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A REVIEW ON BARRETT'S ESOPHAGUS

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ABSTRACT

Barrett's esophagus (BE) is a segment of columnar lined epithelium in the distal esophagus, above the gastroesophageal junction. is a potentially serious complication of the GERD [Gastroesophageal reflux disease],in which the lining of the esophagus, becoming more like the lining of the small intestine rather than the area where the esophagus is joined to the stomach. About ≥10% of people with the chronic GERD develops this condition. It does not have specific symptoms, but presents the similar symptoms as in GERD, where these does not affect the likelihood. As BE is a well known premalignant condition, detection of dysplastic epithelium and its severity is the crucial element. Here the chances of cancer is also present but only as fewer as 1% of the patients with Barrett's esophagus develop such cancers. At the current time, diagnosis of this condition is possible only by the endoscopy and evaluating the certain changes in the esophagus lining.

KEYWORDS: GERD, Dysplastic epithelium, Cancer.

INTRODUCTION

In many western countries, the incidence of esophageal adenocarcinoma has risen more rapidly than in any other cancer over the past four decades.

In Barrett Oesophagus (BE) is present, the risk of development of oesophageal adenocarcinoma is significantly higher.

Barrett's oesophagus is a accepted precursor of oesophageal adenocarcinoma. Both oesophageal carcinoma and Barrett's oesophagus are associated with long -standing prior symptoms of gastroesophageal reflux disease. Their is little consensus among practising gastroenterologists for who if anyone should be screened with endoscopy for Barrett's oesophagus.

The prevalence of BE is estimated to be 1.6% in the general population,and higher in patients with GERD. Risk factors associated with development of BE include increasing age,chronic GERD, male gender.

Anatomy

Normally the oesophageal lining (the epithelium) Consists of flat layered cells similar to those in the skin. This Squamous epithelium stops abruptly at the junction of the oesophagus with the stomach near the lower end of the lower oesophageal sphincter. The epithelium of the rest of the gut, down to the anus, consists of single layered of side-by-side rectangular cells, which is called Columnar epithelium.

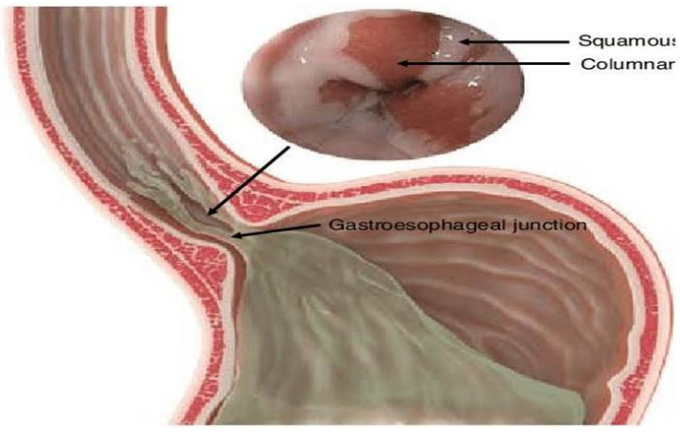


Figure 1 :- Endoscopy view of Gastro-oesophagial junction.

DEFINITION

Barrett's oesophagus is a condition in which the lining of the oesophagus changes,becoming more like the lining of the small intestine rather than the oesophagus. This occurs in the area where the oesophagus is joined to the stomach.

The current definition of Barrett's oesophagus (BE) proposed by the American Gastroenterological Association (AGA) is "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal oesophagus.

BE (or) Columnar lined oesophagus,is an acquired condition that results from chronic gastro-oesophageal reflux. It is characterised by the metaplastic replacement of the normal squamous epithelium of the lower oesophagus by columnar epithelium.

CLINICAL PRESENTATION

Barrett's oesophagus is associated with a increased risk of developing oesophageal cancer. Although the risk of developing oesophageal cancer is small, its important to have regular check ups with careful imaging and extensive biopsies of the oesophagus to check for Precancerous cells (dysplasia). If precancerous cells are discovered, they can be treated to prevent Oesophageal cancer.

Signs and Symptoms

The development of Barrett's oesophagus is most often attributed to long-standing GERD, which may include these signs and symptoms.

