting no significant difference in one-year recurrence rate between patients undergoing hiatal hernia repair using sutures only versus sutures reinforced with a non-absorbable mesh (23.1% *vs.* 12.8%).[10] Furthermore, the group of Watson also did not find any clinically relevant differences in symptomatic outcome between the two procedures, with comparable satisfaction rates as those we describe.

We found no significant difference in total operating time between the suture- and the mesh-group, with comparable difficulty scores reported by the three participating surgeons. Furthermore, the incidence of intraoperative complications did not differ between the two groups, with an overall intraoperative morbidity rate of 6.9%, including minor complications only. This is in line with a recent meta-analysis of Memon et al, in which the previously mentioned trials of Frantzides et al, Granderath et al, Oelschlager et al, and Watson et al were included.[3] After pooling of data, with a total number of included patients of 406 (suture n=186 *vs.* prosthesis n=220), there were no significant differences in recurrence of hiatal hernia or wrap migration, total operating time or complication rate. Only the pooled effect size for reoperation rate favored the prosthesis group.[3]

Although the reported incidence appears to be very low, there are reports of mesh-related complications, with mesh erosion being the most serious type of complication.[19] Since many cases of erosion go unreported, the true incidence still remains unknown. In the present study, no mesh-related complications occurred during one-year follow-up. In all hiatal hernia repairs reinforced with mesh, special care was taken to avoid contact of the mesh with the esophagus, by placing the mesh in a u-shaped non-circumferential fashion posteriorly of the esophagus. However, there appears to be a paucity of studies reporting long-term follow-up of patients who underwent mesh-repair with special focus on these mesh-related complications. Recently, our group published a retrospective cohort-analysis comparing primary repair using sutures versus sutures reinforced with a non-absorbable mesh (n=62).[20] During a mean follow-up period of 39.3 months, there were no mesh-related complications. However, long-term follow-up studies of patients undergoing hiatal hernia repair with mesh-reinforcement remain necessary to determine the true safety of the application of these synthetics.

Depending on the type of postoperative study used, recurrence rates ranged between 13.6% and 20.8%, with no significant differences between the sutures- and mesh-group. The reported recurrence rates reported in the present study are in line with the previous

mentioned study of Watson et al.[10] In the trial published by Frantzides in 2002[7], in which patients were randomized for repair using non-absorbable sutures versus sutures reinforced with a PTFE mesh, a recurrence rate of 0% was found 2.5 years after PTFE mesh, compared to 22% following repair using sutures alone, which is a significant difference compared with our findings and those described by Watson et al. However, follow-up beyond 2.5 years was never published. Oelschlager et al. reported a 6 months recurrence rate of 9% versus 24% following repair using an absorbable mesh versus sutures only.8 However, 2.5 years after surgery, recurrence rates were comparable high for both groups (59% versus 54%).[9] This finding, as well as the results of Watson et al. are used to justify that non-absorbable mesh is superior to absorbable mesh with regards to recurrence rates, which has led to the current study design.

Patients in whom a recurrent hiatal hernia was diagnosed demonstrated a significantly higher heartburn score six months after surgery compared to patients with no objectified recurrence. This finding is in line with the findings of a recent study by Wang et al, in which patients with an initially asymptomatic recurrent hiatal hernia were prospectively followed, and developed significantly higher heartburn scores and more frequently reinstated PPI-use.[21] However, overall symptomatic outcomes, including satisfaction, remained high with low rates of recurrent surgery, as is the case in the cohort of patients we describe.

A possible limitation of our trial is the fact that not all patients underwent routine 6-months barium swallow radiology and upper gastrointestinal endoscopy, with the associated risk of a type II error. However, 68 of the included 72 patients (94.4%) underwent at least one of both types of objective study, and one year symptomatic outcome is provided for 94.4% of the patients. There was a significant difference in the type of partial fundoplication performed within each group, with the majority of patients within the mesh-group undergoing 270 degree posterior fundoplication and 180 degree anterior partial fundoplication being the most frequently performed type of fundoplication in the sutures-group. One could argue that this was a confounding factor when comparing symptomatic outcome between the sutures- and mesh-group. However, we recently published the results of a randomized clinical trial comparing outcome of 270 degree posterior and 180 degree anterior partial fundoplication for the treatment of gastro-oesophageal reflux disease (GORD), in which there were no differences in symptomatic nor objective reflux control or dysphagia between the two procedures up to 12 months after surgery.[22] Therefore, it is unlikely that this has influenced the outcome of the present trial. In the present study, all patients diagnosed with a hiatal hernia of more than 25% intrathoracic stomach were considered eligible for inclusion. One could assume that the benefits of mesh repair, enabling a tension-free hernia repair, apply especially for the larger hiatal hernias. However, subanalysis including only patients with a hernia with at least 50% intrathoracic stomach demonstrated equal recurrence rates between the sutures- and mesh-group. Furthermore, Watson et al randomized patients with a hiatal hernia with at least 50% of intrathoracic stomach and also did not demonstrate any difference in

recurrent hiatal hernia nor symptomatic outcome between patients who underwent repair using sutures alone versus mesh repair.[10]

In conclusion, this randomized clinical trial demonstrates that crural reinforcement using non-absorbable mesh for hiatal hernia results in equal recurrence rates and comparable symptomatic outcome at one year compared to repair using sutures alone. Long-term follow-up of this trial will need to demonstrate whether these findings are sustained, and will help determining the true incidence of mesh-related complications.

Acknowledgments

none

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Chapter 8

Laparoscopic hiatal hernia repair in the elderly patient

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Abstract

Background: Hiatal hernias (HH) are more common among elderly patients, with an increase in incidence with advancing age. Elderly patients frequently suffer from comorbidity, causing them to have an increased risk of perioperative mortality and morbidity. The aim of this study is to assess the safety of this procedure within elderly patients.

Methods: We performed a retrospective analysis of all patients with HH operated between July 2009 and May 2015 at two hospitals in the Netherlands specialized in antireflux surgery and HH repair. Mortality rates and short- and long-term morbidity rates were compared between patients aged under 70 years and aged over 70 years.

Results: A total of 204 consecutive patients underwent laparoscopic HH repair at our institutions, of whom 121 were aged under 70 years and 83 were aged over 70 years. There was no mortality intraoperatively, nor during 30-days follow-up. Intraoperative complications occurred in 7 patients aged 70 years and over, with no significant differences compared to the patients aged under 70. The 30-day morbidity rate did not significantly differ between the age groups, with an overall postoperative complication rate of 9.3%. Only length of stay (LOS) was significantly longer in the elderly patients. Performing univariate analysis, only the occurrence of intraoperative complications was associated with 30-day morbidity.

Conclusion: In the present study, age was not associated with increased 30-day morbidity or mortality following HH repair. Therefore, in carefully selected patients, age should not be used as an argument to withhold laparoscopic HH repair.

Introduction

Hiatal hernias (HH) can be classified into the sliding type (type I), being the most frequent, the 'true' paraesophageal type (type II), which can be further graded according to the severity of the hernia, and the mixed type (type III), consisting of both a sliding and paraesophageal component. Type IV HH's are characterized by the presence of an upside-down-stomach and possibly omentum or colon. Type IV hernias pose a challenge to repair due to the large hernial sac, with increased risk of perforation and insufficient tissue for adequate hiatal closure following dissection.[1, 2] HH may cause a variety of symptoms, including obstruction with dysphagia, chest pain, dyspnea, and anemia due to gastric bleeding caused by Cameron lesions, which can all significantly influence quality of life.

Hiatal hernia, and especially paraesophageal hernias (PEH), are more common among elderly patients, with an increase in incidence with advancing age.[3, 4] With the global increase in life expectancy, it can be expected that the laparoscopic surgeon will more frequently encounter elderly patients suffering from a HH.[5]

Elderly patients frequently suffer from age-related comorbidities, reflected by an increased American Society of Anesthesiologists (ASA) score. Compared to younger patients, elderly can therefore be considered to be more at risk for perioperative complications.

Over the last decades, open repair of HH has been replaced by the laparoscopic approach.[6-11] Although laparoscopy has been shown to be safe in elderly patients, previous studies have reported increased age, extensive comorbidity, and ASA score to be associated with increased morbidity following laparoscopic HH repair.[12, 13]

Based upon our own experience, we hypothesized that there was no difference in outcome following HH repair between elderly and younger patients. Therefore, the aim of the present study was to evaluate the outcome in elderly patients in our centers, with special emphasis on the association between age and 30-day morbidity.

Materials and methods

Design and participants

All adult patients who underwent HH repair between July 2009 and July 2015 in two large teaching hospitals in the Netherlands were analyzed. Patients were operated by two gastrointestinal surgeons (EJH,VBN) specialized in antireflux surgery and HH repair, and who each have performed more than 500 HH repairs and antireflux procedure. Patients suffering from a type I HH, or who had previously undergone esophageal or gastric surgery were excluded. Details of each patient were retrospectively collected. Based on previous studies, patients were grouped according to age under 70 years and 70 years and older.[13] Comorbidity was grouped into categories that were separately analyzed. Cardiovascular disease included a history of hypertension, coronary artery disease, arrhythmia, cerebrovascular accident, and peripheral vascular disease. Diabetes mellitus included both type I and type II diabetes. The presence of chronic obstructive pulmonary disease (COPD) included all types of GOLD-classifications.

Diagnosis

A HH was diagnosed based upon symptoms suggestive of HH confirmed by endoscopy, barium meal examination and/or a computed tomography (CT) scan.

Operative technique

Surgical repair compromised full dissection of the hernial sac from the mediastinum and reduction of the sac's content into the abdominal cavity, while carefully avoiding vagal or pleural injury. The crural defect was repaired using posterior non-absorbable hiatal sutures, supplemented by anterior sutures if necessary. A currently running trial in our institutions compares HH repair using non-absorbable sutures versus sutures reinforced with non-absorbable mesh (Timesh®, PFM Medical, Köln, Germany). Therefore, participating patients could have been randomized for sutures reinforced with mesh. Mesh repair was also used when it was suspected that there was not enough tissue left to adequately approximate the crura following dissection. Mesh repair involved a sutured posterior hiatal repair followed by placement of a U-shaped piece of non-absorbable mesh (Timesh®) over the sutures and the hiatal pillars, but not circumferential. The mesh was anchored with sutures or absorbable tackers to reinforce the repair. Because of the risk of de novo esophageal acid exposure, all patients underwent an additional partial fundoplication consisting of either a 270 degrees posterior (Toupet) or 180 degrees anterior fundoplication, based upon the surgeon's preference.[14]

Postoperative care

Postoperative admission to the intensive care unit (ICU) was only performed if clinically necessary. Patients were allowed oral fluids directly, and soft solid food the next day. Early discharge from the hospital was usual (day 1 or 2 postoperatively).

Outcome

The primary outcome was 30-day morbidity, counting all postoperative events that differed from the standard postoperative course, including bleeding requiring transfusion or re-intervention, esophageal obstruction or stenosis requiring endoscopy, cardiac events, pneumonia, pneumothorax, pulmonary embolism, deep venous thrombosis, surgical site infection (SSI) and urinary tract infection. Intraoperative morbidity, 30-day mortality, length of hospital stay (LOS) and blood loss were secondary outcomes. Follow-up data were based upon chart review regarding routine postoperative outpatient visits or recurrent visits to the emergency department (ED).

Statistical analysis

Statistical analysis was performed after consulting a statistician. The statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was used. Values are presented as numbers (with prevalence) or median with range. The Chi square test, or Fisher's exact test where necessary, were used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. Using uni- and multivariate analysis, the association between 30-day morbidity and different risk factors were analyzed. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

Between July 2009 and July 2015, 204 consecutive patients underwent HH repair in our institutions. There were 155 females (76%) and 49 males (24%). Of all patients, mean age at time of surgery was 66.2±11years. One hundred and twenty-one patients were under the age of 70, with a mean age of 59.4±9 years, and 83 were aged 70 years and over, with a mean age of 76.0±5.0. Mean follow-up of all patients was 26±16 months. In 28% of the patients, the primary indication for surgery was the presence of obstructive symptoms, in 24% chest pain, in 22% reflux or regurgitation, in 18% coughing or dyspnea, and in 3% anemia based on Cameron lesions. The majority of patients (72%) suffered from a mixed-type hernia (type III).

All demographics are summarized in table 1. There were no significant differences in sex, BMI, the number of patients actively smoking, suffering from COPD, diabetes mellitus (DM) or using systemic corticosteroids between the two groups. Fifty percent had a history of abdominal surgery. Patients suffering from cardiovascular disease were significantly more prevalent in the over-70-group compared to the under-70-group (p=<0.001), as were the patients with ASA-score III (p=0.002). There was no significant difference in the hernia types or size between the two groups (p=0.36 and 0.70 resp).

Fifteen patients (7.4%) required non-elective surgery, of whom eight were aged under 70 and seven were aged 70 years and older (p=0.62). All patients presented with symptoms of obstruction with persistent vomiting and nausea. Of the patients undergoing non-elective surgery, five (2.4%) required urgent surgery (within 48 hours) because of the suspicion of strangulation or torsion of the intrathoracic stomach, while the other patients underwent semi-urgent surgery due to persistent obstruction and vomiting. All patients except for one underwent decompression through gastroscopy with duodenal tube placement prior to urgent or semi-urgent surgery.

Only two patients, both aged under 70, underwent primary open repair. All other patients underwent laparoscopic repair, in whom no conversions to open surgery had to be performed. The use of non-absorbable mesh did not significantly differ between the groups. A 360 degrees Nissen fundoplication was performed in one patient (0.5%), a posterior 270 degrees Toupet fundoplication in 79 patients (38%), and a 180 degrees anterior fundoplication in 123 patients (60%).

TABLE 1. Baseline characteristics of study groups based on age

	Age <70 years (n=121) n (%)	Age ≥70 years (n=83) n (%)	*p*-value
Men	32 (26)	17 (20)	0.39
BMI (mean±SD)	29±4.8	28±4.4	0.43
Active smoker	10 (8)	5 (7)	0.67
COPD	19 (16)	12 (14)	0.71
Cardiovascular disease	42 (35)	56 (67)	<0.001
ASA-score*			
III	13 (11)	23 (28)	0.002
I+II	108 (89)	59 (71)	
Previous abdominal surgery	57 (47)	43 (52)	0.55
Non-elective surgery	8 (7)	7 (8)	0.62
Hernia type			0.36
II	12 (10)	5 (6)	
III	88 (73)	58 (70)	
IV	21 (17)	20 (24)	
Intrathoracic stomach*			0.70
25-49%	24 (20)	15 (18)	
50-75%	44 (36)	27 (33)	
76-100%	48 (40)	41(49)	
Approach			
laparoscopic	119 (98)	83 (100)	0.17
open	2 (2)	0	
Conversion	0	0	
Mesh	48 (40)	27 (33)	0.33

BMI: body mass index; SD: standard deviation; COPD: chronic obstructive pulmonary disease; *:N missing=1; ^: N missing=5

Outcome

There were no intraoperative mortalities. The 30-day mortality rate was 0% for the entire group. Only one patient (1%) in the over-70-group died more than three months following surgery. This included an out-of-hospital death secondary to pre-existing heart failure, with subsequent reduced intake, eventually followed by palliation and death (see table 2).

There was no significant difference in mean operating time and occurrence of intra-operative complications (table 2). Intraoperative complications (5.9%) consisted of perforation of the stomach (n=1), bleeding (n=2), atrial fibrillation (AF) de novo (n=4), capsular tear of the spleen (n=2), pleural tears (n=2), and perforation of the esophagus (n=1). Blood loss did significantly differ, with relatively more blood loss in the under-70-group (p=0.039).

