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ORIGINAL ARTICLES

Fundoplication for gastroesophageal reflux and factors associated with the outcome 6 to 10 years after the operation: multivariate analysis of prognostic factors using the propensity score

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Abstract
Background The impact from the mode of operation (partial vs total fundoplication) on long-term outcome after fundoplication still is unknown, although short-term randomized studies have not shown significant differences in the efficacy of reflux control. To obtain some insight concerning the long-term results, the data of a nonrandomized cohort were analyzed using propensity score statistics.
Methods For 134 patients who underwent laparoscopic fundoplication for gastroesophageal reflux disease (GERD), the time until recurrence of reflux symptoms was assessed. The impact of putative prognostic factors and the mode of operation (partial vs total fundoplication) on outcome were tested for significance using univariate and multivariate statistics, including the propensity score, correcting for nonrandomized treatment groups. The follow-up period was 60 to 123 months (median, 93 months). In this study, 45 patients had a partial (Toupet) fundoplication, and 89 patients underwent a total (Nissen) fundoplication.
Results The rate of recurrence after 93 months (the median follow-up interval) was 14% after Nissen and 9% after Toupet fundoplication (nonsignificant difference) as estimated according to Kaplan and Meier. Massive acid exposure to the esophagus was associated with an increased risk of recurrence for 23% of the patients with a DeMeester score of 50 or higher, but only for 9% of the patients with less severe reflux (DeMeester score <50; $p < 0.05$). Multiple proportional hazard regression using the propensity score did not show additional significance for the variables of age, gender, presence of a Barrett esophagus, and mode of operation.
Conclusion The operation method did not have a significant impact on the efficacy of laparoscopic fundoplication in a cohort during a follow-up period of 60 to 123 months (median, 93 months).

Keywords GERD · Gastroesophageal reflux disease · Reflux · Fundoplication · Prognostic factors

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Since first reported in 1991, laparoscopic fundoplication has become a widely accepted alternative to long-term medical treatment for gastroesophageal reflux disease (GERD). Although published experience with follow-up periods exceeding 5 years is scarce, favorable outcomes have been reported.

From the beginning of laparoscopic antireflux surgery, the partial fundoplication (Toupet) has been performed for selected patients to avoid dysphagia. Prospective randomized trials have shown no difference in the efficacy between the two operation methods, but controlled long-term studies have not been reported. Because propensity score analysis allows for comparison of nonrandomized treatment options, we applied this statistical tool to evaluate any influence of the operation method on long-term symptom control. This study aimed to assess the long-term efficacy of laparoscopic fundoplication in controlling reflux symptoms and to evaluate risk factors for recurrence of reflux symptoms.

Patients and methods

Patients

The prospectively collected preoperative and operative data of 194 patients who underwent laparoscopic fundoplication for GERD from 1996 to 1999 at a single institution (Medical University of Vienna) were reviewed. All the operations were performed by or with the assistance of a surgeon experienced in laparoscopic surgery who had a personal record of at least 30 fundoplications. For the purpose of this study, 57 patients were excluded from the analysis for the reasons listed in Table 1. Consequently, 134 patients remained for further analysis.

The information about eventual recurrence of reflux symptoms was obtained by annual phone calls to the patients asking about heartburn or regurgitation symptoms necessitating pharmacologic treatment. The explicit question was "Are the symptoms of GERD that you experienced before the operation still under sufficient control without medical treatment?" If the answer was "no," the patient was classified as a treatment failure. For the purpose of this study, dysphagia without concomitant heartburn or regurgitation was not considered to indicate treatment failure.

In addition to the annual calls to the patients, a questionnaire asking for the aforementioned information was sent to 124 patients in September 2006. An answer was returned in 107 cases after the first inquiry and in 9 cases after the second attempt (total response, 116, 93%). Further investigation showed that all of the patients not responding to the questionnaire had died ($n = 8$) (Table 2).

The allocation to one of the operation methods depended largely on the surgeon's personal choice. In the first 2 years of our series, most of the operations were Nissen fundoplications, with Toupet fundoplication reserved for cases of severe motility disorders. Because some patients experienced significant postoperative dysphagia after the Nissen procedure, the decision to perform a Toupet fundoplication was made more often in 1998 and 1999 (Fig. 1), mostly for patients with mild motility disorders or preoperative dysphagia. Because the decision concerning the operation method was based solely on the surgeon's personal judgment, there evidently is no strict algorithm for the allocation.

