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(Article begins on next page)

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Increased Esophageal Exposure to Weakly Acidic Reflux 5 Years After Laparoscopic Roux-en-Y Gastric Bypass

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Abstract

Objective: To evaluate the long-term effects of laparoscopic Roux-en-Y Gastric Bypass (LRYGB) on gastroesophageal function.

Background: LRYGB is considered the weight loss procedure of choice for obese patients with gastroesophageal reflux disease (GERD). However, long-term instrumental evaluations of GERD after LRYGB are not available.

Methods: Morbidly obese patients selected for LRYGB were included in a prospective study. We performed clinical evaluation with GERD-HRQoL questionnaire, upper endoscopy, esophageal manometry, and 24-hour impedance pH (24-hour MII-pH) monitoring preoperatively and at 12 and 60 months after surgery. This trial is registered with ClinicalTrials.gov (no. NCT02618044).

Results: From May 2006 to May 2009, 86 patients entered the study and 72 (84%) completed the 5-year protocol. At preoperative 24-hour MII-pH monitoring, 54 patients (group A) had normal values, whereas 32 (group B) had diagnosis of GERD: 23 had acidic reflux, whereas 9 had combined reflux [acidic + weakly acidic reflux (WAR)]. The groups were similar in preoperative age, body mass index, and comorbidities. At 12 and 60 months, significant improvement in questionnaire scores was observed in group B patients. No manometric changes occurred in both groups; 24-hour MII-pH monitoring showed a significant reduction in acid exposure, but an increase of WAR in both group A (from 0% to 52% to 74%) and group B (from 35% to 42% to 77%). At long-term follow-up, esophagitis was found in 14 group A (30%) and in 18 group B patients (69%) ($P < 0.001$).

Conclusions: LRYGB allows to obtain an effective GERD symptom amelioration and a reduction in acid exposure. However, 3 out 4 patients present with distal esophagus exposure to WAR.

Gastroesophageal reflux disease (GERD) is a frequent condition in morbidly obese patients.[1] Laparoscopic Roux-en-Y-gastric bypass (LRYGB) is considered the most effective surgical procedure for the treatment of morbidly obese patients with GERD when compared with laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy.[2]

Several studies have shown the benefits of LRYGB on GERD, reporting improvement of GERD-related symptoms and reduction in acid-reducing medications use.[3–6] Physio-pathological mechanisms that have been proposed to explain the favorable effect of LRYGB on GERD include weight loss, reduction in parietal gastric cells, and diversion of the bilio-duodeno-pancreatic juices.[7] However, only a few studies have performed an objective evaluation of the esophageal exposure to acid refluxate after more than 6 months of follow-up.[6,8,9] In addition, very little is known about esophageal exposure to weakly acidic reflux (WAR) after LRYGB.

The aim of this study was to prospectively assess the long-term effects of LRYGB on gastroesophageal function in morbidly obese patients.

METHODS

Obese patients fulfilling the 1991 National Institute of Health criteria for bariatric surgery 10 and eligible for LRYGB were included in a prospective clinical study.

Exclusion criteria were: presence of a large hiatal hernia on preoperative upper endoscopy (any hiatal hernia with more than one-third of the stomach displaced through the hiatus above the diaphragm) and previous gastric surgery. Preoperative work-up data, intraoperative and early postoperative results, and long-term clinical, endoscopic, and functional outcomes were entered into a prospectively collected database.

The study protocol included clinical examination and gastroesophageal function evaluation by using the clinically validated questionnaire Gastroesophageal Reflux Health-Related Quality of Life scale (GERD-HRQoL),11 upper endoscopy with biopsy, stationary esophageal manometry, and 24-hour multichannel intraluminal impedance (MII)-pH monitoring preoperatively and at 12 and 60 months after surgery.

Patients were divided into 2 groups according to the absence (group A) or presence (group B) of GERD at preoperative 24-hour MII-pH monitoring.

Upper Endoscopy

All patients had preoperative upper endoscopy. The presence of hiatal hernia was recorded and macroscopic findings of esophagitis were described according to the Savary-Miller classification.12 Biopsies in the distal esophagus and in the stomach were obtained in all patients to rule out the presence of esophagitis, dysplasia/metaplasia, or Helicobacter pylori (HP) infection. Histopathological changes in esophageal mucosa consistent with microscopic esophagitis were recorded.13–15

Functional Evaluation

Esophageal Manometry

Stationary manometry of the esophagus was performed using 8-channel perfusion catheters. The technique has been described previously.16 We evaluated lower esophageal sphincter (LES) pressure and relaxation, and esophageal body motility.

