UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
AA 2023-24

Esophageal disorders

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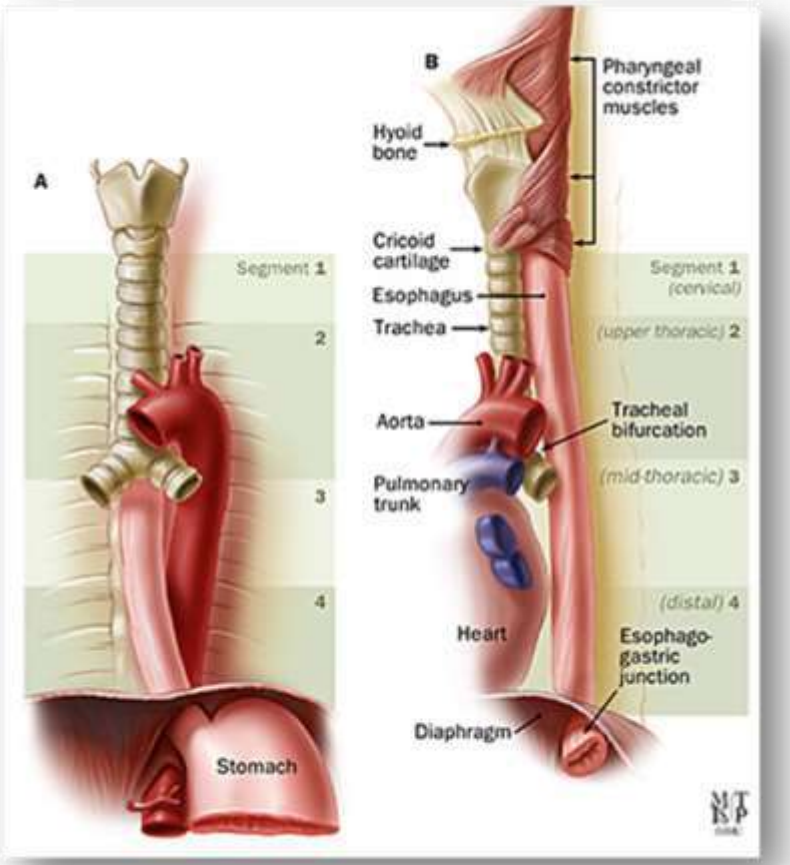
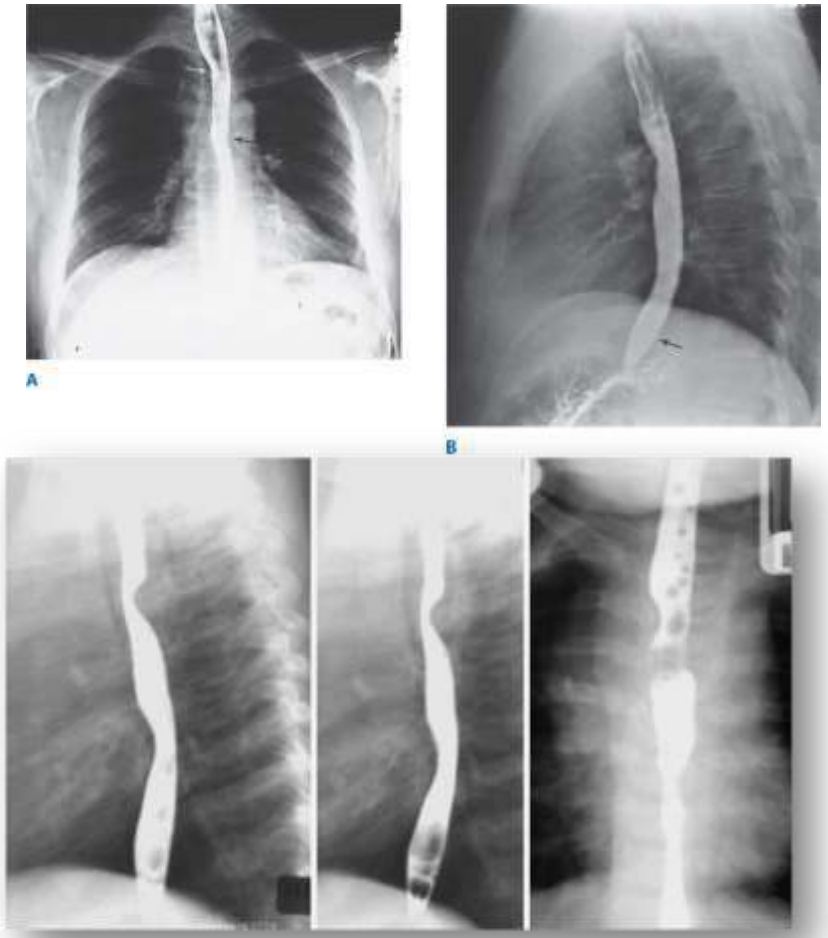
Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Functional anatomy and diagnosis of esophageal disorders

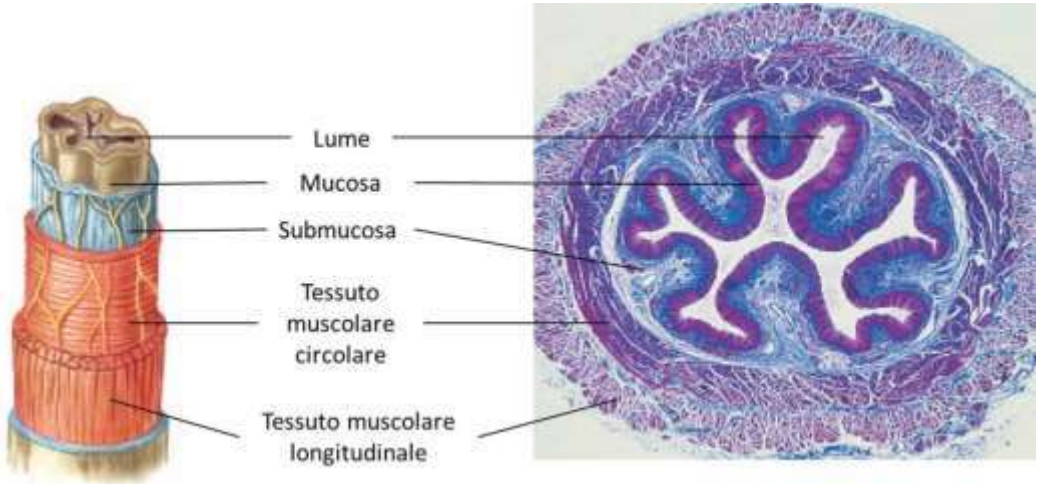
Esophageal anatomy

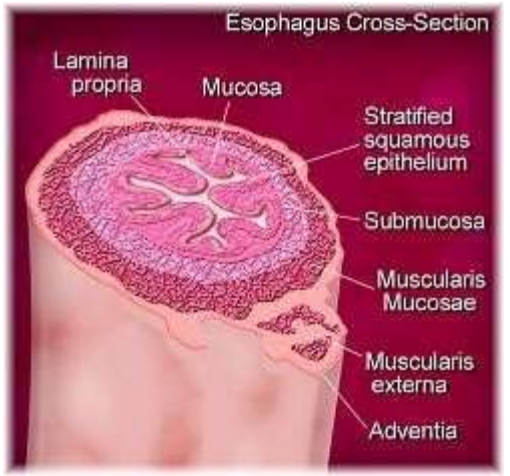




- The esophagus acts as a conduct for the transport of food from the oral cavity to the stomach.
- The esophagus is a 18- to 26-cm hollow muscular tube with an inner skinlike lining of stratified squamous epithelium.
- Between swallows, the esophagus is collapsed, but the lumen distends up to 2 cm anteroposteriorly and 3 cm laterally to accomodate the swallowed bolus.

Esophageal structure



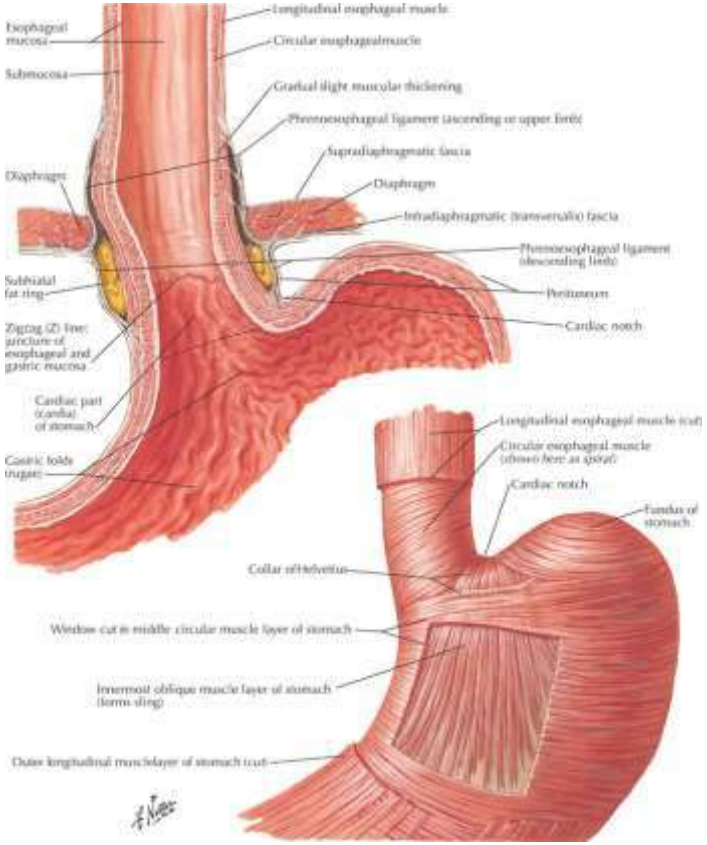


The esophageal wall is composed of four layers:

- innermost mucosa, composed by **nonkeratinized stratified squamous** epithelium;
- submucosa, that comprises a dense network of connective tissue within which are bood vessels, lymphatic channels, neurons of Meissner plexus and esophageal glands;
- muscularis propria that is responsible for carryng out transport function. **The upper 5-33% are composed of skeletal muscle**, the distal **33% are composed of smooth muscle** and in between is a mixture of both types. The muscular wall separates to inner circular and outer longitudinal layers
- outermost avventitia that is an external fibrous layer that covers the esophagus, connecting it with neighboring structures. It is composed of loose connective tissue and contains small vessels, lymphatic channels, and nerve fibers.

Unlike the remainder of the gastrointestinal tract, esophagus has no serosa.

The lower esophageal sphincter (LES)



The esophagogastric junction is the only area of gastrointestinal tract in which contiguous hollows have opposite pressure values: this difference is maintained by a mechanism controlled by LES that permits the presence of a positive intragastric (abdominal) pressure and a negative intraesophageal (thoracic) pressure.

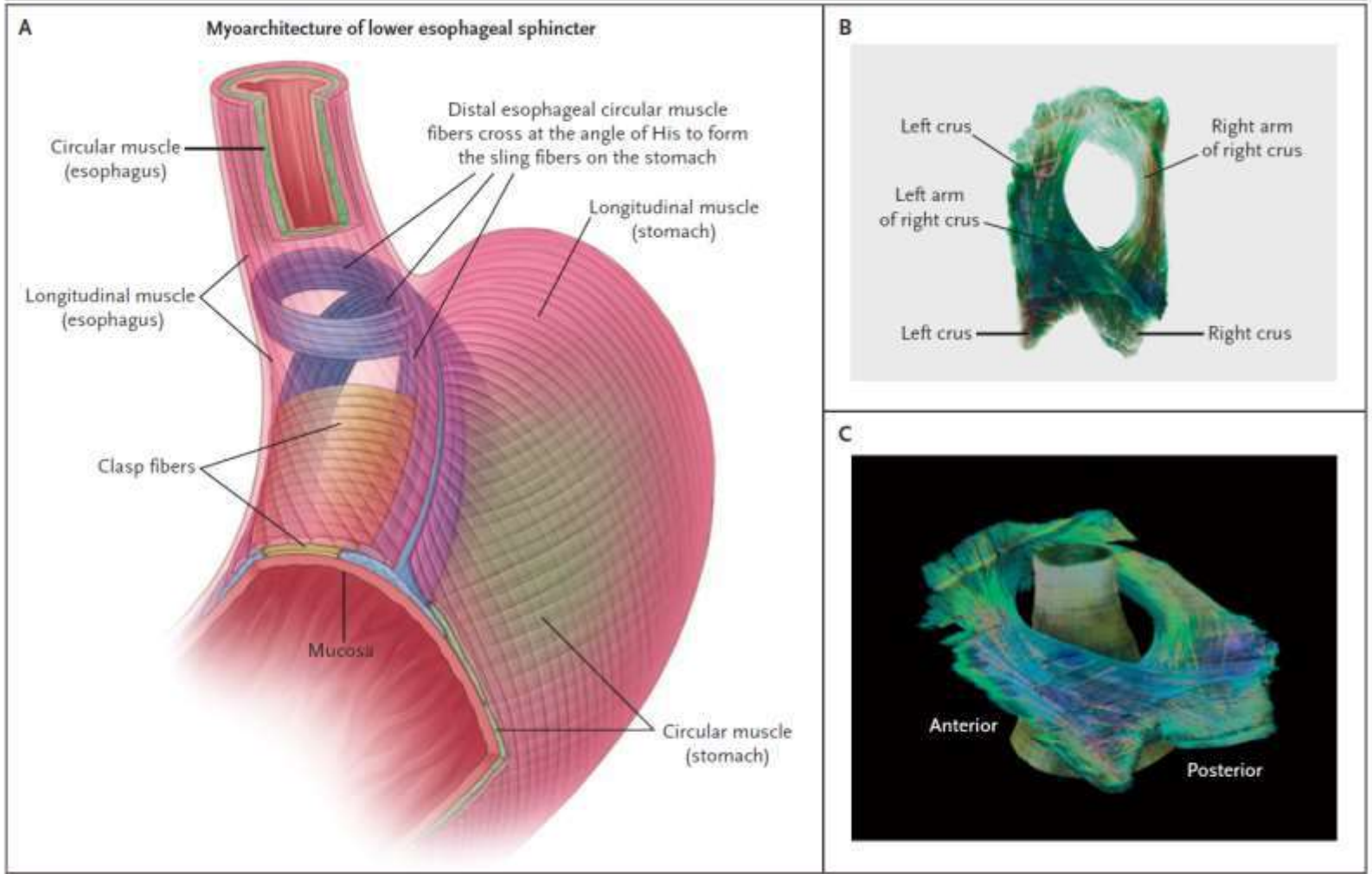
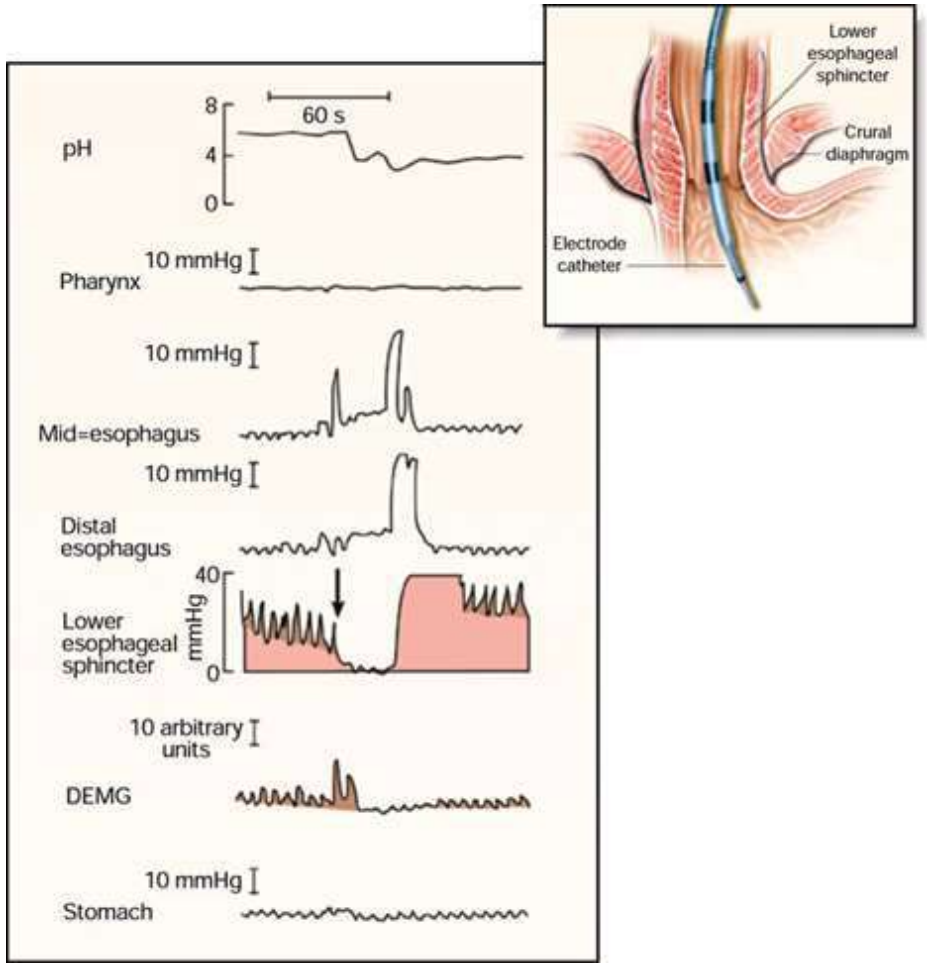


Figure 1. Myoarchitecture of the Lower Esophageal Sphincter and Hiatus.

Panel A shows the microscopic myoarchitecture of the circular and longitudinal muscle layers of the lower esophageal sphincter and stomach. The circular muscle fibers of the esophagus cross each other at the angle of His to continue as the oblique muscle fibers (innermost muscle layer of the stomach) on the ventral and dorsal surface of the stomach. Panels B and C show the microscopic anatomy of the esophageal hiatus in superior view and posterior view, respectively. The two bundles of the right crus cross each other first and then encircle the esophagus to form the esophageal hiatus at the posterior–inferior and anterior–superior ends.

An example of swallow-induced lower esophageal sphincter (LES) relaxation (left) and transient LES relaxation (right)



Esophageal disorders Endoscopy

Diagnosis

Endoscopy

Conventional radiology

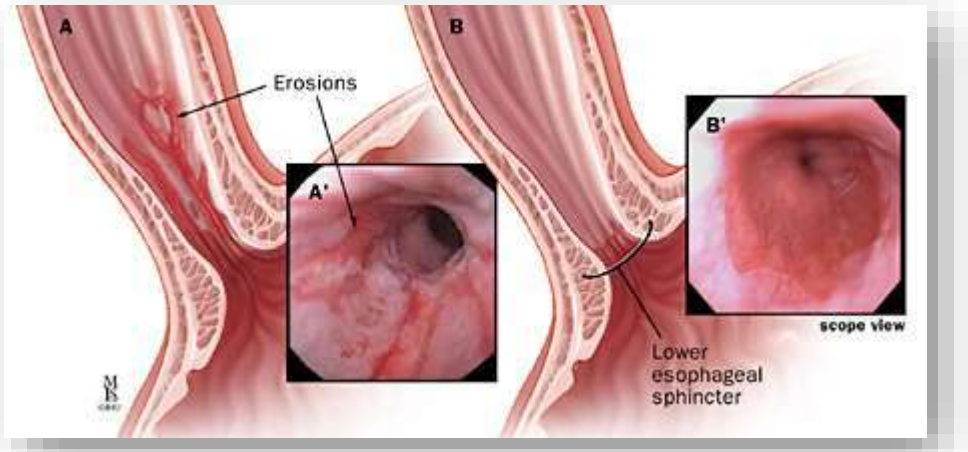
CT

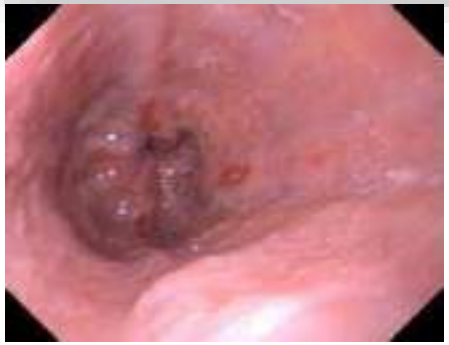
MR

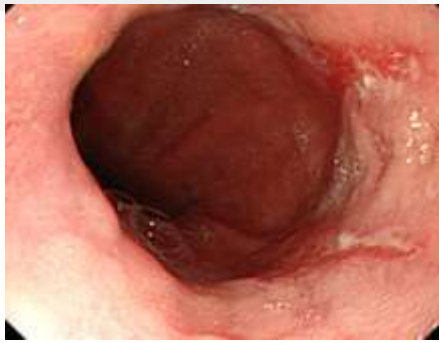
EUS (endoscopic US)

Manometry

pH-metry

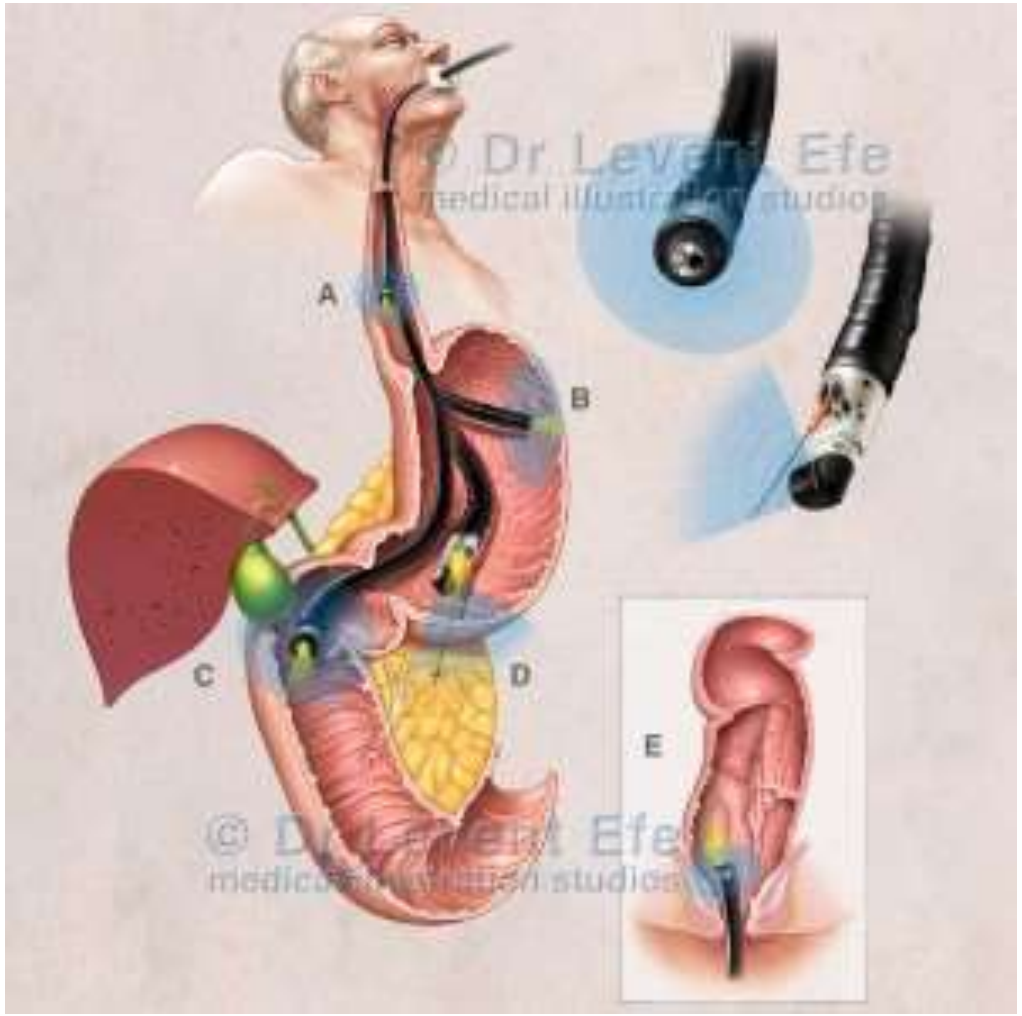






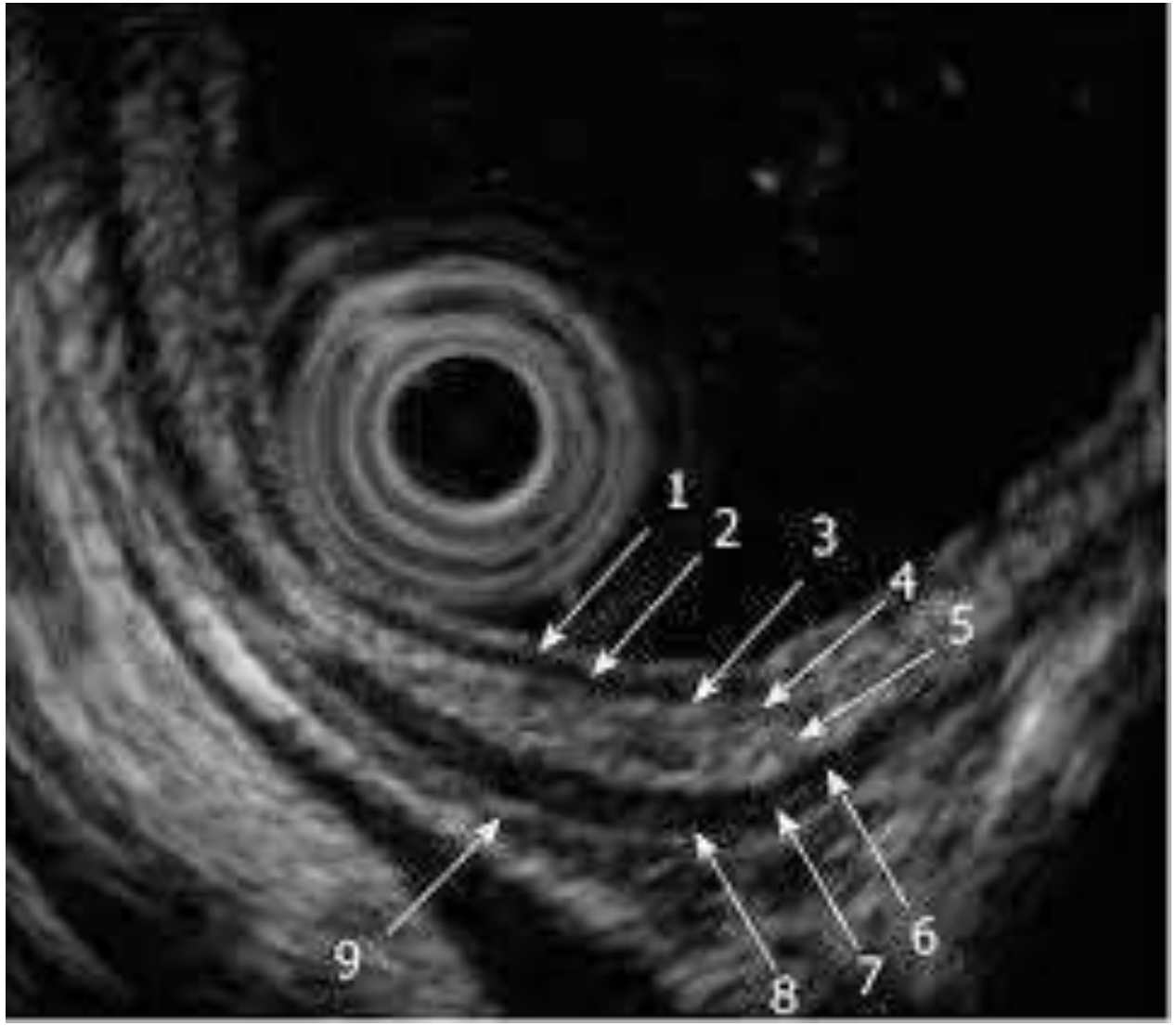
Esophageal disorders

Endoscopic ultrasound

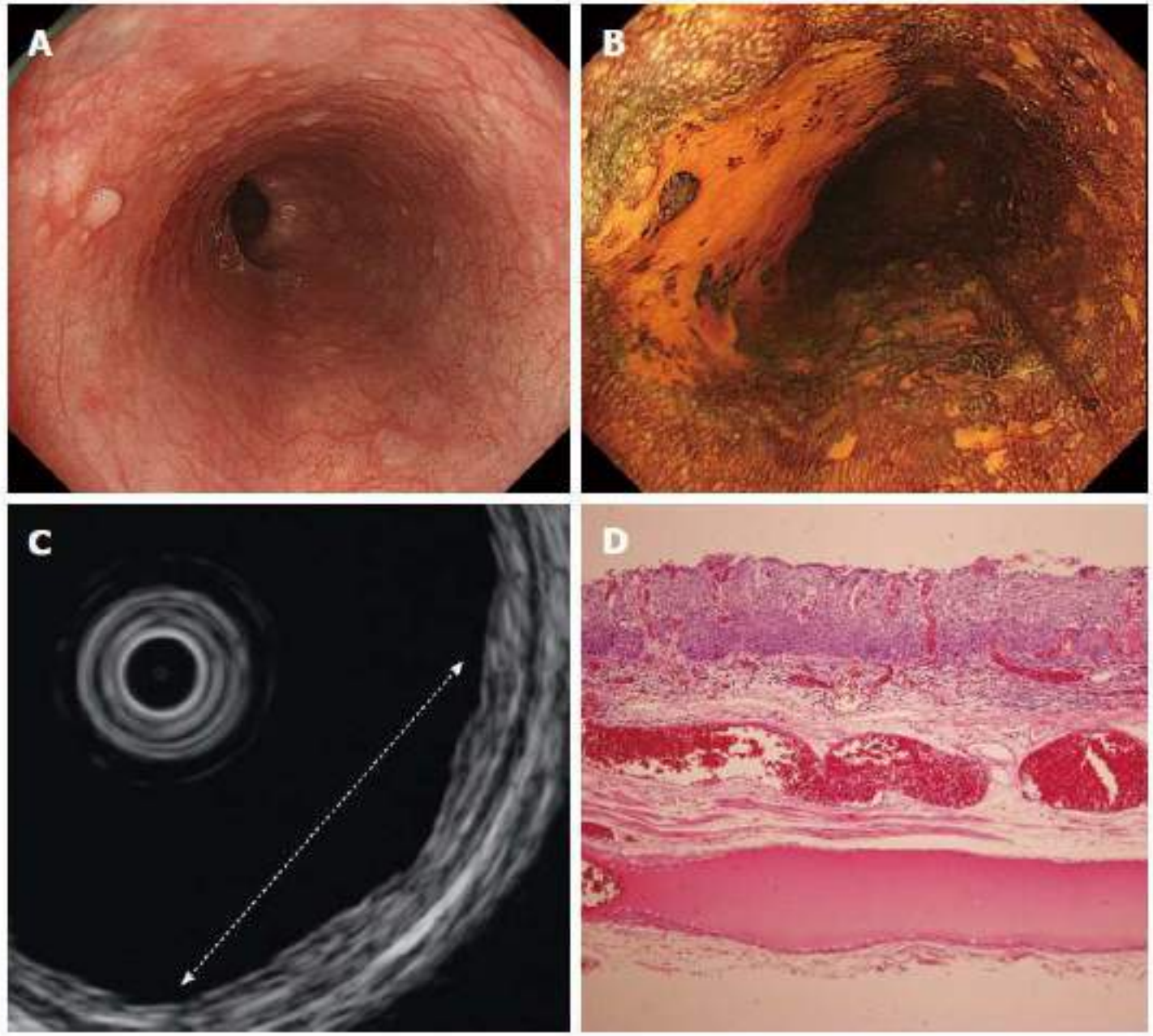


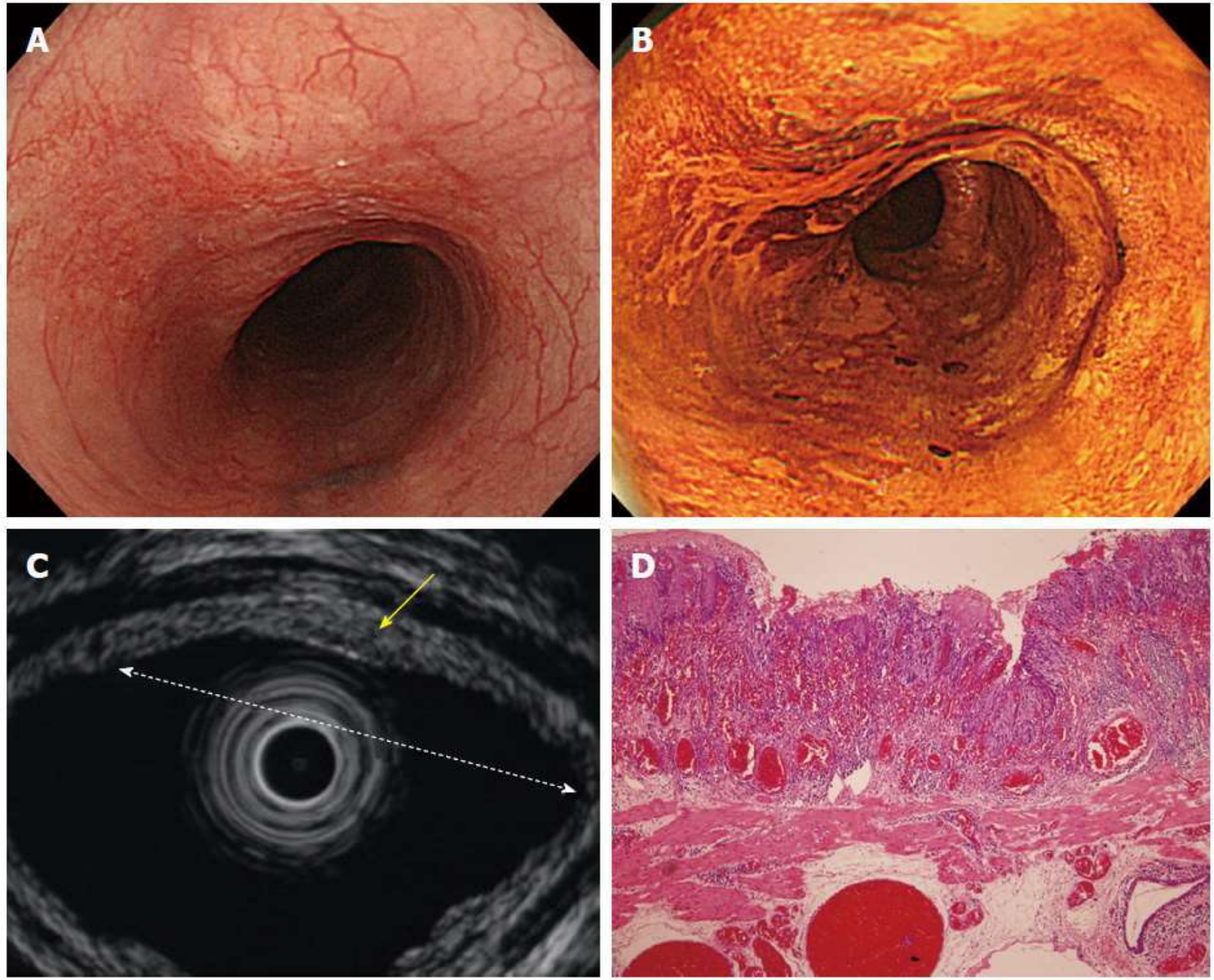
Linear

Radial (360°)



1-4 Mucosa 5 Sottomusa 5-8 Muscular layers 9 Avventia


A
B
C
D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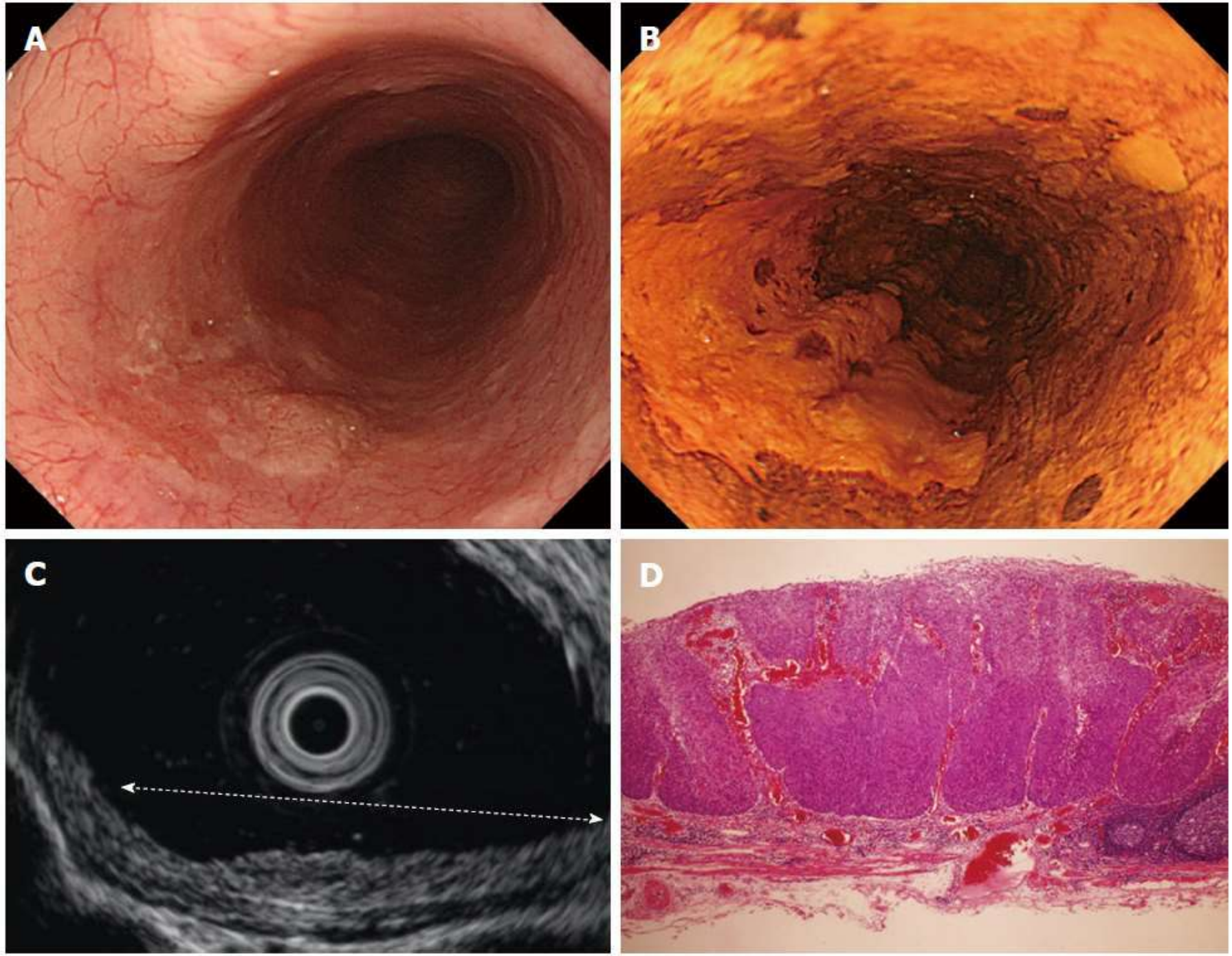
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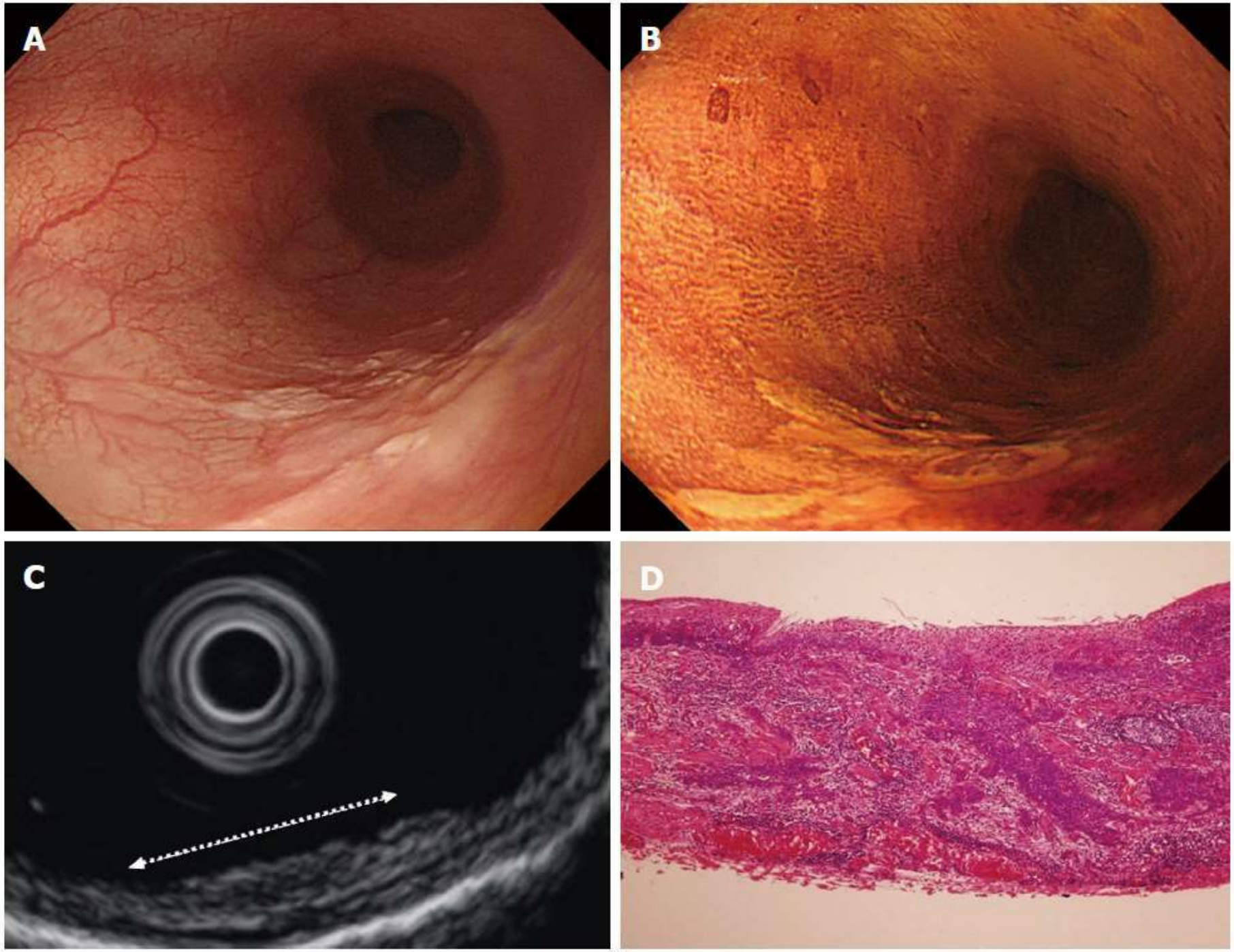
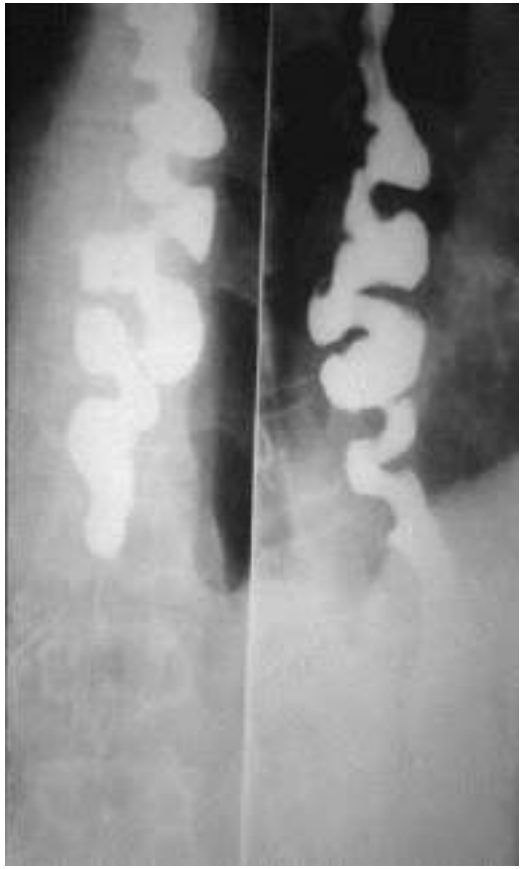
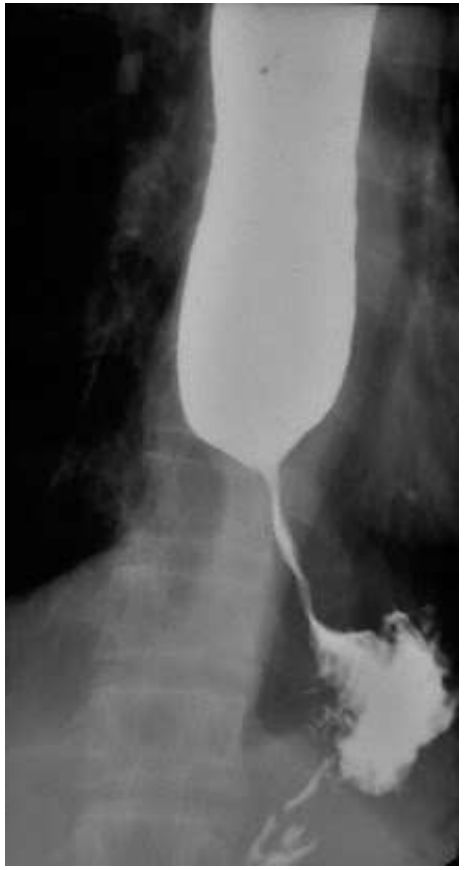
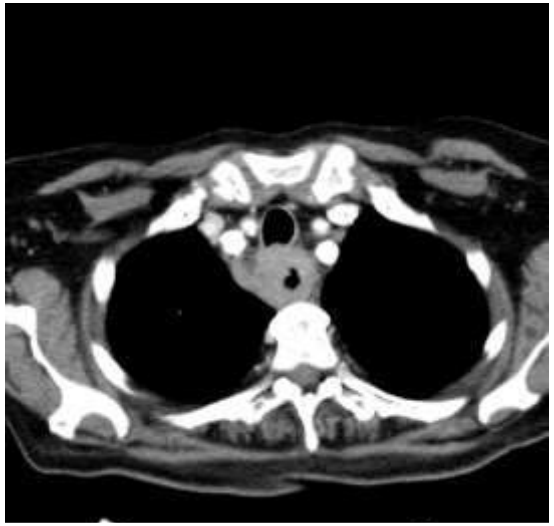