Table 1 Causes for exclusion from the study

194 patients	Fundoplication for reflux 1996–1999	
45	Excluded for	Prior gastric surgery ($n = 17$)
		Prior fundoplication ($n = 10$)
		Personal case load of surgeon <30 ($n = 8$)
		Missing manometric data ($n = 10$)
15	Lost to follow-up within 60 months	
134 patients	Included into further analysis	

Table 2 Patient characteristics

Gender (M:F ratio)	1.83
Age (years)	21–78 (median, 54)
Operation technique	Total fundoplication (Nissen) ($n = 89$)
Partial fundoplication (Toupet) ($n = 45$)	
Follow-up (mos)	2–123; (median, 93)
Patients with recurrence of reflux symptoms	($n = 16$)

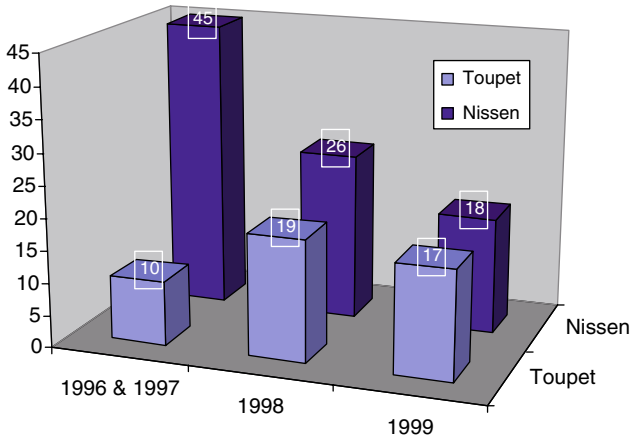

Fig. 1 The choice of operation technique: change with time

The proneness of cases to receive one of the two operation methods (Nissen or Toupet) was analyzed with logistic regression analysis to obtain a propensity score, as described in the following discussion.

Preoperative evaluation

Manometry and 24-h pH-metry

Esophageal manometry and 24-h pH-metry were performed for each patient as described previously [29]. The following variables of ph-metry and manometry were used in statistical analysis: DeMeester score [7], lower esophageal sphincter (LES) pressure, fraction time of pH less than 4, and contraction amplitudes in the distal third of the esophagus.

Preoperative endoscopy and histologic evaluation of the Z-line

Every patient underwent upper gastrointestinal endoscopy preoperatively. Erosive changes in the esophagus were described according to the Los Angeles classification [21].

Table 3 Intestinal metaplasia (IM) and Barrett's esophagus (BE)[a]

	Patients *n* (%)	Nissen *n* (%)	Toupet *n* (%)
Group A (no IM at the Z-line)	105 (79)	67 (76)	38 (84)
Group B ("short segment BE"; histologic evidence of IM in a macroscopically normal GE junction or in a columnar lined esophagus [CLE] <3 cm in length)	19 (14)	14 (16)	5 (11)
Group C ("long segment BE" (IM in a CLE ≥3 cm in length)	9 (7)	7 (8)	2 (4)

GE, gastroesophageal

[a] For the purpose of this study, the patients were grouped according to the presence and extent of intestinal metaplasia presenting at the gastroesophageal junction

Macroscopic changes in the esophageal mucosa suggesting intestinal metaplasia were described according to the Prague classification [28]. Biopsies were taken from the Z-line and from the gastroesophageal border for histologic substantiation. An intestinal metaplasia was defined by the presence of Alcian blue–stained goblet cells in the esophageal squamous epithelial tissue. For the purpose of this study, the patients were classified into three groups with respect to intestinal metaplasia (Table 3).

Operative techniques

Laparoscopic total fundoplication (Nissen) and partial posterior fundoplication (Toupet) were performed. The short gastric vessels were divided in all cases, and a short floppy wrap was created. The diaphragmatic crura (crural repair) were approximated with nonabsorbable sutures.

Conversion to open laparotomy was necessary in 6 cases, 5 of which were among the institution's first 40 laparoscopic fundoplications. Two patients underwent laparoscopic revision for bleeding.

Statistical analysis

Descriptive statistics

The prospectively collected data were entered into a computerized database and analyzed using JMP 6.0.0 (SAS Institute Inc., Cary, NC, USA). Continuous data were presented as mean ± standard deviation or median and range where appropriate.

Propensity score

Propensity analysis was performed to reduce bias caused by the surgeon's decision making. It aimed to identify patients with similar probability of receiving Toupet fundoplication on the basis of observed clinical characteristics such as lower esophageal sphincter (LES) pressure, contraction amplitude, and year of operation. To obtain propensity scores, logistic regression was used as a multivariate tool [18].

Analysis of time until treatment failure

The significance of putative risk factors was assessed using univariate (log rank test) and multivariate (Cox proportional hazards regression) models. The variables under consideration were age, gender, DeMeester score, presence and length of Barrett's mucosa, fraction of time with a pH lower than 4, grade of esophagitis (Los Angeles classification), LES pressure, contraction amplitudes in the distal third of the esophagus, mode of operation, and propensity score.

