Barrett's Esophagus

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ABSTRACT

Barrett's esophagus (BE) is a predisposing factor of esophageal adenocarcinoma. Metaplasia on BE occurs due to imbalance between esophageal defensive and reluxate materials offensive factors. Nowadays, it is believed that gastroesophageal reflux disease (GERD) is one of major risk factors of BE. Patients with BE generally have lower esophageal sphincter (LES) pressure, shorter LES and intra-abdominal esophageal length, and longer acid exposure than patients with severe esophagitis. Acid exposure has pro-proliferation and anti-apoptosis effect which can facilitate BE occurrence.

Currently BE management has gone through various advance, especially in its diagnostic section, from the development of sophisticated endoscopic modality to the finding of biomarker to predict cancer occurrence on BE. Therapeutic section has also been progressing, especially with its endoscopic and chemoprevention therapy. This review article addresses the latest update of BE management.

Keywords: *Barrett's esophagus, GERD, management*

INTRODUCTION

Barrett's esophagus (BE) is a condition where squamous epithelium, which under normal condition lines distal esophagus, turns into columnar epithelium.[1] This abnormal columnar epithelium is an incomplete type of intestinal metaplasia.[1,2] BE is a predisposing factor of esophageal adenocarcinoma.[3,4] Incidence rate of esophageal carcinoma has significantly been increasing, especially on western populations. This associates with poor prognosis, particularly when late stage carcinoma has occurred.[2] Median of adenocarcinoma survival is less than 1 year and less than 10% survive for more than 5 years, with chemotherapy and surgery combination.[2] In 1993 of 11,300 esophageal cancer cases in the United States, death occurred in 10,200 patients. Each year, 0.5-2.0% of BE patients will progress to adenocarcinoma.[1,2,5]

The first reported case of BE was in 1950 by two surgeons, Numan Barrett from England and Jean Louis Jacob from France.Both reported the presence of lesions on distal esophagus which are lined with columnar epithelium. In 1950, Barrett wrote 'Chronic peptic ulcer of the oesophagus and oesophagitis'. He wrote that the epithelium which lined distal esophagus is congenitally short squamous-lined esophagus. In 1953 Allison, a thoracic surgeon, and Johnstone, a radiologist, wrote an article, 'The oesophagus lined with gastric mucous membrane'. This article addressed the presence of columnar epithelium on distal esophagus and encouraged the use of the term Barrett's esophagus. In 1957, Barrett published an article 'The lower esophagus lined by columnar epithelium', which recognized Allison and Johnstone's view of that there is an involvement of columnar epithelium which lines esophagus, and at the same time disposed his earlier analysis about congenital epithelium.[2]

In the last few decades, the definition of BE has slightly changed. Barrett's esophagus is defined as the transformation of distal esophagus epithelium, which can be identified as columnar mucosa on endoscopy, and confirmation of intestinal metaplasia through biopsy. This definition does not differentiate between short and long segmented BE classification.[5]

Epidemiologically, BE occurs more frequently in male, white population, and aged more than 45 years old.[1,2] Gastroesophageal reflux disease (GERD) is be-

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lieved to be the major risk factor of BE occurrence.[4] It is predicted that 10-20% GERD patients have BE.[1,2] In western countries, such as United States, esophagitis as a result of GERD is a frequently found medical condition. Out of 30% adults who had at least once a month heartburn complaint, about one third of them, through endoscopy esophagitis is found with esophagitis. Furthermore, about 10% of the esophagitis then progress to Barrett's metaplasia.[2]

PATHOPHYSIOLOGY

Histologically, Barrett's esophagus is characterized by columnar epithelium and the presence of goblet cells on esophagus tubular.[5,6] Morphological transformation from esophageal squamous epithelium into columnar form is termed as metaplasia. Metaplasia takes place as an abnormal adaptation response from esophagus mucosa in relation to repeated gastroesophageal reflux. Metaplasia is also a part of healing process, aims to protect esophagus from further damage caused by gastroesophageal reflux; despite such mechanism to a degree evolves to dysplasia and adenocarcinoma. The exact mechanism of squamous epithelial transformation into columnar epithelium (metaplasia) is still vague.[6]