A
B
C
D

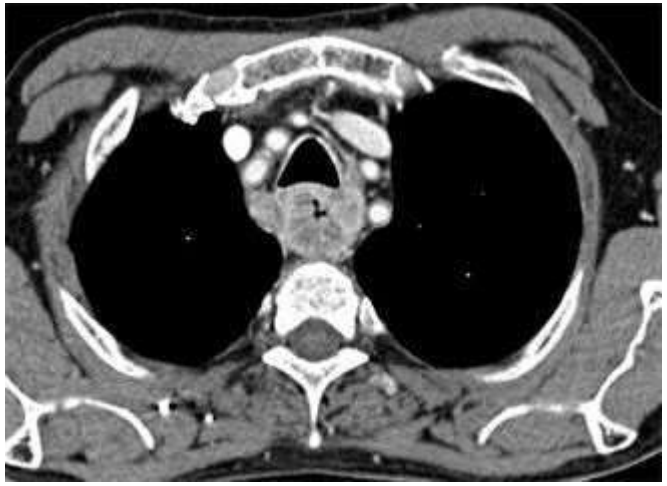
Esophageal disorders

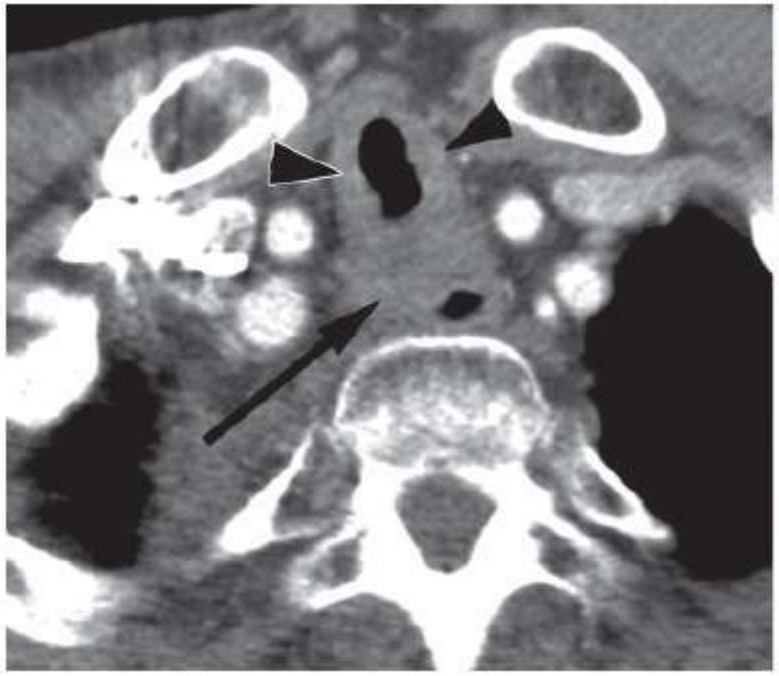


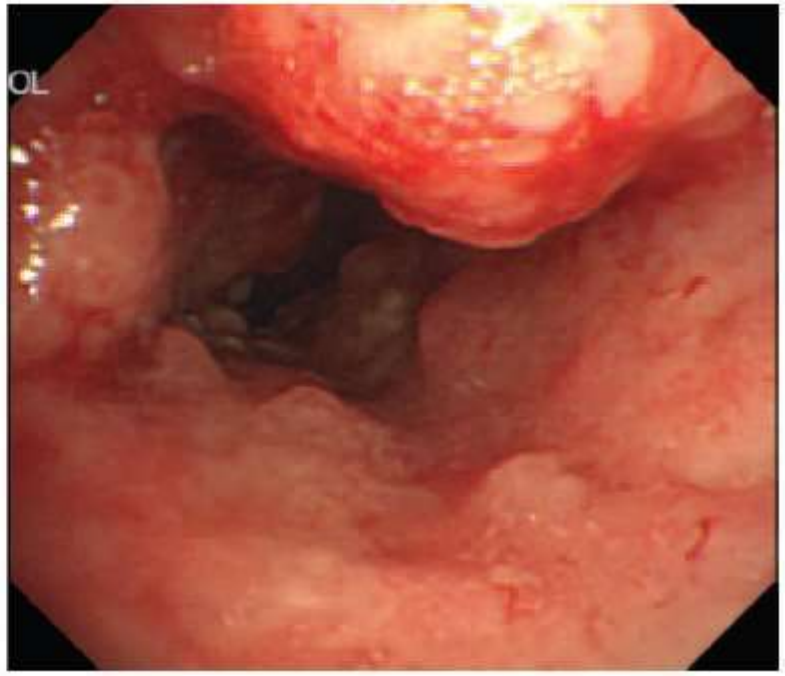


Esophageal disorders

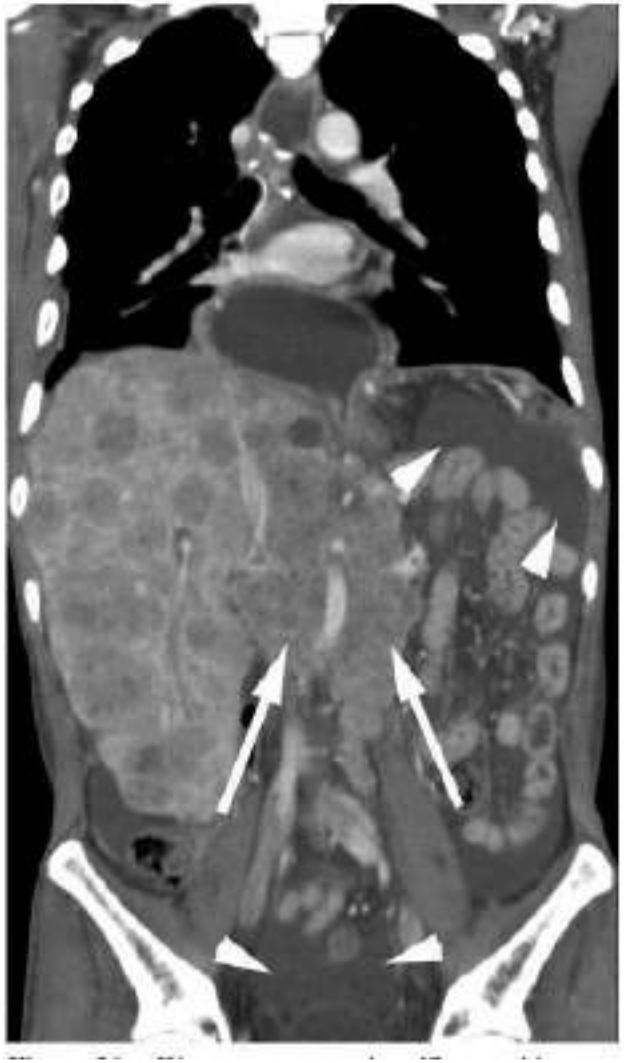








Esophageal disorders



Esophageal motor disorders: esophageal manometry

Diagnostic studies

Conventional radiology

CT

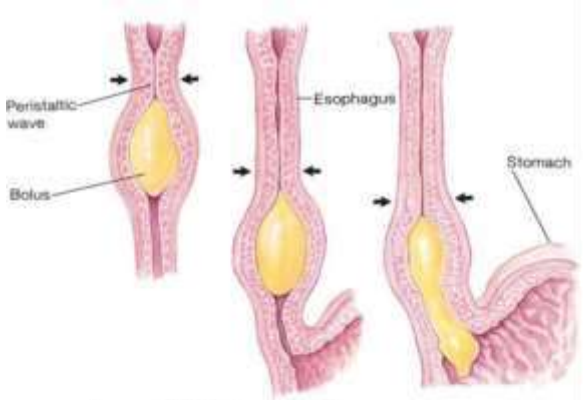
MR

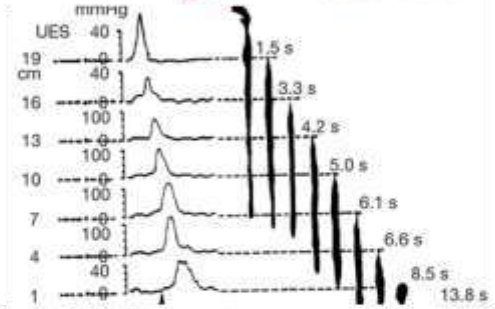
Endoscopy

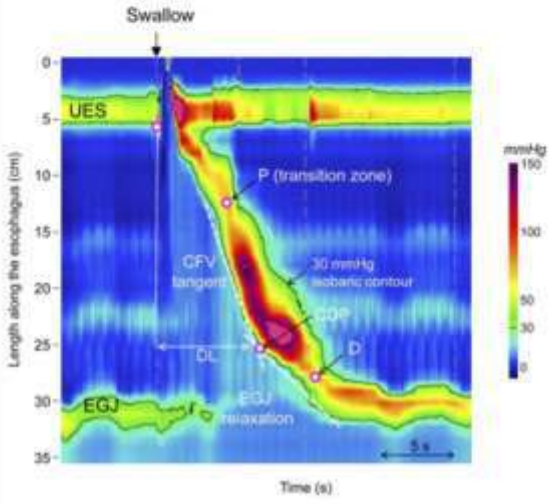
EUS (endoscopic US)

Manometry

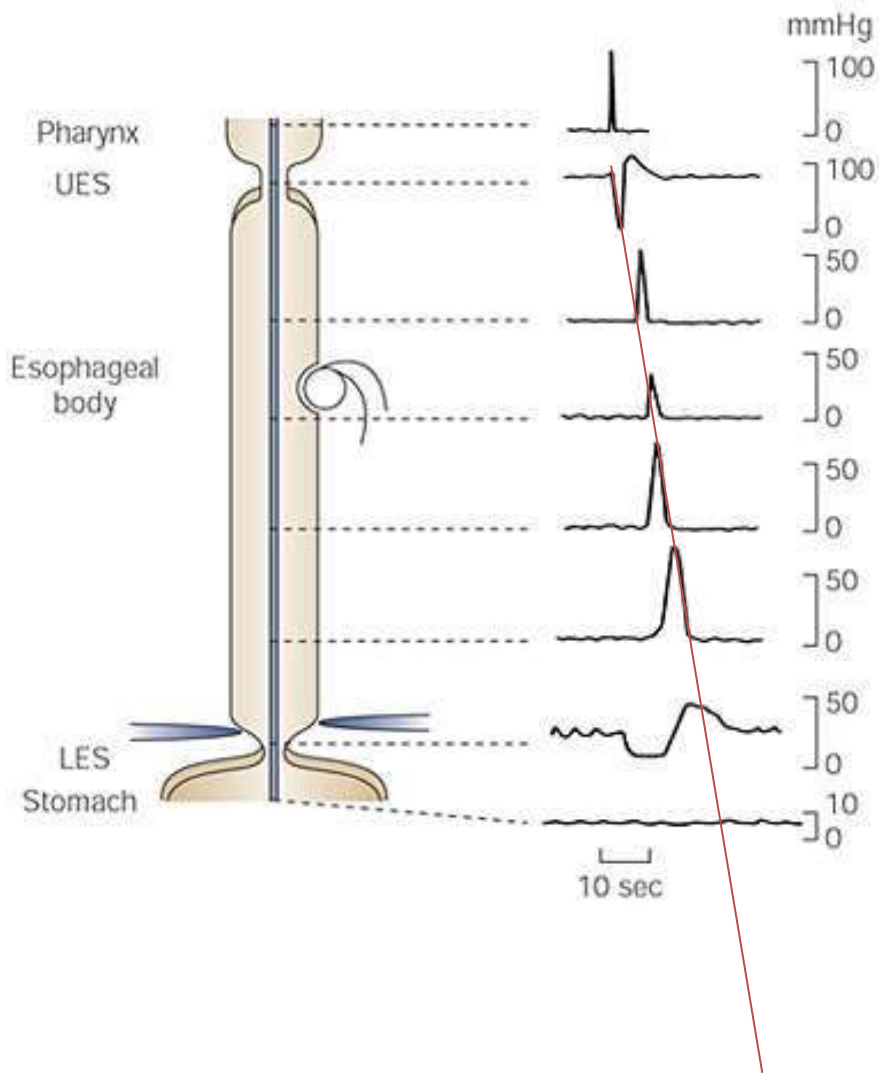
pH-metry

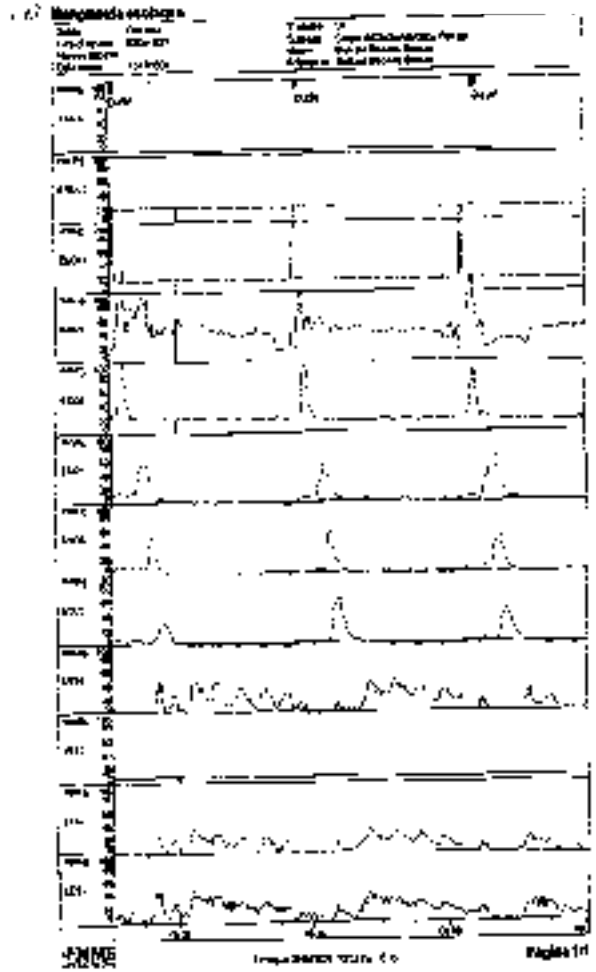




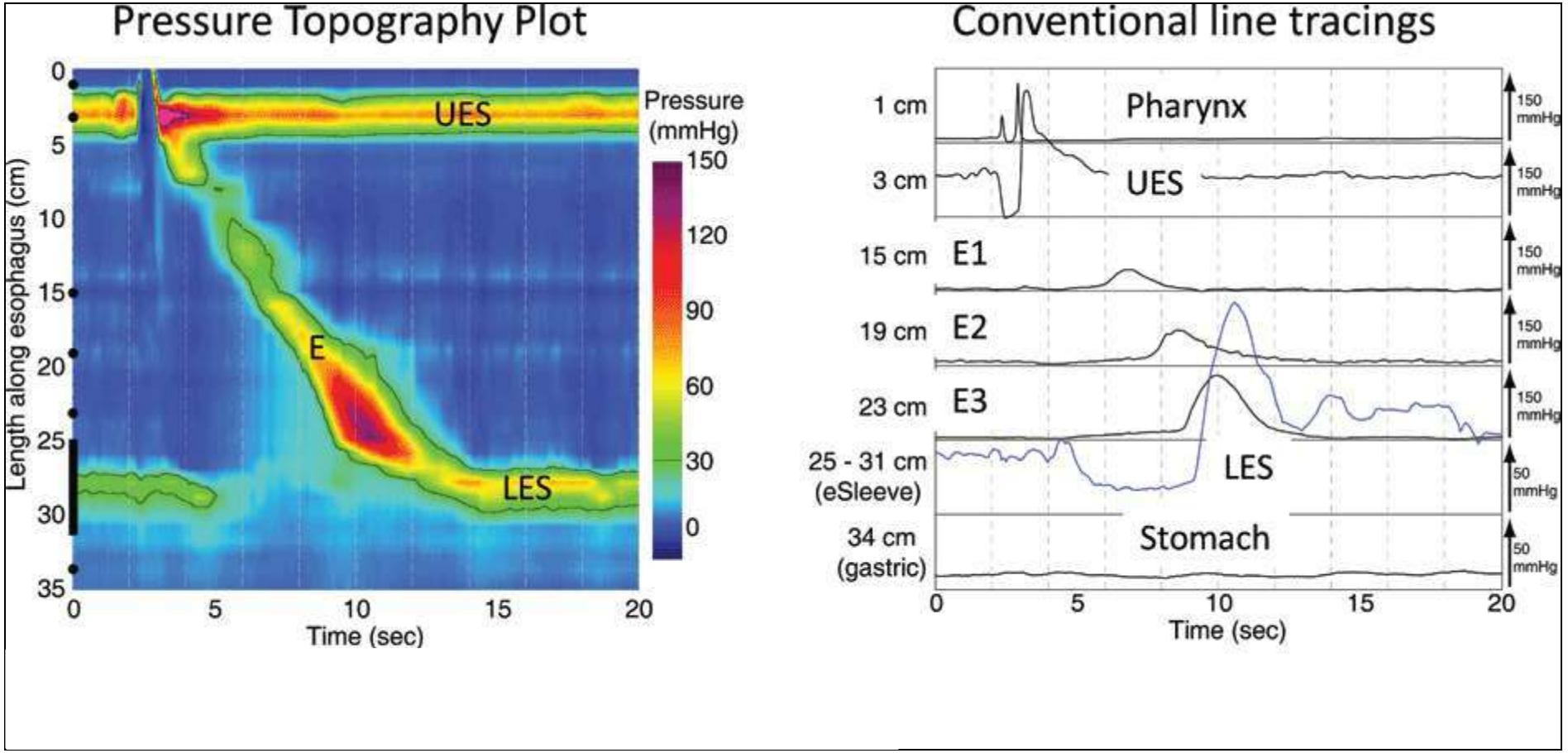


Conventional manometry



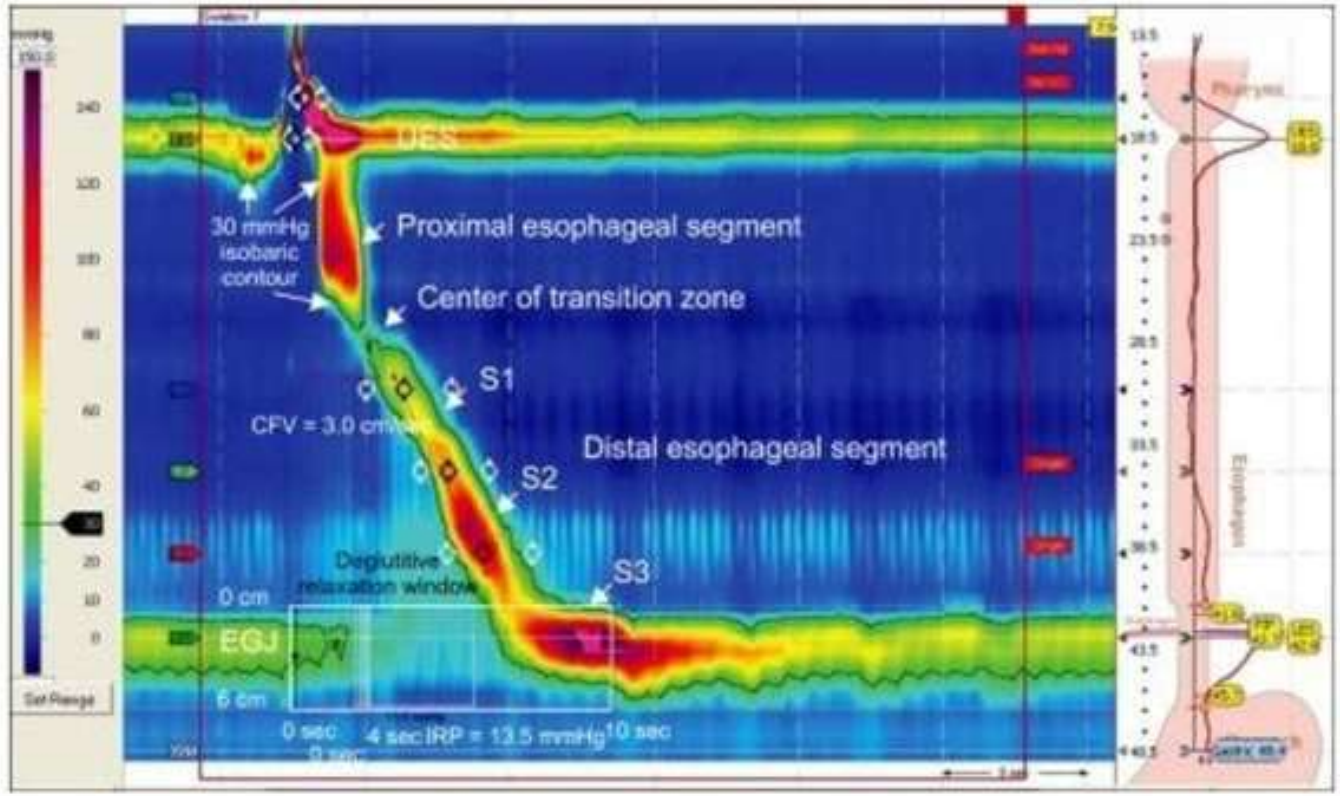


High Resolution Manometry (HRM)



High-resolution esophageal pressure topography (right) and conventional manometry (left) of a normal swallow. LES, lower esophageal sphincter; E, esophageal body; UES, upper esophageal sphincter

- Integrated relaxation pressure (IRP) => LES relaxation
  - The minimal average pressure during a 3 or 4-second relaxation period at the esophagogastric junction (EGJ)
  - CC v3.0 advocates use of median IRP (instead of mean IRP)



High Resolution Manometry (HRM)

Key manometric measures include:

- **integrated relaxation pressure (IRP),**
- **distal contractile integral (DCI),**
- **distal latency**.

These measures are the basis of the diagnostic criteria for esophageal motor disorders.

High Resolution Manometry (HRM)

IRP reflects the adequacy of esophagogastric junction (EGJ) relaxation in response to swallowing. It is calculated by averaging the minimum EGJ pressure over 4 seconds of relaxation within 10 seconds of upper esophageal relaxation. The upper limit of normal IRP depends on patient positioning and which equipment is used.
In the supine position, an abnormal **IRP is at least 15 mm Hg (Medtronic) or at least 22 mm Hg** (Laborie/Diversatek).
In the upright position, an abnormal IRP is at least 12 mm Hg (Medtronic) or at least 15 mm Hg (Laborie/Diversatek).

DCI, a measure of esophageal contractile vigor, is an integrated value of the mean contractile amplitude, length, and time within the distal esophagus.A normal DCI value is between 450 and 8,000 mm Hg•s•cm.
Ineffective swallows include weak (100-450 mm Hg•s•cm), failed (<100 mm Hg•s•cm), and fragmented contractions. Fragmented contractions are represented by a break within the 20-mm Hg isobaric contour that is greater than 5 cm with a normal DCI.[1] A swallow is defined as hypercontractile if the DCI exceeds 8,000 mm Hg•s•cm.

Distal latency is measured as the time from upper esophageal sphincter relaxation to the contractile deceleration point (CDP), the transition point from the proximal rapid to distal slow esophageal contraction. This correlates anatomically with the beginning of the globular phrenic ampulla, a temporary structure formed by the elongated and elevated lower esophageal sphincter (LES).[10]

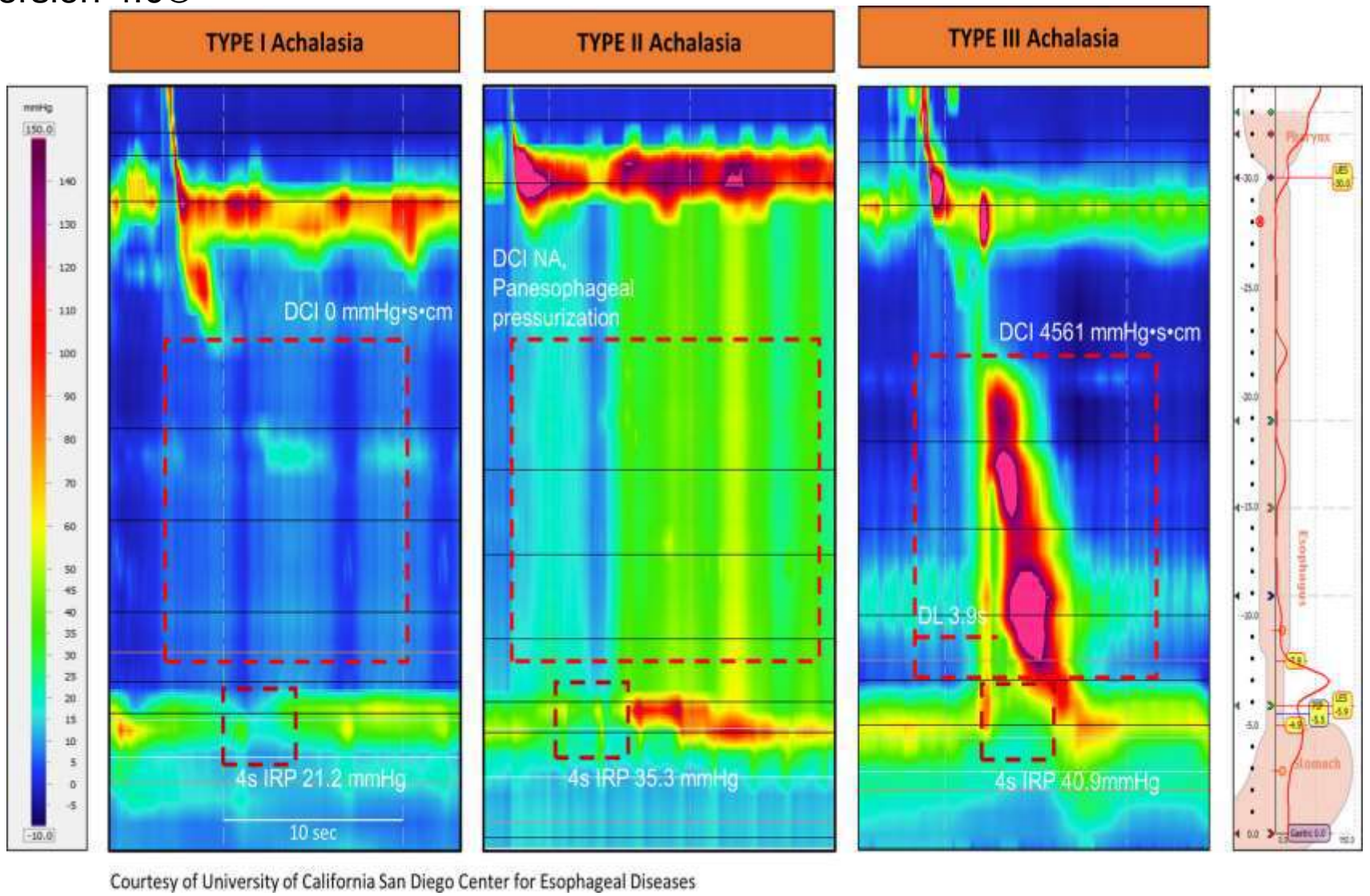
Physiologically, this represents the transition from peristaltic transport to ampullary emptying. Identifying the CDP can be challenging, but it can be pinpointed using the 30-mm Hg isobaric contour on esophageal pressure topographic plots. Two tangent lines are drawn: one along the slope of the initial, rapid contraction, and another extending proximally from EGJ along the slow contraction wave front. The intersection point of the 2 lines represents the CDP. Criteria dictate that the CDP should be within 3 cm of the EGJ proximal border.[11] The lower limit of normal for distal latency is 4.5 seconds, and in the setting of a normal DCI, distal latency less than 4.5 seconds is considered a premature contraction.

HRM parameters

Pressure topography metrics

Metric	Description
Integrated relaxation pressure (mmHg) (IRP)	**Mean EGJ pressure measured for four contiguous or non-contiguous seconds of relaxation of LES in the ten-second window following deglutitive UES relaxation**
Distal contractile integral (mmHg-s-cm)	Amplitude x duration x length (mmHg-s-cm) of the distal esophageal contraction >20 mmHg from proximal (P) to distal (D) pressure troughs
Contractile deceleration point [(CDP) (time, position)]	The inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the phrenic ampulla
Contractile front velocity (cm s−1)	Slope of the tangent approximating the 30 mmHg isobaric contour between P and the CDP
Distal latency (s)	Interval between UES relaxation and the CDP
Peristaltic breaks (cm)	Gaps in the 20 mmHg isobaric contour of the peristaltic contraction between the UES and EGJ, measured in axial length

Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©

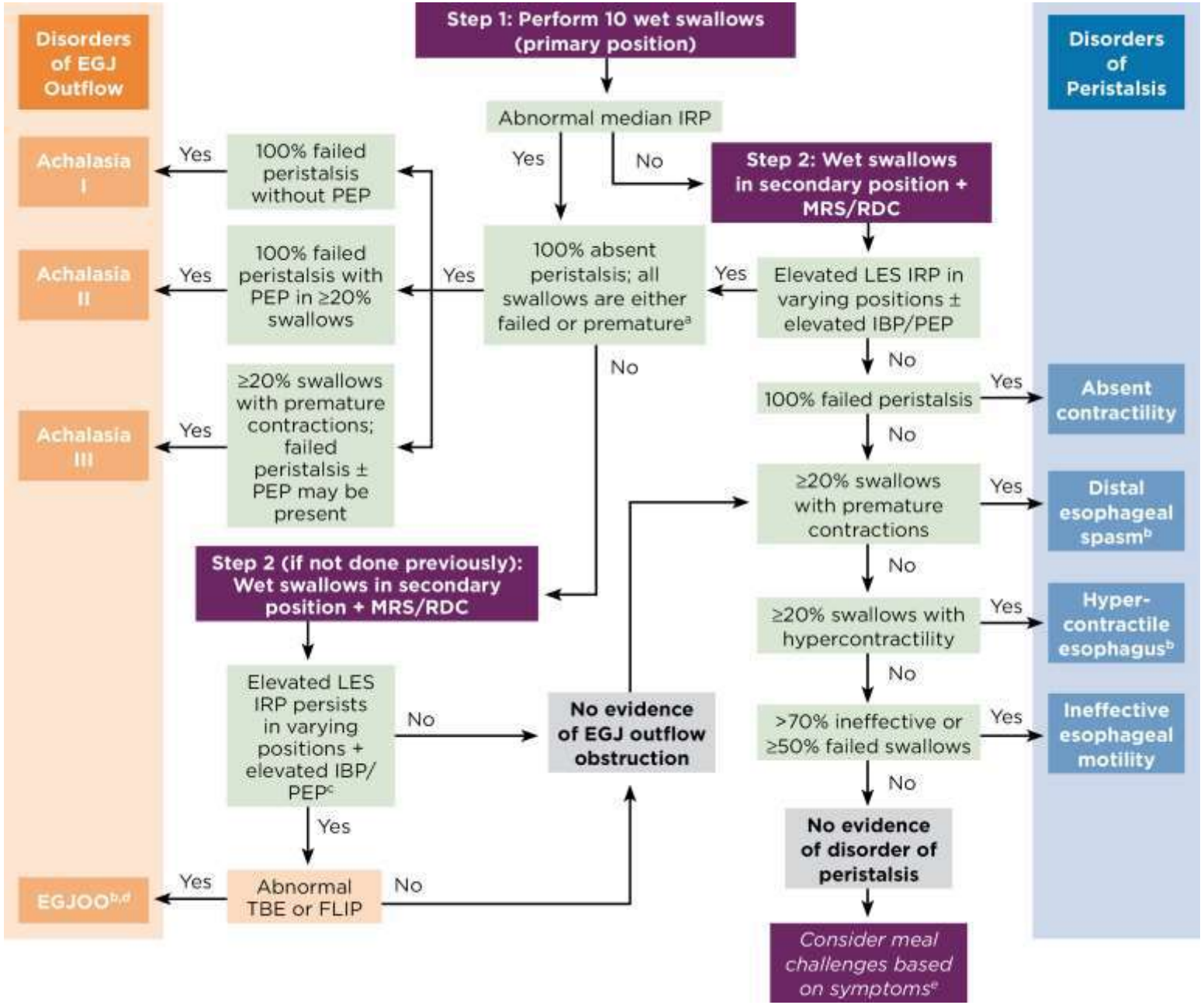


Courtesy of University of California San Diego Center for Esophageal Diseases

Neurogastroenterology & Motility, Volume: 33, Issue: 1, First published: 29 December 2020, DOI: (10.1111/nmo.14058)

Achalasia Subtypes. Type I Achalasia: integrated relaxation pressure (IRP) is elevated with failed peristalsis (distal contractile integral (DCI) <100 mmHg-s-cm), and without panesophageal pressurization. Type II Achalasia: IRP is elevated with failed peristalsis and panesophageal pressurization. Type III Achalasia: IRP is elevated with a normal DCI, and a reduced distal latency. Not applicable (NA)

Diagnostic test	Protocol	Supportive evidence
Endoscopy	Careful attention to esophageal diameter, LES tone, retention of liquid/saliva on insertion	Puckered gastroesophageal junction with resistance to passage of scope with retained liquid in the esophagus is supportive of obstructive process such as achalasia Presence of "foam" in the esophagus suggest dysmotility but is not specific for a manometric diagnosis.
FLIP	Placed transorally with balloon traversing the EGJ Volumetric distention of the balloon to predetermined volumes based on catheter type	EGJ-DI of <2.0 mm^2/mm Hg is abnormal EGJ diameter of <13 mm is likely abnormal Role in various manometric diagnoses is evolving
TBE with barium tablet (13 mm)	Perform in upright position using 8 oz or 236 mL of barium Evaluate barium height at 1, 2, and 5 min	Barium column height to support outflow obstruction (such as achalasia) >5 cm at 1 min >2 cm at 5 min 13-mm barium tablet retention supports obstructive process 3% improvement (decrease) in pre- to post-treatment barium height at 5 min might predict long-term clinical remission in achalasia Corkscrew appearance may be suggestive of distal esophageal spasm
MRS (HRM)	5 swallows of 2-mL liquid at 2–3 s intervals	Absence of esophageal body contractility (DCI <100 mm Hg•s•cm) with complete deglutitive inhibition of LES during MRS Augmentation (peristaltic reserve) present if post-MRS esophageal body peristaltic contraction is normal (DCI >450 mm Hg•s•cm) and any of 3 post-contractions with increased contractile vigor (DCI >single swallow mean DCI)
RDC (HRM)	Rapid drink of 200 mL of liquid	Absence of esophageal body contractility (DCI <100 mm Hg•s•cm) with complete deglutitive inhibition of LES during RDC IRP >12 mm Hg (Medtronic software) and pan-esophageal pressurization (>20 mm Hg) are supportive of outflow obstruction



Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0©. *Neurogastroenterol Motil.* 2021;33(1):e14058.

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Symptoms of esophageal diseases

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Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Dysphagia

Dysphagia is the perception that there is an impediment to the normal passage of swallowed material.

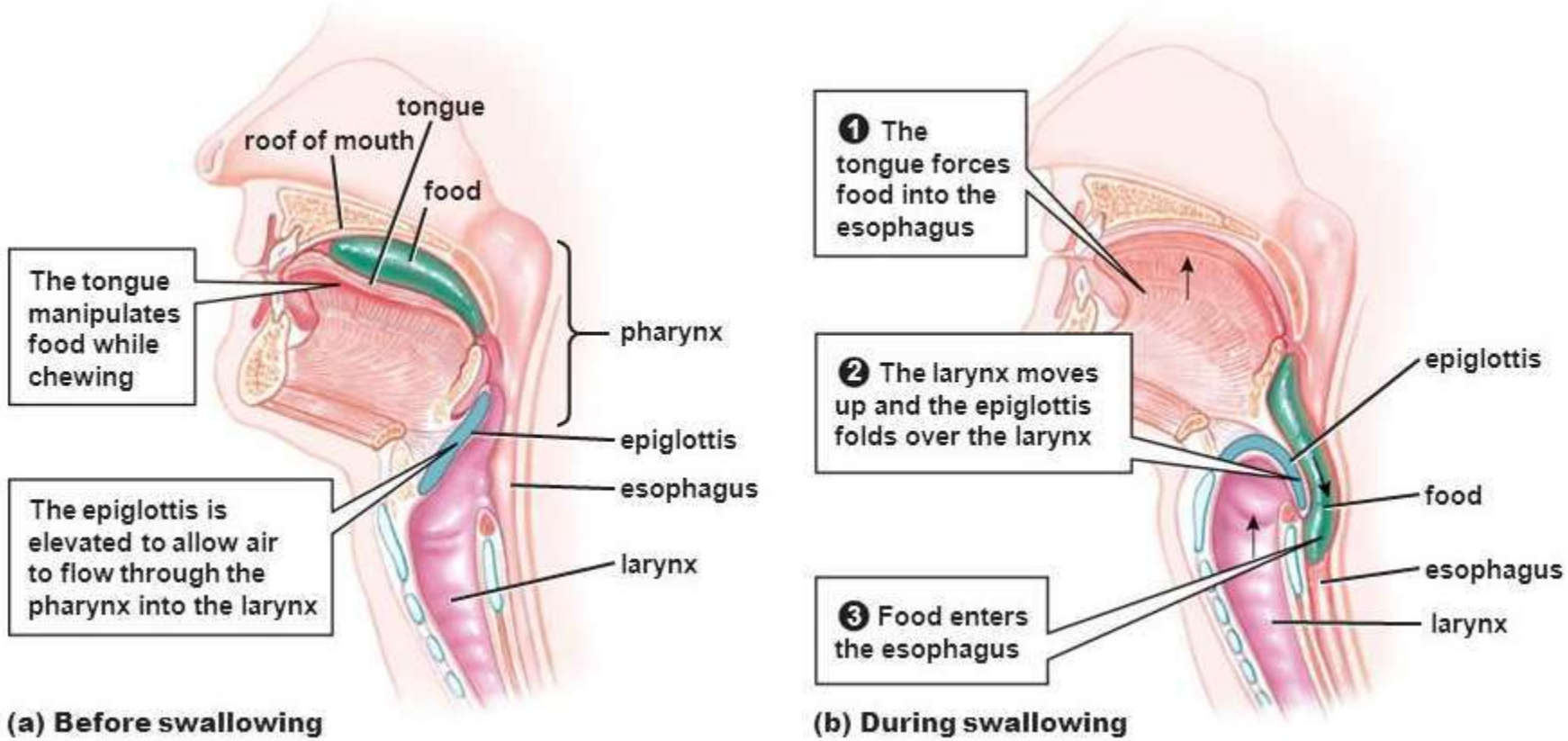
Dysphagia refers either to:

1. the **difficulty with the initial phases of a swallow** (usually described as "**oropharyngeal dysphagia**")

2. or to the **sensation that foods and or liquids are somehow being obstructed** in their passage from the mouth to the stomach

   (usually described as "**esophageal dysphagia**")

Dysphagia


tongue
roof of mouth
food
The tongue manipulates food while chewing
pharynx
epiglottis
esophagus
The epiglottis is elevated to allow air to flow through the pharynx into the larynx
larynx
(a) Before swallowing
❶ The tongue forces food into the esophagus
❷ The larynx moves up and the epiglottis folds over the larynx
epiglottis
food
esophagus
larynx
❸ Food enters the esophagus
(b) During swallowing

Dysphagia

Epidemiology

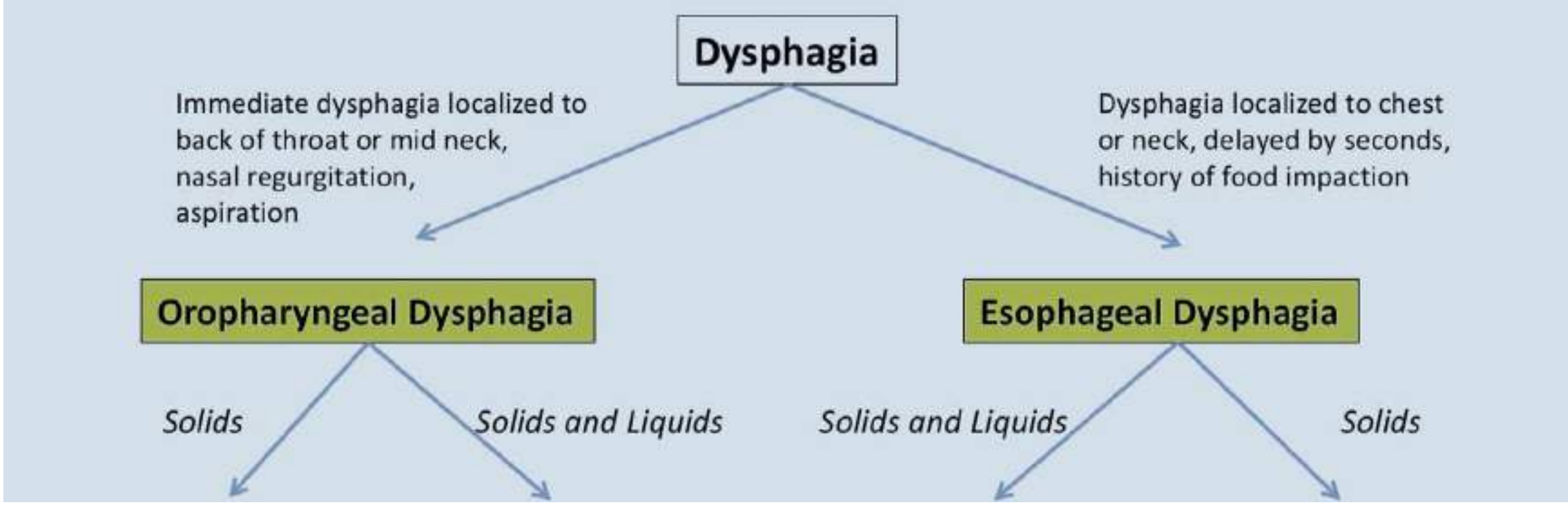
Approximately 8% of the global population suffer from swallowing problems, and research shows that the lifetime prevalence rate of dysphagia is **17.10% in the community-dwelling elderly**, rising to 52.60% in high-risk populations.

Indeed, dysphagia affects **40–70**% of patients with **stroke**, **60–80% of patients with neurodegenerative diseases, up to 13% of adults aged 65 and older** and > 52% **of institutionalized elderly patients**,

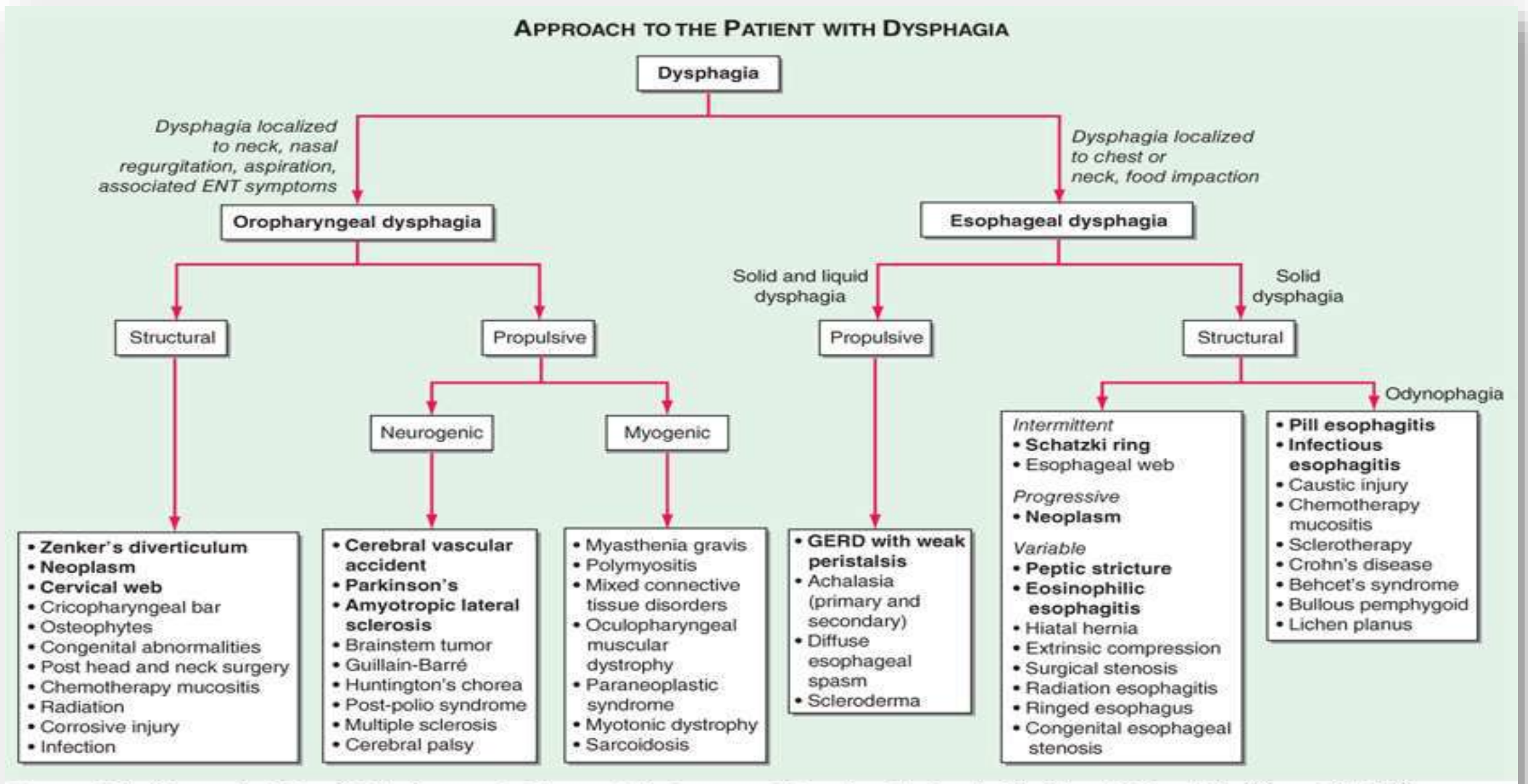
as well as 60–75% of patients who undergo **radiotherapy for head and neck cancer**.

Dysphagia

Oropharyngeal swallowing is a process that is governed by the swallowing center in the medulla, and in the mid-esophagus and distal esophagus by a largely autonomous peristaltic reflex coordinated by the enteric nervous system.



Causes of dysfagia: summary



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition
www.accessmedicine.com

Esophageal dysphagia

Dysphagia that **occurs equally with solids and liquids** often involves an **esophageal motility problem**. This suspicion is reinforced when intermittent dysphagia for solids and liquids is associated with chest pain. In about 20% of patients with achalasia there is a presence of the so-calld **paradoxical dysphagia**, when patients swallow easier solid food than liquids (Achalasia)

Dysphagia **that occurs only with solids but** never with liquids suggests the possibility of **mechanical obstruction**, with luminal stenosis to a diameter of < 15 mm.

If the **dysphagia is progressive**, peptic stricture or **carcinoma should be considered in particular**. It is also worth noting that patients with peptic strictures usually have a long history of heartburn and regurgitation, but no weight loss.

In case of intermittent dysphagia with food impaction, especially in young men, eosinophilic esophagitis should be suspected.

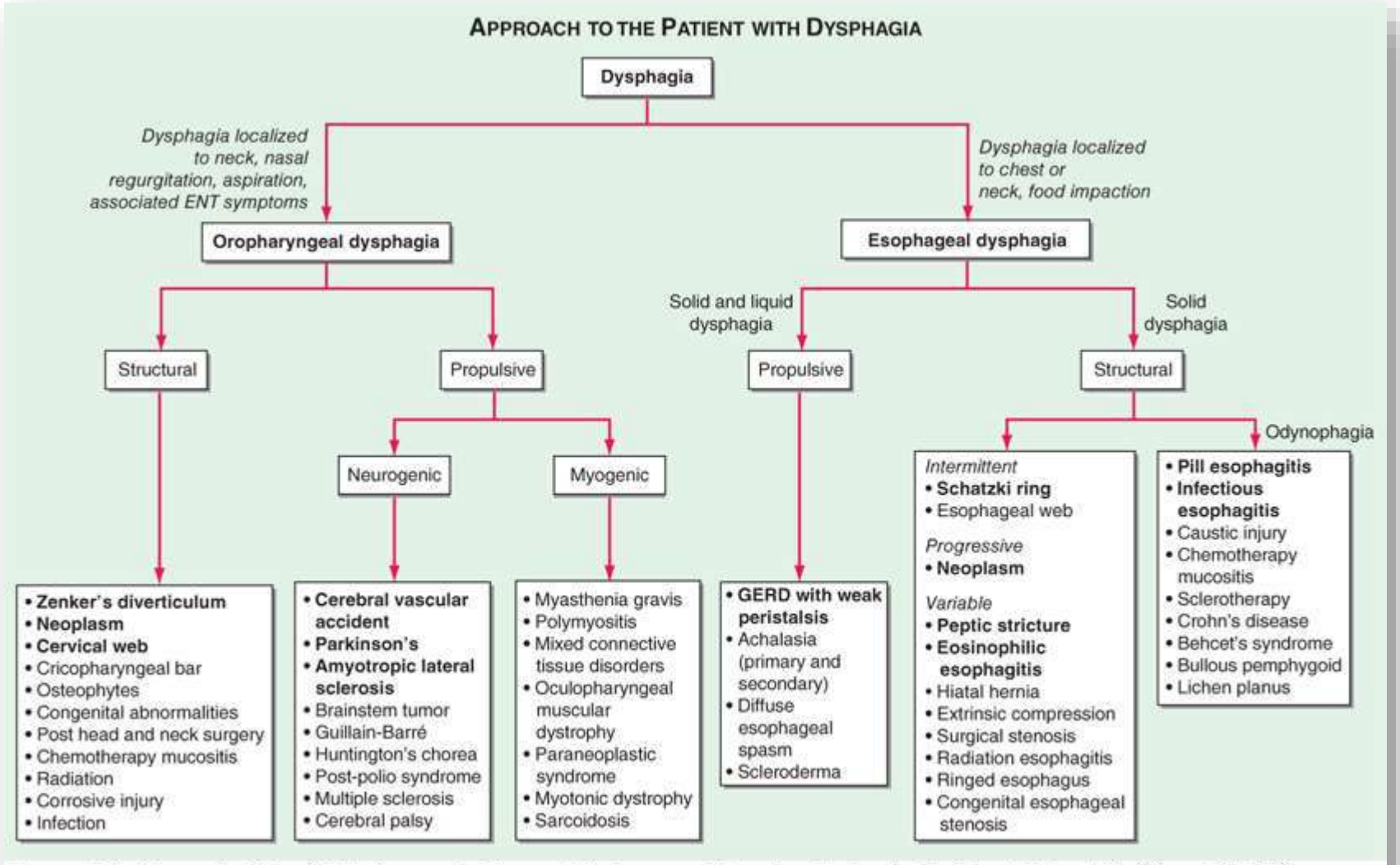
Esophageal dysphagia

A major concern with esophageal dysphagia is to exclude malignancy.
The patient's history may provide clues.

