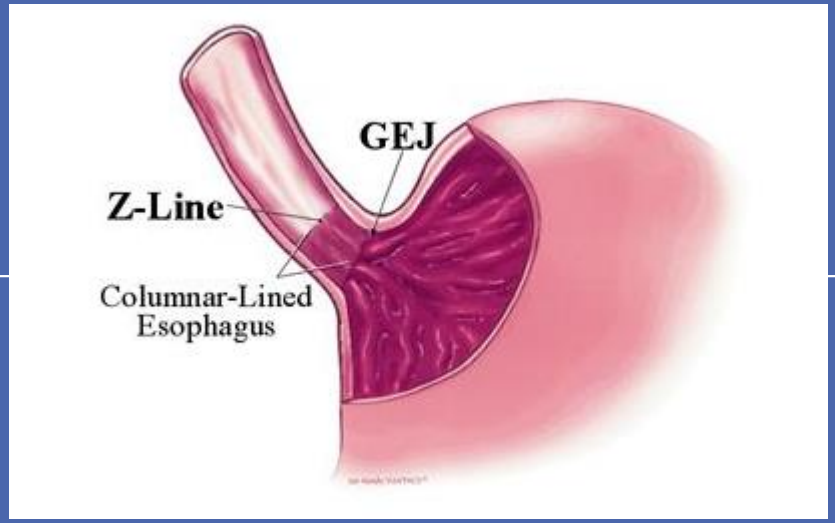
Barrett's esophagus



Masoodi M. MD

- Symptoms of Barrett's esophagus ?

CLINICAL FEATURES

- Barrett's esophagus causes no symptoms.
- Most patients are seen initially for symptoms of associated GERD, such as heartburn, regurgitation, and dysphagia.
- GERD associated with long-segment Barrett's esophagus frequently is complicated by esophageal ulceration, stricture, and hemorrhage
- Erosive esophagitis is an independent risk factor for Barrett's esophagus, conferring a fivefold increased risk of Barrett's
- Studies have suggested that patients with a peptic stricture , White individuals, age > 50 years, central obesity, tobacco use, have a higher prevalence of Barrett's esophagus.

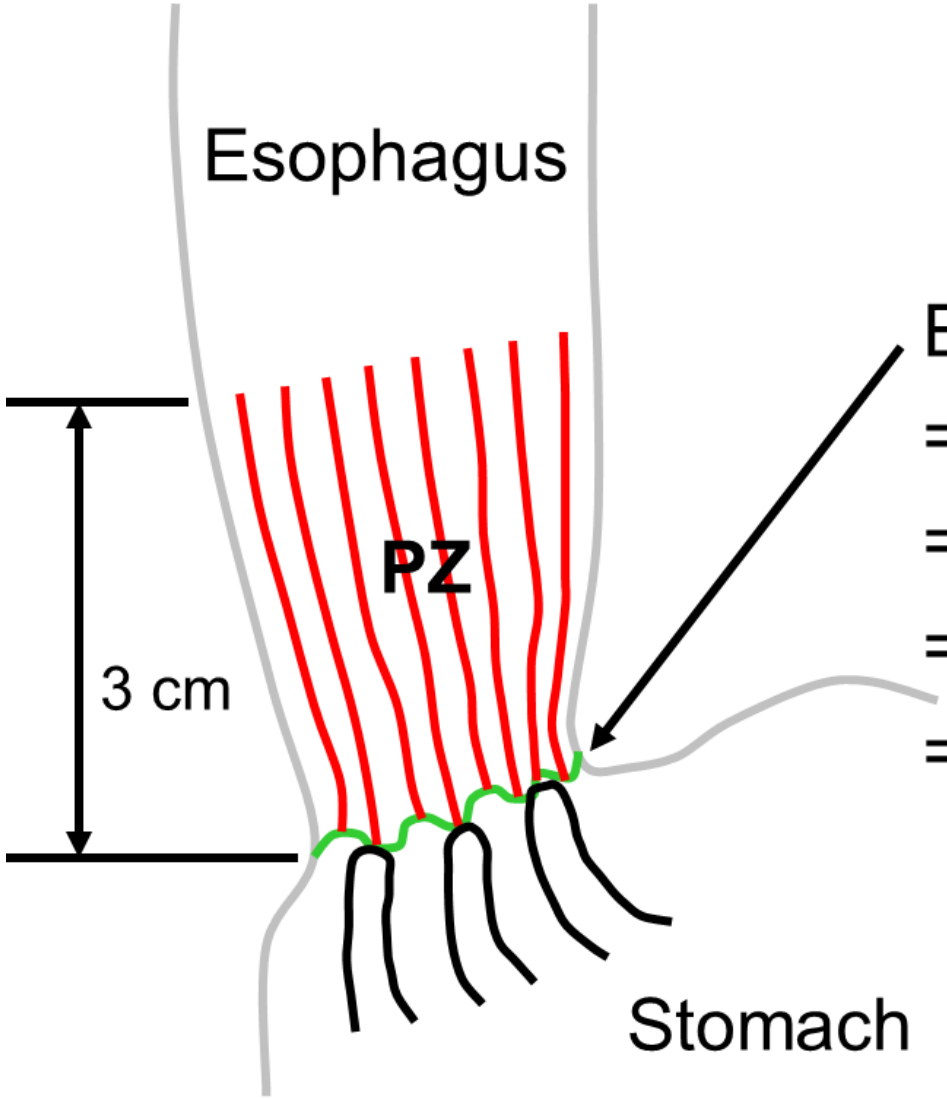
- GEJ is defined as?

GEJ is defined as:

- Distal end of the lower esophageal palisade vessels
  - visualising the distal end of the palisade vessels, which lie in the oesophageal mucosa but penetrate the submucosal layer at the level of the GEJ

- Upper end of the gastric longitudinal folds *with minimal air insufflation*

  - Palisade vessels had lower interobserver reliability
  - Theoretically, the two landmarks should coincide at the GEJ; however, the presence of esophagitis, the degree of insufflation, vascular anatomical variants of the oesophageal vessels, as well as respiration and peristalsis can make the correspondence between these two landmarks inconsistent



Esophagogastric junction (EGJ)

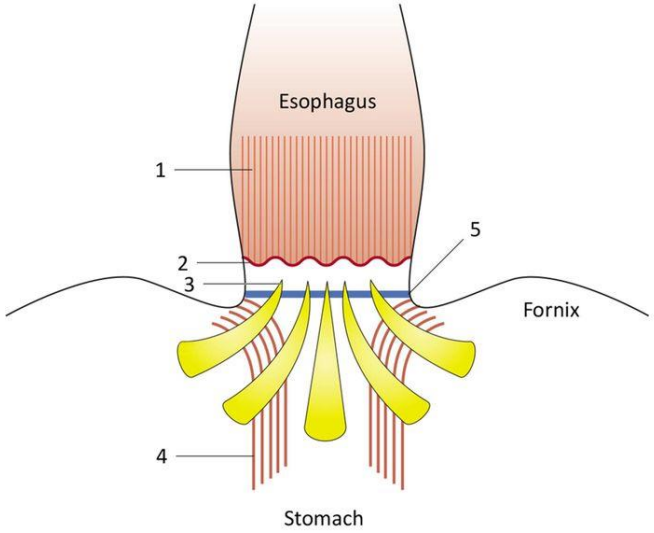
= Proximal margin of gastric folds

= Distal end of palisade zone

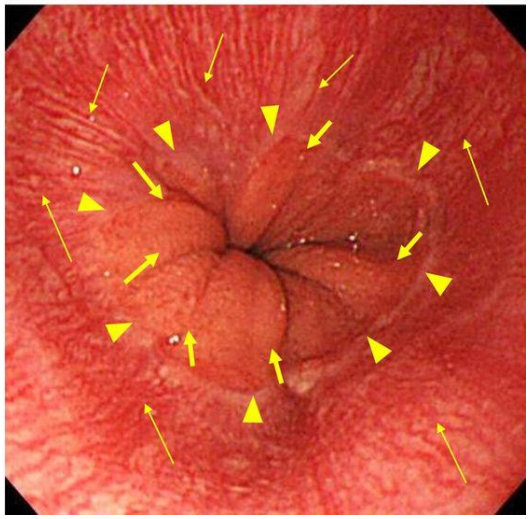
= Pinchcock action (PCA)

= Squamocolumnar junction

A



B



(A) Schema of the landmarks used for GOJ. Endoscopic view of the GOJ.

- (1) palisade vessels
- (2) squamocolumnar junctional line (Z line)
- (3) proximal end of the gastric folds
- (4) gastric sling fibres
- (5) angle of His.

(B) Palisade vessels (thin arrows), squamocolumnar junctional line (Z-line) (arrow heads) and the end of gastric folds (thick arrows) are shown. These three landmarks (distal end of palisade vessels, Z-line and proximal end of gastric folds) are closely aligned with each other in normal subjects.

Barrett's esophagus

- **Endoscopic grading ?**
- **Diagnostic criteria ?**

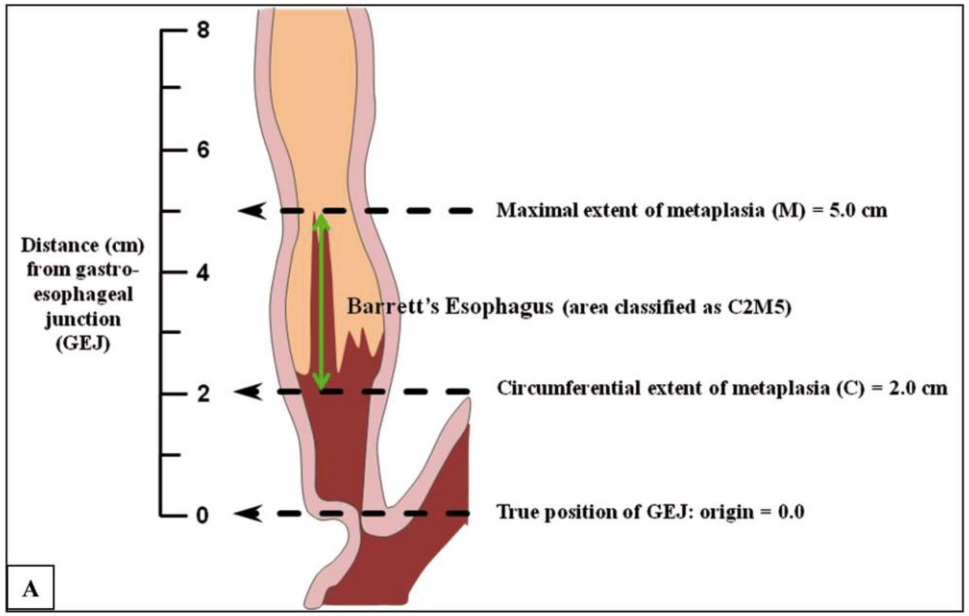
An endoscopic grading system (The Prague C & M Criteria)

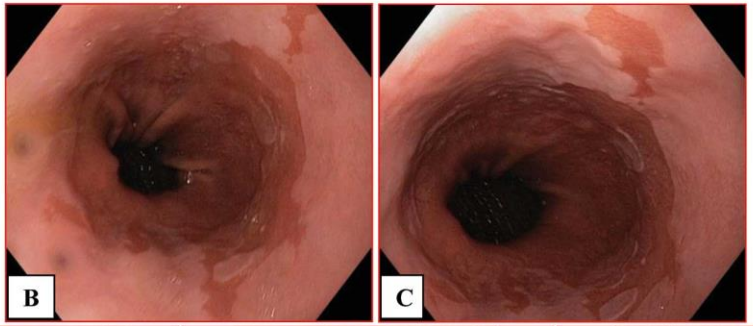
The criteria are based upon assessment of the:

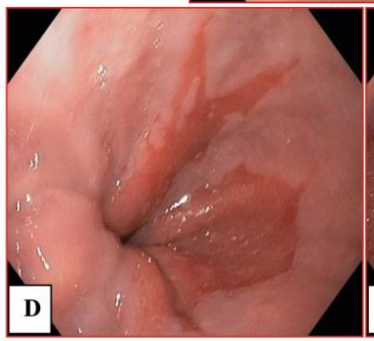
- Circumferential extent (the C value)
- Maximum extent (the M value)

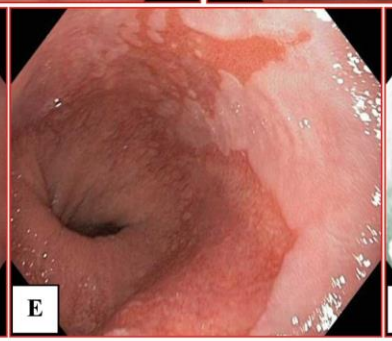
of metaplastic epithelium above the GEJ

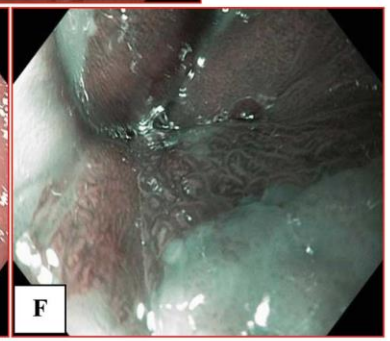
- It should be noted that isolated segments or lesions with appearance of intestinal metaplasia are not measured or included in this classification system











PRAGUE CRITERIA
For Endoscopically Suspected Esophageal Columnar Metaplasia/Barrett's Esophagus

Developed by the Barrett's Oesophagus Subgroup of the International Working Group for the Classification of Reflux Oesophagitis (IWGCO)

IWGCO – International Working Group for the Classification of Oesophagitis

5 Measure Depth Of Endoscope Insertion* At The **Maximum** Extent Of Suspected Columnar Metaplasia# = 29 cm

4 Measure Depth Of Endoscope Insertion* At The Most Proximal **Circumferential** Extent Of Suspected Columnar Metaplasia# = 33 cm

Depth of Endoscope Insertion (cm)

28
30
32
34
36

6 Subtract the Depth of Insertion for **Circumferential** and **Maximum** Extents from the Depth of Endoscope Insertion at the Gastroesophageal Junction†
:36cm - 33cm = **C3**
:36cm - 29cm = **M7**
Prague C3 and M7

3 Look For Displacement Of Squamocolumnar Junction Above Gastroesophageal Junction

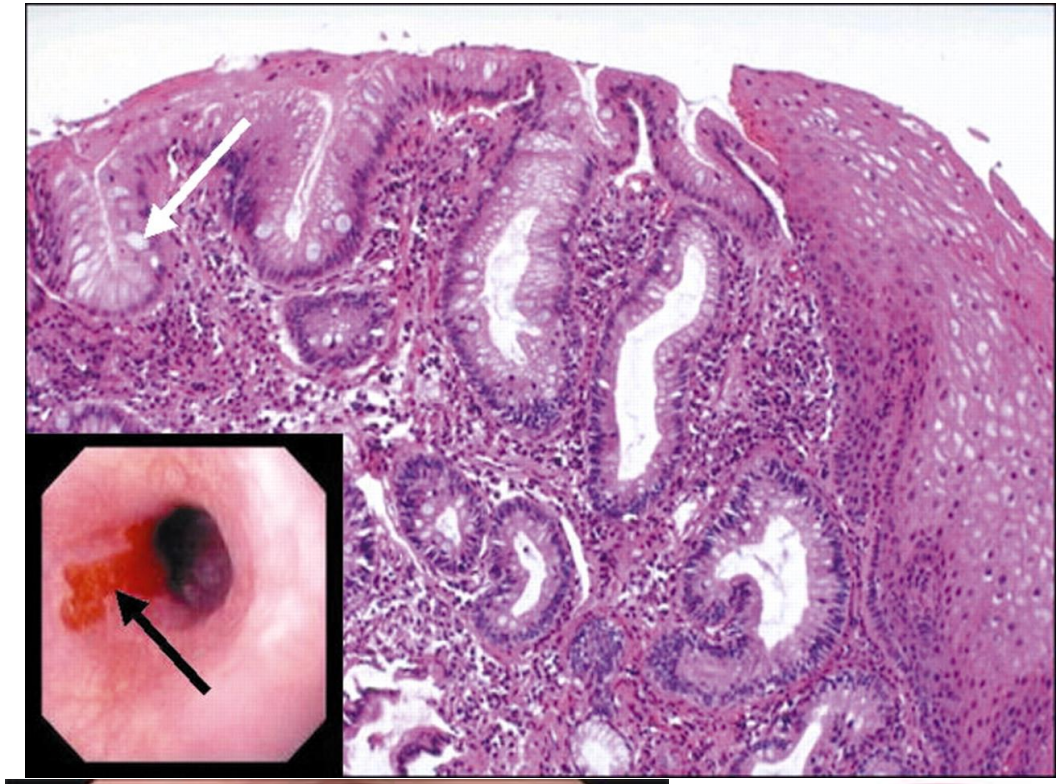
2 Locate Gastroesophageal Junction By Depth Of Endoscope Insertion* At Level Of:
– tops of gastric mucosal folds
– sphincter "pinch"
= 36 cm

