

GASTROESOPHAGEAL REFLUX DISEASE: TREATMENT, OUTCOME AND SPECIAL
ASPECTS

PhD Thesis
(Summary)

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1. Introduction

Gastroesophageal reflux disease (GERD) is probably the most frequently occurring functional foregut disorder and accounts for approximately 75% of esophageal pathology in the industrial countries. Beside its frequency it is also very expensive in both primary and secondary care. The annual direct cost for managing GERD in the USA is estimated to be more than \$ 9 billion dollars. The precise prevalence of GERD is unknown, in western populations, 25% of people report having heartburn at least once a month, 12% at least once a week and 5% describe daily symptoms. In East Asia the prevalence of heartburn is lower with 11% reporting heartburn at least once a month, 4% weekly and 2 % daily. There is a lack of information about the prevalence of heartburn in other geographical regions, but symptoms of GERD are less common in non-western populations. Recent population-based studies revealed a 15-31% overall prevalence of GERD in Europe. The first ever antireflux operation was published by Rudolf Nissen in 1956 with the title: „a simple surgical technique to influence reflux esophagitis”. Later this so called Nissen fundoplication was performed on several hundred patients in Europe and in the USA for more than two decades. In 1991 Dallemagne et al. published their initial experience with laparoscopic Nissen fundoplication. The initial operative outcome of laparoscopic approach was similar to the open procedure, but mortality and morbidity were less than 0,2% and 5% respectively. Since its introduction in 1991 the number of performed laparoscopic Nissen fundoplication has risen significantly and become the most widely applied antireflux procedure.

2. Results and outcome of laparoscopic antireflux surgery

2.1. Patients and methods

Study population

From January 1998 to December 2006, 241 patients with GERD underwent a laparoscopic Nissen fundoplication in the Department of Surgery Medical Faculty University of Pécs. There were 140 women and 101 men with a mean age of 48,7 years (range18-80). Before the operation all patients underwent our routine functional foregut investigations, which contain barium X-ray esophagogram, endoscopy with biopsies from the distal esophagus, stationary water perfusion manometry and 24-hour esophageal pH monitoring. In selected cases 24-hour Bilitec (bilirubin monitoring) was also performed.

Esophageal Manometry

Manometry was performed using a water-perfused system (perfusion manometry and portable data recording system, Medtronic, Sweden) with a multiple-lumen catheter with 5 measurement points with 0,8 mm opening, located 5 cm apart. A pneumohydraulic pump was used for perfusion with distilled water at a rate of 0.5 mL/min. The mean end-expiratory LES pressure, length (overall, intraabdominal) of the LES, and LES relaxation were determined. Intraluminal esophageal pressures were recorded at 5, 10, and 15 cm above the upper margin of the LES. The manometric response to 10 standardized wet swallows (5-mL water bolus) was recorded. Mean amplitude and duration of the esophageal contractions in response to the wet swallows were determined.

24-hour esophageal pH monitoring

pH monitoring was performed (portable pH recording system, Medtronic, Sweden) by placing an antimony multi-use electrode 5 cm above the upper border of the manometrically determined LES. After 24 hours of measurement the probe was removed and data was downloaded into a computer and analyzed using a commercial software (Polygram, Medtronic, Sweden). DeMeester score was used to define esophageal acid exposure.

24-hour Bilitec monitoring

In selected cases where duodenogastric or duodeno-gastroesophageal reflux was suspected long term bilirubin monitoring (Bilitec 2000, Medtronic, Sweden) of the esophagus or stomach was performed and analyzed by a commercial software (Polygram NET, Medtronic, Sweden). The probe was placed in the stomach 5 cm below the lower border or in the esophagus 5 cm above the upper border of the LES.

Surgical procedure

In all patients a floppy Nissen-DeMeester fundoplication was performed. Patient is placed in the lithotomic position. Pneumoperitoneum of 13-15 mmHg is created inserting a Veres needle above the umbilicus at approximately one third of the line connecting the navel and the xyphoid cartilage. A 10 mm trocar is placed at this site for the 30° telescope. The other trocars are then inserted under direct visual control. A 10 mm trocar for the liver retractor is placed in the right anterior axillary line, a 5 mm trocar for an atraumatic grasper in the midclavicular line under the costal margin and two further 10 mm trocars under the left costal margin, one in the midclavicular line for dissection and one in the anterior axillary line for an additional atraumatic grasper or later, at the changed position, for the camera. As soon as all instruments are in position, and the left liver

lobe is retracted upwards the hiatal hernia can be visualized. After identifying the hernia the upper portion of the stomach is pulled back to the abdomen and the gastric fundus is mobilized by dissecting the short gastric vessels and the detachment of the retrofundic area. After complete dissection of the fundus, the left crus is identified. The right crus is visualized after dividing the hepatogastric ligament above the hepatic branch of the vagal nerve. The peritoneal layer between the right crus and the gastroesophageal (GE) junction is split and the division of the peritoneum continues anteriorly, along the phrenoesophageal ligament to the left crus. The dissection is then extended posteriorly behind the GE junction. Once the crura are dissected the distal esophagus is mobilized in the lower mediastinum. The hiatus is then closed using non-absorbable single stitches, starting at the preaortic membrane. Finally the fundus was pulled through behind the esophagus and a 360 degree floppy fundoplication was performed with three single stitches. One of the stitches was also sutured to the muscle of esophagus to anchorage the fundoplication. During the hiatoplasty and the fundoplication a 60 Ch bougie was inserted through the esophagus to prevent dysphagia.

Postoperative management

All patients were started on regular doses of antiemetic for the first 24 hours. No postoperative nasogastric decompression was used. A Gastrografin swallow was performed on postoperative day 1 to check wrap integrity, rule out leakage, and assess esophageal clearance. Patients were then started on a liquid diet. If they tolerated the liquids, solid food was allowed and they were discharged home on the 3rd postoperative day. Patients were routinely examined in our gastrointestinal surgery outpatient department 6 weeks postoperatively, then again at 6 months, and thereafter at 1-year intervals. All patients were asked to undergo repeat barium esophagogram if they were free of symptoms. If any symptoms of dysphagia or recidiv reflux appeared functional testing, including endoscopy, 24-hour pH recording and esophageal manometry was performed.