- Frequent heartburn and regurgitation of stomach contents.
- Vomiting blood or vomit that resembles coffee grounds.
- Dysphagia.
- Chest pain (less commonly).
- Passing black, tarry and bloody stools.
- Unintentionally losing weight.

Call your doctor if you have any of the above symptoms.

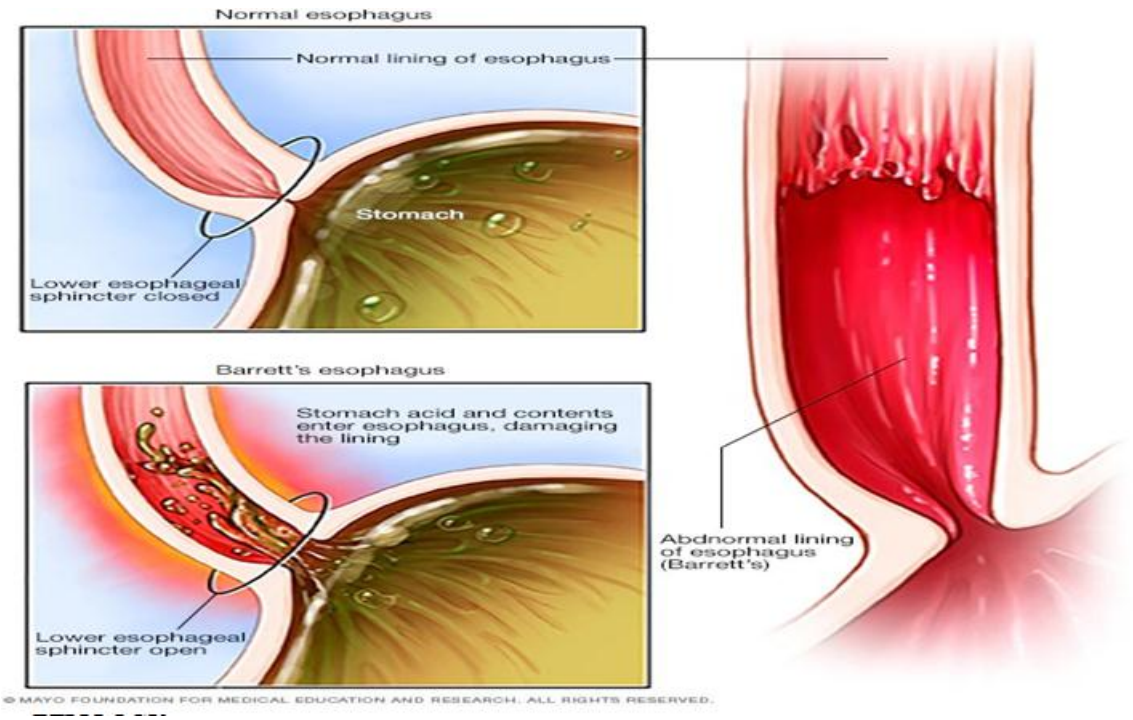


Figure 2:- Mechanism of BE.

ETIOLOGY

The exact cause of Barrett's oesophagus is not yet known.

- GERD occurs when the muscles at the bottom of the oesophagus do not work properly.
- Its believed that the cells in the oesophagus can become abnormal with long term exposure to stomach acid.
- It is estimated that only about 0.5 percent of people with Barrett's oesophagus develop cancer.
- Other risk factors for developing Barrett's oesophagus include:
  - being male
  - being caucasian
  - having H.pylori gastritis

The risk factor for BE highlight again the role of reflux in its pathogenesis. Given the response to injury model of BE, reflux-associated erosive esophagitis (EE)is considered a likely intermediate step on the path towards development of metaplasia.

The relationship among GERD, BE and oesophageal adenocarcinoma are clearly established. Duration and severity of GERD symptoms increases risk not only for BE ,but also for oesophageal adenocarcinoma; in fact, patients with severe and prolonged symptoms of GERD have an odd ratio of 43.5 for development of oesophageal adenocarcinoma compared with patients who do not report any recurrent GERD symptoms.

Interestingly, while duration of GERD symptoms is clearly a risk factor for both development of BE and greater length of BE segment. Additional factors that appear to be risk factors for the presence of BE include presence of HIATAL HERNIA, and interestingly, the absence of Helicobactor pylori infection.

