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Transoral incisionless fundoplication with Medigus ultrasonic surgical endostapler (MUSE) for the treatment of gastro-esophageal reflux disease: outcomes up to 3 years

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Abstract

Background Transoral incisionless fundoplication (TIF) with Medigus Ultrasonic Surgical Endostapler (MUSE) is a new intervention for treatment of gastro-esophageal reflux disease (GERD). We aimed at assessing the clinical, functional, and endoscopic effects of TIF by MUSE.

Methods Forty-six patients underwent TIF. Proton pump inhibitor (PPI) consumption, GERD-health-related quality of life (HRQL) and reflux symptom index (RSI) questionnaires, upper gastrointestinal (GI) endoscopy, esophageal 24-h pH-impedance recording, and high-resolution manometry (HRM) were done before TIF and scheduled 6 and 12 months later (HRM only at 6-month). PPI consumption and symptoms were then assessed yearly. Data up to 3 years are reported in this study (PP- and ITT-analysis).

Results TIF was successfully performed in 45/46 patients; in one patient esophageal intubation was impossible. Perforation occurred in two cases. One patient required surgery within 6 months. Clinical follow-up was available for 42 patients at 6 months and 1 year, 35 patients at 2 years, and 31 patients at 3 years. At 1, 2, and 3 years, PPI consumption was stopped, respectively, in 64.3%, 62.9%, and 74.2% of cases (ITT-analysis: 58.7%, 56.4%, and 65.7%). GERD-HRQL and RSI scores decreased at least 50%, respectively, in 71.5% and 76.2%, 71.4% and 68.6%, and 67.7% of cases (ITT-analysis: 65.2% and 69.6%, 64.1% and 61.5%, and 60%). A significant improvement of both scores was observed up to 3 years. 6-month and 1-year functional follow-up were possible in 31 and 20 patients. HRM showed significant increase of the median lower esophageal sphincter length and rate of peristaltic waves. Esophageal pH-impedance recording found significantly fewer acid, proximal and total refluxes, and percentage of esophageal pH < 4 total time at 6 months, but not at 1 year.

Conclusion TIF by MUSE significantly improved symptoms and PPIs consumption up to 3 years. However, esophagitis still persisted in one-third of cases at 1 year and functional improvement at 6 months was not confirmed at 1 year. Severe complications requiring surgery occurred in two cases.

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Keywords Gastro-esophageal reflux disease · Transoral incisionless fundoplication · Medigus Ultrasonic Surgical Endostapler (MUSE)

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Abbreviations

CI	Confidence intervals
CT	Computed tomography
DCI	Distal contractile integral
GERD	Gastro-esophageal reflux disease
GI	Gastrointestinal
HRM	High-resolution manometry
HRQL	Health-related quality of life
ITT	Intention to treat

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LES	Lower esophageal sphincter
MUSE	Medigus ultrasonic surgical endostapler
NERD	Non-erosive reflux disease
PEEP	Positive end-expiratory pressure
PP	Per protocol
PPI	Proton pump inhibitor
RSI	Reflux symptom index
TIF	Transoral incisionless fundoplication

Transoral incisionless fundoplication (TIF) has proved to be an effective therapeutic option in alternative to medical and surgical therapy for treatment of gastro-esophageal reflux disease (GERD) [1, 2], with good outcomes persisting also in the long term [3–10]. TIF can be performed by either EsophyX® device or, more recently, Medigus Ultrasonic Surgical Endostapler (MUSE™).

MUSE™ (Medigus, Omer, Israel) creates a 180° fundoplication by stapling the gastric fundus to the esophagus below the diaphragm under ultrasound guidance. TIF by MUSE™ was first tested in animal studies [11] and then in ex vivo models [12]. In three studies the technique was found safe and effective up to four years [5, 6, 13].

The aim of this prospective, single-center, observational study was to evaluate the effect of TIF performed by a new-generation MUSE™ device on use of proton pump inhibitor (PPI) medication and GERD-related symptoms up to 3 years, as primary endpoint and functional and upper gastrointestinal (GI) endoscopic findings up to 1 year, in a consecutive series of patients suffering from GERD since at least 6 months with daily consumption of PPI. Other aims of the study were to assess the safety of TIF with the MUSE™ device and the durability of the intervention.