2.2. Results

A total of 261 procedures were performed for 241 patients. The principal presenting symptoms before the operation were heartburn (n = 180, 74,7%), regurgitation (n = 123, 51%), epigastric pain (n = 106, 43,9%), dysphagia (n = 31, 12,9%), and respiratory symptoms (n = 41, 17%). The mean duration of symptoms was 59,4 months (range, 1–396 months). Endoscopic findings showed that 58 (24,1%) of the 241 patients had no esophagitis, 65 (27%) had esophagitis Savary-Miller grade 1, 61 (25,3%) had grade 2, 30 (12,4%) had grade 3, and 27 (11,2%) had grade 4 esophagitis. Barrett's metaplasia was observed in 24 (9,9%) patients. The mean preoperative DeMeester score was 50,8 (range, 8,2–222,4), average LES pressure was 9,7 mmHg (range, 3,1-35 mmHg).

Major intraoperative complications occurred in 15 cases (6,2%). There were 6 bleeding, 1 injury of the spleen, 3 stomach and 5 esophageal perforations. 3 of the 5 esophageal perforation was identified only on the second, third and fifth postoperative day. These complications were manifested by a rapid onset of tachycardia, pyrexia, and peritonism. Unfortunately Gastrografin swallows showed no sign of leakage. The patients were returned to the theater, and the perforation was repaired through a midline laparotomy. Two of the 3 delayed reoperated patients died (0,82%). Conversion to laparotomy was performed in 13 (5,4%) of 241 patients. Indication for conversion was 6 bleeding, one splenectomy, 3 stomach and two esophageal perforation and one cardiopulmonary insufficiency due to pneumoperitoneum. Pneumothorax was observed in 11 patients, which was managed by a thoracic drainage. The average hospital stay was 6,4 days (range 3-16).

The mean postoperative follow-up was 48,5 months (range 2-107 months). From the 241 operated patients with GERD revisional surgery was necessary in 20 patient, which makes an overall failure rate of 8,3%. Indication for redo was therapy resistant dysphagia or recurrent reflux symptoms with objective evidence of failure with pathologic reflux on 24-hour esophageal pH monitoring. Reason for failure was dysphagia in three (15%), slippage of the fundoplication on the stomach (“telescope phenomenon”) in three (15%), disruption of the wrap in one (5%), paraesophageal hiatal hernia and disruption of the wrap in two (10%) and recurrent hiatal hernia in 11 (55%) patients. In addition another 10 remedial operations were performed, in whom the primary fundoplication was performed by other hospitals. In all but one of these cases the cause for failure was a recurrent hiatal hernia. One patient had recurrent hiatal hernia with disruption of the wrap. This makes a 67% of overall failure rate due to recurrent hiatal hernia.

In our series patients with revisional fundoplication were presented between 3 and 83 months (mean 23,4) after their initial operation. 7 redo fundoplications were completed laparoscopically, 3 were converted to laparotomy, 7 were open fundoplication and 3 were performed through a thoracolaparotomy. Intraoperative complication occurred in 2 cases (10%) cases. There were 1 stomach perforation and one delayed splenectomy due to left subdiaphragmatic abscess. From all 30 patients with remedial surgery the complication rate was 13,3% with two additional gastric perforation. Both conversion rate and major intraoperative complications were significantly higher in the remedial surgery group, compared to primary laparoscopic antireflux patients.

3. Factors predicting outcome of antireflux surgery

3.1. Introduction

The surgical management of gastroesophageal reflux disease (GERD) has improved with a better understanding of the underlying pathophysiology of the disease and technical refinements of the antireflux repair. However, the failure rate of all antireflux procedures, both open and laparoscopic, is reported to be 10%, ranging from 3%–30%. The most common pattern of fundoplication failure is anatomical; this includes fundoplication disruption, crus closure failure, paraesophageal hernia formation, a slipped Nissen, and a too tight fundoplication. The purpose of this analysis was to objectively identify factors that predispose to antireflux surgical failure. In order to do so we investigated the correlation between various prognostic factors and failure of antireflux procedure. Failure was defined symptomatically and functional testing basis and requirement of remedial surgery. Those patients who required resumption of medical therapy without redo surgery were not identified as failed antireflux operation cases.

3.2. Patients and methods

A retrospective case-control study was completed to determine the influence of different factors on antireflux surgery failure by retrospectively analyzing the data accumulated prospectively before the primary antireflux procedure, regarding to our standard preoperative investigations. Twenty study cases that underwent reoperative antireflux surgery and 221 control group patients without clinical evidence of failure after primary antireflux surgery were compared. Our prospectively collected data was maintained on an Excel spreadsheet, and statistical analysis was performed using SpSS Version 13.0. All predictors, such as symptoms (regurgitation, heartburn, dysphagia, epigastric pain), presence of Barrett's metaplasia, supraesophageal symptoms, preoperative response to PPI, use of antidepressant medications and short esophagus on endoscopy were recorded as "Yes" or "No", except age, sex, onset of symptoms and the objective assessors of the disease severity, which included grade of esophagitis, size of hernia, lower esophageal sphincter pressure and DeMeester score. The alpha level for the entire analysis was set at 0.05. The univariate analysis was performed using the Student *t* test and the chi-square test when appropriate.

3.3. Results

Baseline characteristics

The two groups were comparable regarding to patients characteristics. In the study group the average age was 45,2 years (range 22-70) compared to a mean age of 49,4 years (range 18-80) in the control group ($p=0,40$). There were 60% female in the case group, and 58% female in the control

group ($p=0,85$). The univariate analysis showed that age and gender have no role in the outcome of antireflux surgery.

Symptoms

Of the preoperative registered symptoms investigated none of them were found to be associated with failure of antireflux surgery. Although heartburn, regurgitation and epigastric pain were more frequent in the study group (90 % vs. 73%, 65% vs 49% and 45% vs. 43,9%) univariate analysis did not reached the level of significance ($p=0,1$; 0,19; 0,92). Dysphagia were recorded only 5% of redo patients compared to 13,5% of the control group ($p=0,27$). Respiratory symptoms were almost similar (15% vs. 17,2%) between the two groups. Analysis of the length of the symptoms also showed no significant difference ($p=0,13$).

Medications

From medications, patients used before the operation, the daily usage of antipsychotic drugs (antidepressant or tranquillizer) and the response to PPI were investigated. We found that almost one quarter of the patients with GERD (24,5%) uses some kind of antipsychotic drug daily. In the study group this ratio was 40 % compared to 23 % in the control group, which was not a statistically significant difference ($p=0,092$). Also the percentage of patients in the study group, who did not respond well to PPI, was higher (30%) compared to the control group (9%). This difference was statistically significant ($p=0,004$), which means that no response to PPI has influence on the outcome of antireflux surgery.