Twenty-four-hour MII-pH Monitoring

Twenty-four-hour MII-pH monitoring was obtained off medical therapy using an ambulatory MII-pH monitoring system (Sleuth; Sandhill Scientific INC, Highland Ranch, CO) as previously described.16 Data were analyzed using a customary reflux detection algorithm (Autoscan; Sandhill Scientific, Inc), and manually reviewed by 2 experts (F.R. and C.G.). On the basis of pH values, a reflux episode was classified as “acidic” if pH dropped below 4 for at least 4 seconds, or “weakly acidic” if at least 1 pH unit decrease in the pH during the reflux episode was observed for at least 4 seconds, with pH remaining between 4 and 7. The total number of acidic, weakly acidic, liquid, and mixed (liquid + gas) reflux episodes was calculated.

The number of total, acidic, and weakly acidic reflux episodes was considered normal below 75, 50, and 33 in 24 hours, respectively.17 Based on the manual review of combined 24-hour MII-pH monitoring findings, patients were classified as follows: patients with acidic reflux alone if only pathological acidic reflux episodes were observed; patients with WAR if only pathological WAR episodes were recorded; and patients with combined reflux (CR) if both acidic reflux and WAR episodes were detected. Symptoms were defined as reflux-related if the symptom index (SI) was higher than 50%.18 SI is the percentage of symptom episodes related to reflux. Bioview analysis software was used for calculation of SI. According to the setting of this software, symptoms were

considered as being related to reflux if they occurred within a 5-minute time window after the onset of the reflux episode.

Surgical Technique

Laparoscopic Roux-en-Y-gastric bypass was performed using a standard technique. Cruroplasty in the presence of small hiatal hernia was not routinely performed. The gastric pouch was created in a standardized fashion, starting 6 cm from the esophagogastric gastric junction using a 45-mm laparoscopic linear stapler and calibrating the pouch size with a 12-mm bougie. The proximal jejunum was transected with a 45-mm linear stapler at 50 cm from the ligament of Treitz. The alimentary tract was then measured using a marked grasper to create a 100-cm limb. The following steps of the procedure included the construction of a mechanical side-to-side jejuno-jejunostomy with a 45-mm linear stapler and the creation of a mechanical end-to-side gastro-jejunostomy by using a 25-mm circular stapler.

Outcome Assessment

Gastroesophageal function was assessed by GERD-HRQoL questionnaire, upper endoscopy with biopsy, esophageal manometry, and ambulatory 24-hour MII-pH monitoring at 12 and 60 months after LRYGB. The primary endpoint was the occurrence of WAR at 24-hour MII-pH monitoring at 12 and 60 months after LRYGB.

Secondary endpoints were: the occurrence of acidic reflux at 24-hour MII-pH monitoring, changes in GERD-HRQoL score, manometric changes, and occurrence of esophagitis or intestinal metaplasia at 12 and 60 months of follow-up.

Statistical Analysis

Quantitative data are reported as mean and standard deviation, whereas categorical data are given as percentages. Continuous variables were compared by the Student t test or the Mann-Whitney U test, depending on distribution. Categorical variables were compared by chi-square test, with Yates correction, and the Fisher exact test (2-tailed) when necessary. All P values were 2-sided. A difference was considered statistically significant when P value was less than 0.05. The data were collected on an Excel spreadsheet, and the statistical analysis was conducted using SPSS software (version 10.0) (SPSS Inc. Chicago, IL). This trial is registered with ClinicalTrials.gov (no. NCT02618044).