Materials and methods

Over a 5-year period, consecutive patients suffering from symptomatic-proven GERD or hypersensitive esophagus for at least 6 months previously or Barrett's esophagus, seeking an alternative to medical or surgical treatment, were considered to be enrolled in the study. All patients were PPI dependent for symptom control.

The indication to intervention was established according to the guidelines issued by the Society of American Gastrointestinal and Endoscopic Surgeons [14].

Inclusion criteria for enrollment in the study were as follows: (a) age > 18 and < 70 years; (b) chronic (at least 6 months) GERD-related symptoms, both esophageal and extra-esophageal, with complete or partial response to PPI therapy; (c) endoscopic findings of GERD or Barrett's esophagus < 3 cm); (d) evidence of non-erosive reflux disease (NERD) or hypersensitive esophagus at functional tests; (e) body mass index < 40 kg/m^2; (f) seeking an alternative to medical or surgical treatment; and (g) availability for a long-term follow-up.

Exclusion criteria were as follows: (a) functional pyrosis; (b) hiatal hernia ≥ 2.5 cm and non-reducible hernia (assessed through barium swallow contrast X-ray) as contraindication to TIF with MUSE device; (c) Barrett's esophagus ≥ 3 cm; (d) malignant upper GI neoplasia; (e) previous GI or thoracic surgery; (f) esophageal varices, stenosis, or diverticula; (g) portal hypertension; (h) scleroderma; (i) body mass index > 40 kg/m^2 and bleeding disorders; (j) age < 18 years and > 75 years; (k) GERD symptoms for less than 6 months; and (l) inability to give consent and unavailability to long-term follow-up.

All patients gave written informed consent for the procedure and data management for scientific purposes. The protocol (N. MUSE/2015) was approved by the medical Ethics Committee of the San Raffaele Scientific Institute of Milan and registered at ClinicalTrials.Gov (ID: NCT03669874).

Study design

Symptoms and daily PPI consumption were scheduled to be assessed before TIF-MUSE, 6 and 12 months, and then yearly after the procedure, for at least 5 years.

All patients completed the GERD-Health-Related Quality of Life (GERD-HRQL) [15] and Reflux Symptom Index (RSI) (validated Italian version, [16]) questionnaires, 14 days after stopping PPI. The GERD-HRLQ is a validated 10-item questionnaire that measures the symptom severity of GERD patients. Six items measure satisfaction for the degree of heartburn, two for dysphagia/pain while swallowing, one for the impact of medication on daily life, and one item measures overall satisfaction with the present condition. The RSI is a self-administered nine-item questionnaire for symptoms assessment in patients with suspected laryngopharyngeal reflux. In both questionnaires the score for each item ranges from 0 (no problem) to 5 (severe problem). Clinical efficacy of TIF was considered the reduction by at least 50% of symptom scores.

Post-TIF daily PPI consumption was considered "unchanged," "halved," and "stopped" when the daily drug dose was, respectively, the same as before the procedure, half that used before the procedure, and when no PPIs were taken during the follow-up.

Functional parameters were assessed before TIF by high-resolution esophageal manometry (HRM) and 24-h ambulatory esophageal pH-impedance recording (always off-PPI) and scheduled to be measured, respectively, 6 months (both HRM and 24-h esophageal pH-impedance) and 1 year (24-h esophageal pH-impedance) after TIF.

Upper GI endoscopy was done before TIF and scheduled to be performed 6 months and 1 year after the procedure.

Follow-up symptom assessment and endoscopy were performed by physicians other than those who performed TIF and unaware of the post-procedure outcomes.

Study endpoints

Primary endpoints were the percentage of patients who stopped or at least halved the PPI consumption and the GERD-HRQL and RSI questionnaires scores (off-PPI), calculated both as median values and percentage of patients who experienced at least 50% reduction, compared with before TIF. Secondary endpoints were the followings: (a) endoscopic findings assessing the presence and grade of esophagitis, hiatal hernia and Hill's grade of the gastro-esophageal valve compared with before TIF; (b) HRM and 24-h pH-impedance findings compared with before TIF; (c) feasibility, durability and safety of TIF by MUSE™.

MUSE procedure

The MUSE™ device comprises the endostapler and a console connected with the endostapler, containing a camera and ultrasonic range finder, various sensors, a pump for insufflation and irrigation, and a suction system.