Disease severity

Endoscopic severity of esophagitis showed no significant difference between the two groups by univariate analysis. The only factor from the endoscopic parameters, which had prognostic value by univariate analysis on the success of the antireflux surgery, was the esophageal shortening. Short esophagus described by the endoscopist was present 60% of the patients who later had failed antireflux procedure compared to 6,8 % of the patients who have no signs of failure ($p=0,0001$).

Functional tests

From the routinely used esophageal functional tests, DeMeester score, LES pressure and motility disorders of the esophageal body were investigated. The latter was defined if any problem with the amplitude, velocity or propagation of a swallow wave was observed on manometry. Although more severe reflux on pH monitoring was recorded in the study group (mean DeMeester score: 51,1 vs. 48,7) and the LES pressure was also lower (11,2 mmHg vs. 13,5), none of these

factors reached the statistical significance ($p=0,94$; $p=0,60$ respectively) to be related to surgical failure. Esophageal body motility disturbances had no influence on outcome of laparoscopic antireflux surgery ($p=0,67$).

Hiatal hernia

Because we found that the most common reason for failure is a recurrent hiatal hernia this factor was examined in details. Regardless of hernia size, hiatal hernia is not a predictive factor on outcome of the antireflux surgery ($p=0,83$). Although the percentage of patients with a hiatal hernia preoperatively was almost the same in the two groups (57,5 % vs. 55%), the percentage of patients with hernia of more than 3 cm in size was significantly higher in the study group ($p=0,007$). We found that patients with preoperative hiatal hernias greater than 3 cm were significantly associated with failure after antireflux surgery.

3.4. Conclusion

From the several factors investigated only three had effect on the outcome of laparoscopic Nissen fundoplication by univariate analysis. We found that large hiatal hernia and short esophagus can predict a possible failure after laparoscopic fundoplication and patients who had no response to PPI are also at greater risk for failure. All other factors (i.e age, gender, symptoms, endoscopic severity of esophagitis, functional tests results) had no influence on the outcome of laparoscopic Nissen fundoplication.

4. Special aspects of gastroesophageal reflux disease

4.1. Hypertensive conditions of the lower esophageal sphincter

It is well known that one of the most important factors in the pathogenesis of gastroesophageal reflux disease is the insufficient pressure of lower esophageal sphincter (LES). This can be due to an inadequate overall or intraabdominal length of the sphincter and/or hypotension of LES. Although the association between GERD and hypertensive conditions of lower esophageal sphincter has always seemed paradoxical, several studies reported that such conditions (i.e Hypertensive lower esophageal sphincter, Achalasia) can be accompanied with GERD. Both achalasia and hypertensive lower esophageal sphincter (HLES) is characterized with elevated lower esophageal sphincter pressure. The difference between the two diseases is the capability of the LES to relax. In HLES there are no esophageal body motility disturbances and relaxation of the LES is normal, while in achalasia the loss of inhibitory neurons of the LES resulting in an incomplete relaxation of LES during swallow. The normal peristaltic activity of the esophageal body

disappears, or simultaneous wave forms are generated by the initiation of a swallow. The exact cause of both achalasia and HLES is still unknown.

4.1.1. Hypertensive lower esophageal sphincter

HLES was first described by Code et al in 1960. It is classified as a primary esophageal motility disorder and characterized by a high resting pressure of LES, which exceeds the upper limit of LES pressure measured in normal population. It is distinguished from diffuse esophageal spasm and achalasia, which also presented with elevated pressure of LES, by normal esophageal body motility and LES relaxation. The most common symptoms in patients with HLES are dysphagia and chest pain, and therefore, therapy was mostly focused on decreasing the pressure of LES by surgical or medical means. Recent reports showed that HLES can also be associated with symptoms of GERD and abnormal esophageal acid exposure, measured by 24-h pH monitoring. Therefore, therapy recommendation for reducing sphincter pressure raises questions of worsening gastroesophageal acid reflux. On the other hand, therapy for abnormal acid exposure with a fundoplication carries a possible risk of more severe obstructive symptoms. A prospective study was performed on patients with HLES associated with GERD to evaluate the effect of laparoscopic fundoplication.

4.1.2. Patients and methods

Overall Patients' Characteristics

Between January 1999 and 2006, a total of 241 patients underwent laparoscopic fundoplication for GERD. Out of them, six patients had GERD associated with HLES. Inclusion criteria were HLES detected by stationary manometry and typical symptoms of GERD. HLES was defined if the pressure of LES was above 35 mmHg (>95 th percentile of normal population), relaxation of LES was normal and no esophageal body motility disorder was present. Patients with achalasia or other esophageal motility disorders were excluded. All patients underwent endoscopy, 24-h esophageal pH monitoring, stationary esophageal manometry, and barium swallow as well. There was no disturbance in esophageal clearance on barium X-ray. Out of the six patients who entered the study, there were five women and one man with a mean age of 40.5 years (range 19–74). Four patients had endoscopic signs of esophagitis and 3 presented with a hiatal hernia. In all patients, laparoscopic floppy Nissen fundoplication was performed. No intra- and perioperative morbidity was observed. There was no mortality. Patients were first called back for manometry and 24-h pH monitoring 6 weeks after the operation. Then, they were yearly followed by symptom questionnaire and barium swallows. At later follow-ups, patients who agreed underwent 24-h

esophageal pH monitoring and stationary esophageal manometry. The mean follow up time was 56 months (range 50–61). At late follow-up, only two patients agreed to undergo functional testing.

4.1.3. Results

24-hour esophageal pH monitoring

Before the operation the mean DeMeester score was 41,7 (range 16,7-86). Six weeks after surgery the score returned to a normal value of 2,9 (range 0,3-4,1). At late follow-up only two patients agreed to undergo 24-hour pH monitoring. The mean DeMeester score was 1,2.

Stationary esophageal manometry

The mean pressure of LES was 50,55 mmHg (range 35,6 - 81,3) before surgery. After the operation the average LES pressure was 24,7 mmHg (range 23,2 - 26,6) at six weeks and 15,7 mmHg at late follow-up.

Symptoms

Besides major symptoms of reflux, two patients also had a slight dysphagia. Although the pressure of LES was higher in the two patients who had dysphagia besides their reflux symptoms, there was no significant difference regarding LES pressure (54.8 vs. 48.4) or DeMeester score (41.5 vs. 41.9) between the two patients with slight dysphagia and the other four without dysphagia. The only difference was that the two patients with dysphagia had the more severe esophagitis on endoscopy, and they both had a hiatal hernia. No chest pain was observed before the operation. Six weeks after the operation, all patients were symptom-free. No new onset dysphagia or chest pain developed in the first year of follow-up. The dysphagia, in the two patients who had minor dysphagia before the operation, was also resolved. One patient developed dysphagia 2 years after surgery. He needed a redo surgery. A laparoscopic exploration was performed. As a reason for dysphagia, a too tight posterior hiatoplasty was diagnosed, which was managed laparoscopically. No abnormality with the wrap was observed. After this remedial operation, the patient became symptom free. The annually performed symptom assessments revealed no recurrence of any of the three major reflux symptoms, and no further case of dysphagia was observed during the average of 56 months follow-up.

