Review Article

Does anti-reflux surgery disrupt the pathway of Barrett's esophagus progression to cancer?

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Abstract: In patients with Barrett's esophagus (BE), anti-reflux surgery aims to sustainable control reflux symptoms and heal reflux induced esophageal mucosal inflammation and prevent progression of BE to adenocarcinoma. There is growing evidence that beside gastric acid, bile salts in refluxed duodenal juice are responsible for the development and progression of BE. However, the pathogenesis of BE progression and the metaplasia-dysplasia-carcinoma sequence of the adenocarcinoma of the esophagus (EAC) is multifactorial and occurs over long natural time course. After anti-reflux surgery significant levels of regression from metaplastic Barrett's to non-metaplastic epithelium as well as from dysplastic to non-dysplastic BE have been observed and a randomized trial showed that sufficient surgical reflux control reduces the risk of Barrett's progression significantly when compared to medical treatment. Thus, large cohort studies show significant reduced risk of EAC in patients suffering from gastroesophageal reflux disease (GERD) with and without BE after anti-reflux surgery. Even after anti-reflux surgery the risk for EAC remains elevated in patients with BE and the right moment of intercepting the progressive nature of GERD has to be discussed in future. The paper also addresses the impact of anti-reflux surgery, endoscopic ablation and life style therapies for the management of GERD, BE and cancer prevention.

Keywords: Anti-reflux surgery; Barrett's esophagus (BE); esophageal adenocarcinoma

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Introduction

Incidences of adenocarcinoma of the esophagus have dramatically risen over the past decades and despite significant improvements in the medical and surgical treatment all over 5-year survival rate remain below 30% and prevention strategies are urgently needed (1-3).

Gastroesophageal reflux disease (GERD) is believed to be responsible for more than 60% of esophageal adenocarcinomas whereas patients with weekly reflux symptoms are known to have a 7-fold increased risk for developing adenocarcinoma (4). Around 12% percent of patients with chronic GERD develop mucosal metaplasia so called Barrett's esophagus (BE) which is, via low- and high-grade dysplasia, associated with an up to 125-fold increased risk for esophageal adenocarcinoma (5,6).

BE, the only known precursor for esophageal adenocarcinoma, is a potentially reversible conditions if the reflux-induced chronic inflammatory process is treated effectively (7-9). This short review brings together data we have on the discussion if anti-reflux surgery can be expected to disrupt the pathway of BE and with this the development of esophageal adenocarcinoma.

Pathogenesis of Barrett development

Despite various theories, the pathogenesis of BE is still poorly understood. Direct extension of gastric cells adjacent to the esophagus, reprogramming of squamous stem cells or repopulation from submucosal esophageal glands are discussed as origin of the metaplastic columnar Barrett's epithelium (10). Traditionally, acid reflux was considered playing the main role in the pathogenesis of BE (11). However, evidence is growing that rather chronic, cytokine mediated inflammation of the distal esophagus than chemical injury from acid reflux alone is significant for the development of metaplastic epithelium (12,13).

Further it was shown that duodenogastro-oesophageal reflux including low pH and bile acids both increase the risk of epithelial erosion and are independent risk factors for the development of BO (14).

Under normal physiologic gastric conditions, bile acids irreversibly precipitate and are of minimal significance but in a more alkaline gastric environment, as found in patients under acid-suppression medication, bile salts are mainly dissociated and more likely to cause cellular damage bile acids cause DNA damage (15). Dissociated bile salts are further thought to, which can prevent the apoptosis that should be induced by DNA damage, enabling Barrett's cells that have sustained potentially carcinogenic genetic alterations to survival (16).

Various studies in rat reflux models that have been established as validated and reproducible models for the development of BE and EAC showed that reflux of a mixture of acid and bile components results in a PPI independent induction of chronic inflammation, BE and EAC (17).

In patients with GERD an increased exposure of a mixture of acid and bile was clearly associated with progressed GERD disease (long-segment BE and early EAC) (18).