The endostapler has a handle, where controls are located, an insertion tube of 15.5 mm in diameter containing operative channels, electrical and mechanical cables that operate the device, a cartridge containing five 4.8 mm titanium staples, the ultrasound mirror, one alignment pin funnel, and two anvil screw funnels. The distal tip can be articulated to align with the cartridge.

Under general anesthesia with endotracheal intubation and a positive end-expiratory pressure (PEEP) of at least 5 mmHg, the device was introduced through an overtube retroflexed in the fundus and pulled back to place the staple cartridge in the esophagus approximately 3 cm proximal to the gastro-esophageal junction. As the tissues were compressed, the ultrasonic range finder automatically engaged to display the tissue thickness. When the tissue thickness was 1.4–1.6 mm, the operator delivered at least three quintuplets of staples. Antiemetic prophylaxis and full muscle relaxation throughout the procedure are mandatory for TIF. Antiemetic prophylaxis was maintained i.v. for 24 h, with broad-spectrum antibiotic therapy i.v. for 48 h, and then orally for five more days. Analgesic prophylaxis with paracetamol and ketorolac for the first 24 h after the procedure was also routine.

All patients were kept in hospital for two nights after the procedure. In case of pain requiring major analgesics or fever persisting for two days a computed tomography (CT) scan and hydrosoluble contrast X-ray investigation were carried out (possible esophageal or gastric leakage).

At discharge, patients were instructed to follow a liquid diet for the first week and then a soft diet for the next two weeks. PPIs were discontinued four weeks after the procedure.

Statistical analysis

Continuous variables are reported as mean values ± standard deviation or as median values with estimated 95% confidence intervals (CI), based on test for normal distribution (Shapiro–Wilk test). Categorical variables are expressed as numbers and percentages. Before- versus after-treatment variations for each patient are computed within three separate blocks of comparisons: (a) clinical, (b) endoscopic, and (c) functional. Statistical significance is assessed through separate paired samples two-tailed Wilcoxon signed-rank sum test. Both per protocol (PP-set), including all patients that did not violate the protocol, and intention-to-treat (ITT-set), including all enrolled patients, analyses are performed. The thresholds of statistical significance are adjusted for multiple comparisons, taking into account, separately, the number of tests executed within the three blocks. Accordingly, thresholds of statistical significance are set at 0.0125 (alpha of 0.05/4) for clinical parameters and at 0.01 (alpha of 0.05/5) for functional parameters. *P*-values below these thresholds are considered statistically significant.

Results

Between September 2015 and June 2019, 46 consecutive patients (25 males and 21 females, mean age: 50 ± 8 years) were enrolled in the follow-up study.

The mean duration of symptoms was 9 ± 6 years. Thirty-one/46 patients (67.4%) complained of both esophageal and extra-esophageal symptoms.

22/46 patients (47.8%) required double-standard dose PPI therapy and 19/46 patients (41.3%) required single-standard dose PPI to control symptoms, while 5/46 patients (10.9%) assumed PPIs at halved standard dose or occasionally.

At pre-TIF upper G.I. endoscopy, 14/46 patients (30.4%) had grade A esophagitis and 2/46 patients (4.3%) had Barrett's esophagus (C1M1 and C1M2, according to Prague's classification) without dysplasia. Thirty/46 patients (65.2%) had a diagnosis of non-erosive reflux esophagitis, confirmed by pathological 24-h pH-impedance recording. A hiatal hernia < 2.5 cm was reported in 18/46 patients (39.1%). The Hill's grade of the gastro-esophageal valve was II in 40/46 cases (87%) and III in 6/46 cases (13%). Demographics, clinical, and endoscopic features of enrolled patients at baseline are reported in Table 1.

Table 1 Demographic and pre-transoral incisionless fundoplication clinical and endoscopic findings of the 46 enrolled patients

Demographic features	
Gender, *N*. (%)	
Male	25 (54.4)
Female	21 (45.7)
Age (years), mean ± SD	50 ± 8
BMI (kg/m^2), mean ± SD	24 ± 3.2
Clinical features	
Symptoms, *N*. (%)	
Esophageal	15/46 (32.6)
Esophageal and extra-esophageal	31/46 (67.4)
Duration of symptoms (years), mean ± SD	9 ± 6
PPIs dose, *N*. (%)	
Double standard	22/46 (47.8)
Single standard	19/46 (41.3)
Halved standard or occasional	5/46 (10.9)
Endoscopic features	
Grade A esophagitis, *N*. (%)	14/46 (30.4)
Barrett's esophagus, *N*. (%)	2/46 (4.3)
Normal esophagus, *N*. (%)	30/46 (65.2)
Hiatal hernia < 2.5 cm, *N*. (%)	18/46 (39.1)
Gastro-esophageal valve Hill grade II, *N*. (%)	40/46 (87)
Gastro-esophageal valve Hill grade III, *N*. (%)	6/46 (13)