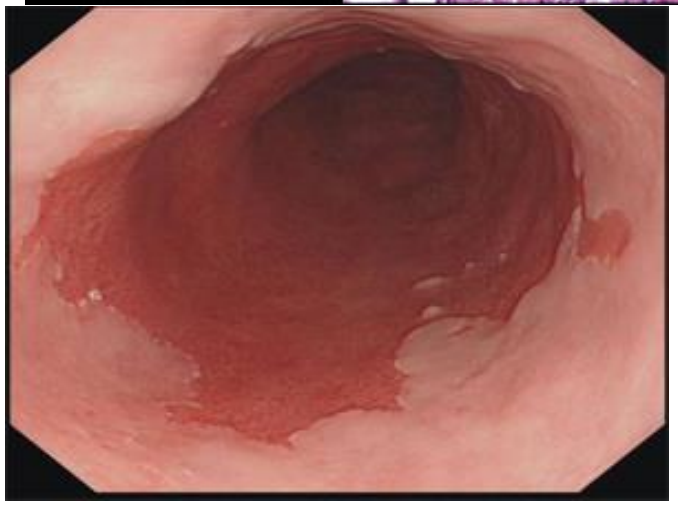
Hiatus Hernia

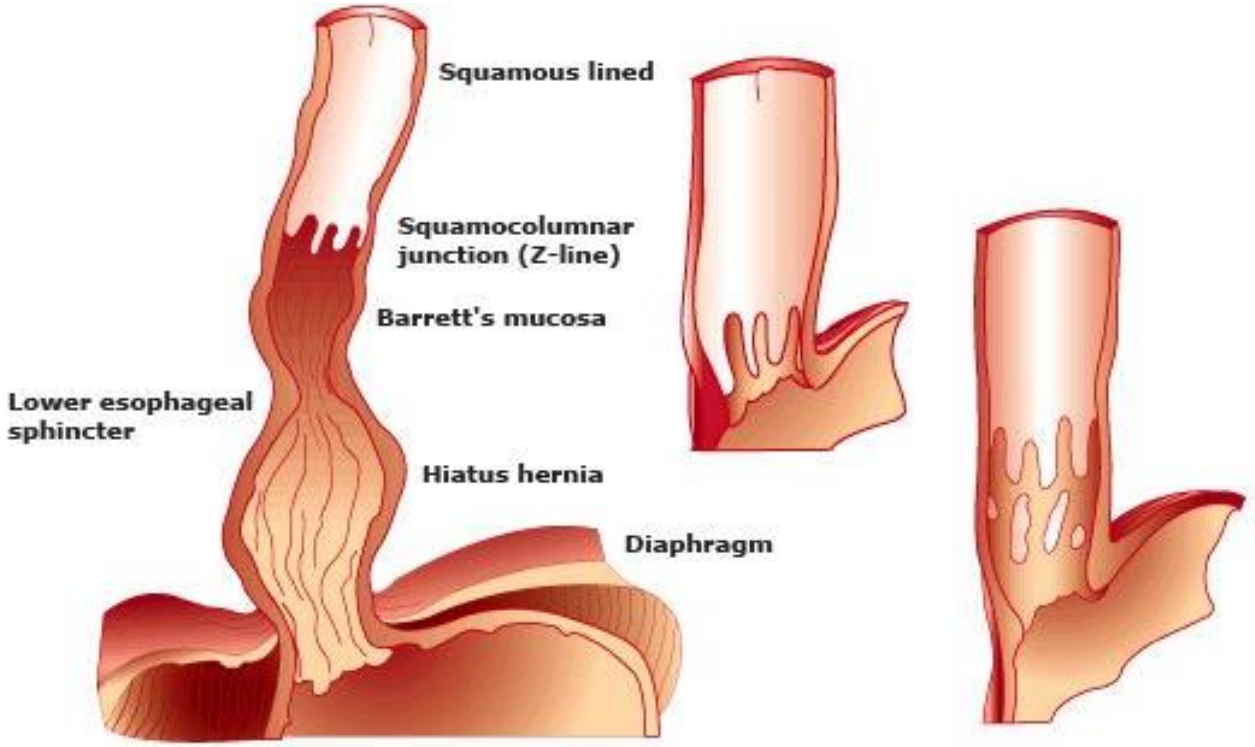
1 Ensure Hiatus Hernia Is Recognised By Distinguishing Diaphragmatic Hiatal Impression From Gastroesophageal Junction

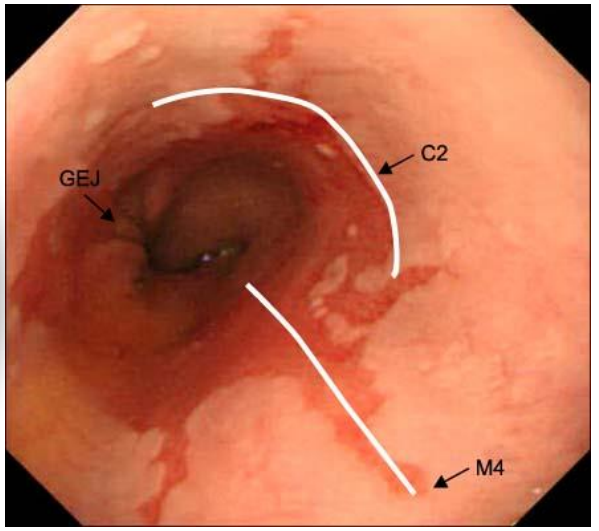
* To the nearest centimeter
# Squamous and columnar islands do NOT contribute to measures of extent
† To the nearest centimeter, except when areas of columnar metaplasia are estimated to be less than 1 cm: report this as <1cm

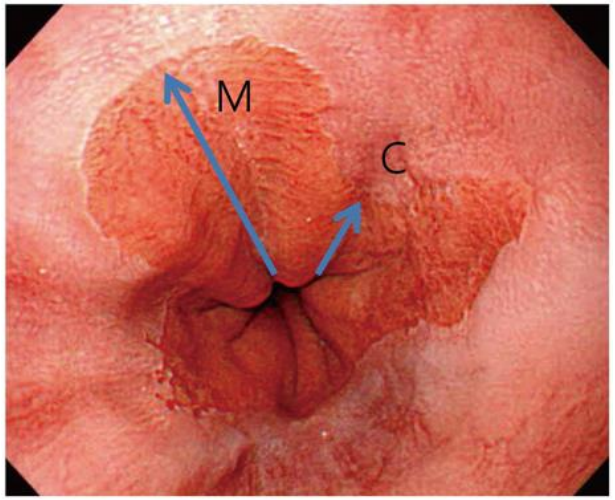
Supported by an educational grant from AstraZeneca






Squamous lined
Squamocolumnar junction (Z-line)
Barrett's mucosa
Lower esophageal sphincter
Hiatus hernia
Diaphragm


GEJ
C2
M4


M
C

Simply, Barrett's esophagus segment length can be defined as :

- Ultra-short (<5 mm)
- Short (5 mm–3 cm)
- Long (>3 cm)

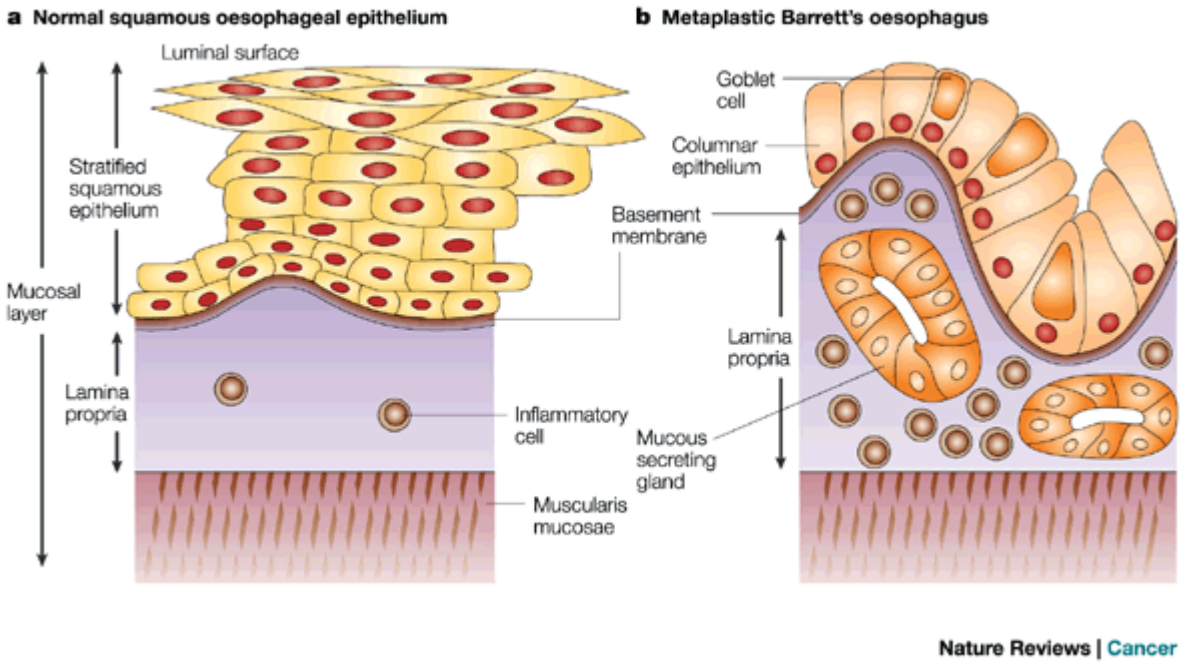
Minimum endoscopic dataset required when reporting the finding of Barrett's esophagus

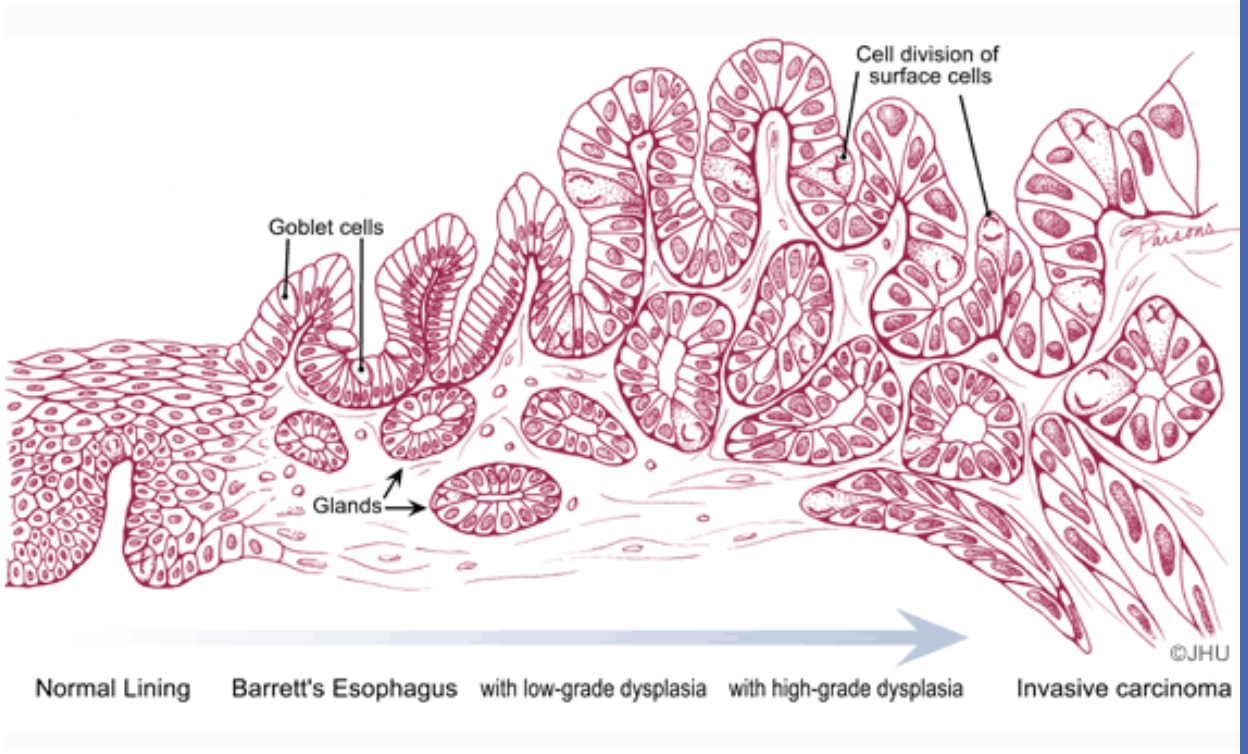
Finding	Reporting system	Nomenclature
Barrett's oesophagus length	Prague classification	CnMn (where n is length in cm)
Barrett's islands	Describe distance from the incisors and length in cm	Descriptive in the text
Hiatus hernia	Distance between diaphragmatic pinch and GOJ	yes/no; cm
Visible lesions	Number and distance from incisors	yes/no; cm
Classification of visible lesions	Paris classification	o-Ip, protruded pedunculated
		o-Is, protruded sessile
		o-IIa, superficial elevated
		o-IIb, flat
		o-IIc, superficial depressed
		o-III, excavated
Biopsies	Location and number of samples taken	n cm (distance from incisors) Xn

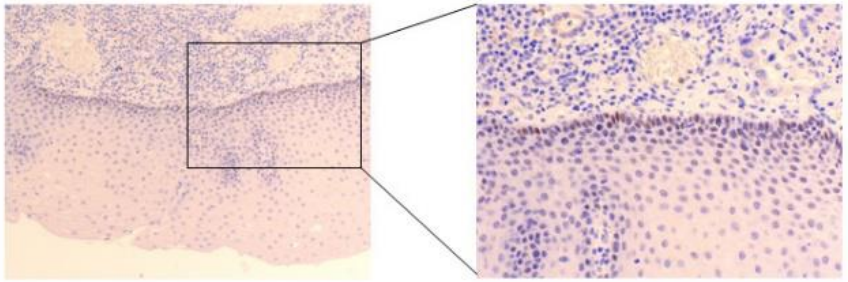
DIAGNOSTIC CRITERIA

Two criteria must be fulfilled:

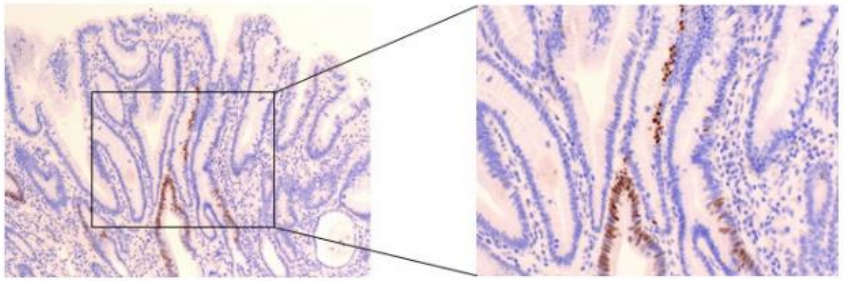
- The endoscopist must document that columnar epithelium lines the distal esophagus.
- Histologic examination of biopsy specimens from that columnar epithelium must reveal intestinal metaplasia.
  - Some data suggest that gastric cardia-type epithelium in the esophagus also might predispose to cancer and thus might be considered "Barrett's esophagus," but most authorities still require the presence of intestinal metaplasia for an unequivocal diagnosis .
- *Columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GEJ*


a Normal squamous oesophageal epithelium
Luminal surface
Stratified squamous epithelium
Mucosal layer
Lamina propria
Inflammatory cell
Muscularis mucosae
b Metaplastic Barrett's oesophagus
Goblet cell
Columnar epithelium
Basement membrane
Lamina propria
Mucous secreting gland
Nature Reviews | Cancer

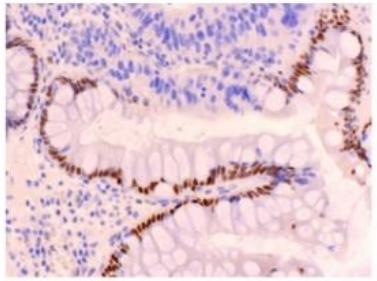

Cell division of surface cells
Goblet cells
Glands
©JHU
Normal Lining
Barrett's Esophagus
with low-grade dysplasia
with high-grade dysplasia
Invasive carcinoma