RESULTS

Between May 2006 and May 2009, 86 patients (72 women/14 men; mean age 40.8 ± 9.1 yrs) were included in the study. Mean preoperative weight and body mass index (BMI) were 126.9 ± 23.3 kg and 44.3 ± 5.1 kg/m^2, respectively. Patients were divided into 2 groups according to the preoperative 24-hour MII-pH monitoring data. Preoperative 24-hour MII-pH monitoring was negative for pathologic reflux in 54 patients (group A). Pathologic reflux was present in 32 patients (group B): 23 patients with acidic reflux and 9 with CR. The 2 groups were similar in age, sex, BMI, and comorbidities (Table 1). Table 1 summarizes the preoperative prevalence of symptoms, GERD-HRQoL score, and endoscopic findings in each group. Preoperatively, 3 (6%) group A patients and 4 group B patients (12%; P = 0.416) had an HP infection that was eradicated with amoxicillin-clarithromycin-containing triple therapy. Eight (14.8%) group A patients with gastric symptoms and all group B patients were receiving proton pump inhibitor (PPI) therapy before surgery with an adequate symptom control.

Baseline esophageal manometry and 24-hour MII-pH monitoring data are reported in Table 2.

The mean operative time of LRYGB was 98.6 ± 21.2 minutes, with no conversion to open surgery.

There was no mortality. The morbidity rate was 3%: 3 patients (1 in group A and 2 in group B) required blood transfusion for anemia on the first postoperative day. At hospital discharge, all patients were instructed to consume a semiliquid diet and received PPI therapy (30 mg/d for the first 30 d, 15 mg/d for the subsequent 6 mos).

All patients completed the follow-up protocol at 12 months. Eight (15%) group A patients and 6 (19%) group B patients were subsequently lost to follow-up. Therefore, 72 patients (84%) were included in the 60-month analysis (Fig. 1).

At 60 months, BMI had decreased to 31.5 ± 5.3 kg/m2, with 54% excess weight loss percentage (EWL%) in group A, and to 30.6 ± 4.8 kg/m2, with 56% EWL% in group B at the end of follow-up (P = 0.477).

Functional Results

No significant changes were observed in LES pressure and esophageal peristalsis amplitude at 12 and 60 months in group A patients (Table 2).

In this group, the number of WAR episodes significantly increased both at 12 and 60 months when compared with baseline (Table 2). The rate of patients with WAR who completed the follow-up protocol increased from 0% to 74% (34/46) (Fig. 2A). The mean SI score decreased at 12 and 60 months (31.7 ± 6.3 vs 10.3 ± 3.6 vs 13.5 ± 2.7; P < 0.001). The proportion of patients with SI greater than 50% was 20% (n = 11/54) preoperatively, 9% (n = 5/54) at 12 months, and 20% (n = 9/46) at 60 months.

Among group B patients, LES pressure and esophageal peristalsis amplitude did not change significantly during the follow-up period (Table 2). In particular, mean LES pressure was 10.8 mm Hg preoperatively, 11.1 mm Hg at 12 months, and 11.3 mm Hg at 60 months. Mean distal esophageal waves amplitude was 85.3 mm Hg preoperatively, 88.6 mm Hg at 12-month manometry, and 89.1 mm Hg at 60-month manometry.

In this group, we observed normalization of esophageal exposure to acidic reflux at 60 months (Table 2). The mean number of WAR significantly increased at 12 and 60 months (Table 2). Among the patients who completed the follow-up protocol, the rate of those with WAR increased from 35% (9/26) to 77% (20/26) (Fig. 2B). The mean SI score significantly decreased at 12 and 60 months (81.5 ± 9.1 vs 17.4 ± 11.5 vs 21.4 ± 14.8; P < 0.001). The percentage of group B patients with SI greater than 50% decreased from 91% (n = 29/32) preoperatively to 12% (n = 4/32) at 12 months, and 23% (n = 6/26) at 60 months (P < 0.001).

Clinical Results

In group A, no significant differences were observed in mean GERD-HRQoL at 12 and 60 months follow-up compared with baseline values (24.6 ± 9.5 vs 22.9 ± 8.2 vs 21.7 ± 5.8; P = 0.198). At 60 months, a total of 37/46 (80%) did not report typical or atypical GERD-related symptoms; among these patients, WAR was detected in 25 patients (68%). Nine patients (20%) experienced episodes of heartburn and regurgitation of sour and bitter liquid; symptoms were only partially responsive to medical treatment (double dose of PPI, prokinetic and alginate-containing drugs). All these patients had a significantly increased exposure to WAR at 12 and 60 months.

