

**MINIMALLY INVASIVE SURGICAL PROCEDURES IN THE TREATMENT OF  
BARRETT'S ESOPHAGUS**

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- I. **Simonka Zs, Paszt A, Ábrahám Sz, Pieler J, Tajti J, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Rárosi F, Lázár Gy.** The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: long-term results. *Scand J Gastroenterol* 47:13-21, 2012. IF: 2,019
- II. **Simonka Zs, Paszt A, Géczy T, Ábrahám Sz, Tóth I, Horváth Z, Pieler J, Tajti J, Varga Á, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Refluxbetegség és Barrett-nyelőcső miatt műtétre kerülő betegek összehasonlító vizsgálata. Comparison of surgical patients with gastroesophageal reflux disease and Barrett's esophagus. *Magy Seb* 67:287–296, 2014.
- III. **Rokszin R, Simonka Z, Paszt A, Szepes A, Kucska K, Lazar G.** Successful endoscopic clipping in the early treatment of spontaneous esophageal perforation. *Surg Lapar Percutan Tech* 21: e311-e31, 2011. IF: 1,227
- IV. **Lázár G Jr, Paszt A, Simonka Z, Bársony A, Abrahám S, Horváth G.** A successful strategy for surgical treatment of Boerhaave's syndrome. *Surg Endosc* 25:3613-9, doi: 10.1007/s00464-011-1767-1. Epub Jun 11, 2011. IF: 4,013

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- I. **Simonka Zs, Paszt A, Géczy T, Ábrahám Sz, Tóth I, Horváth Z, Pieler J, Tajti J, Varga Á, Lup M, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Barrett nyelőcső miatt végzett antireflux műtét hosszú távú eredményei. In: *Magyar Sebész Társaság Sebészeti Endoszkópos Szekció XVI. Kongresszusa Sebészeti Továbbképző Tanfolyam*. Eger, 2015. november 12 -14. Eger: p. 100.

- II. **G Lazar, Zs Simonka, A Paszt, Sz Abraham, J Pieler, J Tajti, L Tizslavicz, I Nemeth, F Izbeki, A Rosztoczy, F Rarosi.** The effects of laparoscopic Nissen fundoplication on Barret's esophagus: longterm results. *Surg Endosc* 26:(Suppl. 1.) p. S38, 2012.
- III. **Lázár Gy, Paszt A, Ábrahám Sz, Pieler J, Tajti J, Tizslavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Rárosi F, Simonka Zs.** The effects of laparoscopic Nissen fundoplication on Barrett's esophagus:: long-term results. *Dis Esophagus* 25:(S1) Paper P01.07, 2012.
- IV. **Rokszin R, Simonka Zs, Paszt A, Szepes A, Kucska K, Lázár Gy.** A spontán nyelőcső-perforatio korai ellátása endoscopos klippeléssel. *Magy Seb* 65:314-315, 2012.
- V. **Simonka Zs, Paszt A, Ábrahám Sz, Bársony A, Horváth G, Lázár Gy.** A Boerhaave-syndroma sebészi kezelésének stratégiája. *Magy Seb* 65:270-271, 2012.
- VI. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Pieler J, Tajti J, Izbéki F, Rosztóczy A, Wittmann T, Tizslavicz L, Németh I, Lázár Gy.** A laparoscopos antireflux műtét szerepe a Barrett-nyelőcső sebészi kezelésében. *Magy Seb* 64:163, 2011.
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- VIII. **Simonka Zs, Paszt A, Géczi T, Ábrahám Sz, Pieler J, Tajti J, Izbéki F, Rosztóczy A, Wittmann T, Tizslavicz L, Németh I, Lázár Gy.** A laparoscopos antireflux műtét szerepe a Barrett nyelőcső sebészi kezelésében. *Magy Seb* 63:237-238, 2010.
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- X. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Pieler J, Tajti J, Mészáros P, Dargai S, Horváth Z, Tizslavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Efficiency of laparoscopic procedure in Barrett's esophagus. *Nihon Geka Gakkai Zasshi* 111:(suppl.2) p. 263, 2010.

- XI. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Tóth I, Horváth Z, Pethő I, Tizslavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Comparison of efficiency of laparoscopic procedures in GERD and Barrett's esophagus (short term functional and histological results). *Br J Surg* 96:(Suppl.5) 55-56, 2009.
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- XIII. **Simonka Zs, Paszt A, Ábrahám Sz, Géczi T, Tóth I, Horváth Z, Pethő I, Tizslavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár Gy.** Comparison of efficiency of laparoscopic procedures in GERD and Barrett's esophagus (short term functional and histological results). *Hepatogastroenterology* 55:(Suppl.1) A186, 2008.
- XIV. **Simonka Zs, Paszt A, Ábrahám Sz, Pethő I, Tizslavicz L, Németh I, Izbéki F, Rocztóczy A, Wittmann T, Lázár Gy.** Laparoscopos antireflux műtét szerepe a Barrett-nyelőcső kezelésében. *Magy Seb* 61:187, 2008.
- XV. **Simonka Zs, Paszt A, Ábrahám Sz, Pethő I, Tizslavicz L, Németh I, Izbéki F, Rocztóczy A, Wittmann T, Lázár Gy.** Laparoscopos antireflux műtét szerepe a Barrett-nyelőcső kezelésében. In: *A Magyar Sebész Társaság 59. Kongresszusa: Sebészeti Továbbképző Tanfolyam. Debrecen, 2008. június 18-20.* Paper 143.

**ABBREVIATIONS**

*BE, Barrett's esophagus*

*BMI, body mass index*

*CM, cardiac metaplasia*

*COX-2, cyclooxygenase-2*

*D, dysplastic (group)*

*ERD, erosive reflux disease*

*FM, fundic metaplasia*

*GERD, gastroesophageal reflux disease*

*GEJ, gastroesophageal junction*

*HGD, high-grade dysplasia*

*I, intestinal (group)*

*IH, immunohistochemistry*

*IM, intestinal metaplasia*

*LES, lower esophageal sphincter*

*LGD, low-grade dysplasia*

*lLES, length of lower esophageal sphincter*

*LSBE, long-segment Barrett's esophagus*

*NBI, narrow band imaging*

*NERD, non-erosive reflux disease*

*NI, non-intestinal (group)*

*pLES, pressure of lower esophageal sphincter*

*PPI, proton-pump inhibitor*

*PTFE, polytetrafluoroethylene*

*PTX, pneumothorax*

*rLES, relaxation time of lower esophageal sphincter*

*SD, standard deviation*

*SSBE, short-segment Barrett's esophagus*

*pRBC, packed red blood cells*

*UES, upper esophageal sphincter*

## **1. INTRODUCTION**

Gastroesophageal reflux disease (GERD) can be summarized as mucosal irritation, inflammation and consequential symptoms caused by the reflux of gastric contents into the esophagus due to the impaired function of the gastroesophageal junction (GEJ). It may be accompanied by a wide range of symptoms. Most often, the main symptom is heartburn, a retrosternal pain which may be caused by the regurgitation of gastric acid into the esophagus. In certain cases, it may also be accompanied by dysphagia. Extraesophageal symptoms may often be misleading: in case of proximal (high) reflux, airway symptoms may often be expected; hoarseness, cough, asthma-like episodes, sinusitis or otitis media may also occur. A chest pain of non-cardiac origin or dental caries may also raise the possibility of GERD.

The incidence of GERD shows a significant increase in developed Western countries. The traditional classification of reflux disease (the Los Angeles Classification)<sup>[6]</sup> was based on the endoscopic picture, differentiating between cases without signs of inflammation (non-erosive reflux disease, NERD) and those with erosive esophagitis (ERD) or with complications of severe erosion. The Montreal Classification<sup>[7]</sup>, besides the esophageal symptoms, also takes the extraesophageal symptoms, i.e., the complaints of the patients, into account. In parallel with the severity and duration of GERD, the risk of possible complications also increases. Ulcers and/or strictures developed on the basis of inflammation may lead to severe dysphagia. The condition of acute abdomen/acute chest due to the perforation of an ulcer or stricture may require an urgent (surgical) intervention. Additional possible complications are Barrett's esophagus (BE) and, ultimately, adenocarcinoma developed based on this in the lower third of the esophagus.

