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The effects of laparoscopic Nissen fundoplication on Barrett's esophagus: Long-term results

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Abstract

Objective. The aim of our study was to conduct a retrospective investigation of the efficacy of laparoscopic Nissen fundoplication in patients with Barrett's esophagus. ***Material and methods.*** A total of 78 patients with Barrett's esophagus underwent surgery. Patients were divided into three groups on the basis of the preoperative endoscopic biopsies: a non-intestinal group (n = 63) with fundic or cardiac metaplasia, an intestinal group (n = 18) with intestinal metaplasia, and a dysplastic group (n = 7) with low-grade dysplasia. Clinical follow-up was available in the case of 64 patients at a mean of 42 ± 16.9 months after surgery. ***Results.*** Check-up examination revealed total regression of Barrett's metaplasia in 10 patients. Partial regression was seen in 9 cases, no further progression in 34 patients, and progression into cardiac or intestinal metaplasia in 11 patients. No cases of dysplastic or malignant transformation were registered. Where we observed the regression of BE, among the postoperative functional examinations results of manometry (pressure of lower esophageal sphincter) and pH-metry were significantly better compared with those groups where no changes occurred in BE, or progression of BE was found. ***Discussion.*** Our results highlight the importance of the cases of fundic and cardiac metaplasia, which can also transform into intestinal metaplasia. ***Conclusions.*** Antireflux surgery can appropriately control the reflux disease in a majority of the patients who had unsuccessful medical treatment, and it may inhibit the progression and induce the regression of Barrett's metaplasia in a significant proportion of these patients.

Key Words: *antireflux surgery, Barrett's esophagus, laparoscopic Nissen fundoplication*

Introduction

Barrett's esophagus (BE) is a premalignant condition which is thought to progress from Barrett's metaplasia (BM) through low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and subsequently to adenocarcinoma [1–5]. The estimated annual risk for adenocarcinoma in subjects with BE ranges from 0.2% to 2.0%, a risk that is 30–125 times that of the general age-matched population [6–8].

BE is associated with gastro-esophageal reflux disease (GERD): it is found in 15–20% of patients with GERD [9,10]. The incidence of BE appears to have risen dramatically in the past 20 years [11], a fact that has been linked to the 10-fold increase observed in the incidence of adenocarcinoma of the esophagus during the last decade [12]. All of these facts underline the importance of the need for the correct treatment of BE.

The aim of treatment for BE is to bring the symptoms under control, cure the associated inflammatory lesions, and prevent the appearance of dysplasia and adenocarcinoma. The therapeutic options are life-long medical treatment or antireflux surgery.

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Although both these options are equally efficient in controlling the symptoms, some clinical studies suggest that effective surgical treatment leads to a higher rate of cure of the associated inflammatory lesions [13,14]. Surgical treatment is also better than medical treatment in preventing BE from progressing into adenocarcinoma [13,15,16]. Laparoscopic antireflux procedures are generally accepted surgical methods for the treatment of patients with GERD and BE with the exception of HGD.

The aim of our study was to conduct a retrospective investigation of the efficacy of laparoscopic Nissen fundoplication in patients with BE.

Materials and methods

In all, 78 consecutive patients with symptomatic BE underwent laparoscopic Nissen fundoplication in our institution between 2001 and 2008, 40 males and 38 females, with a median age of 53 years (range: 24–78). The mean body mass index (BMI) was 28.3 ± 5.4 (range: 19.8–37). All of the patients had previously participated in unsuccessful proton-pump inhibitor (PPI) treatment for persistent reflux symptoms and BM for an average of 20 ± 2.73 months (range: 7 months to 14 years). The mean length of time between the first symptoms and the beginning of medical treatment was 3.65 ± 4.67 years (range: 8 months to 20 years). Hiatus hernia was observed in 50 cases (64.1%) with a mean size of 3.93 ± 1.95 cm (range: 2–8).

Patients were divided into three groups on the basis of the histological results of their preoperative endoscopic biopsies: a non-intestinal group (NI, 63 patients) with fundic (FM) and cardiac metaplasias (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 (85.9%) of the cases and a long segment (>3 cm, LSBE) in 11 (14.1%) patients.