In group B, symptoms significantly improved during the follow-up period, with the mean GERD-HRQoL score decreasing from the preoperative values (33.8 ± 8.3 vs 23.5 ± 7.5 vs 22.3 ± 3.5; P < 0.001). At 60 months, a total of 20/26 (77%) were asymptomatic; among these patients WAR was detected in 14 patients (70%). The other 6 patients (23%) experienced episodes of heartburn and regurgitation of sour and bitter liquid; these patients were receiving medical therapy (double dose of PPI, prokinetic and alginate-containing drugs) with partial and transient symptom control. All these patients had a significantly increased exposure to WAR at 12 and 60 months.

No patient in both groups complained of symptoms related to gastric stasis.

Endoscopic Results

At long-term follow-up, esophagitis was found in 14 group A (30%) and in 18 group B patients (69%). All patients with esophagitis had WAR at 24-hour MII-pH monitoring. The endoscopic findings after LRYGB at 12 and 60 months in group A and B are reported in Figure 3. No patients developed esophageal metaplasia during the follow-up period. No signs of gastric pouch dilatation or intestinal stump abnormalities were detected in both groups at 12 and 60 months after LRYGB.

DISCUSSION

Laparoscopic Roux-en-Y-gastric bypass is considered the most effective bariatric operation with durable effects, and is widely accepted as the procedure of choice in obese patients with GERD. Several studies have shown a significant decrease in GERD-related symptoms and in the use of PPIs.3–6,19–25 The positive impact of LRYGB on esophageal acid exposure has also been demonstrated in the short follow-up by 24-hour pH monitoring.6,8,9,26

In this prospective study, we report the long-term effects of LRYGB on esophageal function, showing a significant improvement in GERD-related symptoms in the majority of patients and normalization of esophageal acid exposure at the 24-hour MII-pH monitoring in all patients with GERD both at 12 and 60 months. However, despite a good control of GERD, 3 out of 4 patients experienced distal esophageal exposure to WAR.

Even though most patients experience improvement or resolution of symptoms after LRYGB, some continue to be symptomatic after surgery. In our study, the rate of patients who experienced GERD-related symptoms after surgery was 20% among those with no preoperative GERD and 23% among those with preoperative GERD. These results are consistent with those reported in other studies.17,27–30 For instance, the early results of the Swiss Multicentre Bypass or Sleeve Study trial 29 that randomly compared laparoscopic sleeve gastrectomy and LRYGB showed an improvement of symptoms in 75% of patients and a 4% rate of new-onset GERD at 1 year follow-up after LRYGB. DuPree et al 30 performed a retrospective review of the Bariatric Outcomes Longitudinal Database including 33,867 patients undergoing RYGB for morbid obesity. GERD-related symptoms were completely resolved in 62.8% of patients, whereas they persisted in 17.6% of patients or worsened in 2.2% of patients. Very recently, a prospective study showed a significant reduction in pathological esophageal acid exposure rate from 58% preoperatively to 30% at 6 months and to 17% at 39 months. Pathologic esophageal acid exposure was detected at 39 months after surgery in 9% of patients with preoperative normal pH monitoring. Interestingly, half of the patients who developed postoperative erosive esophagitis had normal 24-hour pH monitoring, suggesting that causes other than acid reflux might contribute to the esophageal injury.9

Recently, the clinical manifestations of WAR and the effects of antireflux surgery in patients with WAR have been investigated 31–34; however, no specific studies aiming to evaluate the esophageal exposure to WAR after LRYGB have been conducted. This is the first study that demonstrates a high incidence of WAR at 60 months follow-up in obese patients undergoing LRYGB regardless of the presence of GERD before surgery. Overall incidence of postoperative WAR was 74% in group A patients and 77% in group B patients; most patients were asymptomatic [25/34 (74%) in group A and 14/20 (70%) in group B].

