



Secrets for successful laparoscopic anti-reflux surgery: patients with Barrett's esophagus

Adam J. Bograd, Daniela Molena

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Daniela Molena. Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, USA. Email: Molenad@mskcc.org.

Abstract: Barrett's esophagus is a common condition resulting from gastroesophageal reflux with the potential for dysplastic and even neoplastic transformation. The mainstays of treatment of Barrett's esophagus are control of reflux via medical therapy, namely PPIs, or anti-reflux surgery. Fundoplication provides excellent long-term reflux control and may provide the added benefit of preventing progression of dysplasia in those with Barrett's esophagus. Furthermore, effective anti-reflux surgery may promote regression of already present dysplasia. The purpose of this article is to review the potential advantages of utilizing anti-reflux surgery over medical management by summarizing the available literature detailing the ability of anti-reflux to control reflux, possibly prevent cancer progression, and induce regression of dysplasia. Furthermore, we review some of the alterations that occur on a molecular level that may be promoting these beneficial changes post-fundoplication.

Keywords: Barrett's esophagus; fundoplication; gastroesophageal reflux; esophageal adenocarcinoma

Received: 08 February 2017; Accepted: 28 February 2017; Published: 07 April 2017.

doi: 10.21037/ales.2017.03.09

View this article at: <http://dx.doi.org/10.21037/ales.2017.03.09>

Introduction

Barrett's esophagus, squamous to columnar esophageal metaplasia, is a known complication of gastroesophageal reflux disease (GERD). An acquired abnormality as a result of overexposure of esophageal mucosa to caustic refluxate, Barrett's esophagus develops in ~10–20% of patients with GERD (1). Barrett's esophagus represents a pre-malignant condition in some patients, with previous studies identifying between a 30- to 125-fold increase in risk of progression to esophageal adenocarcinoma (1,2). Barrett's esophagus may progress to low-grade dysplasia, then to high-grade dysplasia, with eventual transformation into invasive adenocarcinoma in 30% of those with high-grade dysplasia. Hence, Barrett's esophagus is an identifiable, pre-malignant precursor lesion to one of the fastest increasing cancers in the United States, esophageal adenocarcinoma.

The current treatment options for GERD, and therefore Barrett's esophagus, are either medical therapy (the

mainstay of which is proton pump inhibitors, "PPIs") or anti-reflux surgery (Nissen fundoplication). Medical therapy with PPIs is often inadequate for both symptom control and preventing dysplastic progression, while ablative therapies for Barrett's esophagus can be complicated and incomplete, often requiring multiple procedures. Anti-reflux surgery has both the ability to halt esophageal mucosal exposure to gastric-duodenal refluxate and induce quiescence in Barrett's mucosa, possibly reducing progression to cancer. Furthermore, the vast majority of fundoplication procedures may be performed in a minimally invasive manner, either laparoscopic or robotic-assisted.

Potential advantages of anti-reflux surgery over medical therapy

PPIs, while excellent at reducing gastric acid production, do nothing to reduce bilious reflux. Previous studies have

demonstrated that combined gastro-duodenal refluxate is more harmful to esophageal mucosa than that of gastric juice alone (3). Fundoplication reduces not only esophageal acid exposure but also provides a barrier to biliary reflux. Continued use of PPIs has also been associated with several untoward complications including *C. difficile* infection, osteoporosis with subsequent pathological fractures (secondary to deranged calcium absorption), and increased cardiovascular disease risk.

Anti-reflux surgery is a safe, effective alternative to long-term medical therapy for patients with Barrett's esophagus which in the majority of cases may be performed minimally invasively. An effective fundoplication forms a competent neo-lower esophageal sphincter while repairing concomitant hiatal hernias, thereby protecting esophageal mucosa from gastro-duodenal refluxate. Control of reflux may lead to healing and regression of Barrett's mucosa, which in turn may reduce the risk of progression to esophageal cancer. From a practical standpoint, anti-reflux surgery also eliminates reliance on patient compliance with medical therapy, which may reduce the overall cost of treatment compared to lifelong PPIs. Complete, rather than partial, fundoplication is chosen—if the patient has adequate esophageal function—as it is crucial to completely eliminate pathologic gastro-duodenal reflux and prevent the subsequent disease progression of Barrett's patients through the metaplasia-dysplasia-carcinoma sequence.

Clinical trials utilizing fundoplication for Barrett's esophagus

Multiple clinical trials (randomized and nonrandomized) comparing medical versus surgical management of Barrett's esophagus patient have been published. Most have demonstrated a reduced incidence of esophageal cancer or dysplasia in patients who've undergone anti-reflux surgery compared to those treated medically.