Barrett's Esophagus occurs because of the imbalance between esophageal defensive factor and refluxate material offensive factor. When this esophageal mucosa defense mechanism (intralumen mucous, bicarbonate, growth factors, and more) fails to protect and repair (healing process), mucosal injury process takes place. Hydrogen ions, pepsin, trypsin, and bile acids are toxic agents which synergistically invade esophageal mucosa. The damaged squamous epithelial zone will progressively re-epithelialized into squamous epithelium, but on certain cases metaplasia to columnar epithelium takes place. Columnar epithelium derives from multipotent stem cells, which are situated in basal layer and esophageal sub-mucosal ducts. Barrett's mucosa consist of 80% incomplete metaplasia of particular epithelium with goblet cells; and 20% of cardia type and gastric fundus type.[4,6]

Esophagus and stomach are separated by high pressure zone, which is generated by lower esophageal sphincter (LES) contraction. On normal individuals, such separation is maintained, except while there is antegrade flow during swallowing, or retrograde flow during belching or vomiting. Back flow from stomach to esophagus through LES occurs only if LES tone is absent or very low (< 3 mmHg). Gastroesophageal reflux occurs through 3 mechanisms: (1) Spontaneous reflux during inadequate LES relaxation; (2) Retrograde flow which proceeds tone recovery while swallowing; (3) Increased intra abdominal pressure. Thus, it can be elucidated that esophagus integrity greatly depends on the equilibrium between esophageal defensive factor and refluxate material offensive factor.[4]

The roles of esophageal motility and LES function are other important factors of GERD and BE pathophysiology (figure 1). As many as 10-20% of GERD patients progress into BE. Generally BE patients have lower LES pressure, shorter LES and intra abdominal esophageal length, and longer duration of acid exposure compared to those who only have severe esophagitis. Motility disorder which causes reflux, poor refluxate material clearance, and duration of refluxate material exposure towards esophageal mucosa are important risk factor of BE occurrence. Other risk factors, though less significant, are cigarettes and alcohol.[6]

Data from ex-vivo and in-vitro model system show that acid exposure has pro-proliferation and anti-apoptosis effect, which may facilitate BE occurrence. Although it is still not clear whether this effect is a direct mechanism due to its acid exposure or an indirect mechanism due to its stimulation of inflammation process.[7]

Acid exposure can cause esophagitis. This is proven by findings of inflammation cells, basal cell hyperplasia, and increasing squamous cell proliferation on esophagus. Inflamed esophagus mucosa will undergo healing process with new squamous cell regeneration. But on several cases, this healing process undergoes metaplasia (figure 1).[7]

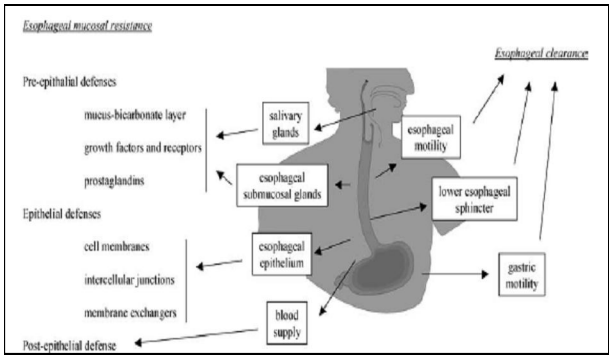

Figure 1. Mechanisms of defense of the esophageal mucosa against gastroesophageal reflux induced injury[6]

There are two plausible mechanisms on how acid triggers cancer. The first one is by means of indirect mechanism, i.e. acid induces inflammation process, which injures cellular components such as protein, lipid, and deoxyribonucleic acid (DNA). Some will activate pro-oncogenic factors and inactivate tumor suppresor genes. This will facilitate tumorigenesis. The second one is by means of direct mechanism, i.e. the acid directly impairs DNA with or without activating

pro-proliferation factors which makes cells grow rapidly and become cancer (figure 2).[7]

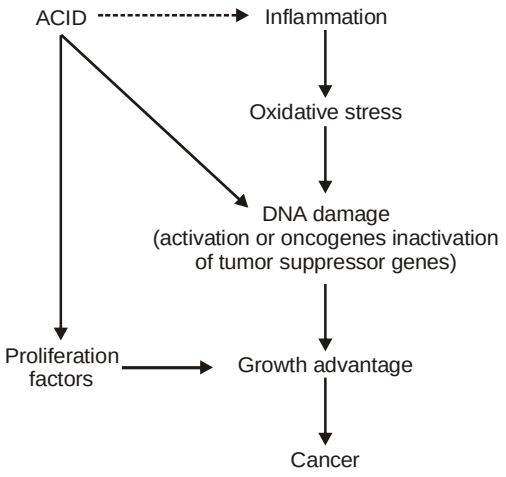

Figure 2. Potential mechanism of acid exposure in cancer formation in Barrett's esophagus.[7]