4.1.4. Conclusion

On the basis of our results, we must assume that there are two types of HLES. One is a primary esophageal motor disorder with symptoms of dysphagia and chest pain and with good response to myotomy. The other is the HLES, which is probably secondary to abnormal

gastroesophageal acid exposure. In these patients, primary symptoms include typical symptoms of gastroesophageal reflux, and abnormal esophageal acid exposure can be observed on pH monitoring. Therefore, we suggest that in this subgroup of HLES patients, a 360° fundoplication should be performed instead of a cardiomyotomy, to control reflux and thereby eliminate the cause of HLES.

4.2. Achalasia and gastroesophageal reflux disease

Achalasia is a primary motor disorder characterized by usually a hypertensive lower esophageal sphincter, which fails to relax completely after swallowing and by aperistalsis of the thoracic esophagus, due to a loss of Auerbach's plexuses. Since the LES of achalasia patients is normo- or hypertensive and relaxation is absent or impaired, there is controversy whether gastroesophageal reflux can occur in these patients prior to treatment.

There are several prospective 24h pH studies which have shown, that untreated achalasia patients are capable of demonstrating true acid reflux. Heartburn was described in one third of patients with achalasia, furthermore esophagitis and Barrett's esophagus were also found in some patients and some reports showed that the prevalence of hiatal hernia in achalasia patients varies between 4-10 % which can be as high as 25 % in the elderly population. And not even axial but paraesophageal hiatal hernia is published with associated achalasia. It is still not clear whether two coincidental diseases (i.e. achalasia and GERD) are present or one disease can transform into the other.

Since all treatment of achalasia is directed toward elimination of the outflow resistance to obtain a good esophageal emptying into the stomach one can assume that patients with GERD associated achalasia need different treatment because standard cardiomyotomy could worsen gastroesophageal reflux. In order to rule out this possibility we changed our therapeutic strategy in patients with GERD associated achalasia and instead of the routinely used laparoscopic Heller myotomy with anterior Dor fundoplication, we performed laparoscopic myotomy with 360 degree Nissen fundoplication. In the time interval 1998-2006 26 patients underwent laparoscopic surgery for achalasia. From them 3 patients had suspected gastroesophageal reflux associated achalasia and therefore they all underwent laparoscopic myotomy but instead of an anterior fundoplication, a 360 degree Nissen fundoplication was performed.

4.2.1. Case reports

Case 1.

A 44-year-old male, with a two year history of classic heartburn and dysphagia, presented in February 1999. His heartburn and symptoms of gastroesophageal reflux started in 1997, heartburn

was decreased after meal. These symptoms were transformed into dysphagia within a year. Symptoms were progressive over a 6-months period until dysphagia occurred with every meal when he stopped to eat and drank cold water. 15 kg-s weight loss was observed in this two year period. Esophagogastrosopy was performed in 1998, showing erosive esophagitis, inflammation was found in the squamocolumnar junction by histology as well. Patient was treated with lansoprazole 30 mg once a day and cisapride 10 mg three times daily resulting in improvement of the symptoms. Clinically, dysphagia progressed rapidly when reendoscopy was performed which revealed a dilated esophageal body with intact mucosa. Cardia was closed, but the endoscope could pass through the cardia suspected to be fibrotic. Barium swallow showed dilated esophageal body with a short smoothly tapered segment at the esophagogastric junction, decreased peristalsis and retention of barium thought to be consistent with achalasia. Esophageal manometry demonstrated LES average resting pressure of 34.4 mm Hg. LES did not relax properly (relaxation < 90%). Deglutitory waves were of low amplitude and simultaneous, „mirror image” wave forms were generated by the initiation of a swallow. 24hr pH-metry showed acid reflux, with total DeMeester score of 94,9. Using pH 3 as a discriminant threshold for GERD the reflux score was: 62,3. Hypertrophy of the LES was found during operation, with the rigidity of the cardia. After a follow-up of 72 months the patient is symptom free. On esophagogram no signs of dysphagia or reflux were seen.

Case 2.

42-year-old man presented in September 2000 with the chief complaint of dysphagia. Symptoms were progressive over a four months period. He felt heartburn, regurgitation, gastroesophageal reflux was experienced the same time that was inhibited by on demand taking of H2 blocker, nizatidine (150 mg). Endoscopy revealed dilatation and atony of the esophageal body, closed cardia that did not open during the procedure. Mild inflammation was found in the distal portion of the esophagus, the instrument passed through the sphincter with an increased pressure. Barium swallow showed a slightly dilated esophageal body with nonpropulsive contractions, tight, nonrelaxing sphincter that allowed contrast material to escape in small quantities from the esophagus. Sequentially propagated waves transversing the distal esophageal body were absent, low amplitude simultaneous contraction waves were observed. Baseline pressure of the esophageal body was elevated. The resting pressure of the LES was not increased (24,4 mm Hg) however incomplete relaxation could be observed. 24 h pH-metry revealed nocturnal acid reflux that was not related to meal. Patient was last seen on follow-up 58 months after the operation. He had no dysphagia and a reflux symptom was also not recorded. Barium X-ray still showed some dilatated esophagus but no outflow obstruction was detected. Gastroesophageal reflux was not seen by esophagogram.

Case 3.

A 65-year old woman was admitted to our clinic in 2003. She had a history of seven years of typical reflux symptoms with heartburn, regurgitation. No dysphagia was observed at that time. The first endoscopy was performed in 2001 where Savary-Miller II stage esophagitis was described with *Helicobacter pylori* infection from the stomach. Patient was put on PPI therapy and eradication of *H.pylori* was performed. Control endoscopy in 2002 showed no signs of esophagitis with normal cardia and stomach. Before the admittance the patient's reflux symptoms disappeared and dysphagia progressed. Endoscopy found esophageal dilatation, with esophagitis and the cardia was narrowed. Histology of biopsies from the distal esophagus showed chronic esophagitis and Barrett's metaplasia. Manometry and 24 hour pH monitoring was performed. The LES pressure was 34,3 mmHg with percent relaxation of 11,5. Esophageal motility showed that 25 % of the swallows was simultaneous and 75 % were uncoordinated with the mean pressure of 23,4 mmHg. At that time there was no abnormal acid reflux on pH monitoring. The first two follow-up of the patients was uneventful. No dysphagia or reflux was observed. At three years follow-up the patient was still symptom free, but esophagogram revealed a small amount of reflux in Trendelenburg position, without any signs of obstruction of the distal cardia. The patient was very satisfied with the result of the operation and she did not agreed to undergo 24-hour pH monitoring, so she was advised to take PPI regularly.

