Barrett’s esophagus and esophageal cancer

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Introduction

Barrett’s esophagus is a transformative process, in which metaplastic columnar epithelium replaces the endogenous stratified squamous epithelium in the lower portion of the esophagus

This adaptation is a consequence of GERD which damages the endogenous stratified squamous epithelium and over time has the potential to predispose to the development of adenocarcinoma of the esophagus.

Components of the definition

- Endoscopic recognition of salmon-colour mucosa into the tubular esophagus
- Extending 1cm or more proximal to the gastroesophageal junction
- Must be confirmed pathologically to contain goblets cell (AGA)

- Consensus from most professional guidelines including AGA is that a diagnosis of BE requires the presence of IM (the presence of goblet cells) because of an increased risk of EAC associated with IM,
- Although guidelines from the British Society of Gastroenterology and the Asia Pacific region do not require this.
- The strongest evidence comes from a large population-based study of 8,522 patients with BE from the Northern Ireland Cancer Registry. The risk for EAC was elevated in patients with IM at index endoscopy compared with those without IM

  hazard ratio [HR] 3.54; 95% confidence interval [CI] 2.09–6.00)

Controversies on real definition of Barrett's esophagus

In a case series of 45 patients with BE or EAC, frequent copy number alterations targeting cancer-associated genes were found in tissue with IM, but no such changes were encountered in columnar metaplasia without goblet cells

On the contrary, A single-center UK study of 688 patients with a median follow-up of 12 years found no difference in cancer risk for those with a columnar-lined esophagus with or without IM: 0.37% vs 0.30%/year . Similarly, a multicenter UK study of 1,751 patients found a similar cancer risk in patients with and without IM (HR 1.36; 95% CI 0.63–2.96)

Any effort to delete goblet cells from the diagnostic criteria for BE is problematic, - increase the pool of patients undergoing surveillance

- concomitant cost and quality of life implications.
- It may also denote that samples collected where take from the proximal stomach

Pathophysiology

Barrett’s esophagus is believed to occur as a two-step process.

The first step, which occurs relatively quickly over a period of a few years, involves transformation of normal esophageal squamous mucosa into a simple columnar epithelium which lacks parietal cells, known as cardiac mucosa.

And results from chronic repeated episodes of refluxing gastric acid onto the squamous mucosa.

Continue

It is said to be associated with increased intercellular spaces which allow for hydrochloric acid molecules to permeate down to the stem cells in the basal layer and stimulate afferent nerves, leading to symptoms and squamous cell transformation to simple columnar cells

The second step of intestinal metaplasia, is thought to progress more slowly, over 5 –10 years, influenced by genetic and environmental factors and follows two pathways

A) One pathway is known as gastric differentiation-

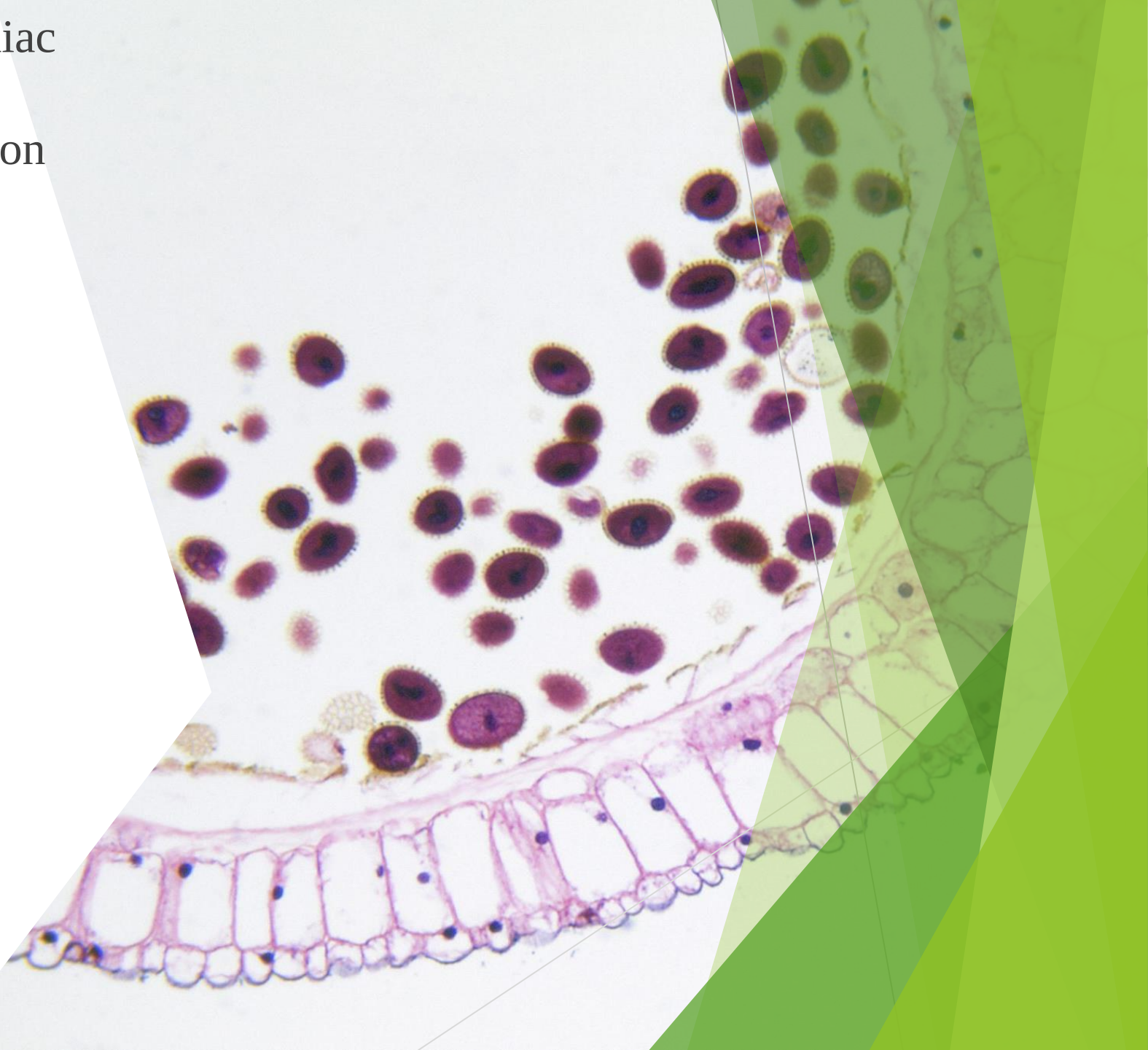
Leading to formation parietal cells within glands below the columnar mucosa through the expression of **gastric genes**

This forms an oxynto-cardiac mucosa, which is not premalignant and favorable since it confers protection from further metaplasia.

The presence of this initial transformation into a cardiac mucosa has been supported by objective markers of GERD, including

- Incompetence of the lower esophageal sphincter (LES),
- Increased acid exposure in the esophagus on 24-h pH monitoring,
- Erosive esophagitis, and
- The presence of a hiatal hernia

- B) In the second pathway, the cardiac mucosa undergoes expression of **intestinal genes** causing the formation of goblet cells within the columnar mucosa, this is known as **intestinal differentiation**



The Role of gastro-biliary Reflux

- There is a substantial evidence that the development of intestinal metaplasia is a consummation from the interplay of both the acid and bile reflux into the esophagus.
- The Acid reflux results in the formation of a pH gradients along the metaplastic segments that enables the optimal bile salt solubility and hence its entrance into the epithelial cells causing activation of signaling pathways involved in BE
- The bile salts also cause injury to the epithelial organelles including the mitochondria leading to generation of ROS, oxidative stress and DNA damage
- Bile salts also induces a pro-inflammatory cytokines which activates the NF-kB P.W therefore preventing apoptosis

Other activities of Bile salts in the esophageal epithelium

- NF-kB activation by the bile salts leads to activation of CDX2, which in necessary in the intestinal differentiation and development of intestinal metaplasia.
- NF-kB also directly activates MUC2 which is needed for cellular reprograming from squamous to intestinal differentiation.
- Inhibition of NOTCH signaling PW: Bile acid inhibition of Notch signaling in esophageal cells is correlated with an increase in Hath1 and CDX2 and may be one of the key processes contributing to the formation of BE.
- Bile salts also activates the Hedgehog signaling pathway, a pw that is normally observed during embryogenesis, and absent in squamous epithelium. Hh also leads to the expression of SOX9 which is normally expressed in the colon.