Our retrospective study was approved by the ethical committee of the University of Szeged.

Assessment of symptoms and objective measures of outcome

We have compared the results of preoperative functional examinations, BMI, the extent of hiatus hernia, duration of reflux symptoms, and the length of PPI therapy, looking for connection with severity of BE (NI, I, and D groups) in case of all patients to be operated ($n = 78$).

Postoperative endoscopy was performed in 64 patients (82%, 64/78); 14 patients who did not participate in upper gastrointestinal endoscopy were excluded from the comparison of the pre- and postoperative functional examinations and the postoperative endoscopic long-term analysis.

Postoperative functional examinations, such as esophageal manometry, 24-h pH-metry, and bile exposure (Bilitec) monitoring, were performed in the early postoperative period with an average follow-up time of 16.7 ± 17 months (range: 3–23). In the later postoperative period, a further upper endoscopy with biopsy was carried out to check the changes in BE. The overall average follow-up time was 42 ± 16.19 months (range: 3–61).

The results of the pre- and postoperative medical examinations in the three groups were compared to identify the possible factors that promote the malignant transformation of BE into an adenocarcinoma.

The efficacy of laparoscopic surgery was studied with regard to the regression or progression of BM or LGD on histology, the lower esophageal sphincter (LES) function, and the postoperative 24-h pH-metry and bile exposure findings.

Clinical investigation

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 [17,18].

Endoscopy

The presence of BE (as a result of reflux) was confirmed by endoscopy and histological examination of the biopsy samples.

The location of the gastro-esophageal junction was defined as the point where the proximal extent of the gastric rugal folds met the tubular esophagus. According to the Prague C&M criteria [19], the length of Barrett's epithelium is measured from this point to the highest point of the squamocolumnar junction. The level of the diaphragm was also recorded. Hiatal hernia was diagnosed when the crural impression was separated from the top of the gastric rugal folds by >2 cm. The size of the hiatus hernia was recorded in centimeters. Biopsies were taken from the columnar mucosa at 2-cm intervals in a four-quadrant fashion.

Histopathology

The specimens were processed separately by formalin fixation and paraffin embedding for hematoxylin

and eosin staining, and immunohistochemistry was performed to identify the type of columnar metaplasia. The same expert pathologist reviewed all biopsy specimens. When HGD was suspected, the opinion of a second independent pathologist was sought to confirm the diagnosis. The pathologists were blinded to the treatment regimen.

Esophageal manometry

Standard water perfusion stationary manometry was performed according to the Castell criteria [20–23]. The manometric catheter was introduced into the esophagus through the nares. The motility of the LES, the esophageal body, the upper esophageal sphincter, and the pharynx was evaluated. The sphincters were studied by the station pull-through technique. Esophageal body peristalsis was also assessed during wet and dry swallows.

24-h esophageal pH monitoring

The procedure was performed on an inpatient basis, following the previously published protocol of our laboratory [24]. A naso-esophageal pH probe was positioned in the distal esophagus, at 5 cm above the LES, and the esophageal pH was recorded for 24 h. Esophageal pH parameters were analyzed with regard to the DeMeester's standards [20,25–27].

24-h esophageal bile exposure (Bilitec) monitoring

The procedure was performed simultaneously with the 24-h pH-monitoring study. A naso-esophageal fiberoptic catheter was positioned in the distal esophagus, at 5 cm above the LES, and the optical density at 450 nm of the esophageal content was recorded for 24 h [20,25–27].

Bilitec was carried out only in the selected cases (51 patients) in which a biliary reflux (duodeno-gastro-esophageal reflux) was proved by endoscopy.

Surgery

All patients underwent standard laparoscopic 360° Nissen fundoplication. The operation took place in all cases after full mobilization of the esophagus, division of the short gastric vessels, and posterior crural repair. At the time of the construction of the wrap, a 57 F bougie was introduced through the esophagus. The operation was always performed by the same team of surgeons.