### **1.1. BARRETT'S ESOPHAGUS (BE)**

The definition of BE can be understood based on its pathogenesis. As "regeneration" of the mucosal inflammation and, later, mucosal damage developed due to the persistent acid and/or mixed reflux, a columnar epithelium that is more resistant to the acidic environment appears next to or replaces the squamous epithelium in the lower third of the esophagus. The polymorphism of Barrett's metaplasia is reflected by the fact that the regeneration starting from the esophageal Schaffer glands may have varying histological appearance, possibly with multiple histological entities next to each other. Besides intestinal metaplasia (which is

considered to be the classic form of BE), numerous other forms may appear, including fundic or cardiac columnar epithelium, ciliary columnar epithelium, or even pancreatic acinar or tubular metaplasia.<sup>[8]</sup> Although the literature describes the possibility of dysplastic transformation in the case of intestinal metaplasia, non-intestinal forms should not be disregarded either because of the heterogeneity of the condition (histological forms present next to each other or that may transform into each other).

The endoscopic appearance of the metaplasia can be described most accurately with the “Prague C and M” classification<sup>[9]</sup>, which also gives the extension and distance of the lesion from the gastroesophageal junction. An extensive BE longer than 3 cm is a so-called long-segment BE (LSBE), whereas a condition shorter than this is a short-segment BE (SSBE).

## **1.2. DIAGNOSTICS OF GERD AND BE**

Besides the proper evaluation of the patient’s symptoms, many instrumental examination methods are available to clarify the diagnosis. Flexible endoscopy, with its advance and widespread use, has clearly become the gold standard in the assessment of the esophagus. Without a proper endoscopic background, a thorough investigation of neither GERD, nor BE can be performed. The new endoscopic examination methods (such as chromoendoscopy, NBI, etc.) may help map GERD and BE more precisely. The need for proper professional experience and technical equipment warrants the investigations to be performed in centers.

The objective confirmation and description of reflux and, ultimately, making the indication for surgery are also inconceivable without proper functional examinations. The gastroenterologist may decide about the correct treatment strategy in the knowledge of the presence of acid or bile reflux obtained with pH-metry, impedance monitoring and Bilitec monitoring.<sup>[24]</sup> The information about the function, motility disorders and impairment of the esophageal body and sphincters gained during manometry may influence the choice of surgical procedure.<sup>[25]</sup> A proper biopsy sampling procedure (Seattle protocol)<sup>[26]</sup> and a well-prepared pathological background are also indispensable for detecting the presence of BE.

## **1.3. TREATMENT OF GERD AND BARRETT’S ESOPHAGUS**

The conservative (non-surgical) treatment is extremely complex and involves losing weight (besides other lifestyle advices), increasing stomach emptying (with prokinetics), protecting the esophageal mucosa, and decreasing the acid content of the refluxate.

Nowadays, the medical treatment is primarily based on effective gastric acid-reducing therapies. The symptoms of reflux can be considerably improved with proton-pump inhibitor therapy, the use of which may mean an adequate long-term control of reflux. Similarly, they can be effective in the treatment of some patients with BE (but there is only indirect evidence of their efficacy in the treatment of metaplasia and dysplasia).<sup>[27]</sup> In case of BE, aspirin in increased dose may be added to antacids as chemoprevention, which may reduce the risk of transition from metaplasia to dysplasia through the inhibition of COX-2.

The purpose of the endoscopic treatment of BE is to remove or destroy the affected mucosa when dysplasia appears, after which the regeneration restores the squamous epithelium or results in a dysplasia-free columnar epithelium if the treatment is combined with successful acid inhibitor therapy. Numerous procedures are known from endoscopic mucosal resection to submucosal dissection. Ablation may be achieved with radiofrequency therapy but laser therapy, argon plasma coagulation, cryotherapy and photodynamic therapy may also be used. Out of these methods, however, the depth of the dissection can be reconstructed and an actual histological examination can be performed only in the case of endoscopic resections. In the rest of the procedures, there is less control of the ablation depth, and the rate of potential complications (stricture and, more rarely, perforation) is higher. The indication for endoscopic procedures is not clear in case of LGD. A special issue is recurrence in the submucosal glandular structures after the endoscopic treatment. In case of LGD, the rate of this may be up to 10% in the year following the procedure. However, an advantage of the endoscopic procedure is that it can be repeated.<sup>[28]</sup>

In case of HGD, the higher relapse rate after endoscopic procedures or the appearance of carcinoma may require surgical intervention. The presence of in situ carcinoma is almost certain in the case of HGD; however, neither this, nor an early carcinoma means a contraindication to endoscopic procedures.<sup>[28]</sup>

### **1.3.1. Surgical Treatment**

The various antireflux procedures have long been accepted in the surgical treatment of GERD and BE. Nowadays, with the spread of minimally invasive surgical methods, laparoscopic antireflux procedures that have low mortality rates have become equivalent alternatives to conservative treatment. In case of proper indication, the correctly performed procedure successfully decreases the acid and bile reflux, and also restores the function of the lower esophageal sphincter. In case of BE, with the reflux gone, we may suppose that the

progression of metaplastic and dysplastic processes is stopped and that regression is achieved. The long-term success of antireflux procedures, similarly to that of medical treatment, is contradictory, as well as their role in the prevention of adenocarcinoma. In cases of BE with LGD, better results may be expected from the combination of mucosal ablation and medical or surgical treatment. In cases of HGD, in situ carcinoma and early cancer, distal esophageal and cardiac resection may be considered an oncologically adequate treatment from a surgical point of view. In case of invasive adenocarcinoma, esophageal resection may be performed.

## **2. Problem and objectives**

The increase in the incidence of esophageal adenocarcinoma calls the importance of this condition to our attention. The key for the successful treatment of esophageal adenocarcinoma is the prevention of its development or its early recognition. The only precancerous condition of esophageal adenocarcinoma confirmed to date is BE. In our clinical study, we intended to establish the clinical risk factors of the development of BE, the prevention of its development, and the possible strategy for its surgical treatment.

*1. An objective of our work was to understand the potential clinical risk factors and relationships playing a role in the development of BE and the process of the Barrett's metaplasia—dysplasia—carcinoma transformation through the study of patients with GERD and BE (Study 1).*

*2. A further objective was to study the efficacy of surgical treatment (laparoscopic antireflux procedure) among patients subjected to surgery because of either GERD or BE (Study 2).*

*3. During our short-term and long-term follow-up, the effect of laparoscopic antireflux procedure on the histological changes of Barrett's esophagus, as well as its possible preventive effect in the process of carcinogenesis were studied (Study 3).*

*4. The early and late complications of the antireflux procedure were studied (Study 4).*

*5. The successful endoscopic treatment of spontaneous esophageal perforation, a rare complication of BE, is presented through one of our cases (Study 5).*

### **3. PATIENTS AND METHODS**

#### **3.1. COMPARISON OF PATIENTS SUBJECTED TO SURGERY BECAUSE OF GERD OR BE (STUDY 1)**

Our retrospective clinical study was based on patients subjected to surgery because of GERD or reflux disease accompanied by Barrett's esophagus at the Department of Surgery of the Faculty of Medicine of the University of Szeged between January 1, 2001 and December 31, 2008. Nissen's laparoscopic antireflux procedure was performed in 176 cases because of GERD (Group 1) and in 78 cases because of BE (Group 2).

In Study 1, the results of the preoperative assessment were compared between the above two patient groups.

#### **3.2. CLINICAL RISK FACTORS OF THE DEVELOPMENT OF BE**

As a continuation of Study 1, patients in the BE group (78 patients) were divided into three further groups on the basis of the histological results of their preoperative endoscopic biopsies: a non-intestinal group (NI, 53 patients) with fundic (FM) and cardiac metaplasia (CM), an intestinal group (I, 18 patients) with intestinal metaplasia (IM), and a dysplastic group (D, 7 patients) with LGD. BE involved a short segment (< 3 cm, SSBE) in 67 cases (85.9%) and a long segment (> 3 cm, LSBE) in 11 patients (14.1%). We compared the results of the preoperative assessment between these three groups.