One of the first studies to address the effectiveness of treated Barrett's esophagus with anti-reflux surgery, is from McCallum *et al.* in 1991 (4). In a prospectively followed study cohort of 181 Barrett's esophagus patients, 152 were treated medically, while 29 patients received anti-reflux surgery. With adequate mean follow-up time in both treatment groups dysplasia was approximately six-times more common in the medical group compared to the group treated with anti-reflux surgery (19.7% vs. 3.4%, respectively). Two patients medically treated developed

esophageal adenocarcinoma during follow-up, while zero patients treated with anti-reflux surgery progressed to esophageal cancer.

Several years later, the first randomized control trial comparing conservative treatment versus anti-reflux surgery for Barrett's esophagus patients was undertaken by Ortiz *et al.* (5). In this study, 59 patients were randomized to either medical treatment (n=27) or anti-reflux surgery (n=32). Following median follow up time of 4 years of the medically treated group and 5 years for the anti-reflux surgery group, no dysplastic changes nor progression to esophageal adenocarcinoma occurred within the surgical cohort. Meanwhile, rates of dysplasia and incidence of esophageal cancer were 18.5% and 3.7% respectively within the cohort treated with acid-reducing medications. Interestingly, this study also followed the length of Barrett's esophagus segments during follow-up. Decreased Barrett's esophagus segment length was observed in 25% (n=8) surgical patients compared with only 7% (n=2) treated medically. Furthermore, increasing Barrett's esophagus length was identified in 11 patients within the medically treated group versus only 3 patients among those who underwent anti-reflux surgery. Despite these differences in outcomes, no differences in symptom control were observed between study groups.

A larger, randomized clinical trial was conducted by the aforementioned group subsequently (6). Forty three patients were randomized to be treated medically, while 58 were randomized to the surgical arm to be treated with anti-reflux surgery with median follow-up of 5 and 6 years respectively. Similar to this group's previous findings, no differences in symptom control were noted between the two cohorts, however a statistically (and clinically) significant reduction in the rate of dysplasia in the surgical group was observed during follow up.

Similarly, Oberg *et al.* examined the rates of dysplasia and esophageal adenocarcinoma prospectively during long-term endoscopic and histologic surveillance in 140 patients with Barrett's esophagus without dysplasia (7). Risk factors for progression to dysplasia and adenocarcinoma were evaluated during a median follow up of 5.8 years. During follow up 31% developed low-grade dysplasia and 5% developed high-grade dysplasia or esophageal adenocarcinoma. Previous anti-reflux surgery was the only prognostic factor associated with a reduced risk of low-grade dysplasia development, with a relative risk of 0.44, corresponding to a risk that is 2.3 times less than that

found in patients receiving medical treatment. Additionally, patients treated medically developed high-grade dysplasia or adenocarcinoma significantly more often than those treated with anti-reflux surgery (7.4% vs. 0%).

Chang *et al.* published a meta-analysis reviewing 25 publications comparing anti-reflux surgery with medical therapy, all of which had at least 1 year endoscopic follow-up post-treatment initiation (8). The meta-analysis pooled results of 996 patients treated with anti-reflux surgery and 700 patients treated with medical therapy. Their surgical analysis included patients that underwent either partial or complete funduplications. The authors observed that the esophageal cancer rate was significantly lower in surgically treated patients. However, this difference may have resulted from inclusion of a large number of uncontrolled case-series, leading to a publication bias, as the authors suggested in their publication. This statistically significant difference in the esophageal cancer incidence disappeared when only controlled studies were considered, leading the authors to conclude that anti-reflux surgery was no better than medical therapy in attenuating the risk of esophageal cancer.

More recently, a systematic review was published including 10 studies comparing esophageal adenocarcinoma risk after anti-reflux surgery versus medically treated GERD patients, 7 of which examined patients with Barrett's esophagus, while 2 studies compared the esophageal cancer risk following surgery to that of the non-Barrett's population (9). A meta-analysis of 7 studies of patients with Barrett's esophagus demonstrated a decreased pooled esophageal adenocarcinoma incidence following anti-reflux surgery compared to the medically treated group. Subgroup analysis limited to the four, post-2000 publications of Barrett's implied a further decreased cancer risk following anti-reflux surgery compared to medical treatment. It's somewhat discouraging however that the esophageal cancer risk post-surgery does not appear to return to that of the background population.