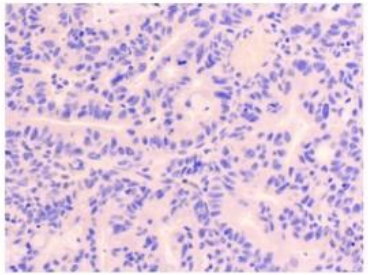
3 A. Normal esophagus



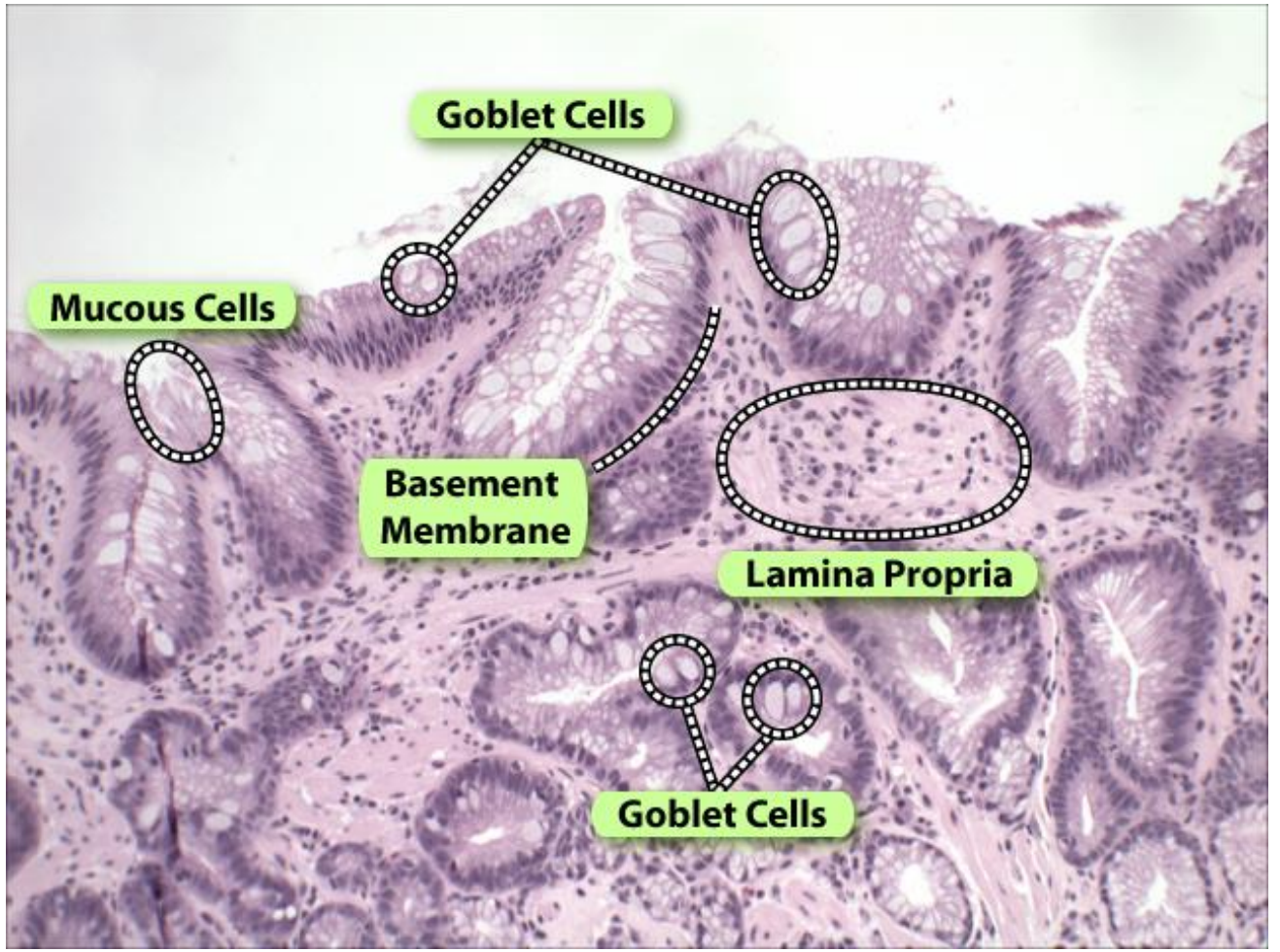
3 B. Barrett's esophagus

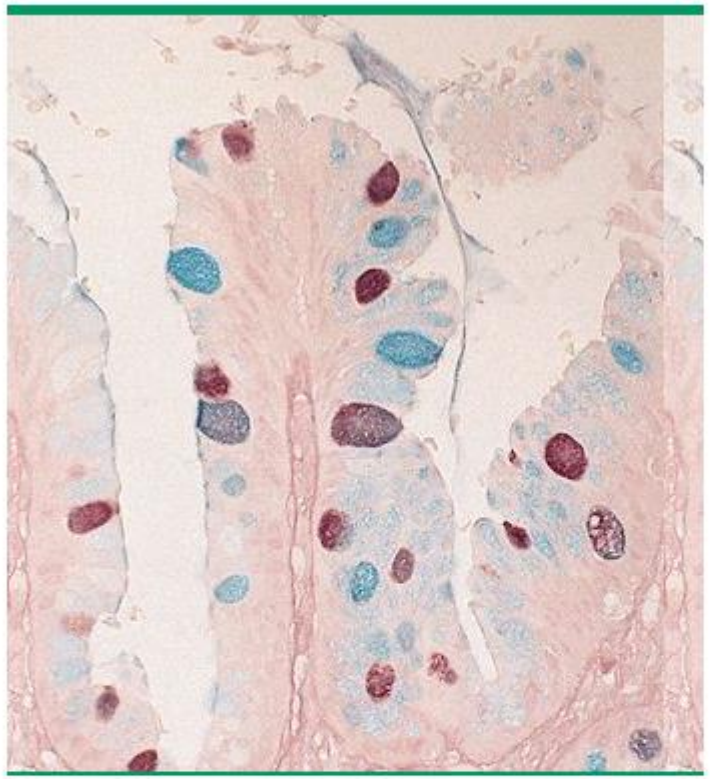


3 C. Metaplasia and dysplasia

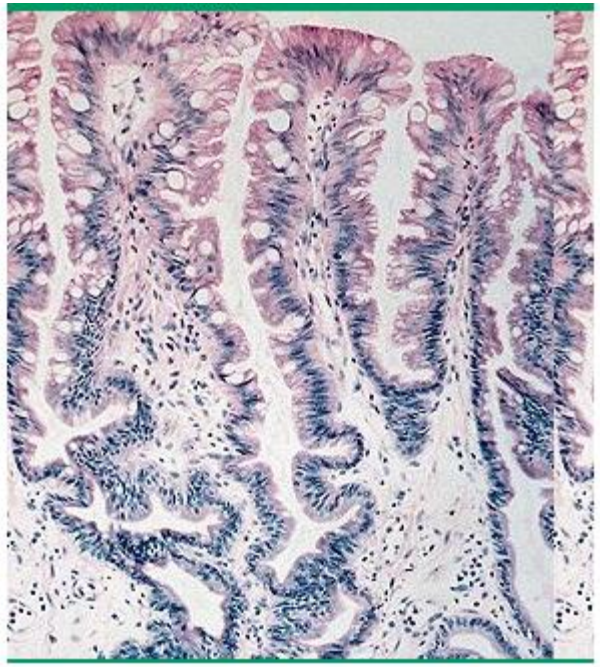


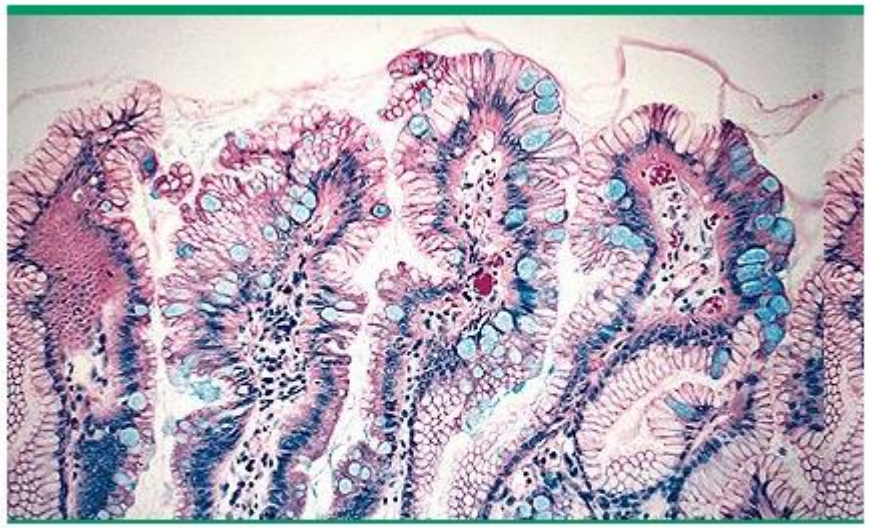
3 D. Adenocarcinoma





High power view of a biopsy specimen from a patient with Barrett's esophagus has been stained with diamine. This stain demonstrates goblet cells containing sulfated mucins (brown) and nonsulfated mucins (blue).





Low power view of a biopsy specimen from a patient with Barrett's esophagus has been stained with Alcian blue, which demonstrates the abundant goblet cells.

What is your plan?

- *Barrett's oesophagus without IM or dysplasia*
  (gastric cardia-type epithelium in the esophagus)

Barrett's oesophagus without IM or dysplasia

- *For patients with Barrett's oesophagus shorter than 3 cm, without IM or dysplasia, a repeat endoscopy with quadrantic biopsies is recommended to confirm the diagnosis.*
- *If repeat endoscopy confirms the absence of IM, discharge from surveillance is encouraged, as the risks of endoscopy probably outweigh the benefits (Recommendation grade C).*

- **Are you recommended Biopsies if there is an irregular Z-line?**

Intestinal metaplasia at the GEJ

- Barrett's oesophagus should be endoscopically distinguished from an irregular Z-line, whereby the squamocolumnar junction appears with tongues of columnar epithelium shorter than 1 cm and with no confluent columnar-lined segment.
- In a case–control study, an irregular Z-line has been found with higher frequency in patients with reflux disease
- Although one study found that about 40% of cases of irregular Z-line harbored IM on biopsy samples, the significance of this endoscopic finding is still unclear
- If the Z-line and the GEJ coincide and biopsy specimens at the Z-line show intestinal metaplasia, the condition is called intestinal metaplasia at the GEJ

Intestinal metaplasia at the GEJ

- As stated in the definition 'columnar epithelium should be clearly visible endoscopically above the GEJ. Since the diagnosis of an irregular Z-line is subjective and there is no accepted length cut-off to distinguish between an irregular Z-line and Barrett's oesophagus, we would suggest that 1 cm (M of Prague criteria) should be the minimum length for an endoscopic diagnosis of Barrett's .
- Intestinal metaplasia of the GEJ appeared to have substantially lower rates of progression to esophageal adenocarcinoma than those with Barrett's esophagus
- For patients found to have intestinal metaplasia at the GEJ, a conservative management approach is to assume a worst-case scenario in which the condition is considered to represent short-segment Barrett's esophagus.
- Biopsies are generally not recommended if there is an irregular Z-line. However, according to the degree of suspicion, biopsies may be performed to aid the diagnosis.
- Presence of pure fundic/oxyntic mucosa is a very rare finding in Barrett's oesophagus, this pathological finding would suggest sampling of the GEJ

British Society of Gastroenterology Guidelines

- *Surveillance is generally not recommended in patients with IM at the cardia or in those with an irregular Z-line regardless of the presence of IM (Recommendation grade C).*

Classification	Association with GERD	Association with carcinoma	Endoscopic surveillance
Columnar lined esophagus **with** specialized intestinal metaplasia	Variable	Yes	Yes
Columnar lined esophagus **without** specialized intestinal metaplasia	Variable	Unlikely	Probably not
Specialized intestinal metaplasia at the esophagogastric junction	Unclear	Probable	Unclear

Distinguishing Between True Barrett's esophagus and IM of the Cardia with?

a) Pattern of cytokeratin 7 and 20 immunocytochemical staining
b) Presence of colonic-type sulfomucins
c) Made endoscopically
d) Made by IM subtype

Intestinal metaplasia at the GEJ or in the gastric cardia

- These conditions cannot be distinguished reliably because the morphological and histochemical features of gastric and esophageal intestinal metaplasia are similar
- Circumstantial evidence suggests that the risk of malignancy is substantially higher for intestinal metaplasia in the esophagus than for that in the stomach
- Medical societies recommend endoscopic cancer surveillance routinely for patients with Barrett's esophagus, but not for patients with intestinal metaplasia in the stomach

Intestinal metaplasia at the GEJ or in the gastric cardia

- The true GEJ is distal to the end of the tubular oesophagus and proximal to rugal folds as shown by the presence of submucosal oesophageal glands in this region'.
- Hence, the distinction between columnar-lined oesophagus and IM at the gastric cardia (CIM) can only be made definitively histologically when columnar mucosa with or without IM is seen juxtaposed with native anatomical oesophageal structures such as submucosal glands and/or gland ducts.
- Reports also suggest that multilayered epithelium or squamous islands are helpful, as the former is reported as pathognomonic of Barrett's, and the latter are almost always seen in continuity with the superficial portion of gland ducts.
- But in large studies, however, native structures are seen in only 10–15% of biopsy samples
- IM in Barrett's is most commonly of an incomplete (type II or III) subtype

Intestinal metaplasia at the GEJ or in the gastric cardia

- In view of the lack of reliable markers to distinguish between IM of the cardia and oesophagus, this distinction needs to be made endoscopically, and the endoscopist is therefore required to carefully label the site from which biopsy samples were taken in reference to the endoscopic landmarks, in order to inform the clinico–pathological correlation.

- **Biopsy Protocol ?**

Biopsy Protocol

- Confirmation of the presence of IM can be limited by sampling error
- In a study by Harrison *et al* of 1646 biopsy samples from 125 patients with long-segment Barrett's oesophagus, the optimum number of samples needed to demonstrate goblet cells in 67.9% of endoscopies was eight, but, in contrast, if only four were obtained, only 34.7%
- single endoscopy with a low number of biopsy samples is not sufficient to exclude IM, particularly in a short segment of Barrett's oesophagus

Biopsy Protocol and Site Mapping

- The Seattle biopsy protocol, which entails four-quadrant random biopsies every 2 cm in addition to targeted biopsies on macroscopically visible lesions, is recommended at the time of diagnosis and at subsequent surveillance
- Targeted biopsy samples from visible lesions should be taken before random biopsies.
- Distal areas should be biopsied first starting 1–2 cm above the GOJ and advancing proximally to minimize obscured view from bleeding

The pathologist should record the following elements in the histopathological report:

- Number of biopsy samples analysed at each level
- Type of mucosa present (squamous or columnar)
- Presence of any native esophageal structures
- Presence of gastric- (cardiac/fundic) or intestinal-type metaplasia
- Presence and grade of dysplasia

Barrett's Endoscopic Biopsies	
Number of levels	
Total number of biopsies	
Squamous mucosa (Y/N)	
Native oesophageal structures (Y/N)	
Glandular mucosa (Y/N)	
Intestinal metaplasia (Y/N)	
Glandular dysplasia (Y/N)	
- Indefinite (Y/N)	
- Low grade (Y/N)	
- High grade (Y/N)	
- Intramucosal ca (Y/N)	
SUMMARY	
Barrett's oesophagus with gastric metaplasia only **or** ***Barrett's oesophagus with intestinal metaplasia*** **(state degree of dysplasia) or** ***No evidence of Barrett's oesophagus***	

Barrett's Endoscopic Biopsies						
Specimen Number	1	2	3	4	5	6
Level/cm						
Number of biopsies per level						
Squamous mucosa (Y/N)						
Glandular mucosa (Y/N)						
Native oesophageal structures (Y/N)						
Intestinal metaplasia (Y/N)						
Glandular dysplasia (Y/N)						
- Indefinite (Y/N)						
- Low grade (Y/N)						
- High grade (Y/N)						
- Intramucosal ca (Y/N)						
p53 Significant immuno staining pattern (Y/N/ equivocal / Not performed						
Highest grade of inflammation :						
Acute (none, mild, moderate, severe)						
Chronic (none, mild, moderate, severe)						
Highest grade of dysplasia:						
SUMMARY						
Barrett's oesophagus with gastric metaplasia only **or** ***Barrett's oesophagus with intestinal metaplasia*** **(state degree of dysplasia) or** ***No evidence of Barrett's oesophagus***						

Risk Factors for Barrett's esophagus except?

a) Male gender
b) Oral bisphosphonates
c) Cigarette smoking
d) Statin
e) Positive Familial history

Prevalence of Barrett's esophagus

- Italian study 1.3%
- Swedish population 1.6%
- United States Estimated 5.6% of adults

  - Risk of selection bias resulting in a possible overestimate of the prevalence.

Risk Factors for Barrett's esophagus

- Male gender 2:1
- Older age > 50
- History of reflux symptoms
- History of peptic stricture and erosive esophagitis
- White individuals
- Obesity
- Cigarette smoking

- Familial clustering for Barrett's oesophagus is reported in about 7% of individuals with Barrett's oesophagus or esophageal adenocarcinoma
  - Up to 28% of first-degree relatives of patients with esophageal adenocarcinoma or Barrett's HGD also have Barrett's oesophagus
  - Germline mutations in the MSR1, ASCC1, and CTHRC1 genes have been associated with the presence of Barrett's esophagus and esophageal adenocarcinoma

Risk Factors for Barrett's esophagus

- 44% of Barrett's esophagus patients lacked "troublesome heartburn and/or acid regurgitation during the past three months" suggesting that screening programs based upon reflux symptoms alone may be inadequate to identify patients with Barrett's esophagus.
- More than 40% of patients with esophageal adenocarcinoma have no history of heartburn
- Among patients who have chronic GERD symptoms:
  - long-segment Barrett's esophagus 3 - 5 %
  - short-segment Barrett's esophagus 10- to 15%
- Barrett's esophagus appears to be uncommon in blacks and Asians

Oral bisphosphonates

- Oral bisphosphonates were associated with a significant

  2.33-fold increase in the risk of Barrett esophagus.