#### **3.3. COMPONENTS OF THE PREOPERATIVE ASSESSMENT**

##### **3.3.1. Endoscopy**

The esophagogastroscope performed as part of the preoperative gastroenterological assessment to confirm the reflux disease was the first step of the standard examination, during which the gastroesophageal junction was examined. Hiatal hernia is diagnosed if the impression of the diaphragmatic crura is widened by more than 2 cm. Its size is given in centimeters. The reflux disease was described based on the Los Angeles Classification.<sup>[6]</sup> Biopsy was performed (in all four quadrants, with 2-cm intervals) to confirm or rule out Barrett's metaplasia (Seattle protocol).<sup>[26]</sup> Barrett's esophagus was characterized based on the Prague C & M Criteria.<sup>[9]</sup>

### **3.3.2. HISTOLOGICAL EXAMINATION**

The formalin-fixed, paraffin-embedded histological samples were assessed for Barrett's metaplasia or dysplasia after hematoxylin-eosin and immunohistochemistry staining. In our study, samples with either fundic or cardiac or intestinal metaplasia were included. In case of BE with LGD described during the histological examination, two experienced pathologists also examined the slides.

### **3.3.3. Functional Examinations**

#### **Esophageal pH-metry**

Of the functional examinations, 24-hour pH-metry was performed in each case. The acid reflux was measured with a pH electrode inserted nasally and secured 5 cm above the upper margin of the lower esophageal sphincter (LES). The probe recorded the acid reflux episodes for 24 hours—esophageal pH decrease below 4, number of reflux episodes longer than 5 minutes, duration of the longest reflux episode, percentage of time of exposure to pH below 4, and the DeMeester composite score, out of which the DeMeester score and the percentage of time of exposure to pH below 4 have the highest sensitivity (96%) and specificity (100%). Their normal value, based on studies conducted with health volunteers, is 14.7 and 4.2%, respectively.<sup>[29,30,31,32,33]</sup>

#### **Esophageal manometry**

During the manometry, the motor function of the esophagus was examined with a catheter inserted nasally into the esophagus, using the standard distilled water perfusion method, and mapping the function of the entire esophageal body, the pharyngoesophageal junction and the LES: the length of the sphincter (ILES), its mean pressure (pLES), its relaxation (rLES), the amplitude and duration of the contractions of the esophageal body, and (optionally) pharyngeal motility. The generally accepted values for the UES are a length of 2 to 5 cm and a mean pressure of 40 to 100 mmHg; and for the LES, a length of 2 to 4 cm and a mean pressure of 10 to 40 mmHg. The pressure in the lower third of the esophagus during swallowing is 20 to 170 mmHg.<sup>[29,34,35,36]</sup>

**Bilitec**

In both groups, Bilitec monitoring was performed only in cases where bile regurgitation was suspected during endoscopy. The nasally inserted catheter was positioned 5 cm above the LES, and the photoabsorption (at 450 nm) of bile acids reaching the esophagus was detected with a fiber optic spectrophotometer.<sup>[29, 30,31,32]</sup>

**3.4. SURGICAL TREATMENT, SURGICAL TECHNIQUE**

After the gastroenterological assessment, patients with GERD and BE underwent elective surgery. Laparoscopic antireflux procedure with Nissen's 360-degree fundoplication was performed on the patients of both groups. During the standardized steps of the procedure, the flaccid part of the lesser omentum was opened while retracting the left lobe of the liver, and then the diaphragmatic crura were prepared (first the right, and then the left one), going around the entire circumference of the esophagus, mobilizing this way its abdominal segment. The fundus was mobilized by transecting the gastrosplenic ligament and the short arteries and veins running within it. The posterior reconstruction of the diaphragmatic crura was performed with interrupted stitches (using non-absorbable suture). After this, 360-degree (Nissen's) fundoplication was performed in each case. Partial (Toupet) and anterior (Dor) funduplications were excluded from the study.

During the surgeries, a mesh was placed because of the large hiatal hernia in 14 cases. The indication for this was the unsuccessful tension-free closure of the diaphragmatic crura. A PTFE mesh was used for the reconstruction, which was secured with a spiral clamp. Gastropexy was performed in 6 cases in the GERD group, and a mesh was also placed in each of these cases because of a large hiatal hernia. In 26 cases, cholecystectomy was also performed in the same session because of the accompanying cholelithiasis.

### **3.5. POSTOPERATIVE FOLLOW-UP (STUDY 2)**

During Study 2, the efficacy of procedures performed because of GERD or BE were compared based on subjective measures (Visick score) and the results of early functional examinations.

#### **Assessment of symptoms and objective measures of outcome**

Visick grading was used to assess the effect of surgery on the symptoms: complete resolution (Grade I); an improvement (Grade II); no effect of surgery (Grade III); or deterioration relative to the preoperative state (Grade IV). This scoring system was devised to give an overall impression of the benefits of antireflux surgery because it exhibits good correlation with heartburn, the most prominent symptom of GERD.<sup>[37]</sup>

In the postoperative period, patients were subjected to follow-up surgical and medical examinations. Postoperative functional examinations, such as esophageal manometry, 24-hour pH-metry and, in reasonable cases, bile exposure (Bilitec) monitoring and endoscopy were performed in the early postoperative period with an average follow-up period of  $13.8 \pm 19.31$  months in the GERD group and  $16.7 \pm 17.00$  months (range: 3–23) in the BE group.

### **3.6. ENDOSCOPIC AND HISTOLOGICAL FOLLOW-UP OF PATIENTS SUBJECTED TO LAPAROSCOPIC ANTIREFLUX PROCEDURE BECAUSE OF BE (STUDY 3)**

During the study, in the later postoperative period, an additional upper endoscopy with biopsy was carried out in the BE subgroups to assess the changes in BE. The overall average follow-up time was  $42 \pm 16.19$  months (range: 3–61).

### **3.7. STUDY OF THE COMPLICATIONS OF THE ANTIREFLUX PROCEDURE (STUDY 4)**

#### **Complications of the antireflux procedures**

The *early* complications of laparoscopic antireflux procedure are well known. *Bleeding* may start from the vessels that supply the stomach (left gastric artery and vein and short gastric

arteries and veins). Spleen injury during the mobilization of the fundus may be a severe condition that often requires conversion. Injury to the hepatic capsule and bleeding of the liver are rarely severe complications. Rarely, the iatrogenic or ischemic *perforation* of a hollow organ (esophagus, stomach) may require an intraoperative solution or early reoperation. *Subcutaneous emphysema* due to the insufflation, which involves less risk, rarely requires surgical intervention. *Pneumothorax* accompanying pleural injuries in the posterior mediastinum, however, may require pleural drainage in certain cases. Impaired gastric emptying as a consequence of *injury* to the *vagus* nerve fibers may cause complaints in the long term.

Among the *late* complications of the surgical treatment, persistent cases of *dysphagia* must be mentioned first, the treatment of which, similarly to making the indication for surgery, requires a close cooperation between the gastroenterologist and the surgeon. In case of an unsuccessful dilation with bougies, balloon dilation may be required. In case of large *hiatal hernias*, the placement of a mesh exposes the patient to special hazards. *Erosion* of the esophageal wall may be a severe or even life-threatening condition, and it is to be treated surgically with relative urgency: often, cardiac resection and jejunal interposition (Merendino's procedure) are required.

### **3.8. COMPLICATIONS OF BE (STUDY 5)**

*Stricture*, *bleeding*, perforation and, ultimately, *malignant transformation* on the basis of Barrett's ulcer are well-known complications. Perforation as a consequence of Barrett's ulcer or a stricture is most often iatrogenic. Spontaneous perforation is an extremely rare, life-threatening condition. The successful endoscopic treatment of this rare complication will be presented through a case report.

### **3.9. STATISTICAL ANALYSIS**

The values measured and summarized during the clinical study of the GERD and BE groups were evaluated using SigmaStat<sup>®</sup> 3.1 Further statistical calculations were performed with SPSS 17.0 for Windows, whereas the special Poisson-distributed ANOVA method was performed with SAS for Windows 9.1.<sup>[38]</sup> To compare changes in the patients' parameters before and after the operation in the three BE groups, a generalized mixed model repeated

measurements ANOVA method was applied (multivariate analysis), using the GLIMMIX procedure of SAS 9.1.