Conceptually, dysfunction of the lower esophageal sphincter fosters increased gastro-esophageal reflux, which in turn provokes a neurohumoral-orchestration-induced inflammatory response in the esophagus, involving immune cells, nerve cells, fibroblasts (19). This neurohumoral flush stimulates genetic, cellular and functional changes leading to the development of columnar lined esophagus and BE. Thus, not the gastric acid, not the reflux *per se* represents the cause of GERD and BE. In contrast to that, the dysfunction of the lower esophageal sphincter and the loosening of its fixation and attachments within the diaphragm (i.e., hiatal geometry) are to be regarded as the cause of the disease (20). Consequently it seems reasonable to consider, that effective anti-reflux surgery and repair of the hiatus (hiatal closure) may contribute to normalize reflux and prevent the progression of BE to cancer. Going in line with this suggestions, recent studies demonstrated that dysfunction of the lower esophageal sphincter i.e., shortened abdominal (<1.0 cm) and total lower LES length (<2.0 cm); decreased LES pressure (≤6.0 mmHg) positively correlated with increased reflux and the presence of BE (21-24). Furthermore, the correlation of endoscopic and function test data demonstrated a positive association between increased dysfunction of the lower esophageal sphincter, acid exposure and higher Hill grade of the esophagogastric valve (25). The Hill valve represents a valuable endoscopic marker for the integrity of the geometry of the esophagus within the hiatus of the diaphragm. Multiple studies have demonstrated that effective anti-reflux surgery repairs the dysfunction of the lower esophageal sphincter and normalizes the geometry of the diaphragmatic hiatus (26-28). In addition, effective anti-reflux surgery assures, that patients do not require proton pump inhibitor therapy, which alters the pH of the reflux, i.e., towards more alkaline Ph (29). This in fact has been demonstrated to create a pH gradient across the squamocolumnar junction within the esophagus, which changes the biochemical characteristics of the bile salts (see above), which in turn stimulates the development of BE, dysplasia and cancer—i.e., up to 10 folds increased risk for cancer development in persons with chronic PPI therapy (30).

Effect of anti-reflux surgery on BE

Based on these observations, various clinical studies evaluating the effect of anti-reflux surgery on the progression of BE and risk of EAC have been published (see *Table 1*).

The two nationwide and population-based cohort studies comparing the risk of developing EAC in patients after anti-reflux surgery to that of the background population from Sweden and Finland, published in 2010 and 2011, included more than 250,000 and 160,000,000 person-years of follow in the anti-reflux surgery group and in the background group, respectively (31-33). As expected meta-analysis of these two studies showed a significant increased risk of EAC for patients in the anti-reflux surgery (GERD-group) [IRR 10.78 (95% CI: 8.48–13.71)] (33).

Meta-analysis comparing medical treated versus surgical treated GERD patients (100,479 person-years in the anti-

Table 1 Studies with anti-reflux surgery in patients with Barrett's esophagus

Reference	Year	Country	Type of study	Number of patients	Type of surgery	Type of medication
Williamson *et al.*	1990	US	Cohort	37 ARS	NF, Collis gastroplasty	N/A
McCallum *et al.*	1991	US	Cohort	142 MT; 29 ARS	NF, Hill gastropexy, Belsey procedure	N/A
Attwood *et al.*	1992	Ireland	Cohort	19 ARS	Partial anterior fundoplication	H2RA
Gurski *et al.*	2003	US	Cohort	77 ARS	NF, partial fundoplication	PPI
Parrilla *et al.*	2003	Spain	RCT	14 MT; 58 ARS	NF, Collis-Nissen procedure	PPI
Oberg *et al.*	2005	Sweden	Cohort	43 MT; 46 ARS	NF, Hill gastropexy, partial fundoplication	H2RA, PPI
Gatenby *et al.*	2009	UK	Cohort	41 ARS	N/A	H2RA, PPI
Benjamin *et al.*	2017	Australia	Cohort	50 ARS	Nissen, Toupet	N/A
Markar *et al.*	2018	UK	Cohort	22,968 ARS; 16,398 MT	N/A	PPI

NF, Nissen fundoplication; PPI, proton pump inhibitors, RCT, randomized controlled trial; ARS, anti-reflux surgery; H2RA, H2-receptor-antagonist; HGD, high grade dysplasia; MT, medical treatment; N/A, not available.

reflux surgery group and 400 459 person years in the non-surgery group, respectively) revealed a decreased pooled IRR (IRR 0.89. 95% CI: 0.66–1.19) comparing surgical with nonsurgical treated patients (34). Results of subgroup analysis of patients with GERD in the very recently published national population-based cohort study including more than 830,000 patients older than 18 years with GERD with around 3% (around 22,200 patients) undergoing anti-reflux surgery more than support these observations presenting a statistical significant reduced risk of EAC for patients after anti-reflux surgery (HR 0.64; 95% CI: 0.52–0.78) (35).