Malignancy should be suspected :

- A short duration – less than 4 months
- Disease progression
- Dysphagia more for solids than for liquids
- Weight loss
- Anemia

Causes of dysfagia: summary



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition
www.accessmedicine.com

Nausea

- **Obstructing disorders**

Pyloric obstruction

Small bowel obstruction

Colonic obstruction

Superior mesenteric artery syndrome

- **Enteric infections**

Viral infection

Bacterial infection

- **Inflammatory diseases**

Cholecystitis

Pancreatitis

Appendicitis

Hepatitis

- **Sensorimotor dysfunction**

Gastroparesis

Intestinal pseudo-obstruction

Gastroesophageal reflux disease

Chronic idiopathic nausea

Functional vomiting

Cyclic vomiting syndrome

Outside the abdomen

Cardiopulmonary

Cardiomyopathy

Myocardial infarction

Inner-ear diseases

Motion sickness

Labyrinthitis

Malignancy

Intracerebral disorders

Malignancy

Hemorrhage

Abscess

Hydrocephalus

Psychiatric illnesses

Anorexia and bulimia nervosa

Depression

Other

Post-operative vomiting

Medications and metabolic

Drugs

Chemotherapy

Antibiotics

Antiarrhythmics

Digoxin

Oral hypoglycemic medications

Oral contraceptives

Endocrine/metabolic disease

Pregnancy

Uremia

Ketoacidosis

Thyroid and parathyroid disease

Adrenal insufficiency

Vomiting

Causes in the digestive tract

Gastritis acute and chronic, peptic ulcer
Gastroesophageal reflux disease
Pyloric stenosis
Bowel obstruction
Acute abdomen and/or peritonitis
Ileus
Food allergies (often in conjunction with hives or swelling)
Cholecystitis, pancreatitis, appendicitis, acute hepatitis
Food poisoning

Drugs

alcohol
opioids
selective serotonin reuptake inhibitors
chemotherapy drugs

Sensory system and brain

Causes in the sensory system:
Movement: motion sickness (which is caused by overstimulation of the labyrinthine canals of the ear)
Ménière's disease

Causes in the brain

Concussion
Cerebral hemorrhage
Migraine
Brain tumors
Benign intracranial hypertension and hydrocephalus

Metabolic disturbances

Hypercalcemia (high calcium levels)
Uremia (acute & chronic renal failure)
Adrenal insufficiency
Hypoglycemia
Hyperglycemia

Pregnancy

Hyperemesis, morning sickness

UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
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Patologia Sistemica VI (M-Z)
AA 2023-24

Esophageal motility disorders

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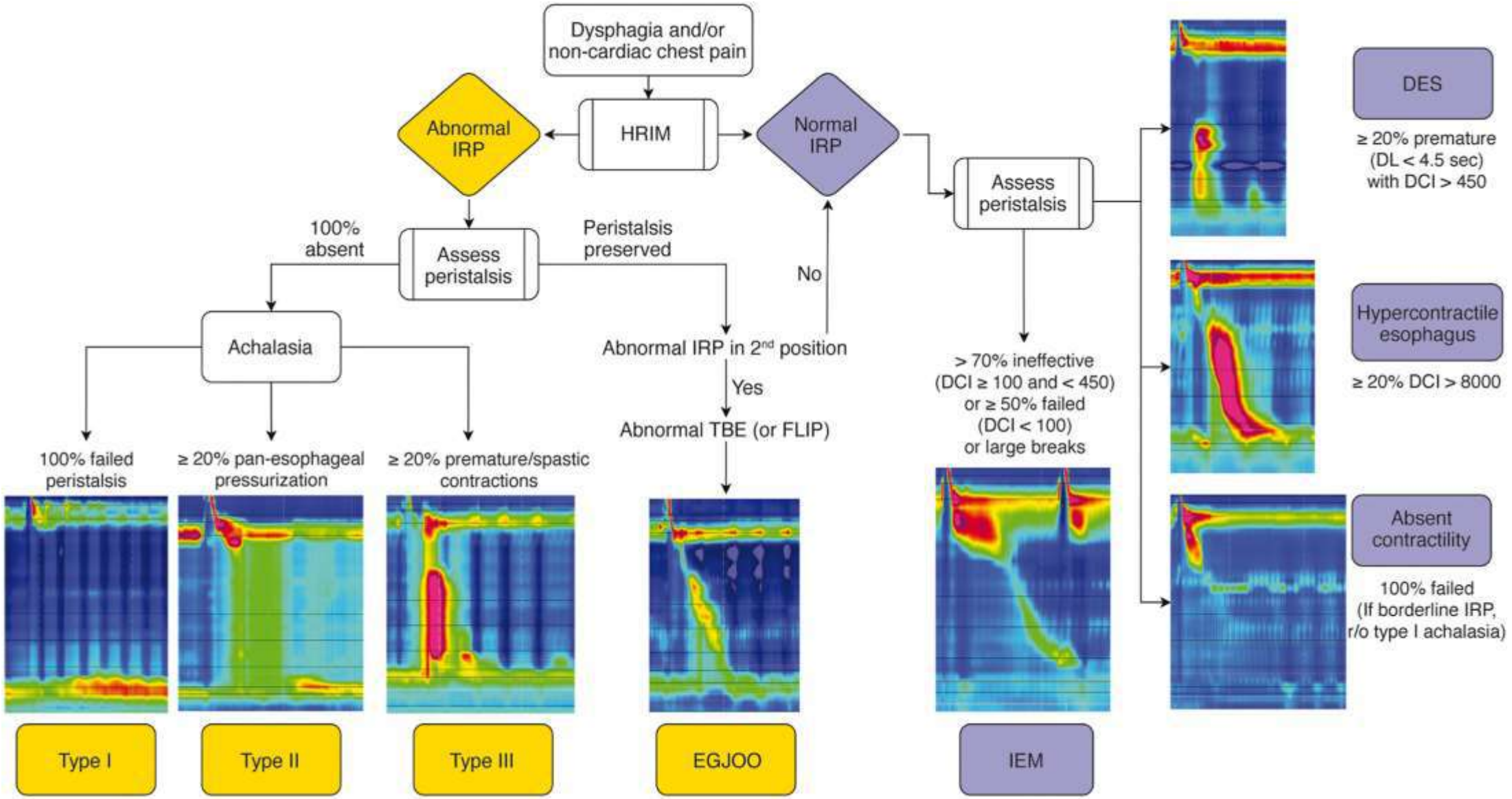
Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Table 1. Primary and Secondary Esophageal Motility Disorders.

Disorder	Details
Primary or idiopathic esophageal motility disorders	
Major	
Achalasia esophagus types 1, 2, and 3	Impaired relaxation of the lower esophageal sphincter and no peristalsis
Esophagogastric junction outflow obstruction	Impaired relaxation of the lower esophageal sphincter and normal peristalsis
Distal esophageal spasm	Normal relaxation of the lower esophageal sphincter and reduced latency of distal esophageal contraction
Hypercontractility of the esophagus	Also called nutcracker or jackhammer esophagus; normal relaxation of the lower esophageal sphincter with high-amplitude peristaltic contractions
Minor	
Ineffective esophageal peristalsis	Low-amplitude esophageal contractions or fragmented esophageal peristalsis
Secondary esophageal motility disorders	
Myasthenia gravis	Low pressure of upper esophageal sphincter and esophageal muscle fatigue with repetitive swallowing
Dermatomyositis	Low pressure of upper esophageal sphincter and esophageal muscle fatigue with repetitive swallowing
Scleroderma esophagus	Low to absent pressure of lower esophageal sphincter; absence of esophageal contractions and peristalsis in smooth muscle of the esophagus
Connective-tissue disorders	Low to absent pressure of lower esophageal sphincter; absence of esophageal contractions and peristalsis in smooth muscle of the esophagus
Diabetes mellitus	Low-amplitude, multipeaked esophageal contractions and low pressure of the lower esophageal sphincter
Secondary achalasia esophagus	Associated with neoplastic infiltration of lower esophageal sphincter or Chagas' disease



Functional Lumen Imaging Probe (FLIP)
Timed barium esophagram[TBE]

Disorders of UES

Neurological lesions causing failed UES relaxation

Failure of EUS to relax causes oro-pharyngeal dysphagia

(difficulty in iniatiating the swalling, passage of food in the hypopharynx and tracheal aspiration and regurgitation in the nasal cavity)

Causes are:

Lateral medullary infarction
Parkinson's disease
Other extrapyramidal movement disorder
Brainstem tumor
Syringobulbia
Brainstem compression secondary to cerebral haemorrhage
Amyotrophic lateral sclerosis
Idiopathic

Failure of UES relaxation is not a diagnosis as such, rather it is a functional abnormality caused by neuronal dysfunction within the central nervous system that may be a manifestation of a number of neurologic syndromes.

Cricopharyngeal myotomy or botulinum toxin injection remains unproven therapy

Disorders of esophageal body and LES

Achalasia

Achalasia is an idiopathic neurodegenerative esophageal motility disorder characterized by impaired relaxation of the lower esophageal sphincter (LES) and the absence of normal peristalsis.

Although the exact etiology of achalasia remains unknown, it may be associated with autoimmune, viral, and neurodegenerative factors.

Inflammatory changes within the esophagus following these causative insults result in the loss of inhibitory neurons in the myenteric plexus of the distal esophagus and cause an imbalance between excitatory and inhibitory neurons, preventing the relaxation of the LES

O'Neill OM, Johnston BT, Coleman HG. Achalasia: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2013;19:5806–5812.

Achalasia

Achalasia is an esophageal motility disorder with reported global **incidence** and **prevalence** ranging from **0.03 to 1.63 per 100,000** persons per year and **1.8 to 12.6 per 100,000** persons per year, respectively

The peak incidence occurs between 30 and 60 years of age. Patients often present with progressive dysphagia to solids and liquids, heartburn, chest pain, regurgitation, and varying degrees of weight loss or nutritional deficiencies (1,3).

However, because heartburn may be present in 27%–42% of patients with achalasia, patients are frequently initially misdiagnosed as having gastroesophageal reflux disease (GERD) and are treated with proton pump inhibitors (PPI)

Achalasia

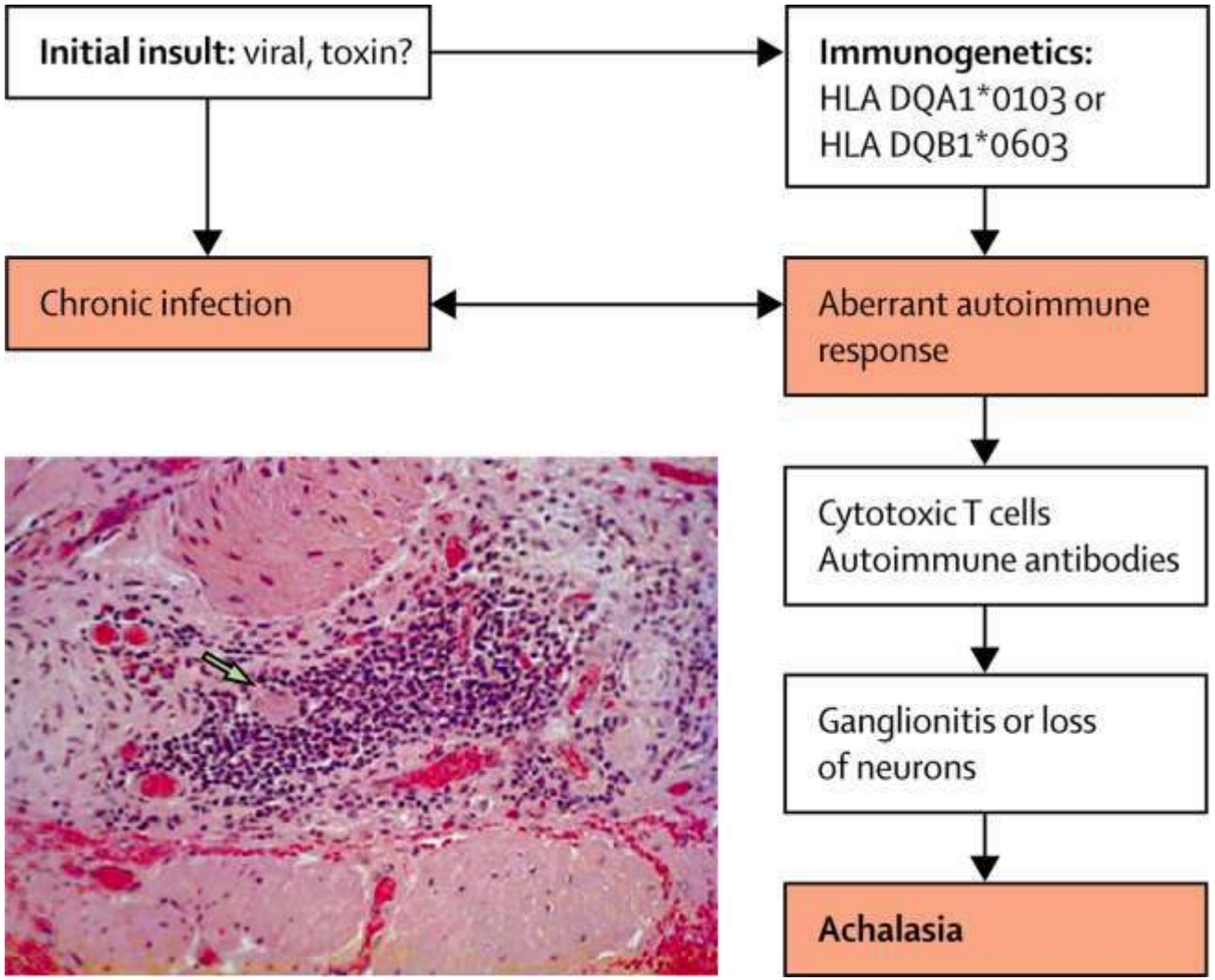
Primary achalasia

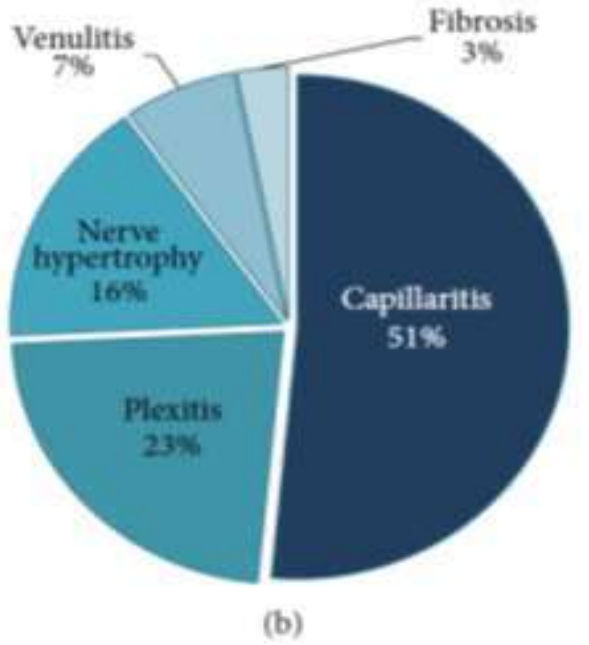
Secondary achalasia(pseudo-achalasia)

- Malignancy (carcinoma of the stomach, esophagus, lung, lymphoma and mesothelioma)
- Paraneoplastic (pancreas, liver, colon, prostate)
- Chagas' disease
- Neuropathic chronic intestinal pseudo-obstruction syndrome
- Eosinophilic gastroenteritis
- Neurodegenerative disorder with Lewy inclusion bodies
- Amyloidosis
- Postvagotomy
- Multiple endocrine neoplasia type IIb
- AAA syndrome: achalasia associated with alachrimia (juvenile Sjögren's syndrome) and achlohydria
- Von Recklinghausen's neurofibromatosis
- Sarcoidosis

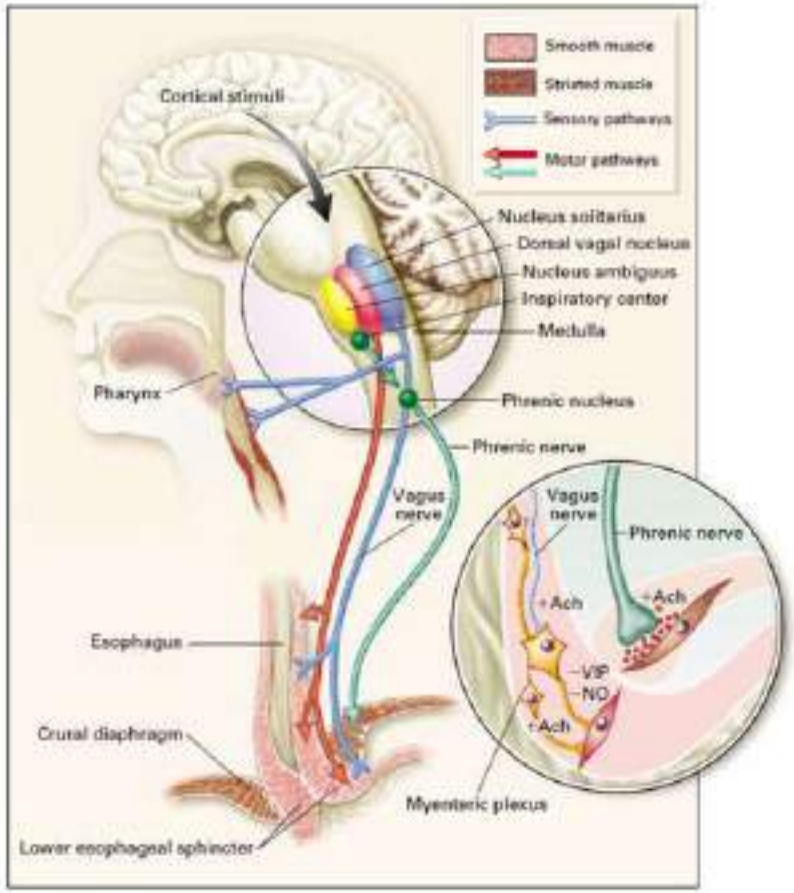
Herpes simplex virus 1

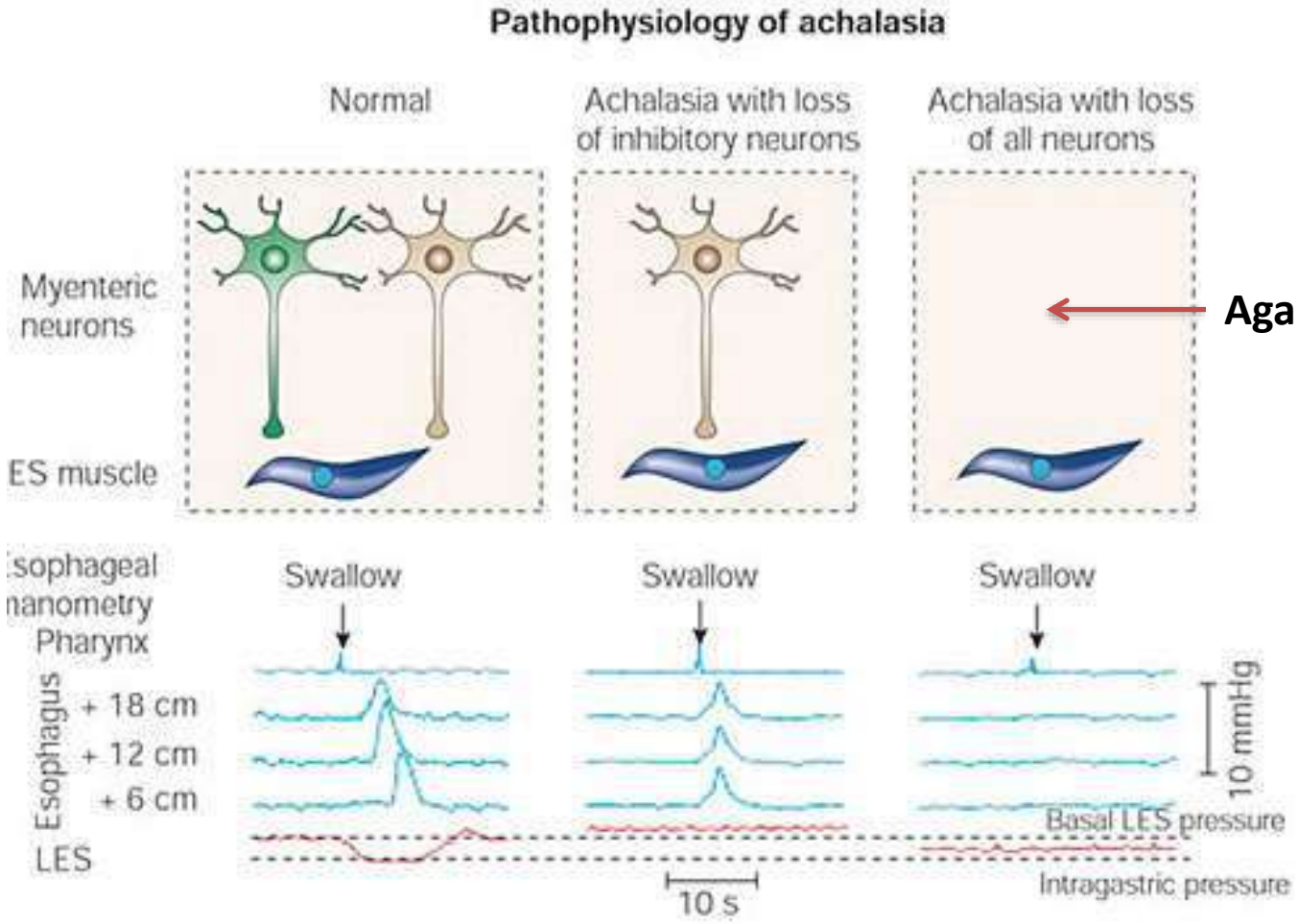
Achalasia: pathogenesis





The Lancet 2014 38383-93DOI: (10.1016/S0140-6736(13)60651-0)





Left: The normal condition where excitatory, cholinergic (Ach) motor neurons innervate the smooth muscle cells of the LES and contribute to the genesis of basal pressure of the LES. Inhibitory, nitric oxide (NO) motor neurons **also act on the LES to produce the relaxation that accompanies a swallow.**
Middle: Achalasia resulting from the loss of inhibitory neurons. In this situation, the absence of NO motor neurons results in an elevation in the basal LESP and absence of swallow induced relaxation of the LES. Esophageal aperistalsis is defined by simultaneous esophageal body contractions.
Right: Achalasia with complete loss of myenteric neurons. Here the basal LESP is below normal owing to the absent excitatory neurons, and swallow-induced relaxation is absent owing to the lack of inhibitory neurons. Esophageal aperistalsis is defined by the absence of esophageal body contractions

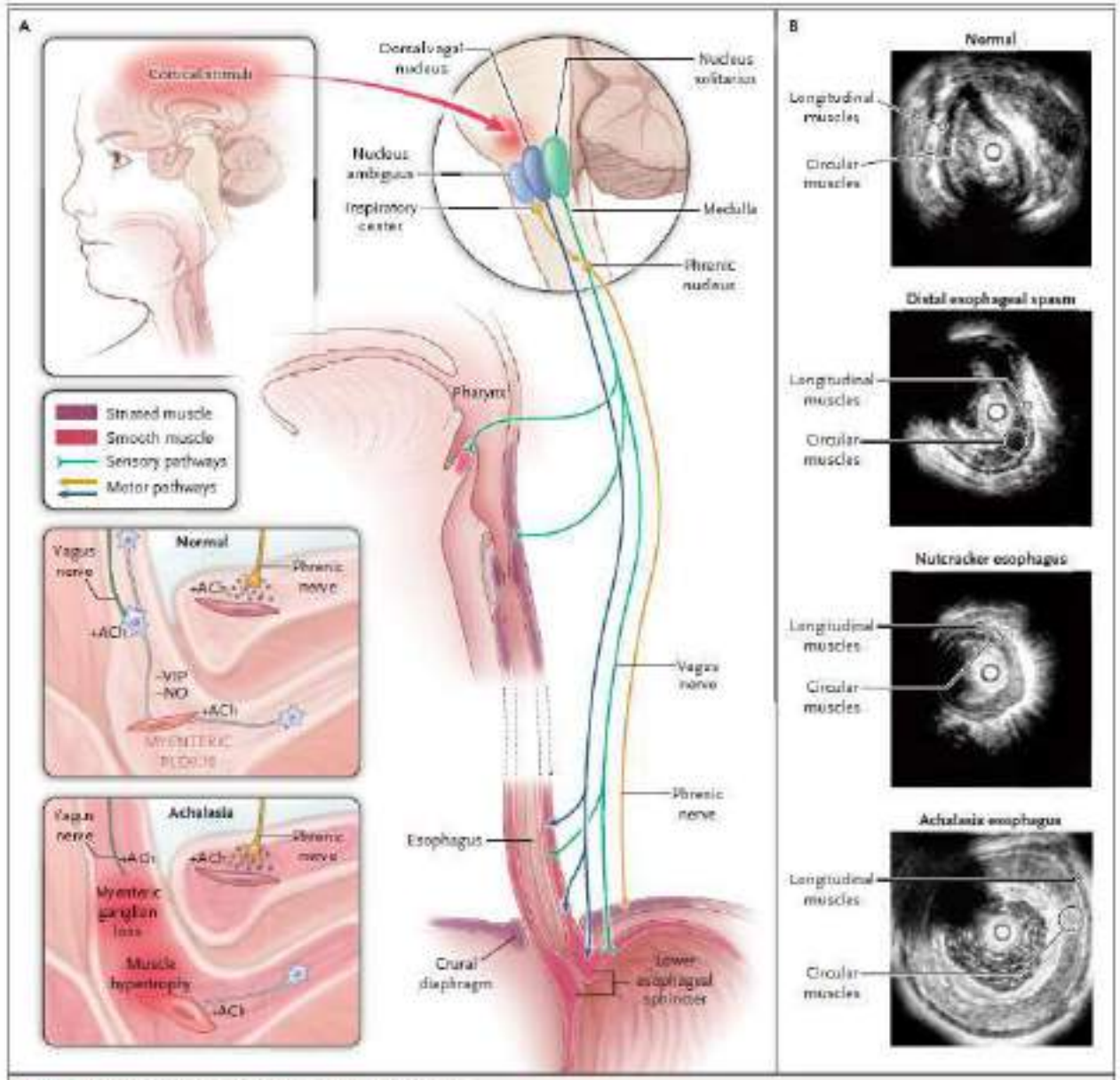


Figure 3. Pathogenesis of Esophageal Motility Disorders.

Panel A shows extrinsic (vagus) and intrinsic (myenteric plexus) innervation of the esophageal wall and the defect in patients with achalasia esophagus. ACh denotes acetylcholine, NO nitric oxide, and VIP vasoactive intestinal peptide. Panel B shows ultrasound imaging of the distal esophagus in a person with normal function, a patient with distal esophageal spasm, a patient with nutcracker esophagus, and a patient with achalasia esophagus. The muscle layer of the esophagus is thicker in patients with esophageal motility disorders; the thickest muscle is seen in patients with achalasia esophagus.

Achalasia: Symptoms

Long standing achalasia is characterized by progressive dilatation and sigmoid deformity of the esophagus with hypertrophy of the LES.

Clinical manifestations include:

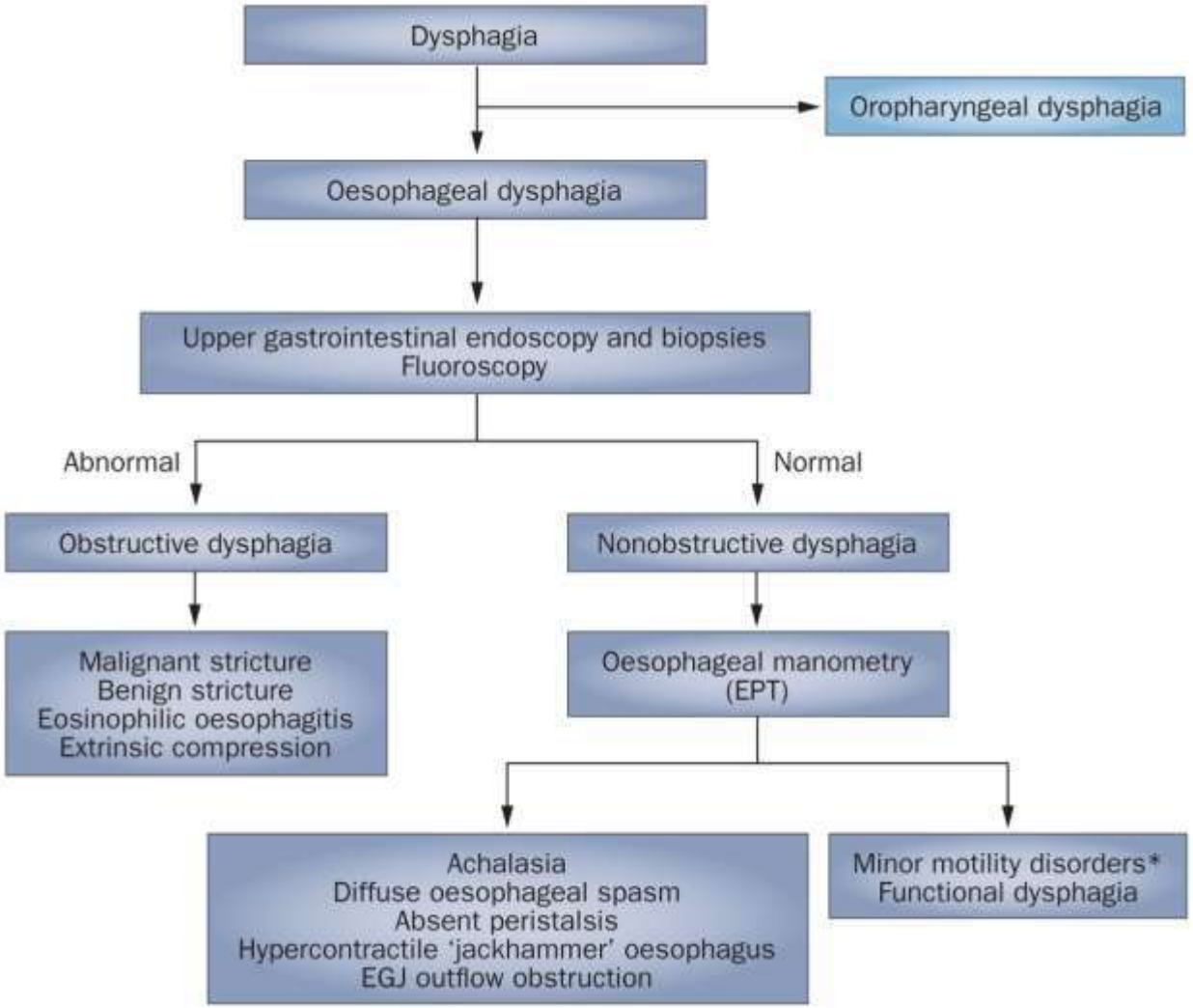
- **Dysphagia** for both solid and liquid or only liquid (paradoxal dysphagia) and then complete
- **Regurgitation** occurs when food, fluids and secretions are retained in the dilated esophageal lumen
- **Chest pain** as the result of esophageal spasm, described as a pressure-like retrosternal pain irradiating to the neck, arms and back
- **Hearthburn**
- **Weight loss**

Achalasia: complications

Patients may also present with a complication of long standing achalasia:

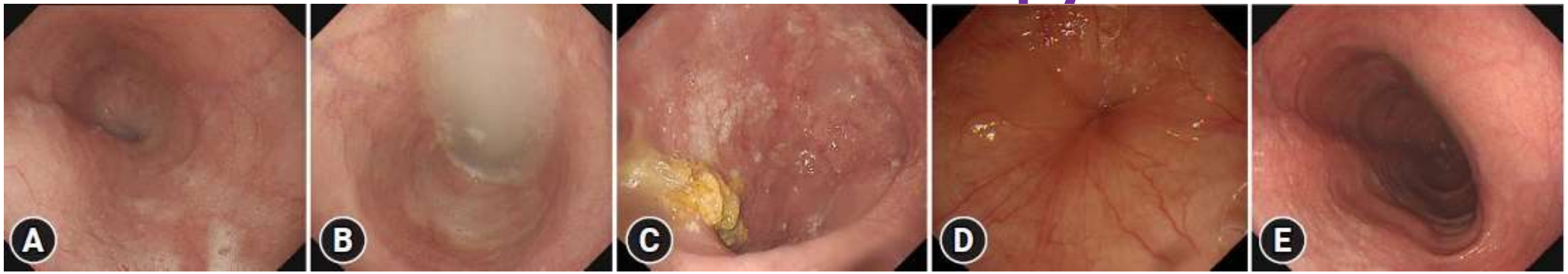
- esophageal carcinoma: is seen in approximately 5%, and most often in the mid esophagus. It is thought to relate to the chronic irritation of the mucosa by stasis of food and secretions. The hystological type is represented by squamous cell carcinoma (SCC)
- aspiration pneumonia and eventually abscess formation
- candida esophagitis
- acute airway obstruction: this is a rare complication requiring immediate esophageal decompression with nasogastric tube

Diagnosis algorithm for oesophageal dysphagia



Zerbib, F. & Omari, T. (2014) Oesophageal dysphagia: manifestations and diagnosis
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2014.195

Achalasia endoscopy



Diagnostic features of achalasia on endoscopy. (A) **Dilatation of the esophageal lumen. (B) Abnormal retention of food and/or liquid remnants in the esophagus. (C) Whitish change and thickening of the esophageal mucosal surface. (D) Functional stenosis of the esophagogastric junction (EGJ), where the endoscope passes through the stenotic segment but the EGJ fails to be dilated by insufflation. (E) Abnormal contraction waves of the esophagus**

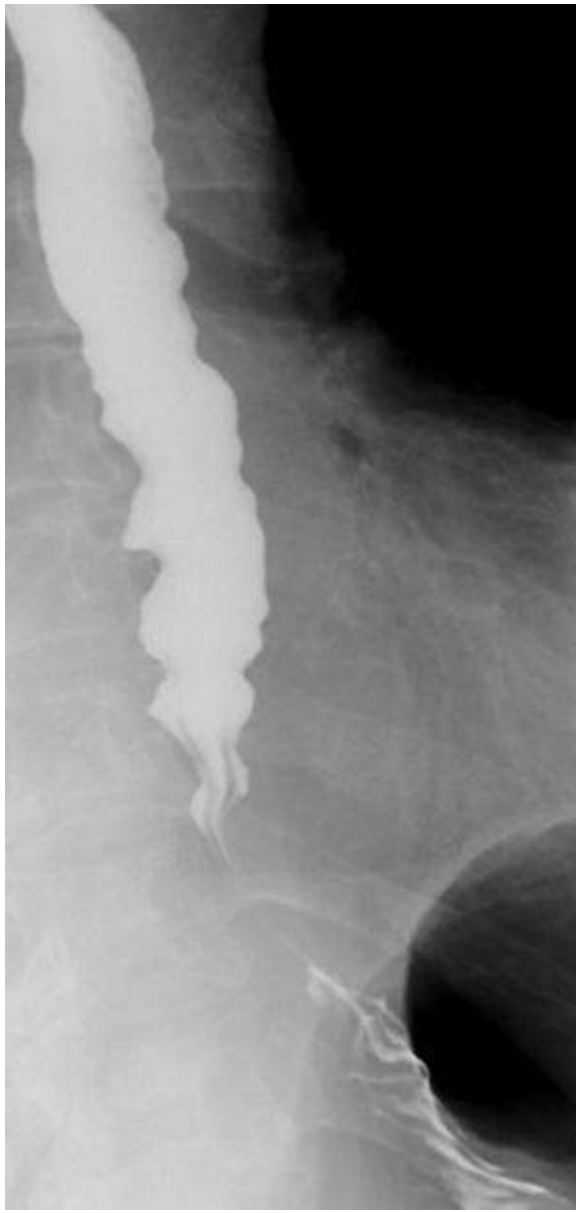
(A) Pinstripe pattern. (B) Rosette-like esophageal folds. (C) Champagne glass sign.

Achalasia: radiological findings

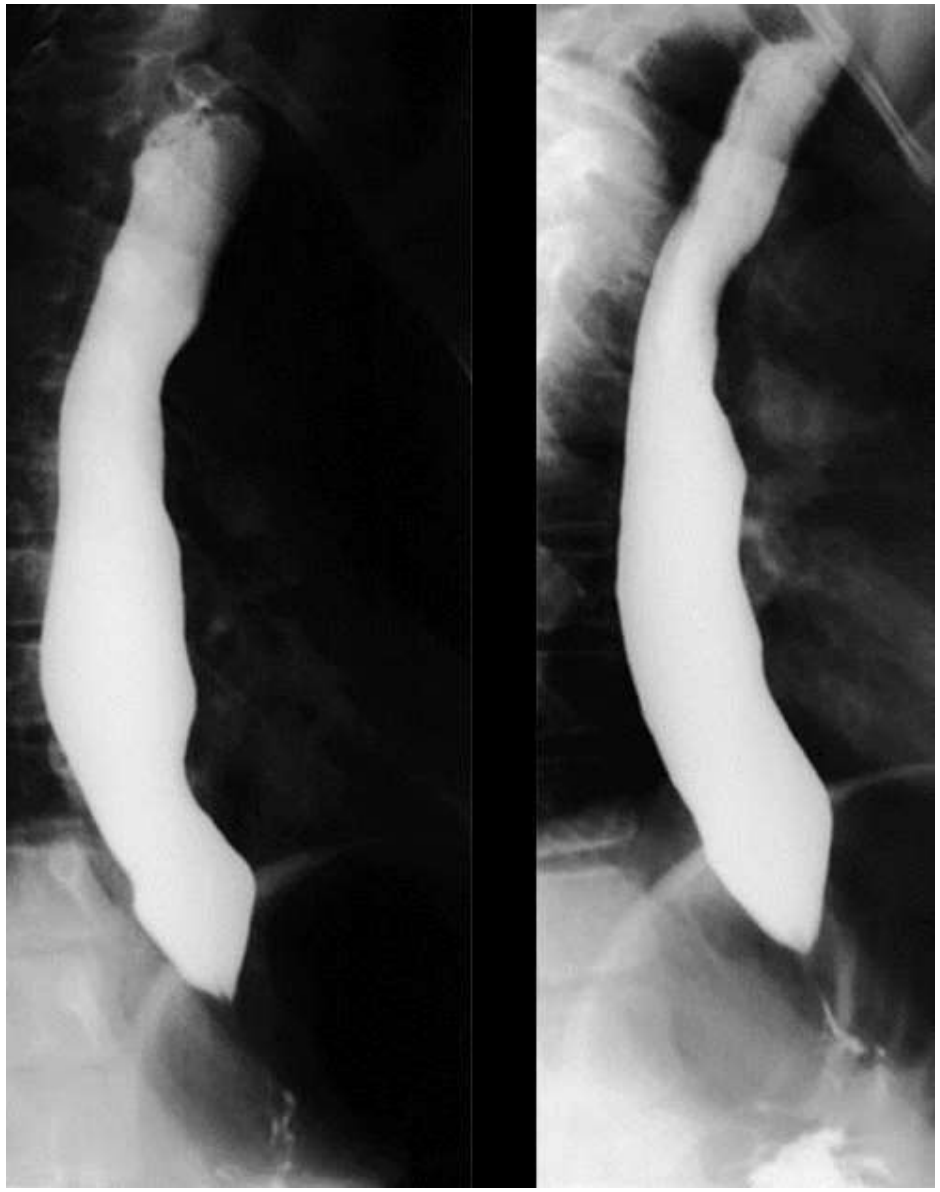
A barium swallow is able to not only confirm that the esophagus is dilated but is also able to assess for mucosal abnormalities.

Findings include:

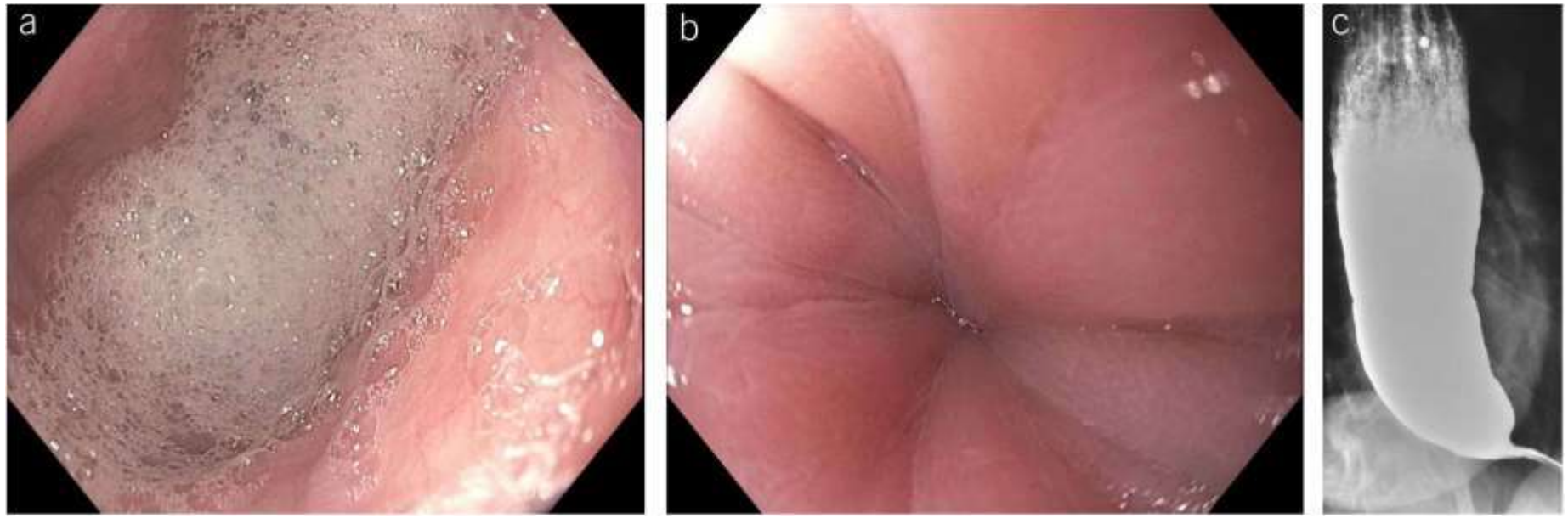
- **failure of normal peristalsis** to clear the esophagus of barium when the patient is in the recumbent position, with no primary waves identified
- **uncoordinated, non-propulsive, tertiary contractions**
- **esophageal body dilatation,** which is typically maximal in the distal esophagus
- **pooling or stasis of barium in** the esophagus when the esophagus has become atonic or non contractile (late feature in the disease)
- **when barium column is high enough** (patient standing) the hydrostatic pressure can overcome the LES pressure allowing passage of esophageal content
- **incomplete LES relaxation** that is not coordinated with esophageal contraction
- **bird beak sign**



Uncoordinated, non-propulsive, tertiary contractions

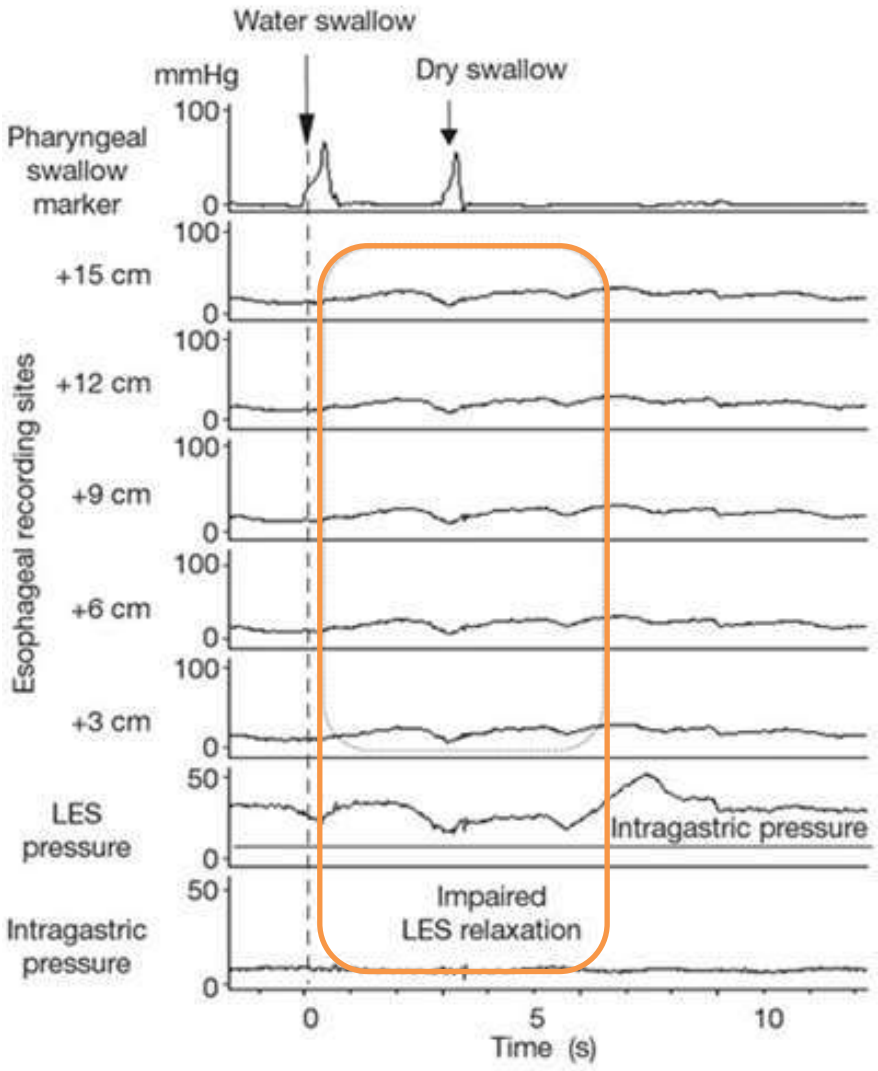


Bird beak sign (a becco d’uccello- coda di topo)



Achalasia with esophageal dilatation, tapering at the gastroesophageal junction and an air-fluid level within the esophagus.

