The Impact of Weight Loss on the Regression of Barrett's Esophagus after Roux-en-Y Near Esophagojejunostomy as an Anti-reflux Operation

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Abstract

Objective: Gastroesophageal reflux (GERD), obesity and Barrett's esophagus (BE) have been implicated in the dramatic rise in esophageal adenocarcinoma (EAC), particularly in western countries. Previous studies have shown that obesity correlates with GERD. Roux-en-Y gastric bypass (RNYGB) can address obesity and be effective as an anti-reflux procedure. We investigated our hypothesis that weight loss associated with RNYGB for GERD, may lead to regression of BE.

Methods: This was a retrospective analysis of patients who underwent RNYGB as anti-reflux procedure. Patients with BMI≥25kg/m^2 with biopsy-proven diagnosis of intestinal metaplasia (IM), confirmed endoscopic BE segment measurement, and post-operative surveillance endoscopy were included in the study. Pre-operative and post-operative weights at each follow-up endoscopic visit were recorded; post RNYGB weight loss was quantified using percent total weight loss, with ≥20%TWL within two years classified as successful weight loss. Events of BE regression were analyzed using survival analysis. Estimation of the BE regression events were obtained using the Kaplan-Meier estimator.

Results: We identified 29 patients that met all inclusion criteria. During median follow-up of 25 months, after RNYGB, 15 patients experienced regression. 14 patients did not. The regression group was significantly younger than the no-regression group ($p=0.04$), and had a trend towards having shorter preoperative BE segments and achieving greater %TWL within two years. There were no significant differences for other variables. Younger age and successful weight loss were found to significantly contribute to early BE regression.

Conclusions: There was regression of BE in over 50% of patients who had undergone Roux-en-Y for GERD. Successful weight loss and young age were associated with a trend in achieving early regression of BE. Future studies with a larger group of patients are necessary to further delineate the effects of RNYGB and weight loss on BE, and other factors associated with regression of BE.

Public Health Relevance: Results of this study offer further evidence to update current practice guidelines in support of the use of RNYGB to manage GERD in the obese population by simultaneously addressing reflux and weight loss.

Table of Contents

List of Tables

List of Figures

1.0 Background

Gastroesophageal reflux (GERD), obesity and Barrett's esophagus (BE) have been implicated in the dramatic rise in esophageal adenocarcinoma (EAC), particularly in western countries(Coleman, Xie, & Lagergren, 2018; Pennathur, Gibson, Jobe, & Luketich, 2013). In patients with GERD, BE develops when the stratified squamous epithelium in the distal esophagus is replaced by metaplastic columnar epithelium; and it predisposes to the development of esophageal adenocarcinoma (EAC) (American Gastroenterological et al., 2011; Pennathur et al., 2013). BE is a known precursor to EAC. The risk of developing EAC is 30-fold above general population in patients with BE compared to the general population(Hvid-Jensen, Pedersen, Drewes, Sorensen, & Funch-Jensen, 2011). Metaplasia develops with chronic tissue injury associated with acid exposure by GERD (Souza, 2007). Carcinogenesis occurs when Acid and bile salts induce DNA damage, causing genetic and epigenetic changes(Huo et al., 2011; Morales, Souza, & Spechler, 2002). In addition to acid exposure, obesity is correlated with GERD(Fisher, Pennathur, Mutnick, & Little, 1999), and is an additional risk factor for developing BE. Increased BMI is associated with development of long segment BE(Abdallah, Maradey-Romero, Lewis, Perzynski, & Fass, 2015; Almers, Graham, Havel, & Corley, 2015). In addition, it is also a predictor for EAC regardless of the presence of GERD symptoms (Hoyo et al., 2012). Roux-en-Y gastric bypass (RNYGB) is an appealing option for obese patients with intractable GERD. It has been shown effective in treating intractable GERD after prior failed anti-reflux operations(Awais et al., 2014; Awais et al., 2008; Frezza et al., 2002; Makris et al., 2012; Perry et al., 2004) and in promoting BE regression (Andrew, Alley, Aguilar, & Fanelli, 2018; Braghetto et al., 2012; Csendes, Burgos, Smok, Burdiles, & Henriquez, 2006; Gorodner et al., 2017; Houghton, Romero,

& Sarr, 2008). It combines the advantage of reducing acid reflux, reducing bile reflux, and weight loss. However, little is known about the effect of any confounding factors in the patient population in affecting BE's disease process. In this study, we investigated our hypothesis that weight loss associated with RNYGB for GERD may be an important contributor to regression of BE.