4.2.2. Conclusion

If preoperative examinations produce a strong suspicion of achalasia, which developed on the basis of GERD, we suppose that instead of an endoscopic dilatation a Heller's myotomy should be considered with a proper 360 degree fundoplication, as anterior hemifundoplication does not protect fully against reflux.

4.3. Large hiatal hernias

4.3.1. Introduction

Once the diagnosis of type II or type III paraesophageal hiatal hernia is made, because they imply a greater risk for the patient such as hemorrhage, strangulation, volvulus and perforation, it is recommended to perform elective repair. Although laparoscopic repair of type I sliding hernia is well established with a proven record of efficacy and safety, results regarding laparoscopic paraesophageal hiatal hernia seems to be controversial. Short and intermediate results of feasibility and efficacy were promising, but recently several series showed a variable incidence of recurrence ranging between 0 and 40 % on midterm follow-up. Outcome results usually depend on how the recurrence is defined, anatomically or subjectively. Although the dissection and posterior closure of

the crura, the so called posterior hiato-plasty is an essential step in any antireflux operation, the breakdown of this repair and the recurrent hiatal hernia is the one of the most common reason for failure of antireflux surgery. This is probably due to the constant movement of the diaphragm and the pressure gradient between the negative intrathoracic and positive intraabdominal pressures during coughing, sneezing or laughing. Another problem of hiatal repair is the lack of a strong fascia adjacent to the hiatal aperture for which the closing sutures encompass predominantly the muscle of the crura. In some cases, especially in large hiatal hernias, the hiatal closure can be performed only with tension between the cruras. So it seems that the hiatal closure is the weakest link in the otherwise well elaborated methods of antireflux surgery.

To overcome this problem several attempts were made to reinforce the closure. In order to avoid using any foreign material around the cardia the employment of the teres ligament, as described earlier for cardiopexy, seemed suitable. In 2003 a prospective study was introduced in our department which was design to evaluate the safety and efficacy of a new laparoscopic procedure. Midterm result of this study led us to start another prospective study from 2006 with a modification of mesh hiato-plasty to prevent recurrence and mesh related complications. In order to compare the results and outcome of the different procedures for large hiatal hernia retrospective analysis of our prospectively collected data was performed. A historical control group was set up, which contained patients without any reinforcement of the repair for large hiatal hernia. The further two groups included patients from the above mentioned two prospective studies.

4.3.2. Patients and method

From the 241 patients in the time interval from 1998-2006 there were 60 patients presented with large hiatal hernia. Another 10 patients, who had large hiatal hernia secondary to a failed antireflux operation performed in other hospitals, were also enrolled in this study, which made a total of 70 patients with large hiatal hernia. 31 patients underwent laparoscopic Nissen-DeMeester fundoplication with posterior hiato-plasty between 1998-2002 (Group A). In 26 patients from 2003-2006 reinforcement of the hiatal closure was performed with ligament teres hepatis (Group B) and in 2006 a further 13 patients underwent a modified mesh repair (Group C). The mean age was 57 years (range 33-74) in Group A, 62,8 (range 39-80) in Group B and 59 (range 43-72) in Group C respectively. Patients were followed with our standard follow-up procedure, to obtain objective data and to discover any possible anatomic recurrence. On a regular basis (3 months, 6 months, 1 year after the operation and then yearly) patients were called back for evaluation. All patients were questioned for symptoms including heartburn, regurgitation, dysphagia, chest pain. Barium swallow were also performed in all cases at all follow-up times. If any symptom of reflux was detectable functional foregut testing was performed. Anatomic recurrence was defined if a recurrent sliding

hiatal hernia, without subjective symptoms was detected. Symptomatic recurrence was defined if large axial or paraesophageal hiatal hernia was observed with subjective symptoms confirmed with functional testing and if a remedial surgery was indicated.

Surgical procedure

In Group A our standard antireflux procedure was performed as described earlier. In patients in Group B the surgical procedure was the same until the hiatal closure. After the hiatoplasty the position of the camera is changed to the left lateral port and the liver retractor is changed to a grasper. The teres ligament is stretched downward with a grasper and is dissected with ultrasonic dissector from the parietal peritoneum. Great care has to be taken to preserve the blood supply of the ligament and to avoid haematoma formation. In order to do so the dissection should proceed between the two vascular arcades (liver and peritoneal attachment), which supplies the ligament, and should stop at the hepatic branch, which feeds the hepatic vascular arcade. After mobilization of the ligament teres the initial position of the instruments are restored and the ligament is pulled through the GE window (between the closed crura and the posterior esophageal aspect). The stronger part of the ligament, which is covered by peritoneum, is sutured to the left crus with two non-absorbable stitches at the level of the esophagus. The right crus is then also sutured to the ligament at the same level creating a U-shaped reinforcement of the crura around the posterior aspect of the esophagus. Finally a Nissen-DeMeester fundoplication is performed.

In Group C after the hiatal closure a polypropylene “U” shape mesh is introduced. It is then placed on the hiatoplasty at an onlay position and fixed with staples (Protac, Autosuture). To avoid connection between the mesh and the esophagus or stomach, and therefore reduce the risk of mesh erosion, the omentum of the dissected great curvature is used. It is brought behind the esophagus and fixed to the right crus with non-absorbable stitches. In this position the omentum is between the mesh and the cardia and covers the mesh completely. In all cases a Nissen fundoplication is also added.

Statistical analysis

Statistical analysis was performed with Chi² with Yates correction. P values < 0.05 were considered significant.

4.3.3. Results

Perioperative data

In Group A the mean operative time was 93 minutes (range 78-110). The conversion rate was 16%, 2 cases due to bleeding, 1 because of cardiopulmonary reasons and 2 for adhesions due to

previous operations. Mean hospital stay was 7,3 days (range 4-16). No mortality was observed, perioperative morbidity was 9,6 % which included 2 bleedings and one pneumothorax. In Group B the mean operative time was 115 minutes (range 96-130). There was no perioperative mortality. 6 conversions (23%) to open surgery were performed all of them were redo operation. The morbidity was 11,5% which included 1 intraoperative pneumothorax, 1 wound disruption after conversion and 1 late subdiaphragmatic abscess on the left side. Mean hospitalization time was 7,4 days (range 4-30 days). In Group C the mean operative time was 110,5 minutes (range 90-145). There were no conversions to open procedure. Mean hospital stay was 5,7 days (range 3-7). Mortality rate was 7,7%. One patient died due to the consequence of esophageal perforation. In this latter case we think that the perforation was caused by the bougie, because it was at the level of tracheal bifurcation. Unfortunately the routinely used esophagogram on the first day did not show any leakage and the perforation was discovered only the fifth postoperative day. Reoperation was performed with esophageal suture and drainage but the patient died on the 10 th postoperative day.