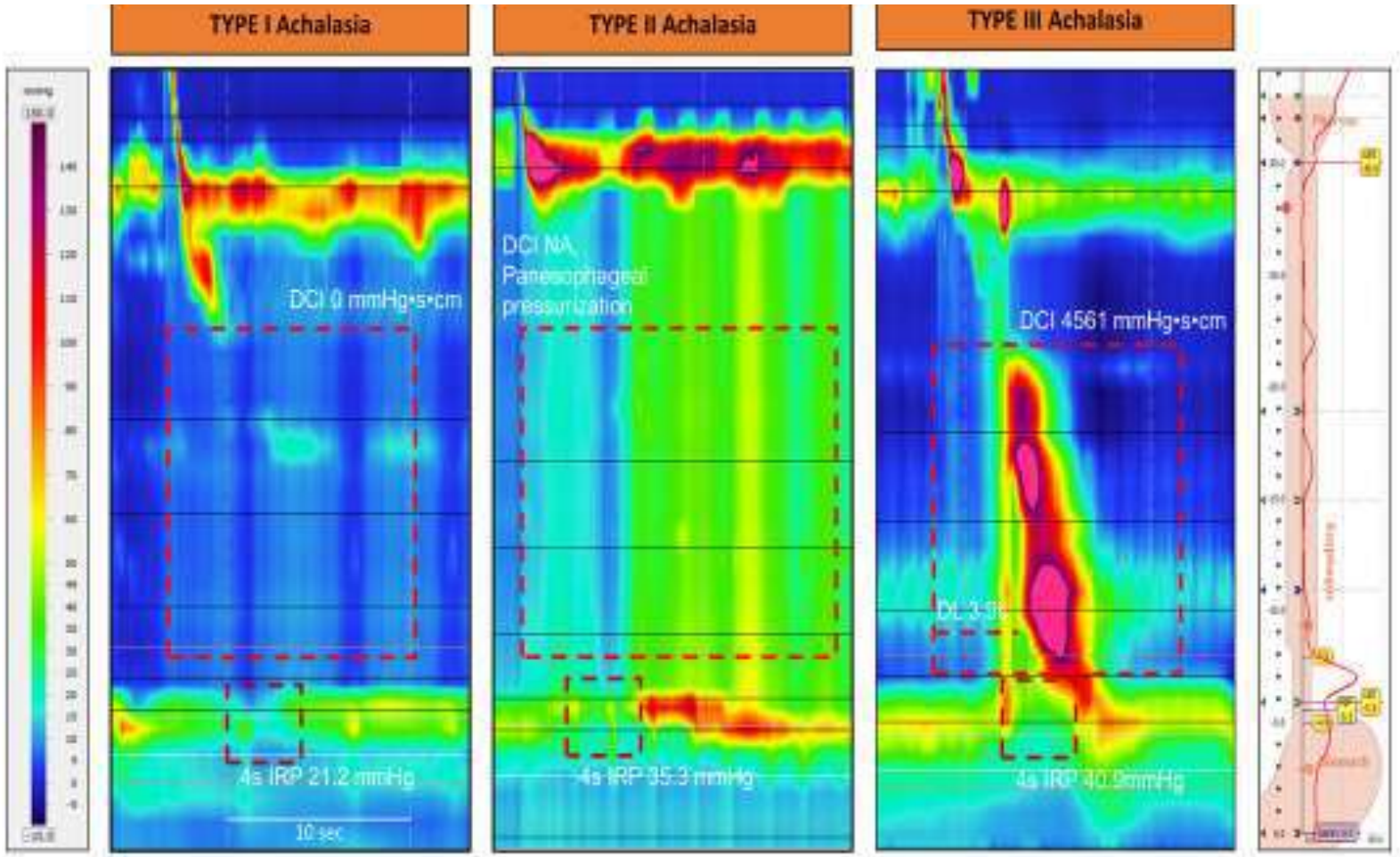
Conventional esophageal manometry



HRM parameters

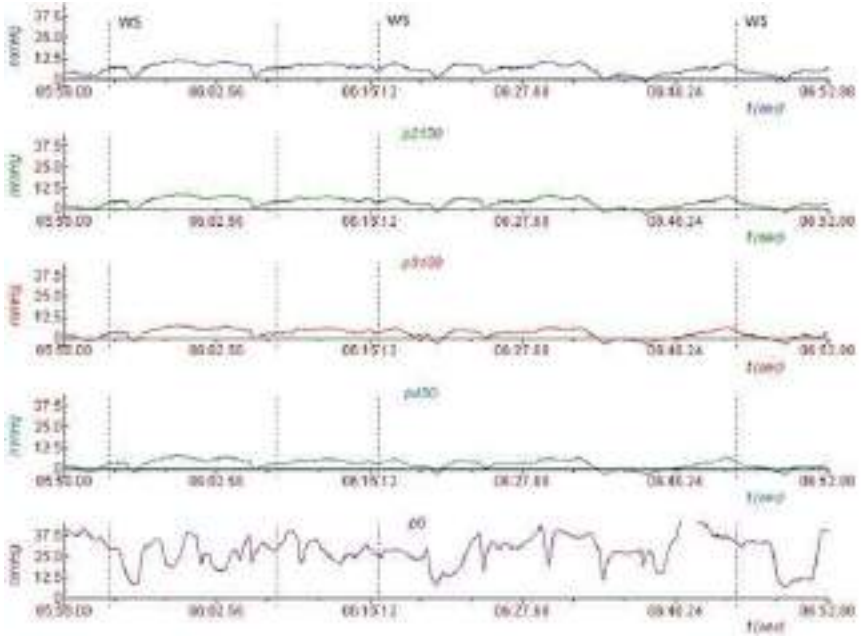
Pressure topography metrics	
Metric	**Description**
Integrated relaxation pressure (mmHg) (IRP)	**Mean EGJ pressure measured for four contiguous or non-contiguous seconds of relaxation of LES in the ten-second window following deglutitive UES relaxation**
Distal contractile integral (mmHg-s-cm)	Amplitude x duration x length (mmHg-s-cm) of the distal esophageal contraction >20 mmHg from proximal (P) to distal (D) pressure troughs
Contractile deceleration point [(CDP) (time, position)]	The inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the phrenic ampulla
Contractile front velocity (cm s−1)	Slope of the tangent approximating the 30 mmHg isobaric contour between P and the CDP
Distal latency (s)	Interval between UES relaxation and the CDP
Peristaltic breaks (cm)	Gaps in the 20 mmHg isobaric contour of the peristaltic contraction between the UES and EGJ, measured in axial length

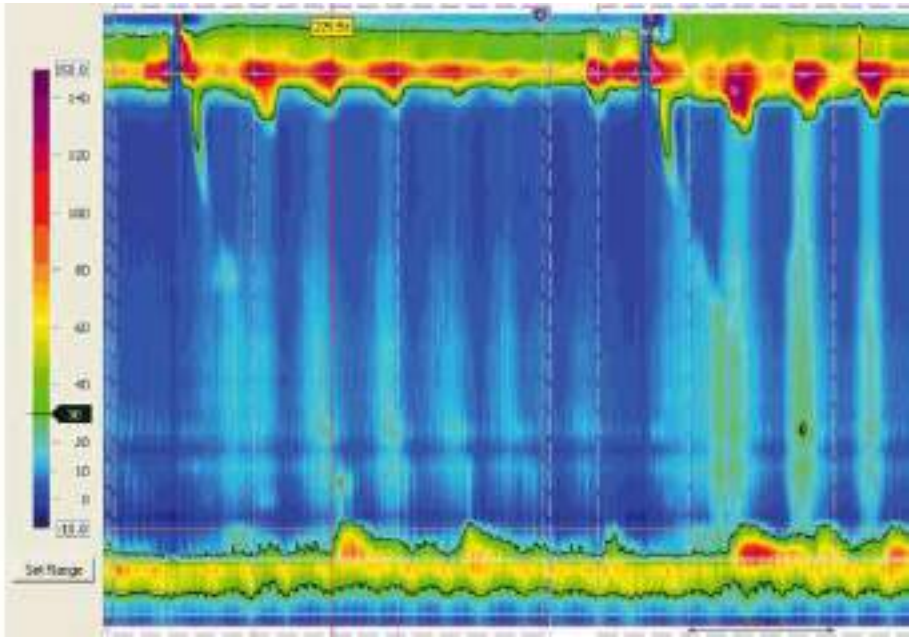
Achalasia: high resolution manometry



High resolution manometry of achalasia phenotypes: type I-absent pressurization (left), type II-pan pressurization (middle), and type III-spastic contractions (right). Lower esophageal sphincter relaxation is impaired for all subtypes.

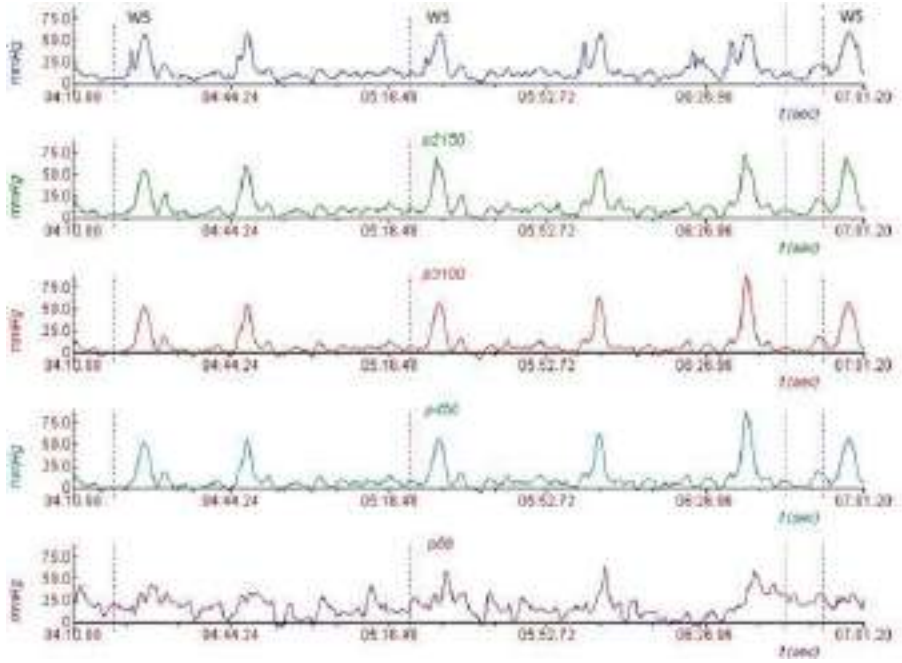
Type I Classic achalasia (A) analogic trace and (B) color pressure topography

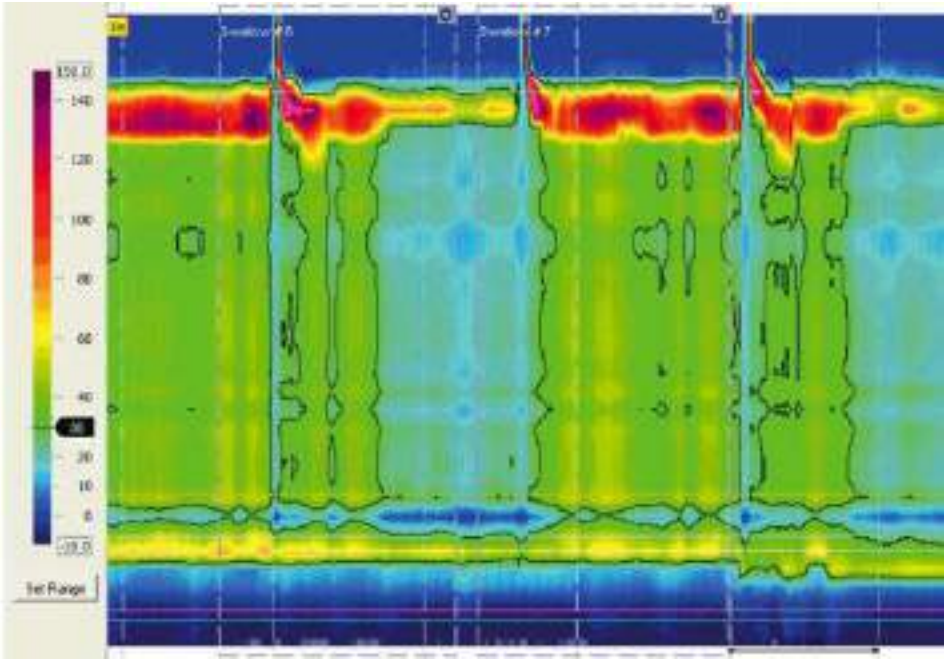




No distal esophageal pressurization is evident and all the contractions elicited by liquid swallows have an amplitude lesser than 30 mm Hg.

Type II achalasia (A) analogic trace and (B) color pressure topography

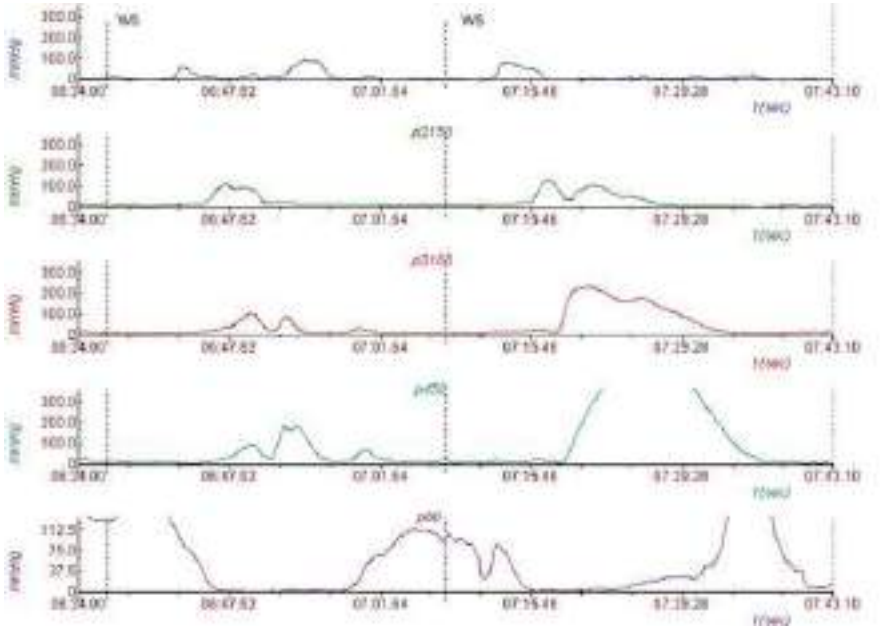


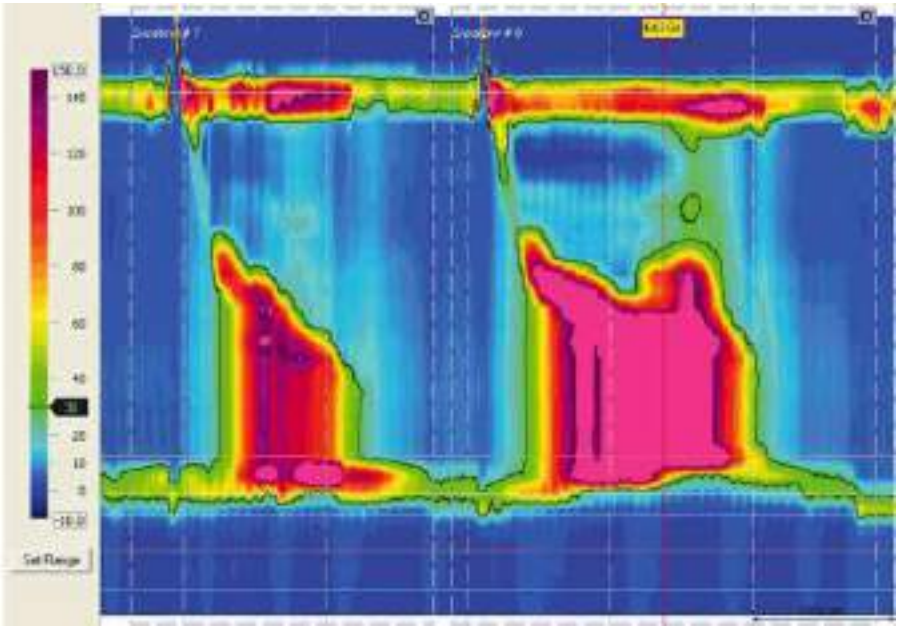


Pan pressurization

Simultaneous isobaric esophageal pressurization is evident at HRM and all the contractions elicited by liquid swallows have an amplitude higher than 30 mmHg, with normal duration.

Type III achalasia (A) analogic trace and (B) color pressure topography.





High-resolution manometric picture of rapidly propagating pressurization with spastic contractions. The high amplitude contractions of the distal esophageal body is represented by the red high-pressure area of the esophageal body contraction. (A) Conventional manometry of long-lasting, high-pressure spastic esophageal contraction.

Medical therapy: Smooth Muscle Relaxers and Neuromodulators That Might Be Used in Patients With Disorder of Esophageal Peristalsis

Smooth muscle relaxers	Peppermint oil	5 drops in 10 mL of water (or 2 Altoid mints sublingual before every meal)	Case series[147]	Might worsen reflux symptoms	Decreases simultaneous contractions and amplitude, but less effect on pain
	Calcium channel blockers	Diltiazem 60–90 mg 4 times a day Nifedipine 10 mg 30 min before meals	RCT in nutcracker esophagus[105]	Hypotension, peripheral edema, headaches, dizziness, and tachyphylaxis	Improves chest pain and decreases esophageal amplitude
	Phosphodiesterase-5 inhibitor	Sildenafil 25–50 mg twice a day	RCT in spastic motor disorder[148]	Headache, hypotension, and dizziness	Might improve manometric findings, but less effect on symptoms
TCAs	Imipramine Amitriptyline	50 mg daily 10–25 mg at night	RCT for NCCP[111,149] RCT for NCCP[150]	QT prolongation, dry mouth, excessive sleeping, dizziness, and constipation	Might use nortriptyline (less anticholinergic effects in hypomotility disorder and NCCP)
SNRI	Venlafaxine	75 mg daily	RCT for NCCP[151]	Sleep disturbances, nausea, hypertension	Less constipation compared with TCA, but similar pain relief
SSRI	Sertraline	50–200 mg daily	RCT for NCCP[152,153]	Nausea, restlessness, dry mouth, diarrhea	Might be beneficial if concomitant anxiety disorder or symptom hypervigilance
	Paroxetine	10–50 mg daily	RCT for NCCP[154]		More drug-drug interactions due to inhibition of P450 isoenzymes Short half-life, risk of discontinuation syndrome if stopped abruptly Fluoxetine preferred in patients who may miss doses (due to longer half-life)
Miscellaneous	Trazadone	100–150 mg daily	RCT in spastic motor disorder[112]	Nausea, dizziness, and drowsiness	Less effect on manometric abnormalities, but significant improvement in chest pain

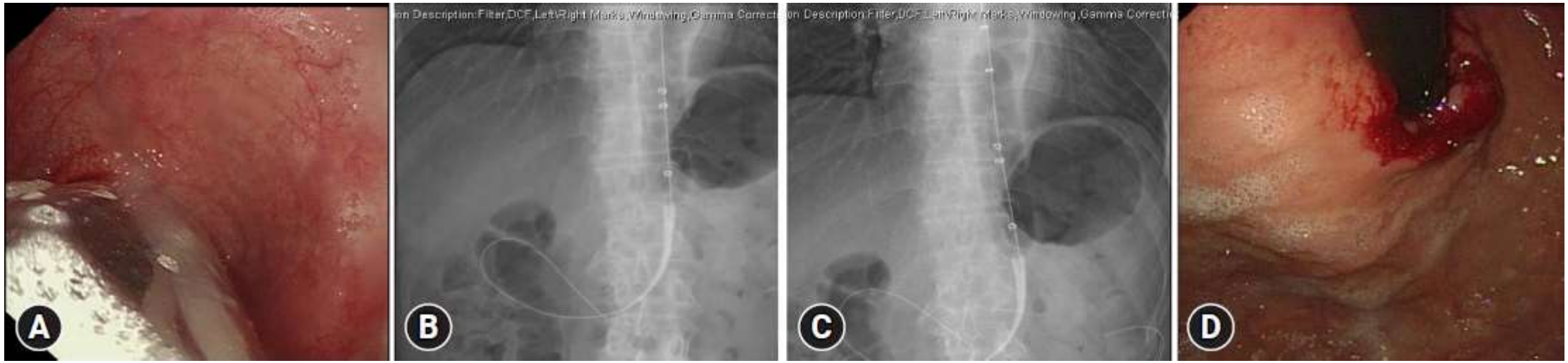
Smooth muscle relaxers should only be used in patients with DES or hypercontractile esophagus.
NCCP, noncardiac chest pain; RCT, randomized controlled trial; SNRI, serotonin-norepinephrine re-uptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants.

Achalasia-medical therapy

Most patients find that long-term drug therapy is inconvenient, ineffective, and often associated with unpleasant side effects, such as headache and low blood pressure.

The drugs tend to become less effective over time.
For these reasons, medications are recommended primarily for patients who are not interested in or not healthy enough for mechanical treatments such as balloon dilatation and surgery (myotomy).

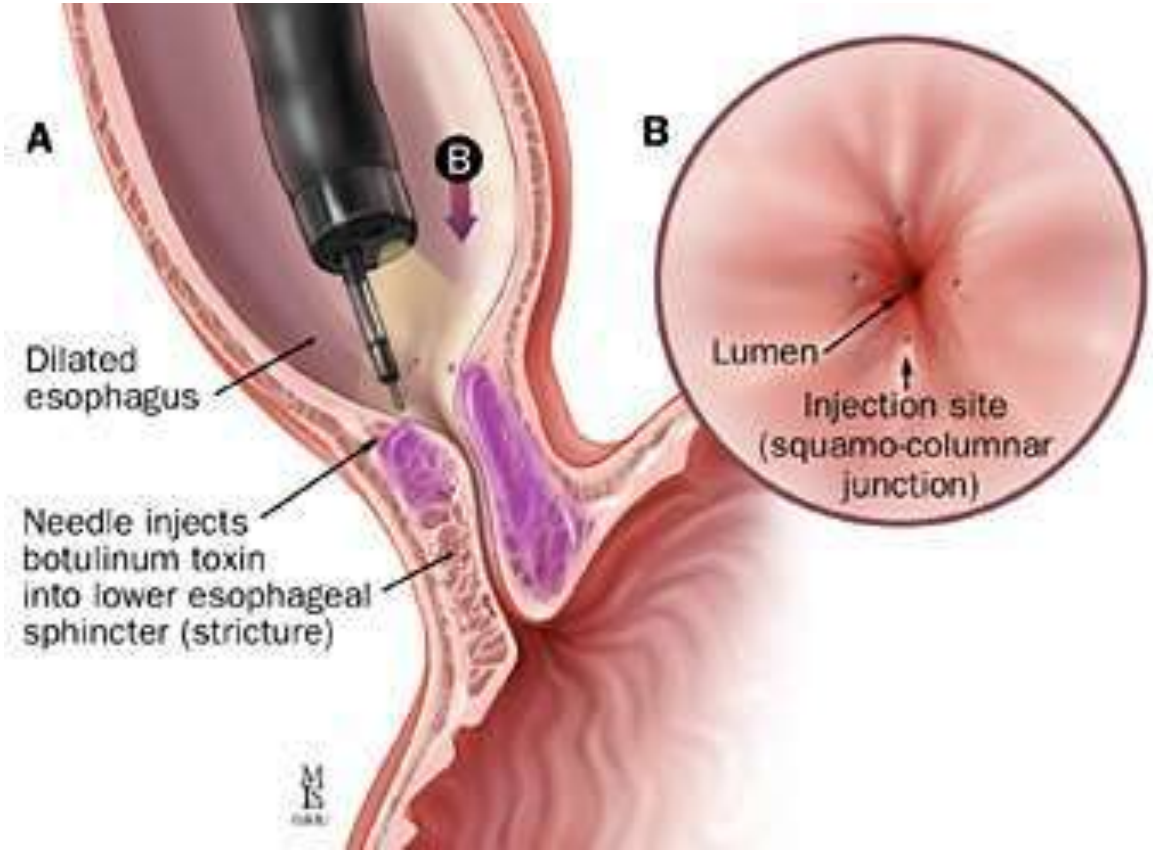
Achalasia: endoscopy treatment
Pneumatic Dilatation



This procedure mechanically disrupts the LES muscle fibers by stretching an air-filled balloon.
The balloon is positioned across the LES and inflated using fluoroscopy until waist obliteration is observed. A graded dilatation approach, starting with a 3-cm balloon and gradually increasing the balloon size by 5 mm when there is insufficient symptom relief, is recommended to minimize the risk of perforation during the procedure.
PD provided relatively long-term symptom relief of over 86% after 2 years of follow-up.

The potential complications of PD include bleeding, chest pain, and most importantly, perforation, which reportedly occurs in **2.9% to 4.3% of patients**. Esophageal perforations may require surgical repair.

Achalasia:endoscopy treatment
Intrasphinteric injection of neurotoxin (botulinum)

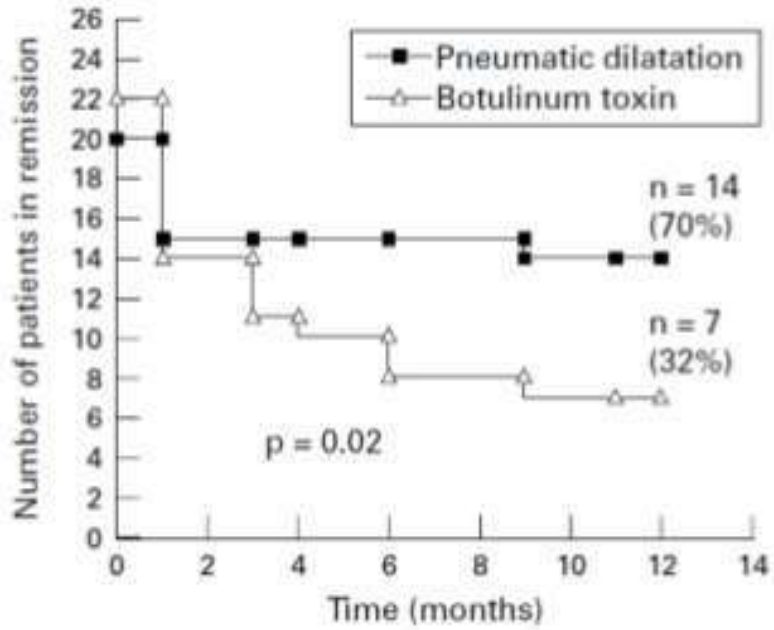


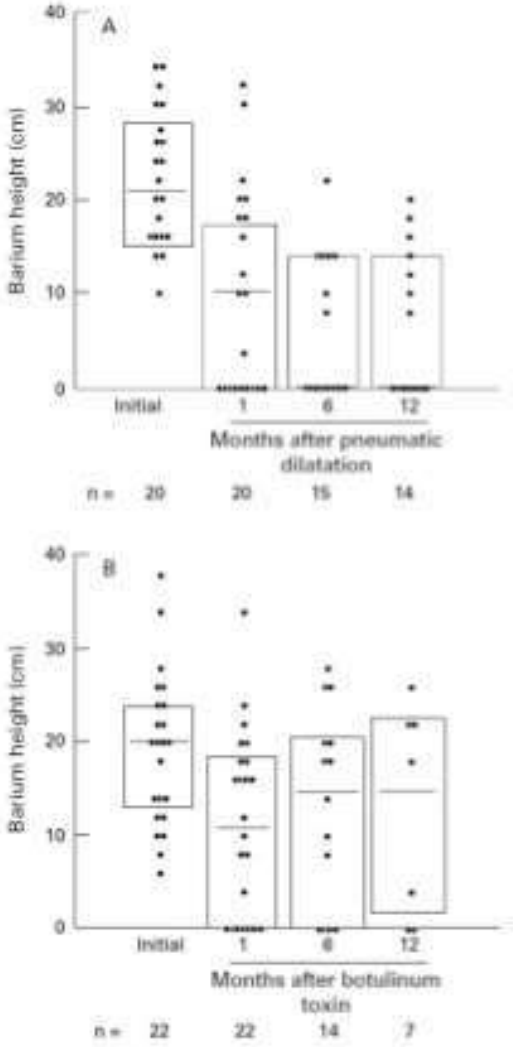
Intrasphincteric injection of the botulinum toxins

The procedure involves injection of the lower esophageal sphincter causing a chemical denervation of the sphincter. Twenty to 25 units of botulinum toxin are injected into each quadrant of the lower esophageal sphincter with a sclerotherapy needle passed through the endoscope. Although it is the safest of available techniques, botulinum toxin injection has a limited duration of effect, lasting on average one year. Repeat treatment is necessary to maintain the effect. Some patients may experience mild chest pain and there have been reports of skin rashes noted after treatment.

Achalasia: endoscopic treatment

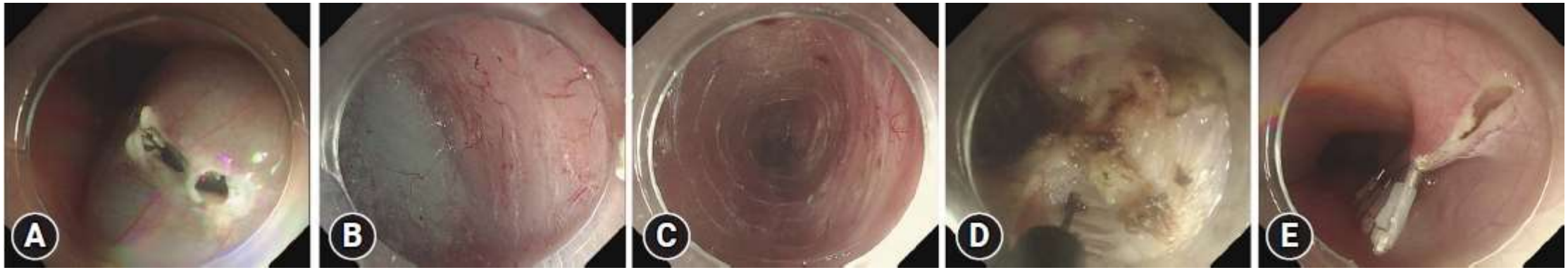
PD vs botox





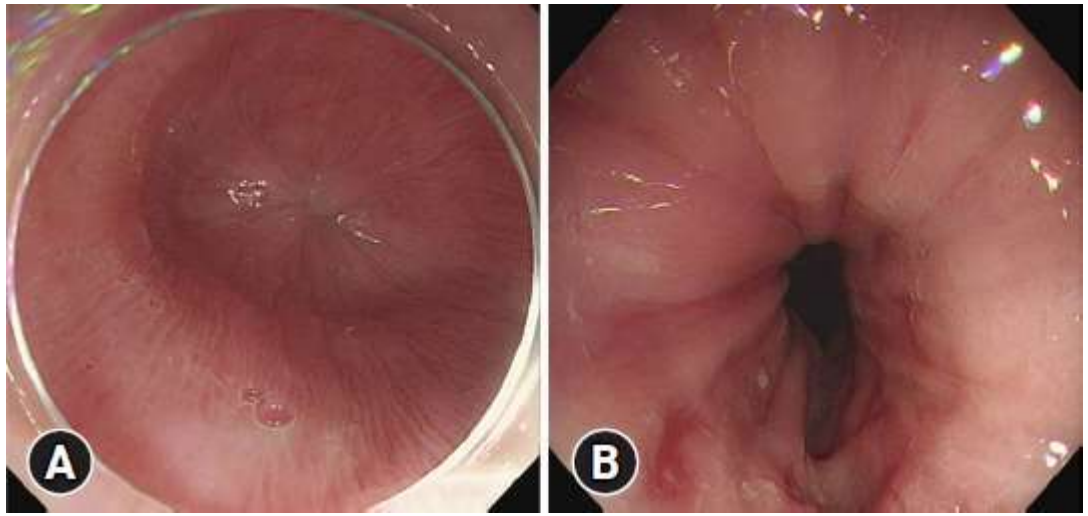
Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, et al. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999 ; 44 : 231-239.

Peroral endoscopic myotomy (POEM)



Four-step procedure for peroral endoscopic myotomy. (A) A mucosal incision approximately 13 cm proximal to the esophagogastric junction. (B) Entry to the submucosal space. (C) Submucosal tunneling. (D) Endoscopic myotomy. (E) Closure of the mucosal entry using hemostatic clips.

Peroral endoscopic myotomy (POEM)



Endoscopic images of a patient with achalasia before (A) and after (B) peroral endoscopic myotomy (POEM). The patient shows improvement in pinstripe pattern after POEM but has developed posttreatment gastroesophageal reflux disease.

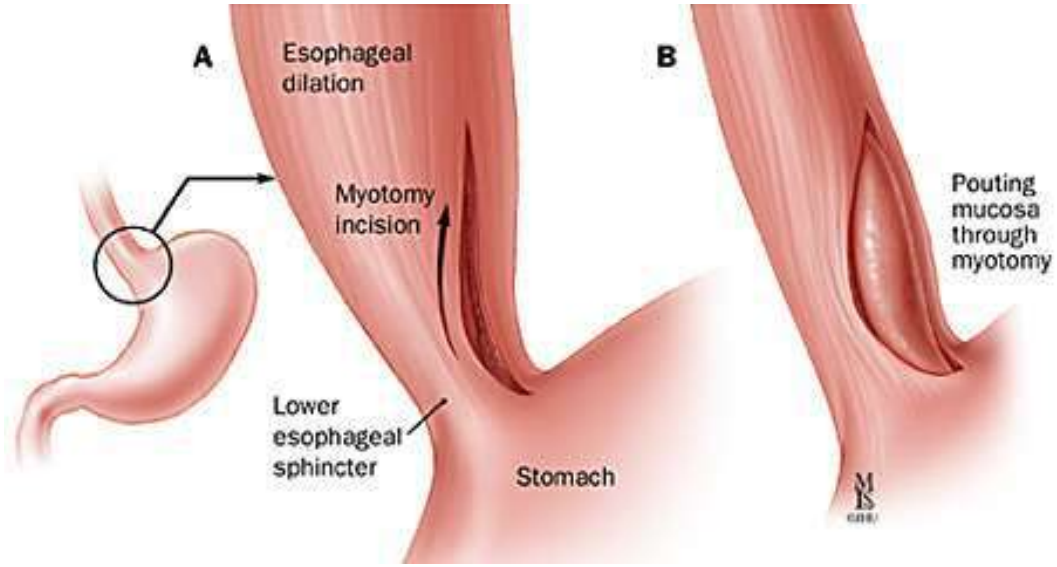
Overview of studies on the long-term clinical efficacy of peroral endoscopic myotomy

Study	No. of total patients	Follow-up period (mo)	Clinical success rate (%)	Eckardt score (before/after treatment)	LES pressure (mmHg) (before/after treatment)	GERD (symptomatic or PPI use) (%)
Li et al. (2018)[52]	564	49 (median)	89.6	8/2	29.7/11.9	37.3
Brewer Gutierrez et al. (2020)[53]	146	55 (median)	95.2	7/1	38.4/16.9	32.1
Nabi et al. (2020)[54]	53 (pediatric)	55 (mean)	88.2	6.9/-	-	33.3
Xu et al. (2021)[55]	278	37 (mean)	95.6	6.9/1.0	32.3/14.1	35.1
Podboy et al. (2021)[56]	69	47 (mean)	72.7	8.7/0.8	-	44.9

LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

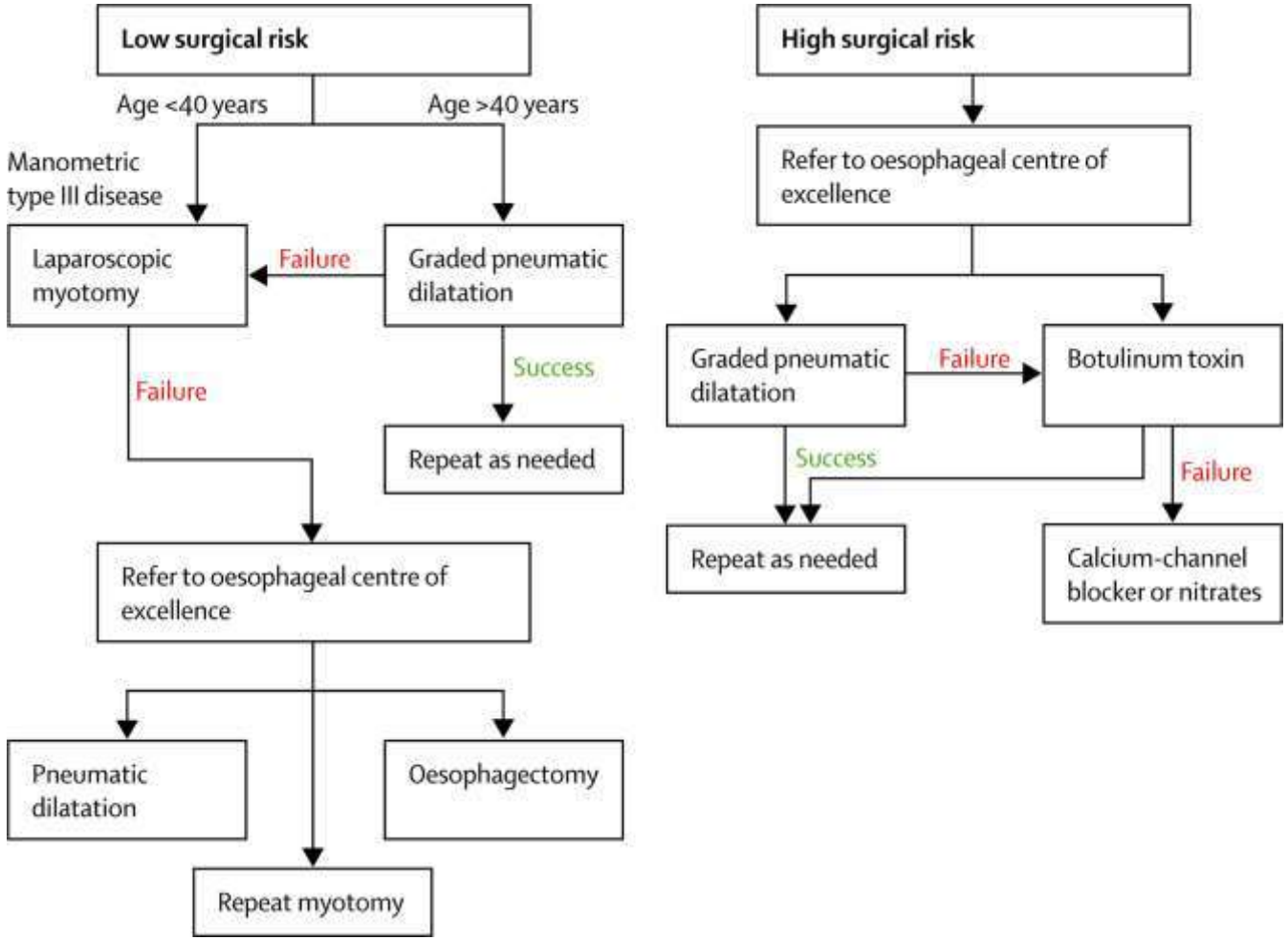
Download Table

Achalasia: Surgical miotomy



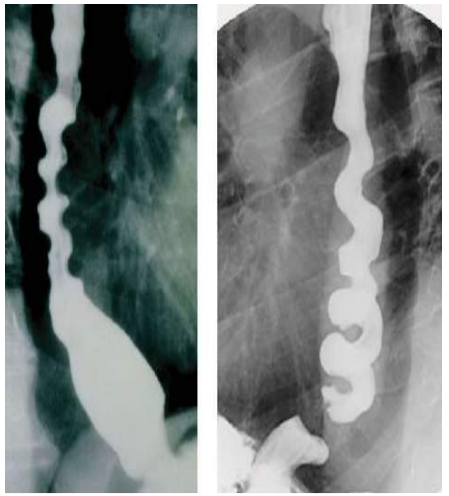
Minimally invasive surgery, using either a laparoscopic or a thorascoscopic technique has significantly decreased the morbidity associated with achalasia surgery.

A single anterior lateral myotomy or a modified Heller myotomy is typically the surgical procedure performed. A lower esophageal sphincter myotomy incises enough muscle to relieve symptoms but not enough to result in gastroesophageal reflux. In many cases, an antireflux procedure is performed at the same time.



Diffuse esophageal spasm (DES)

Diffuse esophageal spasm (DES)



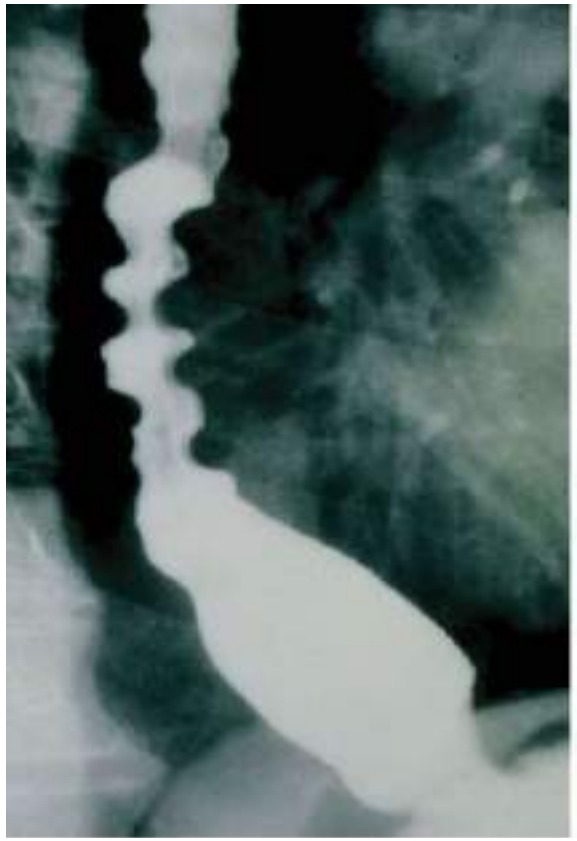
is a condition in which uncoordinated contractions of the esophagus occur.

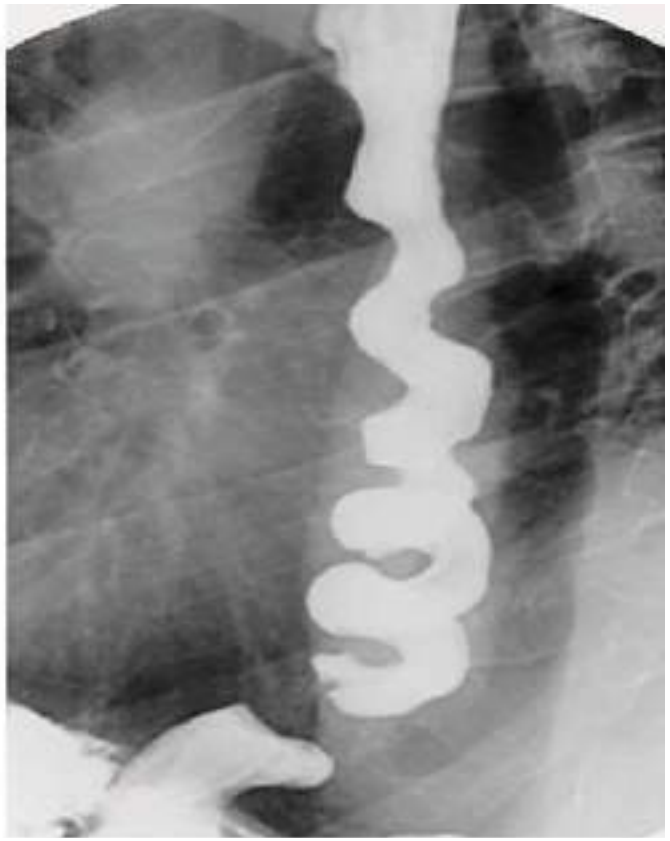
It is thought to result from abnormal esophageal contraction with normal deglutive LES relaxation. As consequence, these spasms do not propel food effectively to the stomach.

Symptoms are dysphagia, regurgitation and chest pain.

The pathophysiology and the natural history of DES are poor defined.
Manometrically, a variety of defining features have been proposed including:
uncoordinated (spastic) activity in the distal esophagus
spontaneous and repetitive contraction
high amplitude contraction
prolonged contraction

Diffuse esophageal spasm: radiological findings

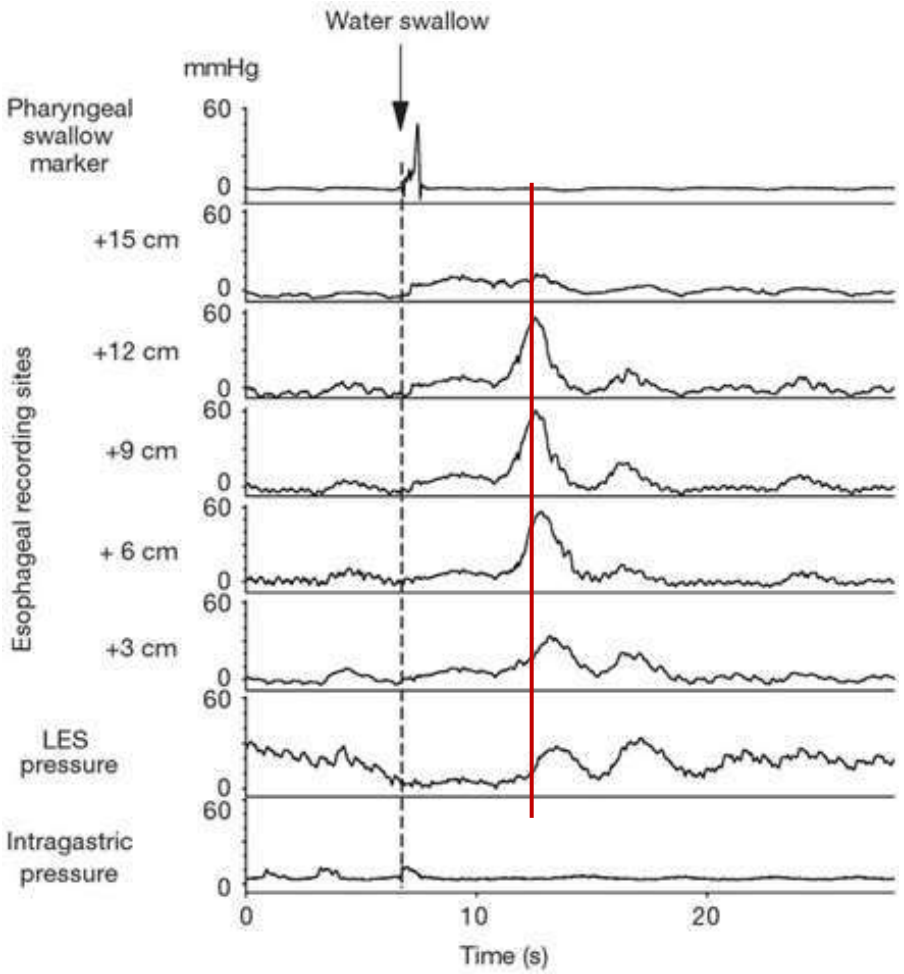




Radiographically, DES has been characterized by tertiary contractions or a “corkscrew esophagus”, but in many instances these abnormalities are actually indicative of achalasia.