2.0 Patients and Methods

2.1 Patient Selection

We retrospectively reviewed our experience with RNYGB as primary and re-operative anti-reflux operation for patients with diagnosis of BE and are overweight (BMI>25kg/m2) at the University of Pittsburgh Medical Center between 2005 and 2019. This study was approved by the institutional review board. Individual patient consent was waived due to its retrospective nature.

We used the following as our inclusion criteria for the study: preoperative diagnosis of GERD unresponsive to medical treatment or failed previous anti-reflux operation(s), preoperative diagnosis of BE confirmed by endoscopic and histological examination, preoperative BMI greater than or equal to 25kg/m^2, and post-operative endoscopic examinations confirming presence or absence of BE segments. Diagnosis of BE requires presence of intestinal metaplasia on histology. A total 282 patients who underwent Roux-en-Y as anti-reflux procedures were identified. Among these patients, 235 were excluded for not having pre-operative diagnosis of BE or having BMI less than 25kg/m^2. Out of the 47 remaining patients, 18 were excluded for not having post-operative surveillance endoscopy. A total of 29 patients met all criteria and were included in the study.

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2.2 Preoperative Evaluation

Patients that were candidates for Roux-en-Y as anti-reflux operation underwent comprehensive preoperative evaluation and testing. Complete history and physical examinations were obtained. All patients were counseled regarding postop dietary modification and potential peri-operative complications. Testing includes barium esophagram, esophageal manometry, gastric emptying study, and esophagogastroduodenoscopy. During endoscopic examinations, BE segment length was measured and recorded. Standard 4 quadrant biopsies every 1cm or 2cm within BE segment were taken (Asge Standards Of Practice et al., 2019) and submitted for pathology. Demographic and clinical variables collected include age, sex, preoperative BMI, smoking history, and redo surgery status.

2.3 Surgical Technique

Our preferred surgical approach, Roux-en-Y near esophagojejunostomy (RNYNEJ) has been detailed in previous publication(Awais et al., 2008). Briefly, on-table endoscopy was performed for all cases. In patients with prior anti-reflux operations, fundoplication was laparoscopically taken down after complete hiatal mobilization. In patients undergoing RNYNEJ as their primary operation, complete hiatal mobilization was also performed if there was evidence

of hiatal hernia. Identification of gastroesophageal (GE) junction was then achieved by removing the GE fat pad. For re-operative patients, the integrity of cardia, fundus, and both vagi were evaluated followed by a leak test by insufflation of air. Next a small, 5- to 10-ml gastric pouch consisting of only cardia was constructed, followed by creation of a 75- to100cm, retro-colic, retro-gastric Roux limb (Figure 1). All potential defects were closed. Gastrostomy tubes and JP drains were selectively placed. A postoperative barium swallow was typically performed on postoperative day 2 or 3.