## 4. RESULTS

### 4.1. COMPARISON OF PATIENTS SUBJECTED TO SURGERY BECAUSE OF GERD OR BE (STUDY 1)

According to the results of Study 1, the gender distribution in the two patient groups showed a predominance of women (112 women, 64 men), with a more balanced ratio in cases complicated with Barrett's esophagus (40 women, 38 men) but, contrary to literature data, there was no male predominance in this group either (Table 1). There was no difference between the two groups in mean patient age (Group 1:  $53.87 \pm 12.04$  years vs. Group 2:  $53 \pm 12.7$  years,  $p=0.495$ ) or mean BMI (Group 1:  $26.91 \pm 4.54$  vs. Group 2:  $28.31 \pm 5.46$ ,  $p=0.451$ ). It must be noted, however, that the majority of patients in both groups were overweight, which is a known potential risk factor of reflux disease.

As to the results of the preoperative assessment, contrary to our hypothesis, there was no difference between the two groups in the mean time from the onset of symptoms to the surgery ( $p=0.653$ ). A relatively long history was observed in both patient groups ( $68.86 \pm 32.63$  months in Group 1 and  $68.98 \pm 60.89$  months in Group 2) (Table 1). In both groups, the complaints of the patients mostly included heartburn, epigastric or chest pain, acid or bile belching, dysphagia, loss of appetite, nausea, and vomiting.

In all of the cases, surgery was performed after an unsuccessful acid-reducing medical therapy (mean duration of treatment:  $19.87 \pm 25.17$  months in Group 1 and  $19.20 \pm 27.31$  months in Group 2). As expected, hiatal hernia was common among the patients (in 75.42% in Group 1 [133 cases] and in 64.10% in Group 2 [50 cases]). Its mean size, however, was almost the same in the two groups ( $3.48 \pm 1.59$  vs.  $3.73 \pm 1.71$  cm [ $p=0.296$ ]) (Table 1). A mesh was placed because of a large hiatal hernia in 10 cases (5.7%) in Group 1 and in 4 cases (5.1%) in Group 2.

The theory according to which bacterial colonization, and metabolites produced during bacterial metabolism, are potentially carcinogenic, was not supported in the case of BE by the *Helicobacter pylori* infection observed in the stomach (confirmed in 27% in Group 1 and in

only 22% in Group 2). Besides the reflux, the accompanying gastritis was also often observed during the endoscopic examination.

#### **4.1.1. Preoperative Functional Results**

##### **Manometry**

Although it can be established that the LES function measured with manometry was impaired in both groups, thus allowing abnormal acid and/or bile reflux, there was no difference between the two groups in the mean values of LES pressure ( $12.10 \pm 7.93$  mmHg vs.  $12.57 \pm 9.03$  mmHg [ $p=0.892$ ]), relaxation time ( $10.39 \pm 2.99$  sec vs.  $10.36 \pm 2.81$  sec [ $p=0.773$ ]) and length ( $3.30 \pm 1.84$  cm vs.  $3.17 \pm 1.45$  cm [ $p=0.377$ ]) (Table 1).

##### **pH-metry**

Based on the results of pH-metry—in accordance with the pathomechanism of the disease—the acid reflux was more severe in patients subjected to surgery because of Barrett's esophagus than in those with reflux disease alone. During the pH-metry performed 5 cm above the cardia, the total number of reflux episodes (measured over 24 hours), the number of upright episodes, the number of supine episodes, the number of postprandial episodes, the number of episodes longer than 5 minutes, and the value of the longest episode were all significantly higher in Group 2 ( $p<0.001$ ). The DeMeester score was also higher in Group 2 (18.9 vs. 41.9,  $p<0.001$ ) (Table 1).

##### **Bilitec**

Bilitec monitoring was performed only in a limited number of GERD cases, primarily if bile reflux was suspected during endoscopy. Because of the selected cases, a statistical conclusion cannot be drawn; however, in view of the Bilitec results, it can be established that the values of the total time of bile reflux and the number of bile reflux episodes longer than 5 minutes were higher, and the longest bile reflux episode was longer in the case of patients subjected to surgery because of Barrett's esophagus (Table 1).

| PREOPERATIVE FUNCTIONAL RESULTS   | GERD        | BE            | p value |
|-----------------------------------|-------------|---------------|---------|
| LES                               | mean±SD     | mean±SD       |         |
| PRESSURE (mmHg)                   | 12.10±7.93  | 12.58±9.03    | NS      |
| RELAXATION TIME (sec)             | 10.39±2.99  | 10.37±2.81    | NS      |
| LENGTH (cm)                       | 3.02±1.84   | 3.17±1.45     | NS      |
|                                   |             |               |         |
| pH-METRY                          |             |               |         |
| Total time of acid exposure <pH 4 | 65.62±69.39 | 123.11±134.71 | <0.001  |
| Upright acid exposure <pH 4       | 55.37±58.21 | 97.84±112.53  | <0.001  |
| Supine acid exposure <pH 4        | 11.00±23.21 | 25.49±36.68   | <0.001  |
| Postprandial acid exposure <pH 4  | 31.34±34.42 | 55.55±57.77   | <0.001  |
| >5 min acid exposure <pH 4        | 2.20±3.64   | 4.55±6.72     | <0.001  |
| Longest acid exposure <pH 4       | 12.04±17.50 | 25.96±49.80   | <0.001  |
| DeMeester score                   | 18.85±21.39 | 41.93±51.15   | <0.001  |
|                                   |             |               |         |
| Bilitec                           |             |               |         |
| Total time of bile exposure       | 10.50±17.72 | 26.97±28.79   | <0.001  |
| Upright bile exposure             | 10.33±17.79 | 17.41±19.70   | NS      |
| Supine bile exposure              | 0.17±0.39   | 9.80±15.17    | NS      |
| Postprandial bile exposure        | 5.58±10.01  | 8.30±9.84     | NS      |
| >5 min bile exposure              | 2.00±4.24   | 6.69±9.53     | <0.001  |
| Longest bile exposure             | 16.17±20.44 | 82.96±105.14  | <0.001  |

**Table 1.** Results of preoperative functional examinations in patients with GERD and BE.

#### **4.1.2. Comparison of the functional examinations of patients subjected to surgery because of BE based on the histological severity of BE**

##### *Preoperative characteristics of the BE patient population (NI, I and D groups)*

Contrary to our expectations, IM and LGD did not show a longer history of reflux disease when compared with the NI group, and history was longer in the NI group than in the I group ( $p=0.057$ ) (Table 1). The duration of medical treatment showed no difference either. Although patients were overweight in all 3 groups, there was no difference in mean BMI. Hiatal hernia was present with the same incidence in cases of more severe BM and LGD, but it was not significantly higher than in the NI group. No statistical difference was detected between the

3 groups in the LES function (pressure, length and relaxation time). In accordance with literature data, our research results revealed more severe acid reflux in patients with BE than in patients with mild GERD alone. With respect to acid reflux, however, BE did not exhibit any difference. The parameters used to calculate the DeMeester score did not differ significantly between the 3 groups. In comparison with the NI group, a higher DeMeester score was observed only in the D group, but this difference was not significant. The majority of the values measured during the Bilitec monitoring indicated more severe bile reflux in the D group than in the other 2 groups (Table 2). In contrast with the results of the univariate analyses, the multivariate analysis did not demonstrate significant differences between the three preoperative groups.

|                       |                             | <b>Group</b> | <b>Mean</b> | <b>SD</b> | <b>p value</b> |
|-----------------------|-----------------------------|--------------|-------------|-----------|----------------|
| <b>Bilitec</b>        | Total time of bile exposure | I            | 23.33       | 30.53     | p=0.025        |
|                       |                             | D*           | 70.75       | 32.52     |                |
|                       |                             | NI           | 13.88       | 17.64     |                |
|                       | Upright bile exposure       | I            | 16.60       | 15.77     | p=0.027        |
|                       |                             | D*           | 48.75       | 28.36     |                |
|                       |                             | NI           | 8.66        | 12.16     |                |
|                       | Supine bile exposure        | I            | 6.80        | 19.04     | p=0.017        |
|                       |                             | D*           | 23.00       | 14.90     |                |
|                       |                             | NI           | 6.78        | 9.30      |                |
|                       | Postprandial bile exposure  | I            | 8.00        | 7.85      | p=0.087        |
|                       |                             | D            | 20.50       | 16.84     |                |
|                       |                             | NI           | 6.97        | 10.27     |                |
|                       | >5 min bile exposure        | I            | 3.00        | 2.90      | p=0.021        |
|                       |                             | D*           | 17.50       | 14.39     |                |
|                       |                             | NI           | 87.16       | 107.20    |                |
| Longest bile exposure | I                           | 38.60        | 63.72       | p=0.195   |                |
|                       | D                           | 111.25       | 37.95       |           |                |

**Table 2.** Characteristics of the three preoperative groups (NI, I and D) (78 patients).

## **4.2. POSTOPERATIVE RESULTS (STUDY 2)**

In part 2 of the study, the efficacy of the antireflux surgery was assessed in view of the postoperative results.