MANAGEMENT

Screening

BE screening is still controversial. The problems that have to be tackled these days are incapability to predict BE prior to endoscopy, no existing criteria, expensive and invasive endoscopy, and the existence of BE with minimal reflux symptoms.[5] A physician could attempt to predict BE with clinical signs and demographic data. Predictors consist of age > 40 years, heartburn, extended GERD symptoms history (more than 13 years), and male.[8,9,10]

An epidemiological study of esophageal adenocarcinoma in the United States has studied the role of gender and ethnic risk factor. The results are: annual incidence of esophageal adenocarcinoma on Caucasian male is 3.6 : 100,000 compared to 0.8 on African American male population; and annual incidence for Caucasian female is only 0.3. The accuracy of gender, ethnic, and age risk factors is not fully elucidated. A study conducted in Sweden reported that 1.6% are asymptomatic BE, and 44% are in the form of heartburn complaint and minimal regurgitation.[2,11]

We can conclude that symptoms-based BE screening is not recommended for general population (grade B recommendation). Endoscopic screening can be performed selectively and on individuals of certain population who have high risk (grade D recommendation). Patients with the highest likelihood of BE occurrence are old-aged Caucasian male with chronic reflux symptom.[5]

Surveillance

Patients with a recognized BE is a surveillance candidate. Several references report that there is a survival advantage with performing endoscopic surveillance. Several retrospective studies report increased survival rate of cancer patients who have endoscopy surveillance compared to those who are diagnosed based only on symptoms. Population-based study in California United States demonstrates the benefit of BE surveillance in detecting early stage cancer with better survival rate.[12,13]

Endoscopic surveillance is performed on patients with reflux symptoms who are also treated with proton pump inhibitor (PPI). The goal is to cure esophagitis reduce inflammation process, which will disturb biopsy and interpretation.[5] Biopsy is performed on four quadrants, each at 1-2 cm from Barrett's mucosa, and ideally samples are placed on different containers to locate the exact area of dysplasia. If dysplasia appearance is not found on two different endoscopic biopsies, there is still no guarantee of being free from neoplasia risk, follow-up endoscopy every three years is compulsory. It is better to confirm low grade dysplasia (LGD) appearance to a gastrointestinal pathologist; follow up endoscopy after six months time is performed to ensure there is no higher dysplasia grade. If higher grade of dysplasia is not found, then follow-up endoscopy is performed periodically once a year, until the dysplasia appearance disappears on two consecutive endoscopies. Dysplasia appearance disappears on two third of 156 LGD patients after mean follow up of four years, and also 40% of the follow-up biopsy turns out to be negative for dysplasia.[5,13,14,15]

High grade dysplasia (HGD) finding on mucosa has to be confirmed by a gastrointestinal pathologist; follow-up endoscopy and biopsy have to be performed to exclude esophageal adenocarcinoma within 3 months period of time. Mucosal resection per endoscopy has to be done if HGD with mucosal irregularity is found. Although the course of HGD varies, more than 30% are at risk for adenocarcinoma in five years time. The majority of experts refer HGD as a threshold for executing therapeutic intervention or intensive surveillance. Diagnostic procedures such as ultrasonography, computed tomography (CT) scan, and even positron emission tomography (PET) scan can be performed although there is still not enough evidence for routine application (table 1).[5]

Endoscopic surveillance gives indirect benefit. The higher the dysplasia grade, the more surveillance is really needed. Problems on interpretation difference, obtaining of samples, and the need of repeated endoscopy, cause the surveillance protocol to be less ideal, so future improvement is necessary.[5]

Table 1. Dyplasia grade and surveillance interval[5]

Dysplasia	Documentation	Follow–up
None	Two EGDs with biopsy within 1 year	Endoscopy every 3 years
Low grade	Highest grade on repeat EGD with biopsies within 6 months Expert pathologist confirmation	11 year interval until no dysplasia x 2
High grade	Mucosal irregularity Repeat EGD with biopsies to role out esophageal adenocarcinoma within 3 months expert pathologist confirmation	Endoscopic resection, continued 3 months surveillance or intervention based or results and patients