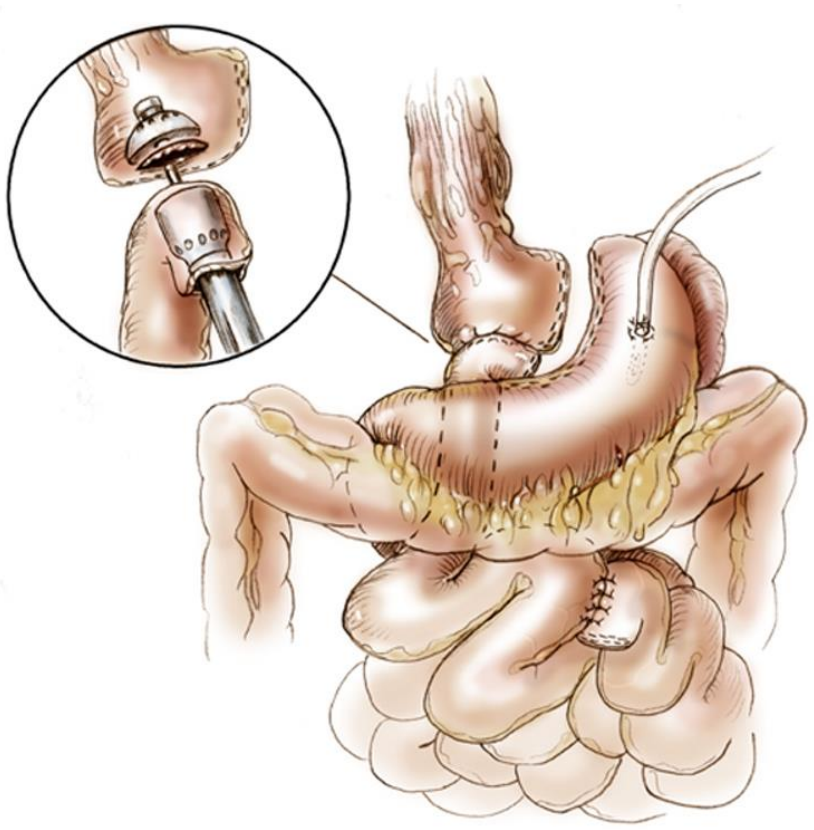

Figure 1. Roux-en-Y near esophagojejunostomy.

This procedure is typically performed laparoscopically. It is characterized by a small gastric pouch consisting only of gastric cardia, and a retro-colic, retro-gastric roux limb. Gastrostomy tubes were placed selectively.

2.4 Postoperative Follow-up

On discharge, all patients were prescribed with lifelong oral vitamins and intramuscular B_{12} injections. Reflux symptoms, postoperative weight loss, and comorbid medical conditions were evaluated during follow-up visits every 3 months for the first year and then yearly after that. Percent excess body weight loss (%EBWL= [Initial Weight - Postop Weight]/ [Initial Weight - Ideal Weight]×100%)(Brethauer et al., 2015) and percent total weight loss (%TWL = [(initial weight) -(postop weight)]/[(initial weight)] × 100%) was calculated for each postoperative visit up to two years. Successful weight loss was defined as ≥20%TWL before the 2-year mark(Grover et al., 2019). Postoperative surveillance endoscopy was performed for all patients. BE segment length was measured when applicable. Regression of BE was defined as absence/resolution of BE or reduced BE segment length. Progression of BE was defined as increase in BE segment length or development of dysplasia.

2.5 Statistical Design and Data Analysis

Events of BE regression were analyzed using survival analysis. The regression curves were constructed using the Kaplan-Meier estimator. The timing of regression events was determined by postoperative endoscopic exams.

3.0 Results

3.1 Patient Characteristics

A total of 29 patients met all criteria and were included in the study. Patient characteristics are summarized in **Table 1**. The median age was 58 years (range 29-70 years); there were 14 (48.3% [14 of 29]) men and 15 (52.7% [15 of 29]) women. The median preoperative BMI was 37.9 kg/m^2 (range 26.9-55.2 kg/m^2). 12 of 29 (41.4%) patients had history of smoking. Median preoperative BE segment length was 3cm (range 0.1-1cm, 0.1 cm indicates focal area of BE with length too small to measure). 14 of 29 (48.3%) patients underwent redo operations while the rest as first-time anti-reflux operation. Median Roux limb length based on operative report was 90cm (range 70-150cm). Median %EBWL at 1-year was 73.7% (range 10.7-194.6%). Median %TWL by two years was 23.9% (range 2.3% - 46.3%). 18 of 29 (62.1%) patients achieved successful weight loss by two years. 15 of 29 patients experienced BE regression. 11 of these patients had complete BE regression evidenced by the lack of intestinal metaplasia on histology. Four patients had partial regression. 14 patients did not experience BE regression. Of these patients, three had no change in BE length; 11 had increase of BE length (seven eventually received radio frequency ablation therapy). None of the patients developed dysplasia. The median follow-up time was 25 months, with range being 2 to 136 months.

Table 1. Patient characteristics

Characteristics	
Age (years): median (range)	58 (29-70)
Sex (male/female)	14/15

Preop BMI (kg/m^2): median (range)	37.9 (26.9 – 55.2)
History of smoking: yes/no	12/17
Preop BE length (cm): median (range)	3 (0.1-11)
BE segment length: SSBE/LSBE	17/12
Redo surgery: yes/no	14/15
Roux limb length (cm)[a]: median (range)	90 (70-150)
Follow up time (month): median (range)	25 (2-136)
%EBWL at 1-year (%)[b]: median (range)	73.7 (10.7, 194.6)
% TWL by 2 years (%)[c]: median (range)	23.9 (2.3, 46.3)
Successful weight loss: yes/no	18/10
BE regression: yes/no	15/14

BE = Barrett's Esophagus. %EBWL = percent excess body weight loss. %TWL= percent total weight loss. LSBE = long segment BE. SSBE = short segment BE.