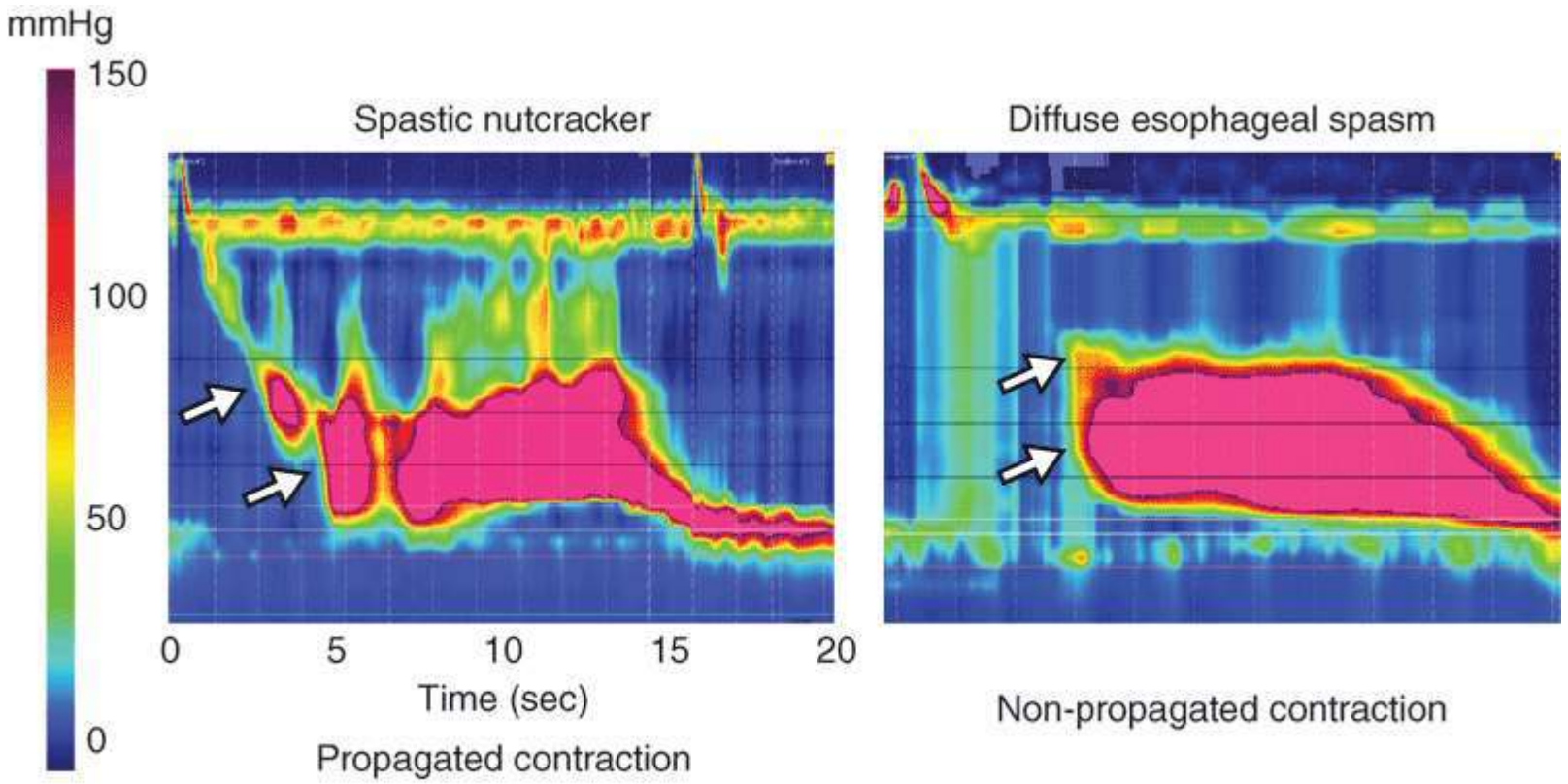
The characteristic “corkscrew” esophagus results from spastic contraction of the circular muscle in the esophageal wall; more precisely, this is actually a helical array of muscle. These findings are also seen with spastic achalas

Diffuse esophageal spasm: conventional manometry



Conventional esophageal motility tracing from a patient with diffuse esophageal spasm demonstrating simultaneous contractions of the esophageal body with intact LES relaxation in >20% of swallows.

Diffuse esophageal spasm: HRM



Esophageal pressure topography of the two major variants of esophageal spasm:
spastic nutcracker (left) and diffuse esophageal spasm (right).
Spastic nutcracker is defined by the extraordinarily vigorous (an amplitude > 180 mmHg) and repetitive contractions with normal peristaltic onset. DES is similar but primarily defined by a rapid propagation at the onset of the contraction.

Diffuse esophageal spasm: therapy

Given this vagaries of defining DES and the resultant heterogeneity of patients identified for inclusion in therapeutic trials, it is not surprising that trial results have been disappointing.

Only small trials exist, reporting response to:

- **Nitrates**
- **Calcium channels blockers**
- **Hydralazine**
- **Botulinum toxin**
- **Anxiolytics**

Surgical therapy (long myotomy or even esopfagectomy) should be considered only with severe weight loss or unbearable pain. These indications are extremely rare.

Esophagogastric junction outflow obstruction (EGJOO)

A diagnosis of EGJOO should be considered in those with high IRP and normal esophageal peristalsis.
The prevalence of manometric EGJOO ranged from 5%–24% of patients undergoing HRM.

Causes include: postoperative anatomic distortion related to fundoplication or bariatric surgery, cancer or other infiltrative processes, luminal stricture or extraluminal compression due to paraesophageal hernia (or cardiovascular compression, etc), or an artifactual increase of the IRP from the catheter effect.
Opioid analgesics have also been associated with impaired LES relaxation resulting in functional EGJOO.
A clinically conclusive diagnosis of EGJOO requires: (1) conclusive manometric diagnosis, (2) appropriate symptom presentation, and (3) confirmation of findings on supportive testing.

Treatment Options for EGJOO

Therapeutic management of conclusive and clinically relevant EGJOO is highly variable and should be based on predominant symptom and severity of symptoms because 52%–92% of patients with mild symptoms might have spontaneous resolution.
Standard endoscopic dilation might provide symptomatic relief with a pooled response rate of 69.6%, whereas botulinum toxin injection to the LES has a pooled response rate of 63.6%.95

Gastroesophageal reflux disease (GERD)

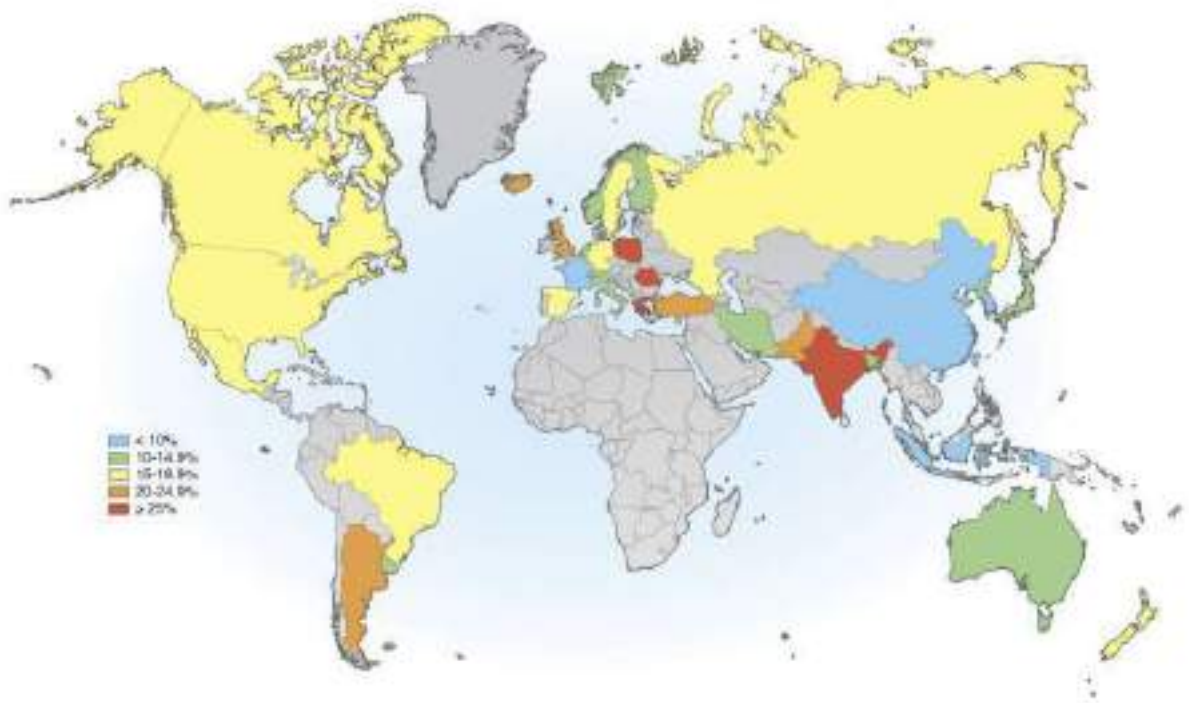
Gastroesophageal disease (GERD)

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by the regurgitation of gastric contents into the esophagus.

It is one of the most commonly diagnosed digestive disorders in the worldwide with a prevalence of 10-15%in the general population, resulting in a significant economic burden in direct and indirect costs and adversely affects the quality of life

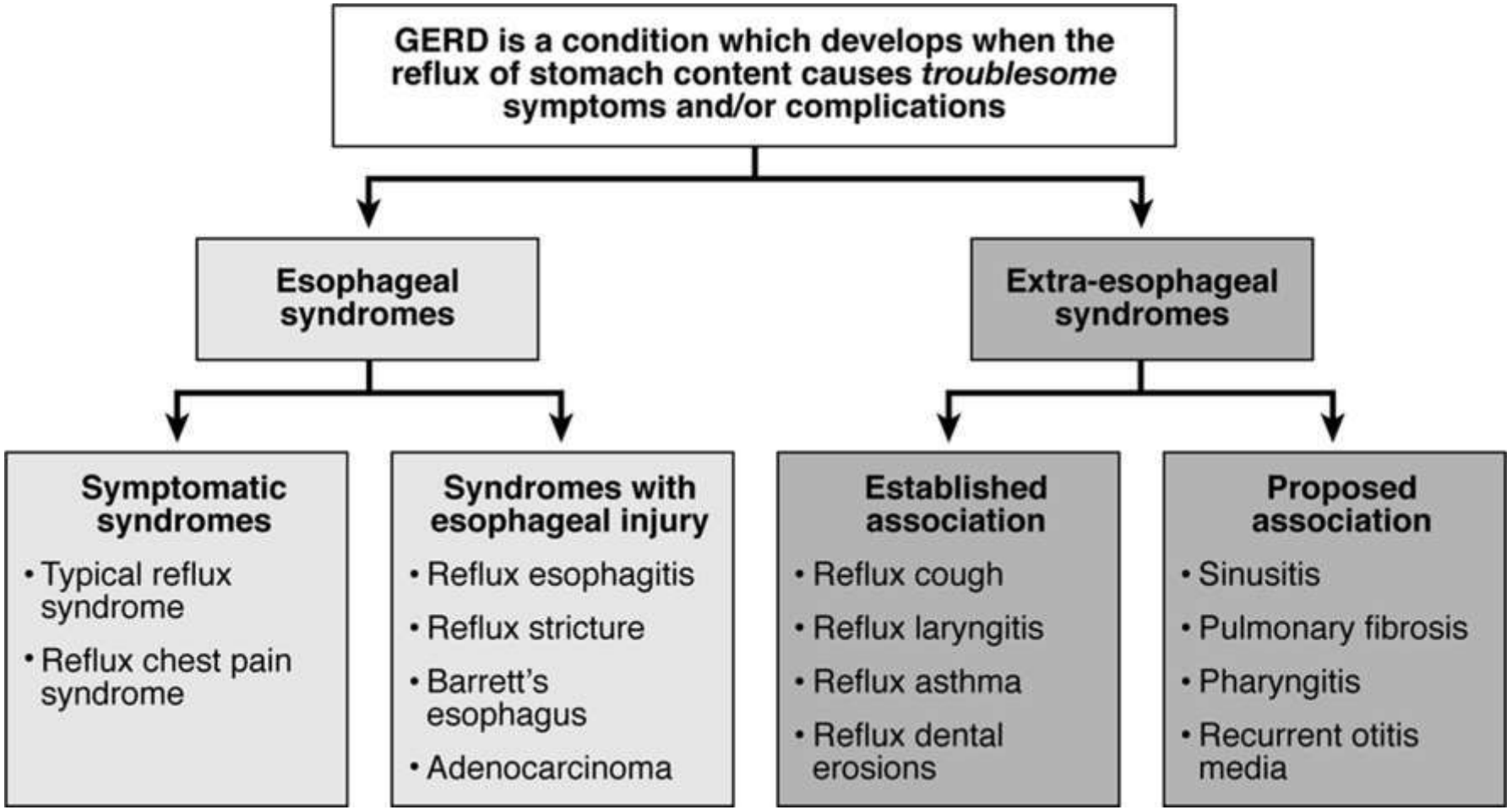
Gastroesophageal reflux disease Prevalence

The estimated prevalence of GERD is 13.3% of the population worldwide and 15.4% in North America, and costs related to GERD in the United States are estimated at $10 billion annually



Prevalence of weekly gastroesophageal reflux symptoms worldwide, based on symptoms at a frequency of once a week or more.
(Eusebi et al. *Gut* 2017. https://doi.org/10.1136/gutjnl-2016-313589)

GERD has several phenotypes



Montreal classification of GERD (Vakil ET AL. AM J Gastroenterol 2006)

GERD has several phenotypes

Typical (esophageal) symptoms are : heartburn, which is described as a burning sensation in the mid-chest, and **regurgitation,** which is the sensation of gastric contents coming up into the esophagus/throat.

In addition patients might develop esophageal lesions, leading to the appearance of endoscopic signs of esophagitis which might progress to **GERD complications, such as esophageal ulceration, stricture, Barrett's esophagus, and adenocarcinoma of the esophagus**

Pathological reflux → Symptomatic GERD → Esophagitis → Complicated esophagitis

GERD Phenotypes

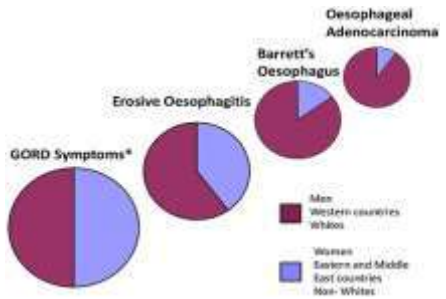
Non erosive Reflux Disease
NERD

Erosive esophagitis

Typical
-Heartburn
-Regurgitation

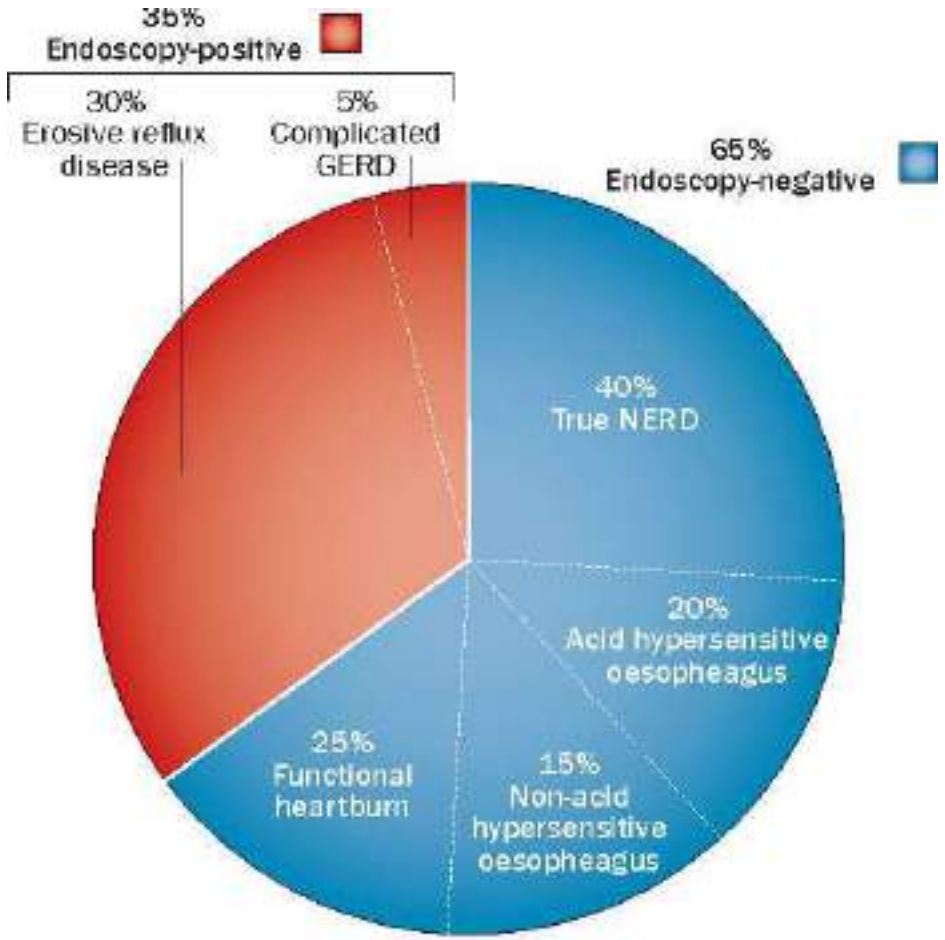
Atypical
Cardiac: Chest pain, arrhyhmia
Respiratory: crhonic cough, asthma, pneumonia
ORL:
Laringitis, otitis, sinusitis

Ulcerations
Stricture
Hemorrhage
Barrett E.
Adeno CR



GERD has several phenotypes

The phenotypic presentations of GERD include **nonerosive reflux disease** (in 60 to 70% of patients), **erosive esophagitis** (in 30%), and Barrett's esophagus (in 5 to 12%).9

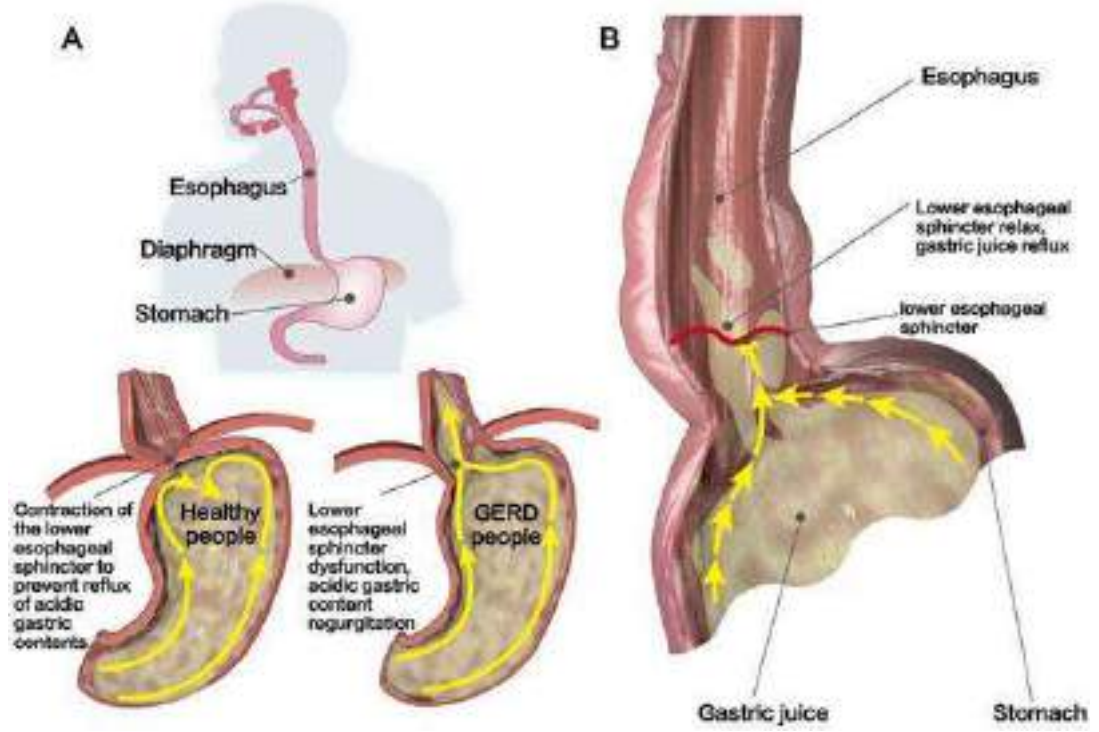


Pathogenesis

GERD: antireflux barrier

- **ntireflux barrier**
  Anatomy and function of LES region (angle of His, LES pressure etc.)
  Esophageal peristalsis
  Esophageal barrier (epithelial and post epithelial, mucus secretion)

- **Aggressive factors**
  Delayed gastric emptying
  Reflux composition (acid and pepsin and bile acids)



GERD pathogenesis

Idhiopathic vs Secondary GERD

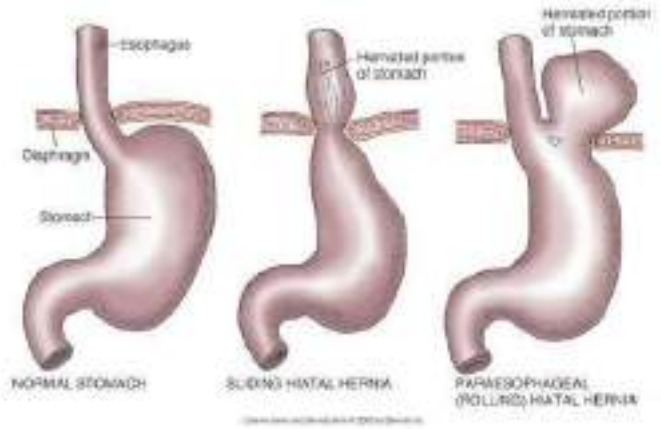
Secondary GERD is caused by failure of the lower esophageal sphincter (LES) or esophageal motility

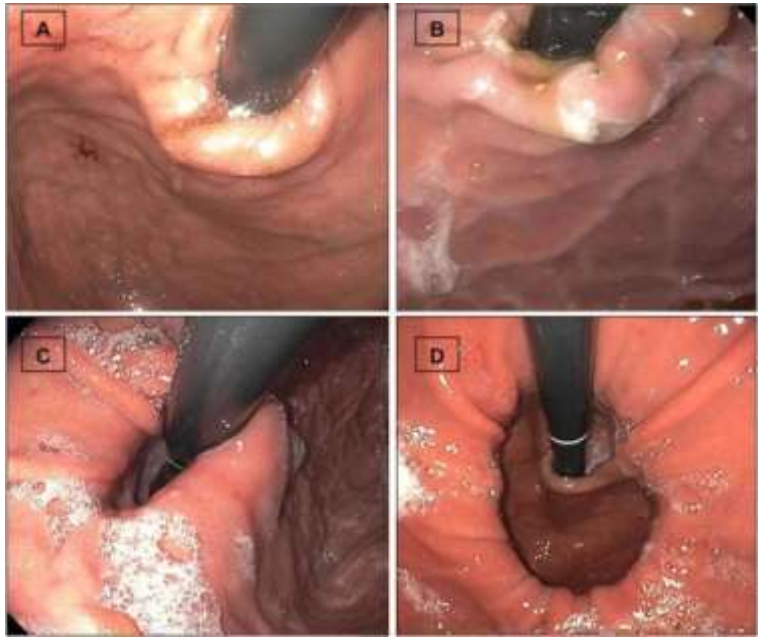
- Hiatal ernia , which increases the likelihood of GERD due to mechanical and motility factors .
- Obesity : increasing body mass index is associated with more severe GERD
- Pregnancy
- Scleroderma and systemic sclerosis , which can feature esophageal dysmotility.
- Drugs, including Ca blockers, Beta agonists, nitrate, steroids, ecc

Secondary GERD pathogenesis

Hiatal hernia

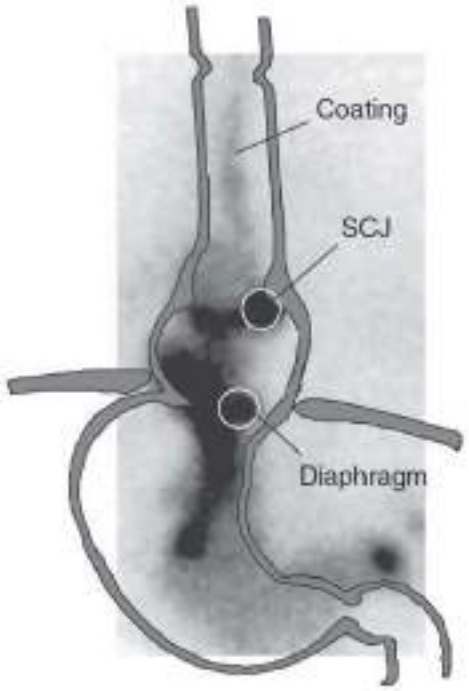
- There are two main types of hiatus hernia, the **sliding and the paraoesophageal**.
- **Sliding hiatus** hernia is strongly associated with GERD and has been shown to be an independent risk factor for the disease, whilst there **is no evidence of an association between paraoesophageal** hiatus hernia and GERD.
- Population-based studies have shown that around **50% of individuals with at least weekly reflux symptoms and 75% of those with esophagitis have a hiatus hernia**

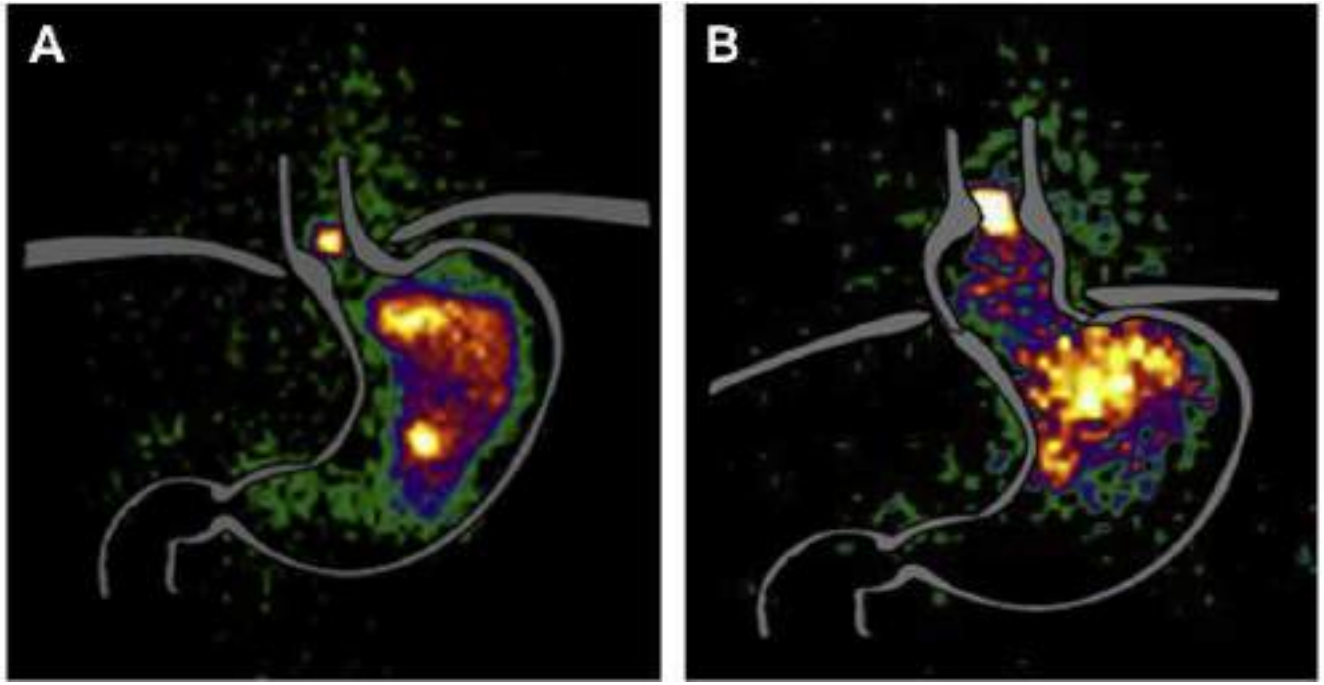




GERD pathogenesis

- Representative scintigraphic images of the postprandial acid pocket and the squamocolumnar junction (SCJ) in a gastroesophageal reflux disease patient with a large hiatal hernia.





Idiopathic GERD

Genetic

A meta-analysis of GERD GWAS studies from three independent population-based cohorts, has identified 30 independent suggestive signals of association that show concordant risk and functional effects on gene expression.

Seven genes associates with GERD

***ABHD10*, *RNF7*, *RASGRF2*, *BTF3P7*, *C8orf4*, *GLDC*, and *ADAMTS17*.**

ADAMTS17 is a member of the *ADAMTS* (a disintegrin and metalloproteinase with thrombospondin motifs) protein family, which comprises 19 secreted proteases primarily associated with the extra-cellular matrix and involved in a wide range of human biological processes with potential roles in arthritis, cancer, angiogenesis, atherosclerosis, central nervous system disorders

03 August 2016 **https://doi.org/10.1111/nmo.12923**

Idiopathic GERD

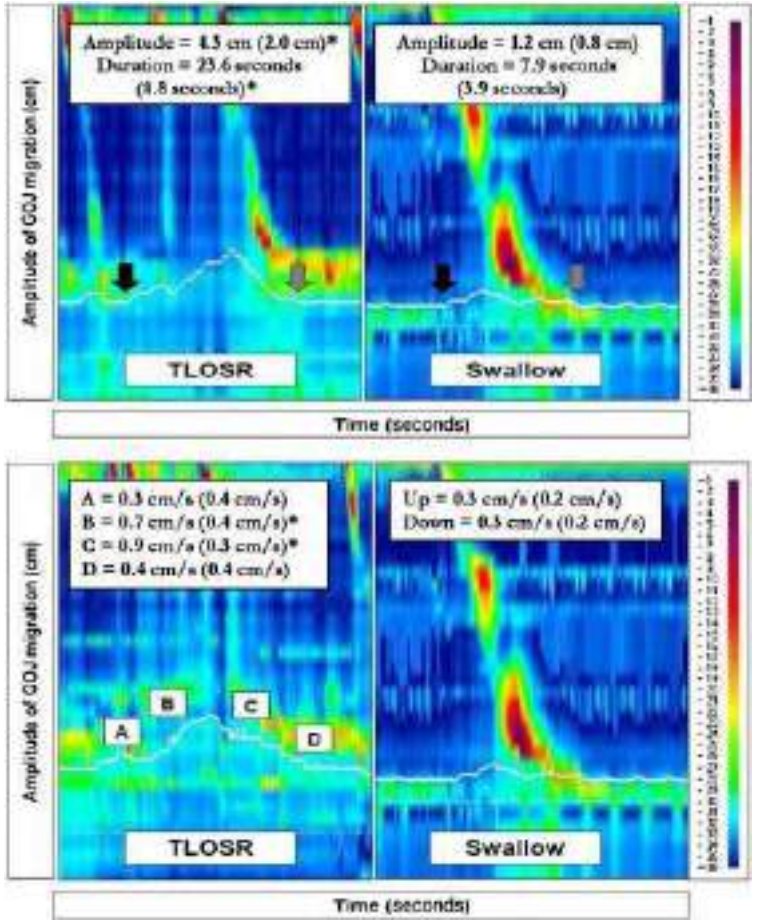
Hypotensive LES

Decreased LES resting pressure and shorter length of LES are associated with increased reflux. These can be caused by physiological factors such as respiration, gastric activity, and body position, as well as **hormones, medication, and certain foods or scleroderma**

Idopathic GERD

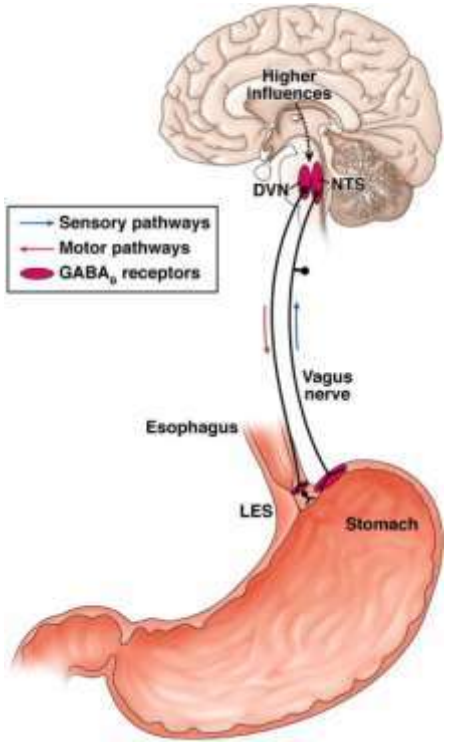
Transient LES relaxations

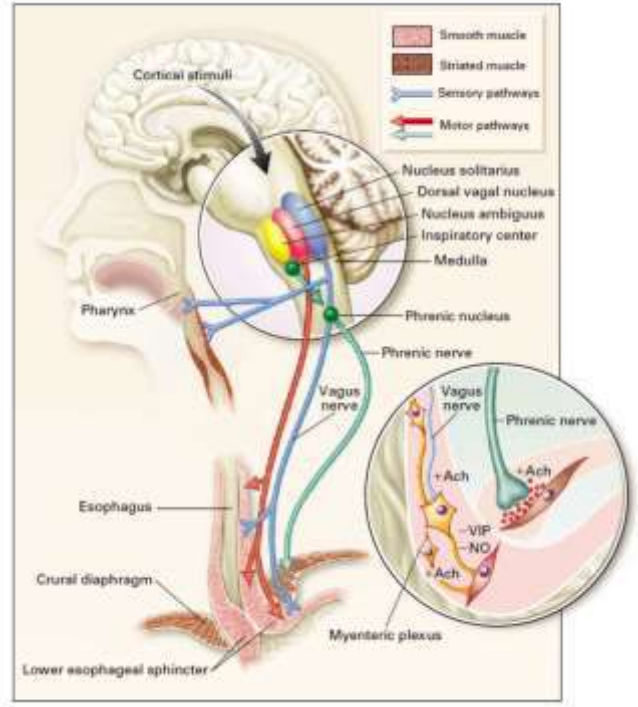
- **Most individuals with GERD have LES pressures within the normal range**. For the majority, reflux episodes occur during relaxations known as **tLESRs**, that **are not induced by swallowing or peristalsis.**
- Gastric distension, which increases the pressure gradient across the GEJ.
- tLESRs are thought to be a **neurally-mediated vago-vagal reflex,** triggered by the activation of stretch receptors in the stomach.

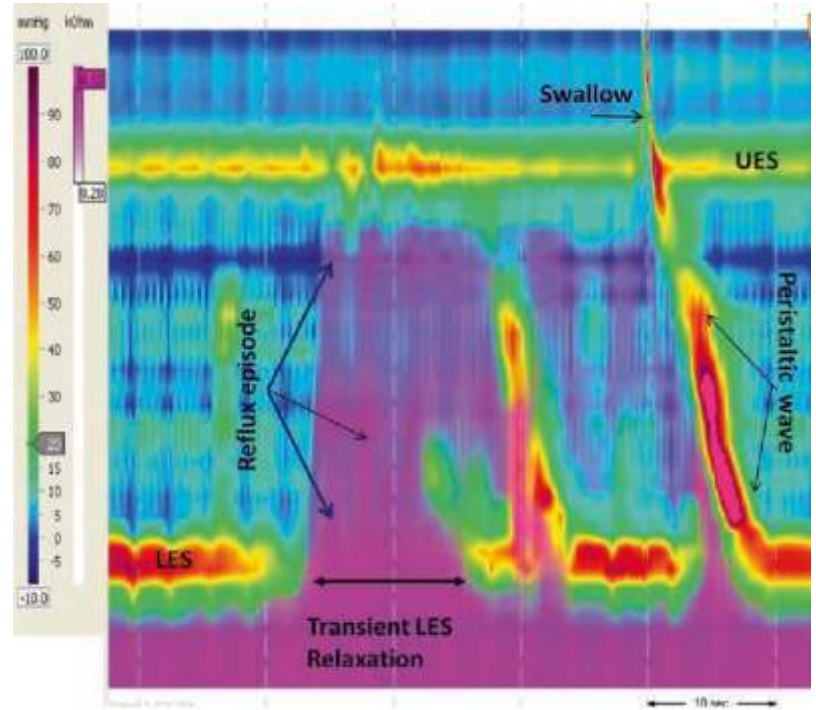


GERD: pathogenesis tLESRs

tLESRs, that **are not induced by swallowing or peristalsis.**







Diagnosis

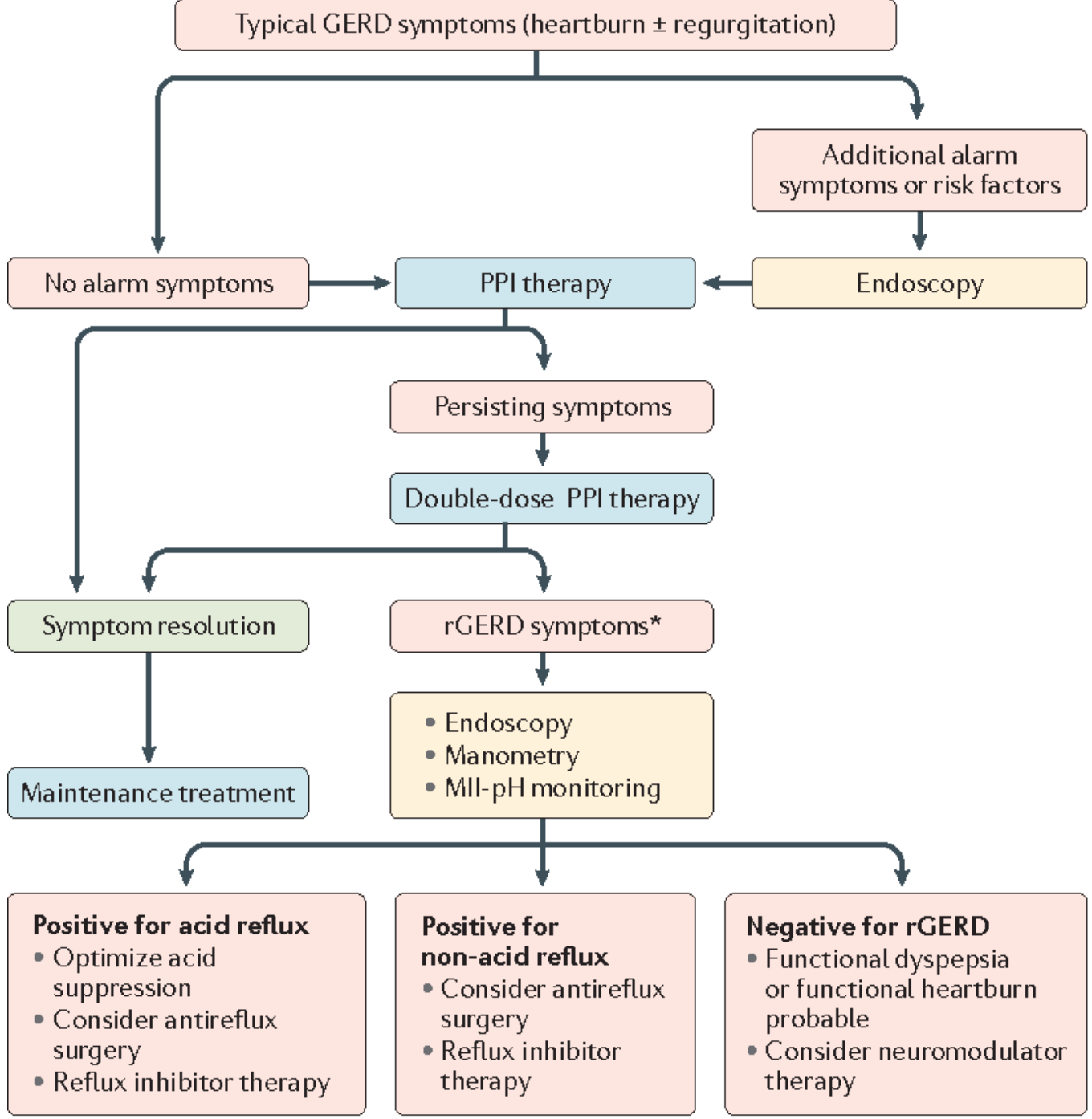


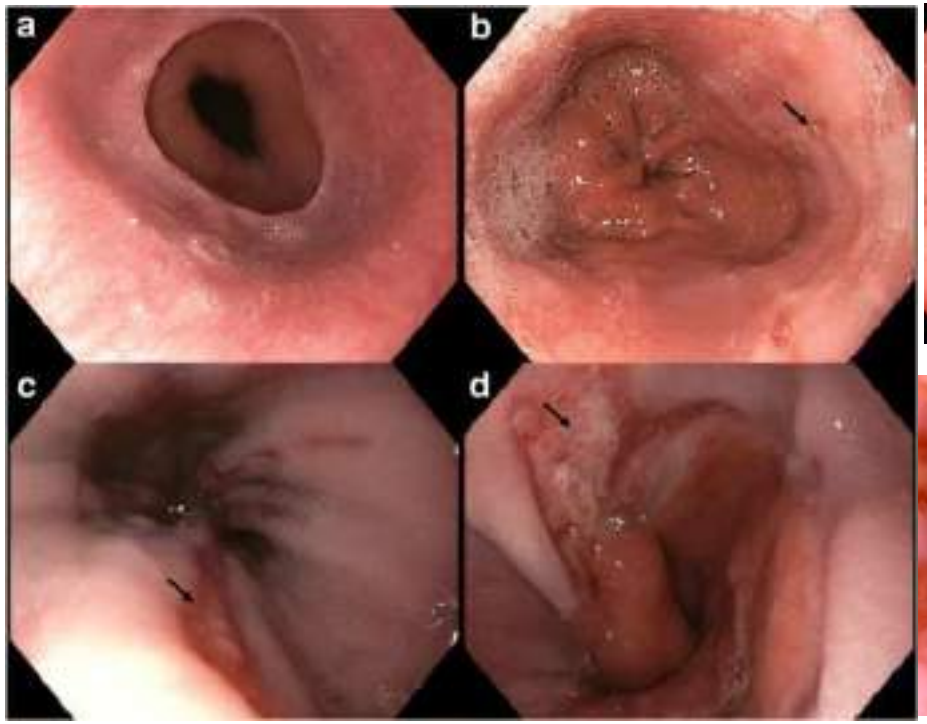
Figure 1 | **Current treatment algorithm for patients with typical GERD symptoms**

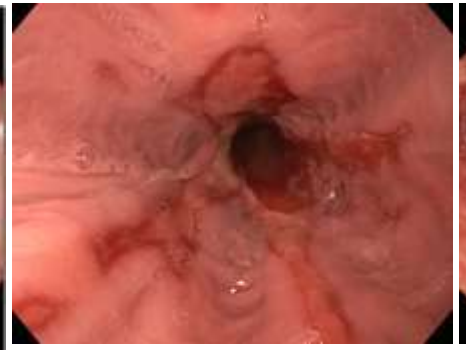
Table 2. Diagnostic testing for GERD and utility of tests

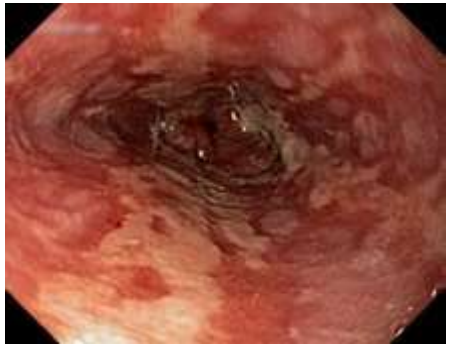
Diagnostic test	Indication	Highest level of evidence	Recommendation
PPI trial	Classic symptoms, no warning signs,	Meta-analysis	Negative trial does not rule out GERD
Barium swallow	Not for GERD diagnosis. Use for evaluation of dysphagia	Case-control	Do not use unless evaluating for complication (stricture, ring)
Endoscopy	Alarm symptoms, screening of high-risk patients, chest pain	Randomized Controlled Trial	**Consider early for elderly, those at risk for Barrett's, noncardiac chest pain, patients unresponsive to PPI**
Esophageal biopsy	Exclude non-GERD causes for symptoms	Case-Control	Not indicated for diagnosis of GERD
Esophageal manometry	Preoperative evaluation for surgery	Observational	Not recommended for GERD diagnosis. Rule out achalasia/scleroderma-like esophagus preop
Ambulatory reflux monitoring pH impedence manometry	Preoperatively for non-erosive disease. refractory GERD symptoms, GERD diagnosis in question	Observational	**Correlate symptoms with reflux,**

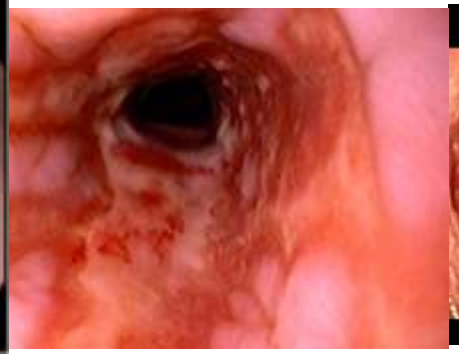
Los Angeles classification of erosive esophagitis

Grade	Endoscopic finding
A	One or more mucosal breaks no longer than 5mm none of which extends between the tops of the mucosal folds
B	One or more mucosal breaks more than 5mm long none of which extends between the tops of 2 mucosal folds
C	Mucosal breaks that extend between the tops of 2 or more mucosal folds but which involve <75% of the esophageal circumference
D	Mucosal breaks which involves at least 75% of the esophageal circumference









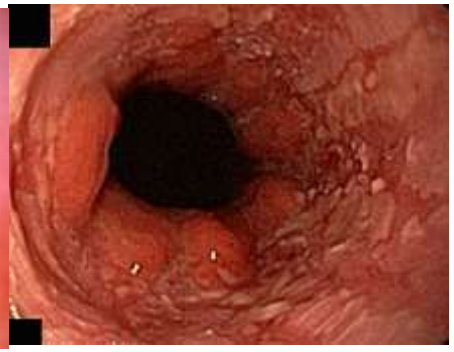
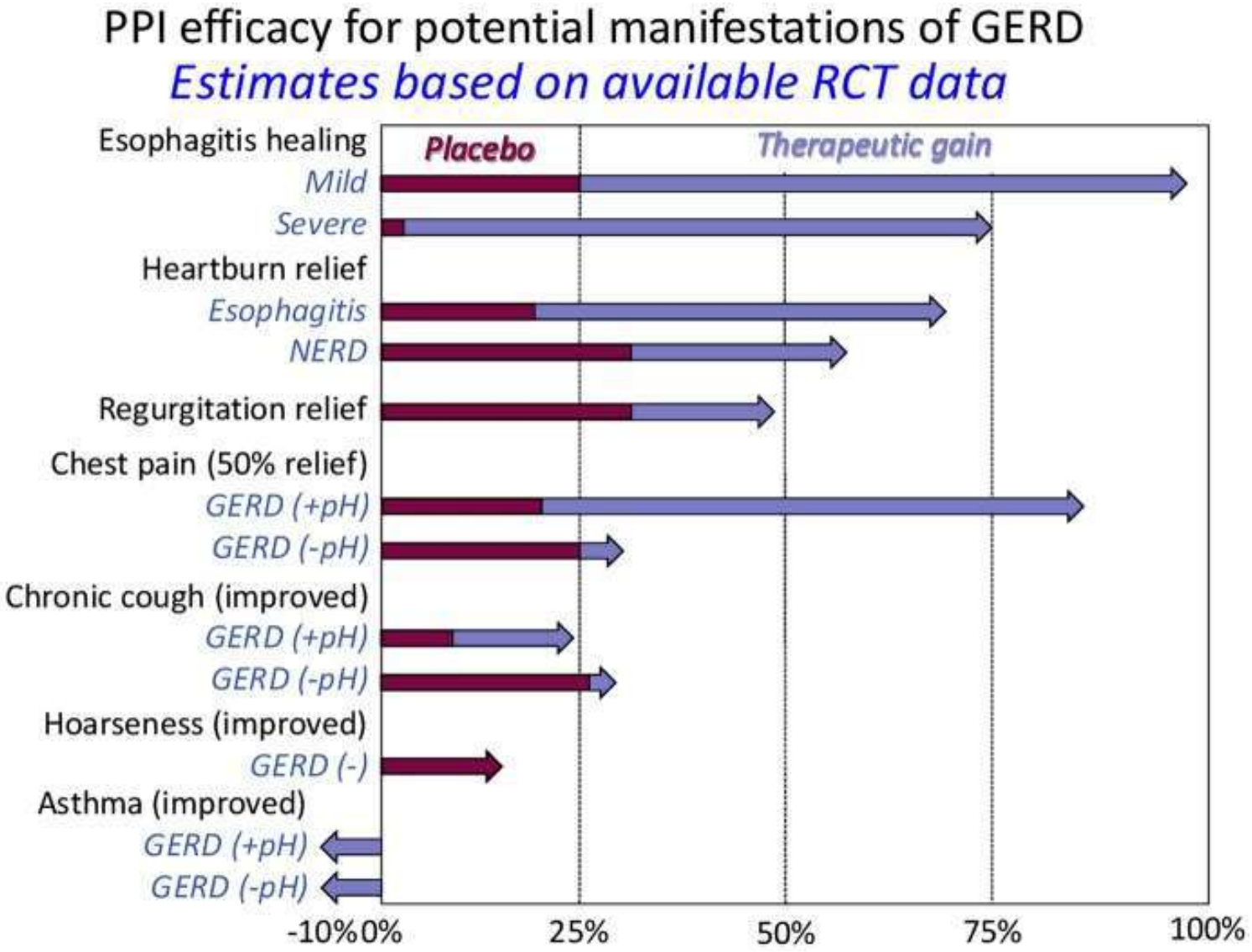


Table 3. Efficacy of lifestyle interventions for GERD

Lifestyle intervention	Effect of intervention on GERD parameters	Recommendation
Weight loss	Improvement of GERD symptoms and esophageal pH	Strong recommendation for patients with BMI>25 or patients with recent weight gain
Head of bed elevation	Improved esophageal pH and symptoms	Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD
Avoidance of late evening meals	Improved nocturnal gastric acidity but not symptoms	Avoid eating meals with high fat content within 2–3 h of reclining
Tobacco and alcohol cessation	No change in symptoms or esophageal pH	Not recommended to improve GERD symptoms
Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages	No studies performed	Not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with elimination

BMI, body mass index; GERD, gastroesophageal reflux disease.



