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Long-term reported outcomes of transoral incisionless fundoplication: an 8-year cohort study

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Abstract

Background Transoral incisionless fundoplication (TIF) offers an endoscopic approach to the treatment of gastroesophageal reflux disease (GERD). Controlled trials have demonstrated the short-term efficacy of this procedure, but long-term follow-up studies are lacking. The objective of this study was to evaluate the long-term impact of TIF on disease-specific quality of life and antisecretory medication use.

Methods We performed retrospective cohort study of all patients undergoing TIF between 2007 and 2014 in a large academic medical center. Reflux symptoms and quality of life were assessed using the gastroesophageal reflux disease health-related quality of life (GERD-HRQL) questionnaire at baseline, short-term, and long-term follow-up.

Results Fifty-seven patients with a median age of 46 (37–59) years and an average BMI of 28.8 ± 4.9 kg/m^2 underwent TIF during the study period. Sixty percent of the patients were female, and all were taking a PPI at least daily. At a median follow-up interval of 97 months, twelve patients had undergone subsequent laparoscopic antireflux surgery (LARS). Of those who had not, 23 had complete long-term follow-up data for analysis and were included in the study. Seventy-three percent reported daily acid-reducing medication use, and the median GERD-HRQL score was 10 (6–14) compared to 24 (15–28) at baseline ($p < 0.01$). Seventy-eight percent of these patients expressed satisfaction or neutral feelings about their GERD management. There were no significant differences in the baseline characteristics of patients who underwent LARS during the study period and those who did not.

Conclusions This study demonstrates that TIF can produce durable improvements in disease-specific quality of life in some patients with symptomatic GERD. The majority of patients resumed daily PPI therapy during the study period, but with significantly improved GERD-HRQL scores compared to baseline and increased satisfaction with their medical condition.

Keywords Transoral incisionless fundoplication · GERD · Long-term outcomes

Gastroesophageal reflux disease (GERD) is a common problem encountered in the Western world resulting in diminished quality of life. Prevalence data suggest 20–40% of the Western adult population suffers from chronic heartburn or regurgitation symptoms [1, 2]. Over 9 million primary care visits are attributed to GERD annually, making GERD the number one disease process leading to visits to a gastroenterologist annually [3].

Management options include medical and surgical therapy, after attempts at lifestyle modification [3]. These strategies effectively manage symptoms in most patients; however, both have significant down sides [3, 4]. Medical therapy with proton-pump inhibitors (PPIs) is ineffective in 25–42% of patients with GERD [4–6]. Further, medical therapy loses effectiveness over time with up to 50% of GERD patients relapsing after 3 years of therapy [4, 7]. Many patients are increasingly concerned about the consequences of long-term high-dose PPI use following reports of increased infectious complications, nutrition deficiencies, and risk of osteoporosis and dementia [3, 8]. Laparoscopic antireflux surgery

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(LARS) is highly efficacious for controlling reflux symptoms, but utilization remains low due to concerns about side effects, particularly bloating [4, 9].

Transoral incisionless fundoplication (TIF) provides an endoscopic therapeutic approach to GERD management and has been associated with improvements in GERD symptoms and medication with minimal adverse side effects at short and intermediate follow-up intervals [1, 10, 11]. The objective of this retrospective cohort study was to assess the long-term impact of the TIF procedure on disease-specific quality of life and antisecretory medication use.

Materials and methods

Patients

Fifty-seven consecutive patients underwent TIF for management of GERD between 2007 and 2014 at the Ohio State University Medical Center by two surgeons. Patient data were maintained in a prospectively created database with institutional review board approval. The patients in this study were referred for surgical management of GERD. They chose to undergo TIF following an informed consent discussion including alternative surgical and medical treatment options. Specific data points included age, gender, body mass index, ASA score, proton-pump inhibitor (PPI) use, barium swallow, esophagogastroduodenoscopy (EGD), manometry, 48-h pH monitoring (Bravo probe, Medtronic, Shoreview, MN, USA), complications, and subsequent procedures. In addition, patients completed the GERD-HRQL questionnaire to assess GERD symptoms and disease-specific quality of life.