The data and observations from these clinical studies evaluating the progression of Barrett's esophagus to dysplasia or cancer seem to imply that successful anti-reflux surgery may protect the non-dysplastic Barrett's mucosa from progression to dysplasia and adenocarcinoma, possibly by better control of gastro-duodenal reflux. Although controversial, these results are promising because they indicate that the natural history of Barrett's esophagus can be affected by successful elimination of reflux via effective fundoplication.

Can anti-reflux surgery reverse dysplastic Barrett's?

There is a paucity of data regarding the ability of anti-reflux surgery to induce regression of dysplastic Barrett's esophagus. Gurski *et al.* investigated the factors leading to histologic regression of metaplastic and dysplastic Barrett's esophagus (10). The pre- and post-treatment endoscopic biopsies from 91 patients with symptomatic Barrett's esophagus were retrospectively reviewed. Seventy seven patients were treated with anti-reflux surgery while 14 were treated medically with PPIs. Statistically significant histopathologic regression was observed in 36% post-surgery, but only in 7% of those treated medically. Regression from low-grade dysplasia to non-dysplastic Barrett's occurred in 68% of patients post-operatively. Furthermore, after surgery regression from intestinal metaplasia to non-metaplastic epithelium was observed in 21%. The aforementioned types of regression more commonly occurred in short segment (<3 cm; 19/33 patients, 58%) than long segment (>3 cm; 9/44 patients, 20%) Barrett's esophagus. All 8 patients who progressed (5 from intestinal metaplasia to low grade dysplasia, 3 from low- to high-grade dysplasia) has long-segment Barrett's esophagus. The presence of short segment's Barrett's and treatment type (namely anti-reflux surgery) were significantly associated with regression on multivariate analysis. The median time of biopsy-proven regression was 18.5 months after surgery, with 95% occurring within 5 years. In addition to hypothesizing that anti-reflux surgery may produce regression of Barrett's esophagus, this study suggested that regression mainly occurs in patients with short segment Barrett's which poses the question of appropriate patient selection to undergo anti-reflux surgery. Importantly in this study, even after anti-reflux surgery in patients with long-segment Barrett's there is progression to low-grade dysplasia and even to high-grade dysplasia in 18% of the cases after 5 years of follow-up.

Subsequently a group from Italy examined the efficacy of anti-reflux surgery versus medical therapy in promoting the regression of low-grade dysplasia in patients with Barrett's esophagus (11). Thirty five patients were identified with low-grade dysplasia of which 19 were treated with high-dose PPIs, while 16 underwent anti-reflux surgery. At 1 year follow-up, regression from low-grade dysplasia to intestinal metaplasia was observed in 63% and 94% of the medically and surgically treated patients respectively. At final 18 month

follow-up, no low-grade dysplasia was identified in the surgical cohort, as all had regression to non-metaplastic epithelium. Controlling for the aforementioned confounders, no factors other than anti-reflux surgery were significantly associated with the probability of remission of low-grade dysplasia.

Zehetner *et al.* more recently retrospectively reviewed the long-term follow-up of patients with Barrett's esophagus after anti-reflux surgery with promising data that anti-reflux surgery likely reduces rates of progression (12). Regression occurred in 23/75 patients (31%). Twenty five percent (17/67) of patients with non-dysplastic Barrett's pre-operatively had complete loss of intestinal metaplasia. In the 8 patients with preoperative low-grade dysplasia, regression was seen in 6 (75%); in five patients there was loss of dysplasia and in one there was loss of intestinal metaplasia. A failed fundoplication was identified as a risk factor for progression. This study also associated Barrett's progression more commonly with long segment Barrett's esophagus.

The meta-analysis by Chang *et al.* also examined the risk of regression and progression of Barrett's esophagus in those treated with either anti-reflux surgery or medical therapy (8). Surgically treated patients were associated with a higher probability of regression than medically treated patients (15.4% *vs.* 1.9%; $P < 0.005$). Limiting their analysis to only controlled studies, this observation also held true. In their analysis while anti-reflux surgery was not associated with preventing development of esophageal cancer, anti-reflux surgery was associated with better regression of Barrett's esophagus as compared to medical therapy.

Allaix and Patti recently summarized the aforementioned data in a thorough review, summarizing that anti-reflux surgery may reduce dysplastic and neoplastic progression of Barrett's esophagus and highlighted its ability to induce regression especially in those with short-segment disease (13).

How does successful anti-reflux surgery affect esophageal metaplasia and carcinogenesis?

