Review Article

Role of radiofrequency ablation in Barrett's esophagus

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Abstract: Barrett's esophagus (BE) with and without dysplasia results from gastroesophageal reflux and harbors and increased cancer risk. Radiofrequency ablation (RFA) represents a novel tool for effective BE treatment and cancer prevention. This web-based research examined the role of RFA for treatment of BE ± dysplasia and early cancer. RFA ± endoscopic resection prevents cancer and cancer progression in those with dysplastic BE and early cancer, respectively. High cancer risk positive individuals with nondysplastic BE should be offered RFA within controlled trials. Post RFA management includes proton pump inhibitor (PPI) therapy. The efficacy anti-reflux surgery (+ hiatal repair) for cancer prevention prior, during or after RFA (± endoscopic resection) awaits further proof and should therefore only be offered within controlled trials. Accurate follow-up endoscopies are required for adequate management monitoring. Regular consumption of concentrated sugar containing food and beverages associates with an increased risk for gastroesophageal reflux disease (GERD), BE and cancer. RFA ± endoscopic resection is recommended for treatment of dysplastic BE and early cancer. Within controlled trials RFA should be offered to persons with cancer risk positive BE without dysplasia. The efficacy of anti-reflux surgery (prior, during, after RFA) for cancer prevention awaits further proof and should be offered within controlled trials. A low carb diet should be included into the management of GERD and BE.

Keywords: Barrett's esophagus; radiofrequency ablation (RFA); low carb diet; histopathology; esophageal manometry; reflux monitoring

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Introduction

Gastroesophageal reflux disease (GERD) affects 30–40% of the Western population (1-3). Due to the typical and atypical symptoms (heartburn, regurgitation, coughing, wheezing, asthma, sinusitis) GERD impairs the life quality and well-being (1-3). In 30% of GERD positive individuals biopsies obtained from the squamocolumnar junction (SCJ) contain Barrett's esophagus (BE) (1,4). BE associates with an increased risk for the development of adenocarcinoma of the esophagus (mean 0.5% annual risk) (1,5).

Conceptually, GERD results from the dysfunction of the lower esophageal sphincter (LES) and its distorted geometry within the diaphragmatic hiatus (i.e., hiatal hernia) (6). This in turn fosters the return of gastric content (acid, bile, food) into the esophagus. As a response to the reflux the squamous lined esophagus is replaced by columnar lined esophagus (CLE) (4,6,7). Going in line with the novel Chandrasoma classification CLE results from reflux and interposes between the normal squamous lined esophagus and the normal mucosa of the proximal stomach (oxyntic mucosa) (7). Histopathology lists the following CLE types: cardiac mucosa (CM; mucus cells only epithelium; superficial type, foveolar type, glandular type); oxyntocardiac mucosa (epithelium consisting of mucus and parietal cells within the subfoveal region of the CLE glands); intestinal metaplasia (IM; CM with goblet cells

instead of parietal cells); BE (4,6,7). While gastric oxyntic mucosa consists of straight tubular glands, the sub-foveolar region of the CLE glands is lobulated and branched (7). Thus, histopathology allows differentiation between normalcy (squamous lined esophagus; normal gastric oxyntic mucosa) and reflux induced CLE [CM, oxyntic cardia mucosa (OCM), IM] (7).

Over time reflux may trigger the progression of BE without dysplasia towards low- (LGD), high- (HGD) grade dysplasia and cancer (CA). Risk factors for progression include long standing GERD (>10 years), proton pump inhibitor (PPI) use, hiatal hernia, esophagitis, family history positive for esophageal cancer and GERD (1,7,8).

Radiofrequency ablation (RFA) represents a new endoscopic treatment for effective and durable elimination of BE (± dysplasia) (1,5,8). As thus RFA has been demonstrated to prevent cancer development in persons with LGD and HGD, when compared to surveillance (1,5,8). Discrepancy still exists, in as much RFA of BE without dysplasia contributes to prevent cancer. Going in line with theory, RFA of BE should contribute to prevent cancer (1,5,6). In contrast to that large numbers are required to proof the assumption.

This review aims to evaluate our current understanding of RFA for treatment of BE with and without dysplasia. Finally, we addressed the impact of life style and nutrition (diet) for the development and management of BE and GERD.