N number, *SD* standard deviation, *BMI* body mass index, *PPI* proton pump inhibitor

TIF by MUSE™ was technically feasible in 45/46 patients (97.8%), with a mean duration of 77 ± 22 min. In one case it was impossible to pass the MUSE™ device through the cervical esophagus because of a compression due to protrusion of a cervical vertebra.

After TIF, all hiatal hernias were reduced and the Hill's grade of the newly created valve was I in all cases.

Two major complications (4.4%) requiring surgical repair occurred: one delayed (48 h after TIF) esophageal perforation and one intra-operative gastric fundus perforation. Esophageal perforation was very likely induced by some severe episodes of cough occurred in the 48-h post-procedure period; gastric perforation occurred 2 cm distally to the cardia as the consequence of an incorrect placement of the stapler because of a difficult ultrasound-guided alignment. Three/45 (6.7%) patients with epigastric pain in the 6 h after the procedure required major analgesics. One patient was unresponsive to TIF and underwent Nissen fundoplication within 6 months after the procedure.

The two patients who experienced post-procedural complications and the patient unresponsive to TIF were excluded from the follow-up.

Clinical follow-up was therefore carried out in all 42 patients (100%) at 6 months and 1 year (46 patients as per ITT-set), 35/42 patients (83.3%) at 2 years (39/46 patients as per ITT-set), and 31/42 patients (71.4%) at 3 years (35/46 patients as per ITT-set). Ten patients were in follow-up at 5 years, but they were not considered for the present study because of the scarce numbers.

None of the 42 patients as per PP-set dropped out or withdrew.

PPI consumption and symptomatic outcomes

The PPI consumption was stopped in 64.3% (58.7% as per ITT-set) of cases at 6 months and 1 year, 62.9% (56.4% as per ITT-set) of cases at 2 years, and 74.2% (65.7% as per ITT-set) of cases at 3 years. The percentage of patients who had stopped or at least halved the PPI consumption was 88.1% (80.4% as per ITT-set) at 6 months, 90.5% (82.6% as per ITT-set) at 1 year, 88.6% (79.5% as per ITT-set) at 2 years, and 87.1% (77.1% as per ITT-set) at 3 years. The detailed number and percentages of patients who had stopped, halved, or unchanged the dose of PPI therapy (both as per PP-set and ITT-set) at each follow-up time-point are reported in Table 2. Results at 6 months were maintained substantially unchanged up to 3 years.

GERD-HRQL and RSI questionnaires median scores (off-PPI) were significantly lower than before treatment ($p < 0.0001$ for both GERD-HRQL and RSI scores) after 6 months and remained significantly lower up to 3 years ($p = 0.007$ for GERD-HRQL score and $p = 0.01$ for RSI score) (Table 3).

Compared with before treatment, a reduction of GERD-HRQL and RSI scores by at least 50% was obtained in 73.8% (67.4% as per ITT-set) and 76.2% (69.6% as per ITT-set) of cases, respectively, at 6-month follow-up. These figures decreased to 67.7% (60% as per ITT-set) of cases 3 years after TIF for both GERD-HRQL and RSI scores. Detailed data (both as per PP-set and ITT-set) for each follow-up time-point are reported in Table 4.

Endoscopic findings

Thirty-eight/42 (90.5%) patients (82.6% as per ITT-set) and 31/42 (73.8%) patients (67.4% as per ITT-set) completed the 6 months and 1 year scheduled endoscopic follow-up, respectively. Four patients at 6 months and 11 patients at 1 year refused to repeat upper GI endoscopy because of symptoms improvement.

Grade A esophagitis was found in 7/38 (18.4%) patients (15.2% as per ITT-set) at 6 months: it persisted in 5/14 (35.7%) patients with prior esophagitis and was seen first in two other patients. At 1 year esophagitis persisted in 6/31 (19.3%) patients (13% as per ITT-set).