Diversion of bilio-duodeno-pancreatic juices from the stomach by constructing a Roux limb that is 100 cm or longer 35–37 is considered one of the major contributors to the antireflux effects of LRYGB. However, the current opinion that reflux is abolished after LRYGB, is based on studies that were focused on the esophageal exposure to acidic reflux, underestimating other chemical components of the refluxate. The high incidence of WAR at 60 months might be secondary to a

postoperative functional disorder of the upper gastrointestinal tract. The absence of changes in LES resting pressure and esophageal peristalsis 26,38 and the rapid gastric emptying after LRYGB 39 with no clinical or endoscopic signs of gastric stasis, as we observed in this study, suggest that WAR through the Roux limb might be related to dysmotility of the Roux limb. Some studies have shown abnormal motility of the Roux limb after gastrectomy.40,41 Herbella et al 41 studied with the aid of manometry Roux-en-Y-limb motility in patients undergoing total gastrectomy. They found that motor activity is present in the proximal part of the Roux limb, but it is characterized by ineffective simultaneous peristaltic waves in 75% of patients. Interestingly, the absence of normally conducted peristalsis was not associated with symptoms. In addition, some studies of the electrical or mechanical activity of the Roux-en-Y-limb have shown several motor abnormalities: inversion of the slow-wave frequent gradient, retrograde slow-wave propagation, retrograde propagation of spike bursts during phase 2 of the migrating motor complexes (MMCs), increased occurrence of ectopic or abortive phase 3 of the MMCs, or inability of the Y-limb to convert its motor activity from a fasting to a fed pattern after meal. Most of these abnormalities may be ascribed to the disconnection of accessory pacemakers from the main intestinal pacemaker in the proximal duodenum during the construction of the Roux limb.36 Based on these pathophysiological findings, the use of prokinetics might improve the Roux limb motility.

Furthermore, the long-term results of our study showed a high incidence of both microscopic and macroscopic esophagitis in patients with WAR. Experimental studies have shown that the exposure of the esophageal mucosa to weakly acidic fluids leads to microscopic esophagitis 42 and might induce changes in the expression of genes linked to esophageal cancer development.43 Therefore, while waiting for further studies that will better clarify the pathophysiological events leading to esophageal adenocarcinoma and the optimal therapeutic strategy in these patients (prokinetics? mucosal protectant? antireflux procedure?),44 a long-term endoscopic surveillance in patients undergoing LRYGB should be taken in consideration.

CONCLUSIONS

Laparoscopic Roux-en-Y-gastric bypass allows to obtain significant long-term weight loss, improvement in GERD symptoms, and reduction in acid exposure. However, 3 out 4 patients present with distal esophagus exposure to WAR. Since many asymptomatic patients with WAR develop esophagitis after LRYGB and the best treatment option is not established, an endoscopic surveillance should be considered.

DISCUSSANTS

AJ Torres (Madrid, Spain):

This study was very well designed and deals with the very controversial issue of obesity, GERD, and different surgical approaches. Some aspects would have to be clarified, for example, it needs to be explained more clearly what does weakly acid reflux mean? The authors define it as “weakly acidic if at least 1 pH unit decrease in the pH during the reflux episode was observed for at least 4 seconds with pH remaining between 4 and 7.”

I have a few questions: Where do you include those episodes with pH > 4 that not decrease more than 1 pH unit? What was the method for evaluating the presence or absence of 1/3 of the stomach above the diaphragm: endoscopy, barium swallow, or other? Does the WAR have the same pathophysiological clinical and pathological consequences as the standard GERD? The authors suggest that some nonacidic content in the esophagus would be involved in the development of macro/micro esophagitis, it would be very important to have more information about some surgical technical details: the way of performing the mechanical gastroyeyunal anastomosis (what stapler machine, size of the stoma, the way of closing the defect after firing the stapler)? Maybe that the

esophageal mucosa inflammatory phenomena could be due to gastric pouch retention, like in achalasia patients, more than truly WAR or standard reflux. Do you explore the crura in a systematic way? Do you close it? When and how? Would you receive any relevant information if you use the Los Angeles instead of Savary-Miller classification for esophagitis evaluation?

Response From ME Allaix (Turin, Italy):

Thank you very much, Prof. Torres, for your comments and questions.

The definition of reflux is based on the pH of the refluxate detected by MII-pH-monitoring; weakly acidic reflux is defined as a pH decrease of at least one unit during the reflux episodes for at least 4 seconds with pH remaining between 4 and 7. The probe measures the pH values with a 1 pH unit interval, therefore episodes with pH changes that are less than 1 pH unit are not detected.

Regarding the method to evaluate the presence of a large hiatal hernia, the diagnosis was performed by upper endoscopy.