Imaging on Barrett's Esophagus

Barrett's esophagus has become the focal point of several imaging modalies development. Old technologies that are previously being used are conventional endoscopy, magnifying endoscopy, and chromo-endoscopy (chromoscopy). Magnifying endoscopy is an endoscopic technique which has zooming ability, and recently its zooming ability almost matches stereomicroscope (80-100x zoom). Other technique that ispreviously being used is chromo-endoscopy. This technique uses dye to mark abnormal mucosa. On BE, the dye is absorbed on the area of metaplastic intestinal mucosa.[16,17] Generally, dye is categorized into four groups, they are: contrast stains (indigo-carmine); absorptive dyes (lugol solution, methylene blue, toluidine blue, cresyl violet); reactive stains (congo red, phenol red); and retention pigment (india ink tatooing).

The latest technology that is available is narrow band imaging (NBI). NBI is an endoscopic technique with high diagnosis accuracy using narrow bandwidth filter on its light illumination system which will be fully absorbed by mucosal and sub-epithelial blood vessels. This technology is named NBI because its white light illumination source has been filtered or narrowed. Mucosal penetrating ability depends on the wavelength being used, blue filter for superficial zone, yellow filter for intermediate zone, and red filter for deep zone. The imaging result gives microstructure image of more vivid mucosa (pits pattern) and capillary network. One study with 51 BE patients who have undergone NBI, demonstrates that seven of them have high grade dysplasia, with NBI sensitivity on detecting irregular mucosal pattern is 100% and 98.7% specificity.[5,18]

Other latest endoscopic technique is Fuji intelligent chromo-endoscopy (FICE). FICE is a new form of endoscopic method based on spectrum analysis. Endoscopic image result is processed by spectrum analysis according to certain wavelength. Available wavelength are 400-600 nm with 5 nm interval. FICE can detect microstructure and capillary of mucosal membrane.[5]

Autofluorescence imaging has also been employed to detect dysplastic zone on BE. This technique utilizes light illumination to detect fluorescence from cell components on esophagus. The dysplastic zone does not emit autofluorescence as strong as normal tissue does, and it looks dark red. Such technique is ideal for extensive mucosal area. In a study with 20 patients, autofluorescence sensitivity for high grade dysplasia reaches 100%, but 40% are false positive.[19]

The latest technologies which are still under development are optical coherent tomography and laser confocal microscopy. This technology is able to enlarge mucosa and cell structure, thus minute mucosal area can be detected. Although the abovementioned technologies seem promising, there is still not enough data to recommend its use for routine clinical method.[5]

Biomarkers for Barrett's Esophagus

Several biomarkers have been proposed, but very few have been proven trough prospective study. There is one big scale cohort study which measures abnormal mucosal DNA content. The technique is using flow cytometry from fresh frozen specimens. This study concludes that cancer risk is nonexistent for five years if there is no evidence of increased tetraploidy (more than 6%) nor aneuploidy. On the contrary: if tetraploidy is found, cancer risk increases (relative risk = 11.7, 95% CI = 6.2-22). Moreover, if aneuploidy is found, cancer risk increases to 9.5 fold (95% CI = 4.9-18).[20] Other study in Seattle, Washington, observes heterozigosity disappearance of specific genes such as p16 and p53 as biomarker to predict cancer. If heterozigosity disappearance is detected, there is 16-fold increase of cancer risk.[21] Clinical validation in multicenter studies for these markers is needed before they are recommended for application in clinical settings.[5]

In recent publication, cancer tissue has been evaluated and compared to the control (case control). Methylation of three genes (RUNX3, HPP1, and P16) is found and this may also help on cancer predicting. Unfortunately, the study is retrospective, thus further big scale prospective research is needed.[5] As a conclusion, there are many biomarkers that have been studied and published, but unfortunately until now there have not been any biomarkers ready for routine use.[5]

Dysplasia Management

Low grade dysplasia needs to be confirmed by gastrointestinal pathologist, as well as surveillance by

means of endoscopy and biopsy. While advanced dysplasia (high grade dysplasia), in addition to the needs gastrointestinal pathologist confirmation, intensive surveillance, and is also a threshold for starting intervention.[5] Intensive biopsy is also needed to eliminate adenocarcinoma. Mucosal irregularities such as nodes or ulcer are ideally resected per endoscopy for extensive histological evaluation and for evaluating cancer occurrence. Nodularity has been proven to be associated with malignancy and regional lymph node metastases. Hidden cancer, without mucosal irregularity, is probably an intramucosal carcinoma without lymph node involvement.