Recurrent hiatal hernia < 2.5 cm was seen in 2/38 (5.3%) patients and further confirmed in 2/31 (6.5%) patients at 6 months and 1 year, respectively (4.4% as per ITT-set).

Table 2 Changes in proton pump inhibitors consumption at 6-month, 1-, 2-, and 3-year follow-up after transoral incisionless fundoplication with the MUSE™ device compared with before the procedure: per protocol and intention-to-treat analyses

PPI therapy, *N* (%)	6 months		1 year		2 years		3 years	
	PP	ITT	PP	ITT	PP	ITT	PP	ITT
	42 pts	46 pts	42 pts	46 pts	35 pts	39 pts	31 pts	35 pts
Stopped	27 pts (64.3%)	(58.7%)	27 pts (64.3%)	(58.7%)	22 pts (62.9%)	(56.4%)	23 pts (74.2%)	(65.7%)
Dose at least halved	10 pts (23.8%)	(21.7%)	11 pts (26.2%)	(23.9%)	9 pts (25.7%)	(23.1%)	4 pts (12.9%)	(11.4%)
Stopped + Dose at least halved	37 pts (88.1%)	(80.4%)	38 pts (90.5%)	(82.6%)	31 pts (88.6%)	(79.5%)	27 pts (87.1%)	(77.1%)
Dose unchanged	5 pts (11.9%)	(10.9%)	4 pts (9.5%)	(8.7%)	4 pts (11.4%)	(10.2%)	4 pts (12.9%)	(11.4%)

PPI proton pump inhibitor, *Pts* patients, *PP* per-protocol analysis, *ITT* intention-to-treat analysis

Table 3 Comparison of median (95% confidence interval) Gastro-esophageal reflux disease Health-Related Quality of Life and Reflux Symptom Index scores (off-proton pump inhibitors consumption) at each follow-up time-point after transoral incisionless fundoplication with the MUSE™ device versus baseline scores

(a) At 6 months and 1 year

Symptoms score, median (95% CI)	Baseline 42 pts	6 months 42 pts	*p* value vs baseline	1 year 42 pts	*p* value vs baseline
GERD-HRQL score	22.0 (16.0–25.0)	9.0 (6.0–12.0)	< 0.0001	7.0 (3.3–10.0)	0.0001
RSI score	19.0 (17.0–24.2)	10.0 (3.0–12.0)	< 0.0001	5.5 (3.0–7.5)	0.0001

(b) At 2 years

Symptoms score, median (95% CI)	Baseline 35 pts	2 years 35 pts	*p* value vs baseline
GERD-HRQL score	23.5 (16.0–26.8)	8.5 (3.0–12.0)	0.0007
RSI score	17.0 (15.4–23.6)	7.0 (3.4–8.6)	0.0003

(c) At 3 years

Symptoms score, median (95% CI)	Baseline 31 pts	3 years 31 pts	*p* value vs baseline
GERD-HRQL score	24.0 (9.7–30.6)	2.5 (0.47–8.7)	0.007
RSI score	23.5 (17.0–25.5)	6.0 (2.3–15.0)	0.01

GERD-HRQL Gastro-esophageal reflux disease Health-Related Quality of Life, *RSI* Reflux Symptom Index, *Pts* patients, *CI* confidence interval

Table 4 Percentages of patients with at least 50% reduction of gastro-esophageal reflux disease Health-Related Quality of Life and Reflux Symptom Index scores (off-proton pump inhibitors consumption) at 6 months and 1, 2, and 3 years after transoral incisionless fundoplication with the MUSE™ device compared with before the procedure: per protocol and intention-to-treat analyses

50% reduction of symptoms score, *N* (%)	6 months		1 year		2 years		3 years	
	PP	ITT	PP	ITT	PP	ITT	PP	ITT
	42 pts	46 pts	42 pts	46 pts	35 pts	39 pts	31 pts	35 pts
GERD-HRQL score	31 pts (73.8%)	(67.4%)	30 pts (71.5%)	(65.2%)	25 pts (71.4%)	(64.1%)	21 pts (67.7%)	(60%)
RSI score	32 pts (76.2%)	(69.6%)	32 pts (76.2%)	(69.6%)	24 pts (68.6%)	(61.5%)	21 pts (67.7%)	(60%)

N number, *GERD-HRQL* Gastro-esophageal reflux disease Health-Related Quality of Life, *RSI* Reflux Symptom Index, *Pts* patients, *PP* per-protocol analysis, *ITT* intention-to-treat analysis

At 6 months and 1 year after the intervention, respectively, Hill's grade of the gastro-esophageal valve was I in 24/38 (63.2%) and 21/31 (67.7%) patients (52.2% and 45.7% as per ITT-set, respectively), II in 13/38 (34.2%) and 9/31 (29.0%) patients (28.3% and 19.6% as per ITT-set, respectively), and III in 1/38 (2.6%) and 1/31 (3.3%) patients (2.2% as per ITT-set).