[a] 1 patient did not have recorded roux limb length

[b] 2 patients did not have weight measurement at 1-year post-op

[c] 1 patient did not have weight measurement at 2-year post-op

3.2 Comparing patients with BE regression and patients without BE regression

Patient characteristics between regression and no-regression group are compared and summarized in **Table 2**. The age was significantly younger in patients who experienced regression than those who did not. Patients who experienced BE regression tend to have shorter preop BE segment length, and higher %TWL compared to those who did not. However, the difference was

not statistically significant. There was no significant difference in sex composition, preoperative BMI, smoking status, pack-year smoking history, redo status, follow up time, Roux limb length, or %EWBL between the two groups of patients.

Table 2. Comparing patients with BE regression and patients without BE regression

Variable	Regression N=15	No Regression N= 14	Statistic	P-value
	Median (range) or N, %	Median (range) or N, %		
Age (year)	54 (39-70)	60 (29-70)	Z^a=2.03	0.04*
Sex (male)	8, 53.3%	6, 42.9%	P^b=0.72	0.72
Preop BMI (kg/m^2)	39.1 (28.7-55.2)	33.1 (26.9-47.7)	Z^a=-0.66	0.51
Smoking (yes)	7, 46.7%	5, 35.7%	P^b=0.71	0.71
Preop BE length (cm)	1 (0.1-7)	4 (0.1-11)	Z^a=1.60	0.11
Redo (yes)	6, 40%	8, 57.1%	P^b=0.47	0.47
Roux limb length (cm)	100 (70-150)	85 (75-150)	Z^a=-0.51	0.61
Follow up time (month)	25 (2-114)	22 (3-136)	Z^a=0.31	0.76
%EBWL (%)	82.8 (10.7-194.6)	72.3 (24.0-176.0)	Z^a=-0.68	0.50
%TWL (%)	29.0 (2.5 - 46.3)	20.6 (2.3 - 39.1)	Z^a=-1.36	0.17

* $p<0.05$

[a] Wilcoxon rank-sum test

[b] Fisher's exact test

%EBWL = percent excess body weight loss. %TWL= percent total weight loss.

3.3 Modeling Regression Events Using Survival Analysis

BE regression events were modeled using survival analysis. The model was first fit by age groups (age ≥ 65 years and age < 65 years) and plotted in Figure 2. The younger group achieved regression significantly sooner than the older group ($p = 0.046$, exact log-rank test). More than 60% of young patients achieve BE regression within the first three years after RNYNEJ. In contrast, after more than 10 years of follow up, less than 40% of older patients experienced BE regression. Next the model was fit by preop BE segment length. Long segment BE (LSBE) represents BE segment greater than 3cm. Short segment BE (SSBE) represents BE segment less than or equal to 3cm. Patients with SSBE showed a trend to experience regression sooner than those with LSBE, but the difference was not significant ($p = 0.32$, exact log-rank test, Figure 3). Next the model was fit by weight-loss status (achieving ≥20% TWL is considered successful weight loss, see Figure 4). The group that achieved weight-loss success experienced BE regression sooner than the group not achieving weight-loss success ($p = 0.019$, exact log-rank test, Figure 4). Among patients with successful weight loss, more than 50% achieve regression within three years. Within this time frame some patients with unsuccessful weight loss experiences regression, too. However, the rest fails to do so at the end of their follow-up period. Finally, the model was fit by combining age and weight-loss status, shown in Figure 5. Young patients with successful weight loss were the group that achieved regression the quickest ($p=0.046$, exact k-sample log-rank test).

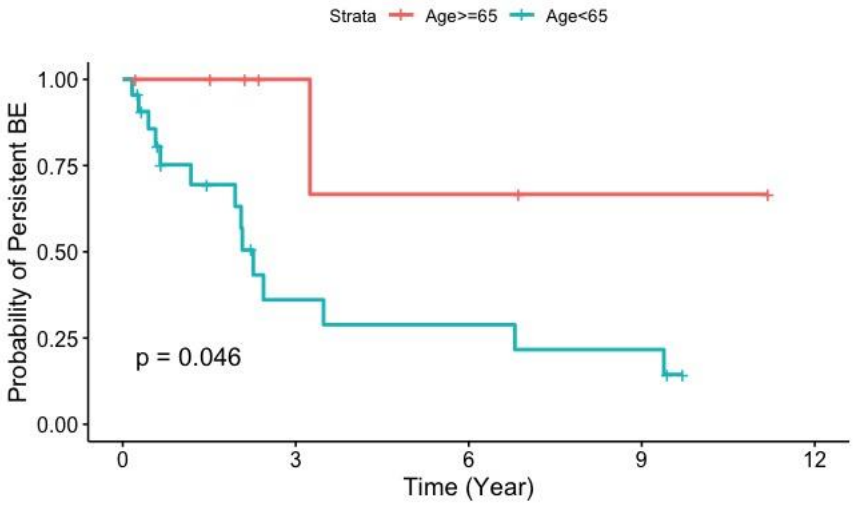

Figure 2. Comparing BE regression by age.