- **Barrett's esophagus progression from short to long segment?**

Barrett's esophagus progression

- For reasons that are unclear, such progression is observed only rarely.
- In most cases, Barrett's esophagus appears to develop to its full extent over a short period of time (ie, <1 year), with little or no subsequent progression. Why this occurs is not well understood
- 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
  - ✓ The second step of intestinal metaplasia, which is thought to progress more slowly, over 5–10 years .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

- **Are you suggest aggressive antireflux therapy in Barrett's esophagus with and without GERD symptom?**

Management of GERD in patients with Barrett's esophagus

- We suggest that all patients with Barrett's esophagus receive treatment with a proton pump inhibitor (PPI) rather than reserving treatment only for patients who are symptomatic .
- We typically start patients on a PPI once daily, and only increase the dose if it is required to eliminate gastroesophageal reflux disease symptoms or to heal reflux esophagitis.

Management of GERD in patients with Barrett's esophagus

- However, for patients with no GERD symptoms and no endoscopic signs of reflux esophagitis, the use of PPIs would be solely to reduce the risk of progression to dysplasia or cancer. The AGA statement notes that the evidence supporting the use of PPIs in patients with Barrett's esophagus solely to reduce the risk of progression to dysplasia or cancer is indirect and has not been proven in long-term controlled trials.
- As a result, the AGA suggests that the risks and potential benefits of long-term PPI therapy be discussed carefully with patients with Barrett's esophagus in the context of their overall health status and medication use.

Management of GERD in patients with Barrett's esophagus

- Antireflux surgery (fundoplication) is another option for controlling GERD in patients with Barrett's esophagus , although fundoplication does not appear to be more effective at preventing esophageal adenocarcinoma than medical therapy
- *Antireflux surgery is not superior to pharmacological acid suppression for the prevention of neoplastic progression of Barrett's oesophagus (Recommendation grade C).*
- *Antireflux surgery should be considered in patients with poor or partial symptomatic response to PPIs (Recommendation grade A).*

- **Treatment of Barrett's esophagus can cause regression ?**

Regression of the specialized intestinal metaplasia in Barrett's esophagus

- Clinical trials suggest that treatment of reflux sometimes results in limited regression of Barrett's esophagus, and observational studies suggest that antireflux therapy prevents progression to high-grade dysplasia (HGD) or esophageal adenocarcinoma in these patients.
- Aggressive antireflux therapy can cause partial regression of the specialized intestinal metaplasia in Barrett's esophagus

Regression of the specialized intestinal metaplasia in Barrett's esophagus

- Regression of Barrett's epithelium has also been observed with fundoplication , and some authorities have suggested that fundoplication might be more effective than antisecretory therapy for preventing cancer in Barrett's esophagus
- Thus, the available data suggest that antireflux surgery should not be advised with the expectation that the procedure will prolong life by preventing esophageal cancer.

- ***Endoscopic screening in patients with chronic GERD symptoms?***

Endoscopic screening

- British Society of Gastroenterology Guidelines
  - *Endoscopic screening can be considered in patients with chronic GERD symptoms and multiple risk factors (at least three of age 50 years or older, white race, male sex, obesity).*
  - *However, the threshold of multiple risk factors should be lowered in the presence of a family history including at least one first-degree relative with Barrett's or* esophageal adenocarcinoma
- Up to date :
  - We suggest that patients with at least weekly GERD symptoms that have been present for at least five years and who have multiple risk factors for esophageal adenocarcinoma undergo screening for Barrett's esophagus.
  - We propose that screening should not be performed in men younger than 50 years or in women of any age, regardless of the frequency of GERD symptoms, due to the very low incidence of esophageal adenocarcinoma in these groups

American Gastroenterological Association

- AGA recommends screening patients with multiple risk factors associated with esophageal adenocarcinoma for Barrett's esophagus
  - Age 50 years or older
  - Male sex
  - White race
  - Chronic GERD
  - Hiatal hernia
  - Elevated body mass index
  - Intra-abdominal distribution of body fat
- The AGA recommends against screening the general population with GERD.

American College of Physicians

- Endoscopy may be indicated for screening for Barrett's esophagus in men older than 50 years with GERD symptoms for more than five years and the following additional risk factors :
  - Nocturnal reflux symptoms
  - Hiatus hernia
  - Elevated body mass index
  - Tobacco use
  - Intra-abdominal distribution of fat

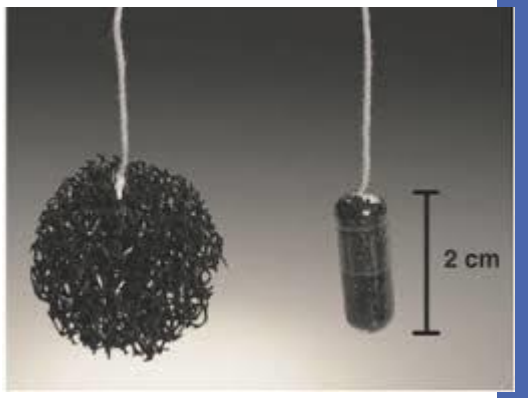
Screening for Barrett's esophagus

Diagnostics 2023, 13, 321. Barrett's Esophagus: An Updated Review

- Although screening for Barrett's esophagus in the general population is not routinely recommended, it may be considered in men with chronic (>5 years) and/or frequent (weekly or more) symptoms of gastroesophageal reflux and two or more risk factors
- These risk factors include age >50 years, Caucasian race, presence of metabolic syndrome, current or past history of smoking, and a confirmed family history in a first degree relative of Barrett's esophagus or esophageal adenocarcinoma

Alternate screening methods ?

Alternate screening methods



- Capsule sponge or cytology collection device
  - (Cytosponge, Surepath; BD Diagnostics, Durham, NC) combined with an immunohistochemical biomarker.
    - Patient ingests a gelatin capsule that is attached to a string and contains a compressed mesh. The mesh is exposed when the gelatin capsule dissolves in the stomach. The mesh is then withdrawn through the esophagus where it obtains samples of the cells
- Ultrathin transnasal endoscopy

Surveillance in detecting curable dysplasia?

Surveillance

- Survival benefit in patients undergoing surveillance has not been demonstrated in randomized prospective trials
- Ethical problems
- None of cost-effectiveness models can be considered definitive
- Decrease in quality of life and risk of the procedure
- No study has established the reliability of surveillance in detecting curable dysplasia
- Furthermore, hazardous invasive therapies for dysplasia like esophagectomy might ultimately do more harm than good.

Cancer incidence in patients with Barrett's esophagus

- Estimates of the annual cancer incidence in patients with Barrett's esophagus have ranged from 0.1 - 2.0 % . Although the risk of developing esophageal cancer is increased at least 30-fold above that of the general population , the absolute risk of developing cancer is low.
- cancer incidence was 5 per 1000 person-years when only studies with well defined criteria for the diagnosis of Barrett's esophagus were included
- For high-grade dysplasia or cancer, the corresponding pooled estimate for cancer incidence was 10.2 per 1000 person-years.
- The incidence of mortality was 3.0 per 1000 person-years due to esophageal adenocarcinoma and 37.1 per 1000 person-years due to other causes.
- The finding that esophageal cancer is an uncommon cause of death in patients with Barrett's esophagus is likely related to the fact that many patients with Barrett's esophagus are elderly and succumb to common diseases

Cancer incidence in patients with Barrett's esophagus

- A prospective study with 713 patients with Barrett's esophagus of 2 cm in length or longer found that the risk of developing high-grade dysplasia or cancer was higher with longer segments of Barrett's esophagus (risk ratio of 1.1 for every centimeter increase in length)
- For patients with low-grade dysplasia, the risk of cancer is so poorly defined that it is not possible to provide a precise estimate. Presumably, the risk is greater than that of the general population of patients with Barrett's esophagus (0.25 % per year) and less than that of patients with high-grade dysplasia (5 to 8 % per year).

Best method for detection of Dysplastic areas?

a) high-resolution, white light endoscopy
b) mucosal staining with vital dyes (chromoendoscopy)
c) endosonography
d) optical coherence tomography
e) high resolution endoscopy
f) narrow band imaging

Detecting dysplasia

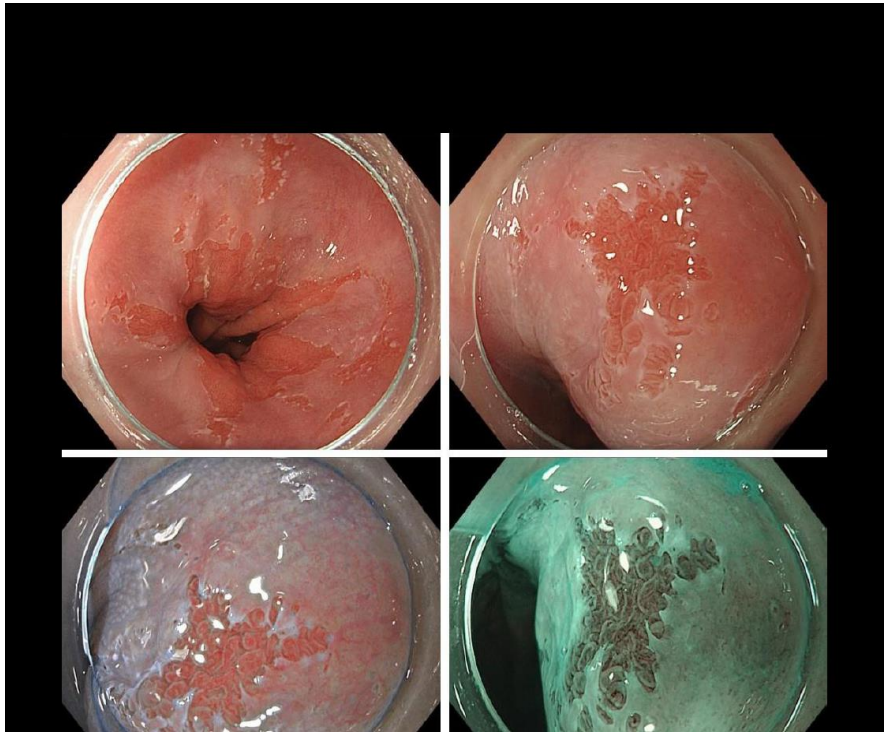
- Dysplasia in Barrett's esophagus is often patchy in extent and severity
- Dysplastic areas can easily be missed because of biopsy sampling error
- Foci of invasive cancer can be missed
- Esophagectomies because endoscopic examination revealed high-grade dysplasia in Barrett's esophagus found that 13 -40% of the resection specimens had invasive cancer
- High-resolution white light endoscopy, however, it has been appreciated that dysplasia is associated with visible abnormalities, albeit subtle ones, in most cases . Therefore, it is now recommended that endoscopists should carefully inspect the Barrett's epithelium and biopsy any visible abnormalities in addition to obtaining random biopsy specimens.

Endoscopic techniques

- high-resolution, white light endoscopy
- mucosal staining with vital dyes (chromoendoscopy)
- endosonography
- optical coherence tomography
- high resolution endoscopy
- confocal microendoscopy
- spectroscopy using reflectance, absorption, light-scattering, fluorescence, narrow band imaging, and Raman detection methods
  - Although initial studies are promising, none of these techniques has yet been shown to provide sufficient additional clinical information (beyond that of high-resolution, white light endoscopy) to justify its routine application for surveillance purposes.

Virtual chromoendoscopy

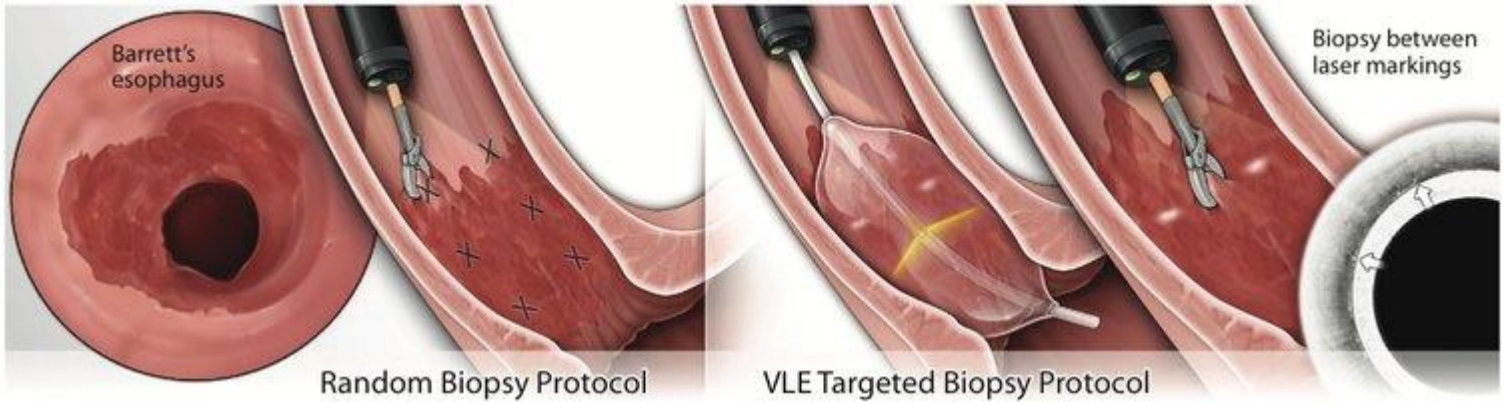
- Virtual chromoendoscopy adds no cost, additional time or risk to the patient while providing a useful adjunct during routine endoscopy.
  - Olympus narrow band imaging (NBI)
  - Fujinon Intelligent Color Enhancement (FICE)
  - Pentax iScan

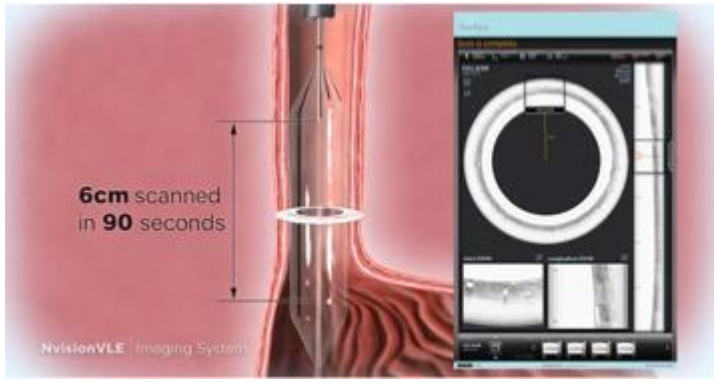


Example of a small Barrett's adenocarcinoma narrow-band imaging (NBI) mode).

VOLUMETRIC LASER ENDOMICROSCOPY(VLE)

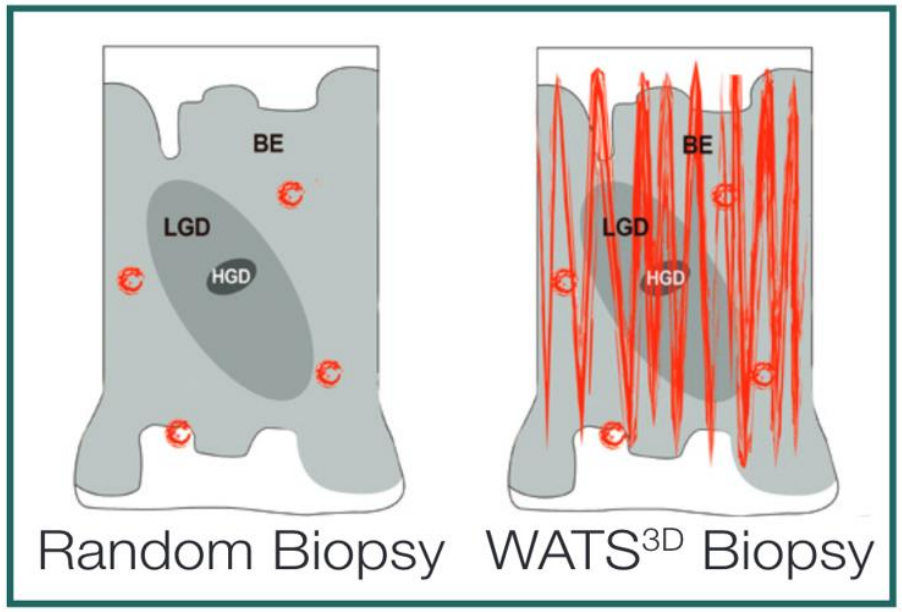
- Experimental studies comparing VLE to endoscopically resected specimens have demonstrated sensitivities of 86–90% and specificities of 88–93% for the etection of dysplasia in BE
- The benefits of VLE are that entire segments of BE can be imaged in a short period of time, abnormalities can be laser marked for targeting and it does not appear to increase endoscopic risk to patients.
- Very detailed microstructures will be visualized for any irregular areas that can be associated with dysplasia (irregular cells). VLE can distinguish between Barrett's with dysplasia versus Barrett's without dysplasia. These areas can be marked with a laser mark on the esophagus (see Video 1) and then targeted for biopsy.