Results

The data derived from endoscopy, 24-h pH-metry, and manometry are listed in Tables 4 and 5. Intestinal metaplasia at least 3 cm in length was seen in 44% of the patients ($n = 4$) with a DeMeester score of 50 or higher and in 56% cases ($n = 5$) with less severe reflux ($p = 0.13$, likelihood ratio test). Seven (78%) of 9 patients with contraction amplitudes lower than 60 mmHg in the distal esophagus had a Barrett's segment of 3 cm or more, but only 2 of 9 patients (22%) cases with higher contraction amplitudes ($p = 0.07$, likelihood ratio test).

Time to recurrence of symptoms

The overall follow-up period was 60–123 months (median, 93 months). Recurrence of reflux symptoms was diagnosed for 16 patients after 2 to 69 months (median, 30 months).

Table 4 Results of preoperative 24-h pH-metry and manometry

Results	Range (median)	Nissen	Toupet
DeMeester score	0.3–168 (32)	0.3–168 (32)	3.4–135 (27) NS
DeMeester score ≥ 50	30	22 (25%)	8 (18%) NS
LES pressure (mmHg)	0–35 (10)	0–25 (10)	1–35 (12)[a]
Contraction amplitudes in the distal third (mmHg)	10–198 (61)	10–198 (64)	12–144 (55) NS

NS, not significant

[a] $p < 0.05$, Wilcoxon test

Table 5 Putative risk factors of treatment failure and percentages of treatment failure estimated according to Kaplan Meyer

Variable	*n*	% Treatment failure after 36 months	% Treatment failure after 93 months	*p*-Value (log-rank test)
All patients	134	9	12	
Mode of operation				
Nissen	89	10	14	
Toupet	45	7	9	0.44
Age				
<54 years	67	8	11	0.63
>54 years	67	9	13	
Gender				
Male	87	6	9	
Female	47	13	17	0.19
Barrett's esophagus				
Absence	105	9	12	
Short BE (<3 cm)	19	5	5	0.37
Long BE (>3 cm)	9	22	22	
DeMeester score				
<50	101	7	9	0.03[a]
≥50	29	13	23	
Mean contraction Amplitudes				
<60 mmHg	65	12	18	0.03[a]
>60 mmHg	68	4	6	

[a] $p < 0.05$ indicates a significant difference

Univariate analysis

The variables tested for significance to predict recurrence are listed in Table 6. A DeMeester score of 50 or higher ($p < 0.05$) and mean contraction amplitudes in the lower distal esophageal third less than 60 mmHg ($p < 0.05$) were significantly associated with an increased risk for recurrence of symptoms. (Fig. 2 and Table 5).

Propensity score

A propensity score was calculated using logistic regression to "predict" the mode of operation. The variables of LES, year of operation, pressure and contraction amplitude in the lower third of the esophagus were independently associated with the mode of operation (Table 6).

Table 6 Logistic regression to "predict" the operation method for obtaining a propensity score

Variable	*p*-Value
Constant	<0.01
Year of operation	0.02
LES pressure (mmHg)	<0.01
Mean contraction amplitudes <60 mmHg	<0.01

LES, lower esophageal sphincter

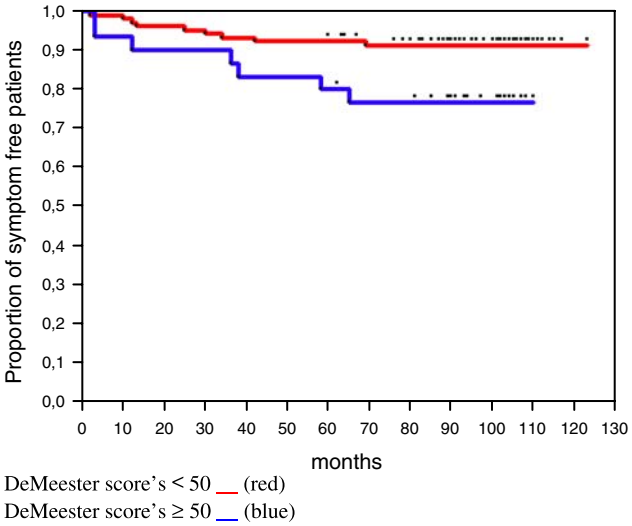

Fig. 2 Survival plot. Proportion of patients remaining without reflux symptoms: the influence of a DeMeester score of 50 or higher

Multivariate analysis of time until treatment failure

Multivariate analysis using Cox's proportional hazards regression showed that after considering the variable of DeMeester score, none of the remaining tested variables was of additional significance for predicting time to symptom recurrence. The operation method (Nissen or Toupet), entered into the Cox model together with the propensity score, also was of no additional significance. An independent influence of the operation method on the risk for recurrence could not be shown (Table 7).