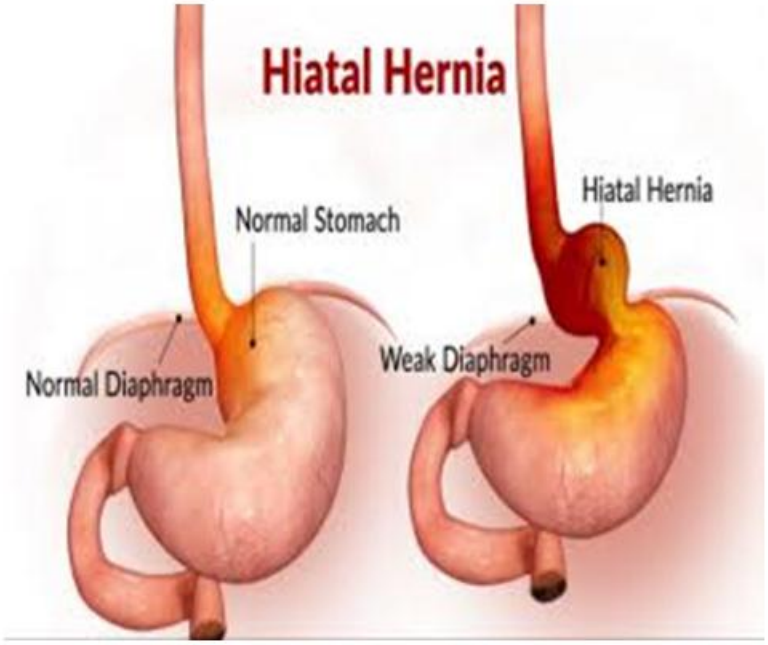


Figure 3:- Depicting Normal stomach & Hital hernia.

Hiatal Hernia distorts the anatomy that normally protects against reflux by reducing pressure at the lower oesophageal sphincter ,creating an acidic hernia sac between diaphragm and the oesophagus, and decreasing the efficacy of peristalsis and other study demonstrated that hiatal hernia correlated with longer segment of BE.

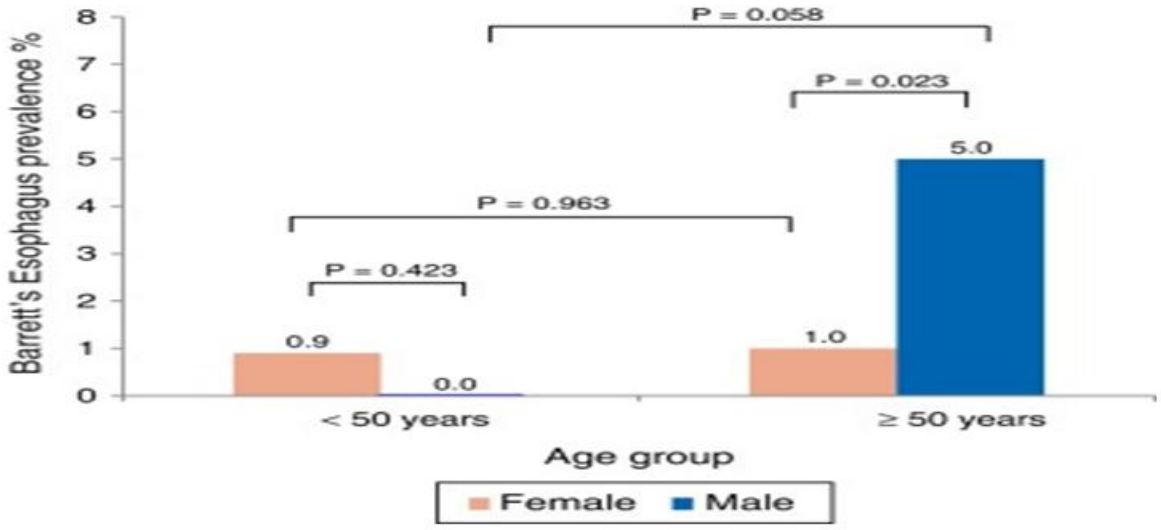
GERD,BE and esophageal adenocarcinoma have all been associated with presence of obesity .The relationship between GERD and obesity is thought to be in part due to increased gastroesophageal sphincter gradient, intra-abdominal pressure and increased incidence of Hiatal hernia in obesity.