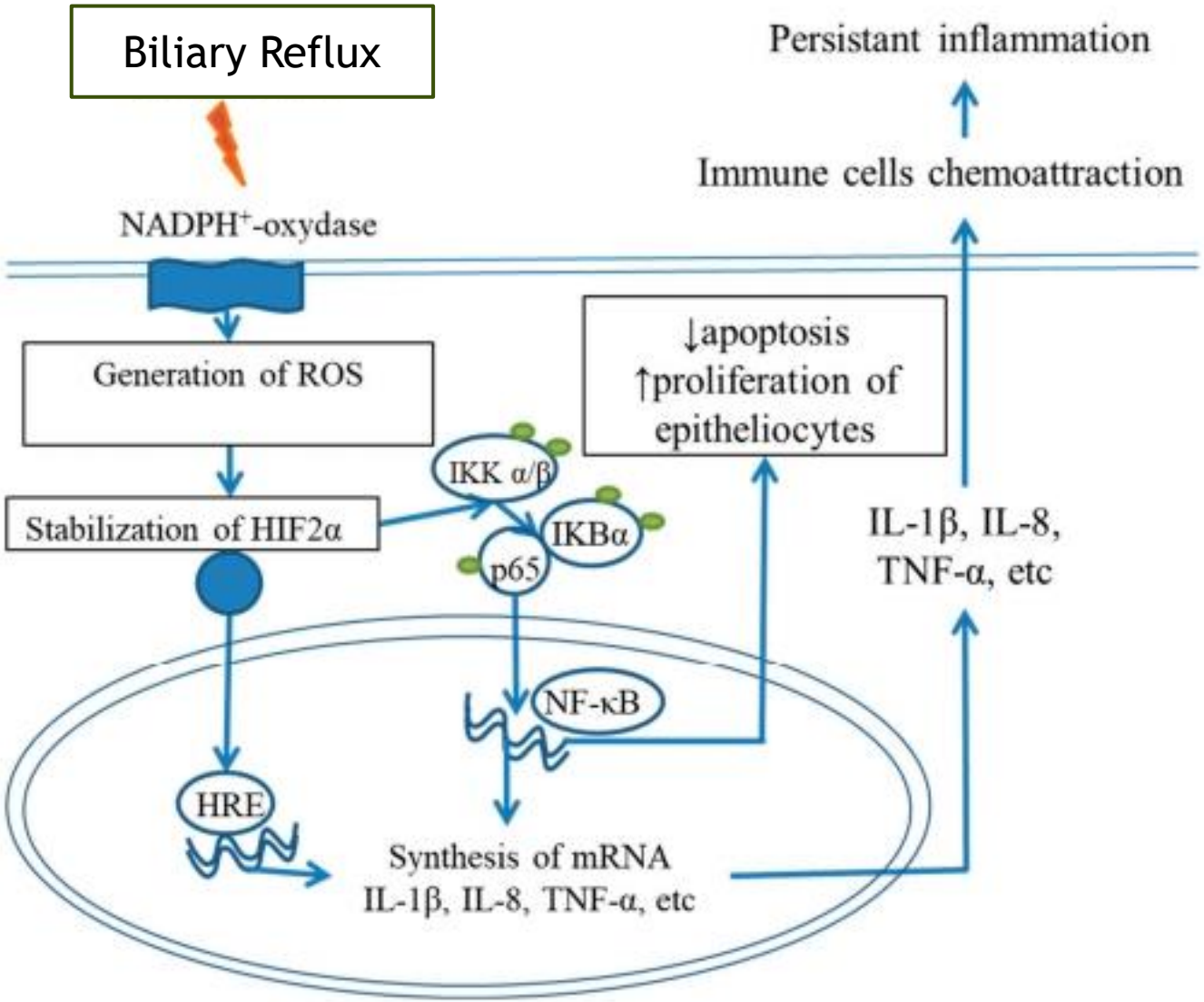


Figure 4. NF-κB signaling pathway in the pathogenesis of reflux esophagitis and BE. Blue arrows indicate positive regulation of a signaling pathway.

Bcl-xL and Bcl2 are anti-apoptotic

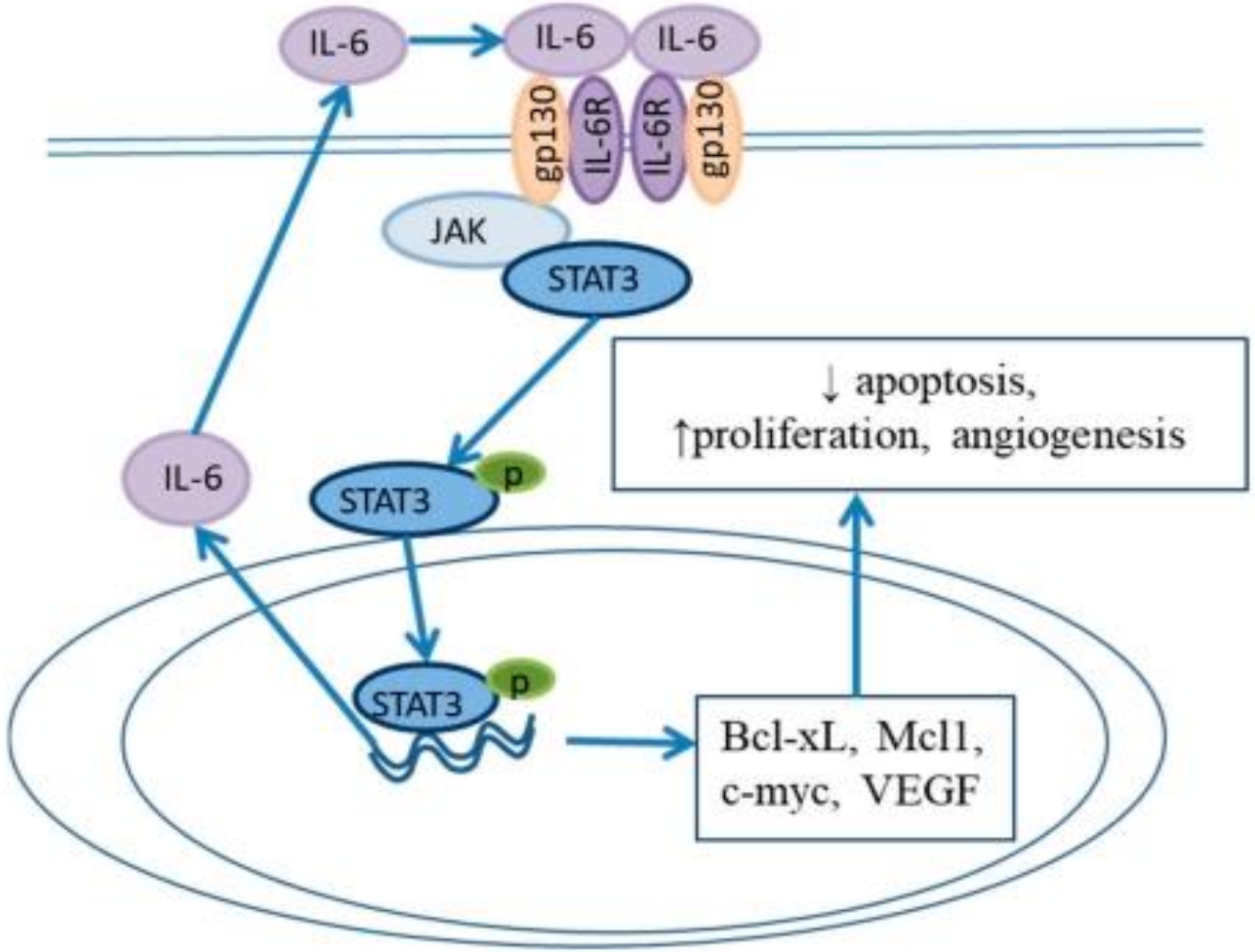


Figure 5. The IL-6/STAT3 signaling pathway in BE. Blue arrows indicate the positive regulation of a signaling pathway.

Possible Cellular origins of the BE-SC&PCells

- The most established hypothesis in the origin of BE is the trans-commitment of multipotent stem cells and progenitor cells
- It has been postulated that different progenitor cells might be involved in the pathogenesis of BE, and hence the heterogeneity and the polyclonal as well as the mosaic-like spread of the metaplastic glands
- The proposed 6 cellular origins are
- 1. Stem cells and Progenitor cells of the squamous epithelium,
- 2. Stem cells and progenitor cells of the GEJ
- 3. SC and progenitor cells of the submucosal glands and ducts,
- 4. SC and progenitor cells of the first Oxyntic glands of the stomach,
- 5. Stem cells and progenitor cells of residual embryonic cells and
- 6. circulating Bone marrow derived multipotent stem cells.