Methods

Using PubMed, Google, and Springer LINK, our research included the following keywords: GERD, Barrett's esophagus, endoscopy, histopathology, Chandrasoma classification, RFA, anti-reflux surgery and diet/nutrition for GERD and BE. Statistics were not applied. Endoscopy images were obtained, using Storz technology, histopathology slide received due to the courtesy of Prof Dr. Fritz Wrba, Vienna.

Results

Diagnosis of BE is established by the histopathology of biopsies obtained from the SCJ (1,3,7) (*Figures 1*,*2*). If SCJ biopsies contain CLE (i.e., CM) with goblet cells, the condition is termed BE without dysplasia (1,7) (*Figure 2*). Irregularities of the cellular and glandular geometry define BE with LGD and HGD (7,8). Extension of HGD beyond the muscularis propria of the CLE and/or towards blood, lymphatic vessels and nerve cells defines the presence of adenocarcinoma of the esophagus (T1a, T2b) (7). An expert pathologist second opinion is recommended for the diagnosis of LGD, HGD and cancer (1). Interestingly the presence of eosinophilic esophagitis (EoE) excludes the diagnosis of BE (9). As such EoE seems to prevent BE. The underlying mechanism has not yet been elucidated.

Due to the significantly increased cancer risk, the treatment of LGD, HGD and early cancer (T1a) should include endoscopic (sub)-mucosal resection (EMR) and RFA of the remaining CLE (1,10-15). RFA represents a new balloon catheter, endoscope tip mounted or through the scope applicable electrode system for the delivery of the RF energy to the mucosa, which in turn ablates the BE positive mucosa (1,10-15) (*Figures 3*,*4*). Three to four treatments may be required or complete elimination of dysplasia and non-dysplastic BE (1). When performed in expert centers the clearance of early cancer/dysplasia (LGD, HGD) and non-dysplastic BE (NDBE) reaches >80% and >90%, respectively (1,10-15). Following the mucosal resection and RFA patients are recommended PPI therapy to support wound healing and prevent recurrence (1,10-15). RFA for NDBE is recommended in persons with increased cancer risk, i.e., GERD >10 years, CLE length >2.0 cm; esophagitis, hiatal hernia, family history positive for esophageal and gastric cancer, history of dysplasia and NDBE (1,16,17). At present RFA for NDBE should be conducted within controlled trials to assess the efficacy for cancer prevention (1).

Advanced stages of cancer (> T1a) are recommended for surgical resection ± oncological therapy. Remains to be questioned and addressed the cause of GERD, BE, dysplasia and cancer (1,7).

Conceptually, gastric acid secretion, gastroesophageal reflux, development of CLE and BE (± LGD, HGD) are not the cause of the disease, they represent manifestations of the cause. The cause of GERD and BE is the dysfunction of the LES and its geometrical distortion within the diaphragmatic hiatus (7). PPI therapy only alters the pH of the reflux, but it does not reduce the reflux per se, PPI therapy does not restore the dysfunction of the LES and PPI therapy does not repair the distorted geometry of the lower esophagus within the widened diaphragmatic hiatus (hiatal hernia) (1,5,7,18,19). Therefore, anti-reflux surgery and hiatal repair should be considered for the elimination of both acid and non-acidic reflux in GERD symptom positive individuals (18,19) (*Figure 5*). Efficacy of anti-reflux surgery for asymptomatic BE ± dysplasia for the prevention of cancer development