Follow-up data and recurrence rates

In Group A through an average of 34,6 months (until the beginning of the teres study) follow-up there were 2 anatomic and 8 symptomatic recurrences with hiatal hernia on barium X-ray. The latter 8 patients all underwent remedial surgery. Unfortunately the primary preoperative data of this historical control group was not sufficient enough to further evaluate these patients in order to determine what led to recurrence. The average time elapsed after the primary operation was 25,6 months (range 6-42).

In Group B the follow-up was 13-46 months with an average of 30,9 months. 2 patients reported reflux symptoms postoperatively one and two years respectively. They were evaluated with esophagogastrosocopy, stationer manometry and 24-hour esophageal pH monitoring. Neither signs of abnormal reflux nor anatomic recurrence was detected by these patients. 1 patient had severe pain after eating 18 months after the operation. Investigations revealed a 3 cm paraesophageal recurrent hernia. This patient underwent remedial surgery. 1 patient had temporary mild dysphagia and fullness after eating 2 years after surgery. Barium swallow showed slippage of the fundoplication into the mediastinum. Barium swallows revealed anatomic recurrence with slipped fundoplication in another two asymptomatic patients, 12 months after the operation. The latter 3 patients are now under strict surveillance, repeated barium swallows showed no changes in the size or type of recurrent hiatal hernia and no renewal of symptoms were recorded until this time. Out of these three patients two were predictable for failure due to the very thin right crus observed during the operation. From the 4 patients who had anatomic recurrence 3 had extreme large hiatal hernia (diameter was ≥ 9 cm) at the primary operation and one was a redo. From the 26 patients

who entered the study 21 patients had a smaller hiatal hernia diameter than 9 cm. Among these 21 patients only one (4,7%) (who had recurrent hiatal hernia at primary operation) anatomical recurrence was observed. From the 5 patients who had a hiatal hernia greater than 9 cm in diameter, 3 (60%) had anatomic recurrence which was statistically significant ($p=0,02$). Regarding to symptomatic recurrence no recurrence was observed from the 21 patients with hiatal hernia size between 6-9 cm and one recurrence was found in the 5 patients who had extreme large hiatal hernia. This difference also reached statistical significance ($p=0,037$). Failed previous antireflux operations did not affect the anatomic recurrence rate. Out of 6 patients who had the ligamentum teres operation as a redo only one (16,6%) had recurrence, while in the remnant 20 patient without previous fundoplication 3 (15%) had anatomic recurrence.

In Group C with a shortest average follow-up of 6,5 months there were no symptomatic or anatomic recurrence on barium X-ray. Summary of the anatomical and symptomatic recurrence of the three groups is shown in table 1. Statistical analysis of the three groups showed that reinforcement of the hiatal closure with teres ligament did not significantly reduce the overall recurrence rate compared to primary closure alone ($p=0,14$). Although the number of patients in Group C is low and the follow-up time is also not comparable to the other groups, modified mesh hiatoplasty seemed to decrease the overall recurrence rate significantly compared to hiatoplasty alone ($p=0,02$), but not compared to teres ligament reinforcement ($p=0,135$). Anatomical recurrences showed no statistical differences at all between the three groups. Symptomatic recurrence was significantly reduced by both teres ligament ($p=0,024$) and modified mesh ($p=0,043$) reinforcement compared to the historical control group, but between the two reinforcement technique no significant difference was found ($p=0,474$).

Table 1. Outcome table comparing the three different surgical procedures for treatment of large hiatal hernia

	I. Group N=31	II. Group N=26	III. Group N=13
Recurrences	10 (32,3%)	4 (15,3%)	0
Anatomic	2 (6,5%)	3 (11,5 %)	0
Symptomatic	8 (25,8%)	1 (3,8 %)	0

4.3.4. Conclusion

Our result suggests that laparoscopic reinforcement of large type II and III hiatal hernias with the teres ligament or with the modified mesh are reduces recurrences. Both are safe and effective. Teres procedure has the advantages that it carries no risk of a foreign material and applies no additional costs, and also prevents recurrences in the majority of patients. It seems that the only

limitation of this technique is the size of the hiatal hernia and possibly the weakness of the right crus, therefore we presume that in such cases of extreme large hiatal hernia a prosthetic mesh would be probably advisable. In order to avoid any mesh related complication we prefer to cover the mesh with the omentum.

4.4. Duodeno-gastroesophageal reflux

4.4.1. Introduction

Pathologic duodenogastric (DGR) and duodeno-gastroesophageal reflux (DGERD) can be detected in 10% to 50% of all reflux patients. Although duodenogastric reflux is a physiologic phenomenon which occurs normally nights and postprandial, excessive or pathologic duodenogastric reflux has been implied in the development of gastritis, gastric ulcer disease, dyspepsia, and even carcinoma. When duodenogastric and duodeno-gastroesophageal reflux present at the same time grade of the esophageal mucosa injury is strongly correlated with the amount of bile and acid refluxated into the esophageal lumen. Studies showed that in patients with more severe complication of GERD such as Barrett's metaplasia or esophageal strictures significantly more acid and bile was detected on esophageal pH and bilirubin monitoring in the esophageal lumen, compared to healthy volunteers or in patients with less severe grade of esophagitis. The effect of pathologic duodenogastric reflux and its toxic components on the esophageal mucosa have been demonstrated also in several experimental animal models.

Although many facts are known about the association of alkaline duodenogastric and gastroesophageal reflux, the therapeutic implications are still controversial. One of the reasons for that is, that the diagnosis of pathologic duodenogastric reflux, the accurate assessment of this abnormal condition, is very difficult to establish. The detection of alkaline reflux and/or the detection of its different components have been difficult and unreliable. Prior methodologies employed for measuring DGER, including endoscopy, aspiration studies (both gastric and esophageal), scintigraphy, and ambulatory pH monitoring, have technical difficulties and do not accurately measure DGER. Currently, the most commonly used means of assessing DGER is the ambulatory esophageal and gastric bilirubin monitoring system (Bilitec). Although measuring bile reflux with Bilitec can help to ensure the diagnosis of abnormal duodenogastric and duodeno-gastroesophageal reflux, indications for surgical intervention is still unanonomous. Furthermore the precise surgical intervention is not yet widely agreed and accepted. The most often used technique is a biliary diversion with Roux-en-Y suprapapillary duodenojejunostomy also called duodenal switch.