Pre-operative evaluations

All patients underwent esophagogastroduodenoscopy, a barium swallow test, and 48-h pH monitoring to confirm the diagnosis of GERD. Manometry was performed in all patients that reported symptoms of reflux or dysphagia. Exclusion criteria for TIF included absence of pathologic reflux, hiatal hernia greater than 2 cm, LA grade C or D erosive esophagitis, and biopsy proven Barrett's esophagus.

Operative technique

TIF was performed as previously described [12]. Briefly, the patient was placed in left lateral decubitus after undergoing general anesthesia with nasotracheal intubation. A preprocedural EGD was preformed to assess for hiatal hernia and the gastroesophageal junction was measured. The EsophyX device was then passed over a standard gastroscope and delivered transorally into the esophagus and stomach. With the endoscope in the retroflexed position, the polypropylene fasteners were delivered serially as the device was rotated around its axis to create a gastroesophageal plication over a circumference of 200° to 300°. Patients were discharged on postop day #1 and PPI therapy was maintained for 2 weeks to allow for healing of traumatized gastric and esophageal tissue. Patients followed a liquid diet for 2 weeks, followed by a soft diet for 2 more weeks before advancing to a regular diet.

Outcome measures

The primary outcome measure of this study was the GERD-HRQL assessment of disease-specific quality of life. Secondary outcome measures included PPI use and satisfaction with the procedure. Questionnaires were administered at the pre-operative clinic visit and each subsequent follow-up encounter. Interval short- and long-term follow-up with questionnaire responses were obtained. Data are based on our institution's experience alone and follow-up via a telephone survey using the GERD-HRQL questionnaire without routine follow-up objective retesting.

Statistical analysis

Data were analyzed using Stata 12 (Stata Corp, College Station, TX, USA) and are presented as mean ± standard deviation or median (IQR) as appropriate. Data were analyzed using *t* tests for continuous data, Fischer's exact test for categorical data, and the Wilcoxon matched pairs test for non-parametric data. A p value less than 0.05 was considered statistically significant.

Results

Fifty-seven consecutive patients underwent TIF during the study period, representing our institution's early experience with TIF. Baseline patient characteristics are summarized in Table 1. Patients had a median age of 46 (37–59) years, an average BMI of 28.8 ± 4.9 kg/m^2, and thirty-four (60%) were female. The median DeMeester score was 30 (23–53). Twelve patients (21%) had endoscopic evidence of mild esophagitis and twenty-six (46%) had endoscopic or radiographic evidence of a small hiatal hernia (1–2 cm). Baseline GERD-HRQL score was 24 (15–28) while taking a PPI, and all patients were taking PPI therapy at least daily.

TIF outcomes were assessed at 12 (11–18) months and 97 (55–109) months post-operatively (Fig. 1). Thirty-six (63%) patients were analyzed at the 12 month time point after excluding twenty-one patients: fourteen were lost to follow-up, two died from causes unrelated to the procedure, and five underwent LARS within 1 year of TIF. Subsequently,

Table 1 Pre-operative patient characteristics for patients undergoing TIF

No. of patients	57
Female, no. (%)	34 (60)
Age (years), median (IQR)	46 (37–59)
BMI (kg/m^2), mean ± SD	28.8 ± 4.9
Daily PPI use, no. (%)	57 (100)
DeMeester score, median (IQR)	30 (23–53)
Hiatal hernia, no (%)	26 (46)
Mild esophagitis, no (%)	12 (21)
ASA, no. (%)	
1–2	42 (74)
3–4	15 (26)
GERD-HRQL score, median (IQR)	24 (15–28)

TIF transoral incisionless fundoplication, *BMI* body mass index, *PPI* proton-pump inhibitor, *ASA* American Society of Anesthesiologists, *GERD-HRQL* gastroesophageal reflux disease health-related quality of life