Functional findings

Thirty-one/42 (73.8%) patients (67.4% as per ITT-set) and 20/42 (47.6%) patients (43.5% as per ITT-set) underwent functional investigation at 6-month and 1-year follow-up, respectively. Eleven and further 22 patients with symptomatic improvement refused to undergo functional investigation at the scheduled times, respectively.

At HRM the median lower esophageal sphincter (LES) basal pressure and length, distal contractile integral (DCI), and percentage of peristaltic waves increased in 16/31 (51.6%) patients (34.8% as per ITT-set), 20/31 (64.5%) patients (43.5% as per ITT-set), 18/31 (58.1%) patients (39.1% as per ITT-set), and 12/31 (38.7%) patients (26.1% as per ITT-set), respectively. The median LES length and peristaltic waves rate increased significantly ($p = 0.03$ and $p = 0.025$, respectively) compared with before treatment. Detailed data are reported in Table 5.

At 24-h impedance recording, total, acid, and proximal refluxes decreased, respectively, in 23/31 (74.2%), 25/31 (80.7%), and 21/31 (67.7%) patients (50%, 54.4%, and 45.7% as per ITT-set) at 6 months and in 12/20 (60%), 12/20 (60%), and 11/20 (55%) patients (26.1%, 26.1%, and 23.9% as per ITT-set) at 1 year. At 6 months there were significantly fewer median number of total, acid ($p = 0.0002$), and proximal ($p = 0.002$) refluxes, compared with before treatment. The figure remained substantially unchanged at 1 year, but no longer significant, likely because of the smaller number of patients investigated (Table 6).

At 6-month and 1-year pH-metric evaluations the DeMeester score decreased in 14/31 (45.2%) and 11/20 (55%) patients (30.4% and 23.9% as per ITT-set), without significant changes compared with baseline. The percentage of total time esophageal pH < 4 decreased in 16/31 (51.6%) and 11/20 (55%) patients (34.8% and 23.9% as per ITT-set), with significant improvement at 6 months ($p = 0.006$), but not at 1 year.

Discussion

Transoral incisionless fundoplication is currently considered as an effective intervention for controlling GERD-related symptoms, in alternative to medical or surgical therapy [1, 2], with favorable outcomes persisting up to 4–10 years after Esophyx procedure [9, 10]. The MUSE™ device has been proposed in the last 5 years as an alternative to EsophyX® device, but only 3 clinical studies are currently available on this technique [5, 6, 13].

The present study assessed the clinical efficacy, safety, and durability of TIF with the MUSE™ device for up to 3 years in a selected group of patients with chronic GERD who were PPI dependent, not satisfied with medical therapy, and seeking for an alternative to medical and surgical treatment, treated consecutively in a single center.

The intervention was performed successfully in all patients except one in whom the insertion of the MUSE™ device was technically impossible. A severe complication arose in two cases (4.4%) as a consequence of delayed esophageal and intra-procedural gastric perforation at the stapler site. Since these complications did not occur in the initial cases, they were independent from the learning curve. The overall complication rate is similar to those reported in the two published meta-analyses and in the previous studies with the MUSE™ device.

PPI consumption was stopped in two-thirds of patients and stopped or at least halved in about 80% of patients

Table 5 Comparisons of manometric findings at 6 months after transoral incisionless fundoplication with the MUSE™ device compared with before the procedure, in patients undergone high-resolution esophageal manometry