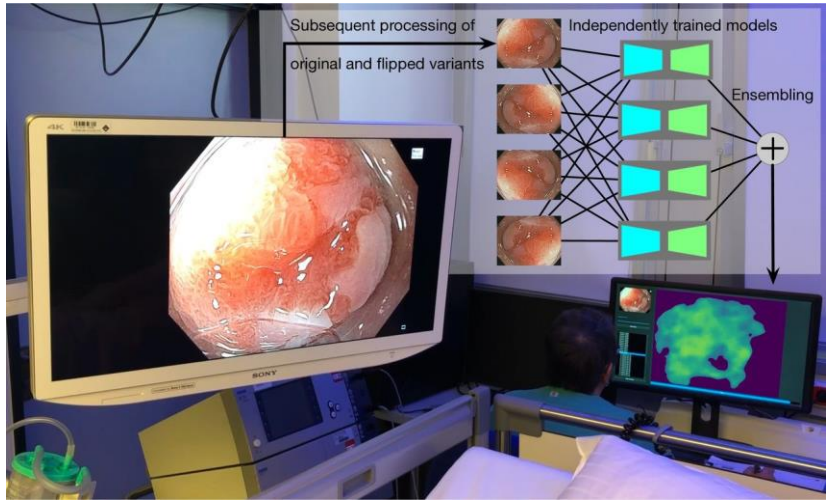
Wide-Area Transepithelial Sampling (WATS)

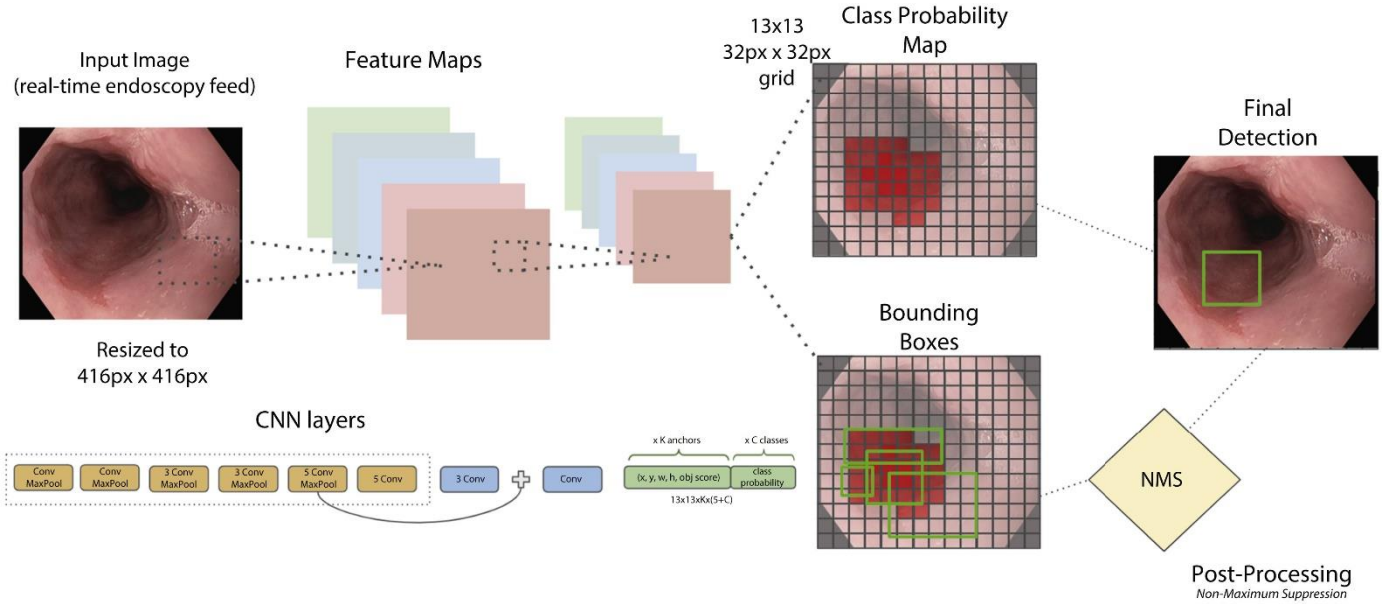
- Wide-area transepithelial sampling (WATS) is a three-dimensional (3D), computer assisted technique which has been used as an adjunct to traditional forceps biopsy
- WATS uses endoscopic abrasive brush biopsy to sample transepithelial tissue circumferentially.
- The biopsy samples are then captured into histologic slices which are synthesized into a 3D image. The 3D imaging is analyzed by software algorithm



Artificial Intelligence (AI) in Detection of Dysplasia in Barrett's Esophagus

AI has enabled endoscopists to target specific lesions and rely less on random sampling





Endoscopic Ultrasound (EUS)

- Often performed prior to endoscopic therapy of BE. EUS has been used to assess for submucosal invasion, given that the initial forceps biopsy does not width and depth of lesions. In early-stage neoplasia, EUS is also used to assess lymph node involvement.
- EUS was found to have poor sensitivity (50%), positive predictive value (40%), and 11% of patients were staged incorrectly, with 7% overstaged and 4% understaged, with EUS compared to EMR . It was found that if staging with EUS alone, 7% of patients would have undergone unnecessary esophagectomy
- It has been discussed that the reason EUS may overclassify dysplasia because it can be difficult to ultrasonically differentiate between microscopic tumor invasion of tissue and peritumoral inflammatory changes.
- Nevertheless, it has been found that EUS remains an appropriate technique to assess for lymph node involvement prior to performing endoscopic treatment of advanced disease

Molecular markers

- A number of molecular markers for cancer risk have been proposed as alternatives to random biopsy sampling to seek dysplasia in Barrett's esophagus .
- Promising molecular markers include abnormalities in p53 and cyclin D1 expression, and abnormal cellular DNA content demonstrable by flow cytometry or methylation arrays, all of which have been associated with carcinogenesis in Barrett's esophagus.
- None has been sufficiently proven for routine clinical use .

- **For patients with no dysplasia or endoscopic signs of neoplasia following 2 biopsy sampling, first surveillance endoscopy be performed within?**

a) one year

b) Three year

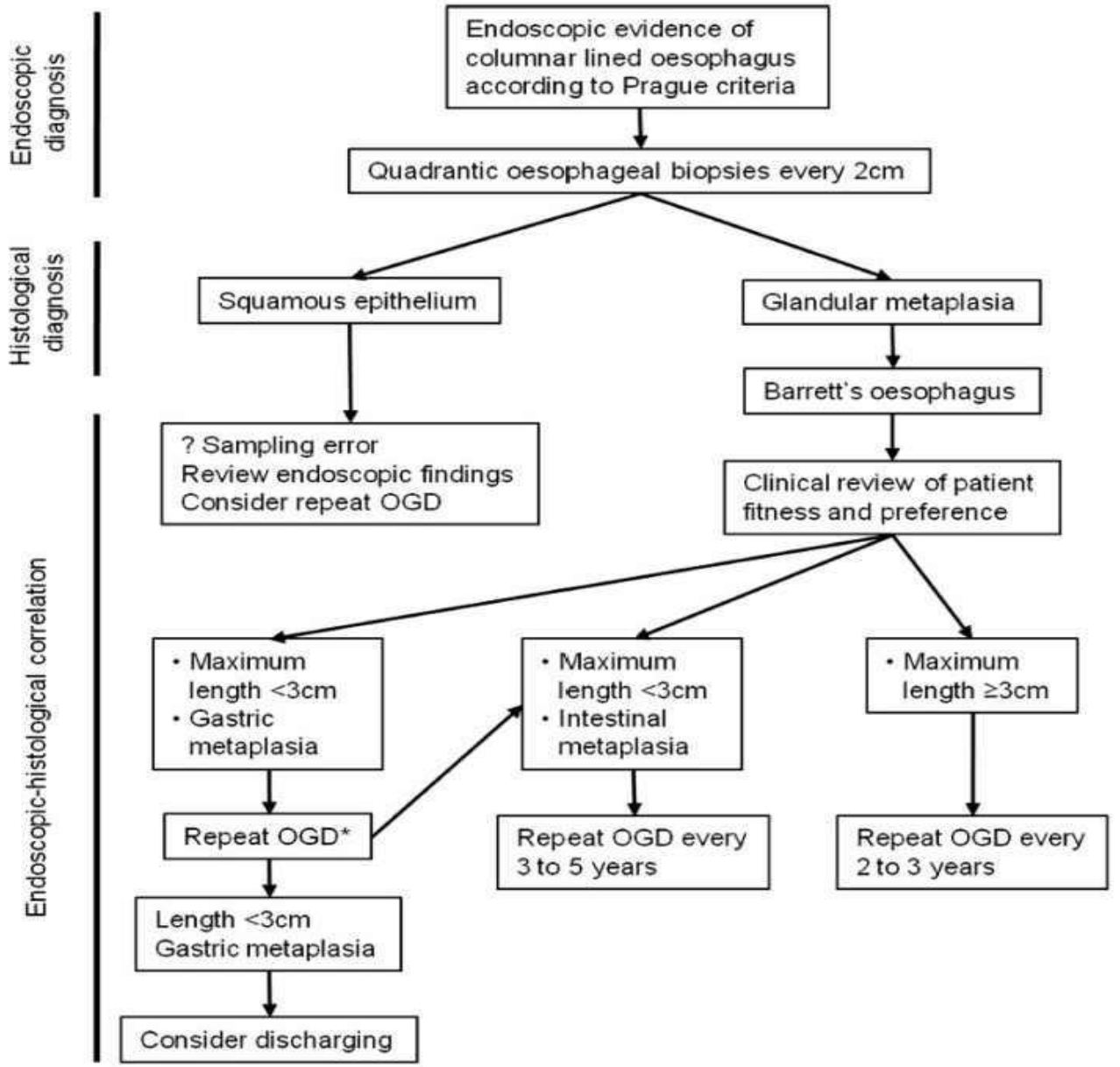
c) Five year

Surveillance in Barrett's esophagus (AGA)

- We suggest that patients with Barrett's esophagus have regular surveillance endoscopy to obtain esophageal biopsy specimens .
- GERD should be treated prior to surveillance to minimize confusion caused by inflammation in the interpretation of dysplasia.
- While not in the AGA guidelines, we suggest that the first surveillance endoscopy be performed within one year of the index diagnosis of Barrett's esophagus if there is any question regarding the adequacy of biopsy sampling (eg, four quadrant biopsies were not obtained) or endoscopic signs of neoplasia during the first endoscopy.
- For patients with no dysplasia or endoscopic signs of neoplasia following adequate biopsy sampling, we suggest surveillance endoscopy at an interval of every three to five years
- The above recommendations apply regardless of whether the patient has long or short-segment Barrett's.

Endoscopic surveillance
British Society of Gastroenterology Guidelines

- *Patients with Barrett's oesophagus shorter than 3 cm, with IM, should receive endoscopic surveillance every 3–5 years (Recommendation grade C).*
- *Patients with segments of 3 cm or longer should receive surveillance every 2–3 years (Recommendation grade C).*



* Interval depends on the degree of clinical confidence about diagnosis (accuracy of endoscopic report and number of biopsies

Indefinite for dysplasia

- *Patients with a diagnosis of indefinite for dysplasia should be managed with an optimisation of the antireflux medical therapy and re-endoscoped in 2-6 months.*
- *If no definite dysplasia is found on subsequent biopsies, then the surveillance strategy should follow the recommendation for non-dysplastic Barrett's oesophagus (Recommendation grade C).*
- *If the repeat endoscopy results are indefinite dysplasia, then it is advised the patient to have a surveillance endoscopy in 2-6 months and if again was indefinite dysplasia surveillance endoscopy was done every 12 months.*

For most patients with verified low-grade dysplasia after extensive biopsy sampling, we suggest surveillance endoscopy at intervals?

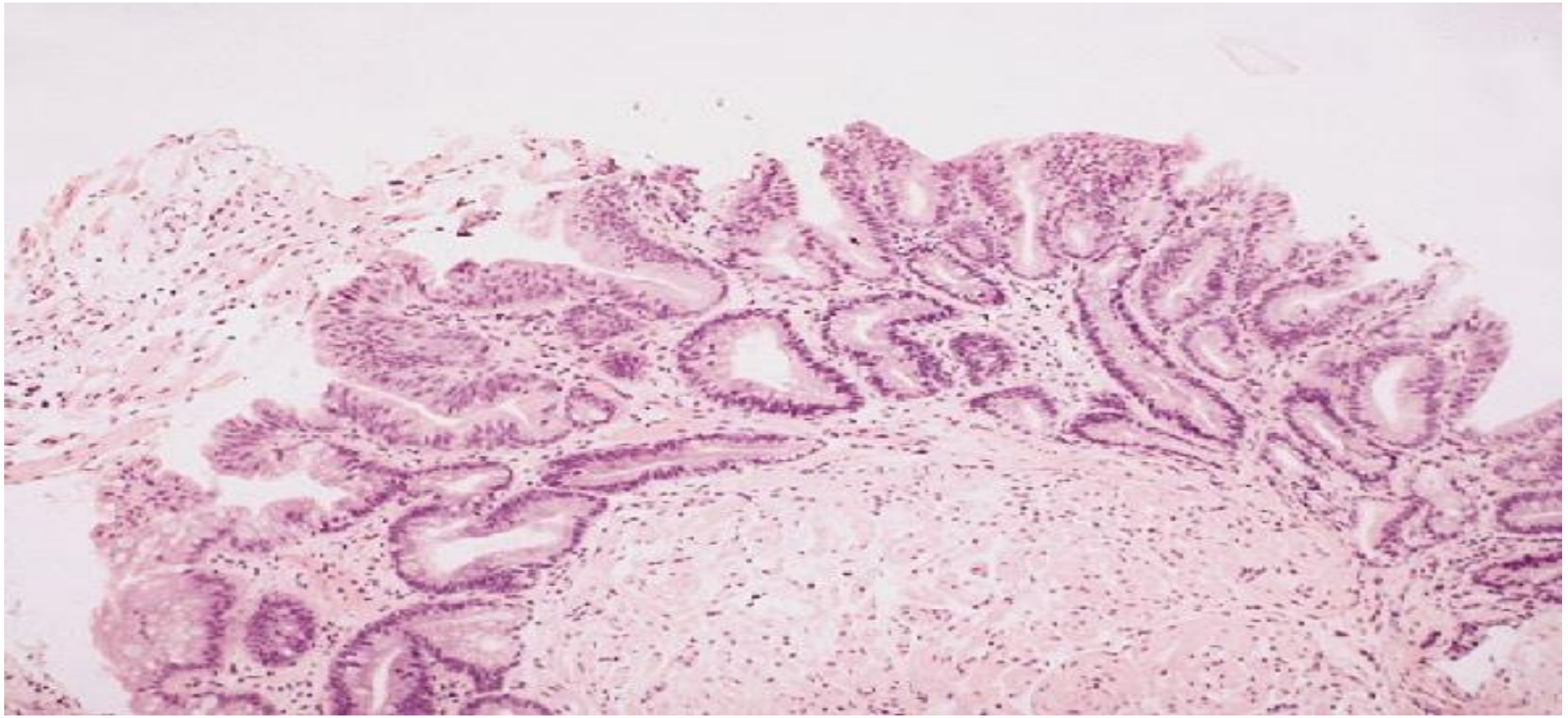
a) Extensive biopsy sampling involves taking four-quadrant biopsies at intervals of no more than 1 cm throughout the columnar-lined esophagus at intervals of 6 to 12 months .

b) Extensive biopsy sampling involves taking four-quadrant biopsies at intervals of no more than 2 cm throughout the columnar-lined esophagus at intervals of 6 to 12 months .

c) Extensive biopsy sampling involves taking four-quadrant biopsies at intervals of no more than 2 cm throughout the columnar-lined esophagus at intervals of 12 to 24 months .