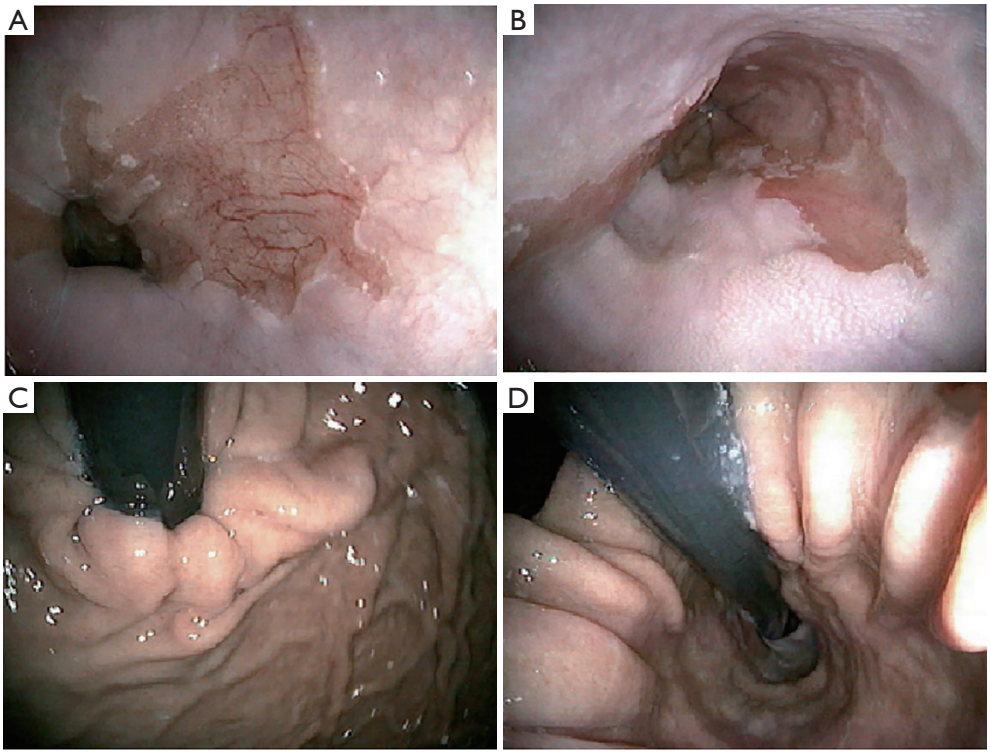

Figure 1 Antegrade (A,B) and retrograde (C,D) endoscopic image towards the esophagogastric junction in short segment columnar lined esophagus (2.0 cm) (A) and long segment columnar lined esophagus (4.0 cm) (B). Histopathology of biopsies obtained from the squamocolumnar junction revealed Barrett's esophagus without dysplasia.

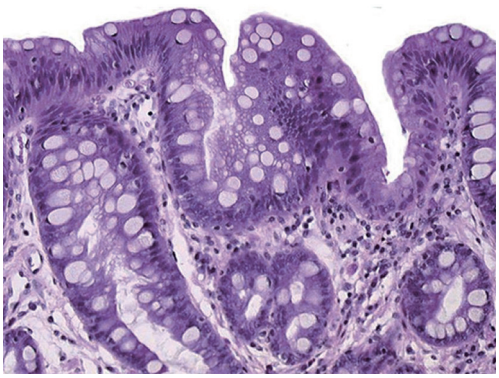

Figure 2 Histopathology of columnar lined esophagus containing goblet cells. This condition describes Barrett's esophagus without dysplasia. H&E stain, ×400.

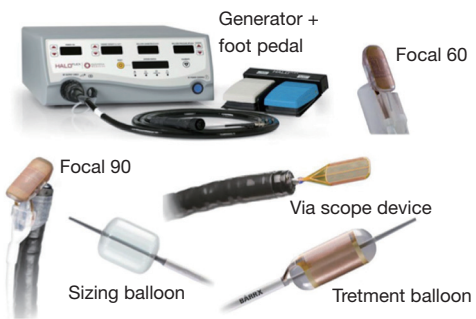

Figure 3 Equipment for radiofrequency ablation, as described in the text.

awaits further proof. However, recent evidence indicates that effective anti-reflux surgery (+ hiatal repair) may be more effective for cancer prevention, when compared to medical (PPI) therapy (1,8,20). Therefore, esophageal function tests (high resolution impedance manometry; pH impedance reflux monitoring) are recommended prior to anti-reflux surgery to assess esophageal function and to exclude motility disorders (achalasia, esophageal spasm, jackhammer esophagus) (21-25). This allows perfect tailoring of the surgical therapy.