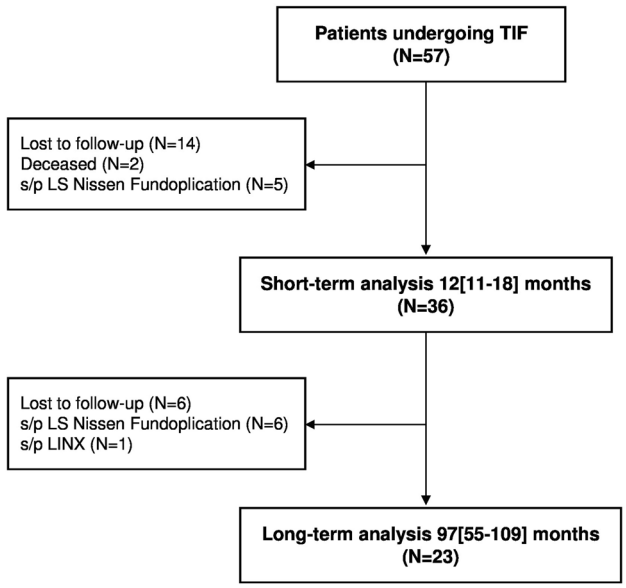

Fig. 1 Flow chart of treated and analyzed patients at baseline, short-term, and long-term follow-up

twenty-three (40%) patients were analyzed at long-term follow-up after six were lost to follow-up and seven had undergone LARS.

The GERD-HRQL score decreased from 24 (15–28) at baseline to 7 (2–18) at short-term follow-up ($p < 0.01$), and to 10 (6–14) at long-term follow-up ($p < 0.01$, Fig. 2). At short-term follow-up 47% achieved PPI cessation and 27% remained free of daily PPI use at long-term follow-up (Fig. 3). At baseline, all patients expressed dissatisfaction with respect to GERD symptom management which decreased to 26% ($n = 6$) at long-term follow-up. While a

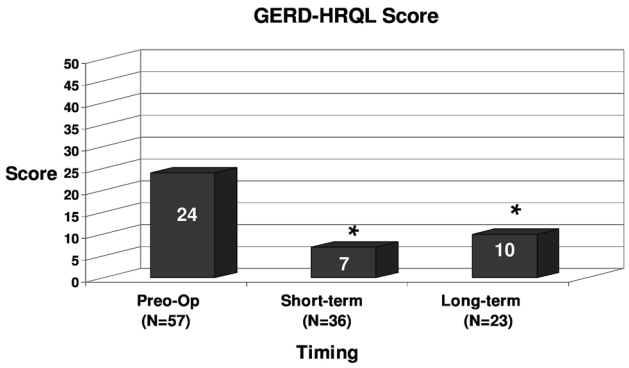

Fig. 2 GERD-HRQL score at baseline, short-term, and long-term follow-up for patients undergoing TIF without a subsequent antireflux procedure

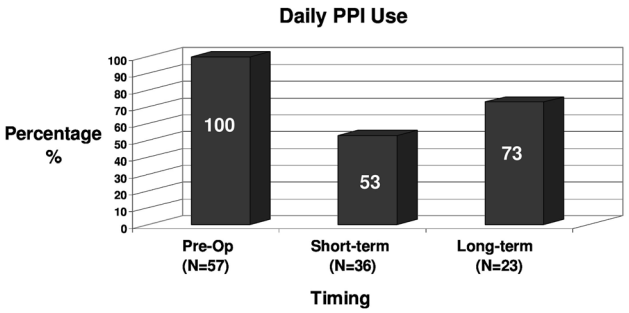

Fig. 3 Daily PPI use at baseline, short-term, and long-term follow-up for patients undergoing TIF without a subsequent antireflux procedure

majority of patients were on BID PPI therapy pre-TIF, 73% of patients who resumed PPI therapy long-term were on daily PPI therapy with either 20 mg or 40 mg.

During the study period, twelve (21%) patients underwent subsequent LARS for recurrent GERD symptoms at a median interval of 24 (10–36) months after TIF.

Five (9%) patients underwent laparoscopic Nissen fundoplication for failed TIF within the first year. At long-term follow-up, an additional six patients underwent laparoscopic Nissen fundoplication and one had a laparoscopic magnetic gastroesophageal junction reinforcement performed. Table 2 summarizes the patient characteristics of those who underwent subsequent antireflux surgery and those who did not. There were no statistically significant differences in patient demographics, hiatal hernia presence, esophagitis, or DeMeester score between these groups.

