DISORDERS OF THE HEAD AND NECK ESOPHAGUS

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Congenital defects

- Esophageal webs
- Generally found in the upper esophagus
- Semi-circumferential
- Composed of epithelial lined fibrovascular tissue.
- Dysphagia a prominent symptom.
- Women
- >40 years old
- Associated with gastroesophageal reflux, chronic graft-versus-host disease, or blistering skin diseases.
- May be accompanied by iron-deficiency anemia, glossitis, and cheilosis (Paterson-Brown-Kelly or Plummer-Vinson syndrome).

Congenital defects

- Esophageal (Schatzki) rings
- Circumferential
- A rings are found in the distal esophagus and are covered by squamous mucosa;
- B rings are found at the squamo-columnar junction and may have gastric mucosa on the surface.
- Dysphagia a prominent symptom
- Acid reflux as cause
- Balloon dilatation therapeutic.
- Ectopic gastric mucosa
- Upper third of the esophagus being the most common site.

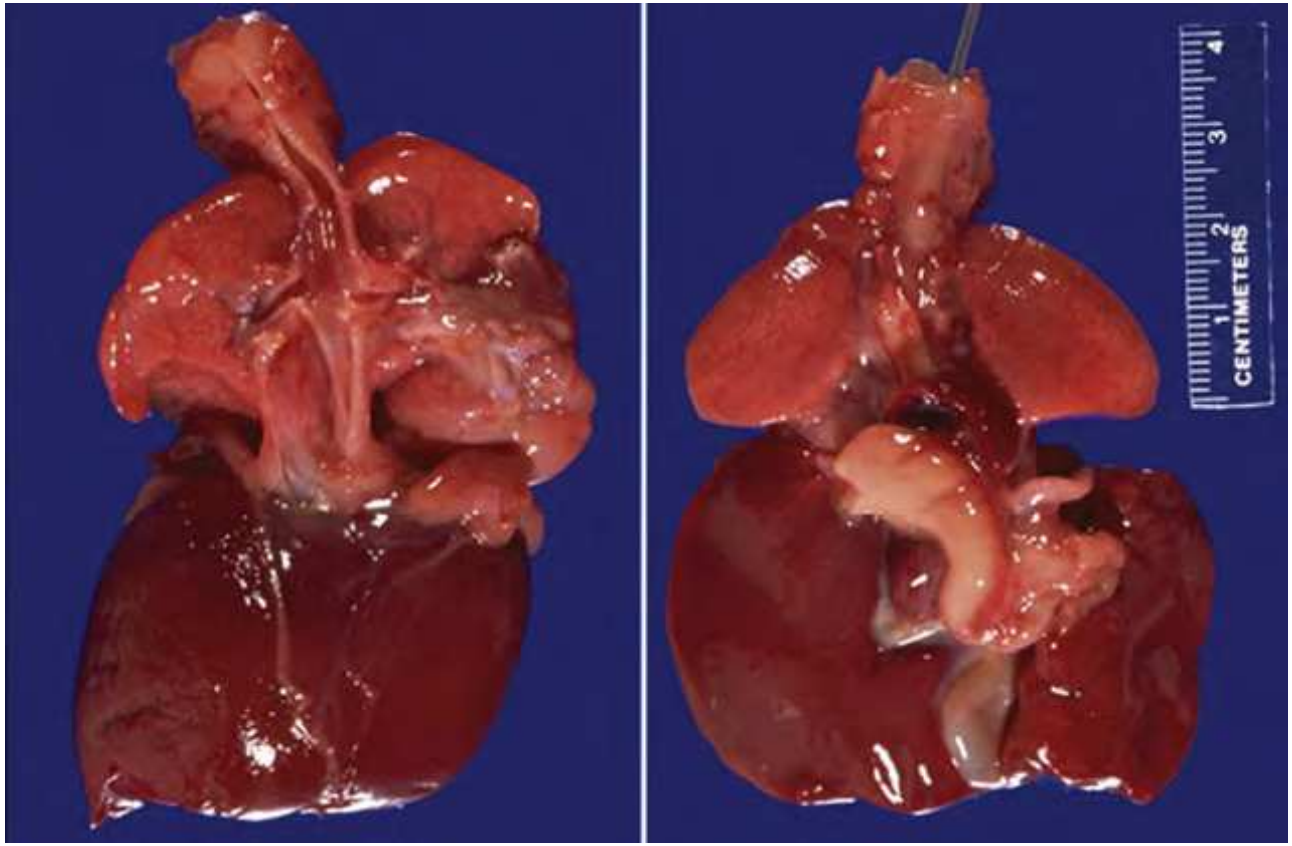
Congenital defects

- Zenker's diverticulum
- Outpouching of the esophagus above the upper esophageal sphincter.
- Leads to saliva and food retention.
- May experience aspiration or postprandial throat clearing with production of food particles.
- Demonstrate with cine-esophagoscopy.
- Cricopharyngeus muscle does not relax when swallowing
- Surgical repair and section of the crico-pharyngeus muscle.