Following endoscopic therapies follow-up endoscopies are scheduled 3, 3 and 6 months after the treatment of HGD,

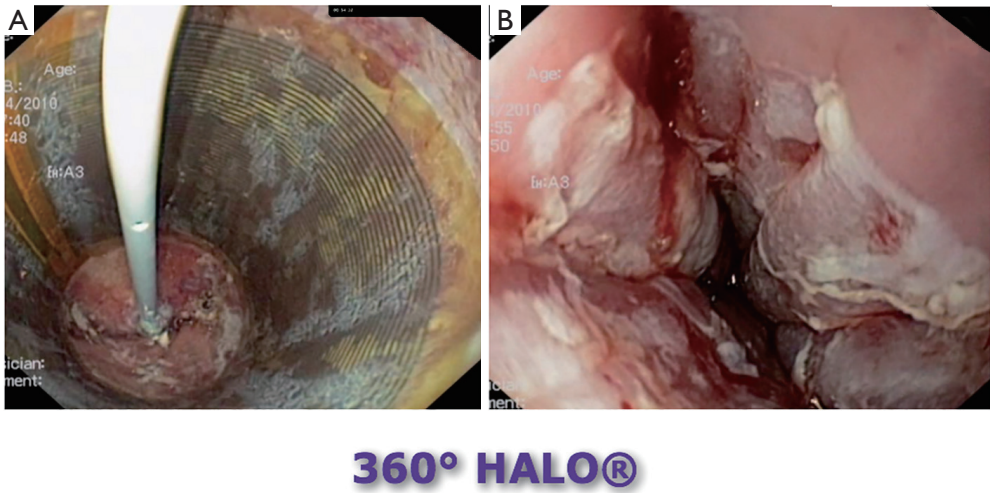

Figure 4 Endoscopic images obtained during radiofrequency ablation (RFA). (A) Vision through the inflated 360 treatment balloon the surface of which harbors the electrode through which the RF energy is delivered to the mucosa; (B) endoscopic image after RFA treatment.

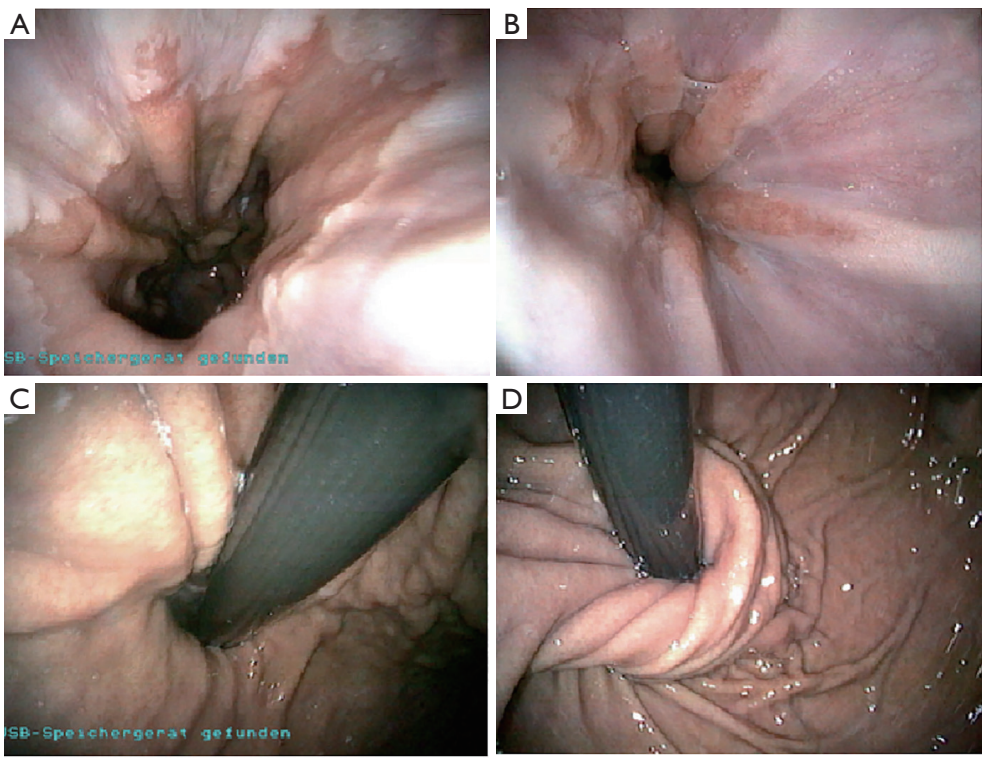

Figure 5 Antegrade (A,B) and retrograde (C,D) endoscopic image towards the esophagogastric junction 2 months before (A,C) and 6 months after Nissen fundoplication (B,D) for the treatment of symptomatic gastroesophageal reflux disease. Adequate geometry of the neo-esophagogastric junction valve parallels with complete symptom relief off proton pump inhibitor therapy (B,D).