Postoperative complications occurred in 19 patients (9.3%). The 30-day morbidity did not significantly differ between the two groups (8% *vs*. 11%, p=0.53). Postoperative complications consisted of mediastinal bleeding requiring surgery (n=1), obstruction (n=3), esophageal stenosis requiring dilatation (n=1), pneumonia (n=4), atelectasis (n=2), pulmonary edema (n=2), pulmonary embolus (n=1), cardiac decompensation (n=1), urinary tract infection (n=2), AF de novo (n=1) and gastro-enteritis (n=1). The LOS was significantly longer for older patients compared to the younger patients (p=0.007) (table 2).

To compensate for possible bias caused by categorizing patients based on age, we re-analyzed the above mentioned outcome variables using 75 years as a cut-off age, after which there were still no significant differences in outcome between elderly and younger patients apart from a significantly longer LOS for the patients aged 75 and older (see table 3). Furthermore, we analyzed the relation between age as a continues variable and 30-morbidity using receiver operating characteristics (ROC) curve analysis, demonstrating low sensitivity and specificity of age as a risk factor for 30-day morbidity (figure 1).

Risk factors associated with morbidity

Performing univariate analysis, only the occurrence of intra-operative complications was strongly associated with 30-day morbidity (table 4). Multivariate analysis could not influence these relations.

TABLE 2. Outcome in patients aged under 70 and over 70

	Age <70 years (n=121)	Age ≥70 years (n=83)	p-value
	n (%)	n (%)	
30-day mortality	0 (0)	0 (0)	1.00
Total mortality	0 (0)	1 (1)	0.40
Intraoperative complications	5 (4)	7 (8)	0.20
Operative time, min. (median, range)*	80 [30-240]	90 [30-213]	0.24
Blood loss^			0.039
0-30cc	76 (63)	67 (81)	
31-100cc	24 (19)	8 (10)	
101-200cc	10 (8)	4 (5)	
201-500cc	5 (4)	0	
>1000 cc	1 (1)	0	
30-day morbidity	10 (8)	9 (10)	0.53
Hospital stay, days [x] (median, range)	2.0 [0-9]	2.0 [1-38]	0.007
Recurrent surgery	3 (2)	3 (4)	0.69

*: N missing=14; ^: N missing=9; [x]: N missing=18

TABLE 3. Outcome in patients aged under 75 and over 75

	Age <75 years (n=159) n (%)	Age ≥75 years (n=45) n (%)	p-value
30-day mortality	0 (0)	0 (0)	1.00
Total mortality	0 (0)	1 (2)	0.22
Intraoperative complications	7 (4)	5 (11)	0.10
Operative time, min. (median, range)*	90 [35-240]	90 [30-150]	0.75
Blood loss^			0.48
0-30cc	108 (68)	35 (83)	
31-100cc	27 (17)	5 (12)	
101-200cc	12 (8)	2 (5)	
201-500	5 (3)	0	
>1000cc	1 (1)	0	
30-day morbidity	15 (9)	4 (9)	0.91
Hospital stay, days^{x} (median, range)	2 (0-13)	2 (1-38)	0.004
Recurrent surgery	3 (2)	3 (7)	0.56

*: N missing=14; ^: N missing=7; ^{x}: N missing=18

TABLE 4. Univariate analysis of risk factors associated with 30-day morbidity

	Univariate analysis OR (95% C.I.)	p-value
Gender (M *vs.* F)	1.3 (0.4-4.0)	0.75
Age ≥70	1.3 (0.5-3.2)	0.54
BMI ≥30	1.7 (0.6-4.3)	0.41
Active smoking	1.4 (0.3-6.8)	0.64
COPD	1.4 (0.4-4.5)	0.96
ASA classification III	2.4 (0.9-6.7)	0.09
Previous abdominal surgery	1.0 (0.4-2.5)	0.86
Intra-operative complications	13 (3.7-45.6)	<0.001

BMI: body mass index; COPD: chronic obstructive pulmonary disease

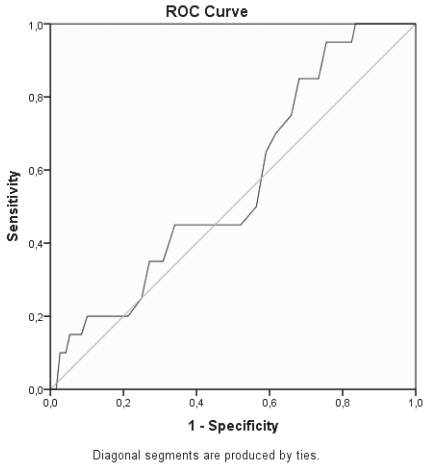

FIGURE 1. Receiver-operating characteristics (ROC) curve of the predictive value of age for 30-day morbidity

Discussion

We found no significant differences in mortality and morbidity rates in elderly patients compared to the younger patients. This was despite the fact that the elderly group included more patients suffering from cardiovascular disease and an ASA score of III, being the principal demographic differences between these two groups in our cohort. There was also no increased rate of intra-operative morbidity or conversions in the elderly patients, despite the fact that half of them had a history of abdominal surgery.

While some studies reported equally outcome of foregut surgery in elderly compared to younger patients, others have shown worse outcome.[11, 13, 15-17] After analyzing 19.388 patients undergoing antireflux surgery or HH repair using the National Surgical Quality Improvement Program (NSQIP) database, Molena et al. found advanced age to be associated with increased rates of 30-day mortality and morbidity and LOS.[18] They found higher complication and mortality rates among all patients aged over 70, and report longer mean procedure times compared to our data (≥150 min. *vs*. 90-92 min.). However, there are important differences in the case mix of our study compared to the study of Molena et al. which could explain these differences in morbidity rate and operating time. The population of Molena et al. includes more patients with ASA III-IV (46.4% *vs*. 28.0%), a BMI≥30 (48.5% *vs*. 28.9%), and more patients operated through an open approach (24.6% *vs*. 0%) in the over-70-group. Furthermore, no differentiation can be made between patients operated in low-volume hospitals, with less experience in HH repair, and those who underwent surgery in specialized centers, such as our hospitals (approximately 80 procedures per year).

Larusson et al. specifically focused on the outcome of laparoscopic HH repair in elderly, based upon a national database.[11] In their analysis, the patients aged over 70 showed a significant higher postoperative morbidity of 24.4%, compared to the 10.1% found in the younger patients. Both advanced age and ASA-score significantly influenced mortality and morbidity rates following surgery. They also report a significant higher postoperative morbidity rate in the over-70-group compared to our results (24.4% *vs*. 10%), possibly explained by the fact that their cohort of elderly patients included more patients with an ASA-score of III or IV (41.8% *vs*. 28%), and more conversions to laparotomy (4.7% *vs*. 0%).

Overall, morbidity rates following laparoscopic repair of HH in elderly patients vary among available studies, ranging from 6.7% to 24.4%, which is mainly because of the heterogeneity of included patients, reflected by differences in ASA scores, urgent versus elective surgery and conversion rates between studies.[12, 13, 15, 17]

The only perioperative variable that significantly differed between the two age groups within our cohort was the mean LOS (2.0 days versus 3.6 days), most likely caused by the domestic setting of elderly patients. We found no association between age and increased mortality or morbidity rates. We believe this is mainly caused by the following principles

implemented in our current selection and treatment strategies for (elderly) patients suffering from HH.

First of all, urgent surgery should be avoided as much as possible. Only in case of acute intestinal obstruction or strangulation, with the risk of ischemic necrosis, urgent surgery should be performed.[19] The risk of incarceration requiring urgent surgery is estimated to be 1% among patients suffering from a HH.[20] Poulose et al. demonstrated that non-elective surgery was associated with a higher mortality rate and longer LOS of 16% and 14.3 days respectively, compared to elective surgery, and that non-elective surgery was the sole predictor of inpatient mortality in their study.[21] In our study, only five patients (2.4%) underwent urgent surgery, which is a significantly lower rate compared to other studies that describe higher postoperative morbidity rates.[18, 22] In case of acute presentation, decompression using endoscopy or nasogastric tube placement frequently causes a stable situation allowing elective or semi-elective surgery.[23] In patients who have been symptomatic for prolonged periods of time, with subsequent reduced dietary intake, elective or semi-elective surgery creates time to optimize the patient's nutritional status, thereby reducing the risk of postoperative events. Also, optimization of lung function through pre-operative pulmonary rehabilitation can be organized in patients suffering from COPD.

Secondly, we believe that despite a history of abdominal surgery, laparoscopy should be the primary approach.[24] Previous studies have demonstrated superiority of laparoscopic abdominal surgery in terms of morbidity, postoperative pain and LOS compared to conventional abdominal surgery in elderly patients.[25, 26] These advantages also account for laparoscopic antireflux surgery and HH repair, with lower morbidity rates and shorter LOS following the laparoscopic approach.[18, 27-29] Indeed our data show a very low overall complication rate, and despite the fact that 50% of the patients reported a history of abdominal surgery, there were no conversions to open surgery, indicating that it is legitimate to initially perform laparoscopic surgery in these patients.

Since the fundamental work of Nissen and others, dating back to 1956, concerning the surgical treatment of gastroesophageal reflux disease and HH, multiple techniques and principles concerning HH repair have been established and further developed.[24, 30-34] Based upon the currently available evidence, we believe HH repair should be performed according to the following principles: (1) complete reduction of the hernial sac, stomach and associated herniated structures with extensive dissection to optimize esophageal mobility, (2) primary closure of the crura using non-absorbable sutures and (3) performing a fundoplication following crural closure.[14, 35, 36] Extensive dissection of the hernial sac is vital for preventing recurrent HH.

There are certain limitations of the present study. Due to the retrospective design there is a potential for selection bias. Despite the fact that less than 1% of the patients referred to our two centers did not receive surgical treatment (data not shown), selection bias might have arisen from selective referral by gastroenterologists, only referring

those patients with the best physical condition. We did, however, include consecutive patients in our analysis, thereby reducing this risk of additional selection bias. Despite our relatively small sample size compared to national studies, including those using the NSQIP database, we have been able to provide a detailed follow-up of patients, with a low risk of missing data and underreporting morbidity. The fact that these nationwide databases also include low-volume hospitals could cause overestimation of the true mortality and morbidity rates of HH repair in elderly patients compared to surgery performed in high-volume centers. Careful selection of patients, balancing the risks of perioperative morbidity against functional outcome, and referral to specialized centers experienced with HH repair and antireflux surgery, could possible reduce perioperative morbidity and lead to better functional outcome in these potential high risk patients.

In the present study, age was not associated with an increased risk of postoperative mortality and morbidity following HH repair. We can therefore conclude that in a carefully selected elderly cohort of patients, being operated in specialized centers, laparoscopic HH repair is as safe as HH repair in younger patients.

Acknowledgments

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Chapter 9

Simultaneous thoraco-laparoscopic repair of giant hiatal hernias: an alternative approach

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Abstract

Laparoscopic repair of giant hiatal hernias with intrathoracic displacement of organs is recommended to relieve troublesome symptoms in patients. During this procedure, incomplete excision of the hernia sac from the mediastinum and omission of creating a 'non-tension-free position' of the cardio-esophageal junction into the abdominal cavity are associated with hiatal hernia recurrence. Giant hiatal hernias therefore often require a thoracotomy or thoracoscopy, to free dense adhesions higher up the chest. These procedures may increase the risk of perioperative morbidity due to lengthy operating times. We developed an operation procedure for giant hiatal hernia repair containing all the benefits of minimal invasive surgery, with overview of both thoracic and abdominal herniated structures. Three patients with a giant hiatal hernia were treated by a simultaneous thoraco-laparoscopic approach, which proved to be technically feasible and safe. Simultaneous thoraco-laparoscopic hernia repair can be considered a reasonable treatment option in selected cases such as type IV hernias, hernia recurrence or traumatic diaphragmatic herniation.

Introduction

Surgical repair of hiatal hernias with intrathoracic displacement of abdominal organs is recommended for relieving troublesome symptoms, such as dysphagia or dyspnea, and prevent potential life-threatening complications, including acute dilatation, perforation, or bleeding, in symptomatic patients.[1, 2]

Complete excision of the peritoneal sac from the posterior mediastinum, reduction of the herniated intra-abdominal organs, a tension-free position of the distal esophagus into the abdominal cavity, and a repair of the diaphragmatic hiatus are the principles of surgical therapy.[2]

The laparoscopic approach is currently considered to be the gold standard in hiatal hernia repair. It has demonstrated superior perioperative outcome compared to conventional surgery, with shorter hospital stay, less requirement of intensive care unit admission, lower overall complication rates and fewer 30-day readmissions.[3]

However, critics claim that the laparoscopic approach may be associated with a higher recurrence rate due to obtaining inadequate intra-abdominal esophageal length when compared to a conventional open procedure.[4] Laparoscopy is sometimes preceded by thoracotomy or thoracoscopy to obtain sufficient exposure of the thoracic part of the adhesive herniated sac.[5] A recent study showed a two-step approach for giant hiatal hernia repair in a single procedure, during which the hernia sac was dissected from thoracic structures through thoracoscopy, followed by laparoscopic completion of the procedure.[6] Although this technique enables all advantages of minimal invasive surgery, the procedure will be prolonged by two phases: the patient has to be repositioned and will require renewed sterile draping. Furthermore, during the abdominal phase, the options of intrathoracic vision or operative techniques are no longer available.

We hypothesized that a simultaneous thoraco-laparoscopic approach could reduce operating time without compromising perioperative morbidity. Through this article, we present our experience with this novel technique.

Materials and methods

The simultaneous thoraco-laparoscopic repair is performed by an experienced thoracic surgeon and laparoscopic surgeon, both accompanied by one assistant and one scrub nurse. The procedure is performed under general anesthesia with double lumen endotracheal intubation. Prophylactic antibiotic (2 grams Cefazolin intravenously) is administered at the time of anesthesia. Patient is placed in the Lloyd Davis position with reversed Trendelenburg tilt. The affected hemithorax is elevated by a pillow below the hemithorax and the ipsilateral arm is lifted. A nasogastric tube is positioned.

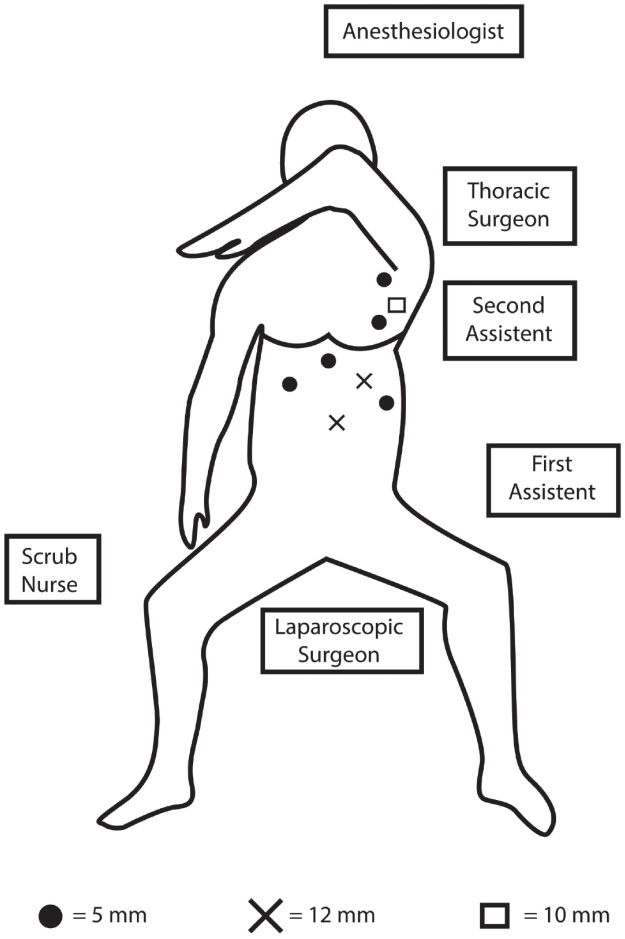

FIGURE 1. Schematic overview of positioning and operating room set-up. The patients' arm is positioned in 90 degree flexion. Trocar sizes are indicated in mm.