Several studies provide biopsy guide for high grade dysplasia. Biopsy is done on four quadrants with 1 cm separating each quadrant, since greater distance (2 cm) provides missing rate more than 50%.[22,23] Big capacity forceps usage can be performed especially on high grade dysplasia cases.[24] Cytological examination from endoscopic brush obtained during BE surveillance can be helpful, with expectation that it will increase diagnosis accuracy.[25] But how valuable the additional information is still being questioned.[5]

GERD Treatment on Barrett's Esophagus

The goal of antireflux administration is to control GERD signs and symptoms. Stomach acid secretion suppressing drugs are generally used for this.[5] Esophageal reflux therapy for BE patients is identical to GERD patients without BE.[1] According to Genval statement and Asia Pacific Consensus 2003 about GERD treatment, it is agreed that the first line GERD treatment is PPI group and is being used with step down therapy approach. A retrospective study reports the decreasing of dysplasia in patients treated with PPI.[2,5] Several studies state that normalization of stomach acid exposure can decrease proliferating markers.[6,7] Unfortunately, until now there is no data which directly support the use of high dose anti-secretion therapy to prevent or slow-down the development of adenocarcinoma.[5]

There is other antireflux therapy other than medicine; i.e. fundoplication, either through surgery or endoscopy. The goal of fundoplication is to build a barrier from gastroesophageal reflux.[1] Medicine and fundoplication therapy are highly effective on improving GERD signs and symptoms, but unfortunately, until now there is still have not been proven to decrease esophageal adenocarcinoma risk. Several studies state fundoplication is more effective compared to anti-secretion therapy on preventing cancer in BE patients.

One randomized trial study compares medicine treatment to surgical therapy in 247 GERD patients with complication. Adenocarcinoma occurs in 4 (2.4%) out 165 patients of medicinal therapy group, and 1 (1.2%) out of 82 patients in surgical therapy group, during 10 to 13 years of follow-up. Unfortunately, the study was not statistically significant. Other study in Sweden, which is a population-based cohort study reported GERD patients who were being followed up for 32 years, adenocarcinoma relative risk of 35,274 males treated with anti-reflux medicinal therapy was 6.3% (95% CI = 4.5-8.7), and relative risk of 6,406 males treated with fundoplication was 14.1% (95% CI = 8-22.8).[1]

Surgical Therapy

Resection surgery (esophagectomy) has become a standard therapy of BE with HGD, based on the notion that endoscopy surveillance protocols cannot detect early stage cancer in almost 43% cases.[5] Recent data states that incidence of adenocarcinoma in resected HGD patients decrease to 17%.[26] Metastases risk on intramucosal carcinoma case is only 4%.[26] Nowadays, esophagectomy can be performed by minimally invasive technique, which are laparascopy or thoracoscopy. However, some studies report the overall possible complication is almost identical with common esophagectomy technique (trans hiatal).[5]

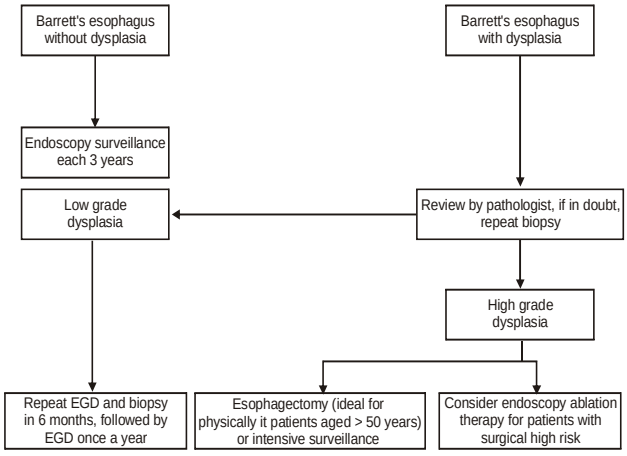

Figure 3. Barrett's esophagus management flowchart.[1]

Endoscopic Therapy

One example of endoscopic therapy on BE is ablation therapy. The goal of ablation therapy is to destroy metaplastic esophagus epithelium, and normal epithelium re-epithelialization is expected. Ablation therapy uses thermal (heat) energy, photodynamic, radiofrequency, and cryotherapy.[1] This therapy is always done simultaneously with acid suppressing drugs.[27] All studies on mucosa ablation use simultaneous treatment with once daily or at lost twice daily PPI.[5]