d) Radiofrequency ablation

Low grade dysplasia



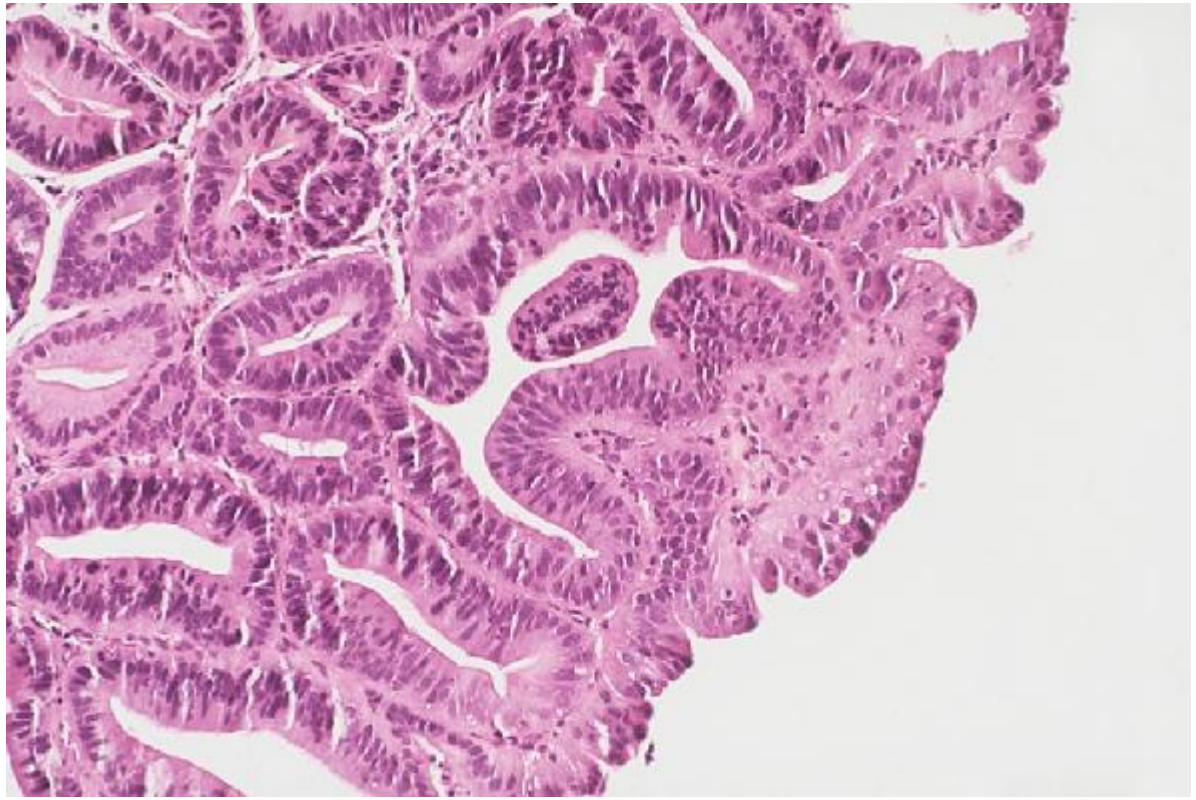
Low-grade dysplasia

- For patients found to have low-grade dysplasia, biopsy specimens should be obtained at 1 cm intervals and any mucosal irregularities should be removed with endoscopic resection.
- If biopsy specimens were not obtained at 1 cm intervals or a mucosal irregularity was not removed with endoscopic resection, endoscopy should be repeated as soon as possible to obtain these specimens.
- A finding of low-grade dysplasia on biopsies should be confirmed by a pathologist with expertise in esophageal histopathology because low-grade dysplasia in Barrett's esophagus is not diagnosed reliably .
- If a diagnosis of low-grade dysplasia is confirmed, we perform endoscopic eradication therapy with radiofrequency ablation (RFA)
- Alternative methods to achieve eradication include spray cryotherapy and endoscopic resection of the entire segment of Barrett's mucosa, but RFA is the preferred ablation technique

Low-grade dysplasia

- If the patient does not undergo endoscopic eradication therapy, surveillance endoscopy should be performed every six months for one year and then annually until there is reversion to nondysplastic Barrett's . Four quadrant biopsies should be obtained at 1 cm intervals.

TREATMENT OF HIGH-GRADE DYSPLASIA?



For younger patients with high-grade dysplasia in long-segment Barrett's esophagus best treatment is?

a) Esophagectomy
b) Radiofrequency ablation or photodynamic therapy
c) Endoscopic mucosal resection
d) Intensive endoscopic surveillance

TREATMENT OF HIGH-GRADE DYSPLASIA

- If biopsy specimens were not obtained at 1 cm intervals or a mucosal irregularity was not removed with endoscopic resection, endoscopy should be repeated as soon as possible to obtain these specimens.
- For patients with verified high-grade dysplasia (also called intraepithelial neoplasia) , there are generally four proposed management options:
  - Esophagectomy
  - Endoscopic therapies eg. radiofrequency ablation, photodynamic therapy
  - Endoscopic mucosal resection
  - Intensive endoscopic surveillance in which invasive therapies are withheld until biopsy specimens reveal adenocarcinoma.
- All four choices are associated with substantial risks and unclear benefits.

The choice of treatment for high-grade dysplasia and intramucosal cancer in Barrett's esophagus depends upon:

- The patient's age
  - (older patients with Barrett's esophagus are less likely to develop cancer due to their shorter life expectancy compared with younger patients)
- The patient's comorbidities
- The extent of dysplasia (short segments or Barrett's esophagus are easier to ablate than longer segments with multifocal dysplasia)
- Local expertise in surgery and endoscopy
- The patient's preferences with regard to undergoing surgery, undergoing repeated endoscopies, and accepting the possibility of recurrent neoplasia in the absence of esophagectomy

High-grade dysplasia

- For most patients with Barrett's esophagus and high-grade dysplasia who are fit to undergo endoscopy, we suggest endoscopic eradication therapy rather than esophagectomy or intensive endoscopic surveillance .
- Endoscopic eradication therapy includes endoscopic mucosal resection for the removal and staging of visible lesions (if present), followed by radiofrequency ablation or photodynamic therapy to ablate the remaining metaplastic epithelium.
- 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. Available data suggest that most patients achieve complete eradication, within three endoscopy sessions

The choice of treatment for high-grade dysplasia

- For younger patients with high-grade dysplasia, especially for those with long-segment Barrett's esophagus and multifocal dysplasia, esophagectomy is a reasonable alternative.
- After a thorough discussion with the younger patient of the risks and benefits of endoscopic eradication therapy and esophagectomy, the choice between the two should be based on patient preferences and the availability of skilled practitioners.
- For very elderly or infirm patients for whom invasive endoscopic procedures pose a substantial risk, intensive endoscopic surveillance is reasonable.

TREATMENT OF HIGH-GRADE DYSPLASIA

- *For HGD and Barrett's-related adenocarcinoma confined to the mucosa, endoscopic therapy is preferred over oesophagectomy or endoscopic surveillance (Recommendation grade B).*
- *Surgical therapy is considered the treatment of choice for early adenocarcinoma that has extended into submucosa because of the significant risk of lymph node metastasis (Recommendation grade B).*

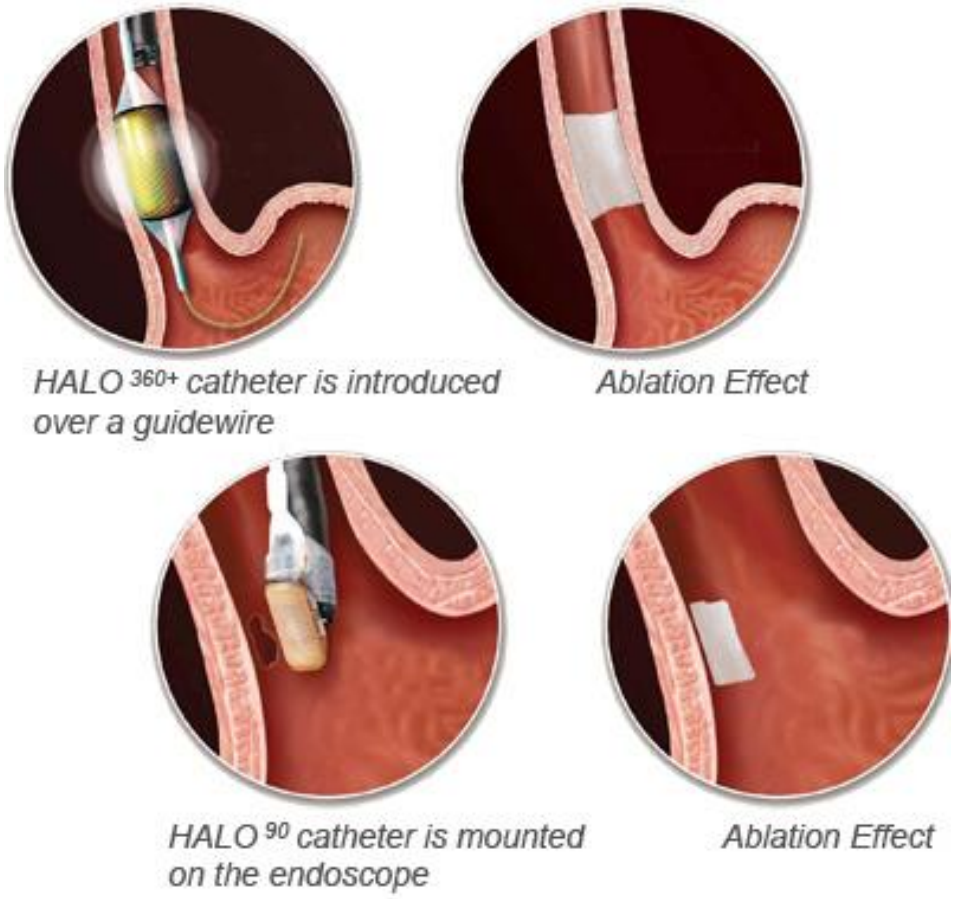
Esophagectomy

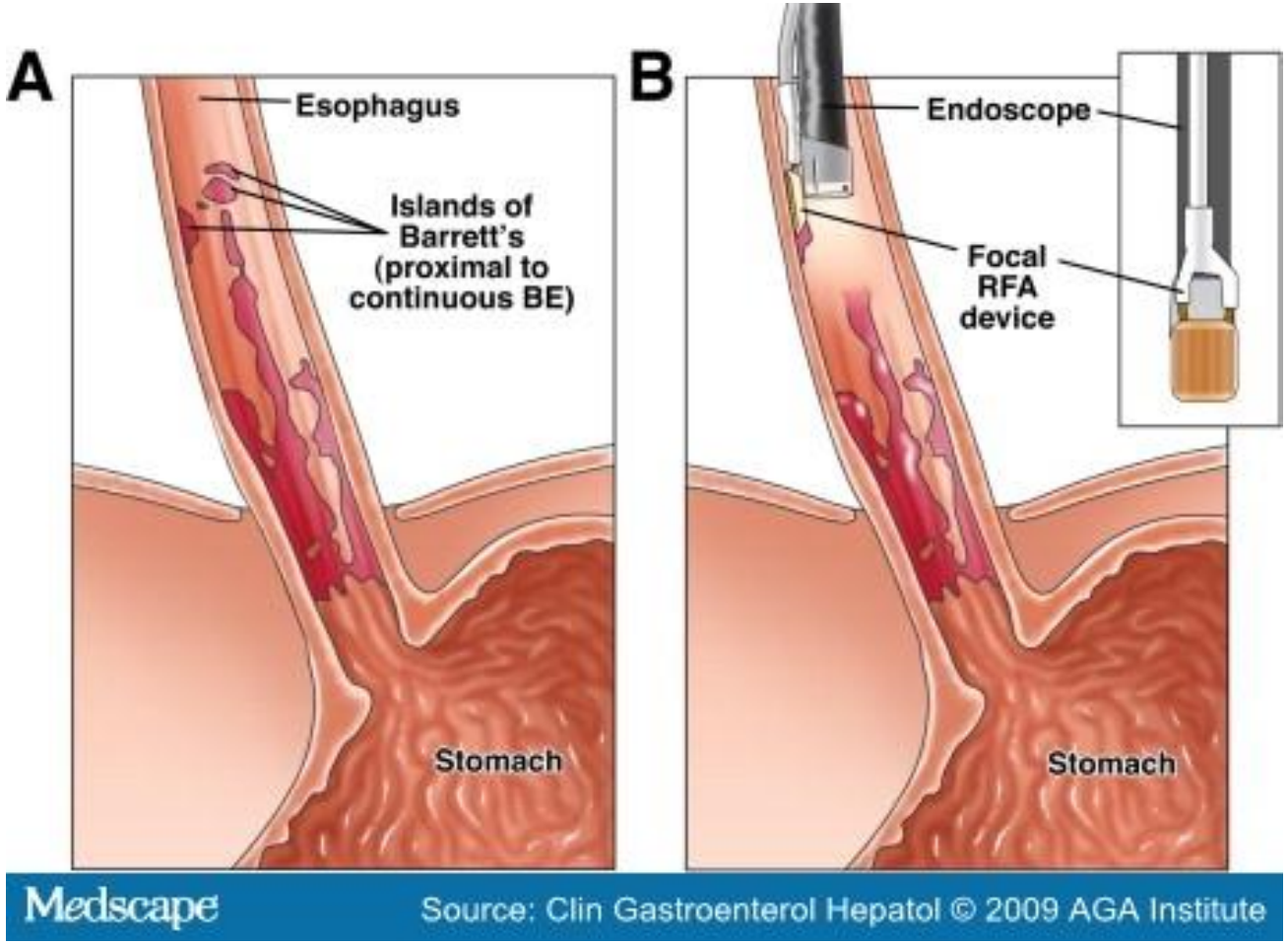
- Esophagectomy is the only therapy for high-grade dysplasia that clearly removes all of the neoplastic epithelium along with any occult malignancy and regional lymph nodes
- However, this definitive therapy also has the highest rates of procedure-related mortality (3-12 %)and long-term morbidity.
- However, the authors argue that the risk of lymph node metastases alone does not warrant the choice of esophagectomy over endoscopic eradication therapy because esophagectomy has a mortality rate that likely exceeds the rate of lymph node metastases. In addition, esophagectomy does not guarantee cure for a tumor that already has metastasized to lymph nodes.
- With the development of efficacious endoscopic therapies, esophagectomy can now often be avoided.

Endoscopic ablative therapies

- Endoscopic ablative therapies use thermal, photochemical, or radiofrequency energy to ablate the abnormal epithelium in Barrett's esophagus .
  - KTP laser
  - argon laser
  - Nd:YAG laser
  - multipolar electrocoagulation
  - argon plasma coagulation
  - photodynamic therapy
  - radiofrequency ablation
- The most commonly used treatments include radiofrequency ablation and photodynamic therapy.
- One major concern is that the procedures may not eradicate all of the dysplastic cells. Partially-ablated metaplastic mucosa can heal with an overlying layer of squamous epithelium that hides the "buried" metaplastic tissue from the endoscopist

Radiofrequency ablation





Radiofrequency ablation

- often used in conjunction with EMR
- RFA has been shown to be highly effective in completely eradicating intestinal metaplasia and all grades of dysplasia and neoplasia, and on average required 3–4 treatment sessions for eradication
- RFA is widely accepted as first-line therapy given efficacy and safety; however, adverse effects can include, most commonly, strictures, bleeding, and pain.

Hybrid Argon Plasma Coagulation (APC)

- Uses the combination of a submucosal injection of saline followed by APC ablation. This hybrid technique was developed to improve tolerability and decrease risk of stricture formation
- Repeat hybrid APC treatment sessions have been performed at 6–12 weeks follow-up with biopsies to assess for successful eradication

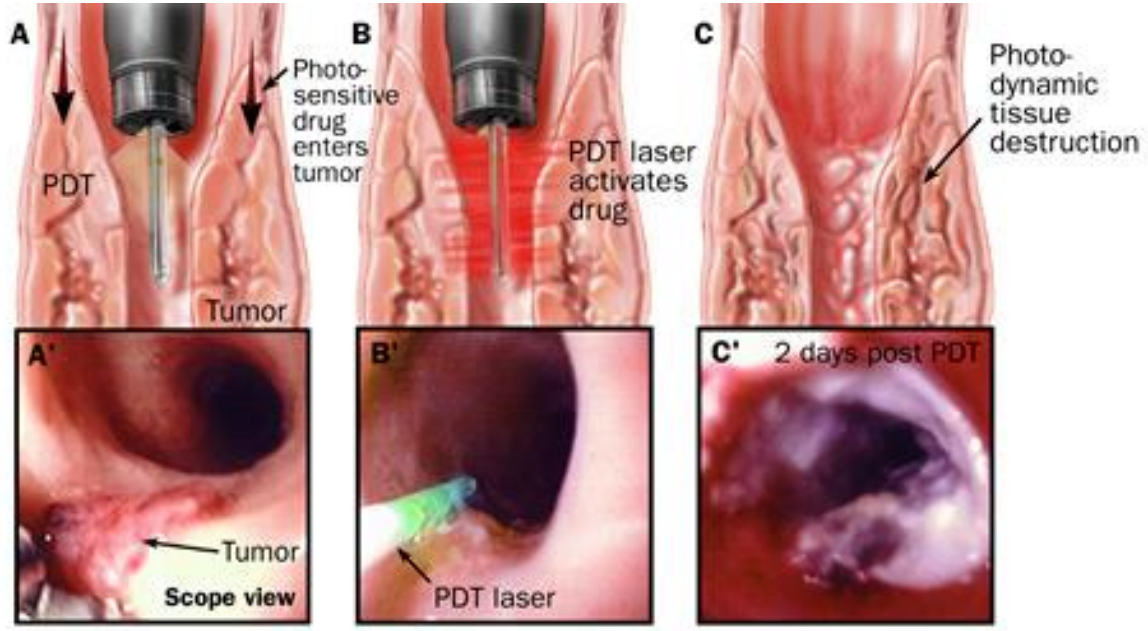
Photodynamic Therapy (PDT)

PDT Technique:

•. PDT patients are injected with a photosensitizer to render their tissue extremely sensitive to laser light.

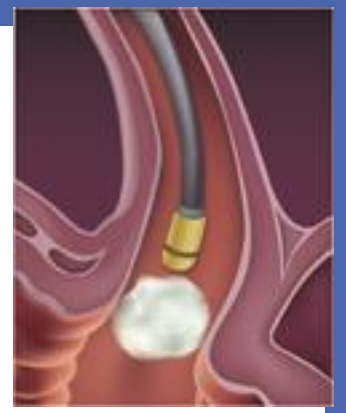
•The lesion is then illuminated with a laser light of proper power and wavelength, or color.

