

Factors Associated with Severe Submucosal Fibrosis in the Treatment of Barrett's Esophagus

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Abstract

Severe submucosal fibrosis (SSF) has been established to significantly increase complications with endoscopic submucosal dissection (ESD) throughout the luminal GI tract. Often, this is attributed to prior therapies such as previous endoscopic mucosal resection (EMR). However, there is little information regarding which forms of treatment increases the risk of severe submucosal fibrosis in Barrett's esophagus therapy. We performed a retrospective cohort study on our patients that underwent ESD to determine the risk factors for SSF (Grade 2 fibrosis).

Methods: We identified consecutive patients who underwent ESD in Barrett's esophagus by a single experienced endoscopist (KKW) who graded the degree of submucosal fibrosis. Submucosal fibrosis can only be reliably identified on ESD or submucosal tunneling to adequately examine the collagen fibers. All resections were performed using a scissor type device (Clutchcutter, Fujifilm Healthcare, Lexington, Ma). Submucosal fibrosis was evaluated as F0 (no fibrosis), F1 (moderate fibrosis with individual strands identified), and F2 (SSF) with solid sheets of fibrotic tissue) as per international standards. All patients had prior therapy identified and categorized as to type and application including EMR, thermal treatments were RFA alone or in combination with multipolar coagulation and APC, as well as cryotherapy either balloon or spray. Patients were excluded if treatments could not be determined.

Results: A total of 205 patients were identified with a mean age of 69 ± 0.7 years with 156 males and a mean Barrett's segment length of 4.4 ± 0.3 cm. Diaphragmatic hernia length was 2 ± 0.2 centimeters. 119 patients had either F0 ($n=57$, 28%) or F1 ($n=55$, 27%), while F2 fibrosis was found in 93 (45%) patients. The patients in each group were similar in terms of age, length of Barrett's esophagus, and histology (Table 1). On univariate analysis, F2 fibrosis was significantly associated primarily with female gender ($p<0.03$), thermal ablation ($p<0.04$), and having a larger hiatal hernia ($p<0.005$). Cryotherapy was not found to be associated with severe F2 fibrosis. EMR was frequently performed in over half the patients with severe fibrosis but was also performed in 41% of those without F2 fibrosis and was not statistically different between the groups ($p<0.08$). On multivariate analysis of variance modeling, thermal ablation was the most significant association with severe fibrosis while length of the diaphragmatic hernia remained significant but gender was not found to be associated.

Conclusions: Severe fibrosis can dramatically decrease the ability for endoscopic resection. It appears that thermal ablation with RFA and size of diaphragmatic hernia are associated with severe submucosal fibrosis. Careful inspection and resection prior to beginning thermal ablation to eliminate potential neoplastic tissue should decrease the need to perform ESD after ablation and the potential severe fibrosis that can be produced. The association with hernia highlights the need for acid control.

Background

- Traditionally, Endoscopic Mucosal Resection (EMR) has been felt to be associated with severe fibrosis in the submucosa
- As shown in **Figure 1** to the right, a prior EMR caused tissue retraction to the point that the EMR site could not be identified.
- Endoscopic submucosal dissection was performed allowing identification of the squamous patch typical following EMR.
- We recently found that EMR was not significantly associated with submucosal fibrosis

Hypothesis

- Our hypothesis was that severe submucosal fibrosis was likely associated with RFA in Barrett's esophagus

Methods

- As submucosal fibrosis can only be assessed using ESD, we identified Barrett's esophagus patients who underwent ESD by a single experienced endoscopist (KKW) who graded the degree of submucosal fibrosis
- All resections were performed using a scissor type knife (Clutchcutter, Fujifilm Healthcare, Lexington, Ma).
- ESD was performed using a VIO 300D generator (Erbe, Tübingen, Germany) using for cutting Endo Cut Q mode, and coagulation with forced coagulation setting 4, 80 watts.
- Submucosal fibrosis was evaluated as F0 (no fibrosis), F1 (moderate fibrosis with individual strands identified), and F2 with solid sheets of fibrotic tissue) as shown in Figure 2.
- All patients had prior therapy identified and categorized as to type and application including EMR, thermal treatments were RFA alone or in combination with multipolar coagulation and APC, as well as cryotherapy either balloon or spray.