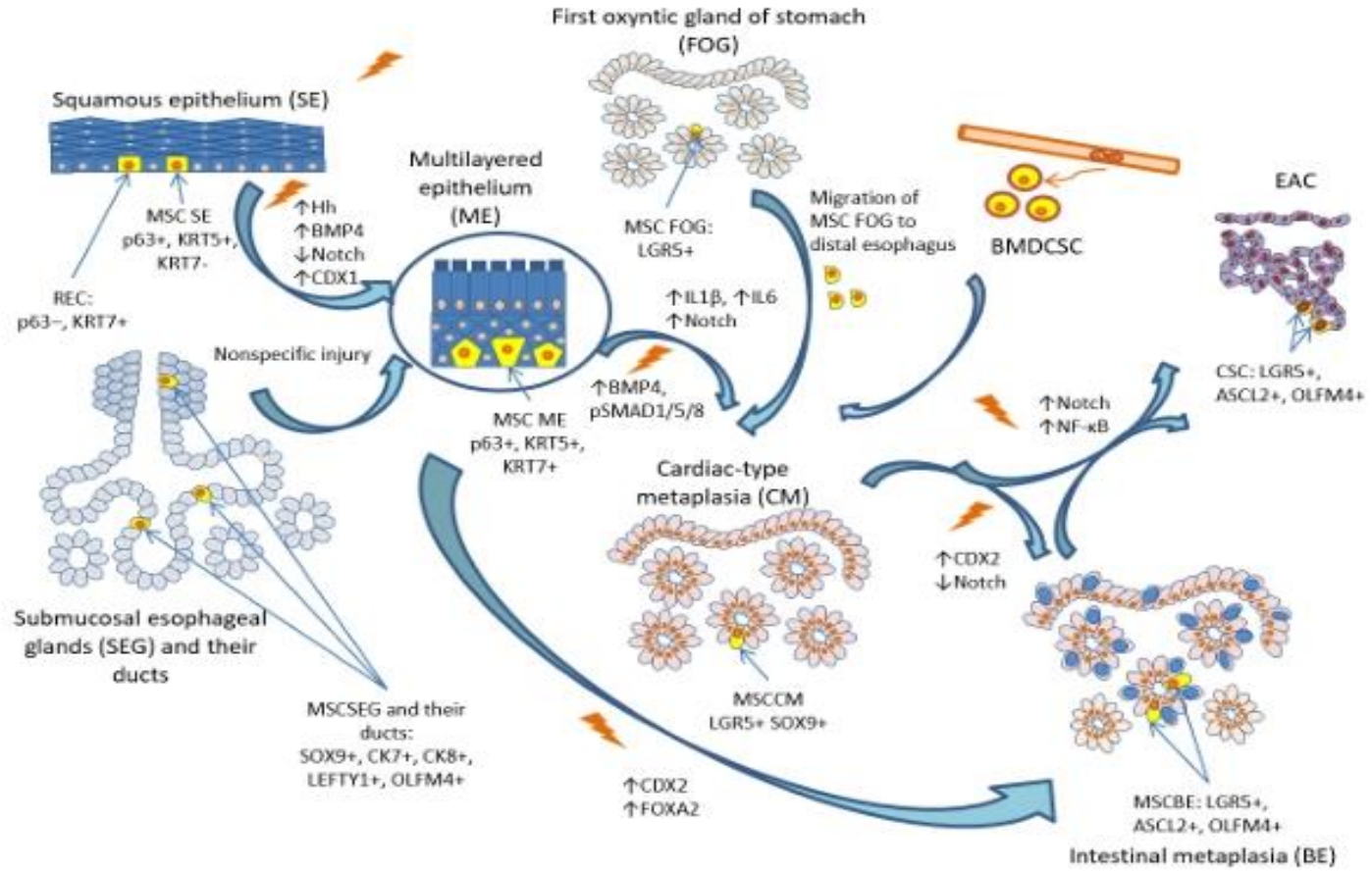


Figure 3. Cellular origins of metaplasia and pathogenesis of BE and EAC. Abbreviations: SE, squamous epithelium; MSCSE, multipotent stem cells of squamous epithelium; REC, residual embryonic cells; ME, multilayered epithelium; MSCME, multipotent stem cells of multilayered epithelium; SEG, submucosal esophageal glands; MSCSEG, multipotent stem cells of submucosal esophageal glands; FOG, first oxyntic gland of the stomach; MSCFOG, multipotent stem cells of the first oxyntic gland of the stomach; BMDCSC, bone-marrow-derived circulating stem cells; CM, cardiac-type metaplasia; BE, Barrett's esophagus; SCBE, stem cells associated with Barrett's esophagus; EAC, esophageal adenocarcinoma; CSC, cancer-associated stem cells.

Genetic events associated with development of Barrett's esophagus

The neoplastic progression in BE and esophageal adenocarcinoma (EAC) can be explained by several important molecular and genetic events, one of which is the loss of heterozygosity (LOH) of a gene.

The commonest LOH in BE and EAC is in locus 9p21 and 17p13, involving genes CDKN2A and TP53.

Inactivation of CDKN2A is believed to be the earliest inciting event of dysplasia and pathogenesis in BE

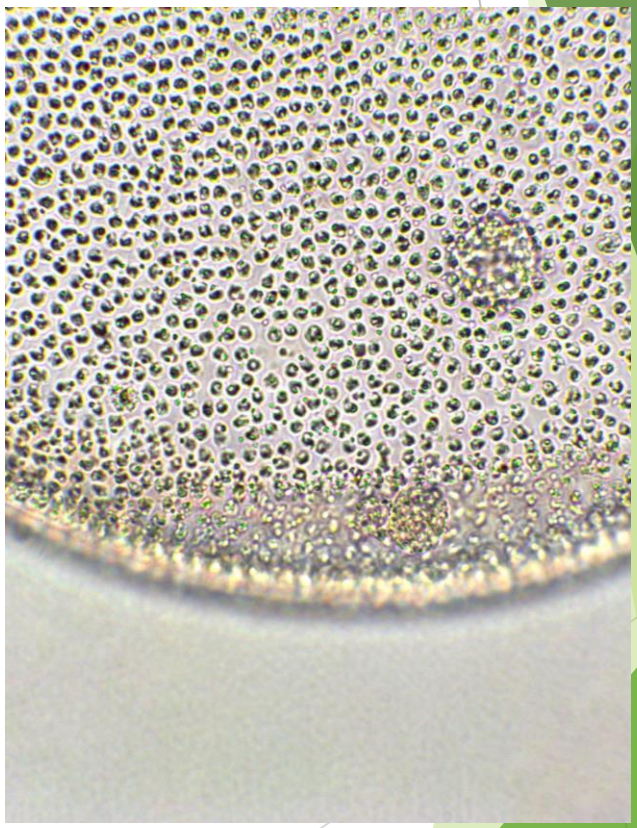
TP53 is responsible for progression and accumulation of mutations, about 72–82.6% of TP53 mutations are identified in EAC, it is also suspected that mutations in TP53 are present before visible endoscopic detection of dysplasia

Risk factors associated with Barrett's

- In the United States, Barrett's esophagus shows the highest prevalence in:
- White individuals over 50 years of age as compared to Hispanic or Asian descent,
- and lowest in Black individuals.

There are several other factors that predispose to the development of Barrett's esophagus, including

- GERD, peptic stricture, and erosive esophagitis—which confers a fivefold increased risk of Barrett's esophagus at five-year follow up (relative risk ratio [RRR] 5.2, 95% CI 1.2–22.9)
- body mass index (BMI) > 30 kg/m2 as compared to patients with (BMI) < 30 (odds ratio (OR) 1.4, 95% CI 1.1–1.6)
- Similar studies have found that a high waist-to-hip-ratio (0.9 in males and 0.85 in females) is associated with an increased risk of Barrett's esophagus



Screening for Barrett's

- Screening with endoscopy is not feasible or justified for an unselected population with gastro-esophageal reflux symptoms
- Endoscopic screening can be considered in patients with chronic GORD symptoms and multiple risk factors, at least three of

  1.age 50 years or older,

  2. white race,

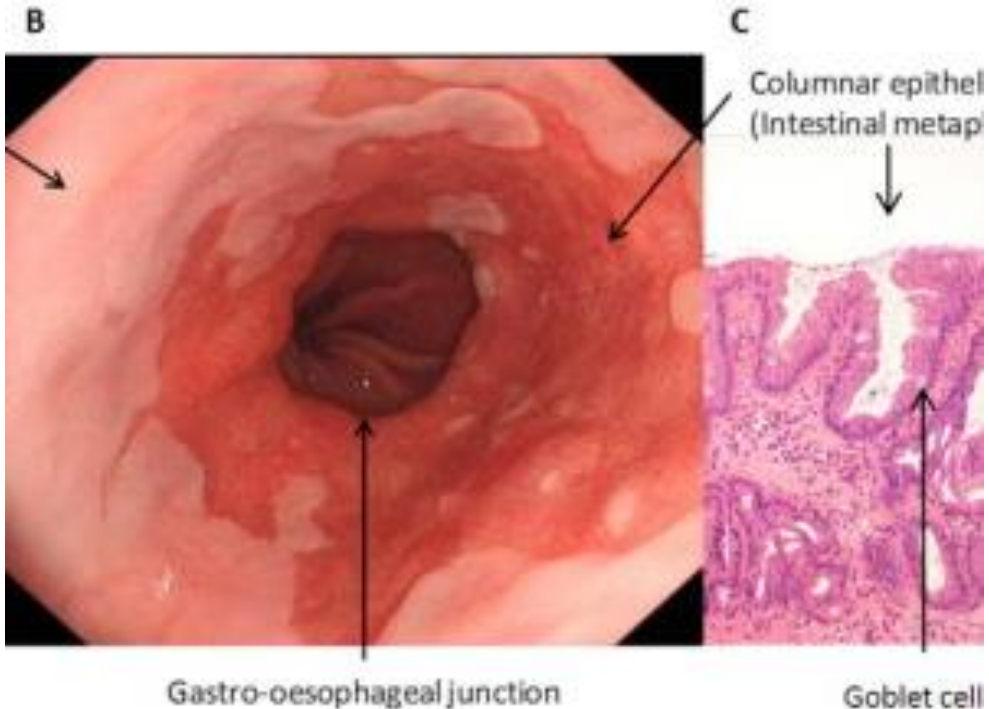
  3. male sex,

  4. obesity.