After sterile draping, pneumoperitoneum is established by inflating the abdomen with CO2 at 12 mmHg. A 12-mm port is placed left to the midline and a 30° telescope is introduced (figure 1). A quick diagnostic laparoscopy is performed to view the diaphragmatic defect and associated pathology. A Nathanson liver retractor (Cook Medical, Bloomington, USA) is placed via a 5mm epigastric incision. A 12-mm port is placed in the left subcostal area and two additional 5-mm ports in the left and right abdomen.

The lung at the affected side is excluded and a 10-mm port with a 30° telescope is placed at the eighth intercostal space over the mid-axillary line together with two 5-mm ports adjacent to it, in a triangular fashion (figure 1). No thoracic gas insufflation is used. The thoracic and abdominal parts of the operation are performed simultaneously and adhesions are taken down by diathermia and ultrasonic dissection (Harmonic® Ethicon, Johnson&Johnson Medical BV, New Brunswick, New Jersey, USA) to dissect the hernia sac. Step by step, the herniated organs are reduced into the abdominal cavity (figure 2). The distal part of the esophagus is mobilized via the thoracoscopic route, hereby identifying both vagal nerves. After gastric fundus mobilization by taking down (some of) the short gastric vessels, the hernia sac is further dissected and resected. The distal esophagus is encircled to enable full mobilization of the cardio-esophageal junction, thereby creating a tension-free position of the distal esophagus into the abdominal cavity.

A posterior crural repair is performed with non- absorbable sutures, with additional anterior sutures if necessary. The cruroplasty is reinforced by an additional non-absorbable mesh (Timesh®, PFM Medical, Köln, Germany) when there is not enough tissue left at the hiatus to establish a sufficient closure. An anterior fundoplication is performed routinely due to the risk of abnormal esophageal acid exposure in case of omission of an antireflux procedure[7].

After hemostasis, all ports are removed under view, a chest tube is placed and connected to a suction device (10 cm H2O suction), the skin is closed with absorbable sutures, and the nasogastric tube removed. Postoperatively, the patients are observed at the post anesthesia care unit and allowed to have oral fluids directly and a soft diet the following day. The chest tube is removed on postoperative day two 2 according to hospital protocol.

All three patients were informed and all agreed on publication of their data in this article.

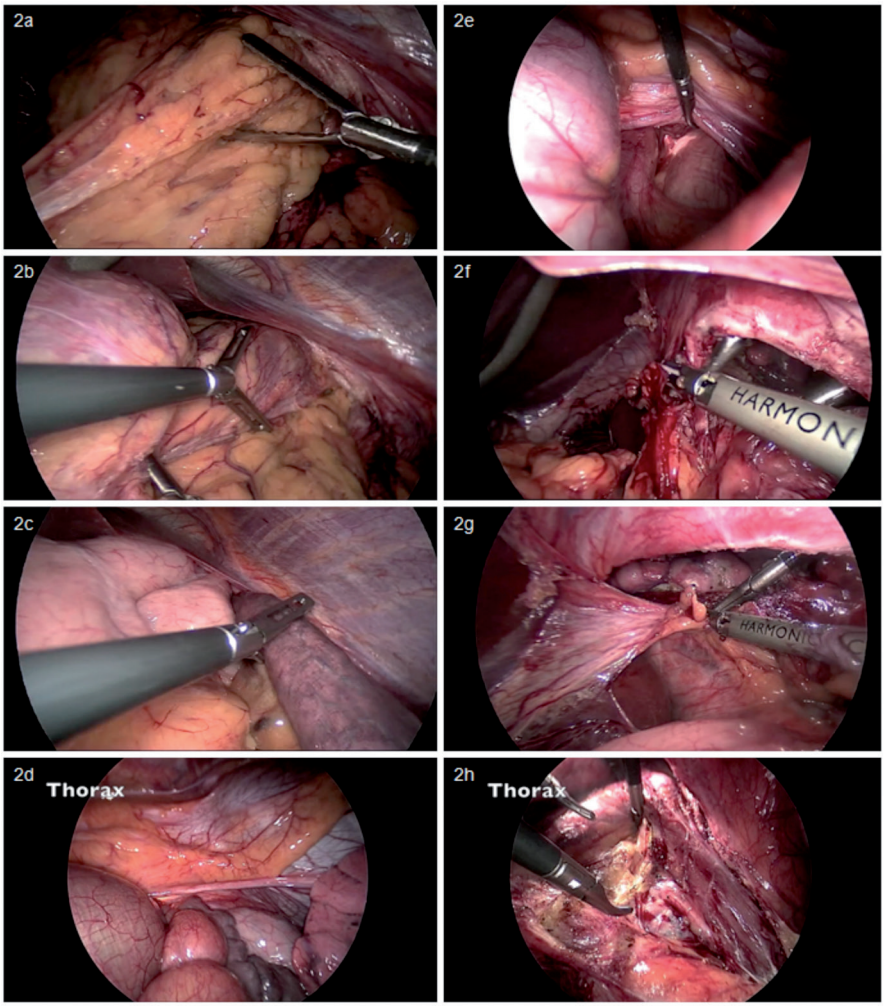

FIGURE 2. Laparoscopic repositioning of intrathoracic omentum (a), colon (b) and small intestine (c). (d) Thoracoscopic view demonstrating intrathoracic colon and small intestine. (e) Laparoscopic view demonstrating right-sided crus and light of simultaneous thoracoscopic approach. (f, g) Thoracoscopic and laparoscopic dissection of hernia sac. (h). Thoracoscopic view demonstrating tension-free position of esophagus.

Results

Case 1:
A 31-year old male presented with symptoms related to regurgitation and exercise depended dyspnea. His history reported an appendectomy and thoracic paraplegia with a left diaphragmatic hernia following a car accident 4 years earlier.

Preoperative tests revealed impaired pulmonary function (Tiffeneau index 78 %). Preoperative computer tomography (CT) scan showed a giant intrathoracic stomach, with herniation of transverse colon and small bowel (figure 3a).

The patient underwent an uncomplicated simultaneous thoraco-laparoscopic diaphragmatic hernia repair. Because of the large hiatal defect, a titanium coated lightweight polypropylene mesh (Timesh®, PFM Medical, Köln, Germany) was used to bridge the gap, which was fixated both intrathoracic and abdominal with non-absorbable sutures and absorbable synthetic polyester tacks (AbsorbaTack™, Covidien, Dublin, Ireland). Care was taken that the mesh was not in direct contact with the esophagus. An anterior fundoplication was performed. Total operation time was 150 minutes with 200 ml blood loss. After postoperative observation, the patient went to the nursing department the same day and was discharged in good clinical condition five days postoperatively. At 4 months follow-up, there were no symptoms of dyspnea, regurgitation, or gastro-esophageal reflux. A normal developed left-lung and no signs of hernia recurrence were seen at control CT-scan (figure 4a). At 2 years follow-up, there were no clinical signs of recurrent disease.

Case 2:
A 47-year-old female presented with symptoms of exercise dependent dyspnea and dysphagia for solid food and fluids. Her medical history mentioned a laparoscopic cholecystectomy. A CT-scan showed a paraesophageal hernia (type IV) with intrathoracic herniation of stomach, transverse colon and small bowel. The abdominal contents were predominantly herniated up to the right chest (figure 3b).

We performed an uncomplicated simultaneous thoraco-laparoscopic hiatal hernia correction, using a right-sided thoracic approach. The hernia was closed with non- absorbable sutures and an anterior fundoplication was performed. Total operation time was 120 minutes with 50 ml blood loss. After postoperative observation, the patient went to the nursing department the same day and was discharged in good clinical condition five days postoperatively. Clinical follow-up was two years without any complaints or signs of recurrent disease.

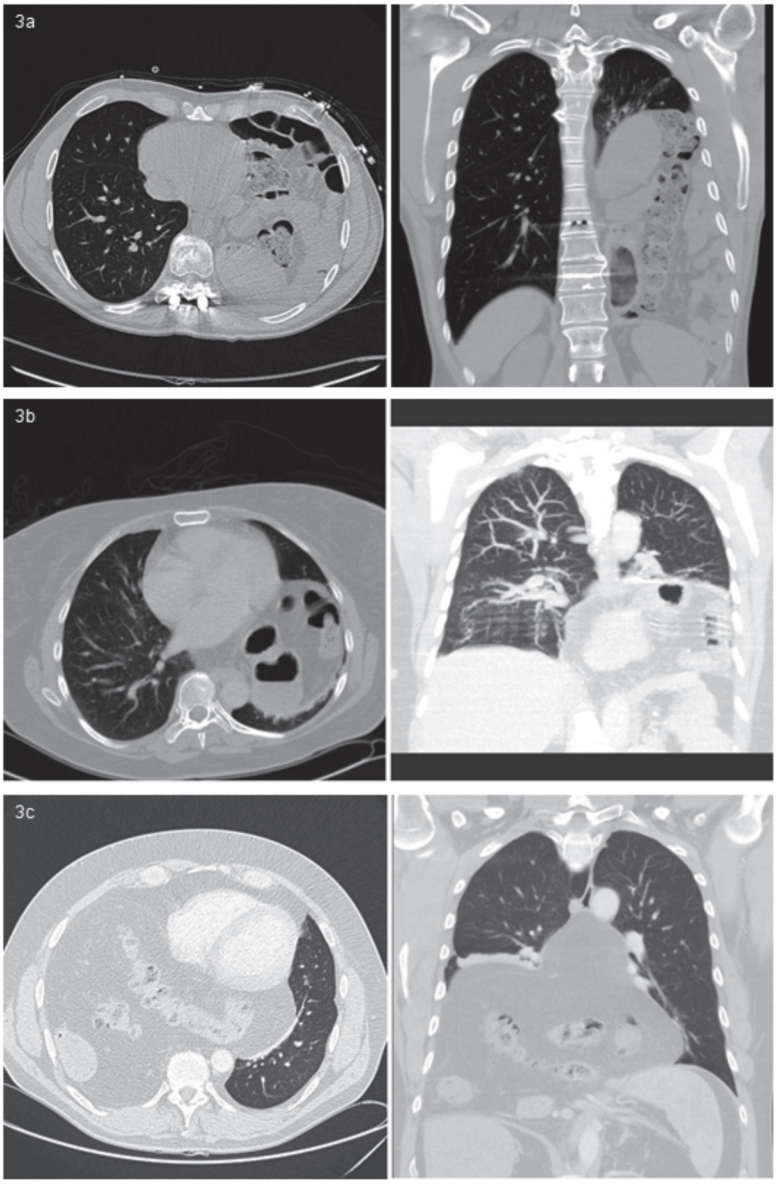

FIGURE 3. (a) Preoperative cross sectional and coronal CT-scan of the chest of patient 1 demonstrating intrathoracic stomach, small intestine and colon. (b, c) Pre-operative cross sectional and coronal CT-scan of the chest of patients 2 and 3, respectively demonstrating intrathoracic stomach, small intestine and colon.

Case 3:

A 47-year-old male was referred to our hospital with thoracic pain, dyspnea and less perseverance. His history reported a left inguinal hernia repair. Pulmonary function tests revealed a decreased pulmonary function (Tiffeneau index 64%). Preoperative CT-scan showed a diaphragmatic hernia (grade IV) with intrathoracic stomach, duodenum, pancreas and transverse colon, causing compression of the right lung (figure 3c).

Patient underwent an uncomplicated simultaneous thoraco-laparoscopic hiatal hernia repair. The hiatal hernia was closed with non-absorbable sutures. A posterior cruroplasty was performed with a polypropylene mesh (Timesh®, PFM Medical), fixated with absorbable synthetic polyester tacks (AbsorbaTack™, Covidien). Total operation time was 240 minutes with 500 ml blood loss. After postoperative observation, the patient went to the nursing department the same day and was discharged in good clinical condition four days postoperatively Three months postoperatively, patient had no symptoms of pain and dyspnea and a normalized physical condition. Five months postoperatively, he suffered from heartburn complaints and regurgitation. A control CT-scan showed a normal aspect of the right lung and no diaphragmatic herniation (figure 4b). His complaints were successfully treated through medication. Patient was practically free of symptoms two years postoperatively.

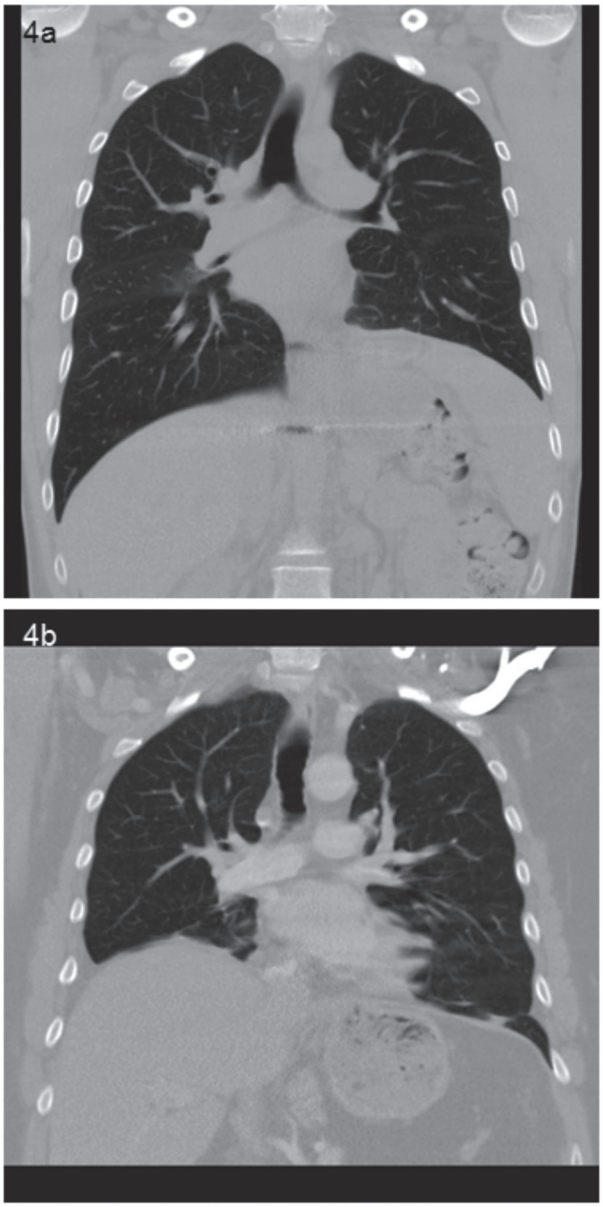

FIGURE 4. (a) Postoperative coronal CT-scan of the chest of patient 1 showing no signs of recurrence. (b) Postoperative coronal CT-scan of the chest of patient 3 showing no recurrent hernia.

Discussion

To our knowledge, this is the first report on simultaneous thoraco-laparoscopic repair of giant hiatal hernias. We have demonstrated that that this novel technique is safe, technically feasible, and offers all the advantages of minimal invasive surgery (figure 5) with the main advantage of a complete overview of herniated structures, hernia sac and esophagus. Both surgeons can work simultaneously and assist each other during various phases of the procedure, with constant thoracic and abdominal view (figure 2). This ensures that all herniated structures are safely reduced, the herniated sac is resected completely and sufficient abdominal esophageal length is obtained to prevent recurrence.