Statistical analysis

Statistical computations were performed with an SPSS 17.0 for Windows software package, while the special Poisson distributed ANOVA method was performed with SAS for Windows 9.1. [28]. Preoperative univariate analyses were performed to identify factors associated with the occurrence of histopathological progression: a non-parametric method (Kruskal–Wallis test) was used for the analysis of variables. Non-parametric univariate analyses (Mann–Whitney test) were performed to estimate the efficacy of laparoscopic antireflux surgery, comparing the variables before and after surgery. To compare changes in the patients' parameters before and after the operation in the three groups, a generalized mixed model repeated measurements ANOVA method was applied (multivariate analysis) using the GLIMMIX procedure of SAS 9.1. One repeated measurement factor (antireflux surgery), one independent factor (groups), and their interaction were examined. The distribution of the variables and the differences of variations in the three groups were also taken into account. P values < 0.05 were considered statistically significant.

Results

Preoperative characteristics of the patient population

In contrast to expectations, IM and LGD did not display a longer history of reflux disease as compared with that in the NI group, whereas the history in the NI group started earlier than in the I group ($p = 0.057$) (Table I). The duration of medical treatments showed no differences either. Though patients in all three groups were overweight, the average BMI values did not differ. Hiatus 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 in the three groups with respect to the functioning of the LES such as pressure, length, and relaxation time. Corresponding with the data in literature, our earlier research results revealed more severe acid reflux in patients with BE than in patients with milder GERD alone. With respect to the acid reflux, however, BE did not exhibit any difference. The DeMeester score parameters used to calculate the score did not differ significantly in the three 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 examination indicated more severe

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

		Group	Mean	SD	*p* Value
Patients' characteristics	BMI	NI	27.70	5.58	0.354
		I	29.93	5.67	
		D	28.30	4.09	
	Hiatal hernia (cm)	NI	3.07	1.95	0.395
		I	3.08	2.4	
		D	4.20	1.17	
	The mean length of time (y) between the appearance of first symptoms and surgery	NI	5.80	4.53	0.057
		I	3.94	5.25	
		D	4.29	5.15	
	PPI's treatment (y)	NI	1.47	2.56	0.537
		I	1.00	0.97	
		D	4.14	5.27	
Manometry	pLES (mmHg)	NI	11.27	8.19	0.382
		I	13.31	8.84	
		D	8.40	8.85	
	rLES (s)	NI	10.51	3.32	0.937
		I	10.09	1.97	
		D	10.00	0.82	
	lLES (cm)	NI	2.98	1.37	0.757
		I	3.54	1.90	
		D	3.00	0.82	
pH-metry	Time of acid exposure <pH 4	NI	100.64	78.11	0.835
		I	111.12	104.80	
		D	274.20	359.82	
	Upright acid exposure <pH 4	NI	80.10	70.91	0.832
		I	93.18	92.16	
		D	229.00	302.06	
	Supine acid exposure <pH 4	NI	20.67	25.10	0.374
		I	18.35	29.21	
		D	45.60	60.65	
	Postprandial acid exposure <pH 4	NI	47.28	38.05	0.748
		I	50.88	55.35	
		D	113.20	136.51	
	>5 min acid exposure <pH 4	NI	3.90	4.76	0.299
		I	5.06	10.05	
		D	8.00	8.80	
	Longest acid exposure <pH 4	NI	25.10	60.13	0.469
		I	15.24	20.97	
		D	43.20	48.98	
	DeMeester score	NI	34.95	43.84	0.145
		I	39.12	61.01	
		D	88.92	67.58	
Bilitec	Time of bile exposure	NI	22.38	22.90	0.025
		I	23.33	30.53	
		D*	70.75	32.52	
	Upright bile exposure	NI	13.88	17.64	0.027
		I	16.60	15.77	
		D*	48.75	28.36	
	Supine bile exposure	NI	8.66	12.16	0.017
		I	6.80	19.04	
		D*	23.00	14.90	
	Postprandial bile exposure	NI	6.78	9.30	0.087
		I	8.00	7.85	
		D	20.50	16.84	
	>5 min bile exposure	NI	6.97	10.27	0.021
		I	3.00	2.90	
		D*	17.50	14.39	
	Longest bile exposure	NI	87.16	107.20	0.195
		I	38.60	63.72	
		D	111.25	37.95	