Functional parameter, median (95% CI)	*N* patients	Baseline	6 months	*p* value vs baseline
DCI (mmHg*sec*cm)	31	530.4 (222.9–1288.4)	755.1 (133.6–1374.6)	0.14
Peristaltic waves (%)	31	90.0 (57.9–100.0)	100.0 (90.0–100.0)	0.025
Fragmented waves (%)	5	10.0 (range 10.0–60.0)	0.0 (range 0.0–10.0)	0.06
Weak waves (%)	11	20.0 (7.4–30.0)	10.0 (0.0–36.1)	0.96
Failed waves (%)	14	23.5 (10.0–70.0)	13.0 (0.0–45.4)	0.50
LES length (cm)	31	4.3 (3.8–5.0)	4.9 (4.3–5.2)	0.03
LES basal pressure (mmHg)	31	23.6 (17.9–27.4)	26.9 (20.0–28.6)	0.88

CI confidence interval, *N* number, *DCI* distal contractile integral, *LES* lower esophageal sphincter

Table 6 Comparisons of 24-h pH and impedance recording findings at each follow-up time-point after transoral incisionless fundoplication with the MUSE™ device compared with before the procedure

(a) At 6 months			
Functional parameter, median (95% CI)	Baseline 31 pts	6 months 31 pts	*p* value vs baseline
N. total refluxes	57.0 (38.3–79.4)	31.0 (24.5–54.1)	0.0002
N. acid refluxes	37.0 (24.5–54.2)	24.0 (12.3–41.2)	0.0002
N. weakly acid refluxes	11.0 (7.0–22.9)	8.5 (6.0–15.9)	0.22
N. alkaline refluxes	2.0 (1.0–3.4)	1.5 (0.0–2.7)	0.81
N. proximal refluxes	26.0 (12.8–37.8)	12.0 (5.8–20.3)	0.002
Longest reflux (min)	8.4 (3.6–11.9)	6.2 (5.0–15.0)	0.68
DeMeester score*	21.1 (12.0–32.8)	20.0 (6.0–37.7)	0.53
% Total time esophageal pH < 4	5.8 (1.5–8.3)	3.8 (1.3–5.1)	0.006
(b) At 1 year			
Functional parameter, median (95% CI)	Baseline 20 pts	1 year 20 pts	*p* value vs baseline
N. total refluxes	41.5 (27.5–76.8)	40.5 (24.7–68.8)	0.37
N. acid refluxes	31.5 (20.6–54.6)	27.5 (13.4–46.6)	0.15
N. weakly acid refluxes	7.5 (4.8–14.0)	10.0 (6.0–19.8)	0.23
N. alkaline refluxes	0.0 (0.0–1.5)	1.5 (1.0–2.5)	0.16
N. proximal refluxes	18.5 (11.0–34.5)	18.0 (7.2–30.5)	0.31
Longest reflux (min)	8.0 (3.4–11.0)	5.0 (4.0–12.0)	0.89
DeMeester score*	17.8 (6.7–35.5)	16.4 (5.6–26.9)	0.46
% Total time esophageal pH < 4	5.7 (3.2–7.1)	4.2 (2.9–5.0)	0.16

N number, *CI* confidence interval, *Pts* patients

*Parameters for DeMeester score: (1) total number of reflux episodes; (2) total number of reflux episodes ≥ 5 min.; (3) longest reflux episode (min); (4) percentage of total time esophageal pH < 4; (5) percentage of upright time esophageal pH < 4; and (6) percentage of supine time esophageal pH < 4

6 months and 1, 2, and 3 years after intervention, either as per PP- and ITT-analysis. Considering only patients who completely stopped PPIs to be responders to TIF, the MUSE™ device proved effective in about two-thirds of patients (74.2% and 65.7% as per PP- and ITT-analysis, respectively) at 3-year follow-up. These data are in line with those already published by our group on symptomatic and functional outcomes on 20 patients followed up to 12 months [13].

Symptomatic assessment by GERD-HRLQ and RSI questionnaires indicated highly significantly lower scores off-PPI therapy 6 months after TIF than before treatment, persisting substantially unchanged up to 3 years. Both typical and extra-esophageal symptoms improved without substantial difference among patient with esophagitis, NERD, and Barrett's esophagus. A reduction by at least 50% of GERD-HRQL and RSI scores was observed in 73.8% and 76.2% (67.4% and 69,6% as per ITT) at 6 months, respectively, and in 67.7% (60.0% as per ITT) at 3 years.

Results at 1 year were maintained up to 3 years, confirming that the new valve obtained by TIF persists over time and are similar to those reported in our experience for patients undergone TIF by EsophyX® device in the same frame-time [17], but without the 10% worsening between 6 and 12 months reported in the latter series, very likely dependent on the patient selection and technique. In fact the MUSE™ technique allows to create a computer- and ultrasound-assisted standardized new flap valve that seem relatively independent from the operator experience.