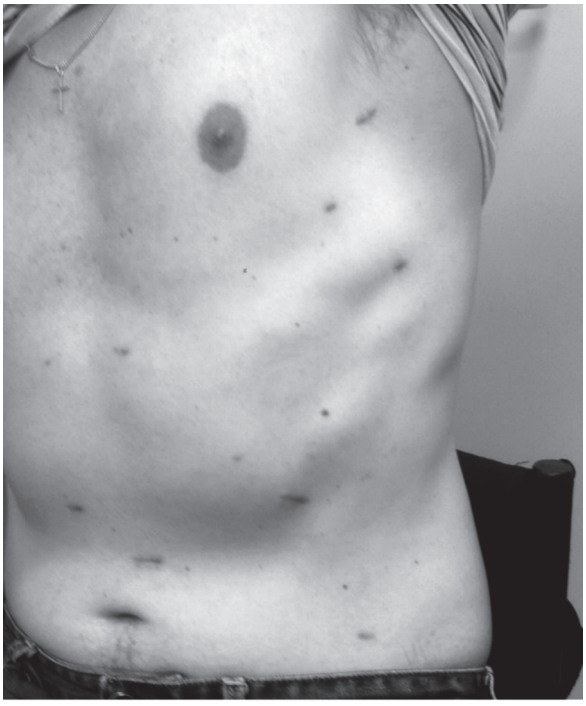

FIGURE 5. Postoperative photograph demonstrating trocar positioning.

One of the main disadvantages of the transhiatal approach is the high recurrence rate due to a lack of mobilization of the esophagus, thus causing a 'short esophagus'. Although the subject of 'short esophagus' is still under debate, some authors have reported that it may be encountered more frequently than appreciated. Lugaresi et al. demonstrated that up to 60% of type II-IV hiatal hernias were measured as 'short' postoperatively.[8] Therefore, some recommend a Collis wedge gastroplasty to increase intra-abdominal esophageal length.[9] One of the advantages of the simultaneous thoraco-laparoscopic procedure is the ability to mobilize the entire esophagus, ensuring a tension-free position of the esophagus, while cruroplasty can be performed when needed. Therefore, an additional plasty to enlarge the native esophagus can be omitted in our opinion. In addition, the hernias described in this article are extreme cases requiring an alternative approach and it can be hypothesized that additional thoracic augmentation of the hernia is of influence in reducing recurrence.

The mean operation time of the three procedures was 170 minutes, mean blood loss 250 milliliters and mean length of postoperative stay 4.7 days, correlating well with literature and as can be expected with minimal invasive surgery. The total duration of procedures was relatively short compared to other published studies, reporting an average operation time of more than 300-400 minutes.[10] Our relatively short operation time can be explained by the simultaneous thoracoscopic and laparoscopic approach, hence facilitating faster dissection and saving time compared to procedures switching between thoracic and abdominal phase. The fact that no pulmonary postoperative complications occurred may be explained by this relatively short operating time.

The simultaneous thoraco- and laparoscopic giant hiatal hernia repair requires two experienced surgeons. It is recommended that procedures as described in this article are only performed in clinics with a large experience in advanced upper gastrointestinal and thoracic surgery. Furthermore the anaesthetic and post-operative recovery team must be well informed and dedicated due to the possible higher perioperative risks when thorax and abdomen will be simultaneously operated upon, as this may cause more severe cardiopulmonary changes than an average hiatal hernia operation. Therefore, this approach should only be used in selected cases, including patients without extensive pulmonary comorbidity, and in whom the risk of inadequate exposure through the transhiatal approach is very likely due to extensive mediastinal adhesions, most likely present in patients suffering from recurrent hiatal hernia, giant type IV hiatal hernia or large traumatic diaphragmatic herniation.

In conclusion, simultaneous thoraco-laparoscopic hernia repair is a feasible and safe technique with acceptable short-term outcome. This approach is not to be considered standard care for hiatal hernias, but a reasonable option in selected cases.

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Chapter 10

Hiatal hernia after open versus minimally invasive esophagectomy: a systematic review and meta-analysis

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Abstract

Purpose: Hiatal hernia (HH) is an infrequent, yet potentially life threating complication following esophagectomy. Several studies have reported the incidence of this complication following both open and minimally invasive esophagectomy (MIE). This meta-analysis aimed to determine the pooled incidence of HH following both types of esophagectomy, and importantly, provide insight in the outcome of subsequent HH repair.

Methods: A systematic search was performed using PubMed, EMBASE, CINAHL and Cochrane databases. Article selection was performed using the PRISMA criteria. Articles describing the incidence of HH following different open and minimally invasive techniques were included. Only when five or more comparable studies reported on the same outcome, data was pooled. The incidence of postoperative HH, and the outcome of HH repair were analyzed.

Results: Twenty-six studies published between 1985 and 2015 were included, describing a total of 6.058 patients who underwent esophagectomy, of whom 240 were diagnosed with a postoperative HH. The pooled incidence of symptomatic HH following MIE was 4.5%, compared to a pooled incidence of 1.0% following open esophagectomy. Eleven studies reported on the outcome of HH repair in 125 patients. A pooled morbidity rate following HH repair of 25% was found. During follow-up, a pooled recurrence rate of 14% was reported in 11 of the included studies.

Conclusion: The pooled incidence of HH following MIE is higher compared to open esophagectomy. Most importantly, surgical repair of these HH's is associated with a high morbidity rate. Both radiologists and surgeons should be aware of this rare, yet potentially life-threatening complication.

Introduction

Esophagectomy is a complex surgical procedure with the potential for significant perioperative morbidity. Both early detection and multimodality therapy have significantly improved the survival of patients diagnosed with esophageal cancer. Due to this increased survival, more data regarding late complications following esophagectomy are becoming available. Multiple studies have reported on different techniques for esophagectomy and their associated short- and long-term complications.

Hiatal hernia (HH) is one of these complications, occurring either immediately or after months or years. During esophagectomy, the hiatus is often widened in order to provide adequate passage of the conduit through the diaphragm. This causes an increased risk of herniation of abdominal contents into the thoracic cavity, with a subsequent risk of potentially life threatening complications, including respiratory distress, incarceration, and perforation.[1-3]

The introduction of minimally invasive esophagectomy (MIE) has significantly enhanced the outcome of esophagectomy, with a decrease in blood loss, pulmonary complications, postoperative pain and reduced hospital stay compared to open surgery.[4, 5] However, several studies report an increased incidence of HH following MIE compared to open esophagectomy, most likely caused by the need to widen the hiatus more extensively during minimally invasive procedures.[6-8]

Several studies have reported on the incidence of HH following different esophagectomy techniques, and the outcome of subsequent repair of these hernia's. The aim of this meta-analysis is to determine the incidence of postoperative HH for open versus minimally invasive esophagectomy, and importantly, to provide insight in the outcome of HH repair following esophagectomy.

Methods

Literature search

Two authors (JO, EH) performed an independent literature search on the 18th of December 2015. The MEDLINE, EMBASE, CINAHL and COCHRANE databases were searched using different combinations of the following Mesh and free search terms: "diaphragmatic hernia" or "hernia", and "esophagectomy", "oesophagectomy" or "esophagus resection". Only studies published in English were considered eligible for inclusion. A full search strategy is available at request.

Quality assessment

After identifying relevant titles, abstracts were read and eligible articles were retrieved. A manual cross-reference search was performed to identify studies that were not found after the primary search. In case of discordant opinions between the authors (JO and EH), a third author (MW) was consulted. The methodological quality was independently assessed by the authors using the Cochrane collaboration and MINORS quality score checklist, with a global ideal score of 16 for non-comparative and 24 for comparative studies.[9]

Inclusion and exclusion criteria

Articles were eligible for inclusion if the following criteria were met: prospective and retrospective studies describing the incidence of HH in patients who underwent esophagectomy, articles published in English, and available full text. Case reports were included when the incidence could be calculated.

Types of participants

Adult patients undergoing esophagectomy for esophageal cancer or benign esophageal disease diagnosed with a postoperative HH. Types of procedures were reported as described in the included articles.

Types of outcome measures

Primary outcome was the difference in incidence of HH following open versus MIE. Secondary outcomes included (median) interval between esophagectomy and diagnosis of HH, the number of patients requiring HH repair, techniques used for repair, and outcome of repair.

Missing data

The corresponding authors of included studies were contacted through e-mail in order to clarify missing data. When the corresponding author did not respond, the study was either excluded or the outcome measure was marked "not specified" (NS) in the accompanying table.

Data analysis

MetaAnalysist software version 3.1 was used for meta-analysis. To provide a reliable outcome and gain sufficient homogeneity of pooled data, only five or more comparable studies were used for pooled analyses. Incidence rates, and morbidity and recurrence rates following HH repair were pooled using a random-effects model. Heterogeneity was determined using a forest plot, and performing a χ^2 ("chi-squared") heterogeneity test and calculating the I^2–index, with a high I^2-value representing a high suspicion for heterogeneity.

Results

Description of studies

Figure 1 demonstrates the flow-chart for the conducted systematic review following the PRISMA guidelines. A total of 544 publications were identified, from which 313 articles were screened bases upon title or abstract. Of these articles, 64 were retrieved for detailed information. After applying our inclusion criteria, we found 26 relevant articles. All authors agreed on including these articles.

Included studies

One RCT, one prospective and 24 retrospective cohort studies published between 1985 and 2015 were included.[1-4, 6-8, 10-26] The studies describe a total of 6.058 patients who underwent esophagectomy, including 240 patients diagnosed with a postoperative HH. The results are summarized in Table 1 and Table 2. All articles were of moderate / good quality based on the MINORS quality score.

Hiatal hernia following open esophagectomy

Thirteen studies reported on the incidence of HH following open esophagectomy, describing a total of 3.621 patients (Table 1).[1-4, 7, 8, 10, 11, 13, 15, 18, 22, 24, 27] The types of open esophagectomy described included transhiatal, thoracotomic-laparotomic, three field/ McKeown, transthoracic esophagectomy, and Ivor-Lewis esophagectomy. The incidence of HH following open esophagectomy ranged from 0 to 10.2%. The median time interval between esophagectomy and diagnosis of HH was reported in five studies, and was 21 months (range 9-31 months).

In order to increase the clinical relevance of the meta-analysis, only studies reporting on the incidence of symptomatic HH's were used for pooling, being reported in nine studies. A pooled incidence of 1.0% (95% C.I. 0.6-1.3) with an I^2-value of 0% was found (Figure 2a).

The lowest incidence of 0% was reported by Willer et al., describing the results of routine computed tomography (CT) scans of 20 patients who underwent open Ivor-Lewis esophagectomy, with follow-up data for at least two years following surgery.[27] The highest incidence was found by Ganeshan et al., who found an incidence of 10.2% among 410 patients in whom CT-scans performed at least one year following surgery were available.[18] Within their cohort of 410 patients, the highest incidence was found in the subgroup of patients who had undergone open transhiatal esophagectomy (THE), with an incidence of 20%.[18] There were insufficient studies to perform a meta-analysis of each of the different open esophagectomy techniques.

Hiatal Hernia following minimally invasive esophagectomy

Twenty studies describing MIE were included, representing a total of 2.437 patients (Table 1).[3, 4, 6-8, 13, 14, 16-23, 25-28] The types of minimally invasive procedures described included thoracotomic-laparoscopic, thoraco-laparoscopic, transhiatal, and Ivor-Lewis esophagectomy. Additionally, one study reported on laparoscopic assisted cardio-esophagectomy (LACO) and one study on the outcome of transhiatal robot-assisted esophagectomy.[20, 23] The incidence of HH ranged from 0 to 26% for all MIE procedures. The median time interval between esophagectomy and diagnosis of HH was reported in six studies, with a median interval of 8.8 months (range 6-29 months).

The incidence of symptomatic HH's following MIE could be pooled for 14 studies, resulting in a pooled incidence of 4.5% (95% C.I. 2.8-6.2), with an I^2-value of 58% (Figure 2b).

The lowest incidence was found by Nobel et al., reporting an incidence of 0% following thoraco-laparoscopic esophagectomy in 53 patients, with a mean follow-up period of 17 months.[22] Willer et al. report the highest incidence of 26.3% following minimally invasive Ivor-Lewis esophagectomy among 19 patients, using CT-scanning during two year follow-up.[27] There were insufficient studies to perform a meta-analysis of each of the different MIE techniques.

Outcome of hiatal hernia repair following esophagectomy

The outcome of HH repair was reported in 11 studies, compromising a total of 125 patients (Table 2).[1, 2, 6-8, 12, 14, 16, 19, 21, 25] Urgent repair was performed in 27 patients (22%) due to acute obstructive or respiratory symptoms and/or suspicion of acute strangulation. Half of the repairs (50%) was performed laparoscopically, with conversion rates ranging between 0 and 18%. Morbidity rates, including minor and major morbidity, ranged from 0 to 60%. Recurrent HH occurred in 21 patients (17%), of whom nearly all required redo HH repair.

Since the morbidity rate was reported in eight studies, data could be pooled. A pooled morbidity rate of 25% (95% C.I. 11.3-38.6) was found, with an I^2-value of 67% (Figure 3a). Eleven studies reported recurrence rates following postesophagectomy HH repair, resulting in a pooled recurrence rate of 14% (95% C.I. 8.4-20.4), with an I^2-value of 0% (Figure 3b).

TABLE 1. Overview of included studies reporting on hiatal hernia following esophagectomy.

Study	Design	Procedure	Total no. of patients	HH (n)
Agha et al. 1985	R	Open, THE	138	2
Barbier et al. 1988	P	Open, THE	50	3
Benjamin et al. 2015	R	MIE, thoraco-laparoscopic	120	7
Biere et al. 2012	RCT	Open, thoraco-laparotomic	56	1
		MIE, thoraco-laparoscopic	59	0
Bronson et al. 2014	R	MIE	114	9
Caputo et al. 2005	R	Open, TTE / transmediastinal	26	0
		MIE, TTE / transmediastinal	45	2
Crespin et al. 2015	R	MIE, THE	192	22
Daiko et al, 2010	R	Open, TTE	168	2
Erkmen et al. 2013	R	MIE, THE	24	3
Fumagalli et al. 2006	R	MIE, thoraco-laparoscopic	44	2
Ganeshan et al. 2013	R	Open, total	410	42
		Open, Ivor Lewis	267	18
		Open, THE	105	21
		Open, 3	38	3
		Field/McKeownMIE, NS	30	2
Kanamori et al. 2015	R	MIE, thoraco-laparoscopic	150	6
Kent et al. 2008	R	Open	494	4
		MIE	581	16
Lowe et al. 2010	R	MIE, LACO	24	3
Messenger et al. 2015	R	Open	205	2
		MIE,thoracotomic-laparoscopic	6	9
Narayanan et al. 2015	R	MIE, THE	194	9
Noble et al. 2013	R	Open, Ivor Lewis	53	1
		MIE, thoraco-laparoscopic	53	0
Price et al. 2011	R	Open, total	1579	14
		Open, Ivor Lewis	978	9
		Open, THE	601	5
Sutherland et al. 2011	R	MIE, transhiatal robot-assisted	36	7

Symptomatic (n)	Incidence	Interval	HH repair	Technique HH repair
NS	1.4%	31 months (median)	2 (100%)	Cruroplasty (n=2)
0 (0%)	6%	9 months (median)	0 (0%)	-
5 (71%)	5.8%	3.4 months (median)	5 (71%)	Cruroplasty (n=3), cruroplasty + mesh (n=2)
1 0	3.6% 0%	NS -	1 -	NS -
4 (44%)	7.9%	13.7 months (average)	9 (100%)	Cruroplasty + mesh + colopexy (n=9)
- NS	0% 4.4%	- NS	- 2 (100%	- NS
7 (32%)	11.5%	7.5 months (median)	5 (23%)	Cruroplasty (n=1), cruroplasty + mesh (n=4)
2 (100%)	1.1%	4 days, 27 days	2 (100%)	Cruroplasty (n=2)
3 (100%)	12.5%	NS	NS	Cruroplasty and cruroplasty + mesh (NS)
2 (100%)	4.5%	4 months, 8 months	2 (100%)	Cruroplasty (n=1), cruroplasty + mesh (n=1)
8 (12%) of total	10.2% 6.7% 20% 7.9% 6.6%	24 months (median) for total	9 (20%)	NS
5 (83%)	4.0%	1 – 8 months (range)	6 (100%)	Cruroplasty (n=6)
83% of total	0.8 2.8	32 months (mean)	22 (100%)	Cruroplasty (n=13), cruroplasty + mesh (n=9)
3 (100%)	12%	4-7 months 6 months (average)	3 (100%)	Cruroplasty (n=1), cruroplasty + mesh (n=2)
2 (100%) 9 (100%)	1.0% 13.2%	44 months , 114 months 4.9 months (average)	2 (100%) 9 (100%)	Omentopexy (n=1), cruroplasty (n=1) Cruroplasty (n=4), cruroplasty + mesh (n=5)
8 (89%)	4.6%	28.8 months (median)	100%	Mesh repair without crural sutures (n=9)
NS -	1.9% 0%	NS -	NS -	NS -
12 (86%)	0.89% 0.92% 0.83%	21 months (median)	15 (100%)	Cruroplasty (n=13), cruroplasty + mesh (n=2)
7 (100%)	19.4%	NS	7 (100%)	Cruroplasty + mesh (n=7)

TABLE 1. Continued.