### **4.2.1. Symptomatic Outcome**

Based on the Visick score<sup>[17]</sup> determined in Group 1 after the surgery, at the early surgical follow-up visit (at 3 months), complaints were gone or improved in 73% of the patients, they were unchanged in 15%, and 12% of the patients reported worsening, primarily with a leading symptom of dysphagia. In Group 2, 81% of the patients were complaint-free or reported improved symptoms, 15% had unchanged complaints, and worsening was observed in 4%. Dysphagia was the predominant symptom also in this group.

### **4.2.2. Postoperative Functional Results**

After the surgery, patients were subjected to follow-up functional examinations and endoscopy; the mean follow-up time was  $13.8 \pm 19.31$  months in Group 1 and  $16.7 \pm 17.00$  months in Group 2. The mean LES pressure was significantly increased compared with the preoperative value in both groups ( $17.58 \pm 7.60$  mmHg in Group 1 and  $18.70 \pm 6.74$  mmHg in Group 2). After the surgery, the LES length and relaxation time did not show a statistically significant difference compared with the preoperative values (Table 4).

Based on the follow-up pH-metry, the number and duration of acid reflux episodes significantly decreased in both groups. The postoperative DeMeester scores returned to the normal range: they decreased to a mean score of  $7.7 \pm 17.41$  in Group 1 and  $12.7 \pm 30.74$  in Group 2. When following the patients subjected to Bilitec monitoring before the surgery, a decrease in the occurrence of bile reflux was also observed (Table 3).

| FUNCTIONAL RESULTS          | GERD        |             |         | BE          |             |         |
|-----------------------------|-------------|-------------|---------|-------------|-------------|---------|
|                             | Preop       | Postop      | p value | Preop       | Postop      | p value |
| LES                         | mean ± SD   | mean ± SD   |         | mean ± SD   | mean ± SD   |         |
| PRESSURE (mmHg)             | 12.10±7.93  | 17.58±7.60  | <0.001  | 12.58±9.03  | 18.70±6.74  | <0.001  |
| pH-METRY                    |             |             |         |             |             |         |
| DeMeester score             | 18.85±21.39 | 7.73±17.41  | <0.001  | 41.93±51.15 | 12.72±30.74 | <0.001  |
| Bilitec                     |             |             |         |             |             |         |
| Total time of bile exposure | 10.50±17.72 | 17.00±22.24 | NS      | 26.97±28.79 | 22.08±30.57 | <0.001  |

**Table 3.** Results of postoperative functional examinations in patients with GERD and BE.

#### 4.2.3. Postoperative Results by BE Subgroup (Study 3)

In part 3 of the study, the rate of BE regression was studied in function of the laparoscopic antireflux surgery. The early quality of life measures, the results of the early postoperative functional examinations and the long-term endoscopic follow-up results were summarized for the three BE subgroups.

##### 4.2.3.1. Early postoperative results

###### 4.2.3.1.1. Symptomatic outcome

The Visick score varied somewhat within the groups—in patients with intestinal BE and also in those with LGD, complaints were alleviated relative to those with NI metaplasia. The assessment of the changes in both the subjective and objective complaints demonstrated that the symptoms recorded during the preoperative period tended to be relieved after laparoscopic Nissen fundoplication. In accordance with our expectations, dysphagia increased.

###### 4.2.3.1.2. Postoperative functional examinations (manometry, 24-hour pH studies and Bilitec)

Postoperative manometry, pH-metry and Bilitec monitoring did not reveal statistically significant differences between the three groups. Changes in the LES function, which also indicate the efficacy of the surgery, demonstrated that the postoperative pressure in the lower esophagus was significantly increased relative to that measured preoperatively, whereas the

relaxation time remained unchanged. As a consequence of the surgical technique (a loose and narrow Nissen floppy), the length of the LES was unchanged after fundoplication, but its function (pressure) was restored, thus preventing acid and bile reflux. Comparison of the results of pH-metry before and after the procedure between the three groups confirmed the above findings, as mean DeMeester scores were clearly decreased after the surgery.

Accordingly, the incidence and severity of bile reflux were reduced, or this symptom was eliminated. The multivariate analysis confirmed significant changes only in LES pressure and the results of pH-metry between the preoperative and postoperative groups.

#### **4.3. RESULTS OF THE ENDOSCOPIC FOLLOW-UP OF THE BE SUBGROUPS (ENDOSCOPIC SURVEILLANCE)—LONG-TERM ENDOSCOPIC SURVEILLANCE**

The mean duration of endoscopic follow-up was  $42 \pm 16.19$  months. Postoperative endoscopy was performed only in 64 patients (82%, 64/78). 14 patients, who were not subjected to upper gastrointestinal endoscopy, were excluded from the long-term analysis.

|                     | Complete regression | Partial regression | No change         | Progression       |
|---------------------|---------------------|--------------------|-------------------|-------------------|
| Overall group       |                     |                    |                   |                   |
| SSBE (n=56)         | 10 (17.9%)          | 5 (8.9%)           | 30 (53.6%)        | 11 (19.6%)        |
| LSBE (n=8)          | 0                   | 4 (50%)            | 4 (50%)           | 0                 |
| NI (n=44)           | 6 (13.6%)           | 4 (9.1%)           | 23 (52.3%)        | 11 (25%)          |
| IM (n=15)           | 3 (20%)             | 3 (20%)            | 9 (60%)           | 0                 |
| LGD (n=5)           | 1 (20%)             | 2 (40%)            | 2 (40%)           | 0                 |
| <b>Total (n=64)</b> | <b>10 (15.6%)</b>   | <b>9 (14.1%)</b>   | <b>34 (53.1%)</b> | <b>11 (17.2%)</b> |

**Table 4.** Endoscopic and histopathological changes of BE after laparoscopic fundoplication (64 patients)

Before the antireflux surgery, SSBE was present in 56 patients and LSBE in 8 patients. Preoperative histological examinations indicated FM in 11, CM in 33, IM in 15 and LGD in 5 patients. The postoperative check-up demonstrated a total regression of BE in 10 patients (15.6%). Partial regression was seen in 9 cases (14.1%), no further progression in 34 patients (53.1%), and progression from FM to CM in 4 patients (6.2%) or from CM to IM in 7 patients (11%), but no cases of dysplastic or malignant transformation were recorded. There was no further progression in the patients with LGD, and in 3 of these 5 patients, LGD disappeared, leaving only residual IM (Table 4).