Discussion

The objective of this study was to assess the long-term impact of TIF on disease-specific quality of life and antisecretory medication use. Using validated questionnaires, we

Table 2 Characteristics of patients who underwent LARS and patients with long-term TIF follow-up

	LARS ($n=12$)	TIF ($n=23$)	p value
Female, no. (%)	6 (50)	11 (48)	0.592
Age, years, median (IQR)	39 (25–49)	48 (35–59)	0.220
BMI, kg/m^2, mean ± SD	28.5 ± 3.9	27.5 ± 5.2	0.852
ASA, no. (%)			
1–2	7 (58)	15 (68)	0.417
3–4	5 (42)	7 (32)	
Hiatal hernia, no. (%)	4 (33)	8 (35)	0.618
Esophagitis, no. (%)	1 (8)	3 (13)	0.575
GERD-HRQL, median (IQR)	25 (18–37)	25 (16–28)	0.763
DeMeester score	28.3 (15–50)	35 (26–75)	0.147

LARS laparoscopic antireflux surgery, *TIF* transoral incisionless fundoplication, *ASA* American Society of Anesthesiologists, *GERD-HRQL* gastroesophageal reflux disease health-related quality of life

found that TIF produces significant durable improvement in patient quality of life at a median follow-up interval of 97 months. However, the majority of patients required PPI therapy to maintain these improvements over time. Also, 21% of patients underwent a subsequent LARS for failure of the TIF procedure during the study period. Please note that durability in this discussion refers to preservation of improved quality of life as assessed by the GERD-HRQL tool ($p<0.01$), and does not refer to the ability to stay off antisecretory medications or the need for additional surgical intervention as noted by the results.

GERD is highly prevalent in the Western world with most patients managed successfully with antisecretory medications. However, a significant number of patients are non-responders, and others experience decline in symptom relief over time [4]. Increasingly, patients are concerned about the long-term effects of chronic PPI use [3, 8]. Nissen fundoplication remains the gold standard antireflux procedure, with excellent long-term efficacy. However, it comes with surgical risks and undesired chronic consequences that affect quality of life including gas/bloat syndrome, inability to vomit, nausea, and diarrhea [4, 13].

The present study demonstrates a significant decrease in the median GERD-HRQL score from 24 to 7 at short-term analysis, and to 10 at long-term follow-up of 97 months. This suggests that patients experienced durable improvement in disease-specific quality of life following TIF, although most patients did require daily PPI therapy to maintain these improvements in the long-term. Studies have shown that TIF is a promising endoscopic procedure with low adverse events, nearly non-existent chronic side effects, and encouraging short- and intermediate-term efficacy [9, 10, 14]. Although we did not directly study chronic side effects in this cohort, side effects of dysphagia, odynophagia, and gas-bloat were rare as assessed by the GERD-HRQL questionnaire. Further study is warranted to assess whether near non-existent chronic side effects following TIF may partly explain why TIF patients have a durable improved quality of life in spite having to resume PPI therapy.

Previous studies have demonstrated significant reductions in PPI use of 61–82% at 6 months, and 42–71% at 3 years [1, 4]. The present study demonstrates similar outcomes, corroborating existing literature with 47% of patients free from PPI use at 12 months. However, complete eradication of daily PPI therapy decreased to 27% at 97 months. This trend is consistent with that reported by Testoni and colleagues at 6-year follow-up with 36% in eradication of daily PPI use compared to 51% at 12 months [15]. However, this series reported that 86% of patients either stopped or halved PPI therapy compared to baseline at 6 years post TIF, implying a sustained partial response [15].

Patient satisfaction rates with GERD symptom management following TIF have been reported as 69% at 6 months, and 70–81% at 3 years [1, 4]. Despite a majority of patients resuming antisecretory medical therapy in the long-term, our study showed a minority (26%) of patients were dissatisfied with the management of GERD symptoms in the long-term, a rate consistent with reported short-term outcomes following TIF. Also, these patients had reported dissatisfaction with their condition at baseline while taking daily PPI therapy, suggesting a sustained partial treatment response following TIF. It remains unclear whether the satisfaction with disease management relates to a durable reduction in reflux volume improving the efficacy of PPIs to control heartburn [9]. Nonetheless, these patients did not seek surgical consultation for conversion to LARS after resuming PPI therapy, perhaps suggesting well-managed symptoms with PPI resumption. In the long-term, PPIs may represent an adjunct to the TIF procedure in patients whose symptoms were uncontrolled preoperatively on high-dose PPIs [11]. On the other hand, TIF may represent a stand-alone GERD intervention for the group of patients who did not resume PPI therapy (27%). We need to study these patients further to understand why TIF was able to control symptoms without the need to resume PPI therapy.