Study	Design	Procedure	Total no. of patients	HH (n)
Terz et al. 1987	R	Open, THE	36	1
Ulloa Severino et al. 2015	R	MIE, Ivor-Lewis	390	32
Vallbohmer et al. 2007	R	Open, TTE MIE, LG+dTTE	168 187	4 5
Van Sandick et al. 1999	R	Open, THE or thoraco-laparotomic	218	9
Warner et al. 2014	R	MIE, thoraco-laparoscopic	96	1
Willer et al. 2012	R	Open, Ivor Lewis MIE, Ivor-Lewis	20 19	0 5
Wu et al. 2015	R	MIE, THE (gasless)	11	1

TABLE 2. Outcome of hiatal hernia repair following esophagectomy.

Study	N	Setting, n	Approach, n	Conversion rate
Benjamin et al. 2015	5	Urgent 1 (20%) Elective 4 (80%)	Lap 5 (100%)	0%
Bronson et al. 2014	9	NS	Lap 7 (78%) Open 2 (22%)	NS
Crespin et al. 2015	7	Urgent 2 (29%) Elective 5 (71%)	Lap 3 (43%) Open 4 (57%)	0%
Erkmen et al. 2015	4	Elective 4 (100%)	Lap 4 (100%)	0%
Kent et al. 2008	22	Urgent 4 (18%) Elective 22 (82%)	Lap 17 (77%) Open 5 (23%)	12%
Kanamori et al. 2015	5	Urgent 4 (80%) Elective 1 (20%)	Lap 1 (20%) Open 4 (80%)	NS
Messenger et al. 2015	11	Urgent 5 (45%) Elective 6 (55%)	Lap 8 (73%) Open 3 (27%)	13%
Naranayan et al. 2015	9	Urgent 3 (33%) Elective 6 (67%)	Lap 0 (0%) Open 9 (100%)	-
Price et al. 2011	15	Urgent 2 (13%) Elective 13 (87%)	Lap 0 (0%) Open 15 (100%)	-
Ulloa et al. 2015	32	Urgent 6 (19%) Elective 26 (81%)	Lap 19 (59%) Open 5 (16%)	18%
Van Sandick et al.1999	6	NS	Open 6 (100%)	-

Symptomatic (n)	Incidence	Interval	HH repair	Technique HH repair
NS	2.8%	7 days	1 (100%)	NS
22 (69%)	8.2%	10 months (median)	32 (100%)	Cruroplasty (n=12), cruroplasty + mesh (n=20)
NS	2.4%	NS	7% of total	Cruroplasty (n=6),
NS	2.7%	NS		cruroplasty + mesh (n=1)
6 (67%)	4.1%	8 montsh (mean)	6 (67%)	Cruroplasty (n=6)
NS	1.0%	NS	1 (100%)	NS
-	0%	18 months (median)	3 (60%)	Cruroplasty (n=2),
0 (0%)	26%			cruroplasty + mesh (n=1)
NS	9.0%	NS	NS	NS

Mortality*, n	Morbidityn	Recurrence, n	Interval**	Redo HH repair
0 (0%)	0 (0%)	1 (20%)	23 months	yes
0 (0%)	2 (22%)	1 (11%)	6 months	yes
0 (0%)	NS	1 (14%)	NS	no
0 (0%)	0 (0%)	1 (25%)	14 months	yes
1 (4.5%)	6 (27%)	6 (27%)	13 months (median)	yes (100%)
0 (0%)	1 (20%)	1 (20%)	2 days	yes
0 (0%)	NS	2 (18%)	2 and 9 months	yes (100%)
0 (0%)	5 (56%)	0 (0%)	-	-
0 (0%)	9 (60%)	2 (13%)	8 and 26 months	yes (100%)
0%	3 (9%)	6 (19%)	NS	yes (67%)
0%	NS	0 (0%)	+	-

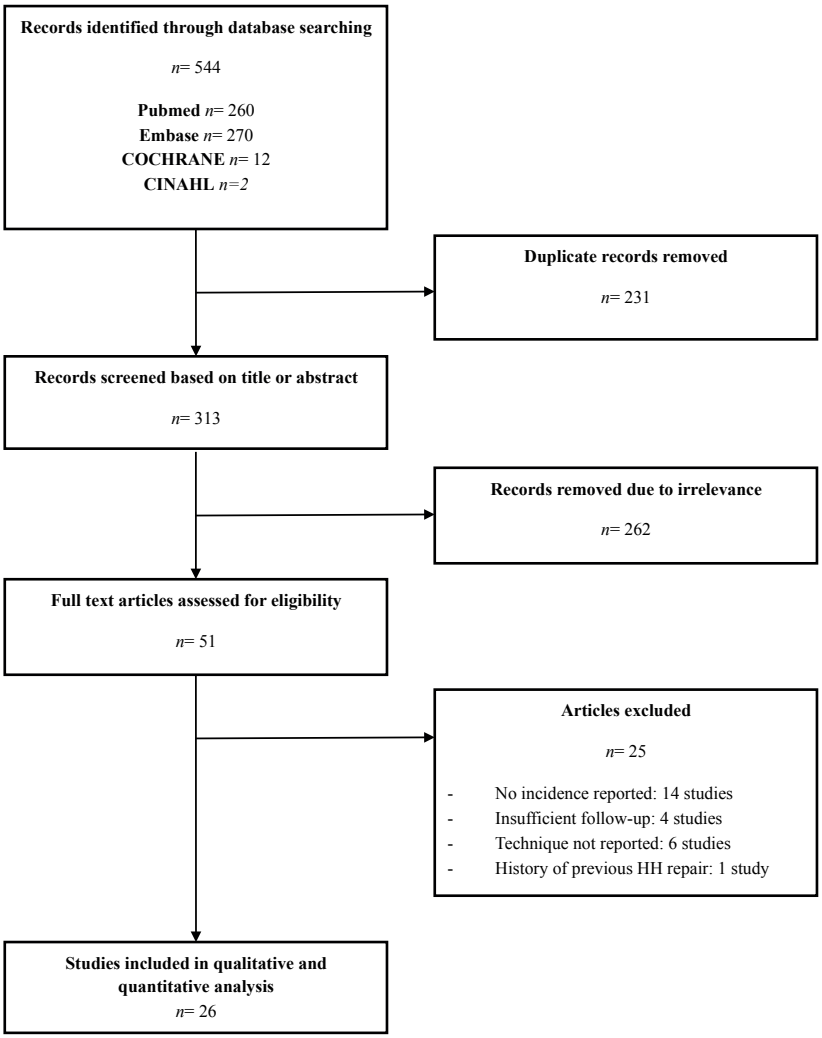

FIGURE 1. Flowchart of search according to the PRISMA guidelines.

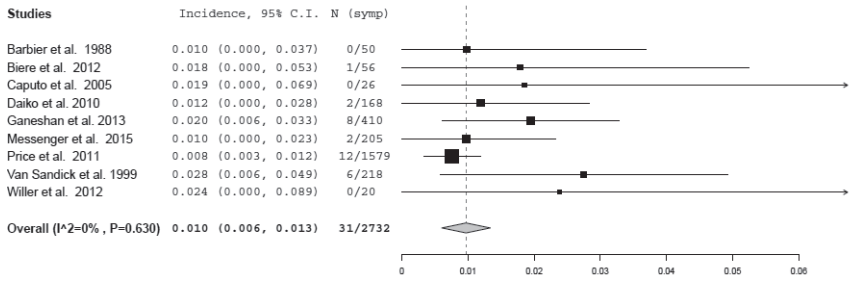

FIGURE 2A. Forrest plot of pooled incidence of symptomatic hiatal hernia following open esophagectomy.

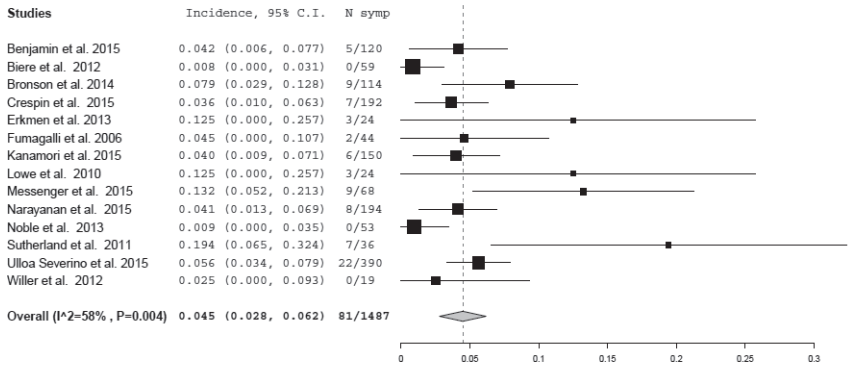

FIGURE 2B. Forrest plot of pooled incidence of symptomatic hiatal hernia following minimally invasive esophagectomy.

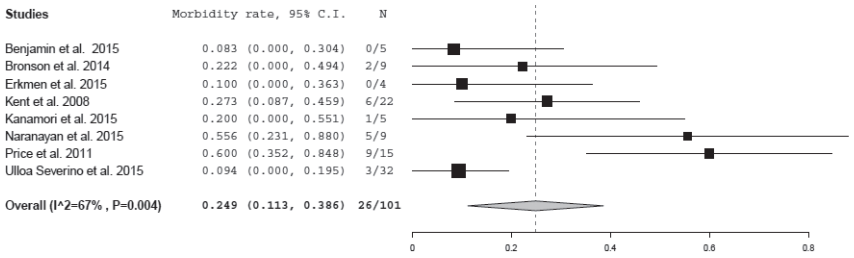

FIGURE 3A. Forrest plot of pooled morbidity rate following hiatal hernia repair.

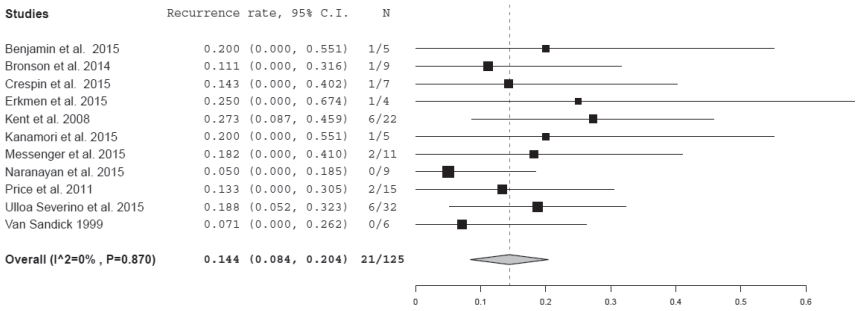

FIGURE 3B. Forrest plot of pooled recurrence rate following hiatal hernia repair.

Discussion

In the present meta-analysis, symptomatic HH's were found to more frequently occur following MIE compared to open esophagectomy, with a pooled incidence of 4.5% versus 1.0% respectively. Importantly, it appears that subsequent HH repair is associated with a high morbidity rate (25%).

Etiology and Risk Factors

Hiatal hernias diagnosed during long term follow-up most likely develop due to progressive hiatal widening caused by an increased intra-abdominal pressure, together with a negative intrathoracic pressure causing suction.[1, 3] With regards to open esophagectomy, Van Sandick et al. found extended disruption of the normal hiatal anatomy, in order to adequately mobilize the esophagus or perform an extended diaphragmatic resection, to be the only significant risk factor for the development of postoperative HH.[2] Ganeshan et al. found the highest incidence of HH (20%) in patients who had undergone open THE, explained by the extended hiatal enlargement performed during the transhiatal approach, resulting in an altered hiatal anatomy.[18]

As demonstrated by our meta-analysis and previous cohort studies, MIE is associated with a higher incidence of HH's compared to open esophagectomy.[7, 8, 13, 27] A frequent reported explanation for this finding is the reduced formation of peritoneal adhesions in the hiatal region following MIE.[1, 3] Furthermore, MIE causes an increasingly dilated hiatus secondary to insufflation, and in case of robot-assisted esophagectomy, more extensive widening of the hiatus is needed to provide adequate mediastinal dissection with mechanical arms.[21, 23, 30] This is reflected by the relatively high incidence (19%) of HH following 36 robot-assisted transhiatal esophagectomies by Sutherland et al..[23] They also found the presence of a pre-existing HH to be significantly associated with postoperative incarcerated hernia.[23] Benjamin et al. found an increased mean body mass index (BMI) to be a risk factor, through the subsequent increase in intra-abdominal pressure.[6] Paradoxically, Ganeshan et al. reported patients with a BMI>25 kg/m^2 to be less prone to develop a postoperative HH, through reduced mobility of intra-abdominal structures in obese patients.[18]

Diagnosis

Patients may present with a variety of symptoms, including respiratory complaints, dysphagia and obstruction, or be totally asymptomatic.[1] Chest roentgenograms demonstrate increased density or air fluid levels in the left or right pleural space, or retrocardiac air.[1, 28, 31] Computed tomography scanning will provide most information since all herniated structures are visualized, and should be considered the golden standard for diagnosing this complication.[1] Not all studies used routine CT-scanning for detecting HH's, hence only symptomatic patients were used for calculating the postoperative incidence, with the

risk of underestimation. Ganeshan et al. reviewed all routine CT-scans following predominantly open esophagectomy in a blinded fashion, and demonstrated an overall incidence of 10%.[18] Only 16% of these patients had been previously diagnosed with a HH by the radiologists during follow-up, whilst of the remaining undiagnosed patients, six ultimately required a surgical reintervention due to HH-related complications. This reflects the difficulty of diagnosing postoperative HH's and the need for increased awareness amongst radiologists.[28]

Hiatal hernia repair following esophagectomy

It is generally accepted to perform HH repair in symptomatic patients deemed fit for surgery.[3, 16] Due to enlargement of previously diagnosed HH's, asymptomatic patients may become symptomatic overtime, with the risk of incarceration and subsequent perforation. Therefore, some authors advocate surgical repair in all asymptomatic patients.[1, 7] However, the risk of incarceration needs to be balanced against the risks and associated morbidity of HH repair, taking the reduced life expectancy of this specific group of patients into account.[16] In the present meta-analysis, a pooled morbidity rate following HH repair of 25% was found, which is considerable higher compared to elective HH repair in the general population. This is an important finding, and most likely caused by the relatively high number of urgent repairs (22%), and that half of the repairs were performed though an open approach (Table 2).