Discussion

Laparoscopic fundoplication, first performed by Dallemagne in 1991, has established itself as a safe and effective

Table 7 Multiple hazards regression for predicting time until recurrence of reflux symptoms

Analyzed risk factors	*p*-Value
Operation method (Nissen vs Toupet)	0.31
Propensity score	0.26
Gender	0.13
Age >54 years	0.39
Mean contraction amplitudes <60 mmHg	0.08
Barrett segment ≥3 cm	0.91
Fraction time (pH >4) >15	0.83
DeMeester score ≥50	0.04[a]

[a] $p < 0.05$

option for the treatment of GERD [1, 9, 19, 22]. Reports on long-term performance (follow-up evaluation >5 years) of laparoscopic fundoplications are rare but promising. From the beginning of the laparoscopic approach, both partial (Toupet) and total (Nissen) fundoplications have been performed. Randomized trials with short follow-up periods showed no differences in antireflux efficacy between Nissen and Toupet fundoplication [3, 12, 13, 20, 27]. Until currently, no long-term results of randomized comparisons have been available, although favorable outcomes with follow-up periods longer than 7 years have been reported for both operation methods [5].

When data of randomized studies are not available, comparison of nonrandomized treatment groups is practicable by means of advanced statistics (e.g., the propensity score) [2]. Using independent (predicting) variables, the likelihood that a patient will be allotted to one of the treatment groups is estimated using multiple logistic regression analysis [8]. If the variables associated with the operation method (i.e., the propensity score) are included as an independent variable in a statistical model to predict time until treatment failure (e.g., Coxs proportional hazards regression), the impact of the treatment method can be evaluated [18].

Not many risk factors for symptomatic recurrence of reflux after fundoplication have been reported until recently. Horvath et al. [15] observed that a high DeMeester score may be a risk factor for recurrence after the Toupet procedure.

Similarly, in our series, only a DeMeester score of 50 or higher was associated with a greater risk for recurrence of heartburn. Because the mechanisms of fundoplication failure to control heartburn are not always clear, the meaning of this finding awaits further reflection. The intensity of acidic reflux, as epitomized by the DeMeester score, correlated with the intensity of reflux sequelae, such as prevalence of Barrett's epithelium, and degree of erosive damage to the epithelium of the esophagus [11, 23]. Conceivably, intense acidic reflux is associated with periesophageal inflammation and fibrosis, which may induce scarry shortening of the esophagus later after fundoplication [14, 16]. Less favorable results of fundoplication for patients with Barrett's esophagus have been reported repeatedly [4, 15]. Although partial fundoplication according to Toupet is associated with a lower incidence of postoperative dysphagia [10, 12, 25, 31], scepticism remains widespread concerning the long-term control of reflux after partial fundoplication [6, 10, 15, 17].

As long as prospective randomized trials with longer observation periods are not available, analysis of the data from observational studies using the propensity score may be favorable. Some authors have proposed tailoring the choice of operation (i.e., partial vs total fundoplication) according to manometric findings, favoring partial wraps for patients with impaired esophageal peristalsis with intent to lessen the risk for dysphagia. However, evidence of the factors leading to dysphagia is scarce, and the necessity to perform partial wraps at all has been questioned [10, 26].

Dysphagia was not within the scope of our study, but there is ample evidence that Toupet fundoplication results in less dysphagia than Nissen fundoplication [24, 25, 30]. If long-term reflux control turns out to be equally effective with both procedures, this would be a strong argument for performing the Toupet operation more deliberately.

In our series, both groups had the same risk for reflux recurrence, even after correction for the covariables (DeMeester score) and the propensity score in the current analysis. The choice of operation was evidently influenced by a changing inclination to perform the Toupet fundoplication throughout the observation period and by an anticipation of dysphagia based on manometric findings.

In the current cohort, the Nissen operation was as efficient as the Toupet procedure in controlling gastroesophageal reflux symptoms. Whether subgroups of patients exist who experience superior long-term results with Nissen remains to be shown, preferably by randomized trials. Because such investigations with long follow-up intervals are not to be expected in the near future, analysis of large unrandomized observations will be the main means for shaping some evidence. Nevertheless, the current analysis is unprecedented evidence that the Toupet procedure may not be inferior to the total (Nissen) fundoplication for guaranteeing long symptom-free intervals after antireflux surgery.

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