Helicobacter pylori, in contrast to obesity and hiatal hernia, may affect the risk of BE by physiologic rather than anatomic means; H. pylori can decrease gastric acidity through activity of urease. The fact that H.pyloru may be protective against BE is a contrast to it's well established status as a risk factor for peptic ulcer disease (PUD)and gastritis, and indeed eradication of H.pylori for PUD may increase risk of BE.

EPIDEMIOLOGY

- Barret's esophagus (BE) is a potentially serious complication of. GERD, which stands for GASTRO ESOPHAGEAL REFLUX DISEASE.
- The prevalence of GERD in India is likely to be between 8 % and 19% which is compared to the prevalence rates in western countries.
- BE is found in 1.6 % of general population and in 10 % patients of those patients who undergo endoscopy for symptoms.
- BE primarily affects older adults in the developed world.
- Males especially Caucasian males, have a strong predilection for the development of BE, with a MALE:FEMALE ratio of 2-3:1 in most studies. The overall ratio of BE cases was 2:1 favoring males, but in younger adults, ratio of MEN to WOMEN approached 4:1.
- It is usually discovered during endoscopic examinations of middle-age and older adults; the large majority of cases go unrecognized. Mean age at diagnosis of BE is approximately 55 years.
- According to a retrospective study, from November 2014 to April 2016, the prevalence of BE was 1.8 %.
- In the group of patients with GASTROESOPHAGEAL REFLUX, BE prevalence is 7.2 %. In multivariate analysis, the factors that were independently associated with BE were GASTROESOPHAGEAL REFLUX and HITAL HERNIA.

- BE is uncommon in children in general and extremely rare in children under the age of 5 years. BE is 2-3 fold more common in men than in women.
- In US, it is estimated that 5.6% of adults have BARRETT'S HuESOPHAGUS.
- In western population, BE appears to have a higher prevalence in whites as compared with Hispanics and Asians and prevalence appears to be lowest in blacks.
- While BE develops in minority of patients with gastro esophageal reflux disease, its diagnosis has markedly increased over the last 30 years.
- Overall mortality rate was 46.7 per 1,000 person-years among Barrett's patients compared with 27.2 per 1,000 person-years in the general population, corresponding to a 71% relative increase in overall mortality risk among Barrett's patients.



Graph 1:- showing Distribution by age and sex in Barrett's esophagus.

Table 1:- showing clinical characteristics of patients with Barrett's esophagus disease.

S.No & contents			
1.Characteristics	**BE (n = 9) n (%)**	**Without BE (n = 491) n (%)**	**p**
2.Age > 50 years	8 (88.9)	315 (64.2)	0.124
3.Sex (male)	6 (66.7)	182 (37.1)	0.069
4.GERD symptoms	9 (100)	116 (23.6)	< 0.001
5.Hiatal hernia, n (%)	6 (66.7)	77 (15.7)	< 0.001
6.Esophagitis, n (%)	0 (0)	41 (8.4)	0.366

In Barrett's esophagus, normally flat, pink cells are replaced with a thick, red lining with potential for cancerous changes, thought to be triggered by long-standing gastro esophageal reflux disease (GERD).

- BE is a condition in which the flat pink lining of swallowing tube that connects the mouth to the stomach (esophagus) becomes damaged by acid reflux; which causes the lining to thicken and becomes red.
- Between the esophagus and the stomach is a critically important valve, the lower esophageal sphincter (LES). Overtime, the LES may begin to fail, leading to acid and chemical damage of the esophagus, a condition called GASTRO OESOPHAGEAL REFLUX DISEASE.
- GERD is often accompanied by symptoms such as heart burn or regurgitation. In some people, this GERD may trigger a change in the cells lining the lower esophagus, causing BARRETT'S ESOPHAGUS.
- BE is associated with an increased risk of developing esophageal cancer.