Some authors advocate an open approach, while others believe HH repair should be performed primarily through laparoscopy.[1, 8, 16] The laparoscopic approach is associated with reduced postoperative pain, enables diagnostic evaluation of the abdomen to rule out metastatic disease, and provides superior visualization of both the herniated contents and the vascular supply to the gastric conduit, lying in close proximity to the herniated contents, thereby reducing the risk of damaging these structures. [8, 16, 25]

In 14 of the included studies mesh was used to establish adequate crural closure (Table 1). Controversy still exists regarding the use of mesh in both elective primary HH repair, as well as HH repair following esophagectomy. A recent RCT performed by Watson et al. demonstrated no significant differences in recurrence rates, or in clinical outcome between primary closure or mesh-reinforced hernia repair.[31] Some authors fear that the mesh, and especially the non-absorbable types of mesh, may erode into the gastric conduit or it's vascular supply.[8, 21] However, if there is a large crural defect, and a tension-free closure cannot be established by primary closure alone, the use of mesh seems legitimate when care is taken that the mesh is placed in a non-circular fashion, thereby avoiding direct contact between the mesh and the esophagus or conduit.[16, 25]

Prevention

The high morbidity rate of HH repair emphasizes the importance of prevention. Several preventative measures have been described in current literature. Minimizing hiatal

enlargement, and single stage repair of intraoperatively diagnosed large hiatal defects seem viable means of prevention. When the crura do need to be divided to allow adequate passage of the conduit, anterior division seems to be the preferred technique.[1-3] Some centers describe standard crural or diaphragmatic fixation of the gastric conduit.[7, 12, 18] However, studies directly comparing outcome of fixation versus non-fixation are lacking, and the risk of compromising the vascular supply of the conduit should be taken into account when performing fixation.[1]

Limitations

There are certain limitations to the present meta-analysis. Most included studies are retrospectively designed, with the risk of selection and patients being lost to follow-up, causing a potential underestimation of the true incidence. Furthermore, there is the risk of heterogeneity among the included studies, caused by different surgical techniques used within both the open- and MIE-group, and different postoperative surveillance programs and follow-up periods.[8] However, meta-analysis showed acceptable I^2-values ranging between 0% and 58%. Next, some studies reported the incidence of asymptomatic HH's or HH's only containing abdominal fat, causing an overestimation of the incidence of clinically relevant HH's. Therefore, we performed a meta-analysis using only those studies reporting the incidence of symptomatic hernias.

Conclusions

Postoperative HH is an infrequent complication, with an increased (pooled) incidence following MIE compared to open esophagectomy. Iatrogenic hiatal enlargement and reduced formation of peritoneal hiatal adhesions are the most likely causes for this increased incidence. Surgical repair is associated with a high morbidity rate. Therefore, in asymptomatic patients, the risk of acute strangulation should be well balanced against the associated risks of repair. Taking the high morbidity rate of repair into account, surgeons and radiologists should be aware of this potentially life-threatening complication when performing esophageal resection and during routine follow-up.

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Chapter 11

Summary and general discussion

Summary and general discussion

Surgical treatment of gastroesophageal reflux disease

Over the last decades, multiple randomized clinical trials have compared different laparoscopic fundoplication techniques for the treatment of GERD. However, there is a paucity of studies providing long-term follow-up of fundoplication, which are desperately needed for adequate patient counseling and selection of patients who will benefit most from surgical therapy.

Although providing excellent long-term reflux control, Nissen fundoplication appears to be associated with an increased risk of developing troublesome dysphagia and gas-related symptoms.[1-3] This is most likely caused by a supracompetent gastroesophageal junction, causing a food bolus to less easily pass, thereby causing dysphagia, and reduced venting of air from the stomach to the esophagus, causing the patient to experience gas bloating and inability to belch. Therefore, partial fundoplications have been developed, in which the fundus of the stomach is wrapped partially around the distal esophagus, either anteriorly or posteriorly, rather than in a 360 degree posterior fashion (Nissen fundoplication). Recent meta-analyses have indeed confirmed that partial fundoplications provide equal short- to mid-term reflux control, with a significant lower risk of dysphagia and gas-related symptoms.[1, 2] These finding have caused an increasing popularity of partial fundoplications for the treatment of GERD.

Long-term outcome of fundoplication

In **Chapter 2**, we compared 17-year outcome of laparoscopic versus conventional Nissen fundoplication, based on the largest randomized clinical trial comparing these two procedures. Seventeen years after surgery, there were no differences in reflux control or dysphagia, with equal quality of life and satisfaction with surgery after both procedures. Patients who underwent conventional Nissen fundoplication more frequently required surgical reintervention during 17-year follow-up compared to those who underwent the laparoscopic approach, which was mainly based on a higher number of surgical corrections for incisional hernia. There were no differences in the number of surgical reinterventions for recurrent GERD or severe dysphagia 17-years following both procedures, thereby confirming the long-term sustainability of laparoscopic fundoplication.

An interesting finding of this study is the fact that 17-years after fundoplication, approximately 40% of the patients had reinstated PPI use. This is an important issue to discuss with patients who are at the doorstep of deciding to undergo a fundoplication and for whom the main reason for surgery is unwillingness to take life-long medication. However, it is unclear why these patients are back on acid-suppressing medication. Previous studies have demonstrated that only a minority of patients who reinstated PPI use in fact have pathological postoperative esophageal acid exposure on 24-hour pH-monitoring. Furthermore, PPI's are frequently prescribed to provide gastric protection for

concurrent medication, such as platelet inhibitors.[4] Another important finding is the fact that during 17-year follow-up, 16% of the patients underwent surgical reintervention for recurrent GERD.

In an era in which shared decision making plays an increasingly important role in daily clinical practice, there is a need for more long-term follow-up studies regarding the outcome of fundoplication in order to adequately counsel patients. These studies will help with the proper selection of those patients who will benefit most from surgery, thereby discriminating between patients suffering from PPI-refractory reflux or invalidating regurgitation, versus those who are unwilling to take life-long medication.

Which type of partial fundoplication is superior?

In **Chapter 3**, we aimed to determine possible superiority of either laparoscopic 270 degree posterior versus 180 degree anterior partial fundoplication for the treatment of GERD, with special emphasis on reflux control and the incidence of postoperative dysphagia and gas-related symptoms. Therefore, data of two randomized clinical trials comparing laparoscopic 270 degree posterior with 180 degree anterior partial fundoplication, performed in the Netherlands and Australia, were combined.[5, 6] This resulted in the largest available dataset comparing these two procedures in a randomized fashion. Two years after surgery, there were no differences in reflux control, dysphagia or gas-related symptoms, with comparable satisfaction scores and no differences in the need for endoscopic dilatation or surgical reintervention for recurrent GERD or severe dysphagia. These finding are in line with the results of our previously published trial comparing one-year outcome of both procedures, in which there were no differences in reflux control, dysphagia or gas-related symptoms as well, with comparable prevalence of esophagitis and no difference in esophageal acid exposure measured three months after surgery.[5] Therefore, we can only conclude that the decision to perform either 270 degree posterior or 180 degree anterior fundoplication should be based on the surgeons' experience with one of these fundoplications. However, long-term follow-up studies of both trials, using symptomatic as well as objective outcome measures, are needed to determine whether these findings are sustained. Currently available long-term studies mainly describe outcome of Nissen fundoplication.[7] While studies have demonstrated partial fundoplications to provide equal short- to mid-term reflux control, with a lower risk of dysphagia and gas-related symptoms compared to Nissen fundoplication, long-term follow-up studies of partial fundoplications are desperately needed in order to determine long-term sustainability of these antireflux procedures.[1, 2]

In **Chapter 4,** we used combined 24-hour pH-impedance monitoring to study differences in effect of laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication on reflux and belching patterns. Using this technique, we were able to manually analyze all movements of gas and liquids during 24-hour monitoring, thereby discriminating between acidic and weakly-acidic reflux episodes, the latter being unde-

tectable using conventional pH-monitoring. Three months after surgery, there were no differences in symptomatic reflux control or total esophageal acid exposure, with a comparable reduction in acidic, liquid and mixed liquid-gas reflux episodes between 270 degree posterior and 180 degree anterior partial fundoplication. Furthermore, there was no difference in the number of postoperative weakly-acidic reflux episodes between the two procedures. Both procedures equally reduced the number of gastric belches and supragastric belches, with no significant reduction in the number of air swallows after either procedure, which was reflected by a similar incidence of the symptoms gas bloat and inability to belch after both procedures.

This study provides the physiological evidence for the results of the previously described trials comparing 270 degree posterior and 180 degree anterior partial fundoplication, reporting no differences in reflux control, dysphagia or incidence of gas-related symptoms both one and two years after surgery.[5, 6] Again, long-term follow-up studies, with the use of combined 24-hour pH-impedance monitoring will need to determine whether these findings are sustained.

Interpretation of routine pH-studies

Recurrent reflux symptoms pose a challenge for surgeons as well as patients, with a major impact on the quality of life and satisfaction with surgery.[8] For patients presenting with typical reflux symptoms following primary fundoplication, 24-hour pH-monitoring is considered the gold standard for objectifying these symptoms by demonstrating pathological esophageal acid exposure. In clinical practice, postoperative pH-monitoring is not routinely performed. However, in research practice, it is more and more common practice to provide objective data when reporting outcome of surgery. This could leave the surgeon with the dilemma of a patient with symptomatic reflux control, but an abnormal postoperative pH-study.

Chapter 5 describes the symptomatic outcome and need for surgical reintervention for patients identified with pathological esophageal acid exposure after laparoscopic fundoplication, demonstrated by routine pH-monitoring performed due to trial participation. During five-year follow-up, there were no differences in heartburn score, use of acid-suppressing medication, dysphagia or satisfaction with surgery between patients with pathological and physiological postoperative acid exposure. Of the patients identified with pathological esophageal acid exposure, 18% underwent redo fundoplication during the follow-up period, which was a significantly higher rate compared to the patients with physiological acid exposure.

This study demonstrates that merely the presence of an abnormal routine postoperative pH-study should not be considered to be an independent marker for "wrap failure", since there appeared to be no major differences in symptomatic outcome between patients with pathological and physiological acid exposure. A possible explanation for this finding is that the reduction in esophageal acid exposure caused by fundoplication

has been enough to stop, or at least significantly reduce the patients' perception of reflux.[9] For the present study, only patients who participated in a randomized clinical trial were included, since in this group of patients routine pH-monitoring was performed. As stated before, postoperative pH-monitoring is not routinely performed in daily clinical practice. When patients do present with recurrent symptoms, full workup should include pH-monitoring and a careful history taking, with assessment of typical reflux symptoms. More importantly, the association between symptoms and reflux episodes needs to be analyzed, together with barium swallow radiology and upper gastrointestinal endoscopy to determine the position of the wrap and the presence of esophagitis and wrap insufficiency respectively.

Outcome of laparoscopic hiatal hernia repair with and without mesh

For patients diagnosed with a symptomatic hiatal hernia, surgical repair is the treatment of choice. Due to the repetitive stress exerted on the diaphragm by respiratory functions (breathing, coughing) and non-respiratory functions (vomiting), dehiscence of the crural repair is an important problem.[10] Several studies have analyzed outcome of laparoscopic hiatal hernia repair using either postoperative barium swallow radiology or upper gastrointestinal endoscopy, reporting recurrence rates ranging between 12% and 42%, indicating that there is significant room for improvement.[10-12] In order to reduce the incidence of recurrent hiatal hernia following primary repair, the use of mesh, both absorbable as well as non-absorbable, has been proposed.

Chapter 6 describes a retrospective cohort study comparing symptomatic outcome and objective recurrence rate following laparoscopic hiatal repair using sutures alone versus sutures reinforced with non-absorbable mesh. During a median follow-up period of 39 months, there were no differences in symptomatic or objective recurrence rate between the two groups. Additionally, in both groups there was a significant and equal improvement in health-related quality of life, significant decrease in dysphagia and comparable postoperative satisfaction with surgery. During follow-up, there were no mesh-related complications.

Despite the fact that this study did not demonstrate any differences in outcome between the primary repair and hernia repair using non-absorbable mesh, there was a risk for selection bias due to the retrospective design of the study. Over the last 15 years, four randomized clinical trials have evaluated the use of mesh in laparoscopic hiatal hernia repair.[13-16] However, these trials have not been able to provide compelling evidence for the routine use of mesh, either absorbable or non-absorbable, in laparoscopic hiatal hernia repair. More importantly, there is a paucity of data regarding long-term outcome of hiatal hernia repair using mesh.

In **Chapter 7**, we describe the results of a multicenter randomized clinical trial comparing hiatal hernia repair using sutures alone versus sutures reinforced with a non-absorbable mesh. A total of 72 patients were included and randomized, and all patients were scheduled for routine postoperative barium swallow radiology and upper gastrointestinal endoscopy six months after surgery. During one year follow-up, there were no differences in presence or severity of the symptoms heartburn, chest pain or dysphagia between the two procedures, with comparable satisfaction scores. Routine postoperative barium swallow radiology and upper gastrointestinal endoscopy demonstrated no significant differences in recurrence rate between the two groups, with no mesh-related complications during one-year follow-up.

Together with our trial, five randomized clinical trials have compared laparoscopic hiatal hernia repair using sutures alone versus sutures reinforced with mesh. Oelschlager et al randomized patients for primary repair with sutures versus crural reinforcement using absorbable mesh.[14] Although the short-term results seemed promising in favor of absorbable mesh, five-year follow-up revealed no differences in outcome.[17] Frantzides et al randomized patients for suture-repair versus repair using PTFE mesh, demonstrating a reduction in recurrence rate from 22% to 0% at 2.5 years.[13] However, follow-up beyond two-and-a-half years was not provided. Watson et al. also did not find any significant differences in either subjective outcome or objective recurrence rate one year after repair using sutures versus absorbable mesh versus non-absorbable mesh.[15]

Based on the currently available trials, their appears to be insufficient evidence for the routine use of non-absorbable mesh in laparoscopic hiatal hernia repair, with comparable symptomatic and objective recurrence rates following both procedures during short- to mid-term follow-up. Long-term follow-up of the above mentioned trials will need to demonstrate whether these results are sustained. Additionally, although the incidence of mesh-related complications appears to be low, long-term follow-up studies are necessary to provide valuable information on the true safety of these synthetic meshes.

Surgical treatment of hiatal hernia repair in specific groups of patients

With an increasing age worldwide and the fact that hiatal hernia has a higher prevalence among elderly patients, the laparoscopic surgeon will more frequently encounter this vulnerable group of patients. Elderly patients frequently suffer from (extensive) comorbidities, causing them to be at increased risk of perioperative mortality and/or morbidty.[18-20] In **Chapter 8**, we analyzed perioperative outcome of laparoscopic hiatal hernia repair in 204 consecutive patients aged under 70 (n=121) versus those aged over 70 (n=83), by combining data from two large tertiary hospitals. There was no 30-day mortality, and there were no significant differences in the incidence of intraoperative or 30-day postoperative complications between the two groups. Univariate analysis only demonstrated the occurrence of intraoperative complications to be associated with 30-day morbidity.

While some studies report equal outcome of foregut surgery in elderly compared to younger patients, others have shown worse outcome. However, the majority of these studies are based on large national databases, not discriminating between hospitals with a large and a small workload of hiatal hernia repair.[21, 22] Furthermore, the wide range of reported morbidity rates associated with hiatal hernia repair appears to be caused by a high heterogeneity among included patients, which is reflected by differences in ASA scores, urgent versus elective surgery and conversion rates between studies. Based on our experience, we believe laparoscopic hiatal hernia repair in carefully selected elderly patients, being operated in specialized centers, is as safe as hernia repair in younger patients.

Giant, type IV, hiatal hernias, characterized by intrathoracic herniation of abdominal organs other than the stomach, such as small intestine or colon, pose a significant challenge to the laparoscopic surgeon. Patients with these type of hernias frequently suffer from severe obstructive or respiratory symptoms. Due to the large crural defect and interposition of small intestine and/or colon, extensive mediastinal adhesions are frequently encountered, causing adequate exposure and mobilization of the esophagus to be challenging, with the risk of damaging important adjacent structures in the mediastinum. Due to the technically challenging exposure, we hypothesized that a simultaneous thoraco-laparoscopic approach would enhance visualization, esophageal mobilization and reduce operating time compared to a two-step procedure (thoracoscopy followed by laparoscopy).[23] **In Chapter 9**, we describe three patients in whom we performed this novel simultaneous thoraco-laparoscopic technique. There were no intraoperative or postoperative complications, and in all patients full esophageal mobilization was achieved. Mean postoperative stay was 4.7 days. All patients were free of their invalidating symptoms at follow-up. This novel technique is a good example of the benefits of a multidisciplinary approach for this challenging type of surgery. By combining these two minimally invasive procedures, we developed a safe and feasible alternative technique for repair of type IV hiatal hernias. This approach is not to be considered the standard approach for hiatal hernia, and should only be performed in clinics with a large experience in upper gastrointestinal and thoracic surgery.