Congenital defects

- Esophageal atresia
- Principal foregut abnormality
- Commonly occurs at or near the tracheal bifurcation
- Thoracic and intestinal organs separate at 7th week of gestation.
- Polyhydramnios (excess amniotic fluid)
- Swallowed amniotic fluid cannot be reabsorbed in small intestine.
- Proximal esophagus ends blindly
- Distal esophagus arises from trachea
- Aspiration common.

Tracheo-esophageal fistula

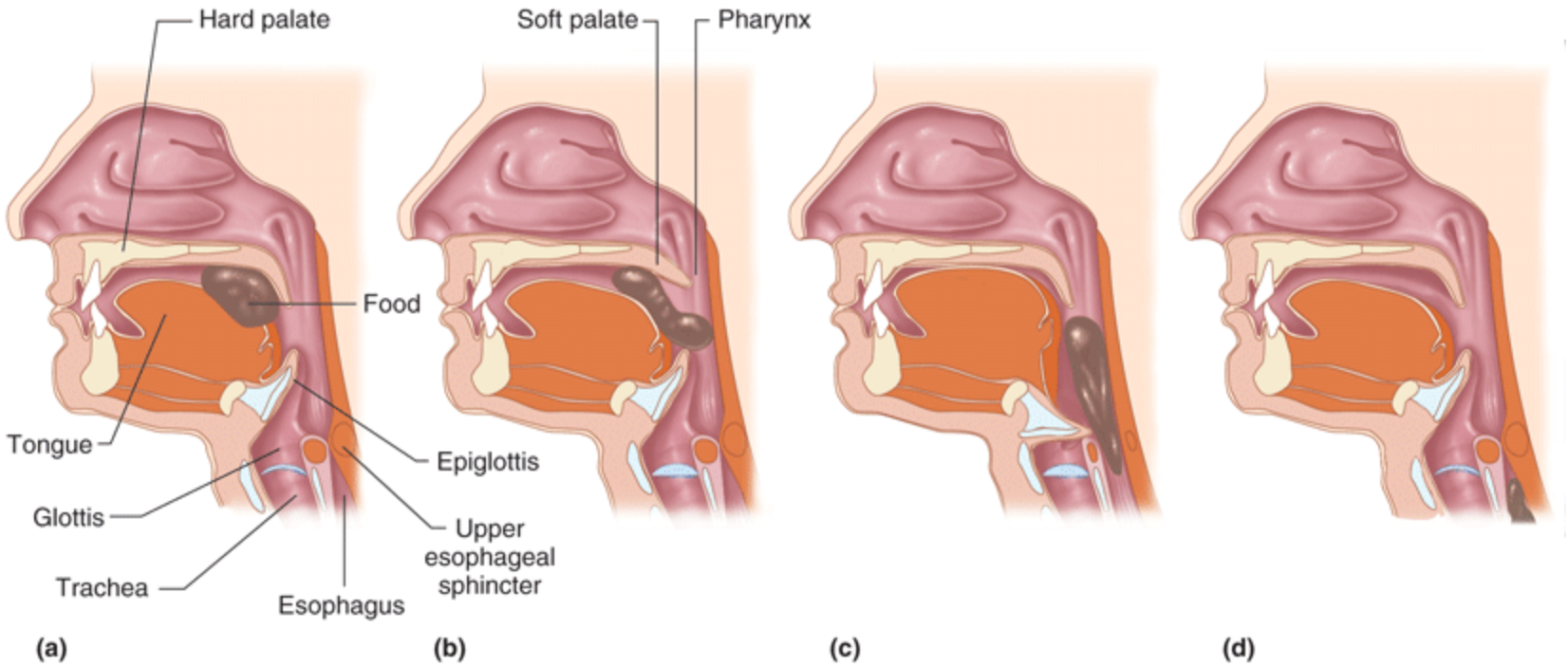


Klatt, EC, Robbins and Cotran Color Atlas of Pathology. Elsevier. Philadelphia. 2015. Figure 7-4 Accessed 11/07/2019