In reply to the question on pathophysiological consequences of WAR, we have to say that WAR is a recently identified pathological entity and therefore its clinical consequences are still under debate. The current evidence seems to show an association between WAR and both typical and atypical symptoms in nonobese patients. In addition, recent studies have shown damage to the esophageal mucosa in patients exposed to WAR. These findings are currently under investigation in clinical and experimental studies in order to better clarify if WAR has the same pathophysiological, clinical, and pathological consequences as the standard GERD. Our study is the first showing a high prevalence of WAR in obese patients with esophagitis after LRYGB.

Regarding your question about surgical details, the procedure is performed so that the pouch is calibrated on a 12-millimeter bougie. Then we use a 25-millimeter circular stapler to perform an end-to-side gastrojejunostomy. The jejunal stamp is then closed quite close to the anastomosis with a 45-millimeter linear stapler.

Regarding the question about the method for evaluating the presence or absence of 1/3 of the stomach above the diaphragm, we have to say that the upper endoscopy performed during the follow-up did not show any gastric pouch dilatation and intestinal stump abnormalities in both groups, and no patients complained symptoms related to gastric stasis.

In reply to your question on the exploration of the crura. Yes, we systematically explore the crura, but we do not routinely perform the cruroplasty in the presence of small hiatal hernia. In this study, obese patients with large hiatal hernia were excluded.

Regarding the last question, in the literature there is no evidence that one classification system is better than the other. In addition, the endoscopists in our institutions use the Savary Miller Classification. These are the reasons why we used this classification in this study.

G. Zaninotto (London, UK):

My question is: What is refluxing back in the esophagus? Did you check what were the contents of the gastric pouch by sampling it? Was it just food coming back? Did you check the quality of your pH-impedance monitoring with an external observer to be sure that you were recording true reflux episodes? In your opinion, what is the clinical significance of this weekly acidity reflux?

Response From ME Allaix (Turin, Italy):

We thank Prof Zaninotto for his questions. In reply to the questions about the contents of the refluxate, there is no consensus among the experts about what WAR is. Probably bile plays a major role, but for sure there is not only bile in the refluxate. The contents of the gastric pouch in these patients could be the object of another study.

Regarding quality of our pH-impedance monitoring, we did not have an external observer group.

However, all tests were performed and all reports were manually reviewed by two expert physicians who treat thousands of people every year in their clinics. So, we are confident that the results observed are correct and really reflect what happens in these patients.

Regarding the question about clinical impact of these results, we personally think that more studies are needed to really understand the role of WAR in terms of damage to the esophagus. What we know, at least from some experimental studies as well as from a few studies conducted on humans is that WAR can cause damage to the esophageal mucosa and might promote changes in the expression of genes linked to esophageal cancer development. In our opinion, the results of this study shed some light on the reason why many papers find that 20% to 25% of obese patients with GERD undergoing LRYGB are still symptomatic postoperatively. A recent study also found that at 30 months or more after gastric bypass, half of patients with esophagitis had normal pH monitoring. That means that probably acid reflux is not the only variable that causes damages to the esophageal mucosa in obese patients undergoing LRYGB and followed for a very long period of time.

TR DeMeester (Los Angeles, USA):

I am more interested in asking about the methodology of pH monitoring. Was the pH probe placed 5 cm above the upper border of the LES base on manometric measurements. Placing the probe based on endoscopy can lead to errors in identifying patients with mild reflux. I am also interested in the method of LES failure. Although the LES may be normal on a motility study done at rest in a fasted patient, it can become abnormal after eating due to gastric distention. In this situation, the LES dynamically fails due to a distal to proximal effacement with gastric distention. As a consequence the length of the LES becomes shortened to where the LES pressure is insufficient to maintain LES closure and reflux occurs. Although, the gastric emptying may be normal when measured using a standardized meal, it might not be normal during the postprandial period of daily living. Very interesting.

Response From ME Allaix (Turin, Italy):

Thank you very much, Prof. DeMeester for your comments and questions.

Regarding the first question, the patient undergoes first a manometry and then after that we position the MII-pH probe 5 cm above the manometrically determined LES.

Regarding the question on postoperative motility. Yes, we did postoperative esophageal manometry in all patients.

Yes, we agree with you. The pouch function should be evaluated in the future to further understand the gastric emptying in these patients.

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