CAUSES

- Exact cause of BE isn't known. While many people with Barrett's esophagus have long-standing GERD, may have no reflux symptoms called "silent reflux".
- Acid reflux accompanied by GERD symptoms or not, stomach acid and chemicals wash back into the esophagus,damaging esophagus tissue and triggering changes to the lining of the swallowing tube, causing BE.
- GERD occurs when the muscles at the bottom of the esophagus do not work properly. The weakened muscles wont prevent food and acid from coming back up into the esophagus. It is believed that the

cells in the esophagus can become abnormal with long -term exposure to stomach acid.

RISK FACTORS

- There are risk factors which increase both BE and GERD.
- The factors that increase risk of BE include
- **Family history:** people with family history of BE or Barrett's esophageal cancer may develop BE.
- **SEX:** Men are more likely to develop than that of women.
- **CAUSCASIAN:** White people have more risks of disease than people of other races.
- **AGE:** BE can occur at any age but more common in adults over 50 years.
- **CHRONIC HEART BURN and ACID REFLUX:** GERD is commonly causing factor of BE.
- **BEING OVERWEIGHT:** Body fat around abdomen increases risk.
- **HAVINH HELICOBACTER PYLORI GASTRITIS**

The factors that aggravate GERD can worsen BARRETT'S ESOPHAGUS. These include:-

- **Smoking**
- **Alcohol**
- **Eating spicy foods**
- **Eating large portions at meals**
- **Frequent use of NSAID's or aspirin**
- **Diet high in saturated fats**
- **Going to bed or lying down less than 4 hours after eating.**

PATHOPHYSIOLOGY

Esophagus:- The digestive tract, with the esophagus marked in red

- It is a 25 cm long fibromuscular tube extending from the pharynx (C6 level) to the stomach (T11 level).
- It consists of muscles that run both longitudinally and circularly, entering into the abdominal cavity via the right crus of the diaphragm at the level of tenth thoracic vertebrae.
- It actively facilitates the passage of food bolus into the stomach under precise nervous regulation.

Histo pathology of Barrett's esophagus

BE is a condition in which columnar cells replace usual squamous cells in the mucosa of the esophagus. The condition is recognized as a complication of GERD. It is a condition marked by abnormality in the lining of the lower esophagus. It is believed to be due to severe, longstanding, GERD.

The mucosa of the normal esophagus is compared of squamous cells similar to those of the skin or mouth. The normal squamous mucosal surface appears white-pink in color, contrasting sharply with the salmon pink to red appearance of the gastric mucosa which is compared of columnar cells.

Chronic exposure to gastric content leads to intestinal metaplasia. Cellular and DNA damage alters the differentiation potential of proliferating epithelial cells. The metaplasia change is macroscopically visible using an endoscopy.

Internal metaplasia may be classified histologically as

- Non-dysplasia
- Low grade dysplasia (LGD)
- High grade dysplasia(HGD)

In HGD, dysplastic cells are still confined by the basement membrane. However, due to large numbers of dysplastic cells there is a high chance of subsequent invasion of the submucosa, and progression to adenocarcinoma.