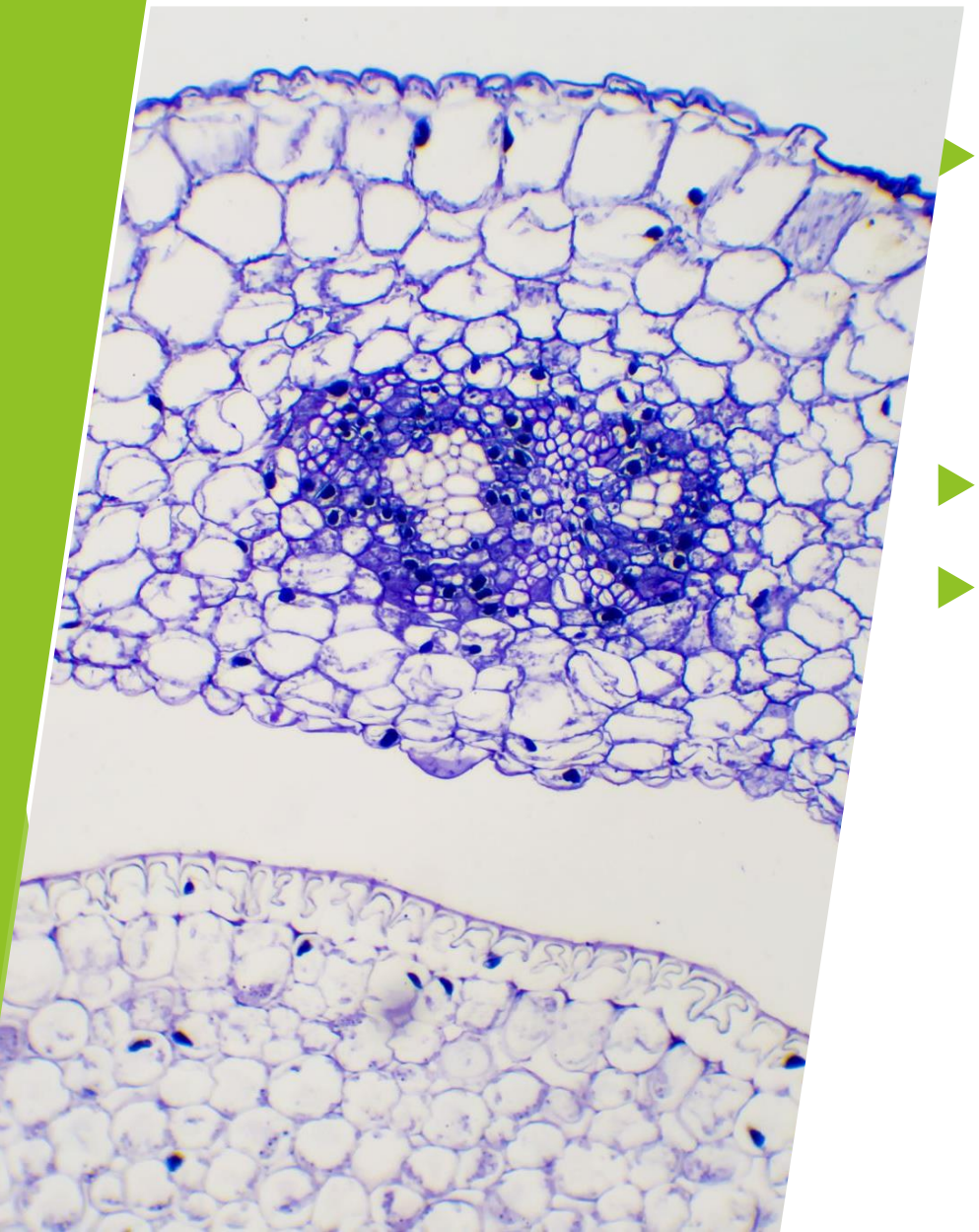
- However, the threshold of multiple risk factors should be lowered in the presence of family history including at least one first-degree relative with Barrett's or EAC

Diagnosis of Barrett’s

- The diagnosis of Barrett’s esophagus is a combination of several components, including
- recognition during endoscopy, (columnar epithelium more than 1 cm above the proximal margin of the gastric folds, based on the universally accepted Prague criteria)
- appropriately targeted biopsies, and
- histologic confirmation of columnar metaplasia Histologic



Histology



- confirmation of Barrett’s esophagus shows a combination of intestinalized columnar cells, gastric fundic and gastric cardia type cells present in the mucosa
- at least eight biopsies are obtained.
- Also, the greater the overall length of columnar lined epithelium, the higher the likelihood in the diagnostic yield of biopsies obtained from that segment

Non-endoscopic technologies in screening

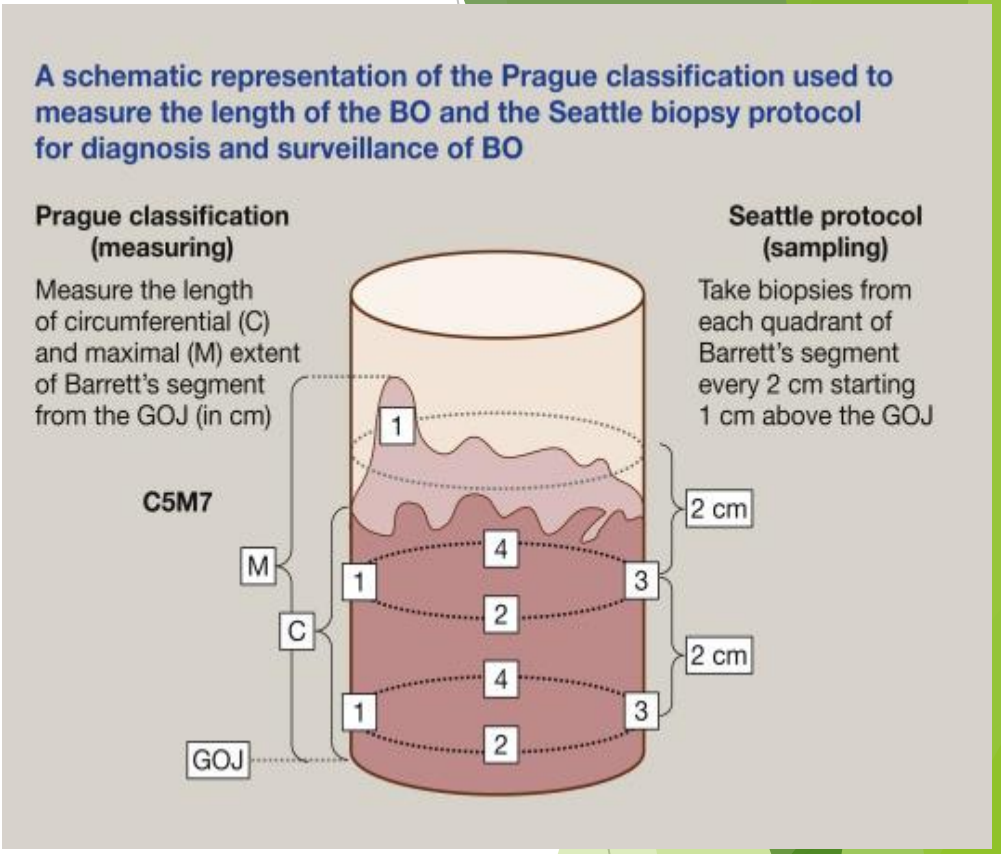
- ESGE recommends that a swallowable non-endoscopic cell collection device such as the Cytosponge, combined with a cytopathologic assessment and biomarker Trefoil-factor3 (TFF3) can be used as an alternative to endoscopy for case finding of BE.
- Other non-endoscopic technologies cannot yet be recommended eg (EsophaCap, or an inflatable silicon balloon, such as the Eso-Check.). **Strong recommendation, high quality of evidence for Cytosponge, low quality of evidence for other non-endoscopic technologies.**

Adjunctive markers of dysplasia

- 1) Markers of cell proliferation(proliferative cell nuclear antigen and Ki-67)
- 2) Cyclin D and 3) P53
- The distribution of Ki-67 staining correlates reasonably well with the degree of dysplasia, however, regenerating epithelium can also demonstrate increase cell proliferation
- Also, P53 staining had been shown to be proportional to the grade of the dysplasia an may have a predictive value in assessing the risk of malignancy. Kastelein et al reported aberrant p53 staining in 11% of biopsies without dysplasia, 38% in LGD, 83% in HGD and 100% in EAC.
- Other markers includes alpha methyl acyl-CoA, and Loss of Membrane Agrin(AGRN) shown in BE related dysplasia and EAC with spec-82.2% and sen. 96.4%

Surveillance

- Surveillance techniques should utilize **high-resolution white light endoscopy** to properly evaluate the mucosa in a thorough manner including insufflation of the lumen, retroflexion and inspection of the gastroesophageal junction
- The gold-standard for tissue sampling of Barrett's esophagus is the Seattle Protocol, first described in 1993, which consists of four-quadrant biopsies at intervals of every 1–2 cm
- and separate samples of areas identified by mucosal irregularity along the entire involved segment



Surveillance(endoscopy)

- A minimum of 1-minute inspection time per cm of BE length during a surveillance endoscopy
- photo-documentation of landmarks, the BE segment including one picture per cm of BE length, and the esophagogastric junction in retroflexed position, and any visible lesions
- use of the Prague and (for visible lesions) Paris classification
- collection of biopsies from all visible abnormalities (if present), followed by random four-quadrant biopsies for every 2-cm BE length.
- In patients with BE undergoing surveillance, we recommend using chromoendoscopy, including virtual chromoendoscopy and Seattle protocol biopsy sampling, compared with white-light endoscopy with Seattle protocol biopsy sampling.