*Comparison of the preoperative groups revealed significantly more severe biliary reflux in the D group than in the other two groups (Non-parametric method – the Kruskal–Wallis test – was applied).
Abbreviations: BMI = body mass index; D = dysplastic (group); I = intestinal (group); lLES = length of lower esophageal sphincter; NI = non-intestinal (group); pLES = pressure of lower esophageal sphincter; PPI = proton-pump inhibitor; rLES = relaxation time of lower esophageal sphincter.

biliary reflux in the D group than in the other two groups (Table II). In contrast with the results of the univariate analyses, the multivariate analysis did not demonstrate significant differences in the three preoperative groups (data not shown).

Operative and early postoperative results

The average operation time was 99 ± 67.40 min. Conversion to open surgery was necessary in one patient (1.3%). There were no major intraoperative complications or deaths. The mean duration of hospitalization was 3 ± 1 days.

Early postoperative results

Symptomatic outcome

The Visick score, which reflects the complaints relating to the reflux, indicated that the patients' complaints were alleviated or ceased in 81% of the cases, remained unaltered in 15%, and worsened in only 4% of the patients. The Visick score varied somewhat within the groups; for the patients with intestinal BM and also those with LGD, complaints were alleviated relative to those in the group 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.

Postoperative functional examinations (manomentry, 24-h pH studies, and Bilitec)

Postoperative manometry, pH-metry, and Bilitec did not reveal statistically significant differences in the three groups. Changes in the functioning of the LES, which also indicate the efficacy of the operation, demonstrated that the postoperative pressure in the lower esophagus was significantly increased relative to that preoperatively, while the relaxation time remained unchanged (Table I). In consequence of the surgical technique (a loose and narrow Nissen floppy), the length of the LES was unchanged after fundoplication, but its functioning (pressure) was restored, thereby preventing acid and biliary reflux. Comparison of the results of pH-metry before and after the operation in the three groups confirmed the above findings, as the average DeMeester scores were clearly decreased after the operation. Accordingly, the incidence and severity of the biliary reflux were reduced, or this symptom was eliminated (Table II). Multivariate analysis proved significant changes between the preoperative and postoperative groups only as concerns the pressure of the LES and the results of pH-metry (data not shown).

Endoscopic surveillance

The mean duration of endoscopic follow-up was 42 ± 16.19 months. Postoperative endoscopy was performed in 64 patients (82%, 64/78). Fourteen patients who did not participate in upper gastrointestinal

Table II. Pre- and postoperative results of functional examinations (64 patients).

		Preoperative		Postoperative		
		Mean	SD	Mean	SD	*p* Value
Manometry	pLES (mmHg)	11.46	8.32	19.35	6.92	≤ 0.001
	rLES (s)	10.39	2.97	9.99	2.10	= 0.510
	lLES (cm)	3.10	1.48	3.28	1.08	= 0.251
pH-metry	Time of acid exposure <pH 4	117.79	132.92	43.39	81.76	≤ 0.001
	Upright acid exposure <pH 4	95.95	114.77	33.74	66.47	≤ 0.001
	Supine acid exposure <pH 4	22.07	30.39	9.71	20.69	= 0.001
	Postprandial acid exposure <pH 4	53.69	57.45	21.00	40.82	≤ 0.001
	>5 min acid exposure <pH 4	4.56	6.91	0.73	2.02	≤ 0.001
	Longest acid exposure <pH 4	23.84	51.18	3.74	6.05	≤ 0.001
	DeMeester score	40.84	52.29	13.11	31.29	≤ 0.001
Bilitec	Time of bile exposure	26.45	28.64	19.04	29.88	= 0.020
	Upright bile exposure	17.41	19.94	15.61	25.48	= 0.095
	Supine bile exposure	9.24	14.96	3.50	7.44	= 0.089
	Postprandial bile exposure	8.22	10.06	6.43	10.85	= 0.072
	>5 min bile exposure	6.63	9.68	2.64	4.47	= 0.008
	Longest bile exposure	74.52	94.29	52.07	125.80	= 0.014

After laparoscopic antireflux surgery the pressure of the LES was significantly increased, and the frequency of acid and biliary reflux was significantly decreased (Non-parametric method – the Mann–Whitney test – was applied).
Abbreviations: lLES = length of lower esophageal sphincter; pLES = pressure of lower esophageal sphincter; rLES = relaxation time of lower esophageal sphincter.