•The interaction of laser light and the photosensitizer causes a chemical reaction, killing the abnormal cells.



PDT, or Photodynamic Therapy, is a treatment that was used as an alternative to surgery in non-surgical candidates for the treatment of high-grade dysplasia and early cancers.

Endoscopic spray cryotherapy



- A cryotherapy system is used to apply cold nitrogen or carbon dioxide gas endoscopically to the BE. The tissue is frozen for a total of approximately 40 seconds (two 20-second applications or four 10-second applications).
- Endoscopic follow-up and as needed serial cryotherapy is performed approximately every 3 months.
- Various techniques, from liquid nitrogen spray to compressed carbon dioxide to cryo-balloon therapy
- Lesser side effect profile in terms of stricture development and post-procedural pain

Endoscopic resection

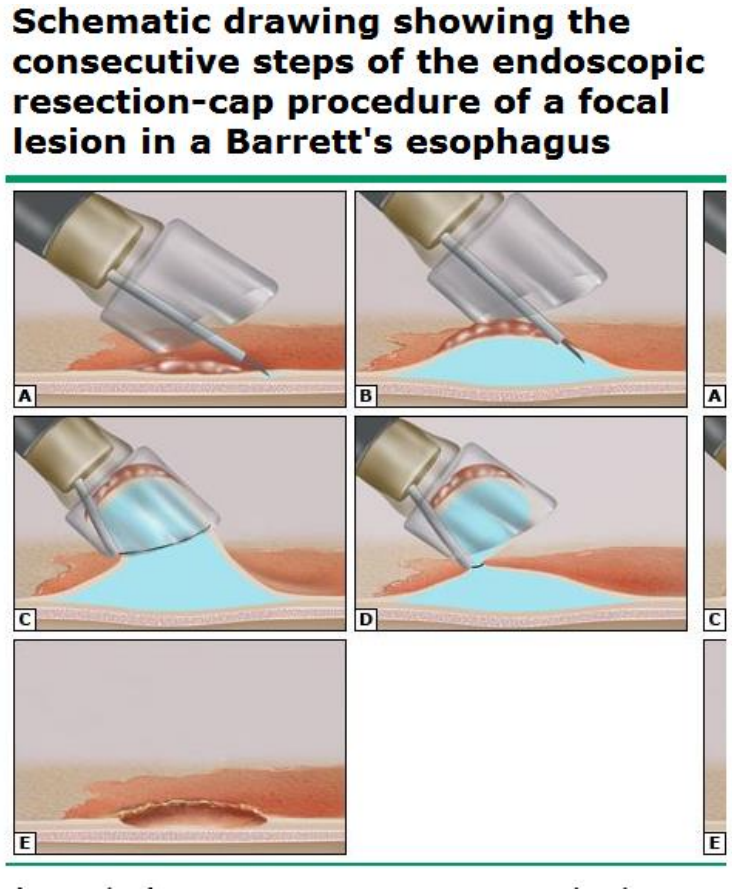
- Endoscopic resection (ER) includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).
- ER provides large tissue specimens that can be examined by the pathologist to determine the character and extent of the lesion, and the adequacy of resection.
- The American Society for Gastrointestinal Endoscopy has issued guidelines that recommend ER for the treatment and staging of nodular BE and suspected intramucosal adenocarcinoma
- EMR for Barrett's esophagus have come from only a handful of highly specialized centers

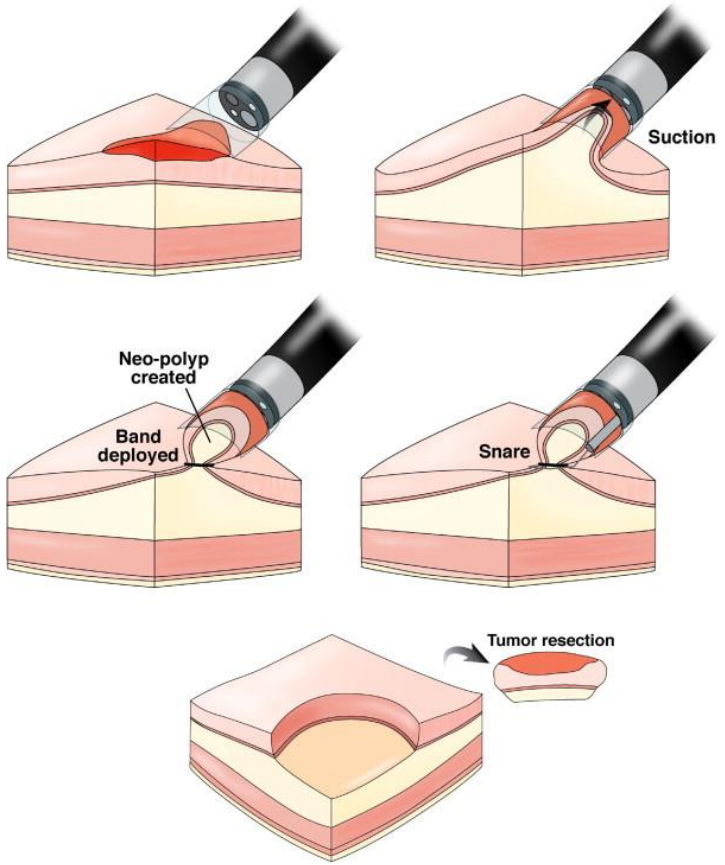
Endoscopic eradication therapy or EMR

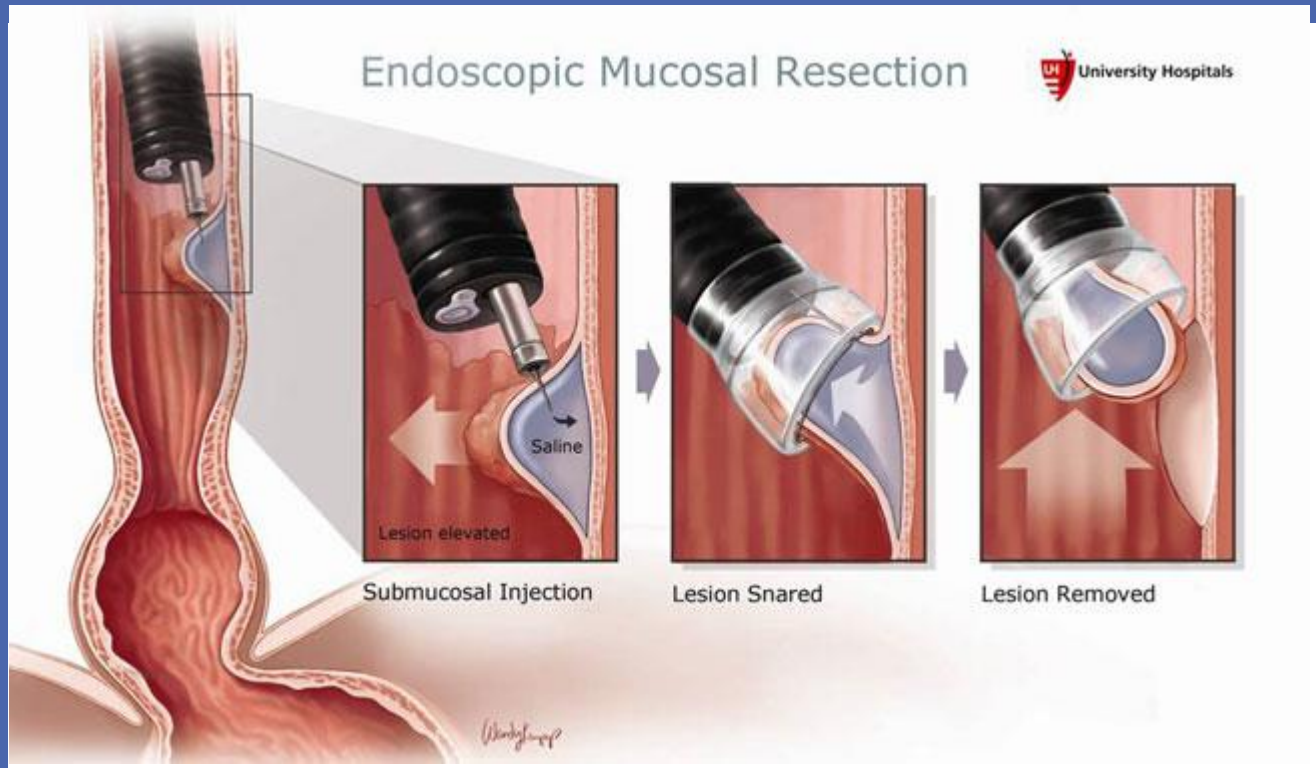
- Endoscopic eradication therapy with radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection (EMR) rather than surveillance is recommended for treatment of patients with confirmed high-grade dysplasia within Barrett's esophagus.
- EMR is recommended for patients who have dysplasia in Barrett's esophagus associated with a visible mucosal irregularity to determine the T stage of the neoplasia.

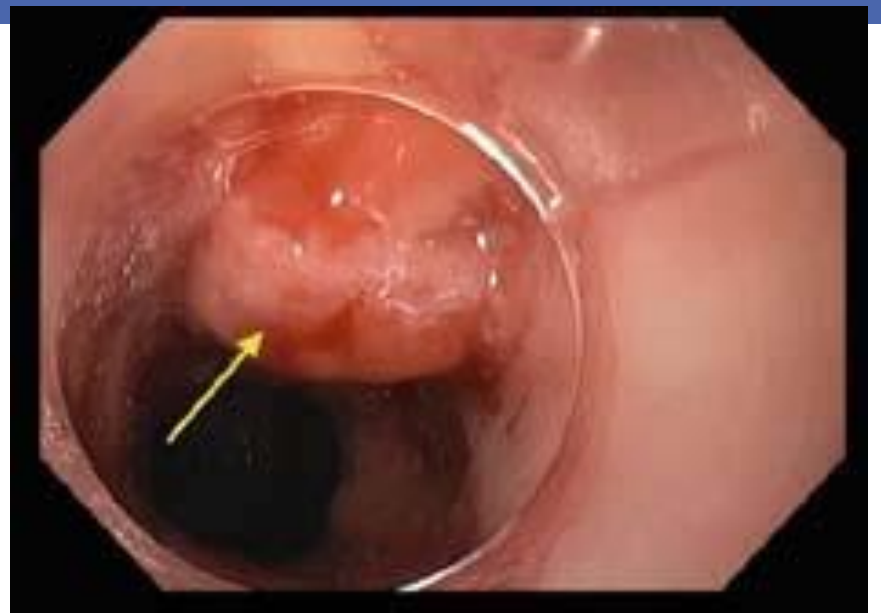
For well-differentiated dysplasia without lymphovascular invasion, EMR can be considered curative if the lesion is superficial and resection margins are negative .

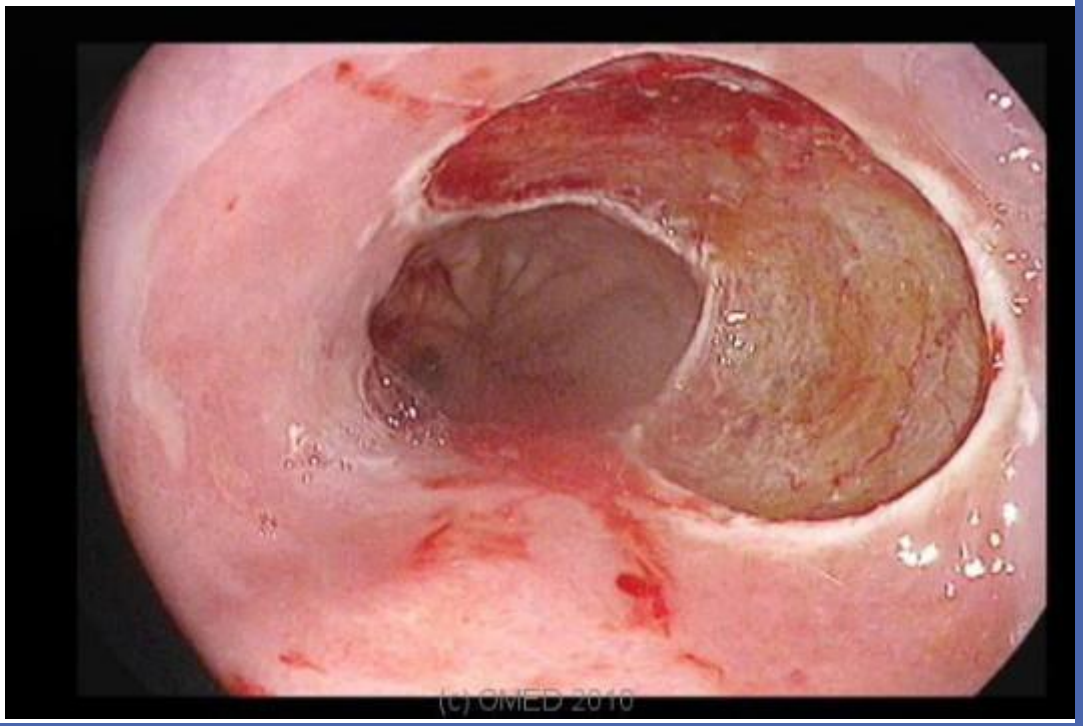
For cases of circumferential, short segment BE, EMR may be a staged procedure and be completed in more than one session.






Endoscopic Mucosal Resection
University Hospitals
Saline
Lesion elevated
Submucosal Injection
Lesion Snared
Lesion Removed

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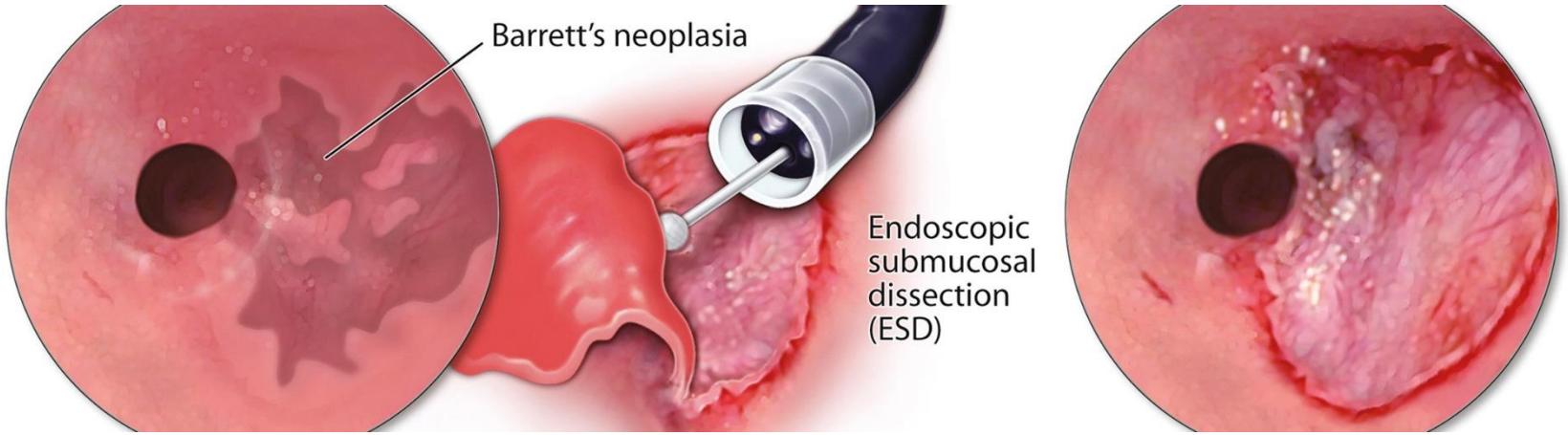
Endoscopic Submucosal Dissection (ESD)