When analyzing the effect of anti-reflux surgery in patients with known BE, the results of a meta-analysis as well as subgroup analysis of a recently published cohort study from England including more than 28,000 patients with BE, describe decreased risk of EAC for patients after anti-reflux surgery (IRR 0.26, 95% CI: 0.09–0.79 and HR 0.47, 95% CI: 0.12–1.90) (31,36-38). These results for patients with and without BE where independent of patients age as revealed in subgroup analysis in patient aged 50 years or older (HR 0.75; 95% CI: 0.58–0.97 and HR 0.76; 95% CI: 0.19–3.09, respectively).

The anatomical, histopathological, functional, genetic and biochemical properties of BE are responsible for BE-dependent, quality-defined difficulties and insecurities for the diagnosis and therapy of the disease. Most importantly the phenomenological interpretation of morphological and functional changes, which parallel the development of NERD, GERD, BE, dysplasia and cancer, reveals a particular spectrum of diagnostic shortcomings due to inadequately assessable and—although technologies profoundly improved—still inaccurately definable changes, alterations and processes within the course of the disease (39). As such we do not know, if the genetic, cellular and biochemical changes responsible for cancer development have already been activated before anti-reflux surgery. Ringhofer *et al.* have demonstrated a patchy distribution of cardiac mucosa, non-dysplastic and dysplastic Barrett's mucosa within a given segment of columnar lined esophagus (40). As a consequence, biopsy error may lead to under or over grading of BE. In addition, there exists no universal agreement regarding the morphological and function (manometry, pH monitoring data) definition of successful anti-reflux surgery. Moreover, patients are referred to anti-reflux surgery, when medical therapy has failed. As a consequence the large majority of these patients present for surgery at advanced stage of the disease, i.e., long history of GERD symptoms, large hiatal hernia, severe esophagitis, long segments of columnar lined esophagus (± BE), failure of the sphincter and esophageal transport function and abnormal reflux monitoring. As mentioned above and below, these qualities define the typical and characteristic profile for an increased cancer risk in patients with GERD and BE. Thus, patients have already drawn bad cards to start with, when being seen by the surgeon. Here, interdisciplinary communication between the gastroenterologist and the

surgeon is mandatory for definition and detection of those patients who benefit from early intervention prior to cancer development. The open-minded approach serves cancer prevention and requires a holistic, tailored approach towards diagnosis, therapy and disease management. Taken together, the above listed disease dependent qualities and characteristics (i.e., staging, genetics etc.) support early intervention in the course of the disease in order to minimize the risk for cancer development.

Remains to be questioned to combine anti-reflux surgery and radiofrequency ablation for cancer prevention in individuals with GERD and BE (7,41). Radiofrequency ablation represents a novel endoscopic technology for durable elimination of BE (± dysplasia and cancer) and has been demonstrated to prevent cancer development in persons with early cancer, high-grade and low-grade dysplasia (42,43). The cancer preventive effect of RFA in persons with non-dysplastic BE awaits further proof. However, data justify to offer RFA to persons with non-dysplastic BE and increased cancer risk profile (i.e., GERD more than 10 years, positive family history for esophageal cancer, large hiatal hernia, esophagitis, history of dysplastic BE) (44). Conceptually, RFA ± endoscopic mucosal resection of BE tissue can be offered before, during or after anti-reflux surgery. At present there exist long no data addressing this issue. However, the group around Skrobić and Simic *et al.* demonstrated that the combination of anti-reflux surgery and RFA may be cancer preventive in BE positive persons with advanced disease, i.e., high volume reflux, large hiatal hernia, esophagitis (45). The results of future studies are to be awaited for allowing a definitive recommendation.