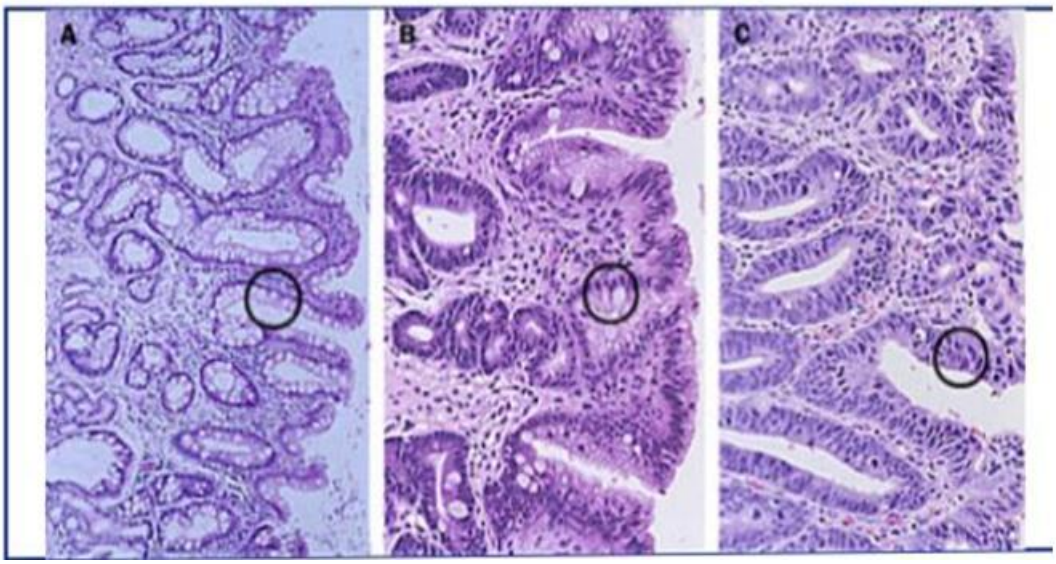


Figure 4:- A. No Dysplasia B. Low grade dysplasia C. High grade dysplasia.

Figure 5:- Histopathology of Barrett's esophagus, showing intestinalized epithelium with goblet cells, as opposed to normal stratified squamous epithelium of the esophagus, and pseudostratified columnar epithelium of the fundus of the stomach. The submucosa displays an infiltrate including lymphocytes and plasma cells, constituting an underlying chronic inflammation. The area between the stratified and the intestinalized epithelium displays reactive changes, but there is no secondary dysplasia.

- The squamocolumnar junction is therefore displaced into the esophagus and no longer marks the esophagogastric junction. BE may extend upwards in a continuous pattern in which the entire circumference of the distal esophagus is covered by columnar mucosa. At its proximal margin, thereare often short extensions of the Barrett's mucosa, referred to as mucosal tongues. There can be skip areas in which islands of columnar mucosa are separated from the main area of Barrett's mucosa.
- A distinction is drawn between patients with more than 3cm of Barrett's esophagus (long- segment BE) and those with less than. 3cm of BE (short-segment BE).

DIAGNOSIS:- Although there are no-depth, published, systemic reviews of the optimal approaches to the diagnosis and management of patients with BE. Given the controversies involving this lesions, workshops conducted by some association scholars and physicians states, the diagnostic, screening and management of BE is necessary to avoid the carcinomas and cancers in the patients with GERD associated BE.

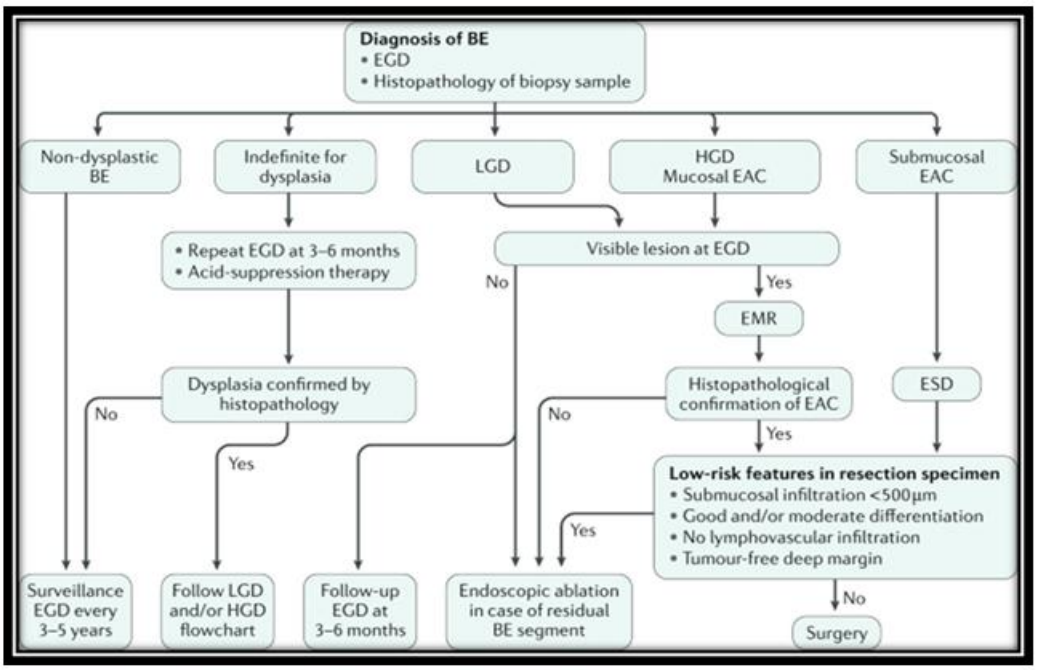


Figure 6:- Showing algorithm for diagnosis of BE.