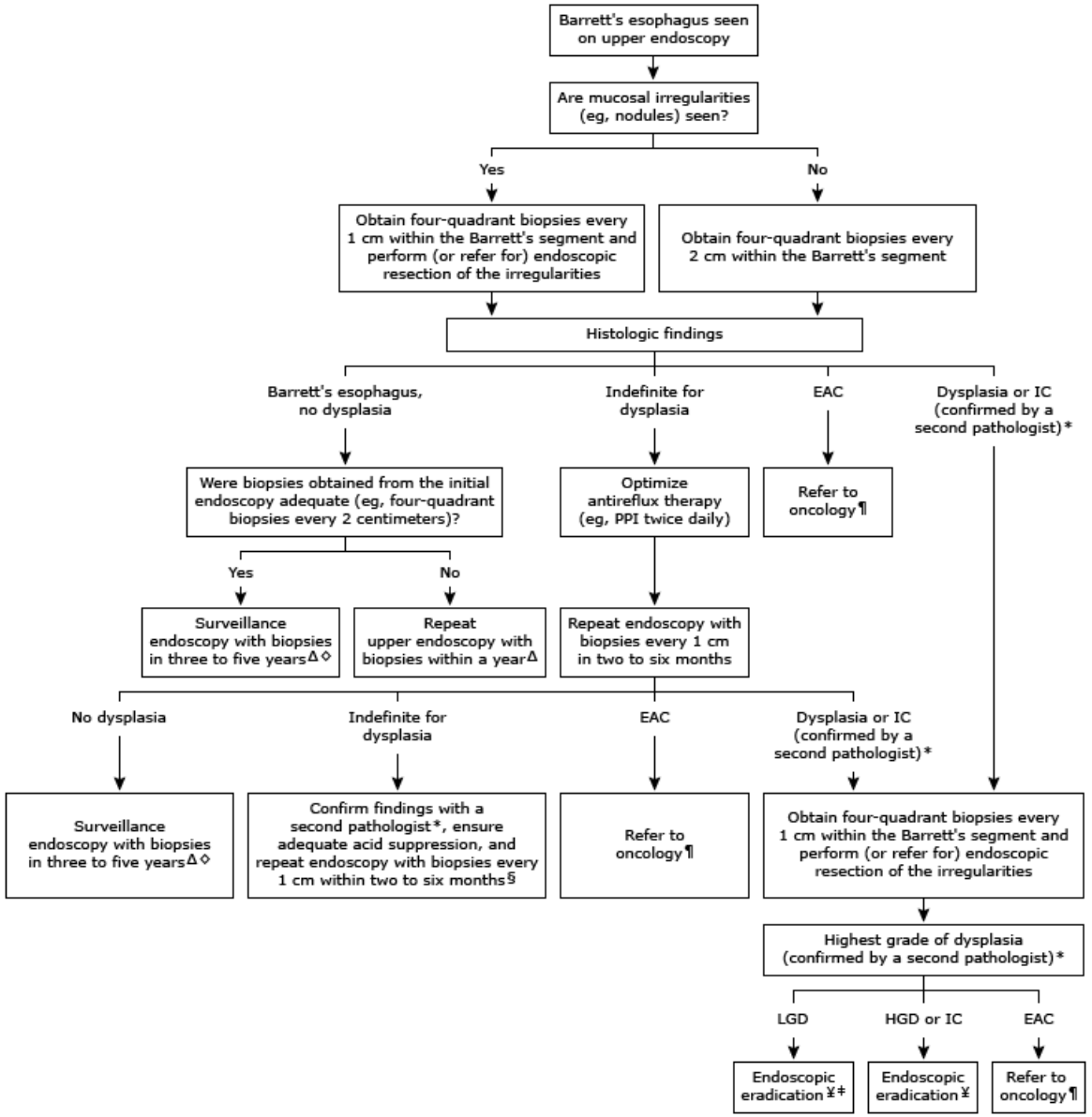
- This modality aims to remove entire lesions, accommodating for varying widths and depths
- ESD cure rate of 92.3% compared to that of EMR with 52.7% cure
- Significantly lower recurrence rate in ESD (0.3%) compared to EMR (11.5%)
- For the same reason, ESD are being used to treat submucosal (T1b-Sm1) lesions.
- Procedure time may be a limiting factor, as the mean EMR time was 36.7 min while the mean ESD time was 83.3 minutes



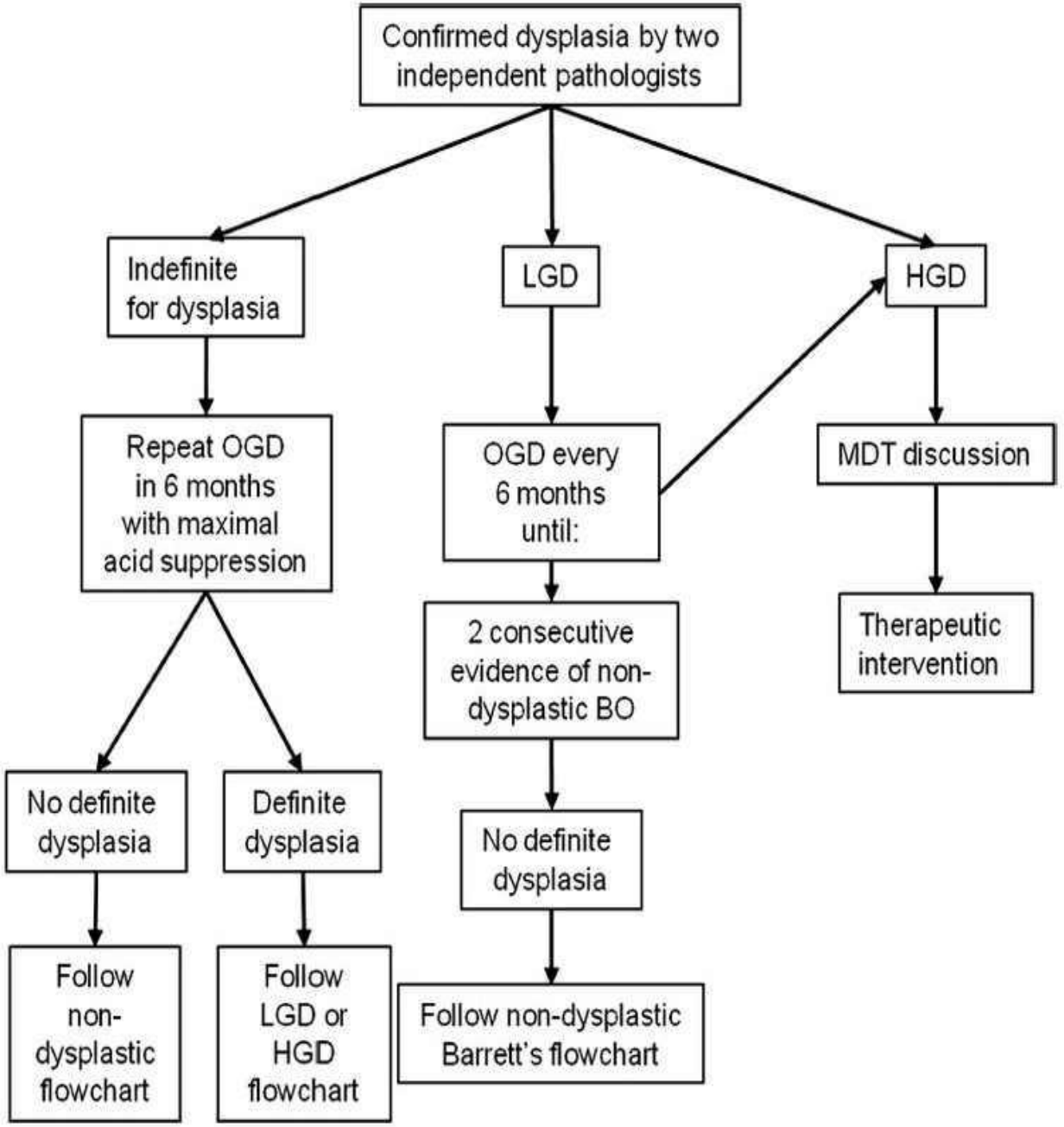
For patients with Barrett's esophagus who are undergoing surveillance, the AGA recommends:

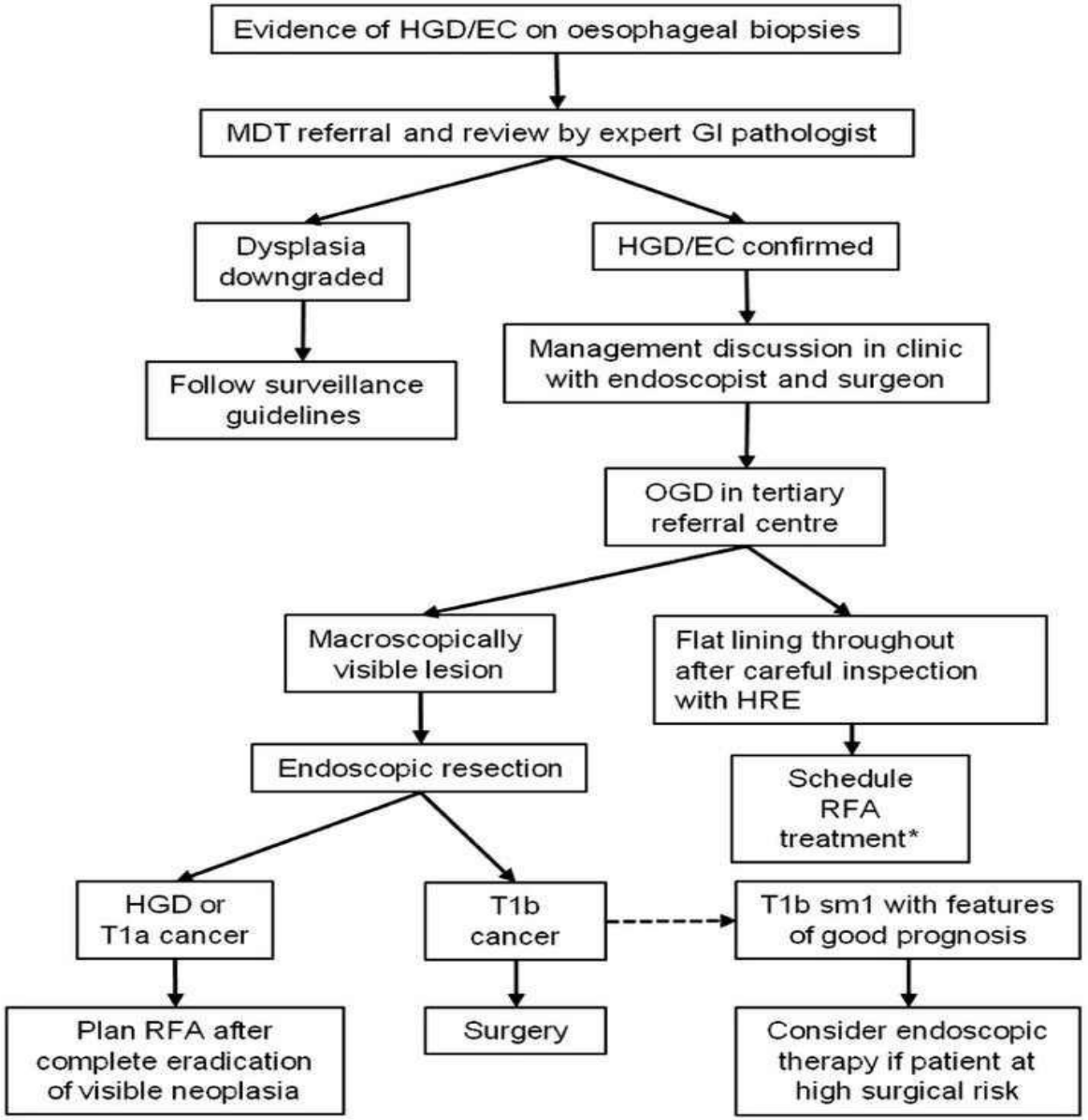
- Endoscopic evaluation using white light endoscopy
- Four-quadrant biopsy specimens be taken every 2 cm
- Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist
- Four-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia

Surveillance and management of Barrett's esophagus



IC: intramucosal carcinoma; EAC: esophageal adenocarcinoma; PPI: proton pump inhibitor; LGD: low-grade dysplasia; HGD: high-grade dysplasia.


Confirmed dysplasia by two independent pathologists
Indefinite for dysplasia
LGD
HGD
Repeat OGD in 6 months with maximal acid suppression
OGD every 6 months until:
MDT discussion
2 consecutive evidence of non-dysplastic BO
Therapeutic intervention
No definite dysplasia
Definite dysplasia
No definite dysplasia
Follow non-dysplastic flowchart
Follow LGD or HGD flowchart
Follow non-dysplastic Barrett's flowchart



* Repeat mapping biopsies may be useful to understand the spatial extent of the dysplasia, however repeat evidence of HGD is not necessary to initiate treatment pathway due to sampling error

Endoscopic surveillance

- We do not recommend routine endoscopic treatment for patients with low-grade dysplasia or nondysplastic Barrett's esophagus.
- Endoscopic surveillance is suggested for patients with Barrett's esophagus using the following surveillance intervals:
  - ✓No dysplasia: 3 to 5 years
  - ✓Low-grade dysplasia: 6 to 12 months
  - ✓High-grade dysplasia in the absence of eradication therapy: 3 months

Are you suggest the use of aspirin solely to prevent esophageal adenocarcinoma in the absence of other indications?

Chemoprevention

- Epidemiological data suggest that aspirin and other NSAIDs, which inhibit cyclooxygenase (COX), may protect against the development of Barrett's esophagus or, in patients with established Barrett's esophagus, the development of cancer
- Even if NSAIDs are effective in preventing the progression to cancer, it is not clear that the high cost and cardiovascular risks of the COX-2 selective NSAIDs will be justified for routine clinical use.
- Aspirin , an inexpensive, non-selective NSAID that can prevent cardiovascular as well as neoplastic complications, might be a useful drug if its protective effects can be shown to outweigh its risk of gastrointestinal complications
- The combination of NSAIDs and statins also appears to provide extra protection against neoplastic progression in patients with Barrett's esophagus.

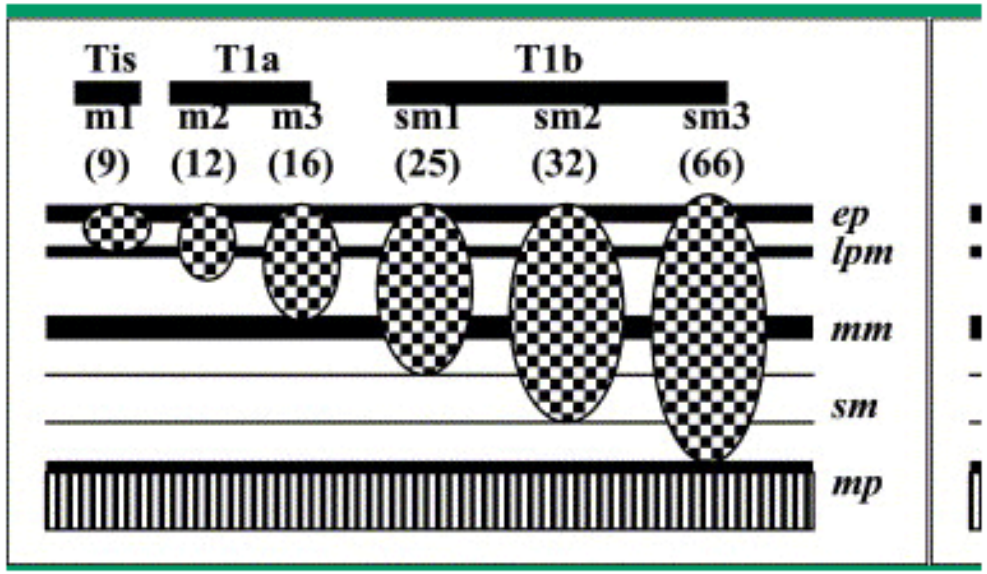
Chemoprevention

- The AGA suggests against the use of aspirin solely to prevent esophageal adenocarcinoma in the absence of other indications. However, it recommends screening patients to identify cardiovascular risk factors for which aspirin therapy is indicated
- *There is currently insufficient evidence to support the use of aspirin, NSAIDs or other chemopreventive agents in patients with Barrett's esophagus (Recommendation grade C).*

GUIDELINES

- No management strategy for patients with Barrett's esophagus has been proven to prolong life.

Subclassification of the depth of superficial esophageal cancer (number of patients)



Proportion of patients without recurrence of Barrett's esophageal cancer according to depth of invasion after esophagectomy (from Westerterp M et al, Virchows Arch 2005; 446:497).

Class	Description
T1a	
m1	Carcinoma in situ or with questionable invasion beyond the basement membrane
m2	Invasion into the lamina propria
m3	Invasion into the muscularis mucosa
T1b	
sm1	Invasion into the upper third of the submucosa within 500 µm
sm2	Invasion into the middle third of the submucosa
sm3	Invasion into the lower third of the submucosa

- *ER should be considered the therapy of choice for dysplasia associated with visible lesions and T1a adenocarcinoma (Recommendation grade B).*
- *For patients at high surgical risk, endoscopic therapy can be offered as an alternative to surgery for treatment of good prognosis T1b adenocarcinomas (T1b sm1, well differentiated and without lymph vascular invasion) (Recommendation grade C).*
- *For T1b adenocarcinomas with involvement of the second submucosal layer or beyond (T1b sm2–sm3), endoscopic therapy should not be considered curative (Recommendation grade B)*

- *Before ER, neither CT nor PET–CT have a clear role in the staging of patients with Barrett's HGD or suspected T1 cancer and neither is routinely required (Recommendation grade B).*
- *Since EUS can both overstage and understage T1 lesions, its routine use cannot be recommended for staging before ER for suspected early lesions (Recommendation grade B).*
- *In selected cases where the endoscopist cannot exclude advanced stage on the basis of endoscopic appearance of nodular lesions, EUS with or without FNA is recommended to inform the therapeutic decision (Recommendation grade C).*
- *EUS with or without FNA of visible lymph nodes is recommended in selected cases with T1b (sm1) disease on staging ER for which endoscopic therapy is selected, because of the significant risk of lymph nodal involvement (Recommendation grade C).*