Deglutition

- Swallowing (deglutition) is coordinated in the medulla.
- In swallowing, a food bolus is pushed to the posterior pharynx by the tongue.
- The soft palate moves upward to prevent reflux into nasal cavities.
- The palatopharyngeal folds narrow to create a small passageway for passage of food.
- The vocal cords tighten and the larynx moves upward, causing the epiglottis to swing backward over the opening to the larynx. (The glottis closes to prevent passage into the trachea.)

Swallowing



Fig/ 28-3 Accessed 03/01/2010

Deglutition

- The upper esophageal sphincter relaxes (resting pressure is 100 mmHg).
- Peristalsis directs food to the stomach.
- The lower esophageal sphincter relaxes (resting pressure, 20).
- Proximal stomach receptively relaxes. Vagal control.
- The stomach contracts 3-5/minute.
- Vagal stimulation increases rate
- Sympathetic stimulation (celiac plexus) decreases contractions.

Lower esophageal sphincter

- The control of the lower esophageal sphincter is critical to esophageal function.
- Maintenance of sphincter tone is necessary to prevent reflux of gastric contents, which are under positive pressure relative to the esophagus.
- During deglutition, both active inhibition of the muscularis propria muscle fibers by inhibitory non-adrenergic and non-cholinergic neurons and cessation of tonic excitation by cholinergic neurons enable the sphincter to relax.

Lower esophageal sphincter

- Gastrin, acetylcholine, serotonin, prostaglandin $F_{2\alpha}$, motilin, substance P, histamine, and pancreatic polypeptide increase tone.
- Nitric oxide and vasoactive intestinal peptide decrease the tone.

Chapman's reflex points

- Smooth, firm, discretely palpable nodules 2-3mm in diameter located within deep fascia or on the periosteum of a bone.
- May represent viscerosomatic reflexes (empirical evidence only)
- T1 adjacent to transverse process associated with somatic dysfunction of esophagus, bronchus, thyroid

Esophageal dysmotility

- Nutcracker esophagus describes patients with high-amplitude contractions of the distal esophagus that are, in part, due to loss of the normal coordination of inner circular layer and outer longitudinal layer smooth muscle contractions.
- Diffuse esophageal spasm is characterized by repetitive, simultaneous contractions of the distal esophageal smooth muscle.
- Hypertensive lower esophageal sphincter dysfunction if dysmotility without the above described changes.

Achalasia

- Presents with dysphagia.
- Usually affects women.
- Occurs due to impaired relaxation of the lower esophageal sphincter.
- Destruction of myenteric (Auerbach) plexus with hypertrophy of circular muscles.
- Loss of NO synthase producing neurons.
- HLA-DQw1 association.
- May see a “bird beak” stricture on x-ray.
- Common complication of scleroderma

Achalasia

- Look for CREST syndrome
- Calcinosis
- Raynaud disease
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia.
- Balloon dilatation therapeutic.
- Laparoscopic myotomy may be necessary.
- Calcium channel blockers or long acting nitrates may be attempted to relax lower sphincter.