Surveillance continue

For BE with a maximum extent of ≥1cm and < 3 cm, BE surveillance should be repeated every 5 years

For BE with a maximum extent of ≥3cm and <10cm, the interval for endoscopic surveillance should be 3 years.

Patients with BE with a maximum extent of ≥ 10cm should be referred to a BE expert center for surveillance endoscopies.

For patients with an irregular Z-line/columnar-lined esophagus of < 1 cm, no routine biopsies or endoscopic surveillance are advised.

Biopsies should not be obtained in mucosal areas with endoscopic evidence of erosive esophagitis until after intensification of anti-reflux therapy to induce mucosal healing

Table 3
Recommendations for surveillance and management of Barrett's esophagus

Society (year)	Negative for Dysplasia	Indefinite for Dysplasia	Low-Grade Dysplasia	High-Grade Dysplasia
AGA (2011)	EGD every 3–5 y	Not specified	• EGD every 6–12 mo • Consider endoscopic eradication therapy	• EGD every 3 mo • Endoscopic eradication therapy rather than surveillance or surgery
ASGE (2012)	• EGD every 3–5 y • Consider no surveillance • Consider ablation in select cases	Repeat EGD with maximal acid suppression	• Repeat EGD in 6 mo to confirm LGD • EGD every year • Consider endoscopic therapy	• EGD every 3 mo (only patients who are not candidates for endoscopic or surgical treatment) • Consider endoscopic treatment • Consider surgical consultation
BSG (2014)	• Irregular Z-line: no surveillance • BE < 3 cm without IM: no surveillance • BE < 3 cm with IM: EGD every 3–5 y • BE ≥ 3 cm: EGD every 2–3 y • Consider no surveillance on the basis of patient's fitness and risk of progression	Repeat EGD at 6 mo with maximal acid suppression	• Surveillance: EGD every 6 mo • Ablation cannot be recommended routinely	• Mucosal irregularity: EMR • Endoscopic therapy is preferred over esophagectomy or surveillance
ACG (2016)	EGD every 3–5 y	• Repeat EGD at 3–6 mo after optimization of acid suppression • Persistent indefinite for dysplasia: EGD after 1 y	• Endoscopic treatment (patients without life-limiting comorbidity) • EGD every 12 mo	Endoscopic treatment (patients without life-limiting comorbidity)

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Table 3
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Society (year)	Negative for Dysplasia	Indefinite for Dysplasia	Low-Grade Dysplasia	High-Grade Dysplasia
ESGE (2017)	• BE < 1 cm: no surveillance • BE 1–3 cm: EGD every 5 y • BE 3–10 cm: EGD every 3 y • BE ≥ 10 cm: referral to BE expert center • Consider discharge for patients with limited life expectancy and advanced age	Repeat EGD at 6 mo with optimization of antireflux medication	• Repeat EGD at 6 mo • If persistent LGD: endoscopic ablation	• Repeat EGD • Visible irregularity: EMR • Persistent HGD: ablation • No dysplasia: repeat EGD 3 mo

Abbreviations: ACG, American College of Gastroenterology; AGA, American Gastroenterological Association, ASGE; American Society for Gastrointestinal Endoscopy, BSG; British Society of Gastroenterology; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection, ESGE; European Society of Gastrointestinal Endoscopy.

Indefinite for dysplasia

If the initial biopsies reveal indefinite for dysplasia, then anti-reflux therapy is optimized, often with a proton-pump-inhibitor to B.D dosing, if the patient has not already been on high-dose therapy. A follow up endoscopy is carried out within 6 months .

If the repeat endoscopy results are indefinite dysplasia, then it is advised the patient to have a surveillance endoscopy every 12 months and if biopsy yields a diagnosis of no dysplasia or LGD/HGD

Then the protocols for each be followed according

LGD

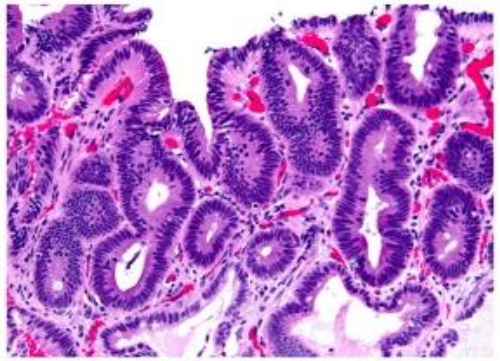


Fig. 3. Low-grade intestinal-type dysplasia in BE. The nuclei are stratified and pencil-shaped but are limited to the lower half of the cytoplasm. The architecture is similar to that of non-dysplastic epithelium.

- If the initial biopsies reveal LGD, then it is recommended that this is confirmed by a second pathologist to ensure the LGD diagnosis is correct and to be certain that there
- is no HGD or EAC present.
- Endoscopic therapy is also suggested to reduce the risk of
- progression to HGD/EAC.
- Endoscopic surveillance is an acceptable option and if selected, is recommended at 6 months, 12 months, and then annually thereafter

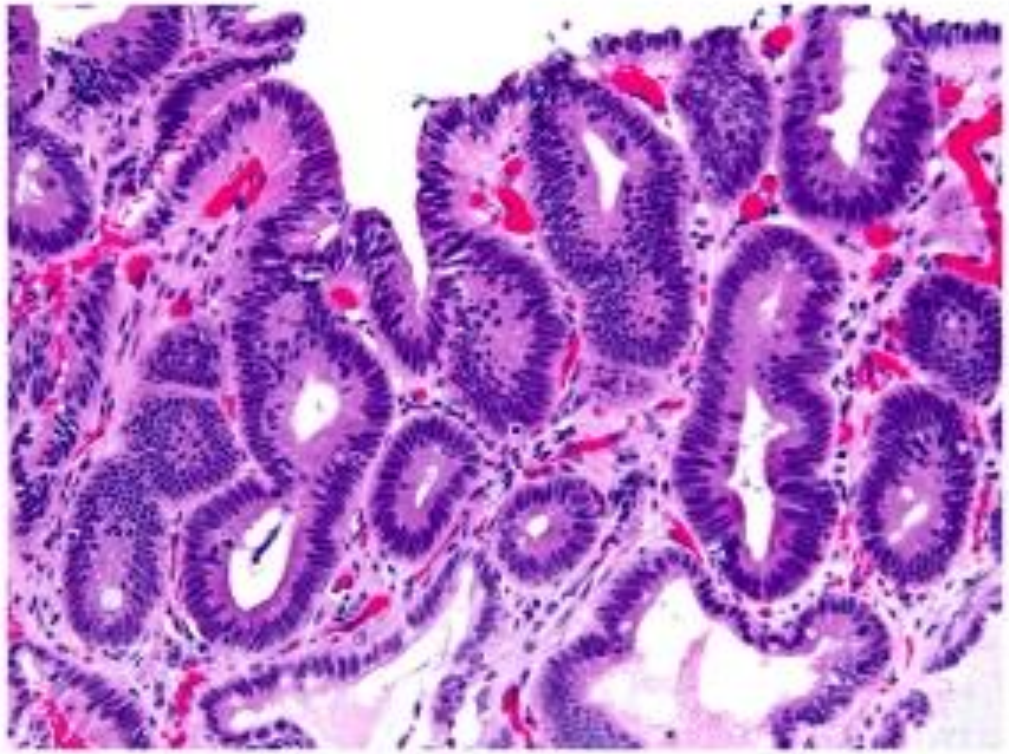


Fig. 3. Low-grade intestinal-type dysplasia in BE. The nuclei are stratified and pencil-shaped but are limited to the lower half of the cytoplasm. The architecture is similar to that of non-dysplastic epithelium.

HGD

- If biopsy initially reveals HGD or if known Barrett's esophagus progresses to HGD then surveillance is no longer recommended and esophagectomy or endoscopic eradication therapy (EET) should be considered.