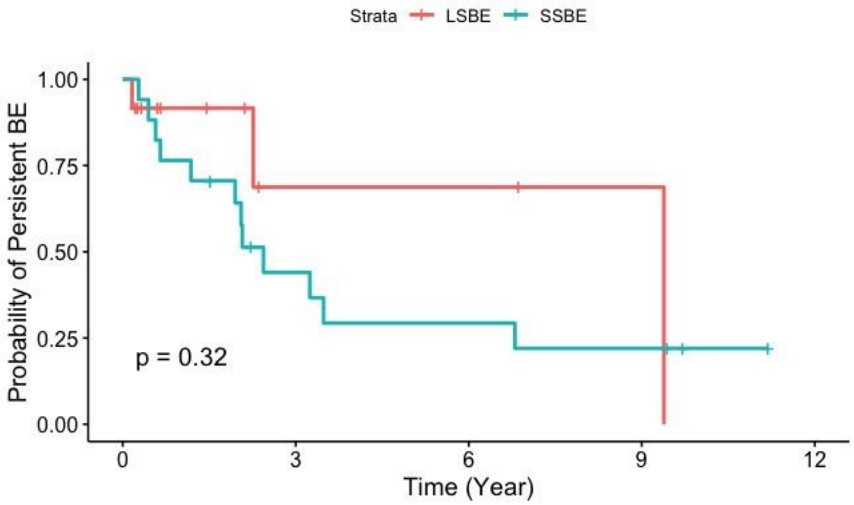

Figure 3. Comparing BE regression by BE segment length.

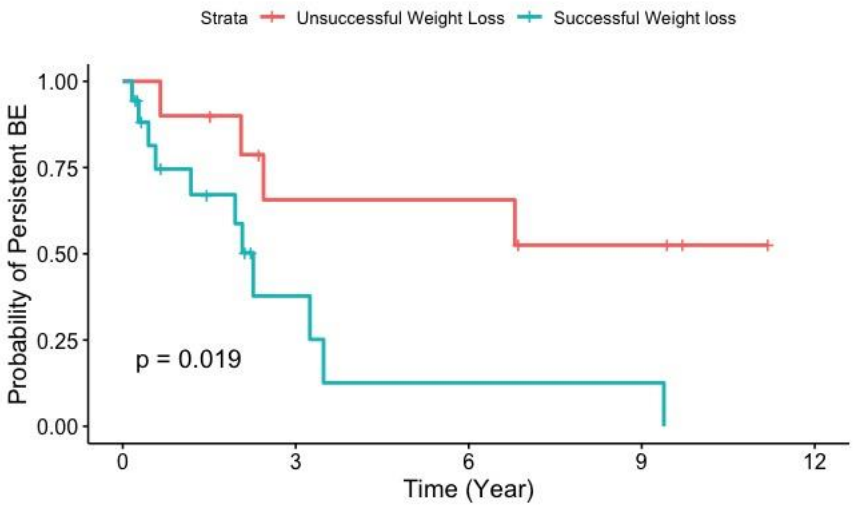

Figure 4. Comparing BE regression by weight loss.

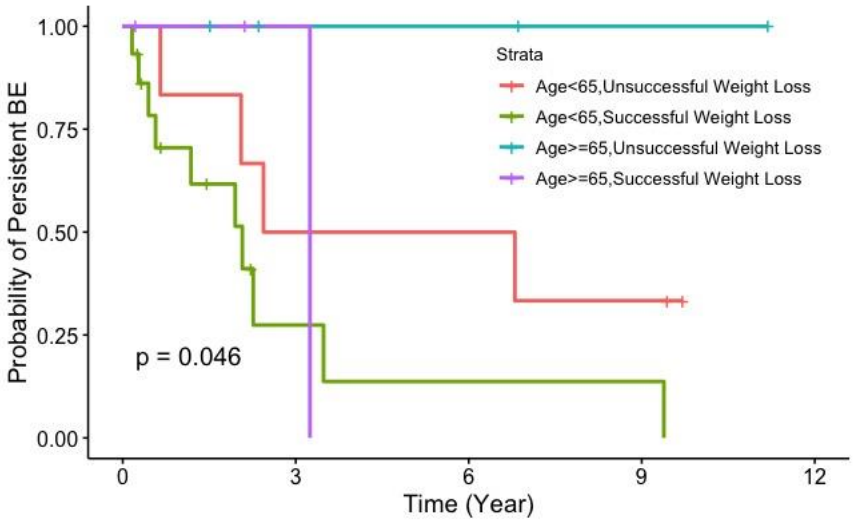

Figure 5. Comparing BE regression by age and weight loss.