The clinical importance of the definition of BE is that it should identify a lesion documented to be at risk of esophageal adenocarcinoma. In addition, both gastroenterologists and pathologists often fail to document adequate diagnostic criteria of BE, some of the diagnostic methods include as follows.

Classic Endoscopy is the test of choice for Barrett's esophagus. During endoscopy, a thin tube with a light and camera on the end are run through the mouth, down your throat and into your stomach. Biopsies, meaning small pieces of tissue is collected and looked under the microscope.

Current recommend that the diagnosis of BE should be based on the presence of columnar epithelium ≥1cm proximal to the gastrointestinal junction with biopsies consistent with intestinal metaplasia (IM).

And other criteria's are followed according to the certain clinical guidelines. These guidelines differ from one to the other (may be country based, may be on the basis of technology, may be based on advanced instruments etc.)

An upper GI barium study can be helpful in finding strictures usually causing trouble swallowing. But this type is rare and not used in general.

SCREENING FOR BE

- Screening for BE may be considered in men with chronic (≥5years) and frequent symptoms of gartoesophageal reflux and two or more risks of the BE or EAC (Esophageal adenocarcinoma).
- Generally females are at lower risk of this condition so screening for BE in females is not recommended except in certain conditions stated in certain guidelines.
- Screening of general population is not recommended.
- Unsedated transnasal endoscopy (uTNE) can be considered as an alternative to conventional upper endoscopy for BE screening.
- If initial endoscopy is negative for BE, repeating endoscopic evaluation for the presence of BE is not recommended. If endoscopy reveals esophagitis, repeat endoscopic assessment after PPI therapy for 8-12 weeks is recommended to ensure healing of esophagitis and exclude the presence of underlying BE.

SURVEILLANCE

- Patients should only undergo surveillance after adequate counseling regarding risks and benefits of surveillance.
- Surveillance should be performed with high-definition/high-resolution white light endoscopy.
- Routine use of advanced imaging techniques other than other than electronic chromoendoscopy is not recommended for endoscopic surveillance at this time.
- Endoscopic surveillance should employ four-quadrant biopsies at 2cm intervals in patients without dysplasia and 1cm intervals in patients with prior dysplasia.
- Mucosal abnormalities should be sampled separately, preferably with endoscopic mucosal resection (EMR). Inability to perform EMR in the setting of BE with nodularity should lead to referral to a tertiary care centre.
- Biopsies should not be obtained in mucosal areas with endoscopic evidence of erosive esophagitis until after intensification of antireflux therapy to induce mucosal healing.
- For BE patients with dysplasia of any grade, review by two pathologists, at least one of whom has specializes experts in gastrointestinal (GI) pathology, is warranted because of interobserver variability in the interpretation of dysplasia.
- Use traditional biomarkers for risk satisfaction of patients should take place at intervals of 3 to 5 years.
- Patients diagnosed with BE on initial examination with adequate surveillance biopsies do not require a repeat endoscopy after optimization of acid suppressive medications 3 to 6 months should be performed. If the indefinite for dysplasia reading is confirmed on the repeat examination, a surveillance interval of 12 months is recommended.
- For patients with confirmed LGD (low-grade dysplasia) and without life-limiting comorbidity, endoscopic therapy is considered as the preferred treatment modality, although endoscopic surveillance every 12 months in an acceptable alternative.
- Patients with BE and confirmed HGD (High-grade dysplasia) should be managed with endoscopic therapy unless they have life-limiting comorbidity.

TREATMENT

Chemoprevention: The utility of chemotherapy is unclear. Because those with baseline dysplasia are often treated with endoscopic ablation and those with NDBE (Non-dysplastic BE) have a very low risk of progression, the safety and cost-effectiveness of long-term use of any agent for chemoprevention needs to be justified. Currently, it is recommended that all patients with BE, regardless of the presence of GERD symptoms, be treated with once daily.