A recent systematic review and meta-analysis demonstrated no difference between EET and esophagectomy regarding overall 1-, 3-, and 5-year survival and EAC mortality. However, lower rates of adverse events were noted in those undergoing EET compared with esophagectomy

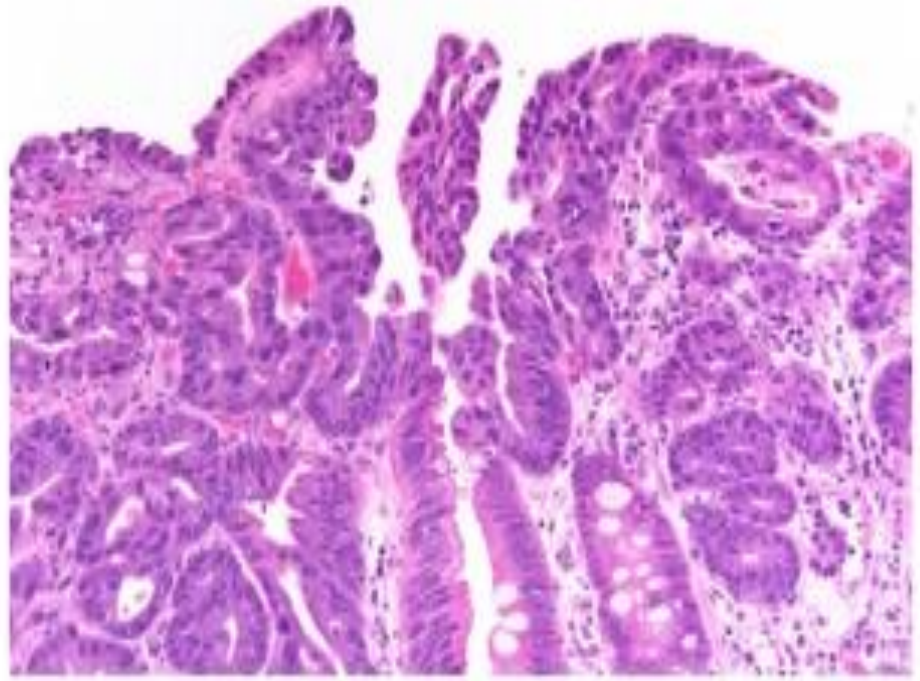


Fig. 4. High-grade dysplasia intestinal-type dysplasia in BE. In contrast to LGD (see Fig. 3), there is a greater degree of nuclear enlargement, pleomorphism, and loss of nuclear polarity. In this example, the glands show crowded architecture with focal cribriform arrangement (left lower aspect of image).

Why confirmation of diagnosis with a second pathologist?

- Several studies have shown significant intra-observer variability in the diagnosis of Barrett's esophagus, particularly with indeterminate for dysplasia (IND) and low-grade dysplasia (LGD).

- There have also been studies demonstrating cases of LGD being mistaken for nondysplastic or IND BE due to esophageal inflammation.

Advanced imaging to detect Barrett's of areas of abnormalities

- Current standards recommend –
- a high-quality endoscopic examination.
- with careful inspection of the BE segment
- and adherence to the Seattle protocol for tissue sampling.

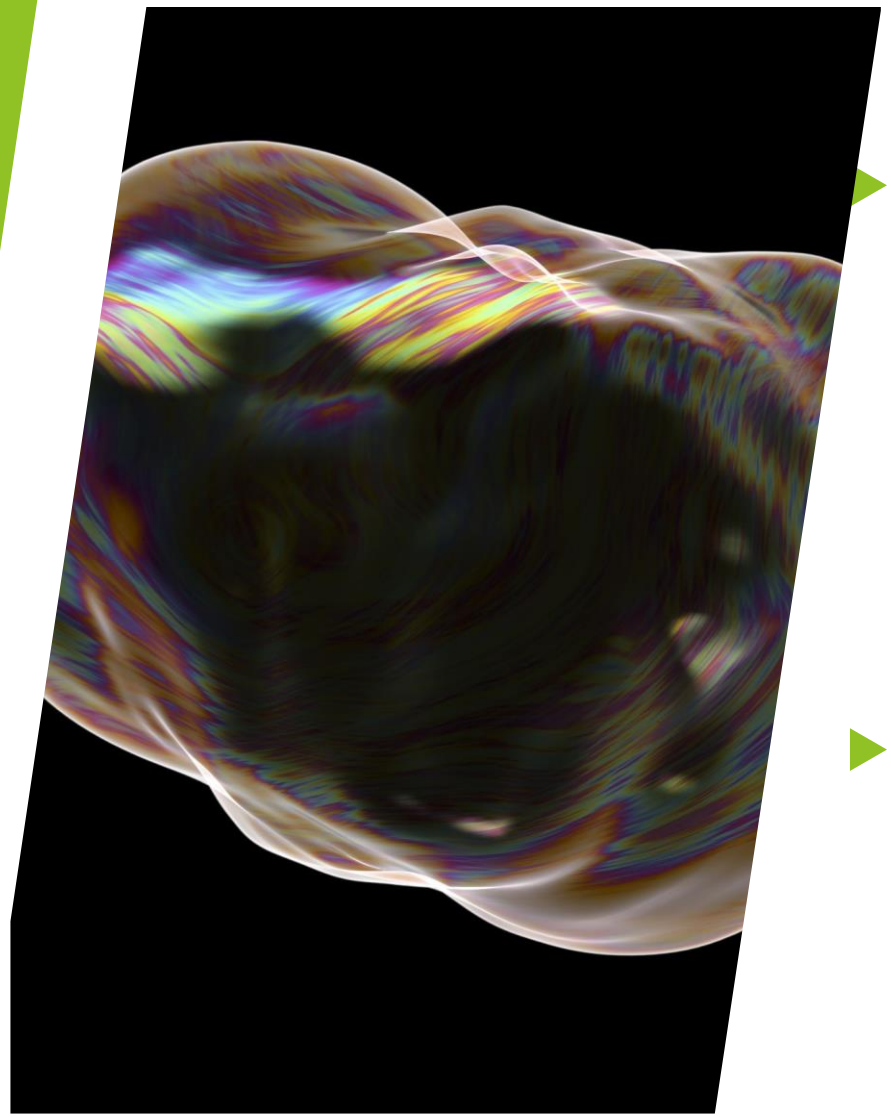
Cont.

- **Other issues to consider-** In depth visualization of abnormalities
- The majority of EAC found in BE are flat and nonpolypoid, hence could be difficult to detect.
- Random biopsy is prone to sampling error as the distribution of affected areas is highly variable; small lesions can be focal and may be easily missed

Examples of advanced endoscopic imaging modalities

- 1. Virtual chromoendoscopy
- 2. Volumetric laser chromoendoscopy uses optical coherence tomography with infrared light to produce high-resolution, cross-sectional imaging of tissue in real-time without the need for contrast
- 3. Wide-area transepithelial sampling (WATS) is a three-dimensional (3D), computer assisted technique which has been used as an adjunct to traditional forceps biopsy.
- WATS uses endoscopic abrasive brush biopsy to sample transepithelial tissue circumferentially. The biopsy samples are then captured into histologic slices which are synthesized into a 3D image.

Advanced imaging cont.



- 3) endoscopic ultrasound (EUS) and endoscopic mucosal resection (EMR) are often performed prior to endoscopic therapy of BE. EUS has been used to assess for submucosal invasion as well as the width and depth of lesion.
- In early-stage neoplasia, EUS is also used to assess lymph node involvement.

When to stop surveillance

- if a patient has reached 75 years of age at the time of the last surveillance endoscopy and/or the patient's life expectancy is less than 5 years, the discontinuation of further surveillance endoscopies can be considered.
- Weak recommendation, very low quality of evidence

Management

- Non-dysplastic Barrett’s can progress to dysplasia and subsequently to esophageal adenocarcinoma. Risk factors for progression includes
- Length of the Barrett's esophagus
- Hiatus hernia
- P53 LOH
- Aneuploidy
- Management option depends on the grade of the Barrett's.

Cont.