Phenotypes of Gastroesophageal Reflux Disease: Where Rome, Lyon, and Montreal Meet
David A.Katzka∗John E.Pandolfino‡Peter J.Kahrilas‡ Clinical Gastroenterology and Hepatology Volume 18, Issue 4, April 2020, Pages 767-776

Risks linked to the PPI use

Box 1. Adverse Events Associated With PPI Use

Adverse nonkidney events

- Atrophic gastritis
- Vitamin B_{12} malabsorption
- Cardiovascular disease
- *Clostridioides difficile* infection
- Community-acquired pneumonia
- Dementia
- Gastric cancer
- Osteoporotic fractures

Adverse kidney outcomes

- Hypomagnesemia
- Acute kidney injury
- Acute interstitial nephritis
- Incident chronic kidney disease
- Kidney failure

Causes of death associated with PPI use

- All-cause mortality
- Death due to cardiovascular disease
- Death due to chronic kidney disease
- Death due upper gastrointestinal cancer

Abbreviation: PPI, proton pump inhibitor.

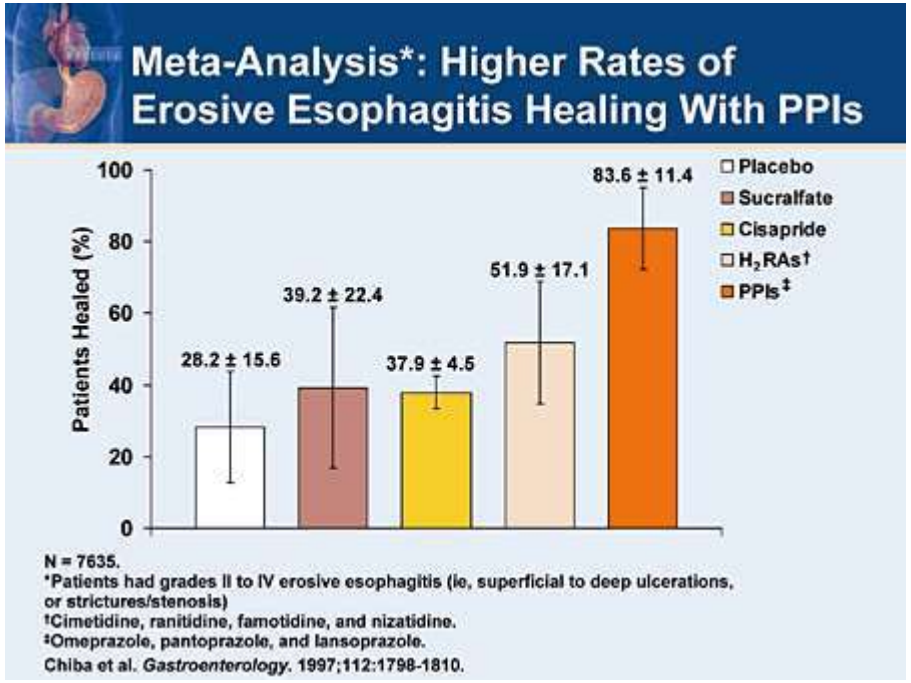
Table 3. Recommendations for Use of PPIs.*

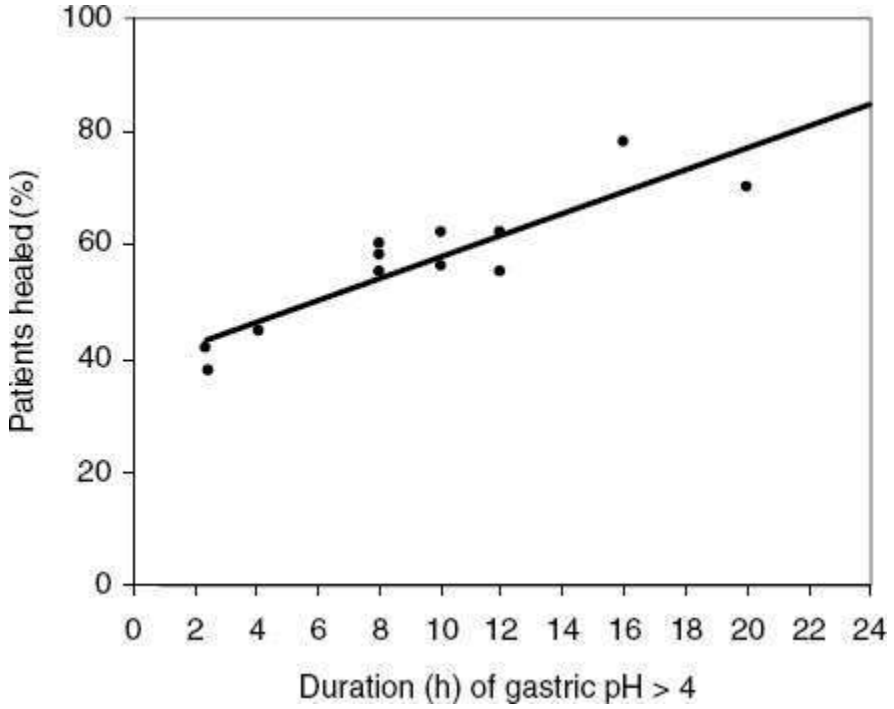
PPIs should be taken 30 to 60 min before a meal, preferably in the morning.
In patients who do not have a response when receiving PPI once daily, therapy should be optimized before doubling the dose:
Confirm daily adherence to PPI regimen and correct timing of ingestion.
If appropriate adherence and timing are confirmed, try splitting the standard dose, giving half before breakfast and half before dinner.
Reemphasize lifestyle recommendations.
Patients with uncomplicated GERD who have a response to short-term PPI therapy should attempt to stop therapy; if symptoms recur, therapy should be reinitiated at the lowest dose that controls the symptoms.†
Long-term PPI therapy should be considered in patients with Barrett's esophagus and symptomatic GERD.
Dose levels that are used for long-term PPI therapy should be periodically evaluated so that the lowest effective PPI dose can be prescribed.
Long-term PPI use is not an indication for routine use of probiotics to prevent infections (e.g., gastroenteritis, *Clostridium difficile* colitis, and pneumonia); increased intake of calcium, vitamin B_{12}, or magnesium beyond the recommended dietary allowance (with the goal of preventing osteoporosis, anemia, or magnesium deficiency); or routine monitoring of bone mineral density or levels of serum creatinine, magnesium, or vitamin B_{12}.
Patients with erosive esophagitis or GERD-related complications (e.g., grade C or D erosive esophagitis, peptic stricture, or esophageal ulcer) should receive long-term PPI therapy for healing, symptom control, and prevention of recurrence.
In patients with nonerosive reflux disease and episodic heartburn, on-demand or intermittent therapy with a PPI can serve as an alternative to daily PPI treatment.

* Recommendations for long-term use of PPIs were adapted from best-practice advice from the American Gastroenterological Association.[38]

† In a patient whose symptoms recur with PPI tapering, an upper endoscopy should be performed if not already done; if findings on endoscopy are normal, reflux testing should be considered to distinguish GERD from functional or other esophageal disorders before committing the patient to long-term PPI use.

Pharmacology of Antacids and Antisecretory agents

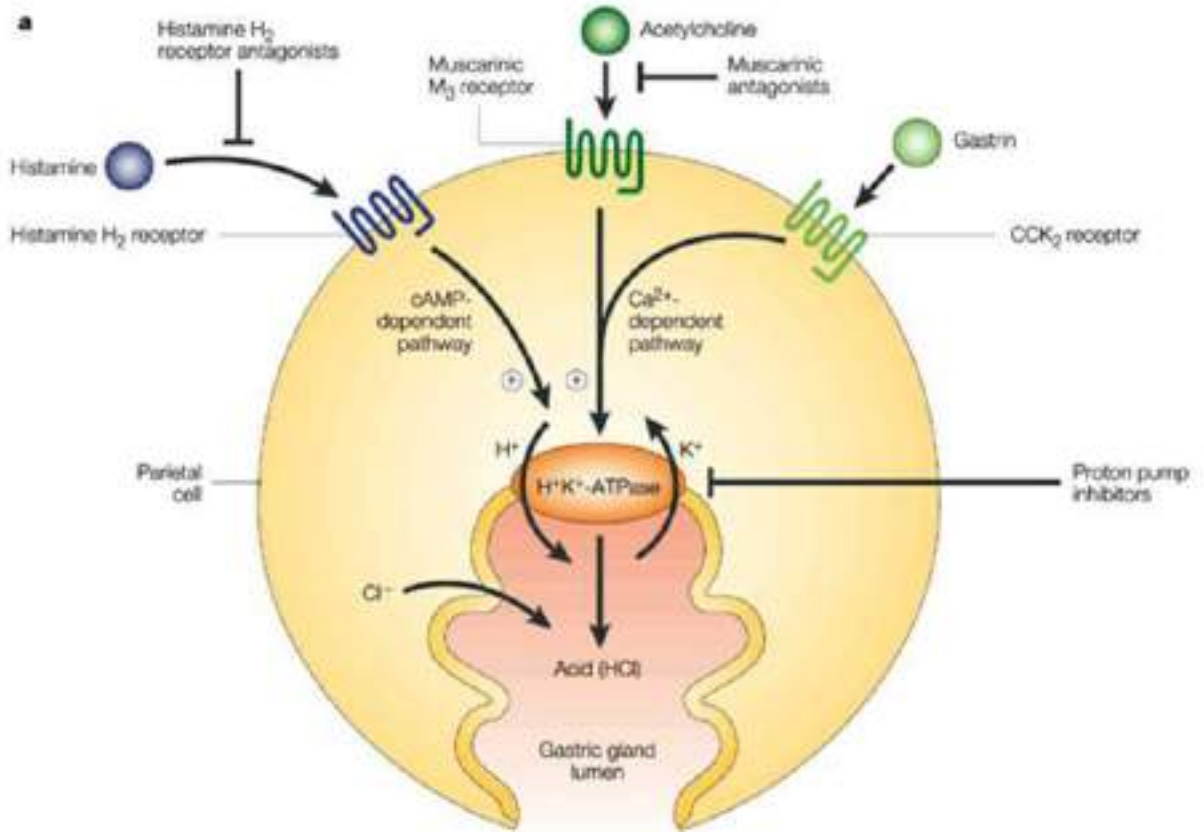




$$pH = - \log H^+$$

Pharmacology of
Antacids and Antisecretory agents

Antisecretory drugs

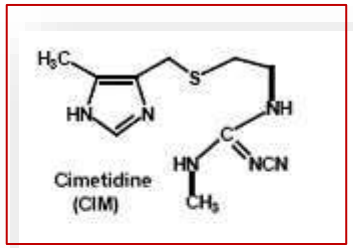


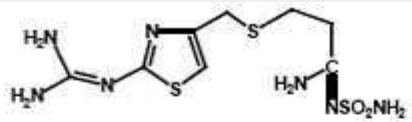
Antisecretory drugs

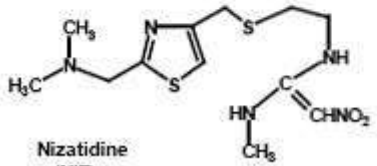

Sir James W. Black

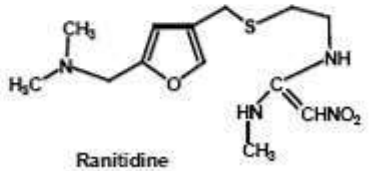

Gertrude B. Elion


George H. Hitchings









H2-Receptor Antagonists

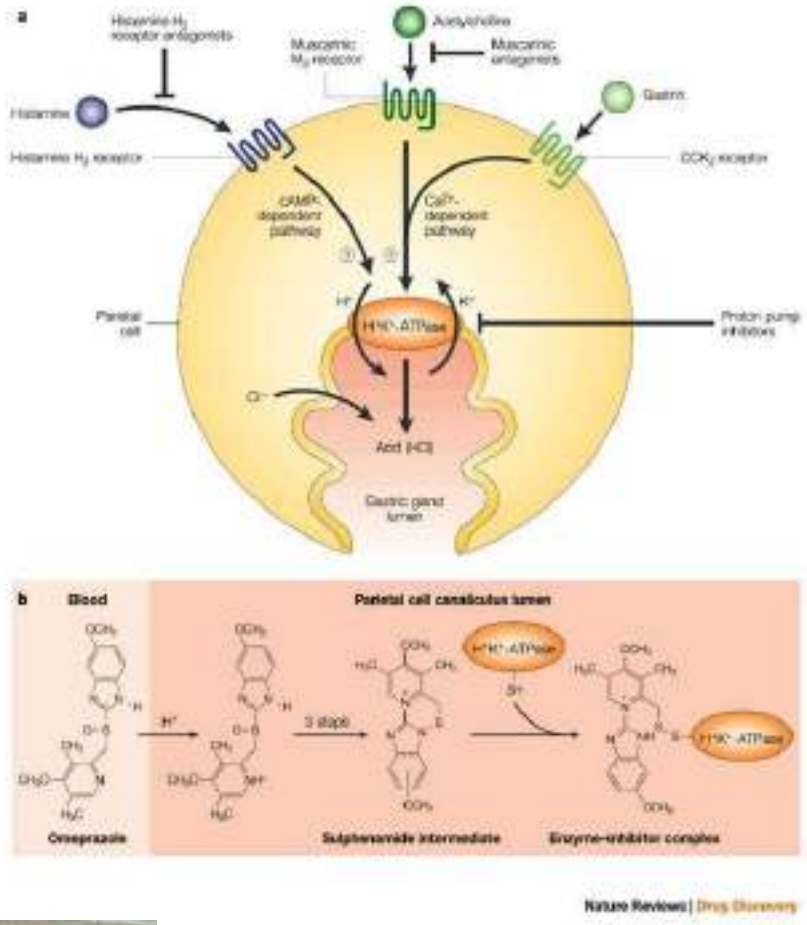
- Typical doses:
  - Cimetidine
    - 200 - 400 mg 2-4 x/day
  - Ranitidine
    - 150 mg 1-2 x/day
  - Famotidine
    - 20 mg 1-2 x/day
  - Nizatidine
    - 150 mg 1-2 x/day

H2As should be dose adjusted for renal insufficiency

Sir James W. Black (1924-2010).
Nobel laureate 1988 who discovered the beta adrenergic receptors and the H2 receptor

Black JW, Duncan WAM, Durant CJ, et al. Definition and antagonism of histamine H2 receptors. Nature. 1972;236:385–390.

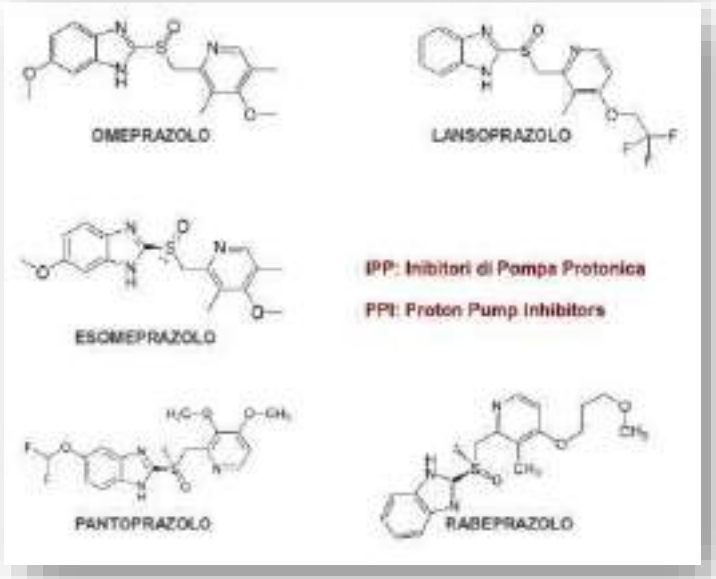
Antisecretory drugs



Proton Pump Inhibitors

- Typical doses
  - Omeprazole or Esomeprazole
    - 20 - 40 mg/day
  - Lansoprazole
    - 15 - 30 mg/day
  - Rabeprazole
    - 20 mg/day
  - Pantoprazole
    - 20 - 40 mg/day

34



George Sachs, Distinguished Professor of Medicine and Physiology at UCLA (1935-2019)

Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H+ + K+)ATPase. Nature. 1981;290:159–161.

GERD: Atypical symptoms

- GERD can be considered as a potential co-factor in patients with **asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients**
- A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings

- **A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD.**

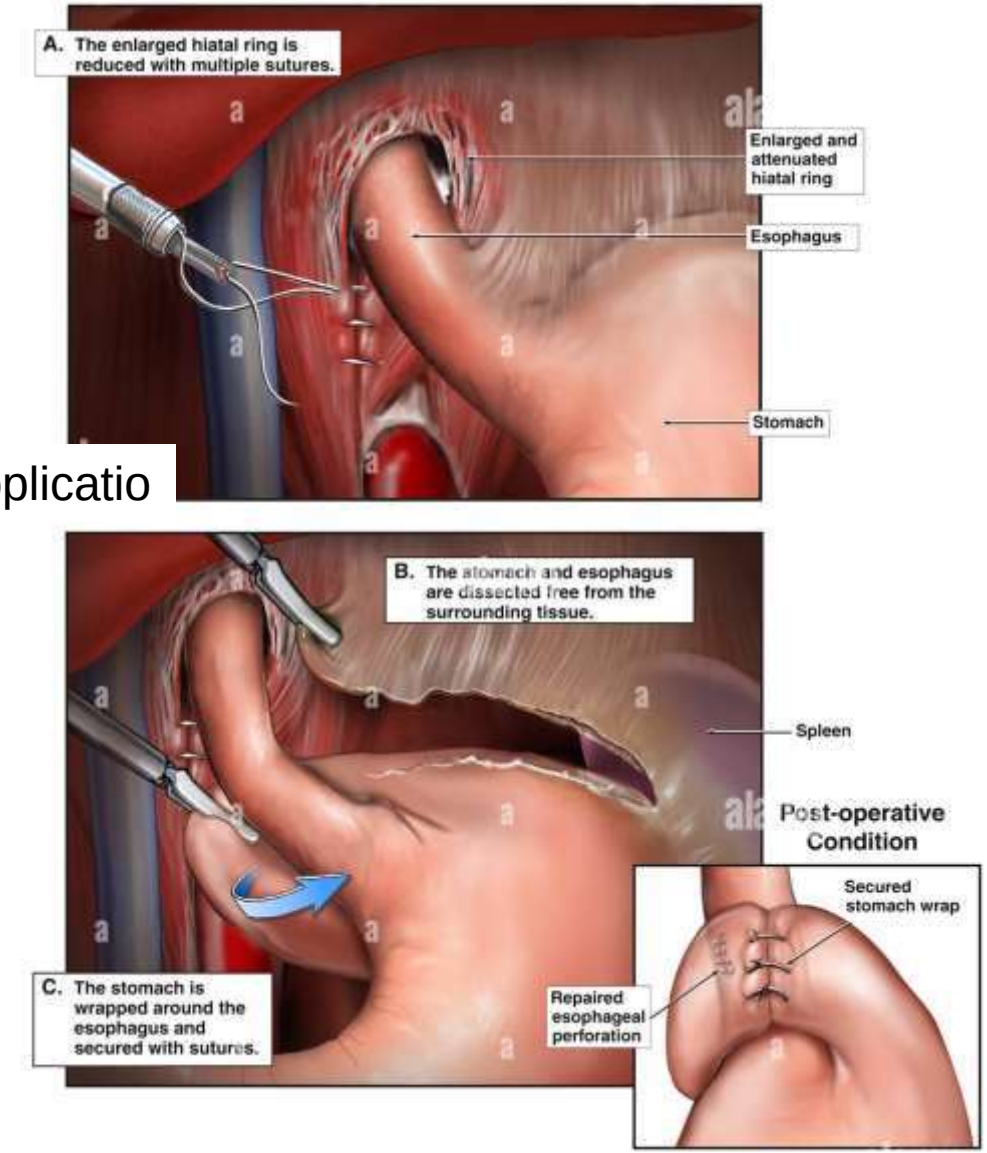
- Upper endoscopy **is not recommended** as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis.
- Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI.

GERD: Surgical therapy

1. Surgical therapy is a treatment option for long-term therapy in GERD patients.
2. **Surgical therapy is generally not recommended in patients who do not respond to PPI therapy.**
3. Preoperative ambulatory **pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus.**
4. **Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon.**
5. **Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients.**
6. The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.

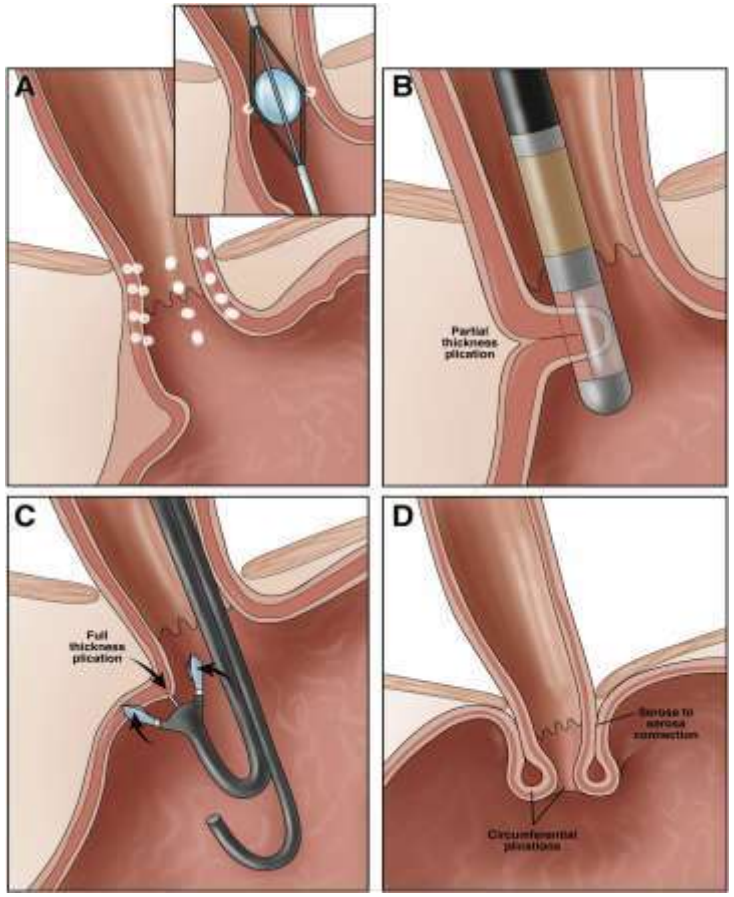
GERD: Surgical therapy

Nissen fundoplicatio



GERD endoscopic procedures

(*A*) The Stretta effect on the EGJ highlighting the focal thermal injury. (*B*) The Endocinch device illustrating the plication technique. (*C*) The NDO plicator using a single plication to recreate a flap valve. (*D*) The effect of the Esophyx illustrating circumferential plications and the resulting flap valve.



Clinical Gastroenterology and Hepatology 2014 12544-554DOI: (10.1016/j.cgh.2013.06.012)

Eosinophilic esophagitis

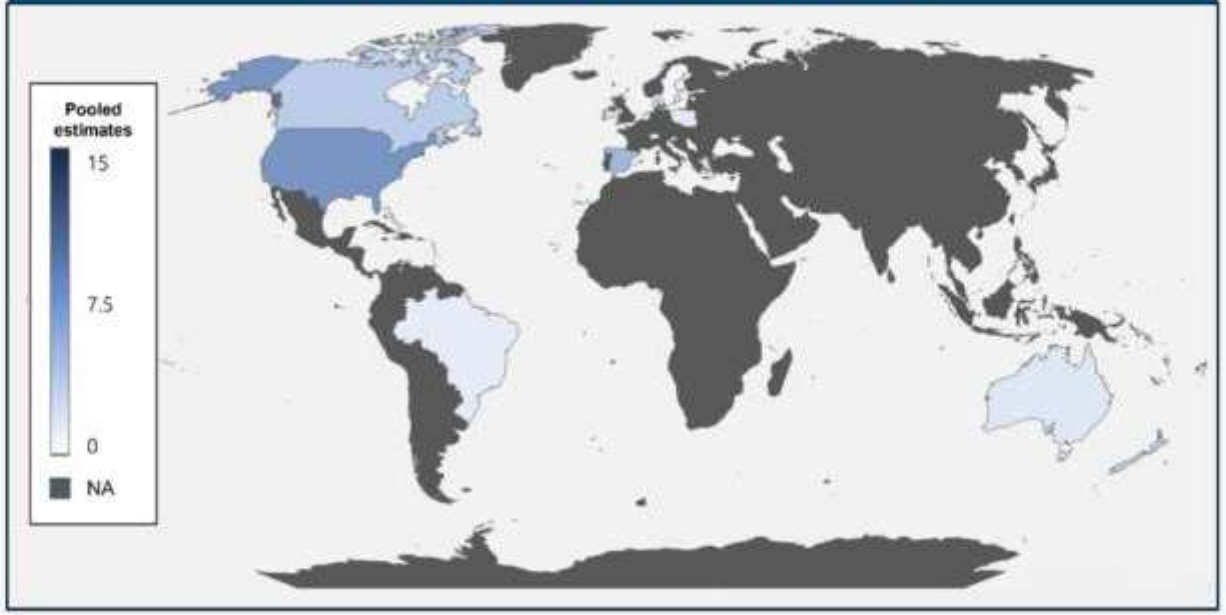
Global incidence and prevalence of eosinophilic esophagitis (EoE), 1976-2022

Systematic review
Meta-analysis

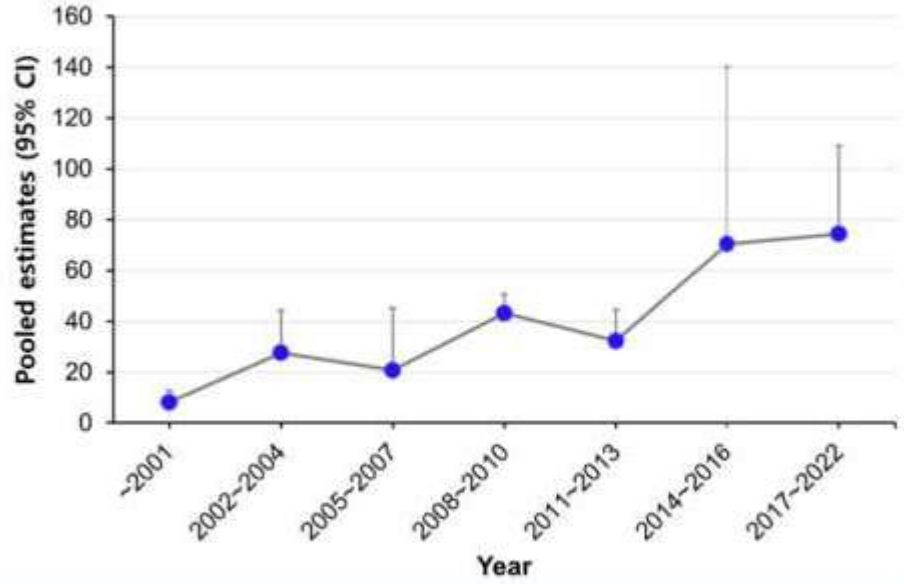
288 million participants

147,668 patients with EoE

Global map
15 countries across the five continents



Time trends of prevalence of EoE
cases per 100,000 inhabitant-years



- **Global incidence of EoE: 5.31 (95% CI, 3.98–6.63)** cases per 100,000 inhabitant-years
- **Global prevalence of EoE: 40.04 (95% CI, 31.10–48.98)** cases per 100,000 inhabitant-years

Clinical Gastroenterology and Hepatology

Eosinophilic esophagitis

Epidemiology

- Among patients undergoing upper endoscopy for evaluation of dysphagia, the prevalence of eosinophilic esophagitis ranges from 12% to 22%.
- Patients may present at any age, though the majority of patients are diagnosed in the second through fifth decade. There is a male predominance, with a **male/female** ratio of 3:1

Eosinophilic esophagitis

- **Symptoms are swallowing difficulty, food impaction, vomiting, and heartburn.**

- Eosinophilic esophagitis was first described in children but also occurs in adults.

- The treatment may consist of removal of known or suspected triggers and medication to suppress the immune response.

Eosinophilic esophagitis

In addition to gender (male predominance)

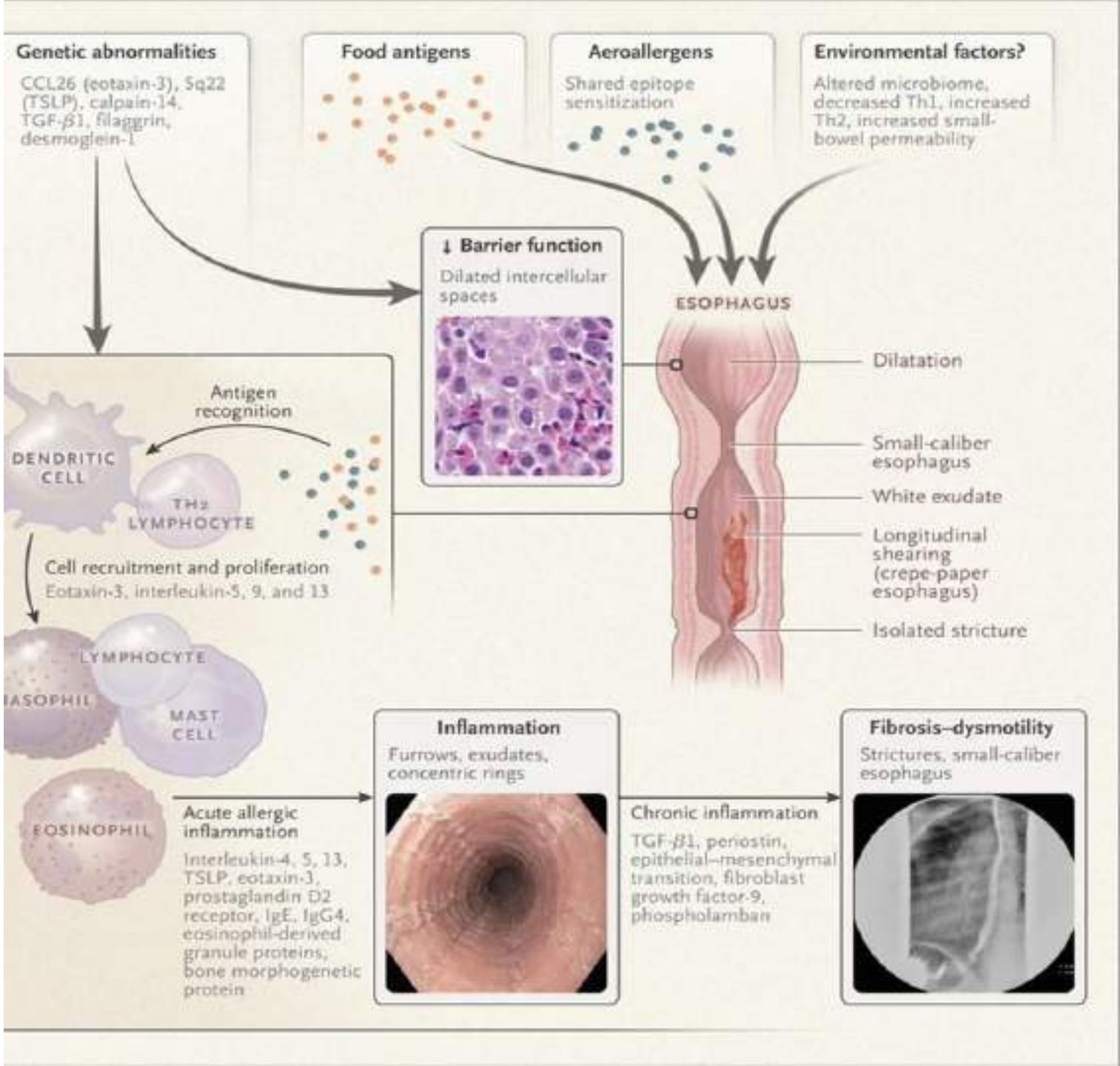
established risk factors for EoE include **atopy and other allergic conditions** (e.g., allergic rhinitis, elevated serum immunoglobulin E [IgE] to common aeroallergens, asthma, and atopic dermatitis).

In fact, patients with concomitant EoE and seasonal allergic rhinitis may have more EoE exacerbations during peak pollen seasons

Eosinophilic esophagitis

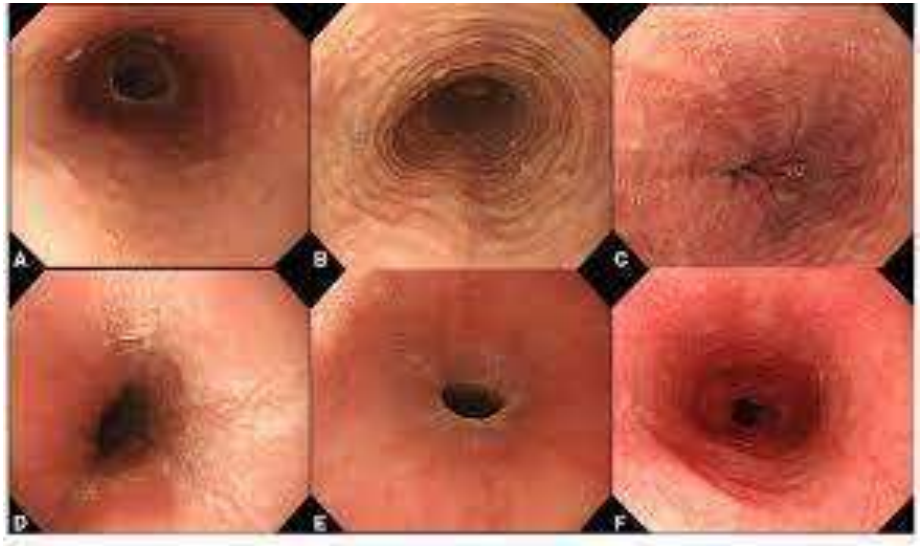
Evidence suggests that the disease is associated with **T helper cell-2 (Th2) type immune responses, which are typical of other atopic conditions**.

Elevated levels of the Th2 cytokines interleukin (IL)-4, IL-5, and IL-13, as well as mast cells, have been found in the esophageal biopsies of EoE

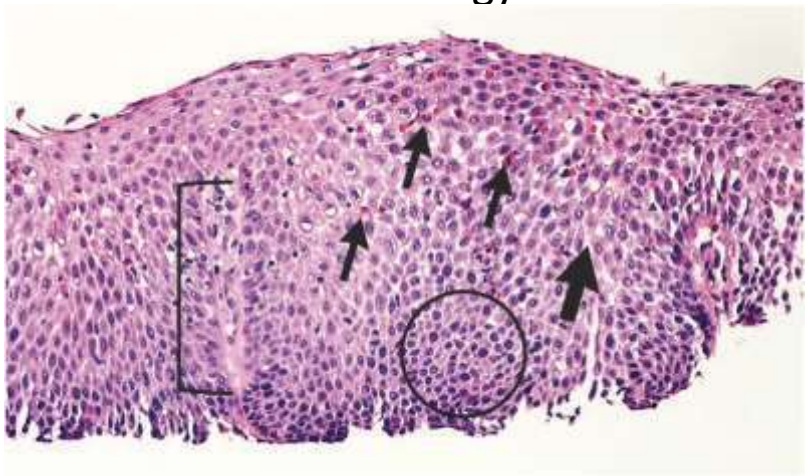


Eosinophilic esophagitis

Endoscopy



Histology

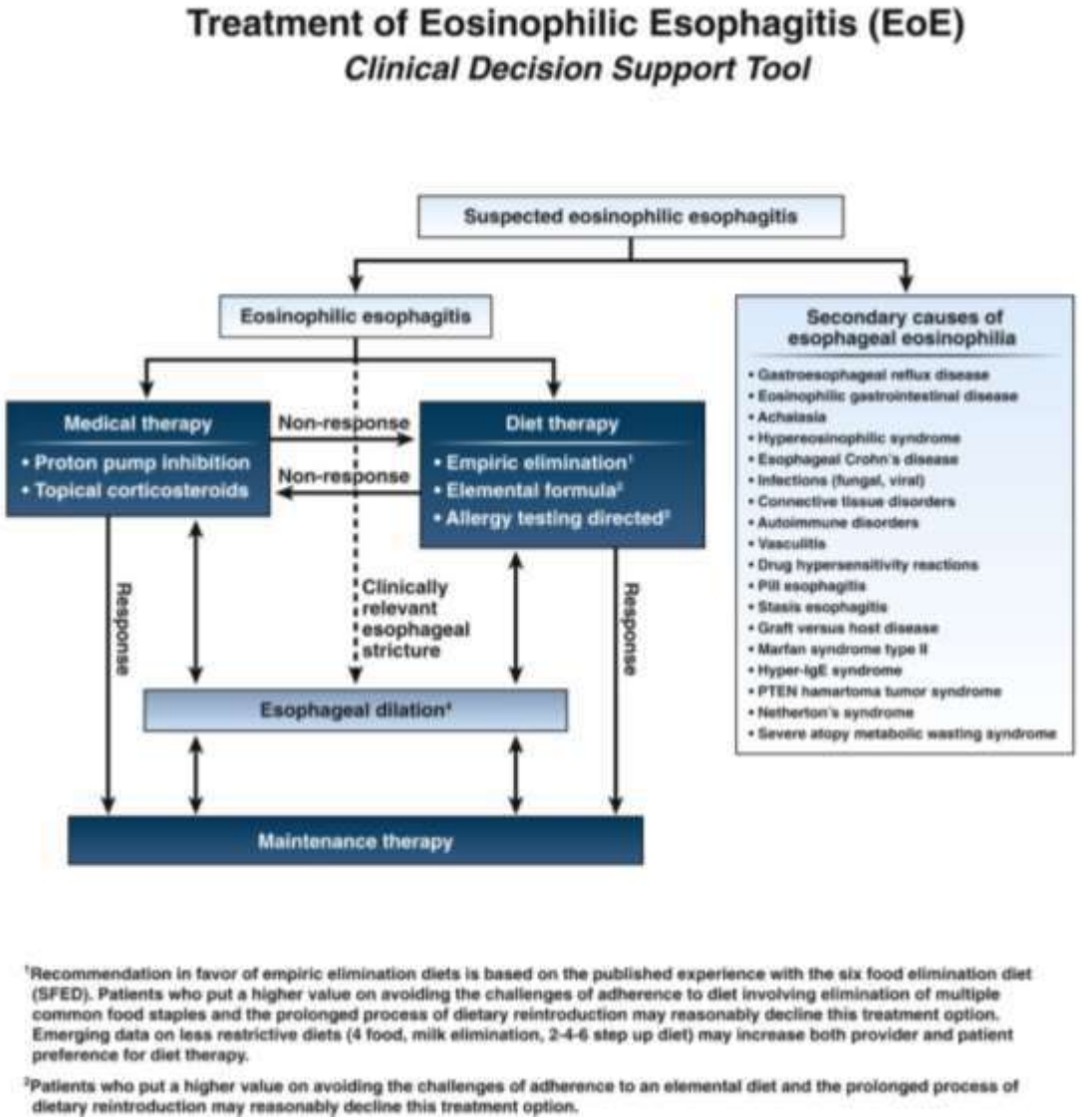


Histologic Characteristics of Eosinophilic Esophagitis.
Routine staining with hematoxylin and eosin reveals numerous eosinophils (thin arrows), dilated intercellular spaces (thick arrow), basal zone hyperplasia (circle), and papillary elongation (bracket).
>15 eosinophils per high magnification field (95% accuracy)

Eosinophilic esophagitis

Current recommendation for first line treatment is PPI

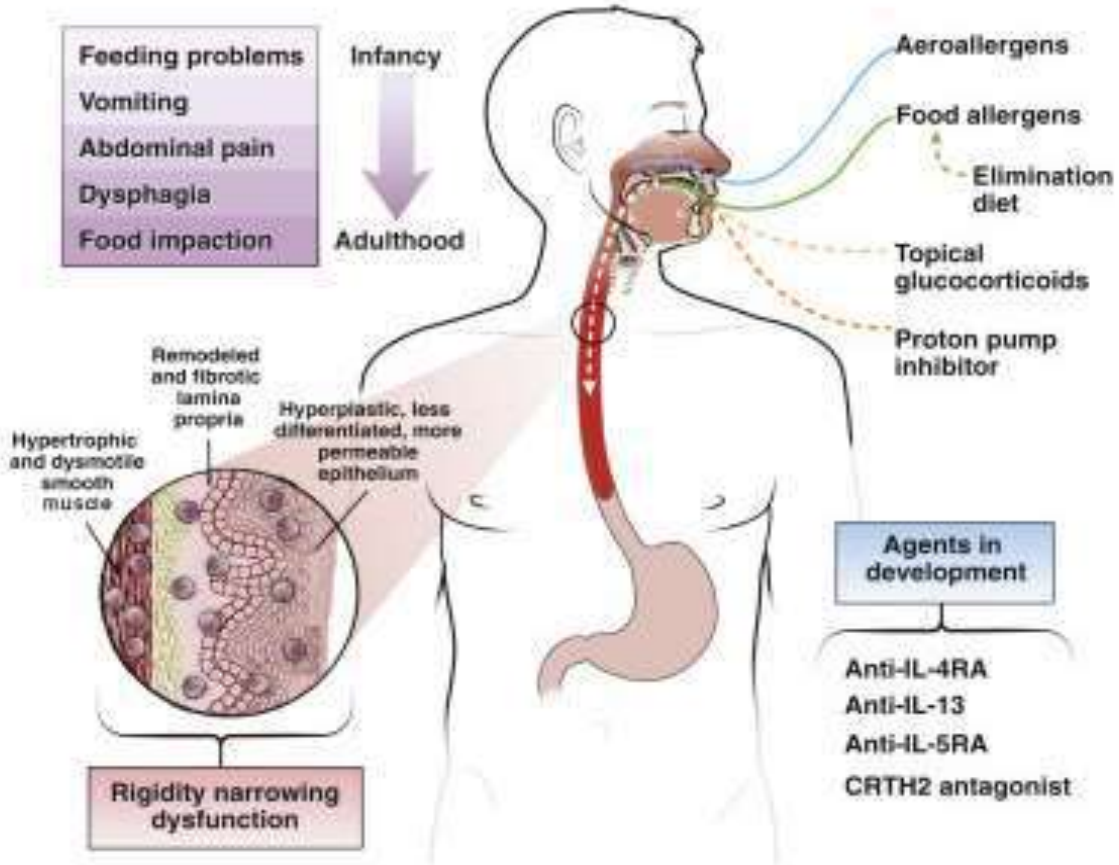
The second and third line therapies are an elimination diet of either the 6 or 4 most common triggers, or topical **corticosteroids, including both fluticasone, and topical viscous budesonide**

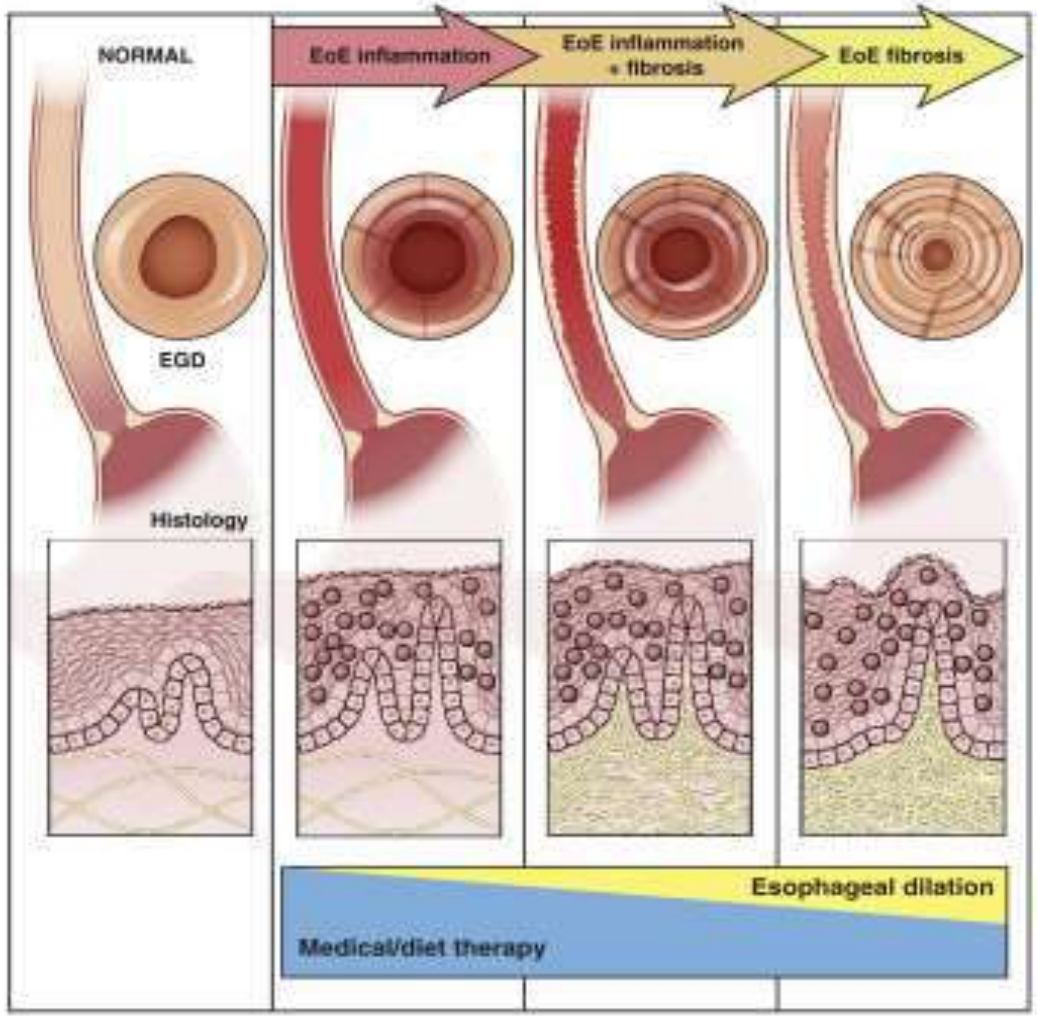


Spotlight: Treatment of Eosinophilic Esophagitis (EoE)

Ikuo Hirano, MD[1]; Ravi Sharaf, MD[2]; Neil Stollman, MD[3]; Kenneth Wang, MD[4]; Yngve Falck-Ytter, MD, AGAF[5]

Collaborators: **Edmond Chan, MD[6]; Matthew Rank, MD[7]; David Stukus, MD[8]; Matthew Greenhawt, MD, MBa, MSc[9]**