4.0 Discussion

In this study, we found that 51.7% (15 out of 29) patients had regression of their BE after RNYGB. These patients had significantly younger age, and trends towards having shorter preop BE segments and achieving more weight loss postoperatively compared to patients who did not experience regression. Furthermore, using survival analysis, we found that young age (<65 years) and successful weight loss (>=20%TWL within two years) contributes significantly to early BE regression. Results suggest that having short segment BE may be associated with early regression, as well. After combining age and weight loss status, we observed that the cohort with younger age and successful weight loss was most advantageous in achieving early BE regression.

The incidence of EAC is on the rise at the global level, particularly in western countries, and is thought to be related to the prevalence of reflux, obesity, and BE(Malhotra et al., 2017; Pennathur et al., 2013; Uhlenhopp, Then, Sunkara, & Gaduputi, 2020). Recognizing and controlling BE is vital in preventing the development of EAC which is associated with high mortality and morbidity. Acid suppression in the form of proton-pump inhibitor therapy and anti-reflux operations is the mainstay of GERD management. However, the development BE and its malignant transformation is multifactorial(Kambhampati, Tieu, Luber, Wang, & Meltzer, 2020). Obesity is an important risk factor for reflux disease(Fisher et al., 1999), BE, and the development of EAC. It is also associated with high failure rates of fundoplication-type anti-reflux operations(Perez, Moncure, & Rattner, 2001). RNYGB, particularly RNYNEJ, offers multiple benefits to obese patients with medically refractory reflux by combining reduction of acid and bile reflux with weight loss. Multiple studies have been carried out to investigate whether RNYGB can

promote regression of BE. Complete regression in 33% to 57% of patients with variable proportions of incomplete regression has been previously reported(Andrew et al., 2018; Braghetto et al., 2012; Csendes et al., 2006; Gorodner et al., 2017; Houghton et al., 2008). Collectively these studies suggest there is an association between RNYGB and BE regression in obese/overweight patients. However, important confounding factors or covariates such as age, BMI and smoking status were not adjusted for in previous studies. In addition, the factors associated with regression of BE were not previously analyzed.

We identified 29 patients with preoperative diagnosis of BE confirmed by endoscopy and histology and performed RNYNEJ as their anti-reflux procedure. 37.9% of all patients experienced complete BE regression postoperatively. Four patients (13.8%) had partial regression. This finding is similar to previous studies. However, in contrast to previous studies, we observed 11 patients who had BE progression postoperatively even with significant weight loss. This shows the complex nature of the disease process with other potential confounders yet to be discovered and understood. We analyzed various modifiable and non-modifiable confounders proposed by existing literature. Age was found to be significantly younger in patients who experienced BE regression than those who did not. Although no statistical difference was observed, BE segment length and %TWL showed potential difference between patients who experienced BE regression and those who did not.

We utilized survival analysis to model the process of BE regression. We are interested in modifiable variables, particularly weight loss associated with RNYNEJ. We found that young patients and patients with successful weight loss postoperatively experience regression

significantly faster than their respective counterparts. Adjusting for both covariates shows that young patients who also had successful weight loss virtually all achieve BE regression 1 year postop. As suggested by previous studies, having short BE segments preoperatively may promote regression. However, the difference did not reach statistical significance.

Our study addresses some of the most important risk factors in BE development and malignant transformation. We observed potential roles that age, weight loss, and preop BE segment length play in the disease process after RNYGB. These results suggest that RNYGB may be considered for obese young patients with short segment BE as anti-reflux operation. To maximize the effect of RNYGB on BE regression, frequent postop counseling and monitoring should be offered to patients to maximize weight loss. Even though some of the analysis did not reach statistical significance, it provided future studies with directions. A major limitation of this study is the small sample size. Due to the retrospective nature, very few patients met all the selection criteria. Future large scale prospective studies are necessary to further delineate the factors contributing to BE regression in patients undergo RNYGB.

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