There was no difference in the length of the follow-up period between the total regression group and the other groups (partial, no change and progression). Where the regression of BE was observed, the postoperative functional examination results of manometry (pLES) and pH-metry were significantly better compared with those measured in the groups where no changes in BE occurred, or progression of BE was found. We did not find differences between the groups in the results of postoperative Bilitec monitoring, except for the longest exposure values (Table 5).

|                            |                                      | Groups                      |                  |                  |              |
|----------------------------|--------------------------------------|-----------------------------|------------------|------------------|--------------|
|                            |                                      | Regression (SD)             | No change (SD)   | Progression (SD) | p value      |
| Manometry                  | pLES (mmHg)                          | 18.04 (±6.405)              | 9 (±7.735)       | 11.02 (±7.815)   | 0.003        |
|                            | rLES (s)                             | 10.04 (±1.613)              | 10.03 (±2.831)   | 9.89 (±4.285)    | 0.988        |
|                            | ILES (cm)                            | 3.21 (±0.699)               | 3.14 (±1.424)    | 2.89 (±1.269)    | 0.571        |
| pH-metry                   | Total time of acid exposure<br><pH 4 | 23.77 (±25.21)              | 105.29 (±89.191) | 112.2 (±82.974)  | <0.001       |
|                            | Upright acid exposure <pH 4          | 21.23 (±24.1229)            | 79.79 (±67.776)  | 87.9 (±74.929)   | 0.002        |
|                            | Supine acid exposure <pH 4           | 2.62 (±3.595)               | 25.75 (±33.216)  | 24.6 (±21.798)   | 0.002        |
|                            | Postprandial acid exposure<br><pH 4  | 12.42 (±16.649)             | 48.63 (±46.04)   | 61.3 (±53.506)   | 0.009        |
|                            | >5 min acid exposure <pH 4           | 0 (±0)                      | 5.46 (±8.495)    | 5.1 (±5.607)     | <0.001       |
|                            | Longest acid exposure <pH 4          | 1.38 (±1.557)               | 19.33 (±27.223)  | 19.6 (±15.82)    | <0.001       |
|                            | DeMeester score                      | 3.52 (±3.617)               | 40.88 (±51.37)   | 43.089 (±6.094)  | <0.001       |
|                            | Bilitec                              | Total time of bile exposure | 4.75 (±6.292)    | 32.05 (±34.861)  | 23 (±28.605) |
| Upright bile exposure      |                                      | 4 (±4.83)                   | 19.21 (±22.062)  | 15.89 (±18.395)  | 0.143        |
| Supine bile exposure       |                                      | 0.75 (±1.5)                 | 13.05 (±19.478)  | 7.44 (±12.69)    | 0.295        |
| Postprandial bile exposure |                                      | 1 (±1.414)                  | 8.11 (±10.954)   | 7.89 (±10.55)    | 0.117        |
| >5 min bile exposure       |                                      | 0.75 (±1.5)                 | 9.05 (±13.206)   | 6.33 (±9.206)    | 0.138        |
| Longest bile exposure      |                                      | 3.25 (±5.188)               | 81.72 (±99.8)    | 72.78 (±93.641)  | 0.050        |

**Table 5.** Comparison of the postoperative functional examinations and the changes in BE (between the three groups: regression, no change, progression (64 patients)).

#### **4.4. COMPLICATIONS OF MINIMALLY INVASIVE ANTIREFLUX PROCEDURES AND THEIR TREATMENT (STUDY 4)**

In part 4 of our study, the risk of the surgical treatment was evaluated. We processed the data on surgical complications of patients subjected to surgery because of GERD or BE between 2001 and 2008. Intraoperative complications, as well as early (within 30 days) and late complications were analyzed in detail.

Conversion was required in 1 case in the GERD group because of adhesions. Open splenectomy (requiring postoperative transfusion) was performed in 1 case in the BE group because of spleen bleeding. Intraoperative chest tube insertion was required in 1 case in the GERD group because of left-sided pneumothorax. Reoperation was not performed in either group in the early postoperative period. In the GERD group, 2 patients were given a total of 6 units of pRBC because of bleeding, and subcutaneous emphysema was detected in 1 case, which did not require further treatment.

During the early and late follow-up in the GERD group, observation at the institution was required in 3 cases because of dysphagia and stenosis: in 1 case, the complaints of the patient resolved spontaneously, in 1 case, endoscopic foreign body retrieval was performed because of food bolus obstruction (in the early period), and in 1 case, endoscopic balloon dilation was performed (in the late period). Usually, a satisfactory result was achieved with dilation, and reoperation has not been required in our practice to date. Endoscopic follow-up described the appearance of ulcer in 2 cases in the GERD group, and in 2 cases, BE was developed. In 1 case, cardiac resection was needed because of erosion due to the implanted mesh 7 months after the surgery. In the BE group, esophageal dilation was performed because of dysphagia in 2 cases. There were no mortalities in either group.

#### **4.5. ENDOSCOPIC TREATMENT OF SPONTANEOUS ESOPHAGEAL RUPTURE, A COMPLICATION DEVELOPED ON THE BASIS OF BE**

In this section, we present the minimally invasive treatment strategy of spontaneous esophageal rupture (Boerhaave's syndrome), a rare condition associated with BE. A 53-year-old male patient with lower-third rectal adenocarcinoma (T2N1) was admitted. He was known to have gastroesophageal reflux disease complicated with Barrett's esophagus (intestinal metaplasia with low-grade dysplasia). On the second postoperative day after a low anterior rectal resection, forceful vomiting occurred and was followed by chest pain without clinical signs of esophageal perforation. The immediate chest x-ray revealed only a small amount of

pleural effusion on the right. The follow-up chest x-ray (acquired 12 hours later), however, demonstrated an increase in the amount of the pleural effusion, and hydropneumothorax was developed. A contrast swallow with a water-soluble contrast agent confirmed the presence of a transpleural esophageal rupture (Figure 1). The immediate upper gastrointestinal endoscopy showed a mucosal rupture of 5 to 7 mm in length on the posterior wall of the esophagus, 4 cm above the gastroesophageal junction. The mucosal tear was successfully closed with 3 endoscopic clips (Olympus Quick Clip 2) (Figure 2). The endoscopic closure was supplemented with right thoracic drainage, gastrostomy and catheter feeding jejunostomy. Eight days after the endoclip application, esophagography demonstrated no further leakage, and oral feeding could be resumed. There were no complications and the patient was eventually discharged 14 days after the endoscopic intervention. Control endoscopy showed only scar tissue at the site of the closed perforation with LGD of BE.

## 5. DISCUSSION

Reflux disease affects more than one third of the population, and it may range from an asymptomatic condition through a condition without inflammatory signs (non-erosive reflux disease) to a symptomatic condition accompanied by severe erosion and its complications that considerably worsen the quality of life. Parallel to this, the incidence of esophageal adenocarcinoma shows an increase in the developed world. In the presence of Barrett's metaplasia developed on the basis of reflux, the risk of developing esophageal adenocarcinoma is 30 to 125 times higher than in the normal population.<sup>[39,40]</sup>

It has been known for a long time that in some cases, depending on the severity of the reflux, the acidic gastric contents regurgitating into the esophagus may cause symptoms only, whereas in other cases, they may damage the squamous epithelium lining the esophagus, resulting in erosion, inflammation and, later, ulceration and stricture.<sup>[5]</sup>

In the development of reflux esophagitis, at the microscopic level, the opening and widening of the gap between mucosal cells play a role. It was successfully triggered under experimental conditions with both mild and severe acid or mixed reflux.<sup>[41]</sup> At the site of the epithelial defect that is developed in case of persistent reflux, the regeneration starting from the submucosal pluripotent Schaffer glands may result in that columnar epithelium, which is more resistant to the acidic environment, replaces the squamous epithelium, i.e., Barrett's esophagus is developed. Its predictive factors are the total time of acid reflux, its severity and the consequentially worsening lower esophageal sphincter (LES) function.<sup>[13,42,43,44,45,46,47,48]</sup>

Our study supports the observation that the exposure to reflux is longer and more severe in the group of patients with Barrett's metaplasia than in the group of patients with reflux alone. In our sample, however, no difference was found between the two groups in the duration of complaints and the LES impairment. Nevertheless, the mean history of 5.6 years is in accordance with the observation of Öberg who found that approximately the same time (6.2 years) is required for the columnar epithelial metaplasia to appear as a result of the increased exposure to acid.<sup>[49]</sup> It can be established, based on the above, that one of the most important factors in the squamous-columnar transformation is the appearance of acid in the esophagus.

The driving force behind the transition within the columnar epithelium and the appearance of intestinal metaplasia and dysplasia is the bile that is mixed with acid reflux.