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

	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
Total ($n = 64$)	10 (15.6%)	9 (14.1%)	34 (53.1%)	11 (17.2%)**

Complete regression of BE was defined as the absence of any visible metaplasia on endoscopy. Partial regression was defined as a regression from LSBE to SSBE, or a regression from dysplasia to metaplasia, or changes within the metaplastic group (IM>CM>FM). Aggravation of the disease was defined as changes within the metaplastic group (such as FM<CM<IM), or progression from metaplasia to dysplasia or from SSBE to LSBE. Results are expressed as numbers of patients with percentages in parentheses.

*NI, including FM and CM.

**Progression from FM into CM in four patients or from CM into IM in seven patients; no further progression in patients with IM or LGD.

Abbreviations: BE = Barrett's esophagus; CM = cardiac metaplasia; FM = fundic metaplasia; IM = intestinal metaplasia; LGD = low-grade dysplasia; LSBE = long segment Barrett's esophagus; NI = non-intestinal (group); SSBE = short segment Barrett's esophagus.

endoscopy were excluded from the long-term analysis.

Before 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. Postoperative check-up examination demonstrated total regression of the BM 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 into CM in 4 patients (6.2%) or from CM into IM in 7 patients (11%), but no case of dysplastic or malignant transformation was registered. There was no further progression in the patients with LGD, and in three of these five patients the LGD disappeared, leaving only residual IM (Table III). There was no difference in the length of the follow-up period between the total regressive group and the other groups (partial, no change, and progression). Where we observed the regression of BE, out of the postoperative functional examinations results of manometry and pH-metry were significantly better compared with those groups where no changes occurred in BE, or progression of BE was found. We did not find differences among the groups in the results of postoperative Bilitec, apart from the results of the longest expositions (Table IV).

Discussion

We present evidence that laparoscopic Nissen fundoplication can appropriately control the reflux disease in a majority of the patients who underwent unsuccessful medical treatment, and it may inhibit progression and induce the regression of BM in a significant proportion of these patients.

Options available for the treatment of BE include medicinal treatment, endoscopic ablation, antireflux surgery, and their combination. The advantage of surgery over medicinal treatment is that it eliminates not only acid, but also biliary reflux due to the fact that it restores the functioning of the LES. Since the first observation by Brand et al., the fact that antireflux surgery can bring about the regression of Barrett's mucosa has become well-known. The results of recent randomized and nonrandomized studies suggest that successful antireflux surgery may be more effective than medical therapy with respect to preventing BE from progression [29–37]. The most recent meta-analysis concluded that antireflux surgery is definitely associated with the regression of BE and/or dysplasia [38]. However, evidence suggesting that surgery reduces the incidence of adenocarcinoma largely stems from uncontrolled studies. Several surgical centers have reported very good overall outcome of laparoscopic fundoplication in controlling reflux diseases [39,40]. However, a recent Swedish population-based study has concluded that antireflux surgery cannot be considered a procedure which prevents the development of esophageal or cardiac adenocarcinoma in individuals with reflux [41]. Postoperative reflux which persists or repeatedly recurs after unsuccessful surgery could be one of the reasons for this [42]. Another reason is that it is common in patients with more severe reflux to undergo surgery after long and unsuccessful medical treatment, and in these cases carcinogenesis cannot be prevented [9]. The extent of the experience of the surgical team could be a third reason that also significantly influences both the short-term and the long-term results.

Inflammation is responsible for the development of BE, but BE would seem to be an indicator of

Table IV. Comparison of the postoperative functional examination and the BE changes (among the three groups: regression, no change, progression) (64 patients) (Non-parametric method – the Kruskal–Wallis test – was applied).