Although the lack of a control group in our study cannot rule out a placebo effect in the short post-TIF period, symptom control persisting up to 3 years very likely indicates that the improvement is objective. Considering the mean 6-year duration of symptoms before TIF, it is also unlikely that such improvement could be related to a spontaneous disease regression.

In all, three-year post-TIF clinical outcomes are substantially similar to those observed in patients who undergone surgical fundoplication [18–21].

Morphological assessment indicated that the Hill's grade of the newly created valve remained I in two-third of patients at 1-year endoscopy. Among the 6 patients with grade III Hill's valve, only one recurred at one year. These

data confirm that MUSE™ is able to create an effective new valve also in presence of a Hill's grade III valve.

In contrast with symptomatic improvement, grade A esophagitis persisted or recurred in about one-third of patients at 1-year endoscopy and was unrelated to the recurrence of hiatal hernia, presence of Barrett esophagus, or severity of the Hill's grade of the valve.

Functional parameters, when assessed, showed at high-resolution manometry a significantly longer esophagogastric junction high-pressure zone without appreciable pressure changes and a significant improvement in the rate of peristaltic waves in the esophageal body.

This confirms that the MUSE™ device creates a durable high-pressure segment longer than at baseline and that very likely it is more than the greater length of the newly created valve than its pressure that acts as an effective barrier to reflux. The improved rate of esophageal peristaltic waves confirms that esophageal motility is negatively affected by long-lasting gastro-esophageal reflux, with reduction of clearing capacity and tends to be restored if reflux is controlled.

Impedance 24-h recordings showed significantly fewer total and proximal refluxes at 6 months but not at one year, while pH recordings did not show significant changes in the Johnson–DeMeester's score and other reflux parameters.

Discordance between improvement of GERD-related symptoms and functional findings has also been reported in most studies on the outcomes of TIF reported in the two meta-analyses and for other endoscopic procedures for GERD.

In this protocol study TIF was proposed only to patients with grade A esophagitis and in those with NERD or hypersensitive esophagus, most of them with Hill's grade II or III of the valve or small hiatal hernias, so we cannot draw conclusions on the efficacy of the intervention in patient with more severe degrees of esophagitis or anatomical changes. We cannot draw conclusions on the efficacy of TIF in patients with hypersensitive esophagus, too, because we did not enroll in the study patients with this functional disorder. However, in clinical practice the vast majority of patients seeking for an effective alternative to medical and surgical therapy suffer from NERD or esophagitis of mild degree. Moreover, most of our patients were taking continuous PPI therapy at different doses since many years, so we cannot exclude that the intervention could be able to cure more severe esophagitis grades, too.

In conclusion, in our prospective observational study, TIF by MUSE™ achieved significant and persistent improvement of GERD-related symptoms and allowed to stop or halve PPI consumption in about 65% and 77% of patients up to 3 years as per ITT-analysis, in a selected subset of symptomatic GERD patients, PPI responsive, with hiatal hernia smaller than 2.5 cm and reducible. However, the procedure did not appear to be as effective in controlling esophagitis and improving functional parameters, and the occurrence of two severe complications requiring surgical repair must be taken into account when proposing the intervention to the patient.

Author contributions SGGT drafted the manuscript, performed statistical analysis, followed the endoscopic case series, and collected the endoscopic data; MBC clinically followed the patients and collected the clinical data; GM, ER, and SP performed functional analysis; GM clinically followed the patients and collected clinical and functional data; SP performed statistical analysis; LF and FA assisted in transoral incisionless fundoplication procedures; GMC, DE, EV, CN, and RAZ performed endoscopic controls; PAT designed the study protocol, performed transoral incisionless fundoplication procedures, provided scientific guidance, and supervised the scientific work.

Declarations

Disclosures Sabrina Gloria Giulia Testoni, Maria Bernadette Cilona, Giorgia Mazzoleni, Lorella Fanti, Emanuela Ribichini, Giulia Martina Cavestro, Dario Esposito, Edi Viale, Chiara Notaristefano, Raffaella Alessia Zuppardo, Francesco Azzolini, Sandro Passaretti, and Pier Alberto Testoni have no conflict of interest or financial ties to disclose. All authors revised and approved the final version of this article.

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