LGD and non-dysplastic BE, respectively (1,26,27). BE negative CLE should be followed in 12 months' intervals (1). BE positive CLE should undergo repeat endoscopic treatment (RFA ± EMR) until complete clearance (1). Complications after RFA include stenosis (4%), bleeding and perforation (<1.0%) (1). The probability for the development of a post RFA ± EMR complication positively associates with advanced disease (presence of dysplasia, esophagitis, hiatal hernia, duration of GERD) (27,28).

Recent literature strongly indicates, that nutrition plays an important role for the development of BE, dysplasia and cancer (29). As such, a sugar rich diet has been demonstrated to associate with a 7–10-fold risk for the development of BE and esophageal adenocarcinoma (29). Therefore, a low carb diet is recommended within the treatment algorithm for GERD and BE.

Discussion

The major finding of our research was, that RFA ± EMR prevents cancer development in persons with BE positive for LGD, HGD and early cancer, when compared to surveillance (10-15,30,31). Thus, dysplastic BE and early cancer should be scheduled for RFA treatment. Management of advanced cancer includes surgical resection ± oncological therapy (1).

Discrepancy still exists regarding the management of BE without dysplasia. At present RFA for NDBE should be offered to persons with an increased cancer risk profile within controlled academical trials (1,4). Risk factors include: long standing GERD (>10 years), esophagitis, hiatal hernia, family history positive for GERD, BE and esophago-gastric cancer, history of BE ± dysplasia (1,4). Remains to be questioned an alternative to PPI therapy for the treatment of GERD in BE positive individuals (19).

Conceptually, the dysfunction of the LES and the distortion of its geometry represent the cause of the disease (7,8). As a consequence, reflux of gastric content into the esophagus occurs and triggers the inflammatory response, which in turn fosters the development of BE and cancer (7,8). While PPI therapy alters the pH of the reflux, it does not repair the dysfunction of the LES and does not narrow the widened diaphragmatic hiatus (20,22). Thus, PPI therapy does not reduce reflux *per se*, it simply alters the acidic into non-acidic reflux. Evidence indicates, that PPI therapy induced alkaline reflux increases the risk for the development of esophageal cancer (20). In contrast to that, recent studies indicated that effective anti-reflux surgery repairs the cause of the disease, eliminates increased reflux and symptoms and contributes to impair progression of BE (1,18,22). Therefore, it is justified to consider anti reflux surgery (+ hiatal repair) for the management of BE ± dysplasia and early cancer within controlled trials. Anti-reflux surgeries (+ hiatal repair) include fundoplication, magnetic sphincter augmentation (LINX) and Endostim (32,33-35). Esophageal function tests are recommended to foster an individualized tailored approach (21,23,24).

Following RFA treatment (± EMR, anti-reflux surgery) accurate follow-up endoscopies are essential for exclusion of recurrence of BE ± dysplasia and to exclude the presence of so called buried glands (<1.0%) (1). Therefore, BE management should be conducted in specialized centers with adequate expertise in the diagnosis and treatment of GERD and BE. Follow-up intervals are tailored according to the base line histopathology and ranges from 3 to 12 months intervals, as described in the results (1).

An interesting finding of our research indicated the importance and relevance of nutrition for the development of BE and esophageal cancer. As such recent studies demonstrated that increased consumption of food and beverages containing concentrated sugar, conservatives and artificial sugar associates with an increased risk for BE and cancer (29). Therefore, life style nutrition should be included into the treatment algorithm of BE and GERD.

Taken together, modern BE management (diagnosis, therapy, follow-up) orchestrates a multidisciplinary approach (endoscopy, histopathology, physiology, nutrition/diet and surgery). The results of ongoing and future studies are to be awaited to proof the efficacy of this novel approach. Otherwise the "Norse" myth will keep on going, that reflux is suggested to be the essential and fundamental cause for the development BE (35,36). Here a sound understanding may offer a possibility for effective cancer prevention for those with GERD and BE (1,7,8).

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