In the study, twelve patients (21%) failed TIF therapy and were excluded from long-term analysis. These TIF failure patients re-presented to clinic electively seeking further management of their GERD symptoms. They all underwent repeat testing for objective confirmation of GERD prior to re-intervention with LARS. Patients undergoing conversion to LARS had poor management of GERD symptoms with PPI therapy alone or did not want to take PPI therapy long-term. Five patients had an early TIF failure and underwent Nissen fundoplication within 1 year. It is unclear why these patients had early failures. One can speculate that it could have been a technical failure. It also could have been poor patient

selection in which these were some of the patients seeking an intervention to eradicate PPI use as they did not want to take long-term medication for symptom control. One patient had a laparoscopic magnetic gastroesophageal junction reinforcement and two patients underwent Nissen fundoplication 2 years following TIF. The remaining four patients underwent Nissen fundoplication: two at 3 years, one at 4 years, and the last at 6 years after TIF. This study suggests that TIF failures requiring reoperation occur in a minority of cases (21%), relatively speaking, and present equally in the short-term and long-term time frames. It is worth noting that the 21% TIF reoperative rate observed in our cohort is higher than LARS reoperative rates reported between 3 and 15% depending on the series reviewed [16, 17]. No differences in pre-operative patient characteristics, reflux severity, or presence of a hiatal hernia were identified between the TIF failures and those with long-term TIF follow-up (Table 2). In addition, it is unclear if the failures were related to the surgeon's learning curve. Further studies are needed to identify patients who are likely to achieve long-term success following TIF to reduce the rate of early failures.

While this study was not aimed at assessing the cost of GERD management using TIF, these data may provide improved data for assessing the cost-effectiveness of GERD therapies in the future. Nissen fundoplication or low-cost PPIs alone have been shown to be cost-effective GERD treatment therapies compared to short-term TIF data [18]. This study shows that many patients require long-term PPI use post TIF associated with durable improvements in disease-specific quality of life, which could not be achieved with medication alone. High-quality cost-effectiveness studies based on this and other long-term follow-up studies are required to model the long-term effect of various GERD treatments on long-term quality of life.

The study is limited by its retrospective nature, small size, single institution cohort, and lack of a matched LARS cohort to compare data. The study was designed to provide long-term data on the natural history of patients undergoing TIF for reflux treatment, considering long-term outcome data are lacking. The study design of a telephone questionnaire also is a limitation, as our ability to study other variables such as diet, weight loss, etc. that may have affected outcomes was hampered. Another limitation of the study has to do with GERD recurrence confirmation. Other than in patients undergoing conversion to LARS for TIF failure, objective testing for disease recurrence was not routine. 73% of patients resumed PPI therapy post TIF either by PMD prescription for GERD symptom recurrence or by self-medicating with over-the-counter PPI therapy for the same without objective retesting. Hence, using the PPI resumption rate as a marker for TIF failure may lead to unreliable and artificially elevated rates of TIF failures [1]. We do think as more institutions acquire long-term data, a metanalysis of these data will certainly increase the weight of our findings.

In conclusion, this study demonstrates that TIF can produce durable improvements in disease-specific quality of life in some patients with GERD. Although a majority of patients resume antisecretory medications in the long-term, a majority of patients are satisfied with GERD symptom management and have a sustained improved quality of life. We believe that this study sheds light to the unanswered question on what the natural history following TIF is. Further studies are required to identify the specific population who may benefit from TIF to avoid need for subsequent antireflux surgery.

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Compliance with ethical standards

Disclosures Munyaradzi Chimukangara, Anahita D. Jalilvand, W. Scott Melvin, and Kyle A. Perry declare no conflicts of interests.

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