In 2005, a group from Italy investigated the histologic changes induced in Barrett's esophagus following anti-reflux surgery (14). More specifically, they examined the histological phenotype, extent of Barrett's, and Cdx2 IHC expression in 35 patients before and after anti-reflux surgery. Briefly, Cdx2 expression in normal tissue is restricted to intestinal-type epithelium and is considered an adequate marker of intestinal immunophenotype in both

the esophagus and stomach (15). In patients who underwent laparoscopic anti-reflux surgery, Barrett's metaplasia significantly decreased in length. A statistically significant decrease in Cdx2 IHC expression was observed to occur only in patients with short segment Barrett's however; those with long segment Barrett's did not demonstrate reduction in Cdx2 expression. Several years later, the same Italian group revisited this molecular change question with an observational, long-term follow-up study of Barrett's patients treated with either medical or anti-reflux surgery. Again, in the short segment Barrett's group only they demonstrated a shift from intestinal metaplasia to normal epithelium in ~30% as well as a reduction in Cdx2 expression. Similar to their previous findings, no changes in Cdx2 IHC expression were identified in long-segment Barrett's esophagus patients' post-antireflux surgery.

Due to the similarity and overlap (at a molecular level) between some pathways involved in injury/inflammation and carcinogenesis, Oh *et al.* examined the NF- κ B pathway (16). The NF- κ B transcription factor is hypothesized to play a role in downstream activation of genes which may promote cancer development and progression. IL-8 is a major downstream mediator of NF- κ B which is known to be upregulated by NF- κ B activation, and interestingly possesses a dual role as both a pro-inflammatory chemokine as well as promoting carcinogenesis. This study measured IL-8 mRNA expression in esophageal mucosal cells taken from patients with varying stages of reflux-induced esophageal injury (esophagitis, Barrett's esophagus, Barrett's with dysplasia, and esophageal adenocarcinoma). They also examined the impact of Nissen fundoplication on IL-8 gene expression. In summary, this study found that IL-8 expression was increased in patients with reflux compared to those without. There was a dose-dependent correlation of IL-8 expression, with the highest IL-8 expression occurring in those with Barrett's esophagus with dysplasia and esophageal adenocarcinoma. Among patients with reflux who underwent anti-reflux surgery, fundoplication significantly decreased IL-8 mRNA expression compared with pre-operative levels. While its clinical implication is currently unclear, the results demonstrate that anti-reflux surgery can affect changes on a molecular level within esophageal mucosa which may mitigate pro-neoplastic changes caused by exposure to gastro-duodenal refluxate.

Management of patients with low- and high-grade dysplasia

Although the optimal treatment of low-grade dysplasia

remains controversial, once Barrett's esophagus with high-grade dysplasia is confirmed, radiofrequency ablation paired with either high-dose PPI or anti-reflux surgery should be administered. Regardless of the methods chosen, close 3–6 months' endoscopic surveillance with 4-quadrant biopsies at every 1 cm of Barrett's segment should be performed. Endoscopic mucosal resection should be used liberally if mucosa's irregularity or nodularity is seen within the area of metaplasia, since early stage cancer can be otherwise missed. Should dysplasia regress post-treatment, endoscopic surveillance may be relaxed to yearly for subsequent 3 years and then to every 2–3 years thereafter should regression continue. Post-antireflux surgery it is imperative that surveillance endoscopy be performed by endoscopist familiar with funduplications as obtaining biopsy specimens from within the wrap is often not straightforward. Barrett's esophagus with low-grade dysplasia should be treated with high-dose medical therapy first, since it often regresses by eliminating gastro-duodenal reflux in the esophagus and ablation should be reserved for patients with persistent disease.

Typically our group waits until eradication of dysplasia is complete before attempting any anti-reflux procedure to preserve the stomach in case needed for esophagectomy. However, if endoluminal therapy is failing due to anatomic limitations, such as a large paraesophageal hernia, a laparoscopic anti-reflux procedure may be considered earlier. It is important to remember that the most commonly utilized organ for conduit creation during esophageal reconstruction is the stomach. If one thinks with a reasonable likelihood that a patient may require an esophagectomy, it may be prudent to hold off on performing an anti-reflux procedure as a prior fundoplication may significantly complicate an esophagectomy, and in some cases may not allow for use of the stomach as a conduit. More specifically, if repeated endoluminal treatments are unable to rid the esophagus of dysplastic Barrett's, esophagectomy is more likely to be appropriate, rather than fundoplication.