Figure 1: ESD of EMR Site

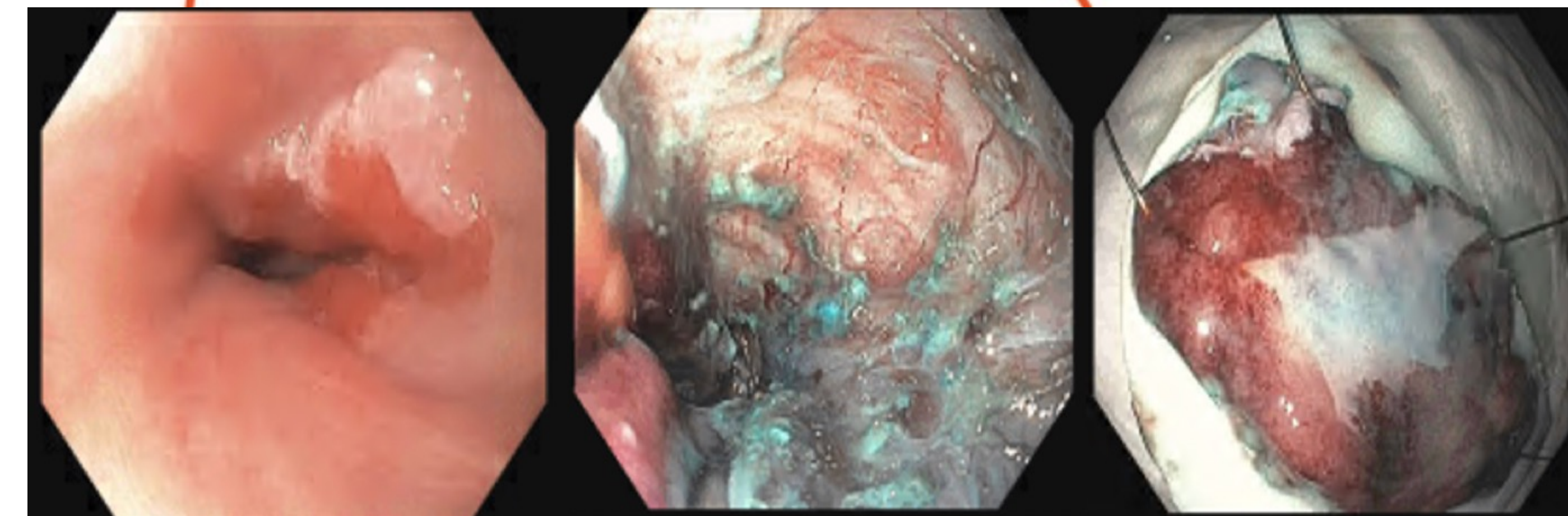


Figure 2: Grading of Submucosal Fibrosis

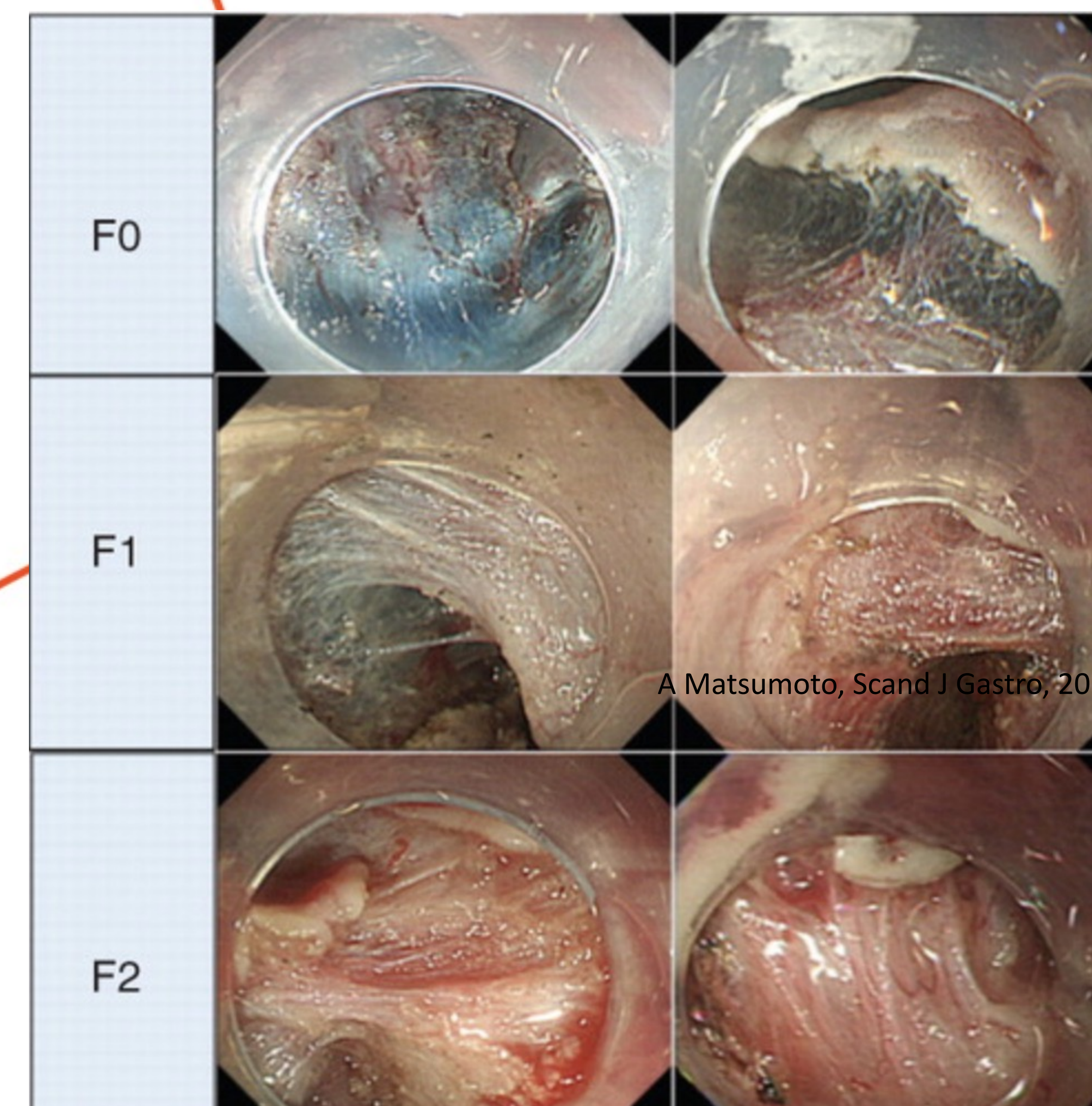


Table 1: Results of Comparison of Minimal Fibrosis to Severe

	None or Mild Fibrosis	Severe Fibrosis
Patients (n,%)	112 (54%)	93 (45%)
Age (yrs)	69.5±0.9	68.4±1.0
Male gender (n,%)	92 (82%)	64 (69%)
Length of BE (cm)	4.5±0.4	4.2±0.4
Length of DH (cm)	1.6±0.2	2.5±0.2
LGD or ND (n,%)	50 (45%)	35 (38%)
HGD or ACA (n,%)	62 (55%)	58 (62%)
Thermal Ablation (RFA) (n,%)	24 (21%)	32 (34%)
Cryotherapy	17 (15%)	21 (23%)
EMR	43 (38%)	47 (51%)

Results

- 205 patients were identified with a mean age of 69 ± 0.7 years with 156 males and 49 females
- 112 patients had minimal F1 fibrosis or F0 no fibrosis while 93 had F2 or severe fibrosis
- Comparison between these two groups found that only a larger diaphragmatic hernia and thermal ablation were significantly associated with severe fibrosis
- Large diaphragmatic hernias may be a surrogate marker for more severe reflux that causes fibrosis
- Spray cryotherapy using liquid nitrogen was not associated with severe fibrosis while balloon cryotherapy had lower stricture rates found using spray cryotherapy
- EMR was not found to be significantly associated with severe fibrosis
- Complications occurred in 4% of patients with mild or no fibrosis while 14% of those with severe fibrosis ($P<0.02$) had complications (stricture, bleeding)
- En bloc resections rates were >91% in both F0,F1 fibrosis and severe fibrosis.
- On multivariate analysis of variance, thermal ablation was the most significant association with severe fibrosis while length of the diaphragmatic hernia remained significant but gender was not associated.

Conclusions

- The most significant factors associated with severe submucosal fibrosis in Barrett's esophagus were thermal ablation therapy and the presence of a large diaphragmatic hernia
- If a patient has high grade dysplasia with suspicion of intramucosal cancer, ESD should be performed prior to ablative therapy
- The association with large diaphragmatic hernia suggests that the fibrosis may be associated with severe reflux and adequate control of reflux should be obtained prior to initiation of therapy