Another specific group of patients includes those who underwent esophagectomy for esophageal cancer. Due to early detection and multimodal therapy, the survival of patients diagnosed with esophageal cancer has been significantly improved. As a result of this improved survival, more data regarding late complications of esophagectomy is becoming available. One of these complications is the development of hiatal hernia. Multiple studies have described series of patients diagnosed with this complication, as well as the outcome of subsequent hiatal hernia repair.[24-26] Based on the available literature, it appears that post-esophagectomy hiatal herniation is more frequent after minimally invasive esophagectomy compared to the conventional approach. Therefore, in **Chapter 10**, we describe a systematic review and meta-analysis regarding the incidence of hiatal

hernia after minimally invasive versus open esophagectomy, and report on the outcome of surgical repair of this specific type of complication. Pooling of data from a total of 26 studies demonstrated a pooled incidence of symptomatic hernia of 4.5% after minimally invasive esophagectomy versus 1.0% after open esophagectomy, which is most likely caused by decreased formation of adhesions after the minimally invasive procedure, as well as iatrogenic hiatal enlargement. Additionally, based on a total of 11 studies, subsequent repair of these hiatal hernias appears to be associated with a 25% morbidity rate. Taking the relatively high morbidity rate of hiatal hernia repair into account, surgeons and radiologists should be more aware of this infrequent but potentially life-threatening complication when performing esophagectomy and during postoperative follow-up.

Conclusions

The studies presented in this thesis lead to the following conclusions regarding the surgical management of GERD and hiatal hernia:

- Laparoscopic Nissen fundoplication provides sustainable and equal reflux control beyond 15 years after surgery, with a lower risk of incisional hernia compared to conventional Nissen fundoplication.
- If a patient is reluctant to take life-long acid-suppressing medication, surgery should be proposed while informing patients that they have a 60% chance of sustained success, and a 16% chance of needing a surgical reintervention for recurrent reflux or dysphagia.
- Laparoscopic 270 degree posterior and 180 degree anterior partial fundoplication provide equal control of acidic and weakly-acidic reflux, with a comparable postoperative incidence of dysphagia and gas-related symptoms.
- Pathological esophageal acid exposure demonstrated by routine postoperative 24-hour pH monitoring should not be used as an independent marker for wrap failure.
- There is insufficient evidence for routine crural reinforcement using non-absorbable mesh in laparoscopic hiatal hernia repair.
- In specialized centers, laparoscopic hiatal hernia repair can be performed equally safe in selected elderly patients as compared to younger patients.
- For patients diagnosed with a giant type IV hiatal hernia, simultaneous thoraco-laparoscopic repair is a safe and feasible alternative.
- Hiatal hernia is more frequent after minimally invasive esophagectomy compared to open esophagectomy, and subsequent repair is associated with a relatively high morbidity rate.

Proposed future research

Long-term follow-up studies are required to determine the sustainability of fundoplication for the treatment of GERD, thereby subanalyzing patients in whom the primary indication for surgery is PPI-refractory GERD, invalidating regurgitation, and unwillingness to take

life-long medication. Additionally, long-term follow-up of studies comparing 270 degree posterior and 180 degree partial fundoplication will need to determine whether one of both partial fundoplications is superior with regards to reflux control, dysphagia or the incidence of gas-related symptoms.

Currently, there is insufficient evidence for the routine use of non-absorbable mesh in laparoscopic hiatal hernia repair for reducing the recurrence rate. However, long-term follow-up studies assessing both symptomatic as well as objective outcome will need to determine if this is sustained, and need to provide further information regarding the safety of these synthetic meshes.

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Chapter 12

Summary in Dutch – Nederlandse samenvatting

Summary in Dutch – Nederlandse samenvatting

De chirurgische behandeling van gastro-oesofageale refluxziekte

De gastro-oesofageale overgang, of maag-slokdarmovergang, wordt gevormd door de lagere oesofageale sfincter (intrinsieke sfincter, ook wel LOS genoemd) en de hiatus van het diafragma (extrinsieke sfincter). De terugvloed van zure maaginhoud, ook wel gastro-oesofageale reflux genoemd, is een fysiologisch verschijnsel. Bij patiënten met gastro-oesofageale refluxziekte (GORZ) is er echter dusdanig veel reflux dat de patiënt klachten ervaart van zuurbranden of regurgitatie, en/of dat er sprake is van objectiveerbare schade van de oesofagus in de vorm van oesofagitis of een Barrett-slokdarm. Oorzaken voor GORZ zijn een hypotensieve LOS (te lage druk van de intrinsieke sfincter), een te hoog aantal relaxaties van de LOS en/of een middenrifbreuk, ook wel hiatus hernia genoemd.

De chirurgische behandeling van GORZ is aangewezen voor patiënten die onvoldoende reageren op leefstijladviezen en medicamenteuze therapie middels H2-receptor-antagonisten of protonpompremmers. Daarnaast is chirurgie aangewezen voor patiënten die niet bereid zijn levenslang medicatie te gebruiken. In 1956 beschreef dr. Nissen de eerste twee patiënten bij wie hij in verband met ernstige refluxklachten een zogenaamde 'fundoplicatie' had verricht. Hierbij werd de fundus van de maag 360 graden posterieur om de distale slokdarm gewikkeld. In 1991 werd de laparoscopische variant van deze procedure geïntroduceerd, wat heeft geleid tot een daling van de morbiditeit geassocieerd met deze ingreep en tot een sneller postoperatief herstel.

Alhoewel de Nissen-fundoplicatie een goede en langdurige refluxcontrole bewerkstelligt, wordt dit type fundoplicaties geassocieerd met een verhoogd risico op postoperatieve slikklachten (dysfagie) en zogenaamde gasgerelateerde klachten (onvermogen te boeren en opgeblazen gevoel). Dit heeft geleid tot de ontwikkeling van partiële fundoplicaties, waarbij de fundus van de maag partieel rondom de distale oesofagus wordt gewikkeld. Op dit moment zijn de laparoscopische 270 graden posterieure, of Toupet-fundoplicatie (LTF), en de 180 graden anterieure fundoplicatie (LAF) de meest uitgevoerde partiële fundoplicaties. Recente meta-analyses hebben inderdaad aangetoond dat beide partiële fundoplicaties een gelijkwaardige refluxcontrole bewerkstelligen, met een kleiner risico op dysfagie en gasgerelateerde klachten in vergelijking met een Nissen-fundoplicatie.

Langetermijnuitkomsten van fundoplicatie

In **hoofdstuk 2** worden de zeventienjaarsuitkomsten beschreven van een gerandomiseerde prospectieve studie waarin laparoscopische en conventionele, of open, Nissen-fundoplicatie zijn vergeleken. Tot zeventien jaar na de ingreep waren er geen verschillen in de mate van refluxcontrole, dysfagie of kwaliteit van leven. Bij patiënten bij wie primair een open Nissen-fundoplicatie was verricht was vaker een heroperatie nodig, waarvan het merendeel de chirurgische correctie van een symptomatische littekenbreuk (hernia cicatricalis) betrof. Een interessant gegeven is dat zeventien jaar na fundoplicatie ruim 40% van de

patiënten aangaf wederom een maagbeschermer te gebruiken. Alhoewel het onduidelijk is wat de exacte reden voor dit gebruik is, is dit een belangrijk punt om te bespreken met patiënten bij wie de wens om niet levenslang medicatie te hoeven gebruiken de belangrijkste reden is om voor een fundoplicatie te kiezen. Bovengenoemd onderzoek benadrukt de behoefte aan studies die de langtermijnuitkomsten van fundoplicatie beschrijven, waarvan de resultaten zullen bijdragen aan verbeterde patiëntvoorlichting en selectie van patiënten die het meest baat zullen hebben bij een operatie van dit type.

Welk type partiële fundoplicatie is superieur?

In **hoofdstuk 3** vergeleken we de tweejaarsuitkomsten van twee gerandomiseerde studies die zijn uitgevoerd in Nederland en Australië, waarin de laparoscopische 270 graden posterieure, of Toupet-fundoplicatie (LTF) en 180 graden anterieure fundoplicatie (LAF) met elkaar worden vergeleken. Twee jaar na de primaire operatie waren er tussen beide groepen geen verschillen in de mate van refluxcontrole, de aanwezigheid van dysfagie of het ontstaan van gasgerelateerde klachten, met gelijkwaardige tevredenheidscores. De resultaten van deze studie zijn in lijn met de eerder beschreven éénjaarsuitkomsten van beide gerandomiseerde studies; door de ruwe data van beide studies te combineren konden we de grootste beschikbare dataset beschrijven waarin beide partiële fundoplicaties met elkaar worden vergeleken. Gebaseerd op de resultaten van deze studie moeten we concluderen dat de keuze om een LTF of LAF te verrichten gebaseerd dient te worden op de ervaring van de operateur met een van beide partiële fundoplicaties. Een langetermijn-follow-up van deze studie moet vaststellen of beide fundoplicaties gelijkwaardige subjectieve en objectieve uitkomsten bewerkstelligen.

In **hoofdstuk 4** beschrijven we een prospectieve studie waarin we middels gecombineerde pH-impedantiemetingen de invloed van LTF en LAF op refluxkarakteristieken en boeren hebben vergeleken. Met deze techniek waren we in staat gedurende 24 uur voor en drie maanden na de operatie alle bewegingen van zowel gas als vloeistof in de oesofagus te analyseren, waarbij onderscheid kan worden gemaakt tussen zure en zwak-zure reflux. Drie maanden na beide typen partiële fundoplicaties waren er geen significante verschillen in symptomatische refluxcontrole of totale oesofageale zuurexpositie, met een gelijkwaardige reductie van het aantal zure, vloeibare en gemengde vloeistof-gasrefluxepisoden. Verder was er geen significant verschil in het aantal postoperatieve zwak-zure refluxepisoden tussen beide procedures. Het aantal postoperatieve gastrische en supragastrische boeren werd gelijkwaardig door beide procedures gereduceerd, zonder significante reductie in het aantal luchtslikken. Dit resulteerde in een vergelijkbare incidentie van de symptomen ‘opgeblazen gevoel’ en ‘onvermogen te boeren’. Deze studie levert het fysiologische bewijs voor de hiervoor beschreven uitkomsten van de gerandomiseerde studies waarin LTF en LAF met elkaar zijn vergeleken en waarbij er sprake was van gelijkwaardige symptomatische en objectieve uitkomsten tot twee jaar na beide partiële fundoplicaties.

Interpretatie van routinematig uitgevoerde pH-metingen

Recidiverende refluxklachten vormen een belangrijke uitdaging voor zowel de chirurg als de patiënten; bij de laatsten is sprake van een significante invloed op de kwaliteit van leven en tevredenheid met de ingreep. 24-uurs-pH-monitoring wordt ook wel als de gouden standaard beschouwd voor het objectiveren van typische refluxklachten na een primaire fundoplicatie. In de dagelijkse chirurgische praktijk wordt niet routinematig bij iedere patiënt een postoperatieve pH-meting verricht. Echter, voor onderzoeksdoeleinden wordt steeds vaker gebruikgemaakt van routinematig uitgevoerde pH-metingen om objectieve data te kunnen presenteren. Hierdoor kan het voorkomen dat de chirurg te maken krijgt met een patiënt die helemaal geen klachten ervaart, maar wel een afwijkende pH-meting laat zien.

In **hoofdstuk 5** vergelijken we de symptomatische uitkomsten en de noodzaak tot heroperatie gedurende vijf jaar bij patiënten bij wie in het kader van wetenschappelijk onderzoek een routine-pH-meting is verricht; waarbij patiënten met pathologische oesofageale zuurexpositie worden vergeleken met patiënten met fysiologische oesofageale zuurexpositie. Gedurende vijf jaar vertoonden patiënten met pathologische en fysiologische zuurexpositie geen verschillen in zuurbrandschaal, het gebruik van zuurremmende medicatie, slikklachten of de tevredenheid met de ingreep. Van de patiënten met pathologische zuurexpositie onderging 18% gedurende vijf jaar een heroperatie voor recidiverende refluxklachten, hetgeen significant hoger was dan het aantal heroperaties onder patiënten met fysiologische zuurexpositie.

Middels deze studie hebben we aangetoond dat alleen de aanwezigheid van een afwijkende routinematig uitgevoerde postoperatieve pH-meting niet als onafhankelijke marker voor 'niet-functionerende fundoplicatie' dient te worden gebruikt. Dit gezien het feit dat er geen klinisch relevante verschillen in symptomatische uitkomsten tussen patiënten met pathologische en die met fysiologische zuurexpositie werden aangetoond. Een mogelijke verklaring hiervoor is dat een fundoplicatie een dusdanige reductie in oesofageale zuurexpositie bewerkstelligt dat een patiënt geheel of vrijwel geen reflux meer ervaart. In de huidige studie hebben we alleen patiënten geïncludeerd die deel hebben genomen aan een gerandomiseerd onderzoek en dientengevolge een routine postoperatieve pH-meting hebben ondergaan. Wanneer een patiënt in de dagelijkse praktijk wordt gezien met recidiverende refluxklachten, dient een pH-meting te worden verricht ter objectivering van de klachten, alsook een uitgebreide anamnesevoering. Nog belangrijker is dat de associatie tussen refluxklachten en de aanwezigheid van refluxepisoden wordt geanalyseerd. Daarnaast dient middels een gastroscopie en een slikfoto respectievelijk de aanwezigheid en ernst van refluxoesofagitis en de positie van de fundoplicatie te worden bepaald.

Chirurgische behandeling van hiatus hernia met en zonder het gebruik van mesh
Bij patiënten bij wie een middenrifbreuk oftewel hiatus hernia is geconstateerd en die daar klachten van ondervinden, is chirurgische correctie de aangewezen behandeling. Door de repetitieve stress die op het diafragma wordt uitgeoefend tijdens respiratoire functies (ademen, hoesten) maar ook bij non-respiratoire functies (braken), is dehiscentie van een eerder aangelegde cruraplastiek een belangrijk probleem. Verschillende studies hebben de uitkomsten van laparoscopische correctie van hiatus hernia onderzocht middels postoperatieve slikfoto's en/of gastroscopie, waarbij recidiefpercentages tussen de 12% en 42% worden beschreven. Dit heeft geleid tot de introductie van het gebruik van mesh, hetzij oplosbaar hetzij onoplosbaar, met als doel het recidiefpercentage te verlagen.

In **hoofdstuk 6** beschrijven we de uitkomsten van een retrospectieve cohortstudie waarin de symptomatische en objectieve uitkomsten van laparoscopische correctie van hiatus hernia met en zonder niet-oplosbare mesh met elkaar worden vergeleken. Gedurende een mediane follow-up-periode van 39 maanden waren er geen significante verschillen in het aantal symptomatische dan wel geobjectiveerde recidieven tussen beide groepen. Daarnaast was er in beide groepen een significante en gelijkwaardige verbetering in health-related quality of life, een significante reductie in dysfagie en een vergelijkbare gerapporteerde tevredenheid met de ingreep. Gedurende de gehele follow-up-periode traden er geen mesh-gerelateerde complicaties op.

Ondanks het feit dat de huidige studie geen verschillen liet zien in de uitkomsten na chirurgische correctie van hiatus hernia met en zonder mesh, bestaat er het risico op selectie-bias gezien het retrospectieve karakter van deze studie. Gedurende de afgelopen vijftien jaar zijn er vier gerandomiseerde studies gepubliceerd waarin het gebruik van mesh bij de chirurgische correctie van hiatus hernia is geëvalueerd. Echter, deze studies hebben tot nu toe geen duidelijk bewijs kunnen leveren voor verbeterde uitkomsten na het routinematig gebruik van mesh. Daarnaast is er een gebrek aan studies die de langetermijnuitkomsten beschrijven van patiënten bij wie dit soort meshes is toegepast.