At first, thermal ablation therapy is only used for therapy of BE with minimal dysplasia. The first thermal coagulation device being used is laser by method of injuring the mucosa. Then after that came argon plasma coagulation and multipolar

coagulation.[5,27,28] In several serial case reports, high-voltaged argon plasma coagulation (80 watt) is proven to cure HGD and even small cancer, although there is still no long term follow-up study being made. Multipolar coagulation has been employed in low grade dysplasia and non-dysplastic BE cases.[29,30]

Photodynamic therapy is BE therapy using photosensitizer which is activated by endoscopic probe. A randomized prospective control trial shows that photodynamic therapy significantly lowers cancer risk on BE. In this study, 208 patients were randomized in 2:1 ratio into 2 groups: (1) patients receiving photodynamic and PPI therapy; (2) patients receiving only PPI therapy. The endpoint goal is HGD elimination. The result shows that photodynamic therapy lowers cancer risk up to 50% but on the follow up did not eliminate cancer after 48 months of time. Therapy with photodynamic can also eliminate HGB in 78% patients who had been treated, although in the control group, it could also eliminate HGB in 39% patients.[5]

Photodynamic therapy with 5 aminolevulinic acid has been widely used in Europe, and several serial case reports show that it is successful for eliminating HGD and early adenocarcinoma. The disadvantage of such therapy is that it causes hypotension, and death has also been reported.[31,32] Radiofrequency ablation using endoscopy has lately been used as BE treatment. This device is made with high voltage radiofrequency energy. Although it is not frequent, esophagus stricture and perforation have been reported. Cryotherapy application using endoscopy has also been reported for its role in eliminating BE; however, data on this technique is still very limited.[5]

Other endoscopic therapy that lately has been developed is ligation therapy. It has similar goal, which is brings causality on Barrett's epithelial zone so that normal epithelium re-epithelialization can take place. This technique uses ligation band for varices. Several advantages of this technique are the scar is not as extensive as the scar made by thermal and photodynamic ablation, and it does not leave behind residue on esophagus. Thus, complication due to performing this ligation therapy is minor. Other advantages are in addition to its safety, this technique is also effective and simple.[33] The decision to choose which technique to use is very individualistic, it depends on the device availability, patients' preferences, and the experience of the gastroenterologist.[5]

Chemoprevention

It seems that pre-malignancy stage chemoprevention of esophageal adenocarcinoma, in this case BE, will be a promising future strategy. Unfortunately, until now, evidence on this therapy is still lacking. Several epidemiological studies show chemoprevention with non steroidal anti inflammatory drug (NSAID) is associated with decreased cancer risk, with odd ratio of 0.57 (95% CI = 0.47-0.71).[33] Such decreased risk is reinforced by decreased biomarkers, such as aneuploidy and tetraploidy.[34] An animal model experiment shows decreased cancer risk in mice receiving cyclo-oxygenase inhibitor (COX inhibitor).[35] A randomized trial has been done and it shows that administration of 200 mg celecoxib twice daily is not more effective than placebo in dysplastic BE patients on intermediate endpoint.[35] Recently a big scale study on administration of aspirin and PPI in BE is being carried out.[36]

CONCLUSION

Barrett's esophagus is defined as epithelial transformation of distal esophagus from squamous into columnar epithelium, which can be identified by endoscopy and confirmed by the presence of intestinal metaplasia through biopsy. Reflux-causing motility disorder, poor refluxate material clearance, and duration of refluxate material exposure on esophagus mucosa are major risk factors of BE. Nowadays, it is believed that GERD is one of major risk factors BE. Management of BE consists of screening, surveillance, antireflux therapy, endoscopic therapy, surgery, and chemoprevention. Endoscopic screening can be performed selectively and individually on certain high-risked population. Surveillance is performed in patients with identified BE, and majority of experts place high grade dysplasia as a threshold for performing intervention therapy or intensive surveillance. Nowadays, BE has been a focal point of several diagnostic and therapy modalities development. The progress of diagnostic section is marked by progression of sophisticated imaging with high accuracy rate such as NBI and FICE, and the finding of several cancer predicting biomarkers. It appears that the progress on therapy and chemoprevention will be a promising future strategy, and also nowadays several therapeutic modalities, which are safer and simpler, are progressing.

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