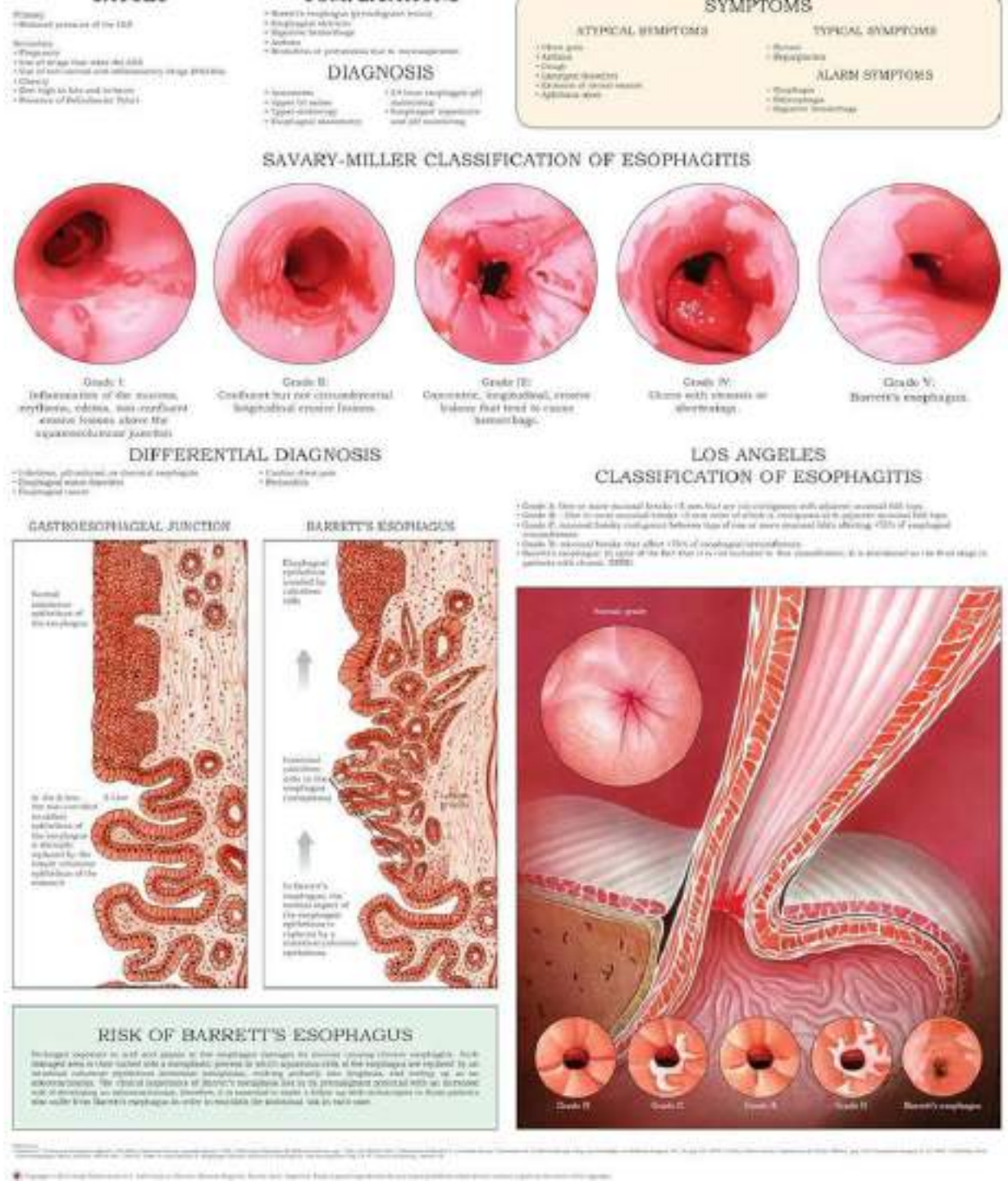




GERD complications

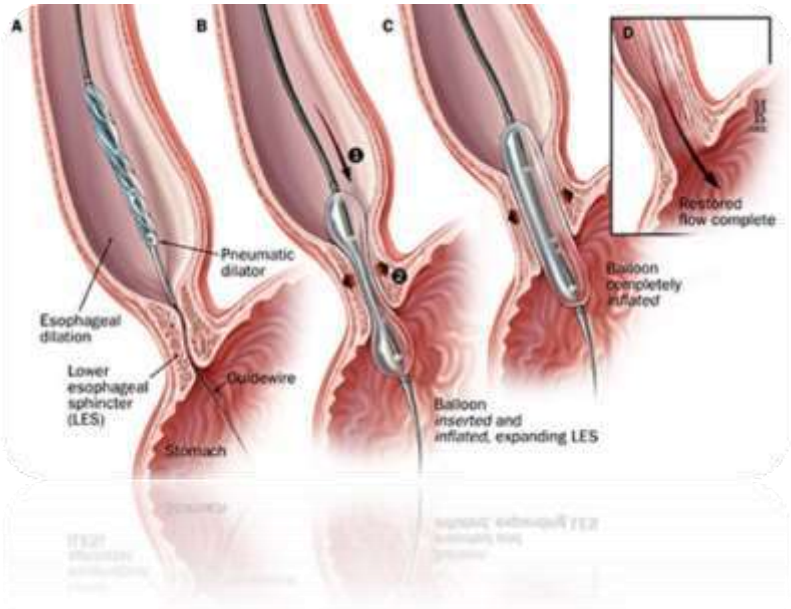
GERD complications

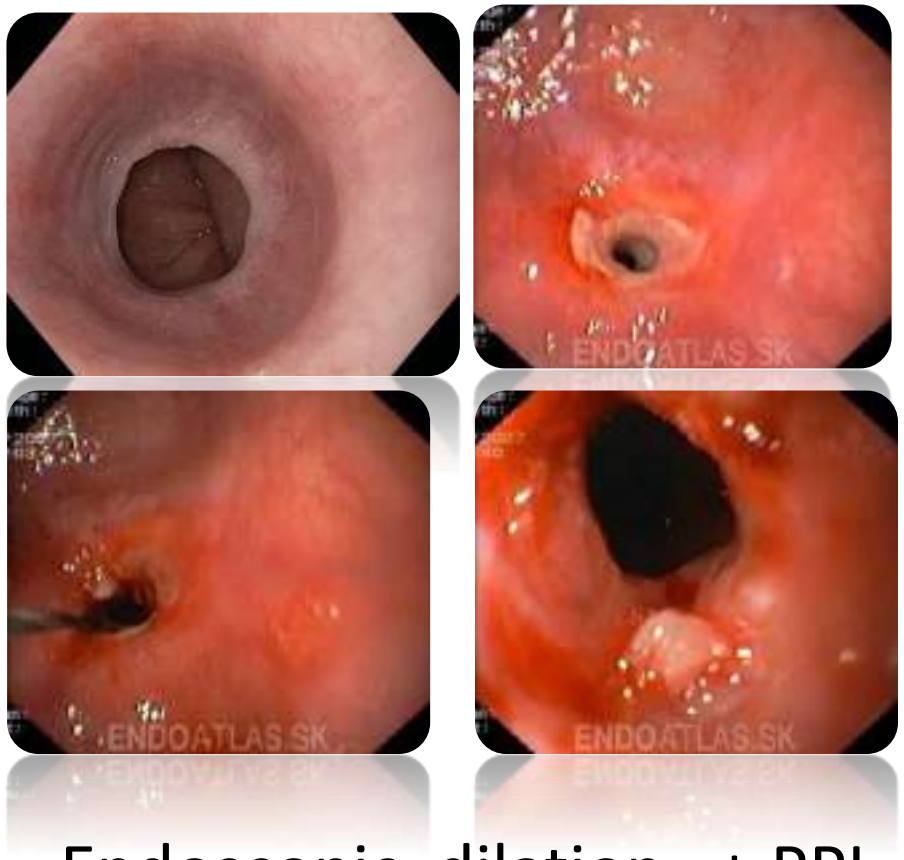
- **Stricture**
- **Hemorrage**
- **Intestinal Metaplasia (Barrett's esophagus)**



GERD complications

- **Stricture**





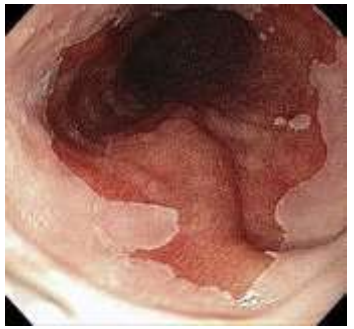
Endoscopic dilation + PPI

GERD complications

Barrett esophagus

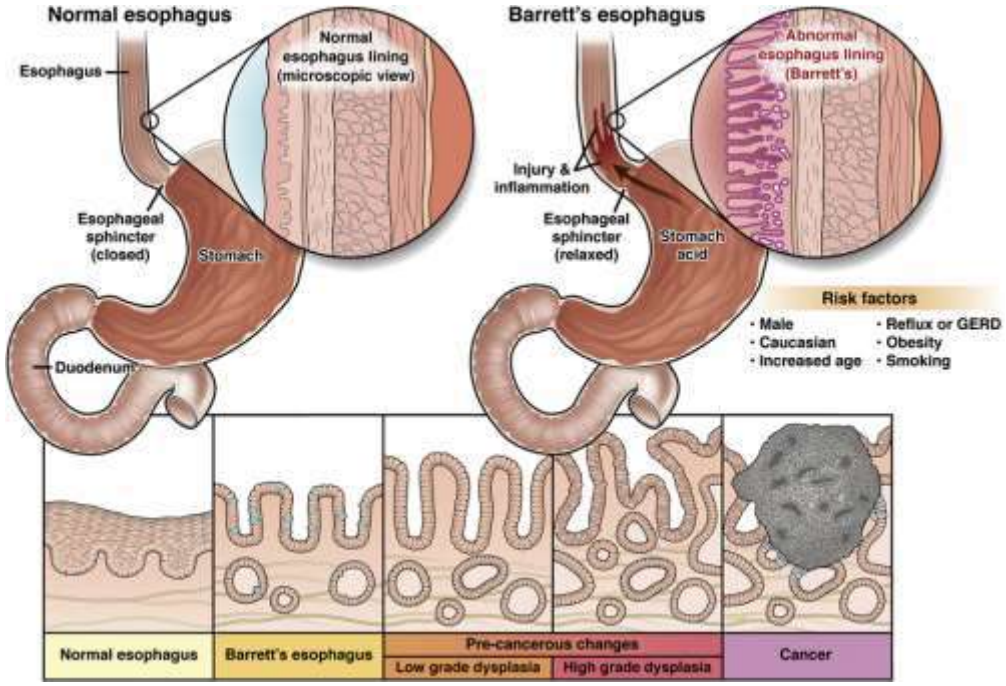
It is characterized by the replacement of the normal stratified squamous epithelium_lining of the esophagus by simple columnar epithelium with **goblet cells** (which are usually found lower in the gastrointestinal tract).

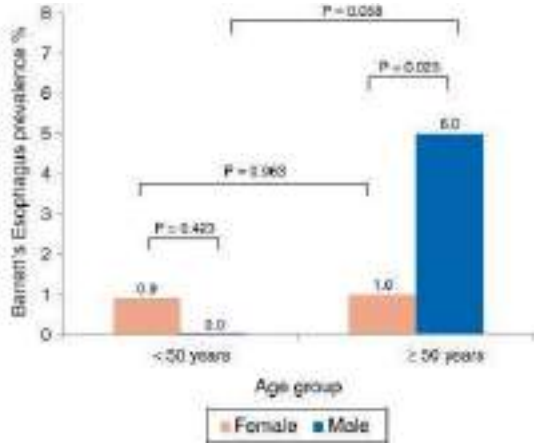
Norman Barrett M.D.
(1903-1979)



Barrett’s esophagus

The prevalence of Barrett's esophagus in the adult population is **0.4% to 1.3%,** although recent reports from gastroenterology-selected populations suggest a higher prevalence





Barrett’s esophagus

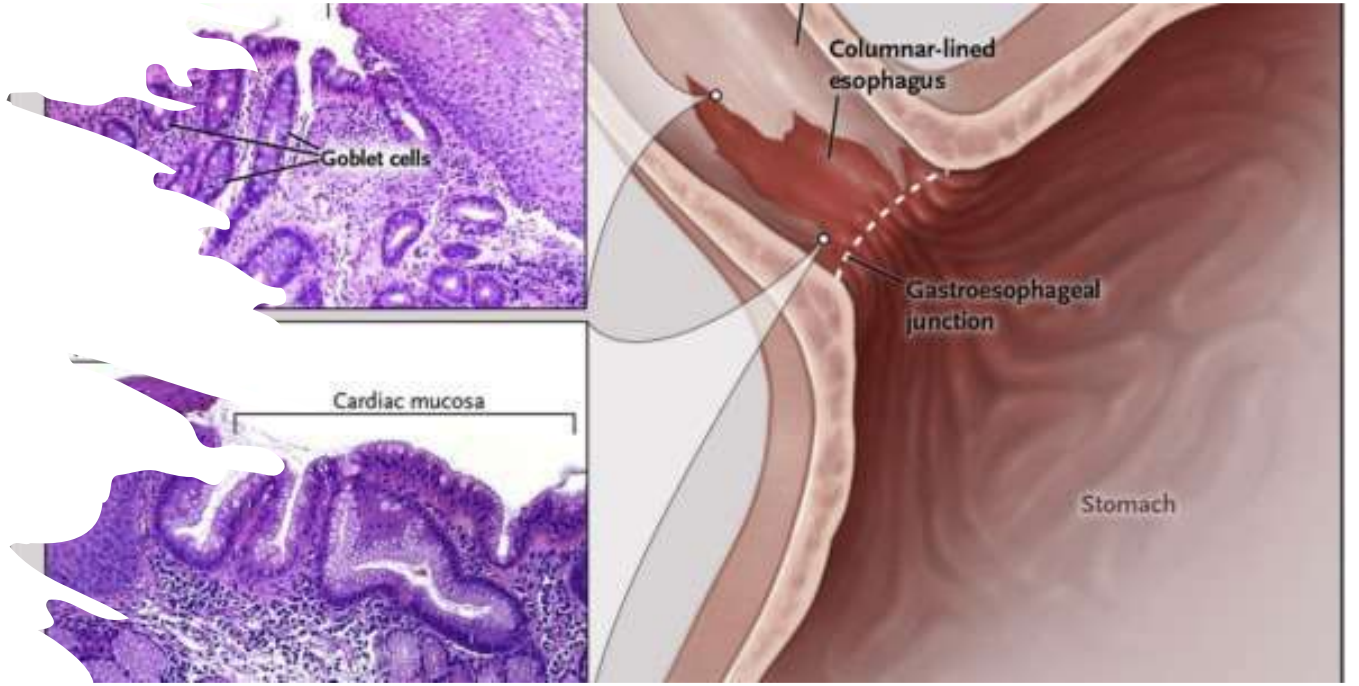
Barrett's esophagus occurs as a result of chronic, GERD

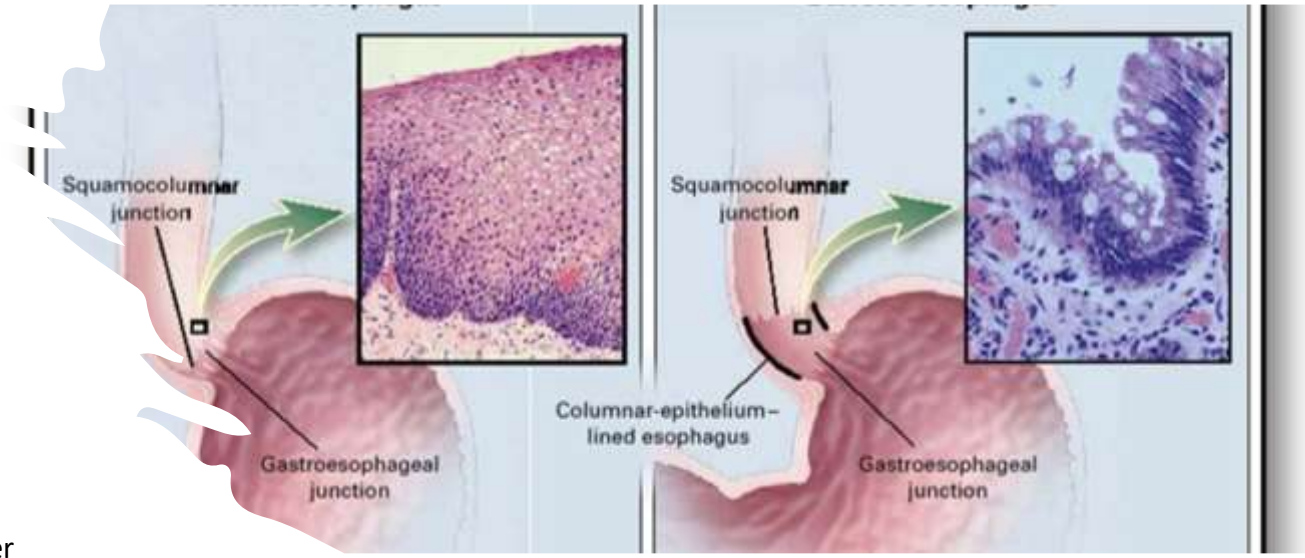
The diagnosis is made by **endoscopy with biopsy**.
Histologically, Barrett's esophagus is a metaplastic change in the distal esophageal (intestinal metaplasia IM).

Barrett's esophagus is classified histologically as either non-dysplastic IM , low-grade dysplasia (IM-LGD) or high-grade dysplasia (IM-HGD)

Barrett’s esophagus: histopathology

Presently, **intestinal metaplasia [with goblet cells] is required for the diagnosis of Barrett's esophagus** because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy.” That statement remains valid to date, and the AGA, the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of Gastroenterology (ACG) all agree that intestinal metaplasia with goblet cells is a requisite diagnostic criterion for Barrett esophagus





Evans, J.A., Early, D.S., Fukami, N. et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc. 2012; 76: 1087–1094

Barrett's criteria

Table 3 | **Criteria for diagnosis of BE**

Society	Year	Endoscopic criterion	Histological criterion
AGA	2011	Columnar epithelium extending for any length above the GEJ into the tubular oesophagus	Intestinal metaplasia
ASGE	2012	Salmon or pink colour, in contrast to the light-grey appearance of the oesophageal squamous mucosa	Specialized intestinal metaplasia
BSG	2014	Distal oesophageal mucosa replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GEJ	Columnar metaplasia (columnar-lined epithelium, regardless of the presence or absence of intestinal metaplasia)
ACG	2016	Extension of salmon-coloured mucosa into the tubular oesophagus for ≥1 cm proximal to the GEJ	Specialized intestinal metaplasia
JSG	2016	Columnar epithelium that continues from the stomach to oesophagus for any length	Columnar metaplasia (columnar-lined epithelium, regardless of the presence or absence of intestinal metaplasia)
ESGE	2017	Distal oesophagus lined with columnar epithelium with a minimum length of 1 cm (tongues or circular)	Specialized intestinal metaplasia

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; ESGE, European Society of Gastrointestinal Endoscopy GEJ, gastro-oesophageal junction; JSG, Japanese Society of Gastroenterology.

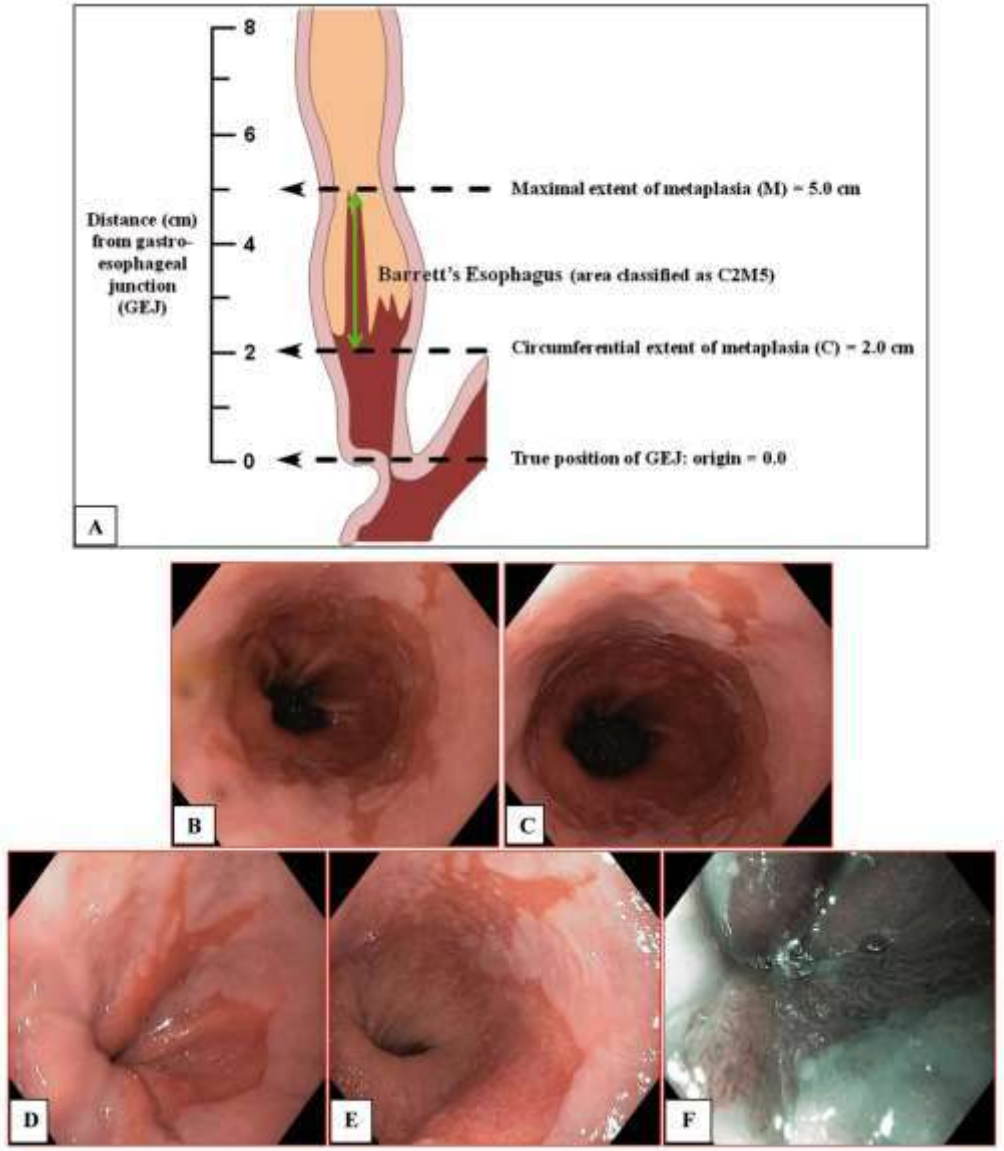
Barrett's dysplasia histology

Table 1 Histological criteria for grading dysplasia in Barrett's oesophagus

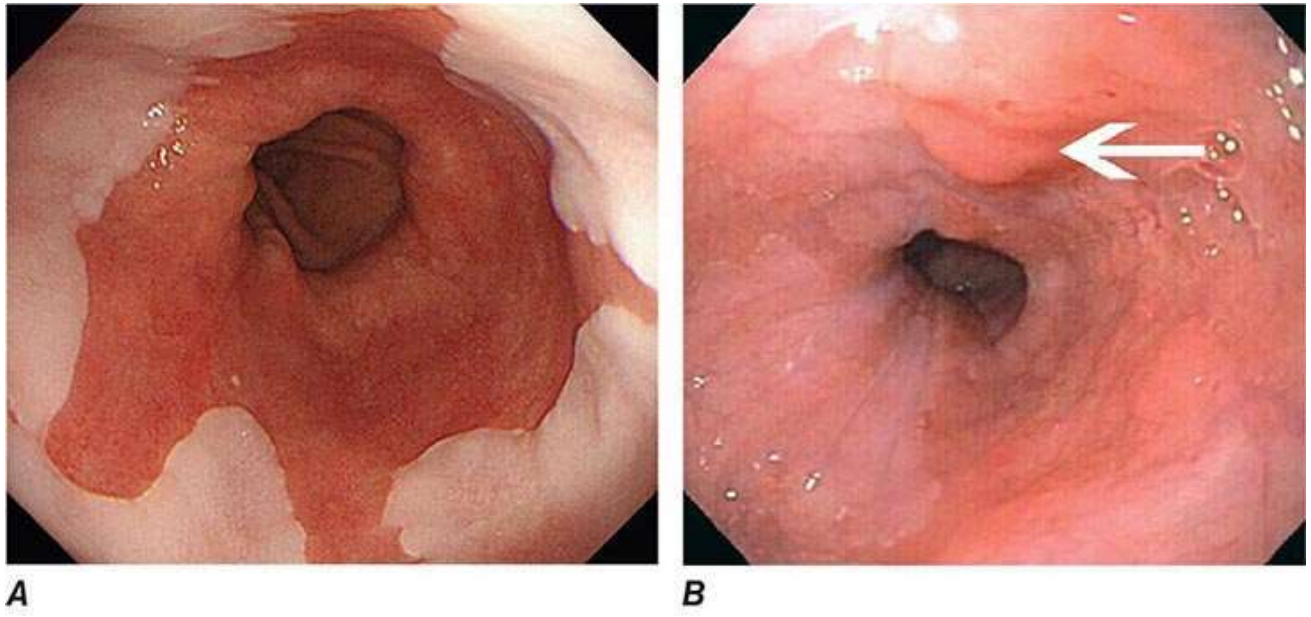
	Criteria
Negative for dysplasia	Architecture within normal limits. No nuclear abnormalities, except focal nuclear stratification. Greater nuclear alterations acceptable when associated with inflammation, erosion, or ulceration.
Indefinite	Architecture may be moderately distorted. Nuclear abnormalities less marked than those seen in dysplasia. Changes too marked for negative but not sufficient for the diagnosis of dysplasia.
Positive for dysplasia	Architectural and cytological changes severe enough to suggest neoplastic transformation. Diagnosis of high grade or low grade based on the severity of changes: high grade dyspasia is diagnosed if either architectural and/or cytological abnormalities are sufficiently prominent. Alterations are especially noteworthy if they involve the mucosal surface.
Intramucosal carcinoma	Carcinoma has penetrated through the basement membrane of the glands into the lamina propria but not yet invaded the submucosa.

Adapted from Geboes and Van Eyken,[30] Riddell *et al*,[31] Montgomery *et al*.[37]

Barrett’s esophagus: endoscopy



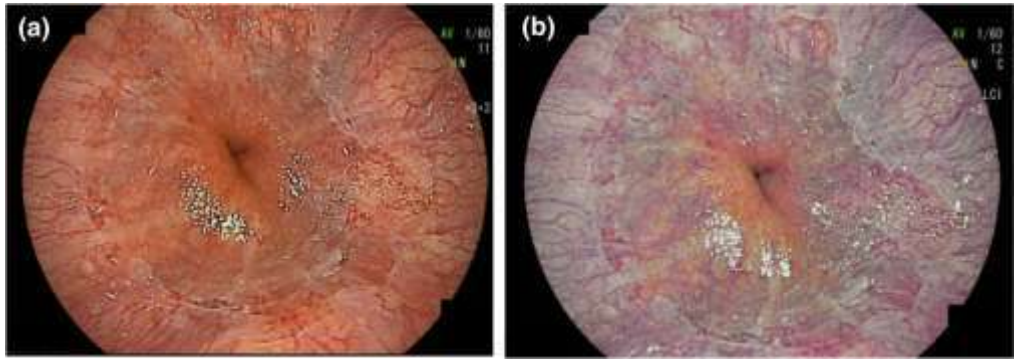
From Barret's esophagus to Adenocarcinoma



Barrett esophagus

Advanced endoscopic imaging for the diagnosis of BE

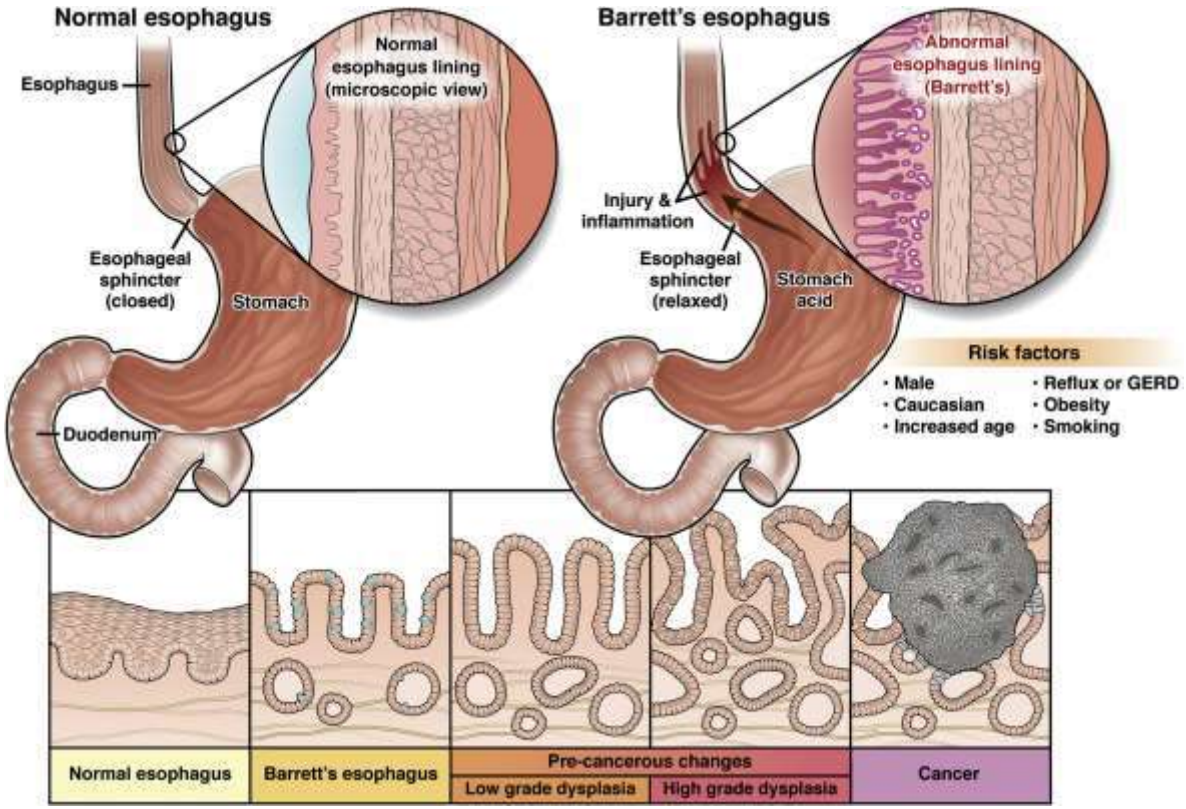
- Magnified endoscopy for BE using indigo carmine
- Crystal violet chromoendoscopy
- Narrow-band imaging (NBI)
- Linked color imaging (LCI)



Barrett’s esophagus

What is the risk of esophageal cancer with Barrett’s esophagus?

Less than 1 percent of people with Barrett’s esophagus develop esophageal adenocarcinoma each year.



The risk of cancer for non-dysplastic Barrett's esophagus is very low: less than 1 percent (0.4 percent to 0.5 percent) per year.

Barrett's esophagus

Who Should be Screened to Identify Barrett Esophagus?

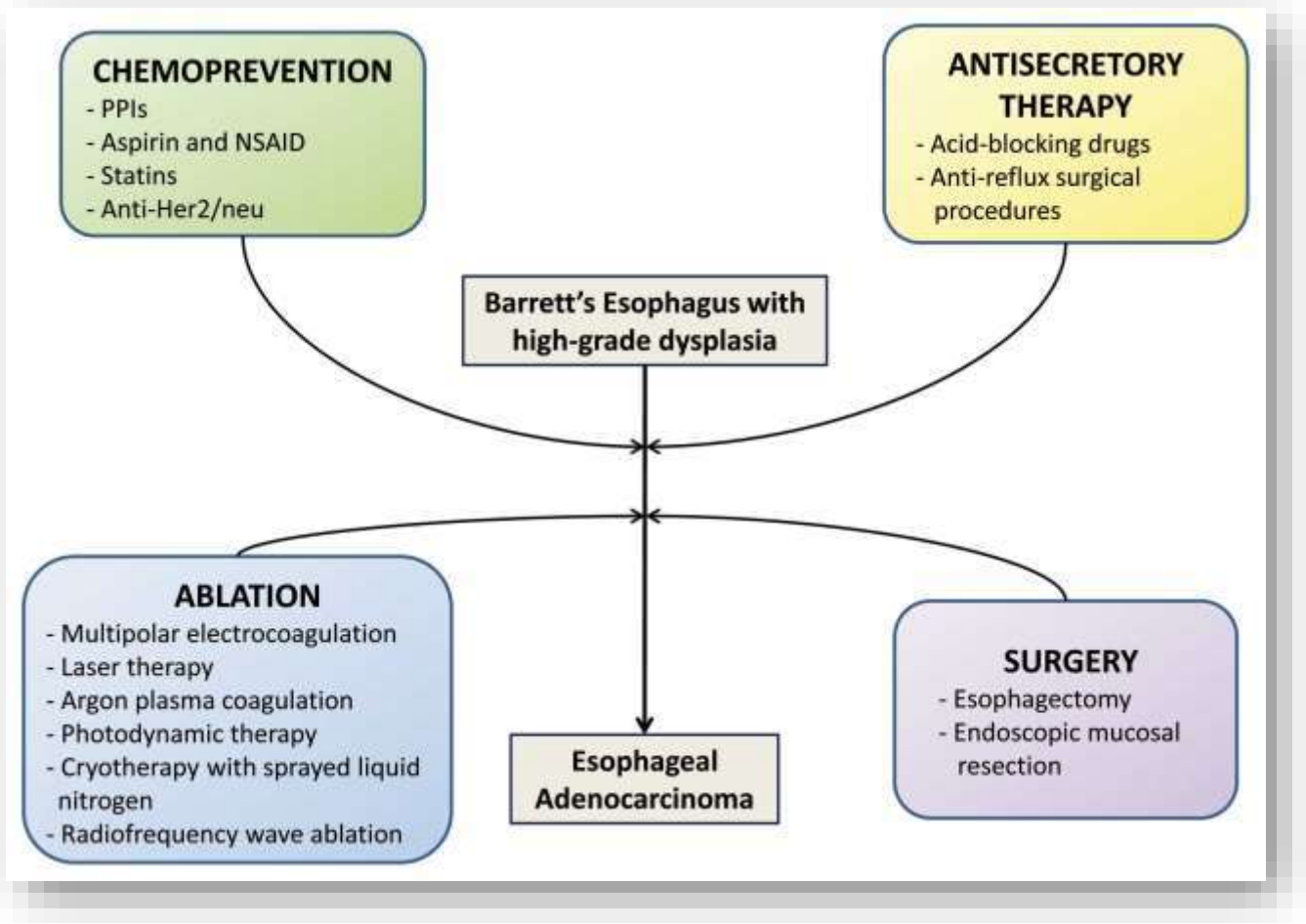
Endoscopic screening shoudl be offered only to patients who have at least one risk factor for esophageal adenocarcinoma in addition to chronic GERD

Table 1 | **Selected risk factors for BE and EAC**

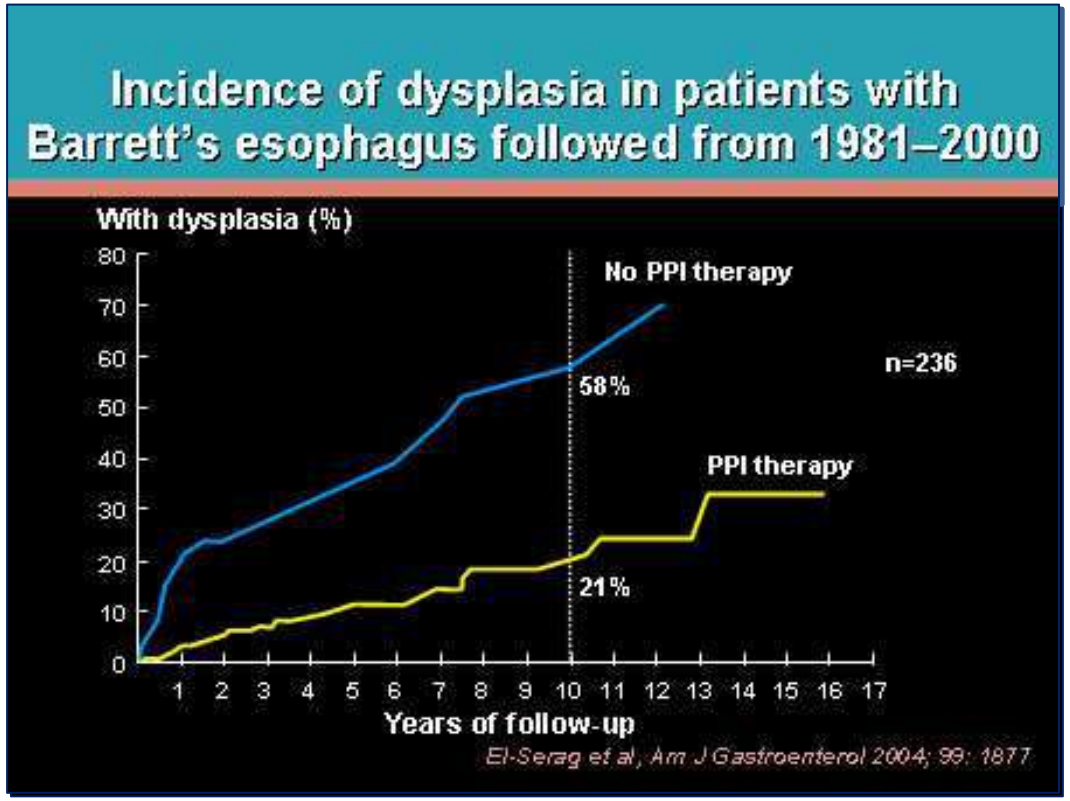
Risk factor	Association with BE (OR (95% CI))[a]	Association with EAC (OR (95% CI))[a]	Refs[b]
Male sex	2.0 (1.8–2.2)	2.2 (1.8–2.5)	24,53–55
White ethnicity	+	+	20,22,33
Increased age	1.0 (1.0–1.1)	1.0 (1.0–1.1)[c]	11,25,53–55
Presence of GERD symptoms	2.9 (1.9–4.5)	7.7 (5.3–11.4)	14,44
Hiatal hernia size	3.9 (3.0–5.1)	Unknown	46
BMI (per unit increase)	1.0 (0.9–1.0)	1.0 (0.9–1.2)[c]	34,35,55
Waist circumference ratio (per 5 cm increase)	1.2 (1.0–1.3)	2.1 (1.3–3.2)	35
Cigarette smoking	1.4 (1.2–1.7)	1.5 (1.1–2.0)[c]	26,55,56,229
Alcohol intake	1.1 (0.6–1.8)	1.1 (0.8–1.5)[c]	55,230
Helicobacter pylori infection	0.7 (0.6–0.8)	0.5 (0.4–0.7)	47,48,231
NSAID use	1.0 (0.8–1.3)	0.7 (0.5–1.0)[c]	51,55
Family history of GERD, BE or EAC	+	+	49,50

BE, Barrett oesophagus; BMI, body mass index; EAC, oesophageal adenocarcinoma; GERD, gastro-oesophageal reflux disease. + indicates positive for risk factor. [a]Odds ratios for family history are not available and in the case of white ethnicity, they depend on the population that is used for comparison. [b]If a recent meta-analysis has been published, it is preferentially listed. [c]Odds ratio for factors associated with progression of BE to EAC.

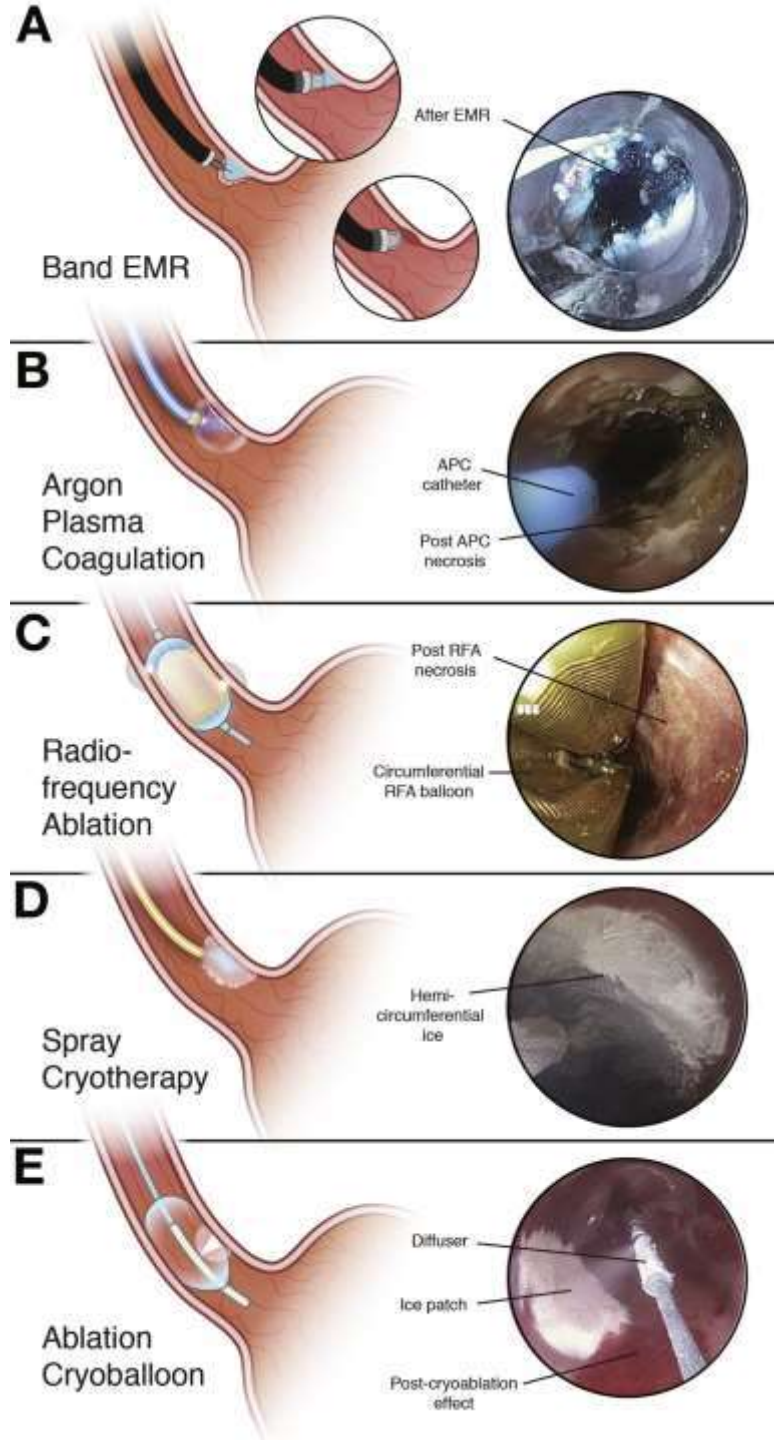
Barrett’s esophagus treatment



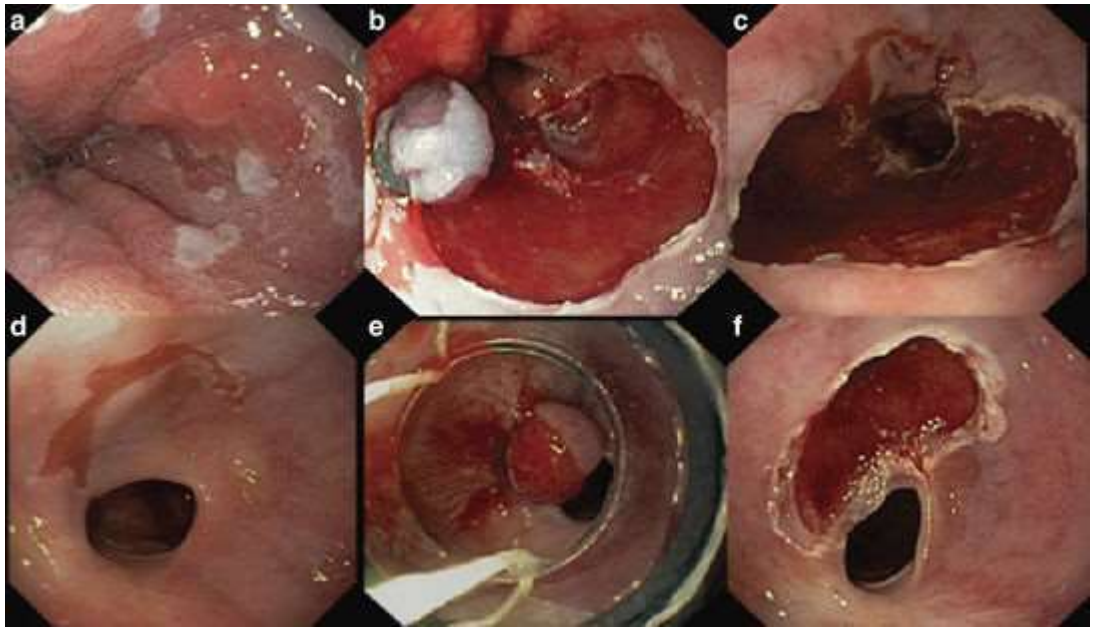
However: PPIs prevent dysplasia



- El-Serag HB, Aguirre TV, Davis S *et al. Proton* pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol 2004;99:1877–83.
- Hillman LC, Chiragakis L, Shadbolt B *et al.* Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004;180:387–91.

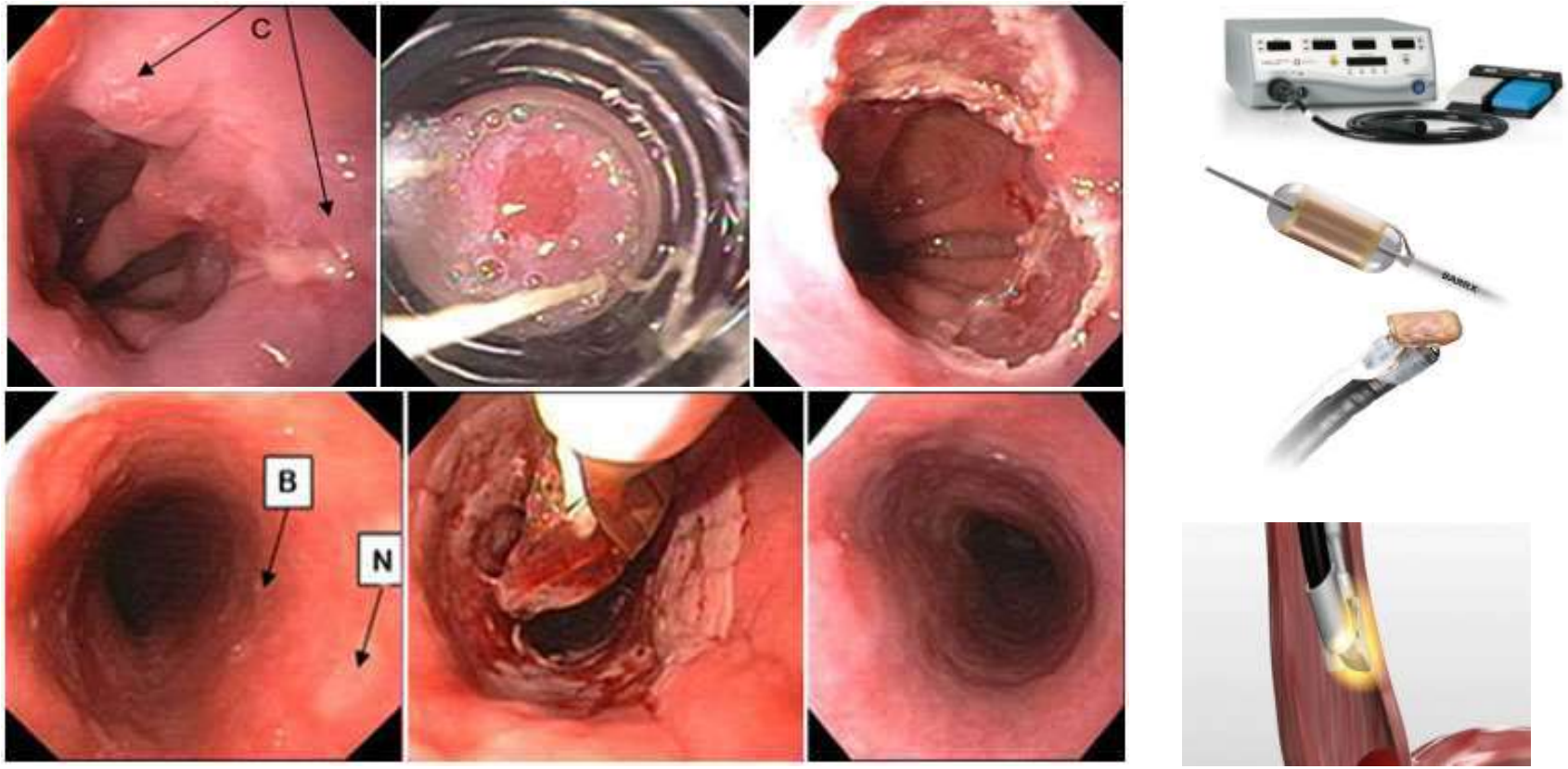

A
After EMR
Band EMR
B
APC catheter
Post APC necrosis
Argon Plasma Coagulation
C
Post RFA necrosis
Circumferential RFA balloon
Radio-frequency Ablation
D
Hemi-circumferential ice
Spray Cryotherapy
E
Diffuser
Ice patch
Post-cryoablation effect
Ablation Cryoballoon

ENDOSCOPIC MUCOSAL RESECTION



Endoscopic mucosal resection of HGD nodule. (**a**) Barrett's nodule (HGD on biopsy). (**b**) Nodule resected, and further band applied for next resection. (**c**) Greater than hemi-circumferential resection at second session. (**d**) Repeat endoscopy at 6 weeks demonstrating a small amount of residual Barrett's tissue and a moderately tight stricture. (**e**) Band applied to residual Barrett's using multiband mucosectomy technique. (**f**) Resection complete. Stricture will require dilatation. HGD, high-grade dysplasia.