In the acidic–biliary environment, several “evolutionary responses” may appear often parallel to each other (fundic, cardiac and intestinal or even respiratory ciliary columnar epithelium, pancreatic acinar or ductal metaplasia, or low-grade, high-grade dysplasia or even in situ carcinoma). It is supposed that Schaffer glands have an important role in the development of this diverse picture, because their pluripotent germ cells may be responsible for the heterogeneous responses to the inflammatory damage.<sup>[8]</sup> Besides the simultaneous presence of metaplasias, transformation into each other may also be supposed. Nevertheless, many of the above forms of metaplasia and dysplasia may be present in the mucosa even at the same time.<sup>[8]</sup> A true risk of potential malignancy is associated with the appearance of IM.<sup>[28, 52]</sup> However, it is a known fact that the malignant transformation of non-intestinal epithelium cannot be excluded either, although its estimated risk is considerably lower (0.07% annually) than in the concomitant presence of intestinal metaplasia (0.38% annually).<sup>[28, 52]</sup> In other publications, the rate of dysplasia and carcinoma was almost the same in case of non-intestinal metaplasia than in IM. It must be added, however, that during the 5-year follow-up of this group, IM appeared in more than 50% of the cases, and this ratio reached 90% after 10 years.<sup>[53]</sup> It appears to support our conclusions below about the possible limitations of biopsy and the ability of metaplastic processes to transform into each other.

Although multiple biopsy samples may help assess the precise status of BE, only the momentary status of a small area can be assessed this way, which makes it hard to evaluate the efficacy of the treatment and the change in the condition. During the endoscopic examinations, multiple sampling is performed as per the Seattle protocol: on the one hand, from the visible Barrett lesions themselves, and on the other hand, from each esophageal quadrant with 2 cm intervals<sup>[26]</sup>. Increasing the number of biopsy samples clearly improves the ability to detect IM. According to the results of Harrison et al., with only 4 samples taken from the same patients, IM could be detected in only half of the IM cases previously confirmed with samples taken from 8 biopsy sites.<sup>[54]</sup>

In view of the above, we still consider it important, when Barrett’s esophagus is developed, not to focus only on intestinal metaplasias (that are confirmed to carry the potential for malignant transformation) but to follow non-intestinal (fundic and cardiac) metaplasias and other histological phenotypes as well.

We suppose that a more severe acid-bile reflux has a pathogenic role in the development of dysplasia. Because of this, patients with BE in our study were assigned to three different groups based on the presence of conditions indicating carcinogenesis or its risk, depending on whether the histological sample taken during the endoscopy showed non-intestinal (i.e., fundic or cardiac) metaplasia (Group 1), intestinal metaplasia (Group 2) or low-grade dysplasia on the basis of the latter (Group 3). Taking into account that parallel metastatic and dysplastic conditions were likely in the biopsy samples, patients were always sorted based on the most severe condition found.

Patients with BE reported a mean duration of complaints of 5.6 years before the surgery. It was not different from the length of history reported by patients who underwent surgery because of GERD. There was no correlation between the severity of Barrett metaplasia (intestinal metaplasia and low-grade dysplasia) and the duration of complaints either and, paradoxically, reflux complaints of longer duration were observed in the non-intestinal group, compared to the intestinal one. There were no differences in patient demographics (age, BMI, etc.) in the case of BE or, within this group, LGD.

When comparing patients who suffer from GERD with those who have BE, the more severe acid reflux confirmed in the BE group may cause metaplasia but a further role of acid reflux in the metaplasia–dysplasia transition in the BE subgroups could not be confirmed in the second half of our study. Nevertheless, our study showed that bile reflux was significantly more common and more severe in the low-grade dysplasia (LGD) group of BE patients than in the groups of patients with non-dysplastic metaplasia.<sup>[58]</sup>

Our hypothesis that changes in the anatomy of the gastroesophageal junction, a larger hiatal hernia or decreased LES pressure, decreased LES relaxation time, or a shorter LES, are more common in case of LGD, was not confirmed.

Conservative and surgical therapies are both accepted in the treatment of reflux, which has a central role in the development of the above mucosal transformation. With minimally invasive surgery becoming part of everyday practice, we can say that the morbidity risk of the laparoscopic antireflux surgery is low compared to its possible benefits to the patients.<sup>[59]</sup> The advantage of laparoscopic antireflux surgery over conservative therapy is that it attempts to restore the previous anatomical situation, i.e., it eliminates hiatal hernia by reconstructing the posterior diaphragmatic crus, restores the angle of His by retracting the lower portion of the esophagus into the abdomen, and restores the LES function with fundoplication. Unlike

proton-pump inhibitors, it may eliminate not only acid reflux but also bile reflux. Compared with the permanent, lifelong medical treatment, it may be considered cost effective. However, opinions are divided on its long-term efficacy.<sup>[60, 61]</sup> A long-term complaint-free status can be expected in case of a correctly performed antireflux surgery. It can be established based in the LOTUS trial that, regarding long-term efficacy, laparoscopic antireflux procedure is as effective as medical treatment.<sup>[62]</sup>

Our patients, therefore, had heterogeneous indications for surgery but the procedure was mostly performed after an unsuccessful conservative therapy. In our study, the patients in both groups underwent surgery after a mean 19 to 20 months of unsuccessful medical treatment. Our early postoperative functional examinations confirmed that laparoscopic antireflux surgery could achieve improvement, i.e., good reflux control, even in this presumably selected patient population with poorer prognosis and poorer response to conservative therapy (unsuccessful after a mean duration of one year and a half). LES pressure returned to the physiological range and the DeMeester score, which best describes acid reflux, decreased to normal values in both groups. Surgical treatment, therefore, may have additional advantages over medical treatment. Our results, however, must be considered to be of limited value because of the short follow-up of the functional examinations. Its mean duration did not exceed eighteen months in either group.

A further advantage of laparoscopic antireflux surgery is that it can be standardized, and therefore the steps of the procedure can be reconstructed later at any time, and the results from different institutions are comparable.<sup>[62]</sup> Nissen's fundoplication creates a relatively stronger reflux barrier than partial fundoplication.<sup>[67]</sup> Dysphagia and also later dilation are more common in case of a 360-degree fundoplication but only among patients with decreased esophageal motility. However Nissen's fundoplication may provide the best reflux control in the long term.<sup>[67, 68, 69, 70]</sup>

Since the first observation made by Brand et al.<sup>[73]</sup> (1980), it has become a generally known fact that antireflux surgery also creates an opportunity for the regression of BE. Based on the results of randomized and retrospective studies conducted to date, it can be established that antireflux surgery is more effective in preventing the progression of BE than medical treatment.<sup>[74, 75, 76, 77, 78, 79, 80, 81]</sup> According to the most recent meta-analysis, antireflux surgery clearly has a beneficial effect on the regression of BE and dysplasia.<sup>[82]</sup> It has been found in some studies that surgery does not lead to an obvious decrease in the occurrence of adenocarcinoma, despite the excellent results published by numerous institutions about the

beneficial effect of laparoscopic fundoplication in the treatment of reflux disease. [83, 84] According to a recent Swedish study, antireflux surgery does not prevent the development of esophageal or cardiac adenocarcinoma in some of the patients with GERD. [85]

The views on the role of antireflux surgery in prevention are quite contradictory in the literature. To date, no meta-analysis confirming or refuting a preventive effect with clear evidence has been published, and no large, prospective studies are expected in the near future either because of the special and small patient population.

This assumption seems to be confirmed by the fact that during the 42-month endoscopic follow-up of our patients subjected to surgery because of Barrett's esophagus, an unchanged status was observed in 53% of the cases, and regression was detected in a further 30%. Progression occurred in only 17%, and all of these cases were observed in the non-intestinal metaplasia group. Dysplasia was not developed in the group of patients with intestinal metaplasia, and no further progression (to high-grade dysplasia or carcinoma) occurred in the low-grade dysplasia group during the study period.