Normal esophagus

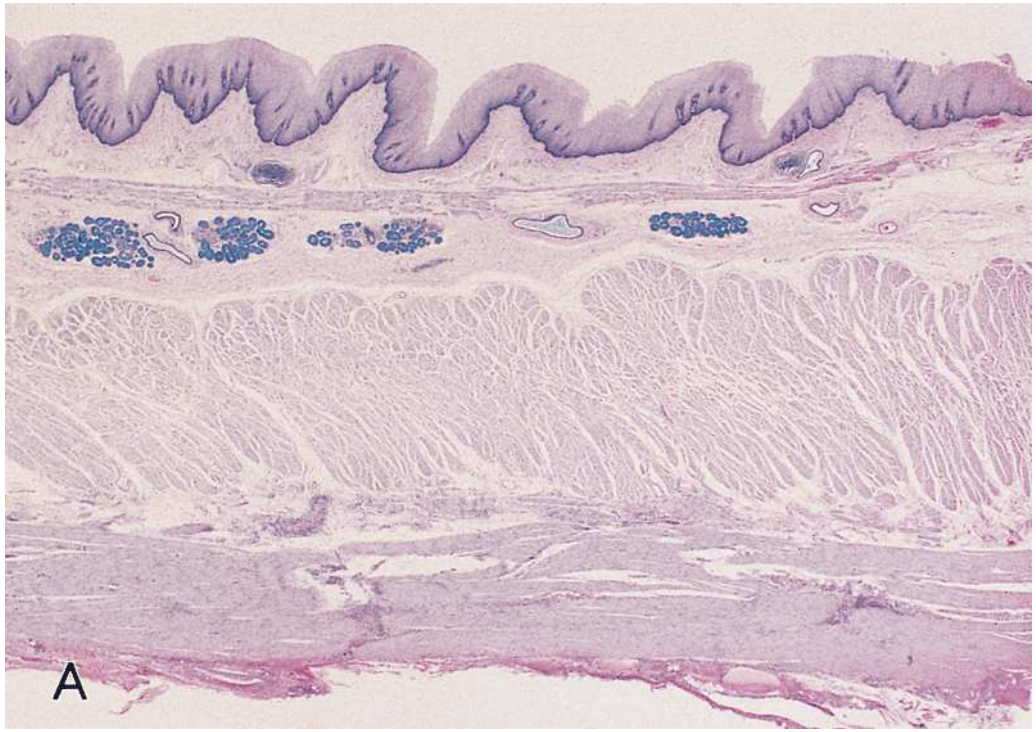
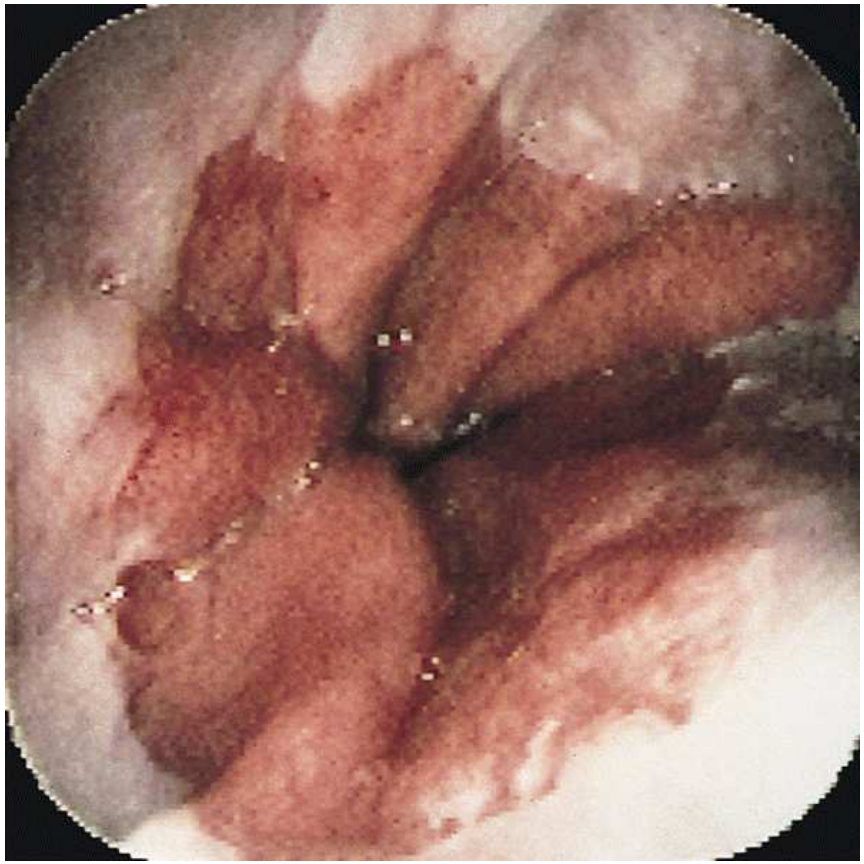


Fig. 2-6A

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Scanning- power view of the full thickness of the esophagus. The mucosa is composed of squamous epithelium, lamina propria, and muscularis mucosae. The latter separates the mucosa from the submucosa. The muscularis propria consists of two layers, the inner circular and the outer longitudinal coats. Note that the circular muscle coat is thicker than the longitudinal coat. Also visible are lymphoid follicles just above the muscularis mucosae. Submucosal glands are present near the z-line.

Esophago-gastric junction



Endoscopic appearance of the z-line (the esophago-gastric junction).