Radiofrequency Ablatation



Shaheen, N. J. *et al*. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N. Engl. J. Med.* **360**, 2277–2288 (2009)

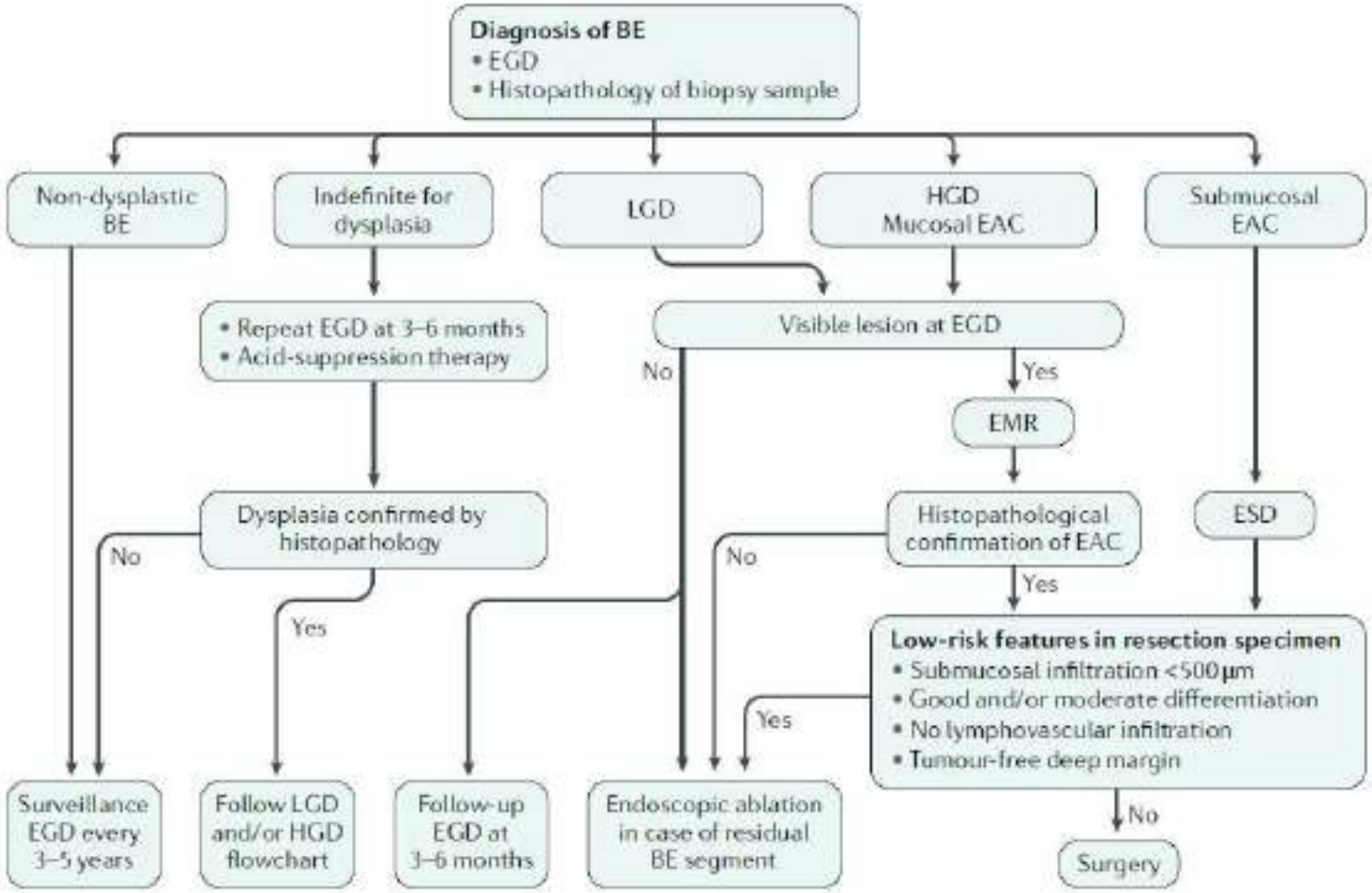


Fig. 7 | **Algorithm for management of non-dysplastic and dysplastic Barrett oesophagus.** In cases of Barrett oesophagus (BE) confirmed by oesophagogastroduodenoscopy (EGD) and histopathological assessment of biopsy samples, BE is staged as non-dysplastic, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD) or mucosal oesophageal adenocarcinoma (EAC), or submucosal EAC. For lower-grade disease (non-dysplastic or indefinite for dysplasia), surveillance at various intervals is recommended. For higher-grade disease with lesions visible by EGD, endoscopic mucosal resection (EMR) followed by ablation of the residual BE segment is recommended. In case of no visible lesion, endoscopic ablation is recommended in patients without life-limiting comorbidity, otherwise strict surveillance is warranted. Endoscopic submucosal dissection (ESD) may be considered in selected cases of EAC (with poorly lifting tumours, >15 mm or lesions at risk of submucosal invasion). If the endoscopic resection does not fulfil low-risk criteria, surgery is needed.

Summary

- **Long term GERD causes Barrett.**
- **About 10%** of people with symptoms of GERD have this condition.
- Barrett's esophagus increases the **risk of adenocarcinoma** of the esophagus. People with Barrett's esophagus are anywhere from **30 to 125** times more likely than people without this condition to develop esophageal cancer.
- **The exact risk of developing cancer in people with Barrett's esophagus is estimated to be only 1 in 200 per year.**
- **The use of PPI prevents the dysplasia (no data on cancer)**
- **Endoscopic ablation is indicated in patients with high grade dysplasia**

UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
AA 2023-24

Cancer of esophagus

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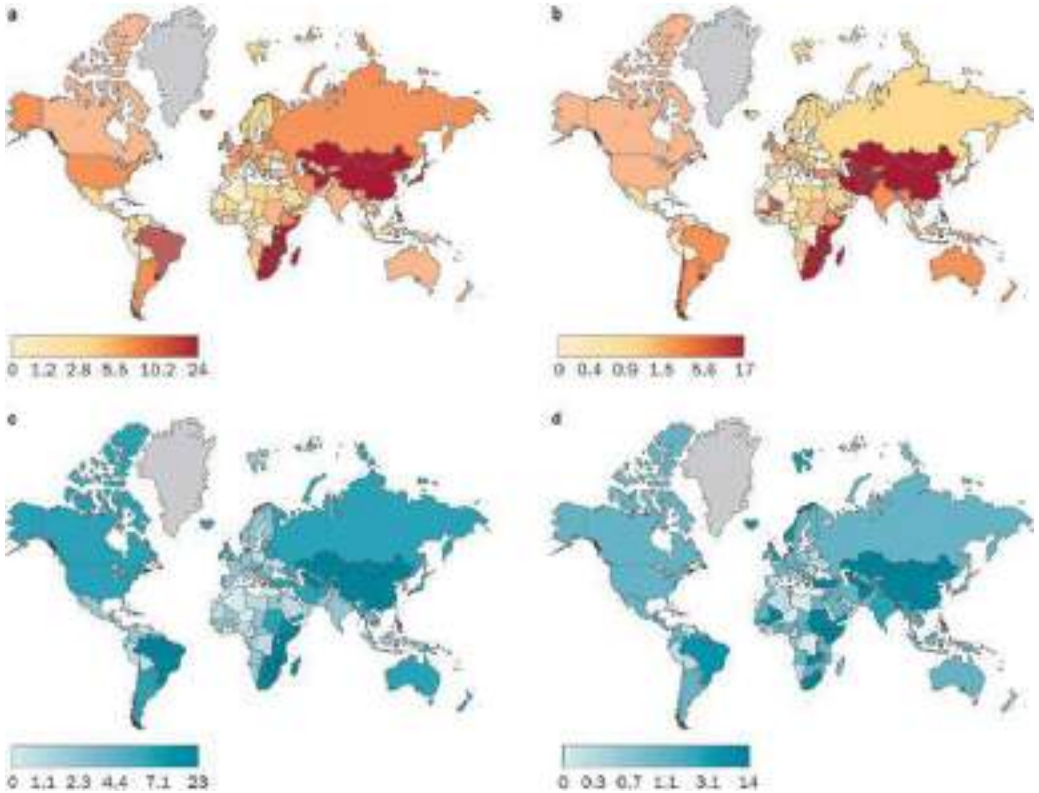
Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Esophageal cancer incidence and mortality worldwide—2012 estimates



Lao-Sirieix, P. & Fitzgerald R. C. (2012) Screening for oesophageal cancer
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2012.35

Cancer of the esophagus

- The most common histologic types are **squamous cell carcinoma (SCC) and adenocarcinoma (AC),** which together constitute more than 90% of esophageal malignancies.

- Rarely, melanoma, sarcoma, small cell carcinoma, or lymphoma may arise in the esophagus.

- Although SCC is more evenly distributed throughout the length of the esophagus, **AC is predominantly a disease of the distal esophagus and gastroesophageal junction**, and is rarely found in the cervical esophagus

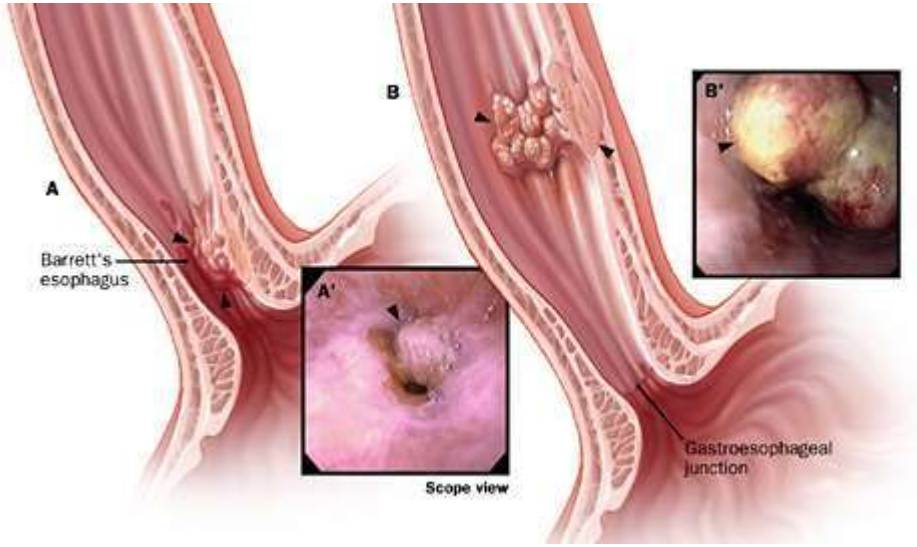
- **Squamous cell carcinoma and adenocarcinoma are distinct malignancies of the esophagus, with different risk factors and different natural histories.**

Cancer of the esophagus

- Cancers arising from the esophagus and gastroesophageal junction account for 14,520 new cases and 13,570 deaths in Europe in 2005.
- Worldwide, esophageal cancer is the **eighth** most common malignancy and the sixth most common cause of cancer-related death.
- The epidemiology of esophageal cancer changed dramatically during the latter half of the 20th century.
- While in the past the **squamous cell carcinoma** accounted for more than 90% of all esophageal tumors in the Western countries, diagnoses of esophageal **adenocarcinoma** have significantly increased and **now represent 80% of cases**.
- **However, SCC remains the most common worldwide.**
- The mean age at diagnosis is 67 years, and men are affected more frequently than women, particularly among patients with AC.

Cancer of the esophagus

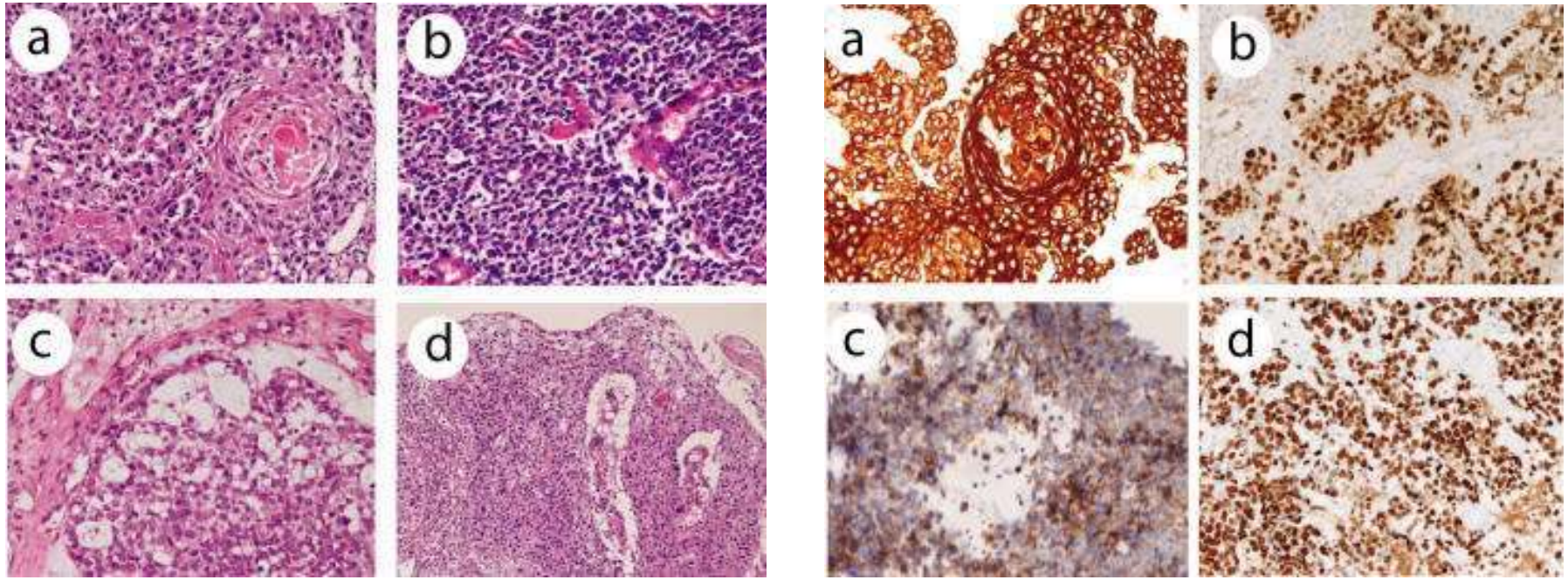
Two histogy types



- **Adenocarcinoma** is the leading histology for esophageal cancer over squamous cell. Adenocarcinoma has increased 350% since 1970 and accounts for 75% of all cases in Caucasian males.
- **Squamous cell** cancer can be estimated based on what level the cancer is in the esophagus. It is seen in 10%-25% of cases involving the upper third, 40%-50% involving the middle third, and 25%-50% involving the lower third

Carcinoma of the esophagus

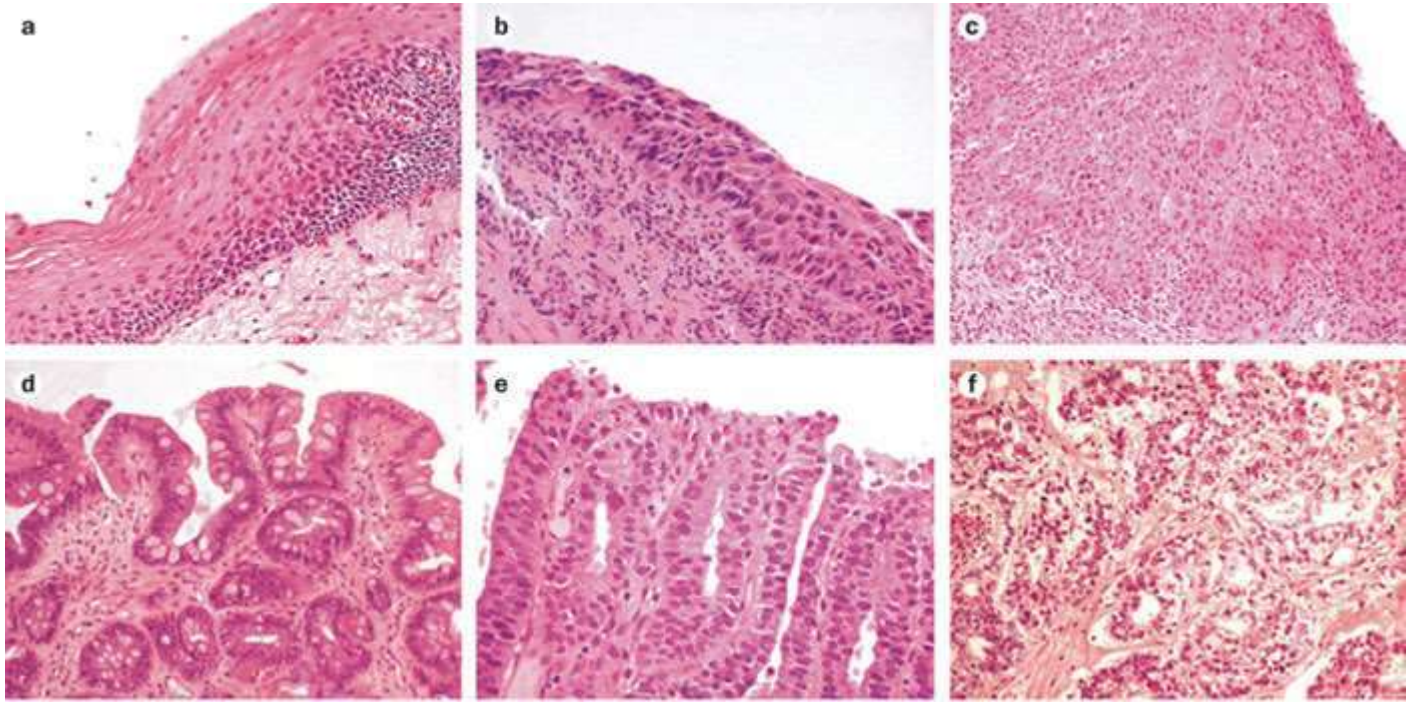
- **SCC**



High molecular weight cytokeratin is positive in the squamous cell carcinoma element.

Carcinoma of the esophagus

SCC and AC have different precursors



Progression of a) normal squamous epithelia to b) squamous high-grade dysplasia and c) squamous-cell carcinoma.
Progression of d) Barrett's oesophagus to e) glandular high-grade dysplasia and f) adenocarcinoma.
The sections were stained with haematoxylin and eosin and are displayed at ×100 magnification.

Cancer of the esophagus

Risck factors

Causative and Risk Factors for Adenocarcinoma and Squamous Cell Carcinoma

Adenocarcinoma

Barrett's esophagus
Gastroesophageal reflux disease (GERD)
Obesity (by increasing the risk of GERD)

Squamous Cell Carcinoma

Smoking
Alcohol
Dietary and environmental factors that cause chronic irritation and inflammation of the esophageal mucosa
Predisposing underlying conditions, such as tylosis, achalasia, esophageal diverticula and webs, Plummer-Vinson syndrome, and human papillomavirus (HPV) infection

Cancer of the esophagus

Symptoms Caused by Local Tumor Effects

Dysphagia
Cough and regurgitation
Odynophagia
Weight loss
Upper gastrointestinal bleeding

Symptoms Related to Invasion of Surrounding Structures

Respiratory fistula
Hoarseness from recurrent laryngeal nerve invasion
Hiccups from phrenic nerve invasion
Pain caused by local spread

Symptoms Related to Distant Disease

Metastatic disease to the lungs, liver, and central nervous system
Hypercalcemia

Cancer of esophagus

Symptoms

- AC and SCC have similar clinical manifestations, which reflect the extent of local esophageal involvement.
- **Dysphagia**, the most common manifesting symptom, usually develops in response to dense solid food, and progresses gradually to interfere with the intake of softer foods and, finally, liquids.
- This can sometimes be accompanied by **vomiting or regurgitation** of saliva or food.
- **Pain** is frequent and can occur in the absence of dysphagia. It can be related to swallowing itself (**odynophagia**) or to the local extension of the tumor into adjacent structures, such as the pleura, mediastinum, or vertebral bodies.
- **Weight loss** is common and correlates with dysphagia, dietary changes, and tumor-related anorexia. Weight loss is noted in more than 70% of patients and, if present, carries a worse prognosis.
- Other manifesting signs and symptoms reflect complications from disease spread, such as cough or fever from a respiratory tract fistula, upper or lower gastrointestinal bleeding, hoarseness from recurrent laryngeal nerve involvement, and hiccups from phrenic nerve

Cancer of esophagus
Staging: anatomic considerations

- Esophageal tumors 5 centimeters (cm) or less in length are often localized.
- Tumors larger than 5 cm have distant **metastasis 75% of the time.**
- The esophagus is at risk for **skip metastasis** and nodal involvement. Lymphatic spread is unpredictable and may occur at a significant distance from the tumor.
- Lymphatics of the esophagus drain into nodes that usually follow arteries, including the **inferior thyroid artery, the bronchial and esophageal arteries from the aorta, and the left gastric artery**. At the time of autopsy, 70% of patients are found to have lymph node metastases.

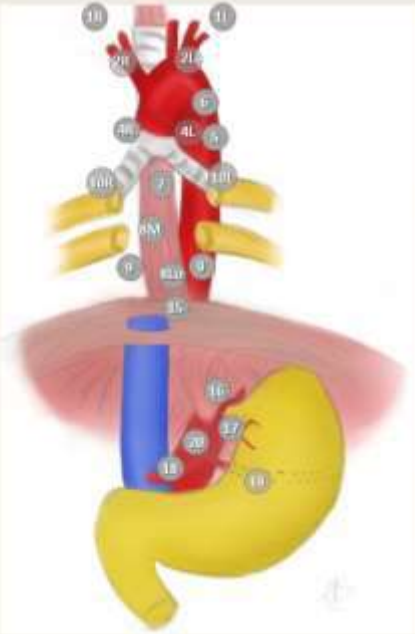


Fig. 1 -Regional lymph nodes according to the eighth edition of TNM for esophageal cancer.
(L – left; R – right)

1 – supraclavicular
2 – upper paratracheal
4 – lower paratracheal
5 – aortopulmonary
6 – anterior mediastinal
7 – subcarinal
8Lo – lower paraesophageal
8M – middle paraesophageal
9 – pulmonary ligament
10 – tracheobronchial
15 – diaphragmatic
16 – paracardial
17 – left gastric
18 – common hepatic
19 – splenic
20 – celiac

Esophageal cancer: staging

Modality	Clinical Utility	Overall Accuracy (%)
Computed tomography (chest, abdomen)	Invasion of local structures (airways, aorta)	≥90%
	Metastatic disease	≥90%
Endoscopy	Local tumor (T) staging (operator dependent)	80%–90%
Ultrasonography (with or without fine-needle aspiration of lymph nodes)	Local nodal (N) staging (operator dependent)	70%–90%
Positron emission tomography	Metastatic disease	≥90%

Esophageal cancer staging

Table

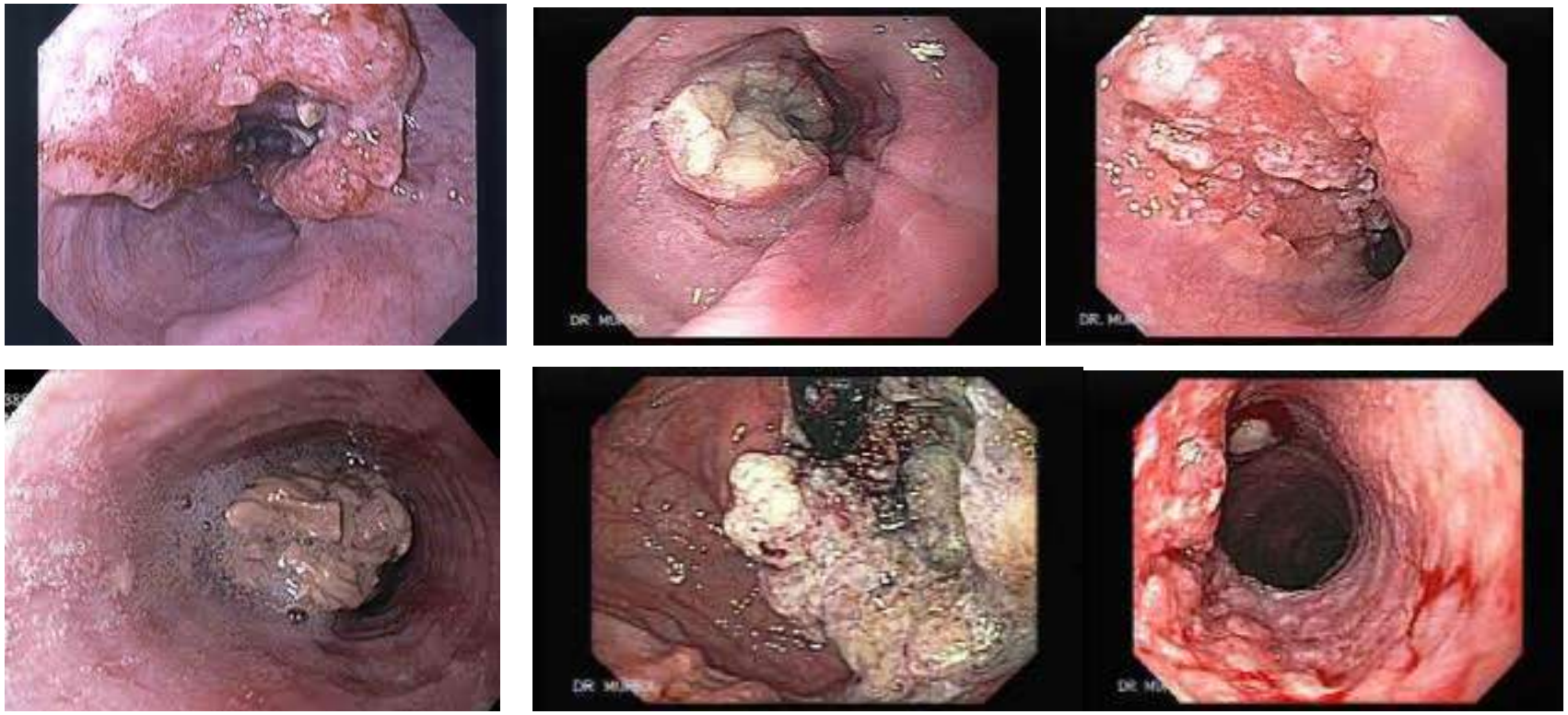
New WECC / AJCC Staging System for Esophageal Cancer

TNM Classifications	
Grade	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated
T stage	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1a	Tumor invading lamina propria or muscularis mucosae
T1b	Tumor invading submucosa
T2	Tumor invading muscularis propria
T3	Tumor invading adventitia
T4a	Tumor invading pleura, pericardium, or diaphragm
T4b	Tumor invading other adjacent structures
N stage	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis involving 1-2 nodes[a]
N2	Regional lymph node metastasis involving 3-6 nodes[a]
N3	Regional lymph node metastasis involving 7 or more nodes[a]
M stage	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Nonregional lymph node metastasis or distant metastasis

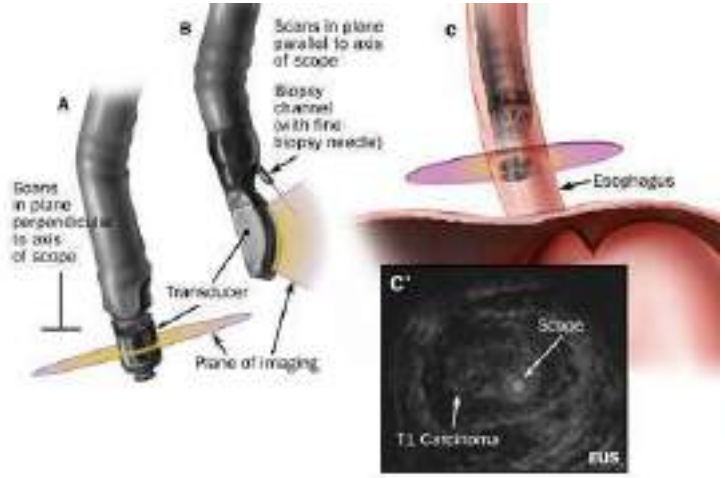
Stage Classifications	
Stage 0	T0 N0 M0, any grade Tis N0 M0, any grade
Stage IA	T1 N0 M0, grade 1-2
Stage IB	T1 N0 M0, grade 3-4 T2 N0 M0, grade 1-2
Stage IIA	T2 N0 M0, grade 3-4
Stage IIB	T3 N0 M0 T0-2 N1 M0, any grade
Stage IIIA	T0-2 N2 M0, any grade T3 N1 M0, any grade T4a N0 M0, any grade
Stage IIIB	T3 N2 M0, any grade
Stage IIIC	T4a N1-2 M0, any grade T4b any N M0, any grade Any T N3 M0, any grade
Stage IV	Any T, any N, M1, any grade

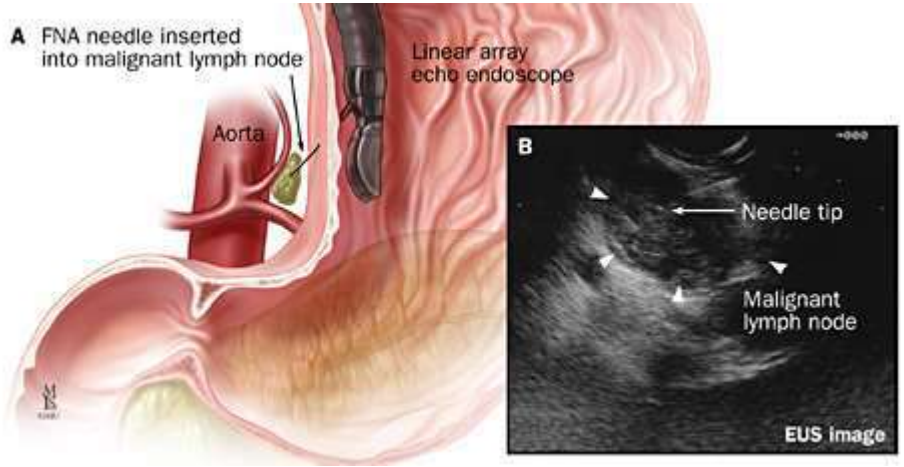
[a]Regional lymph nodes extend from periesophageal cervical to celiac nodes.
WECC = World Esophageal Cancer Consortium; AJCC = American Joint Committee on Cancer; T = Tumor; N= Node; M = Metastasis.

Endoscopy

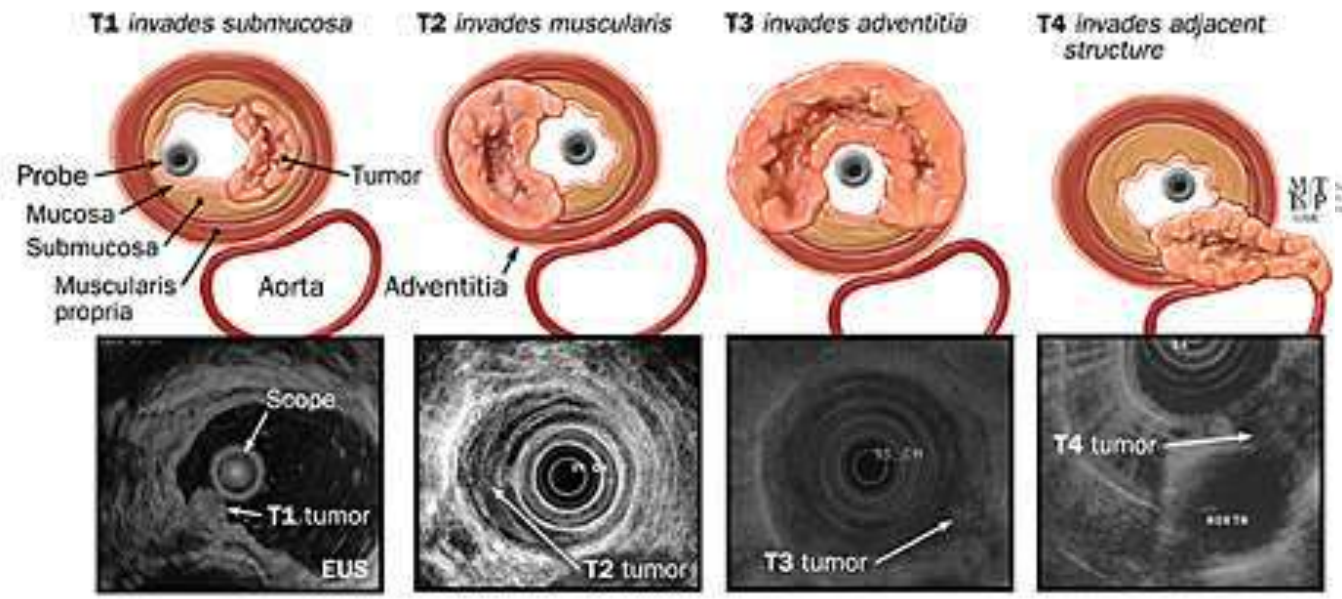


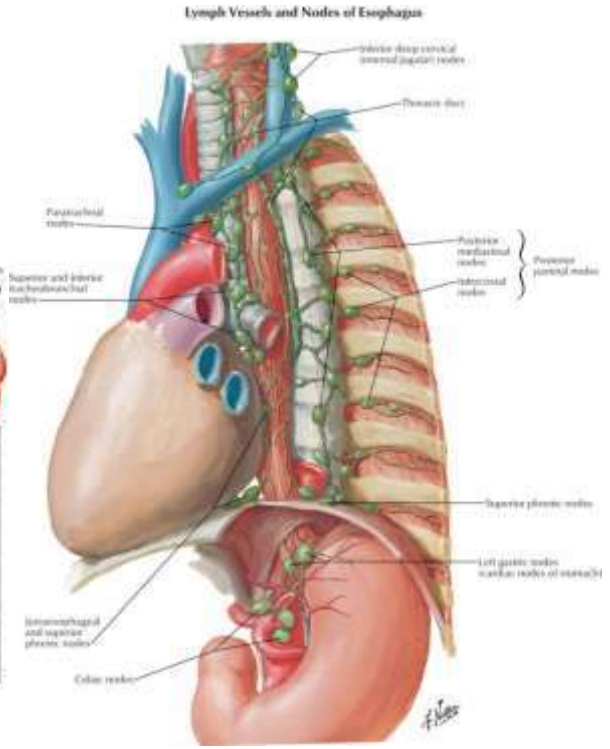
Esophageal cancer: staging
EUS



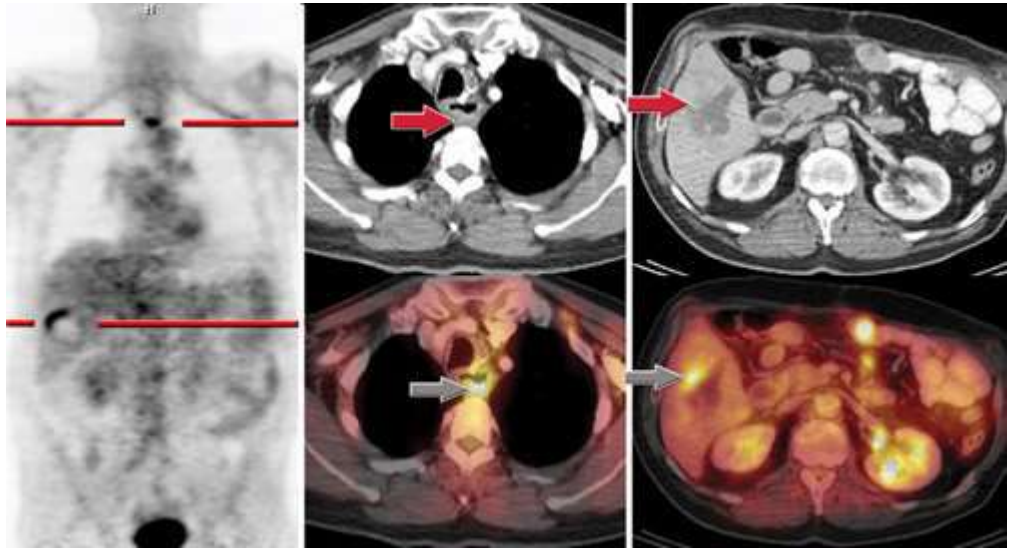


Esophageal cancer: staging
EUS endoscopic ultrasound

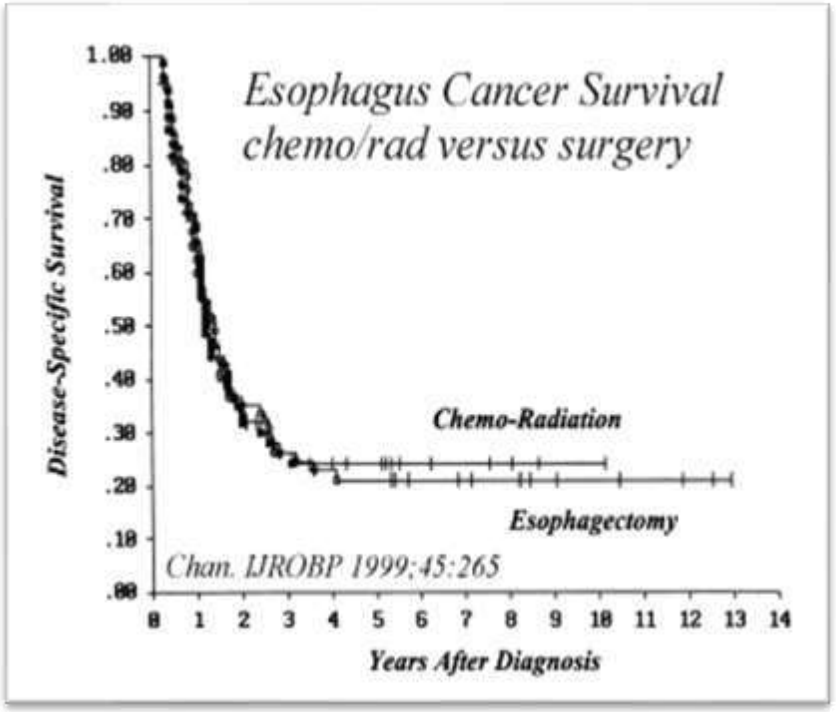


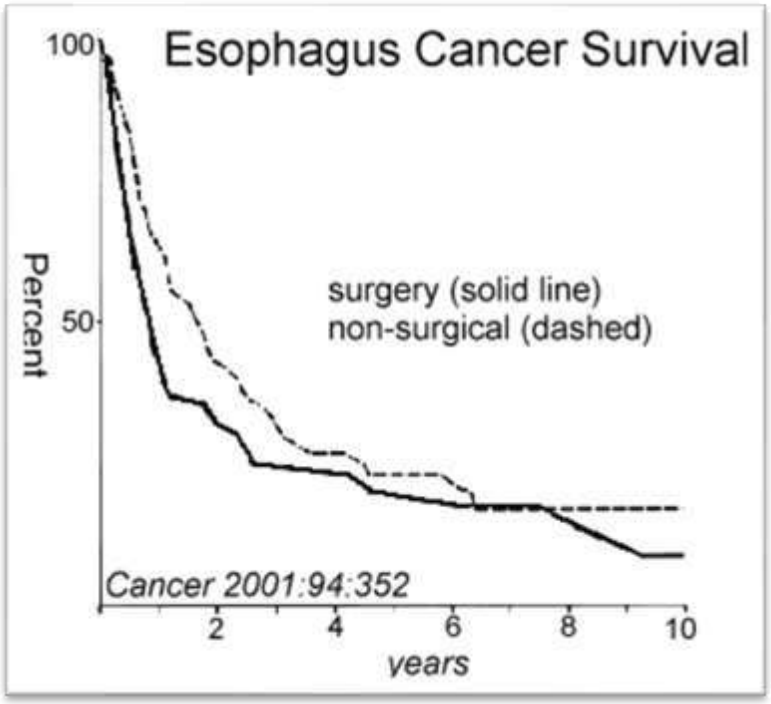


Esophageal cancer: staging PET



Cancer of esophagus survival





Esophageal cancer Treatment

Is Radiation Plus Chemotherapy as Good as Surgery?

Radiation alone has such a poor cure rate for esophagus cancer that many studies have evaluated combining radiation with chemotherapy which improves the cure rates. Some studies have compared chemo/radiation with surgery and found the results similar, suggesting that surgery may not be necessary.

A recent study compared chemotherapy (Mitomycin/ 5FU/ leukovorin) plus Radiation (50-60Gy) and had survival rates by stage: stage I 55%/5y, stage II 16%/5y and stage III 8%/5y.

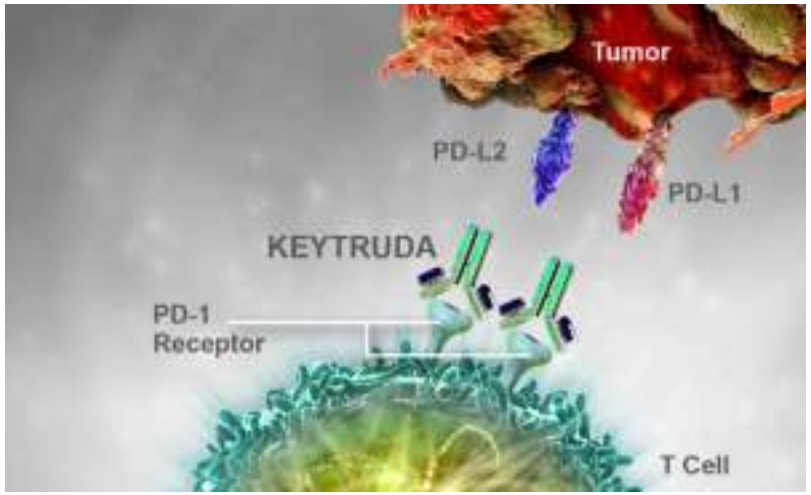
The overall results with chemoradiation (25%/5y survival) were the same as those patients treated with surgery (23%/5y survival.)

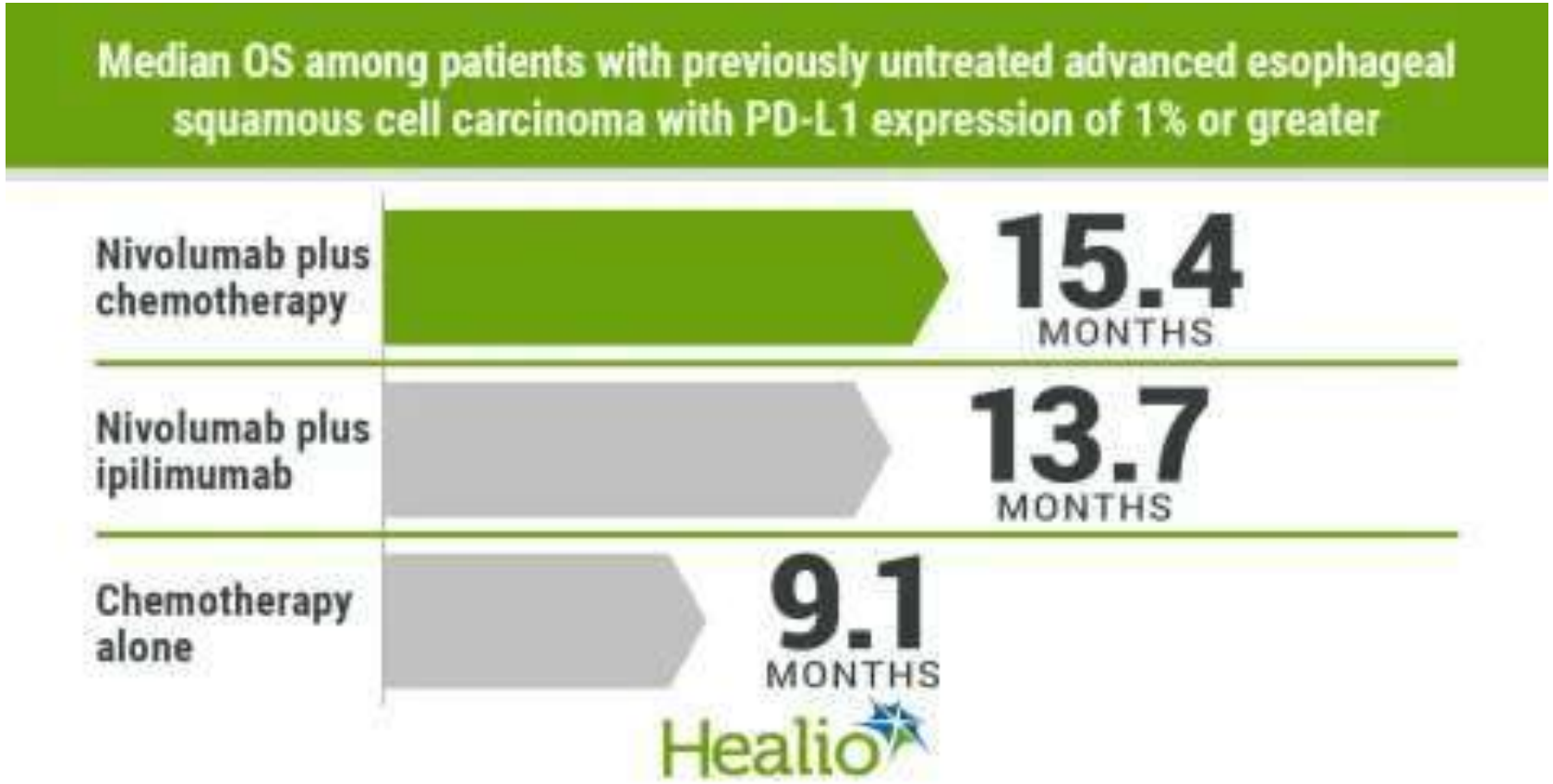
Novel Chemotherapy Agents

- Numerous novel chemotherapeutic and targeted agents have been explored in the locally advanced unresectable and metastatic disease settings for esophageal cancer.
- **Inhibition of the HER-2 receptor by trastuzumab.** Approximately 4,000 patients with either gastric or gastroesophageal junction carcinoma were screened, and 22% were found to be positive for HER-2. These patients were then randomly assigned to either chemotherapy with or without trastuzumab.
- Response, progression-free, and overall survival rates were all improved for those patients who received trastuzumab in combination with chemotherapy.

Novel Chemotherapy Agents

PD-1 Checkpoint Inhibition - prime line treatment





Palliative treatment:

Esophageal stent