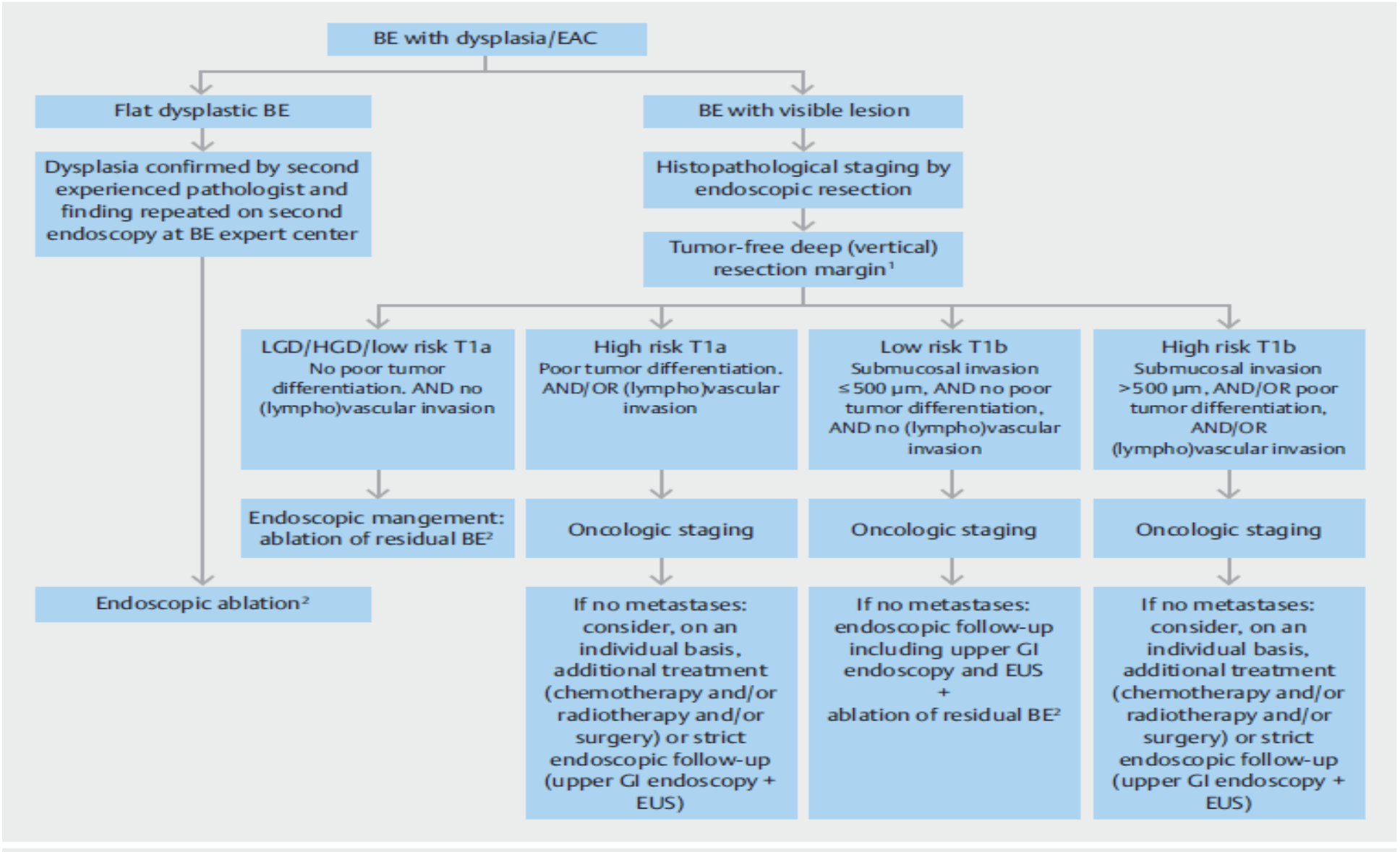
- Treatment modality depends on the grade of the Barrett's.

Options includes-

Endoscopic Eradication therapy

Surgical management

Adjunct medical management


BE with dysplasia/EAC
Flat dysplastic BE
Dysplasia confirmed by second experienced pathologist and finding repeated on second endoscopy at BE expert center
Endoscopic ablation[2]
BE with visible lesion
Histopathological staging by endoscopic resection
Tumor-free deep (vertical) resection margin[1]
LGD/HGD/low risk T1a
No poor tumor differentiation. AND no (lympho)vascular invasion
Endoscopic mangement: ablation of residual BE[2]
High risk T1a
Poor tumor differentiation. AND/OR (lympho)vascular invasion
Oncologic staging
If no metastases: consider, on an individual basis, additional treatment (chemotherapy and/or radiotherapy and/or surgery) or strict endoscopic follow-up (upper GI endoscopy + EUS)
Low risk T1b
Submucosal invasion ≤ 500 µm, AND no poor tumor differentiation, AND no (lympho)vascular invasion
Oncologic staging
If no metastases: endoscopic follow-up including upper GI endoscopy and EUS + ablation of residual BE[2]
High risk T1b
Submucosal invasion >500 µm, AND/OR poor tumor differentiation, AND/OR (lympho)vascular invasion
Oncologic staging
If no metastases: consider, on an individual basis, additional treatment (chemotherapy and/or radiotherapy and/or surgery) or strict endoscopic follow-up (upper GI endoscopy + EUS)

Non-dysplastic Barrett's

- have lower and slower progression to advanced disease.
- developed low-grade dysplasia (LGD) incidence of 4.3% per year
- It was found that 1 in 50 patients with non-dysplastic BE on multiple
- biopsies ended up progressing to high grade dysplasia at an interval of 6 years Pooled
- Incidence of HGD and EAC from non-dysplastic BE was found to be 11.2%
- BE is does not require eradication therapy and
- is recommended for surveillance endoscopy alone every 3–5 years

Low grade dysplasia

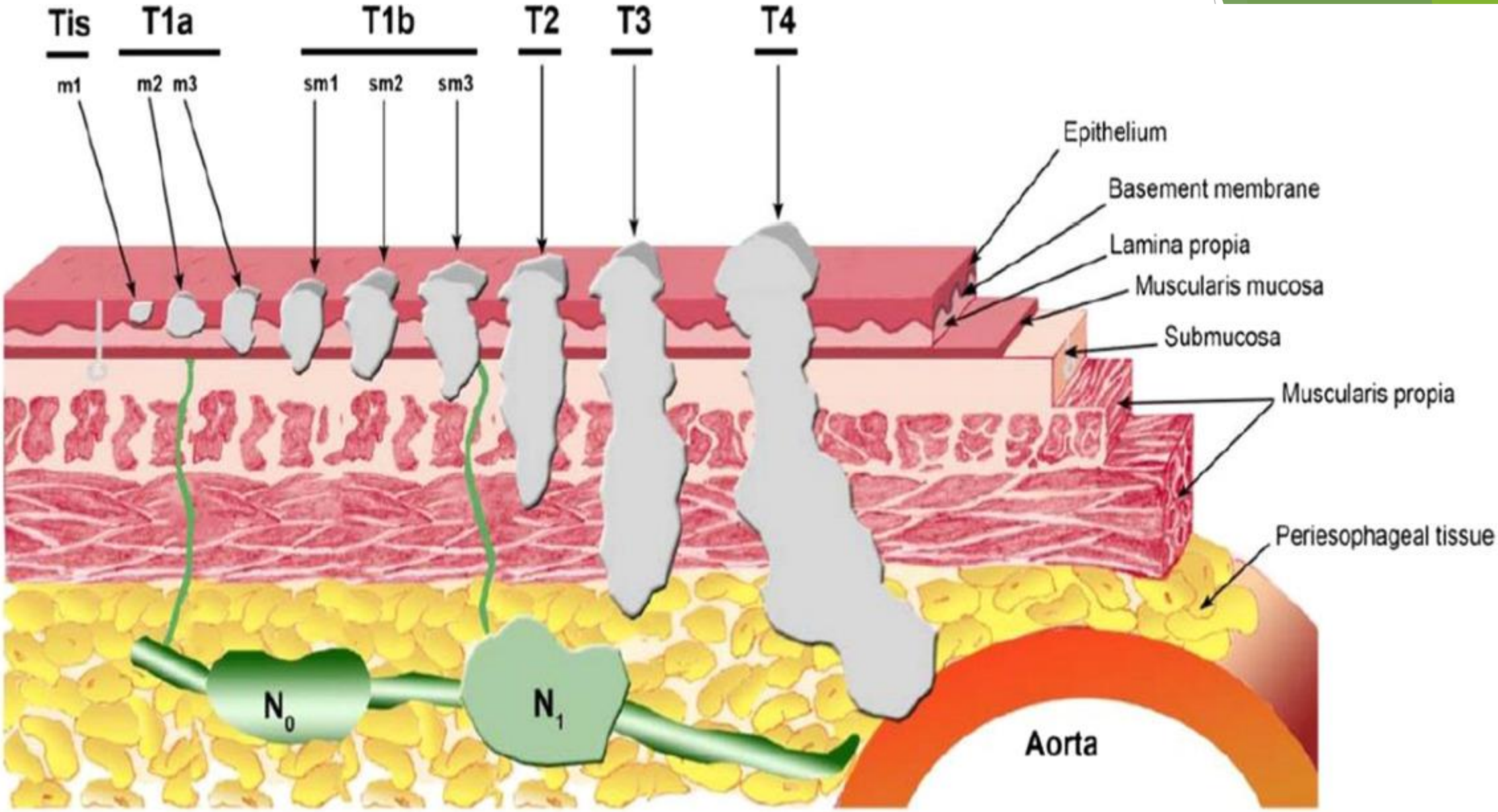
- LGD can easily be mistaken for nondysplastic lesion or indefinite for dysplasia or BE with esophagitis.
- There is a high variability of LGD diagnosis should be confirmed with an expert GI pathologist before starting treatment.
- Patients with LGD should be treated with a high dose PPI
- If repeat EGD demonstrates mucosal abnormalities or confirms LGD by histology, eradication therapy should be performed. Given moderate risk for progression of disease, careful surveillance is acceptable instead of eradication Complete
- eradication of LGD should have surveillance endoscopy 6 months following treatment and annually thereafter.