The above findings show that there exists a rapidly growing evidence that, in addition to the elimination GERD symptoms, anti-reflux surgery contributes to prevent the progression of BE to cancer. Remains to be questioned, who should get the therapies for cancer prevention in GERD and BE and when they should be scheduled during the course of the disease. Thus it seems crucial to define those at increased cancer risk and the ideal time point for the intervention (surgery, ablation etc.).

Patient selection aims to define those who will maximally benefit from the treatment, i.e., those at direct or indirect cancer risk. First of all, the diagnosis of GERD and BE should include cautious patient history, endoscopy, biopsy sampling, histopathology (*Chandrasoma classification*), esophageal manometry and reflux monitoring (46,47). These tests contribute to assess the presence or absence of specific risk factors (see below). Conceptually those with increased cancer risk will benefit from the elimination of reflux and cancer risk. BE positive columnar lined esophagus containing early cancer, high and low grade dysplasia represent stages with increased cancer risk and should be treated by ablative therapies, i.e., RFA, EMR and subsequent anti-reflux surgery (for symptom control). Bridging until anti-reflux surgery should include a proton pump inhibitor (PPI) therapy. BE without dysplasia allows different approaches. Persons with non-dysplastic BE are at increased cancer risk, i.e., equal to low grade dysplasia, if the following criteria are fulfilled: long standing GERD (>10 years), endoscopic visible esophagitis, tongues of columnar lined esophagus exceeding 2.0 cm, large hiatal hernia (>3.0 cm) and a family history positive for esophageal and/or gastric cancer (44). Therefore patients with the above risk profile also benefit from RFA for non-dysplastic BE, i.e., in patients with the above risk profile, non-dysplastic BE harbors the cancer risk of low grade dysplasia.

Going in line with the novel understanding of the pathogenesis underlying GERD and BE, effective management should target the elimination of the *cause*, i.e., the reflux, and target the *manifestation*, i.e., BE. Thus, it seems justified to consider the combination of anti-reflux surgery and endoscopic therapies (RFA ± EMR) for those with non-dysplastic BE and increased cancer risk (above risk profile). As suggested above, the evidence based proof for the ideal sequence of the treatments has not yet been found. Basically, for non-dysplastic BE, anti-reflux surgery can be offered before, during or after RFA (48). Therefore non-dysplastic BE may be managed by anti-reflux surgery first or RFA first or both treatments at the same time. Remains to be questioned the ideal time point for the treatment of GERD and BE for cancer prevention.

Progression of disease, i.e., non-dysplastic to dysplasia, or low to high grade etc. should be managed by ablation of premalignant tissue. Progression of cardiac mucosa positive CLE to goblet cell positive CLE, i.e., BE, may be treated by anti-reflux surgery and RFA (at the same time or subsequently). Based on the above considerations, the ideal time point for the intervention seems to be the progression from cardiac mucosa to non-dysplastic BE during follow up. Future studies will have to proof the value of this approach.

Anti-reflux surgery harbors considerable side effects (gas bloat, dysphagia, break down, failure, slipping) including the relapse of GERD and BE (49). Risk factors for failure of anti-reflux surgery include impaired esophageal function, normal pre-surgical esophageal function test, normal

esophageal function and reflux monitoring (+ absence of positive symptom correlation). As such, accurate pre-operative diagnosis including endoscopy and function tests help to define those, who will benefit from the anti-reflux surgery, i.e., those with LES dysfunction and abnormal reflux monitoring. In addition, it is essential, that the procedures are conducted in centers with high volume experience in the full spectrum diagnosis, treatment and follow up of GERD and BE (44). Finally life style aspects should be implemented into the management of GERD and BE. Future studies will have to proof in as much nutrition contributes to cancer prevention and to support anti-reflux surgery and endoscopic therapies for the management of GERD and BE.

Conclusions

Taken together, increasing evidence justifies to assume that effective anti-reflux surgery and ablative endoscopic therapy contribute to disrupt the progression of BE to cancer. Accurate diagnosis and tailored therapy seem mandatory for effective cancer prevention. Future studies will have to proof the value of novel cancer prevention concepts. A tailored, interdisciplinary approach seems mandatory for cancer prevention in GERD and BE. May these aspects motivate the "act" *vs.* "wait and see" policy for disease management.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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