In the patient group showing regression, the postoperative functional results were significantly better than in the groups that did not show regression. However, we consider it important that the majority of our cases were short-segment BE. Based on the above, it can be established that in certain (presumably early) cases of BE, a laparoscopic antireflux surgery that provides effective reflux control may achieve regression even in patients not responding to medical treatment. Csendes et al. [81] have reached a similar conclusion. According to our observations, laparoscopic antireflux surgery is associated with a low morbidity rate, and may decrease the subjective complaints of short-segment BE patients in the long term (Visick Grade I and Grade II in 86.3 to 100% of the patients), it leads to the regression of intestinal metaplasia (IM) in two-thirds of the patients, and the IM does not progress to LGD, HGD or adenocarcinoma. In case of BE, surgical treatment should be considered also according to DeMeester et al., because they often observed the regression of LGD after antireflux surgery. [13] The regression of IM is more common in the group of patients treated surgically than in those who receive medical treatment. [82] A randomized study comparing the medical and surgical treatment has confirmed that a correctly performed antireflux surgery significantly decreases the rate of reflux esophagitis and stricture, and the segmental length of BE also significantly decreases after the surgery. [80] The rate of new-onset dysplasia was statistically different between the surgery group and the medically treated group (2% vs. 20%, respectively). [75, 86, 87, 88, 89] At the same time, the risk of malignant transformation was not

lower than in the medically treated group. However, the same incidence of developing cancer in the two groups may be influenced by the fact that surgical treatment is performed in patients with more severe reflux - after medical treatment has failed.<sup>[86, 87, 89, 90]</sup> A preventive effect of laparoscopic antireflux surgery on the development of adenocarcinoma was not confirmed by the Swedish cohort study published by Lagergren et al. either.<sup>[91, 92]</sup> It must be noted, however, that this study compared the rate of adenocarcinoma with that in the healthy population and not in patients with reflux.<sup>[93]</sup> A “new-onset” BE developed after the antireflux surgery and the progression of an already present BE raise many concerns against the surgical treatment.

In the GERD patient group, the occurrence of metaplasia during our postoperative observation may have two explanations. The first is unsuccessful surgery. De novo BE may be expected in case of inadequate reflux control. It is contradicted by the fact that the results of our functional examinations did not differ from those observed in patients without progression. The second, more likely explanation lies in the limitation of biopsy already mentioned, that is, that the quadrant biopsy samples “taken blindly” in case of GERD provide a histological picture of a small area only, which does not exclude the prior presence of Barrett metaplasia in other areas, recognized only at the time of the second biopsy. Nevertheless, our opinion is that the clinical manifestation of BE should not be considered a uniform condition.

Although surgery that provides adequate reflux control can lead to regression (primary prevention) in a certain group of patients with BE, Barrett metaplasia was nonetheless observed after surgery in another patient group and, in a smaller portion of the patients, progression is not excluded either. Recognizing this patient group and following it more closely are indispensable for secondary prevention, i.e., the early recognition and successful treatment of cancer.

The conclusion of DeMeester et al. may possibly explain progression - if carcinogenesis already started before the surgery because of the mixed reflux, and the meta- and dysplastic cells already got out of autoregulation control due to the genetic damages, the antireflux surgery, obviously, does not provide protection against advanced dysplastic processes, and in this case, adenocarcinoma may appear within 5 years after the surgery. In case of cancers developed later than this, they confirmed the recurrence of reflux.<sup>[13]</sup> Other studies<sup>[94, 95, 96]</sup> also point out that late adenocarcinoma following antireflux surgery can be explained by postoperative reflux due to an unsuccessful surgery or by recurrent reflux, and they emphasize the importance of pH-metry during follow-up.

It is also possible, however, that BE does not expose to a higher risk of developing adenocarcinoma but appears only as a coincidence. The fact that the histological examination confirmed BE next to adenocarcinoma in only half of the resections performed because of tumor may support this theory.<sup>[97, 98]</sup> Jamieson hypothesized that adenocarcinoma may be developed not or not only from the Barrett epithelium during tumorigenesis but the transformation of a pluripotent germ cell starts in response to inflammation and epithelial damage due to the reflux.<sup>[92]</sup> In this case, although the reflux-induced inflammation is also responsible for the development of BE, BE should be considered an indicator of the severity of reflux rather than a premalignant condition. The most likely case is that carcinogenesis does not occur in one way only, and dysplasia and cancer developed on the basis of BE is just one possible way in this process. Going ahead with this hypothesis, from the perspective of carcinogenesis, therefore, a successful antireflux surgery performed in time may be of preventive effect in certain patients with BE. Nevertheless, taking the slow progression of the condition and the great heterogeneity of BE into account, regular long-term endoscopic follow-up and biopsies are indispensable for the successful treatment of reflux disease and Barrett's esophagus. To confirm whether laparoscopic antireflux surgery can prevent the progression of Barrett's esophagus in the long term, repeat functional examinations to verify the effective functioning of the antireflux barrier are required besides endoscopic follow-up.

The minimally invasive surgical treatment performed at our center was an effective treatment alternative to unsuccessful medical treatment, without mortality and with a low morbidity rate. The conversion rate of 0.6 to 1.3% is considered low. As to late complications, the most common is dysphagia that requires hospitalization (1.7 to 2.6%), which can be considered an "efficacy indicator" of Nissen's fundoplication. The most severe late complication is erosion of the esophageal wall after mesh placement (1.3%). Although it appears to be rare, its rate of 7.1% in patients with mesh placement only is high. Therefore, in our practice, besides the choice of material (Teflon or composite mesh), we avoid wrapping the esophagus around completely.

A similarly rare severe complication is spontaneous perforation or Boerhaave's syndrome developed on the basis of BE ulcer. According to our knowledge, the closure of the perforation opening with endoscopic clips that we performed in our patient is the first documented successful case in Hungary. The condition is the result of a pressure increase in the lumen of the esophagus, which is primarily caused by voluminous vomiting. Since our patient had known reflux disease complicated by BE with LGD, and esophagitis, a weakening

of the distal esophageal wall could be assumed as well. The condition was considered fatal until the first successful surgical treatment performed by Barrett in 1947.<sup>[100]</sup> Today, despite the more effective treatment options, mediastinitis and the rapidly developed septic condition are often irreversible. In cases where surgery is performed after more than 24 hours, the mortality rate exceeds 20 to 30%.<sup>[101]</sup> In the past years, several cases of successful use of endoscopic clips and self-expanding stents in the treatment of esophageal rupture have been reported.<sup>[105, 106]</sup> Closure of an esophageal injury with endoscopically placed clips was first performed in 1995 (the injury occurred during pneumatic dilation in a patient with achalasia).<sup>[107]</sup> In our case, the complete esophageal perforation (with a rupture on the esophageal wall and also the mediastinal pleura) was detected within 24 hours. Since the visible rupture on the esophagus was only 5 to 7 mm, it could be successfully closed with endoscopic clips.-Endoscopic stents have been successfully used in the treatment of different types of esophageal perforation, including Boerhaave's syndrome <sup>[115, 116, 117, 118, 119, 120]</sup> To summarize, we can establish based on the available experience that endoscopic and minimally invasive surgical methods, if proper conditions are met, may be therapeutic alternatives in the treatment of Boerhaave's syndrome developed on the basis of BE.

**SUMMARY, OUR MOST IMPORTANT RESULTS**

1. *The severity of the pathological acid reflux developed parallel to the incompetent functioning of the impaired lower esophageal sphincter potentiates, besides the inflammation in the lower third of the esophagus, the start of metaplastic processes and, ultimately, the development of Barrett's esophagus.*
2. *In response to the bile reflux accompanying the acid reflux, dysplastic changes may start in the metaplastic columnar epithelium (that appeared due to acid reflux).*
3. *In selected GERD and BE patients resistant to medical treatment, Nissen's correctly performed laparoscopic surgery can successfully control (eliminate or decrease) gastroesophageal reflux and is associated with a low morbidity rate.*
4. *The antireflux surgery may stop the progression of Barrett's esophagus and result in regression in some patients. Nevertheless, further long-term follow-up is required to confirm the assumed preventive effect of antireflux surgery in the process of carcinogenesis.*
5. *Endoscopic methods, if proper conditions are met, may be therapeutic alternatives in the treatment of esophageal perforation.*

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