In **hoofdstuk 7** hebben we de resultaten van een gerandomiseerde multicenterstudie beschreven, waarbij de uitkomsten van de chirurgische correctie van hiatus hernia met en zonder gebruik van niet-oplosbare mesh zijn vergeleken. Alle 72 geïncludeerde patiënten werd hierbij gevraagd zowel voor als zes maanden na de operatie een slikfoto en gastroscopie te ondergaan. Een jaar na beide procedures waren er geen verschillen in de aanwezigheid of ernst van de symptomen zuurbranden, pijn op de borst of dysfagie, met gelijkwaardige tevredenheidscores tussen beide groepen. Postoperatieve slikfoto's en gastroscopieën lieten geen significant verschil zien in het aantal recidief hernia's na beide procedures en er traden geen mesh-gerelateerde complicaties op.

Onze studie meegerekend zijn er in totaal vijf gerandomiseerde studies waarin het gebruik van mesh bij de chirurgische correctie van hiatus hernia is beschreven, waaruit geconcludeerd dient te worden dat er op dit moment onvoldoende bewijs is voor het routinematig verstevigen van de cruraplastiek middels mesh. De langetermijnuitkomsten

van de gerandomiseerde studies moeten aantonen of dit gehandhaafd blijft. Alhoewel de incidentie van mesh-gerelateerde complicaties laag blijkt te zijn, moeten deze langetermijnstudies tevens aantonen hoe veilig het gebruik van mesh is met het oog op het ontwikkelen van deze zeldzame maar ernstige complicatie.

De chirurgische correctie van hiatus hernia in specifieke patiëntenpopulaties

Gezien het feit dat de gemiddelde leeftijd wereldwijd steeds verder toeneemt en het feit dat hiatus hernia vaker voorkomt bij ouderen, is het aannemelijk dat de chirurg vaker te maken krijgt met dit type aandoening bij deze kwetsbare groep patiënten. Uitgebreide comorbiditeit is vaker aanwezig bij oudere patiënten, waardoor ze een verhoogd risico hebben op het ontwikkelen van perioperatieve complicaties. In **hoofdstuk 8** hebben we de perioperatieve uitkomsten van de laparoscopische correctie van hiatus hernia vergeleken van 121 patiënten met een leeftijd onder de 70 jaar versus 83 patiënten met een leeftijd boven de 70 jaar. Er waren geen sterfgevallen binnen dertig dagen na de operatie en er waren geen significante verschillen in de incidentie van intra- of postoperatieve complicaties tussen beide groepen. Univariate analyse toonde aan dat alleen het optreden van intra-operatieve complicaties geassocieerd was met het ontwikkelen van postoperatieve morbiditeit.

In tegenstelling tot onze studie hebben sommige andere studies wel een significant slechtere uitkomst van de chirurgische correctie van hiatus hernia bij ouderen aangetoond. Een mogelijke verklaring hiervoor is het feit dat deze studies gebruik hebben gemaakt van grote nationale databases, waarbij geen onderscheid is gemaakt tussen algemene chirurgische centra en centra die gespecialiseerd zijn in de laparoscopische antirefluxchirurgie. Verder is er vaak sprake van een grote heterogeniteit van de beschreven patiëntenpopulatie met betrekking tot verschil in ASA-scores, electieve versus spoedingrepen en het aantal conversies naar open chirurgie. Gebaseerd op onze ervaringen zijn we van mening dat de laparoscopische correctie van hiatus hernia bij zorgvuldig geselecteerde ouderen die geopereerd worden in daartoe gespecialiseerde centra even veilig is als dezelfde operatie bij jongere patiënten.

Een type IV hiatus hernia is een grote hernia diafragmatica waarbij sprake is van intrathoracale herniatie van de maag én andere abdominale organen, zoals dunne darm of dikke darm. Dit type breuken is een ware uitdaging voor de laparoscopische chirurg, met name gezien de grootte van het defect en de interpositie van dikke en/of dunne darm, waardoor er vaak straffe adhesies ter plaatse van het mediastinum aanwezig zijn. Hierdoor wordt met name adequate mobilisatie van de slokdarm bemoeilijkt, met het risico op beschadiging van belangrijke nabijgelegen structuren in het mediastinum. Onze hypothese was dat een simultane thoraco-laparoscopische benadering zou leiden tot een verbeterde visualisatie en mobilisatie van de slokdarm en zou resulteren in een verkorting van de totale operatieduur in vergelijking met een benadering waarbij eerst een thoracoscopie wordt gedaan en daarna een laparoscopie. In **hoofdstuk 9** beschrijven

we drie patiënten bij wie er sprake was van een type IV hiatus hernia en waarbij we deze nieuwe simultane thoraco-laparoscopische benadering hebben toegepast. Er deden zich geen intra- of postoperatieve complicaties voor en bij alle patiënten kon een volledige mobilisatie van de slokdarm worden bewerkstelligd. De gemiddelde opnameduur was 4,7 dagen en alle patiënten waren nagenoeg geheel asymptomatisch ten tijde van poliklinische vervolging. Deze nieuwe techniek is een fraai voorbeeld van de voordelen van een multidisciplinaire benadering bij deze uitdagende soort chirurgie. Door het combineren van twee minimaal invasieve procedures hebben we een veilige en efficiënte alternatieve methode voor de behandeling van dit type middenrifbreuken ontwikkeld, die overigens alleen dient te worden verricht in klinieken met een uitgebreide ervaring met zowel gastro-intestinale als thoraxchirurgie.

Een andere kwetsbare populatie bestaat uit patiënten bij wie een slokdarmresectie voor slokdarmkanker is verricht. Door de verbeterde vroegtijdige detectie en multimodale behandeling van deze aandoening is de overleving van patiënten met slokdarmkanker significant verbeterd. Hierdoor komt er meer informatie beschikbaar met betrekking tot de ontwikkeling van late complicaties na deze soort chirurgie. Een van deze complicaties is de ontwikkeling van een zogenaamde post-oesofagectomie-hiatus hernia. Meerdere studies hebben cohorten van patiënten beschreven bij wie deze complicatie is vastgesteld en daaropvolgend chirurgisch is gecorrigeerd. Hierbij lijkt dit type complicaties vaker voor te komen na minimaal invasieve slokdarmresecties in vergelijking met de open benadering. In **hoofdstuk 10** beschrijven we een systematische review en meta-analyse betreffende de incidentie van hiatus hernia na open versus minimaal invasieve slokdarmresecties, alsook de uitkomsten van chirurgisch herstel van dit type complicaties. Toen de data van 26 studies werd gecombineerd, bleek de incidentie van een symptomatische hiatus hernia na minimaal invasieve slokdarmresectie 4,5% versus 1,0% na open resectie, hetgeen hoogstwaarschijnlijk veroorzaakt wordt door een verminderde vorming van adhesies na minimaal invasieve chirurgie en de noodzaak tot iatrogene verwijding van de hiatus bij dit type ingrepen. Gebaseerd op elf studies waarin de uitkomsten van de chirurgische correctie van dit type complicaties werd beschreven, bleek de incidentie van perioperatieve complicaties 25% te bedragen. Mede gezien dit hoge morbiditeitpercentage dienen zowel chirurgen alsook radiologen zich meer bewust te zijn van dit relatief zeldzame maar potentieel levensbedreigende type complicaties na een slokdarmresectie, zowel tijdens het uitvoeren van een slokdarmresectie alsook gedurende de follow-up van deze groep patiënten.

Conclusies

De studies die in dit proefschrift beschreven zijn, leiden tot de volgende conclusies met betrekking tot de chirurgische behandeling van GORZ en hiatus hernia:

- Laparoscopische Nissen-fundoplicatie bewerkstelligt een duurzame en gelijkwaardige refluxcontrole meer dan vijftien jaar na de primaire ingreep, met een lager risico op het ontwikkelen van symptomatische littekenbreuken in vergelijking met open Nissen-fundoplicatie.
- Wanneer het niet levenslang willen gebruiken van zuurremmende medicatie de belangrijkste beweegreden voor een patiënt is om een fundoplicatie te ondergaan, dient de patiënt geïnformeerd te worden dat hij/zij een kans van 60% heeft dat dit op de lange termijn ook daadwerkelijk niet meer nodig is, en een kans van 16% dat hij/zij een tweede chirurgische ingreep zal moeten ondergaan.
- De laparoscopische 270 graden posterieure en 180 graden anterieure partiële fundoplicatie bewerkstelligen een gelijkwaardige controle van zowel zure als zwak-zure reflux, met een vergelijkbare incidentie van dysfagie en gasgerelateerde klachten.
- De aanwezigheid van pathologische oesofageale zuurexpositie, aangetoond middels routinematig uitgevoerde pH-metingen, dient niet te worden gebruikt als een onafhankelijke marker voor een 'niet-functionerende fundoplicatie'.
- Er is onvoldoende bewijs voor het routinematig verstevigen van de cruraplastiek middels niet-oplosbare mesh bij de chirurgische behandeling van hiatus hernia.
- Uitgevoerd in gespecialiseerde klinieken is de laparoscopische correctie van hiatus hernia bij zorgvuldig geselecteerde ouderen even veilig als bij jongere patiënten.
- De simultane thoraco-laparoscopische benadering is een veilige en efficiënte alternatieve benadering voor de chirurgische behandeling van type IV hiatus hernia.
- Hiatus hernia komt vaker voor na minimaal invasieve slokdarmresecties in vergelijking met de open benadering, waarbij de chirurgische correctie van dit type complicaties geassocieerd is met een relatief hoge morbiditeit.

Chapter 13

Review committee

List of publications

Dankwoord

Curriculum vitae

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List of publications

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Beste Eric, toen ik je in september 2014 voor het eerst sprak, werd de planning van dit promotietraject al grotendeels uitgestippeld. Met jouw enthousiasme voor en expertise op het gebied van partiële fundoplicaties (en Down Under) was het altijd ontzettend fijn en gemakkelijk werken. Een manuscript werd voorzien van enkele wijzigingen, gevolgd door 'ik zou het gewoon insturen'. We dachten hetzelfde over de invulling van mijn tijd als onderzoeker, waardoor we in rap tempo dit proefschrift hebben weten te realiseren. Ik ben er trots op onder jouw supervisie te hebben mogen werken, waarbij ik veel van je heb geleerd over zowel de chirurgie als alle zaken daaromheen, en ik ben ervan overtuigd dat ik zonder jou niet had gestaan waar ik nu sta. De belangrijkste les zal in ieder geval altijd zijn: 'als je eraan denkt, moet je het doen!'. *Have a good one* en veel dank voor alles!

De leden van de leescommissie en de oppositie, prof.dr. R.L.A.W. Bleys (Universitair Medisch Centrum Utrecht), prof.dr. D.C. van der Zee (Universitair Medisch Centrum Utrecht), prof.dr. I.A.M.J. Broeders (Universiteit Twente), prof.dr. W.A. van Klei (Universitair Medisch Centrum Utrecht), prof.dr. R. van Hillegersberg (Universitair Medisch Centrum Utrecht), prof.dr. H.J. Bonjer (VU Medisch Centrum), prof.dr. N.D. Bouvy (Maastricht Universitair Medisch Centrum), prof. D.C. van der Peet (VU Medisch Centrum). Dank voor het beoordelen van dit proefschrift en de bereidheid zitting te nemen in mijn promotiecommissie.

Dr. B. van Ramshorst,
Beste Bert, beklonken op de Chirurgendagen en twee weken later zat ik als onderzoeker in Nieuwegein. Ik wil je danken voor de kans die je me hebt geboden, als ook voor de inspirerende rol die je hebt vervuld. Ik heb helaas nooit direct in de kliniek met je mogen

werken, maar ben trots op het feit dat ik het grootste deel van mijn opleiding in het ziekenhuis mag volgen waar jij zo'n duidelijk stempel op hebt gedrukt. Dank!

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Beste Djamila, nooit geweten dat het in slaap vallen tegen de deur van jouw hotelkamer onze eerste researchbespreking zou zijn! Ik wil je danken voor de kansen die je me hebt gegeven als onderzoeker, AGNIO en opleidingsassistent in de mooiste kliniek van Nederland. Ik kijk uit naar een inspirerende en 'pony-vrije' opleidingstijd onder jouw supervisie.

Dr. V.B. Nieuwenhuijs,
Beste Vincent, samen met Eric heb jij je kennis en ervaring vanuit Australië naar Nederland gebracht. Jullie behoren tot de grootste antirefluxcentra van Nederland en hebben een fantastische onderzoekstrein opgezet; drie proefschriften in één jaar tijd zijn daarvan het resultaat. Het was altijd fijn met je samen te werken, waarbij je elk manuscript van kritisch en bruikbaar commentaar wist te voorzien. Dank voor de vruchtbare samenwerking.

Prof. D.I. Watson,
Dear prof. Watson, in the summer of 2016 you gave me the opportunity to come to Australia and work at the Department of Gastrointestinal Surgery at Flinders Medical Centre in Adelaide. During our weekly meetings, you amazed me with your extensive knowledge regarding antireflux surgery, as well as with your keen and early responses to all my questions. It has been a true honour to have been working with you, and in the beatiful country you live in.

Prof.dr. H.G. Gooszen,
Beste prof. Gooszen, in de zomer van 2016 heb ik met u mogen werken aan de follow-up van de MANCHET-trial, hetgeen in een mooie publicatie heeft geresulteerd. Uw kritische blik op de data heeft geleid tot de huidige insteek van het artikel, en ik wil u dan ook hartelijk danken voor de fijne en vooral ook leerzame samenwerking.

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Beste Jan, dank voor de fijne samenwerking afgelopen twee jaar op het gebied van de antirefluxchirurgie! Allebei naar Down Under, allebei in opleiding, allebei een boekje, niet slecht voor zo'n 'zuur verhaal'!

Dr. J.A. Broeders,
Beste Joris, jouw kritische blik en creativiteit hebben menig manuscript tot een mooier manuscript gemaakt. Dank voor de fijne samenwerking!

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Lieve Daan,

'Slaap je al, ik wilde nog wat kwijt,
Ik maak je even wakker tot mijn spijt
Ik moet je zeggen dat ik van je hou, en dat meen ik
Want alleen is maar alleen.'

(André Hazes, Ik Meen 'T)

Curriculum vitae

Jelmer Erik Oor was born on the 16th of August 1989 in Putten, The Netherlands, where he spent most of his childhood and attended high school at the Christelijk College Groevenbeek. After he graduated in 2007, he started medical school at the VU University Medical Center Amsterdam. In his graduation year, he completed an extended research internship at the Department of Pulmonary Surgery of the VU University Medical Center Amsterdam, followed by a senior internship at the Department of Surgery at the St. Lucas Andreas Hospital (OLVG location West nowadays). After he obtained his medical degree in November 2013, he started as a non-training resident at the Department of Surgery in the St. Lucas Andreas Hospital for a period of 9 months. In September 2014, he started his PhD research on the outcome of different laparoscopic techniques for the surgical treatment of gastroesophageal reflux disease and hiatal hernia at the St. Antonius Hospital Nieuwegein, under the supervision of dr. E.J. Hazebroek (St. Antonius Hospital Nieuwegein) and prof. dr. M.R. Vriens (University Medical Center Utrecht). During the summer of 2016, he attended Flinders University for a research elective at the Department of Gastrointestinal Surgery, Flinders Medical Centre, Adelaide, Australia, under the supervision of prof. D.I. Watson. From September 2016 until June 2017 he worked as a non-training resident at the Department of Surgery at the St. Antonius Hospital Nieuwegein. In July 2017, he started the general surgery training program at the Department of Surgery at the St. Antonius Hospital Nieuwegein (supervisor dr. D. Boerma).