However on occasion, fundoplication is performed to optimize reflux control in order to facilitate complete eradication of dysplastic Barrett's tissue by endoluminal therapy. Therefore, in certain situations, performing a fundoplication may be justified in the presence of high grade dysplasia despite the aforementioned conduit considerations. While there is a lack of data to support that fundoplication for reflux control may make endoluminal therapies more effective, having these patients referred

to surgeons for consideration of fundoplication allows us to take part in the decision making process of the proper surgery. While fundoplication may be the correct choice in some, others, such as those with high-grade dysplasia in the presence of a dilated, aperistaltic esophagus due to long standing reflux, may be better served with esophagectomy. In our experience, performing fundoplication in the presence of low-grade dysplasia is often overlooked as well by many. Rather than multiple ablations over a longer time frame, fundoplication for Barrett's patients with low-grade dysplasia affords good symptomatic and reflux control, while promoting regression of dysplasia, especially in situations of short-segment Barrett's esophagus.

Conclusions

Laparoscopic fundoplication is a reasonable approach to treating symptomatic reflux disease, which affords great symptom control while possibly having the added benefit of preventing neoplastic transformation. While there is no data yet firmly establishing that fundoplication prevents cancer, there is data to support that fundoplication mitigates factors that cause cancer progression more effectively than PPIs. While the data reviewed here within are encouraging, at present time, anti-reflux surgery should be used to cure reflux and its associated symptoms, but not yet as a means of preventing esophageal cancer. Furthermore, its use in the correct clinical scenario, where the esophagus is not damaged, may allow patients to avoid esophagectomy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Fernando A. M. Herbella) for the series "Secrets for Successful Laparoscopic Antireflux Surgery" published in *Annals of Laparoscopic and Endoscopic Surgery*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ales.2017.03.09>). The series "Secrets for Successful Laparoscopic Antireflux Surgery" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Naini BV, Souza RF, Odze RD. Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists. *Am J Surg Pathol* 2016;40:e45-66.
- Dent J, Bremner CG, Collen MJ, et al. Barrett's oesophagus. *J Gastroenterol Hepatol* 1991;6:1-22.
- Kauer WK, Peters JH, DeMeester TR, et al. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. *Ann Surg* 1995;222:525-31; discussion 31-3.
- McCallum RW, Polepalle S, Davenport K, et al. Role of anti-reflux surgery against dysplasia in Barrett's esophagus. *Gastroenterology* 1991;100:A121.
- Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. *Br J Surg* 1996;83:274-8.
- Parrilla P, Martinez de Haro LF, Ortiz A, et al. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg* 2003;237:291-8.
- Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. *Ann Surg* 2005;242:49-54.
- Chang EY, Morris CD, Seltman AK, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. *Ann Surg* 2007;246:11-21.
- Maret-Ouda J, Konings P, Lagergren J, et al. Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. *Ann Surg* 2016;263:251-7.
- Gurski RR, Peters JH, Hagen JA, et al. Barrett's esophagus can and does regress after antireflux surgery: a study of prevalence and predictive features. *J Am Coll Surg* 2003;196:706-12; discussion 12-3.
- Rossi M, Barreca M, de Bortoli N, et al. Efficacy of Nissen fundoplication versus medical therapy in the regression of low-grade dysplasia in patients with Barrett esophagus: a prospective study. *Ann Surg* 2006;243:58-63.
- Zehetner J, DeMeester SR, Ayazi S, et al. Long-term follow-up after anti-reflux surgery in patients with Barrett's esophagus. *J Gastrointest Surg* 2010;14:1483-91.
- Allaix ME, Patti MG. Antireflux surgery for dysplastic Barrett. *World J Surg* 2015;39:588-94.
- Zaninotto G, Cassaro M, Pennelli G, et al. Barrett's epithelium after antireflux surgery. *J Gastrointest Surg* 2005;9:1253-60; discussion 60-1.
- Groisman GM, Amar M, Meir A. Expression of the intestinal marker Cdx2 in the columnar-lined esophagus with and without intestinal (Barrett's) metaplasia. *Mod Pathol* 2004;17:1282-8.
- Oh DS, DeMeester SR, Vallbohmer D, et al. Reduction of interleukin 8 gene expression in reflux esophagitis and Barrett's esophagus with antireflux surgery. *Arch Surg* 2007;142:554-9; discussion 9-60.

doi: 10.21037/ales.2017.03.09

Cite this article as: Bograd AJ, Molena D. Secrets for successful laparoscopic anti-reflux surgery: patients with Barrett's esophagus. *Ann Laparosc Endosc Surg* 2017;2:60.