4.4.2. Patients and methods

In those patients where symptoms were susceptible for DGR or DGER beside our routine preoperative workup (barium X-ray, endoscopy, manometry, 24-hour esophageal pH monitoring) bilirubin monitoring with Bilitec 2000 was performed. Bilirubin exposure was analyzed above the 0,25 absorbance level in the stomach and 0,14 in the esophagus. Abnormal bile reflux was defined when the exposure exceeded the 95th percentile of healthy controls, which was 24,8 in the stomach and 11,8 in the esophagus. From 241 GERD patients who underwent a laparoscopic antireflux procedure 45 patients had two-channel (esophagus and stomach) 24-hour bilirubin monitoring before the operation because suspected duodeno-gastroesophageal reflux or because normal pH monitoring results. A further 16 patients had Bilitec after their initial antireflux operation for recurrent and atypical symptoms with normal 24-hour esophageal pH monitoring. From these 61 patients four (6,5%) underwent a duodenal switch procedure. They all were females with a mean age of 41,8 years (range 32-53).

Surgical procedure

Our preference is to perform the biliary diversion procedure through a right subcostal upper abdominal incision, but other authors prefer an upper midline incision. When the Roux-en-Y suprapapillary duodenojejunostomy is begun, the duodenum is mobilized by a Kocher maneuver to feel the head of the pancreas and especially the position of the papilla of Vater as accurately as possible. Care must be taken to dissect an area around the duodenum well above the papilla and without devascularizing the proximal duodenum. Using the thumb and index finger around the duodenum, it is usually possible to feel the closest approximation at a point along the medial duodenal border just proximal to the papilla at approximately 3 to 7 cm distal to the pylorus, depending on the anatomic situation of the patient. At this point the duodenum is dissected free of the head of the pancreas by carefully dividing the small vessels. It is essential to keep a minimal of 3 cm of postpyloric duodenum because only in this case remains enough receptor in this region for duodenal inhibition of acid secretion. It is important to reduce the risk of jejunal ulcers. Precautions must also be taken to avoid damage to the intrapancreatic common bile duct. When the channel between pancreatic head and duodenum is completed, the duodenum can easily be divided and closed with a linear stapling device. Since the dissection is carried down to the most distal point just proximal of the papilla, it is not advisable to oversew the stapling suture to avoid obstruction of the common bile duct. The first or second jejunal loop, depending on the vascular status of the mesentery, is pulled supracolically into the area of the duodenal bulb through an opening in the transverse mesocolon, and to the right of the midcolic vessels. A dissection point in the jejunal loop is identified to prepare a limb that is long enough to complete the Roux-en-Y jejunojunostomy

without tension. The distal jejunal loop is then sutured to the proximal duodenal stump in an end-to-end anastomosis. The proximal jejunal limb is anastomosed end-to-side to the distal jejunal limb 40 to 50 cm distal to the duodenojejunal anastomosis. The opening in the mesocolon is closed.

4.4.3. Results

From the 45 patients who had Bilitec before their antireflux operation 18 (40%) patients had abnormal duodeno-gastroesophageal reflux. After a successful laparoscopic fundoplication only one (5,5%) patient had remnant symptoms susceptible for duodenogastric bile reflux. In this patient, symptoms appeared after ERCP, EST and stone extraction from common bile duct followed by a laparoscopic cholecystectomy. After the antireflux procedure, reflux symptoms disappeared and only epigastric pain and loss of appetite remained. Conservative treatment was started with sucralfate and prokinetic drugs with little effect. Because persistent symptoms of duodenogastric reflux a duodenal switch was performed half year after the laparoscopic fundoplication. Functional investigation before biliary diversion, showed no recurrent gastroesophageal reflux. At follow up patient was symptom free, and she returned to her normal eating habit.

From the 16 patients who had bilirubin monitoring after the antireflux operation, due to renewal of partially reflux symptoms and atypical epigastric symptoms, 3 (18,7%) had abnormal duodenogastric reflux. They all had epigastric and right subcostal pain, weight loss and loss of appetite. One of them also had typical symptoms of gastroesophageal reflux. The latter patients had a laparoscopic cholecystectomy 2 years ago and in the same time gastrotomy and removal of a gastric polypus was performed. Due to acute gastric hemorrhage reoperation was performed and the site of polypectomy was sutured from a pyloromyotomy. One year after that a Toupet fundoplication was performed because of gastroesophageal reflux disease. Barium swallow and endoscopy showed a small hiatal hernia and esophagitis SM II grade. Abnormal esophageal acid exposure was detected on 24-hour pH monitoring and incompetent LES was observed on manometry. 24-hour bilirubin monitoring revealed abnormal duodenogastric and gastroesophageal bile reflux. A duodenal switch and a revisional Toupet fundoplication were performed. One year after surgery the patient was symptom free and gained 2,2 kg. At two year follow-up, reflux symptoms renewed and functional testing proved recurrent abnormal esophageal acid exposure. Patient was put on PPI and she is now free of symptoms.

The other two patients had antireflux operation for GERD and histologically proven Barrett's metaplasia one and two years earlier. One of them also had cholecystectomy before. They had no reflux symptoms but epigastric and right subcostal pain, weight loss and appetitelessness were present. On 24-hour esophageal pH monitoring no abnormal acid reflux was observed. Bilirubin monitoring showed excessive bile reflux in the stomach, but in the esophagus no abnormal

bile reflux was detected. A duodenal switch was performed in both patients. One of them had a small wound healing problem after surgery and the other had reflux symptoms one year after surgery but functional testing showed no abnormal acid reflux into the esophagus. The patient who had wound healing disturbance had an abdominal hernia repair two years after the duodenal switch.

There were no intraoperative complications, or major perioperative morbidity. Mortality was not observed. After an average of 24,3 months follow-up (range 21-30) all patients were symptom free. There was no progression or regression of the two Barrett's metaplasia. The three patients with symptoms of weight loss regain 2,2; 2,5 and 12 kg respectively. One patient is still on PPI because of recurrent gastroesophageal acid reflux. With this therapy she is symptom free.