		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
	lLES (cm)	3.21 (±0.699)	3.14 (±1.424)	2.89 (±1.269)	0.571
pH-metry	Time of acid exposure <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 <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	Time of bile exposure	4.75 (±6.292)	32.05 (±34.861)	23 (±28.605)	0.097
	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

Abbreviations: BE = Barrett's esophagus; lLES = length of lower esophageal sphincter; pLES = pressure of lower esophageal sphincter; rLES = relaxation time of lower esophageal sphincter.

the severity of the reflux rather than a premalignant condition. In the process of carcinogenesis, the importance of the functional examinations (manometry, pH-metry, and Bilitec) should be emphasized besides endoscopic surveillance. In BE, a larger hiatus hernia, insufficient LES activity, and more severe acid and biliary reflux were observed relatively frequently. It points to the importance of a comparatively frequent and aggressive reflux in the tumorgenesis [13].

Patients' complaints had persisted for more than 5 years on average before surgery was performed. The severity of BM (intestinal and LGD) did not correlate with the duration of the disease. Some published data suggest medical treatment as a possible successful alternative mode of treatment, but in fact our patients underwent surgery after a 20-month period of unsuccessful medical treatment on average. In this group of resistant patients, BM/dysplasia was not decreased measurably after conservative therapy and/or the symptoms of reflux persisted. It may, therefore, be assumed that patients who finally underwent surgery were resistant to medical treatment and generally had worse prospects for recovery.

Severe acid-biliary reflux is presumed to be a factor in the development of LGD. As concerns the three groups of patients who underwent surgery because of BE (the NI group, the I group, and D group), biliary reflux in the D group proved to be the most severe. However, it could not be confirmed that acid reflux that is more frequent and more severe plays a prognostically important role in transforming metaplasia to dysplasia, and that a change in the structure of the gastro-esophageal junction, i.e. hiatus hernia, lower LES pressure, shorter relaxation time, or shorter length of the LES, is more common in LGD.

Our results proved that laparoscopic antireflux surgery on BE patients with severe reflux had a low morbidity rate. Properly performed laparoscopic surgery eliminated the symptoms in a significant proportion of the patients; furthermore, it could successfully restore the activity of the gastro-esophageal junction, and eliminate or decrease both acid and biliary reflux which can prevent the further progression of BM. During endoscopic follow-up, regression was confirmed in 30% of the cases, the condition remained unchanged in 53%, and progression was observed in only 17%, all in the NI metaplasia group. Dysplasia did not develop in the I group, and further progression (HGD or *in situ* carcinoma) did not occur in the LGD.

It must be mentioned, however, that several forms of metaplasia and dysplasia (e.g. FM, CM and IM, pancreatic acinar or pancreatic ductal metaplasia, or even ciliar epithelium, LGD or HGD) and *in situ* carcinoma can be present in the esophageal mucosa at the same time. Our results highlighted the importance of endoscopic and biopsy follow-up in cases of FM and CM. After antireflux surgery, new IM was diagnosed in 17% of the cases of FM and CM. This evidently did not indicate the progression of the disease, but may be a consequence of the heterogeneous form of the disease or of the fact that biopsy samples were not 100% representative. Multiple biopsy sampling can contribute to a more exact

diagnosis of the state of the disease, but it can reveal the current state in only a small area, thus making the correct diagnosis and treatment more difficult. Regression after surgery has been reported in 35–60% of patients with SSBE, whereas its regression is uncommon in LSBE [15,16,30,37,43]. Our results revealed that antireflux surgery could reduce BM in both SSBE and LSBE.

Conclusion

Our results highlighted the importance of the cases of FM and CM, which can also transform into IM.

Results reported here suggest that laparoscopic Nissen fundoplication is a good therapeutic option for patients with BE after failed medical treatment. Technically correct antireflux surgery after unsuccessful medical treatment can ensure a symptom-free state in a majority of the patients and may result in the regression of BM. The evaluation of our results and the conclusions that can be drawn are limited by the retrospective nature of our study and the limited number of patients. To determine whether laparoscopic Nissen fundoplication can halt the progression of BE and prevent the development of adenocarcinoma in the long term, regular endoscopic follow-up and functional examinations should be performed in view of the slowness of the process of carcinogenesis.

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