HGD

- HGD has the highest risk of progression to EAC, with a weighted EAC
- incidence rate of 6.58 per 100 patient years in patients undergoing regular surveillance, not normalizing for BE segment length
- Initial grade of dysplasia had the strongest prognostic factor and development of EAC.
- Endoscopic eradication therapy, including EMR and/or ablation therapy, is indicated in HGD given high risk of progression, complete eradication is seeing in 83.7% of patients requiring a median of two treatment sessions
- Recurrence rate, has been found to be 13.5% following treatment in the same study.
- surveillance is currently recommended more frequently (3–6 months) in the first few years following therapy, and annually thereafter.

Esophageal cancer

- Esophageal carcinoma is staged using the TNM staging system.
- Early stage EAC is divided by depth of invasion, T1a (mucosal) and T1b (submucosal).
- Because EAC prognosis is generally poor, treatment is indicated even in early T1a stage cancer.
- LN metastasis is low- 0-1.8%
- T1a is divided into moderately vs poorly differentiated types with moderately differentiated type having the better prognosis because of less lympho-vascular invasion. Therefore, T1a with moderate diff. should be have EET while poorly diff – surgical resection. Mortality risk is high in esophagectomy


Tis
T1a
T1b
T2
T3
T4
m1
m2 m3
sm1 sm2 sm3
Epithelium
Basement membrane
Lamina propia
Muscularis mucosa
Submucosa
Muscularis propia
Periesophageal tissue
N0
N1
Aorta

T1b lesions

- Submucosal (T1b) cancer has been associated with higher rates of lymph node metastases.
- They are further classified into Sm1-3 with Sm3 having the most depth with poorer prognosis.
- Sm1 and lesions less than 2cm have better prognosis, endoscopic treatment success rate of 97% had been reported in some studies however this was not confirmed in other studies.
- Given confounding results, careful assessment of submucosal invasion and assessment of lympho-vascular involvement imaging by PET, CT, and/or EUS is advised.

T2

- Locally advanced esophageal cancer which invades the muscularis propria (T2)
- It is aggressive, characterized by poor 5-year survival, ranging from 17.1% to 23% even in patients who received treatment.
- Rx-neoadjuvant chemoradiotherapy plus surgical resection which shows survival benefit over treatment by surgery alone; survival rates at 5 years for each has been found to be 47% and 33%, respectively

Treatment modalities

- **Endoscopic mucosal Resection**: (EMR) is a widely used technique for diagnosing and eradicating superficial BE dysplasia and neoplasia.
- This technique involves endoscopic evaluation of mucosal tissue, followed by targeted resection of visible mucosal abnormalities suggestive of dysplasia.
- The pooled efficacy(CE-IM) was 79.6% and complete eradication of neoplasia (CE-N) was 94.9%, with substantial heterogeneity (I2 > 25%) .
- Risk of recurrence is associated with fragmented resection technique and longer BE segment. Pooled recurrence rate for EMR was 0.7% for EAC, 3.3% for dysplasia, and 12.1% for intestinal metaplasia

ESD

- **Endoscopic submucosal dissection** (ESD) is a technique, initially created for resection of gastric tumors, which utilizes en bloc resection.
- This modality aims to remove entire lesions, accommodating for varying widths and depths
- Pooled data demonstrated ESD cure rate of 92.3% compared to that of EMR with 52.7% cure rate ($p < 0.001$) and found significantly lower recurrence rate in ESD (0.3%) compared to EMR (11.5%) ($p < 0.001$) . For the same reason, ESD are being used to treat submucosal (T1b-Sm1) lesions.

RFA

- RFA can be employed to eradicate circumferential areas of dysplastic BE.
- It is often used in conjunction with EMR for complete diagnosis and
- treatment; nodular BE requiring EMR for appropriate resection and non-nodular BE benefiting from targeted or focal ablation.
- RFA is widely accepted as first-line therapy given efficacy and safety; however, adverse effects can include, most commonly, strictures, bleeding, and pain.

Cryotherapy

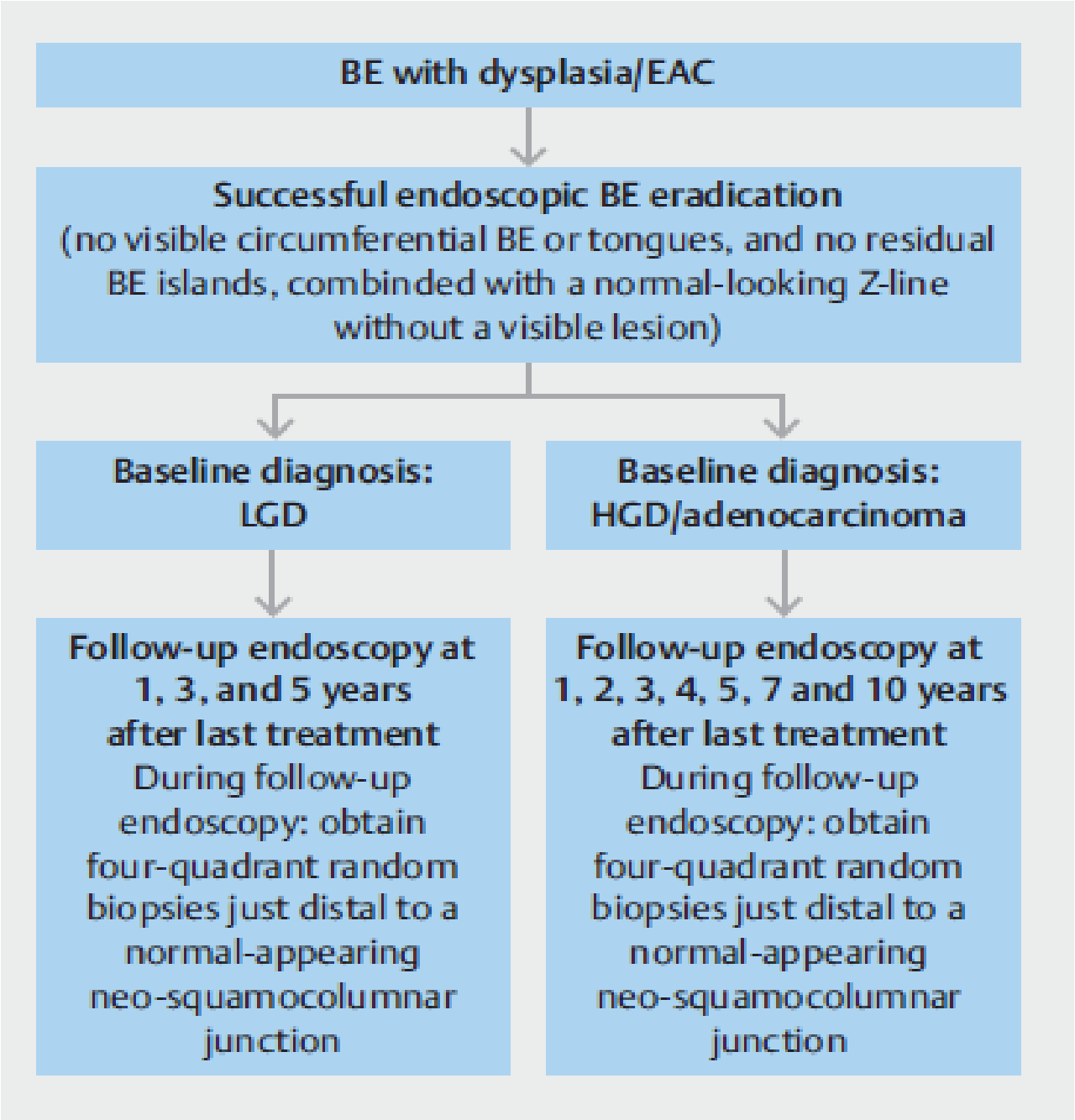
Cryotherapy involves cold-temperature ablation and can be performed via various techniques; liquid nitrogen spray, compressed carbon dioxide or cryo-balloon therapy.

Can be performed 3 monthly

Said to be safer than RFA because of less tissue destruction, less strictures and less pain, however no head –to- head trial

Hybrid argon Coagulation

- Hybrid argon plasma coagulation (APC) ablation is a technique which uses the combination of a submucosal injection of saline followed by APC ablation.
- In a prospective, multi-center study, it was found that CE-IM was achieved in 88.4% of hybrid APC cases and CE-N was achieved in 98%.


BE with dysplasia/EAC
Successful endoscopic BE eradication
(no visible circumferential BE or tongues, and no residual BE islands, combinded with a normal-looking Z-line without a visible lesion)
Baseline diagnosis: LGD
Baseline diagnosis: HGD/adenocarcinoma
Follow-up endoscopy at 1, 3, and 5 years after last treatment
During follow-up endoscopy: obtain four-quadrant random biopsies just distal to a normal-appearing neo-squamocolumnar junction
Follow-up endoscopy at 1, 2, 3, 4, 5, 7 and 10 years after last treatment
During follow-up endoscopy: obtain four-quadrant random biopsies just distal to a normal-appearing neo-squamocolumnar junction

Management post endoscopic eradication of BE

- Acid reflux is the driving force in the initial development of BE
- Adequate acid suppression treatment is therefore considered a cornerstone of patient management after eradication of BE
- Based on common practice in BE expert centers, we recommend double-dose PPI (equivalent to omeprazole 40mg b. i. d.) during EET