4.4.4. Conclusion

Patients with suspected duodeno-gastroesophageal reflux must be studied thoroughly using all current diagnostic measures to determine the probability of the pathophysiologic importance of such a finding. If excessive alkaline reflux into the esophageal lumen is identified, the patient should be clearly informed that the planned antireflux operation, usually a laparoscopic Nissen fundoplication, may possibly be only the first step of the procedures that are necessary to bring constant relief. If complaints diminished after the antireflux procedure there is no need for a duodenal switch. Also in patients after primary antireflux operation for GERD appearance of atypical, epigastric symptoms should always bring attention to abnormal duodenogastric reflux. A preoperative medical therapy to neutralize alkaline refluxed should be the first step in those patient. A duodenal diversion operation after laparoscopic antireflux surgery is indicated only in patients who have had a history of continued severe symptoms despite medical therapy and have clearly documented duodenogastric reflux. In these cases good results can be achieved with duodenal switch procedure.

5. New findings

1. We suppose that there are two types of HLES patient. One with dysphagia and chest pain, who respond well to cardiomyotomy and the other is the GER associated HLES in whom the hypertension of the LES is a consequence or complication of gastroesophageal reflux. In these patients instead of a cardiomyotomy a 360 degree fundoplication should be performed.

2. Achalasia could develop in the settings of long standing gastroesophageal reflux. There are three factors that can predict GERD associated achalasia. First, if there is long standing reflux symptoms in the patients' history and reflux symptoms diminish after dysphagia developed. The second suspicious factor is a hiatal hernia accompanying achalasia. And third is, if pH monitoring shows abnormal acid reflux. The setpoint should be changed to pH 3 in these cases to exclude artifacts from acidic fermentation in the esophageal lumen.

3. We suppose that if preoperative examinations produce a strong suspicion of achalasia, which developed on the basis of GERD, a proper 360 degree fundoplication should be considered after Heller's myotomy, as anterior hemifundoplication does not protect fully against reflux.

4. A new laparoscopic technique was developed in our institute to prevent recurrence after laparoscopic repair of large hiatal hernia. The teres ligament was used to reinforce the hiatal closure in patients treated for large hiatal hernia. This is a completely new operation and it was never published before.

5. Although reinforcement of the hiatal closure with teres ligament was sufficient in most of the cases, recurrence was found in patients with extreme large hiatal hernia and weakened right crus. In these cases a modification of mesh cruroplasty was applied. This modification was also developed by our unit. To reduce the risk of mesh associated complications the mesh was covered with the omentum of the dissected greater curvature to avoid connection of the mesh and the cardia.

6. Experience with duodenal switch procedure, which was designed to eliminate abnormal bile reflux, has not been published in the Hungarian medical literature so far. We reported on four cases.

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7. Publications

1. Articles in Periodicals (In connection with Thesis)

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IF_{Summ}:5,371

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6. Abstracts published in Periodicals (Not in connection with Thesis)

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14. Kelemen D, **Varga G**, Róth E, Horváth ÖP. Kísérletes pancreas transzplantáció új módszere Magyar Sebészet 1999; 52: 210 (Abstract)
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7. Presentations (Not in connection with Thesis)

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2. **Varga G**, Jaberansari MT, Borsiczky B, Róth E, Paroczai M. Does bisaramil (a new anti-arrhythmic drug) have any cardioprotective and haemodynamic effect in an experimental ischemia–reperfusion model? MST Kongresszus 1998 Budapest, Hungary
3. **Varga G**, Cseke L, Pataki N, Horváth ÖP. Mesenterio-axiális gyomorvolvulus műtéti megoldása laparoszópos gasztropexiával – Esetismertetés MST Kongresszus 1998 Budapest, Hungary
4. **Varga G**, Király Á, Horváth ÖP. Relation between different investigating techniques in patients with gastroesophageal reflux disease MGT 41. Nagygyűlése 1999, Balatonaliga, Hungary
5. **G.Varga**, M.Fein, K.H.Fuchs, S.M.Freys, J.Maroske , H.Tigges . Indication, technique and results of laparoscopic treatment of achalasia. ISDE Congress 2001 Sao Paolo, Brasil
6. **G.Varga**, M.Fein, K.H.Fuchs, S.M.Freys, J.Maroske , H.Tigges, A. Thiede Interaction between gastric pH, Helicobacter pylori and duodenogastric reflux in patients with gastroesophageal reflux disease ISDE Congress 2001 Sao Paolo, Brasil
7. **Varga G**.,Fein M.,Freys S.,Marosle J.,Tigges H., Fuchs K. Az achalasia sebészi kezelésének korai eredményei MST Kongresszus 2001 Pécs
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9. **Varga G**, Cseke L, Horváth Ö.P. Subglottic trachea stenosis as a consequence of long time gastroesophageal reflux - Case report MGT 44. Nagygyűlése 2002, Balatonaliga, Hungary
10. A. Papp, L. Cseke, G. Pavlovics, R. Farkas, S. Márton, **G. Varga**, L. Potó, ÖP Horváth. Locally advanced squamous cell cancer of the cervical oesophagus: the role of multimodal therapy. ESS Congress 2007 Dublin, Ireland

8. Invited lectures:

1. **Varga G**, Cseke L, Kalmár K, Horváth ÖP. Nagyméretű hiatus hernia kezelése: Új laparoscopos módszer III. Pécsi Nyelőcsőnap 2004, Pécs, Hungary
2. **Varga G**. Nyelőcső motilitászavarok a sebész szemszögéből. III. Pécsi Nyelőcsőnap 2004, Pécs, Hungary
3. **G. Varga**, L. Cseke, K. Kalmár, Ö. P. Horváth. Difficult closure of hiatus with Ligamentum teres – prevention of recurrence-Early results. EAES Congress 2005 Venice, Italy

4. **Varga G**, Cseke L, Horváth ÖP. A duodeno-gastroesophagealis refluxbetegség diagnózisa és sebészi kezelésére MST Jubileumi kongressusa 2006 Budapest, Hungary
5. **Varga G**. Die Beziehung Achalasie und Hiatus Hernie Symposium und Kurs Gastrointestinale und Kolorectale Funktionsstörungen 2007 Frankfurt , Germany

9. Participation in Research Grants

1. ÖP Horváth, **G Varga**, K Kalmár, Á Király, I Kiss, E Kálmán, T Aikou, H Feussner, KH Fuchs: A gyomor és a gastro-oesophagealis átmenet rosszindulatú daganatainak komplex kezelése. FKFP-0361/2000
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3. ÖP Horváth, L Cseke, D Kelemen, K Kalmár, **G Varga**: Aborális pótyomor prospektív randomizált összehasonlítása hagyományos orális pótyomorra totális gastrectomia után. OTKA T 042726/2003
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