PPI based on evidence that progression to neoplasia is reduced compared with no PPI therapy or with use of H2 receptor blockers.

Although the use of NSAIDS, is associated with a diminished incidence of EAC and a reduced risk of progression of EAC in BE patients up to 30%, the bleeding risk associated with NSAIDS may outweigh

these benefits and therefore they are not currently recommended as a chemopreventive strategy in BE.

ENDOSCOPIC THERAPY

- Patients with nodularity in the BE segment should undergo EMR (Endoscopic mucosal resection) of the nodular lesions as the initial diagnostic and therapeutic maneuver. Histologic assessment of the EMR specimen should guide further therapy. In subjects with EMR specimens demonstrating HDG, of intramucosal carcinoma, endoscopic ablative therapy of the remaining BE should performed.
- In patients with EMR specimens demonstrating neoplasia at a deep margin, residual neoplasia should be assumed, and surgical, systemic, or additional endoscopic therapies should be considered.
- Endoscopic ablative therapies should not be routinely applied to patients with nondysplastic BE because of their low risk of progression to EAC. Endoscopic eradication therapy is the procedure of choice for patients with confirmed LGD and confirmed HDG.
- In patients with T1b EAC, endoscopic therapies the preferred therapeutic approach, being both effective and well tolerated.

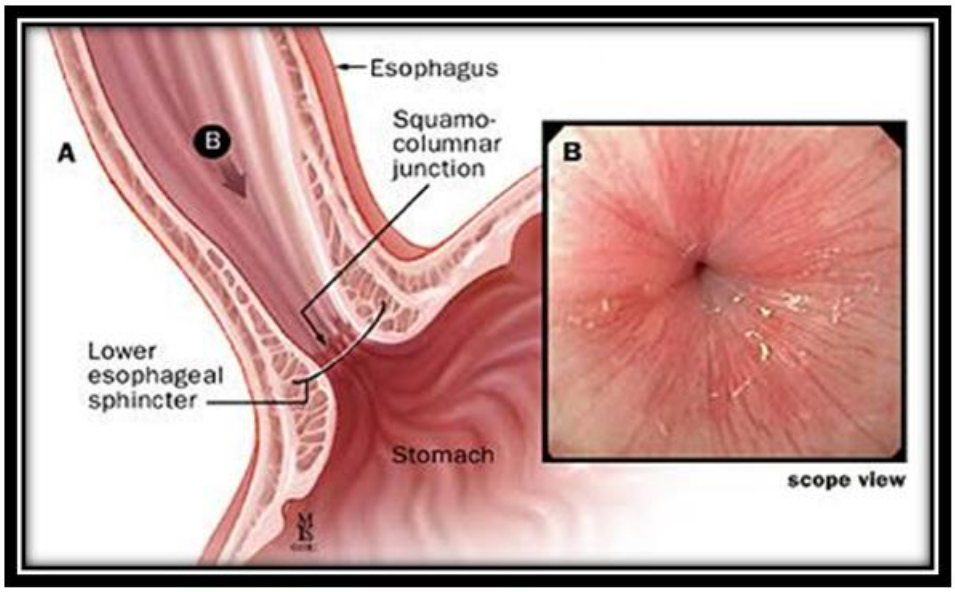


Figure 7:- Endoscopy of stomach.

- In patients with T1b EAC, consultation with multidisciplinary surgical oncology team should occur before embarking on endoscopic therapy. In such patients, endoscopic therapy may be an alternative strategy to esophagectomy, especially in those with superficial disease with a well-differentiated neoplasm lacking lymphovascular invasion, as well as those who are poor surgical candidates.
- In patients with dysplastic BE who are to undergo endoscopic ablative therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablation therapy.

SURGICAL THERAPY

- Antireflux surgery should not be pursued in patients with BE as an antineoplastic measure. However, this surgery should be considered in those with incomplete control of reflux on optimizes medical therapy.
- In case of EAC with invasion into the sub mucosa, especially those with invasion to the mid or deep mucosa, esophagectomy, with consideration of neoadjuvant therapy is recommended in the surgical candidate.
- In patients with T1a or T1b sm1 EAC, poor differentiation, lymphovascular invasion or incomplete EMR should prompt consideration of surgical and/or multimodality therapies.

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