Fig. 2-2

Lewin, KJ, Appelman, HD., “Tumors of the esophagus and stomach.” Atlas of Tumor Pathology, Third Series, Fascicle 18. Armed Forces Institute of Pathology, Washington, DC. 1996.

Mallory-Weiss tears

- Longitudinal mucosal tears near the gastroesophageal junction
- Often associated with severe retching or vomiting.
- Normally, a reflex relaxation of the gastroesophageal musculature precedes the anti-peristaltic contractile wave associated with vomiting.

- Relaxation fails during prolonged vomiting
- Refluxing gastric contents overwhelm the gastric inlet and cause the esophageal wall to stretch and tear
- 10% of hematemesis cases
- Heal spontaneously

Boerhaave's syndrome

- Transmural tearing and rupture of the distal esophagus.
- Pneumomediastinum
- May lead to subcutaneous dissection of chest and neck skin by air
- May produce severe mediastinitis
- May present with severe chest pain, tachypnea, and shock
- May be complication of endoscopy.

Chemical esophagitis

- Dense infiltrates of neutrophils are present in most cases but may be absent following injury induced by lye, acids, or detergent, which can lead to frank necrosis of the esophageal wall.
- Pill-induced esophagitis frequently occurs at the site of strictures that impede passage of luminal contents.
- When present, ulceration is accompanied by superficial necrosis with granulation tissue and eventual fibrosis.
- Esophageal irradiation damage includes intimal proliferation and luminal narrowing of damaged submucosal and mural blood vessels.

Infectious esophagitis

- Nonpathogenic oral bacteria are frequently found in ulcer beds
- Pathogenic organisms account for 10% of cases
- These may invade the lamina propria and cause necrosis of overlying mucosa.
- Candida (usually, albicans)
- Patches of the entire esophagus become covered by adherent, gray-white pseudomembranes teeming with densely matted fungal hyphae.

Infectious esophagitis

- CMV
- Linear ulceration of the esophageal mucosa.
- Both intranuclear and cytoplasmic inclusions are found in capillary endothelium and stromal cells in the base of the ulcer.
- Herpes viruses
- Typically cause punched-out ulcers
- The nuclear inclusions of herpes virus are found in a narrow rim of degenerating epithelial cells at the margin of the ulcer.

Other causes of esophagitis

- Histologic features of esophageal graft-versus-host disease are similar to those in the skin and include basal epithelial cell apoptosis, mucosal atrophy, and submucosal fibrosis without significant acute inflammatory infiltrates.
- The microscopic appearances of esophageal involvement in bullous pemphigoid, epidermolysis bullosa, and Crohn's disease are also similar to those in the skin.
- The microscopic changes noted in autoimmune diseases are similar to those seen in the skin.

Reflux esophagitis

- Presents with substernal chest pain and regurgitation that worsens when bending over and when supine.
- May only see hoarseness or asthma.
- Sliding hiatal hernia most common cause.
- The anatomic changes depend on the causative agent and on the duration and severity of the exposure.
- Simple hyperemia may be the only alteration.

Reflux esophagitis

- Histopathology:
- Elongation of lamina propria papillae with capillary congestion, extending into the top third of the epithelial layer.
- Infiltrates of intraepithelial eosinophils (early)
- Basal zone hyperplasia exceeding 20% of the epithelial thickness.
- Intraepithelial neutrophils are markers of more severe injury such as ulceration.

Eosinophilic esophagitis

- The majority of individuals with eosinophilic esophagitis are atopic and many have atopic dermatitis, allergic rhinitis, asthma, or modest peripheral eosinophilia.
- The cardinal histologic feature is large numbers of intraepithelial eosinophils, particularly superficially

Diagnosis of esophagitis

- Barium swallow x-ray useful to reveal structural abnormalities and motility dysfunction.
- Esophagoscopy-gastroscopy essential for diagnosis of cause of esophagitis.

Therapy of esophagitis

- Calcium channel blockers lower the pressure of the lower esophageal sphincter and can alleviate symptoms.
- Sulfacralate can provide a protective lining for the mucosa in an acid environment.
- Proton pump inhibitors with or without H_2 blockers are the drugs of choice.
- Prokinetic agents (cisapride, metoclopramide) may improve symptoms by promoting gastric emptying.
- Nissl fundoplication wraps a portion of the stomach around the lower esophageal sphincter to increase pressures.

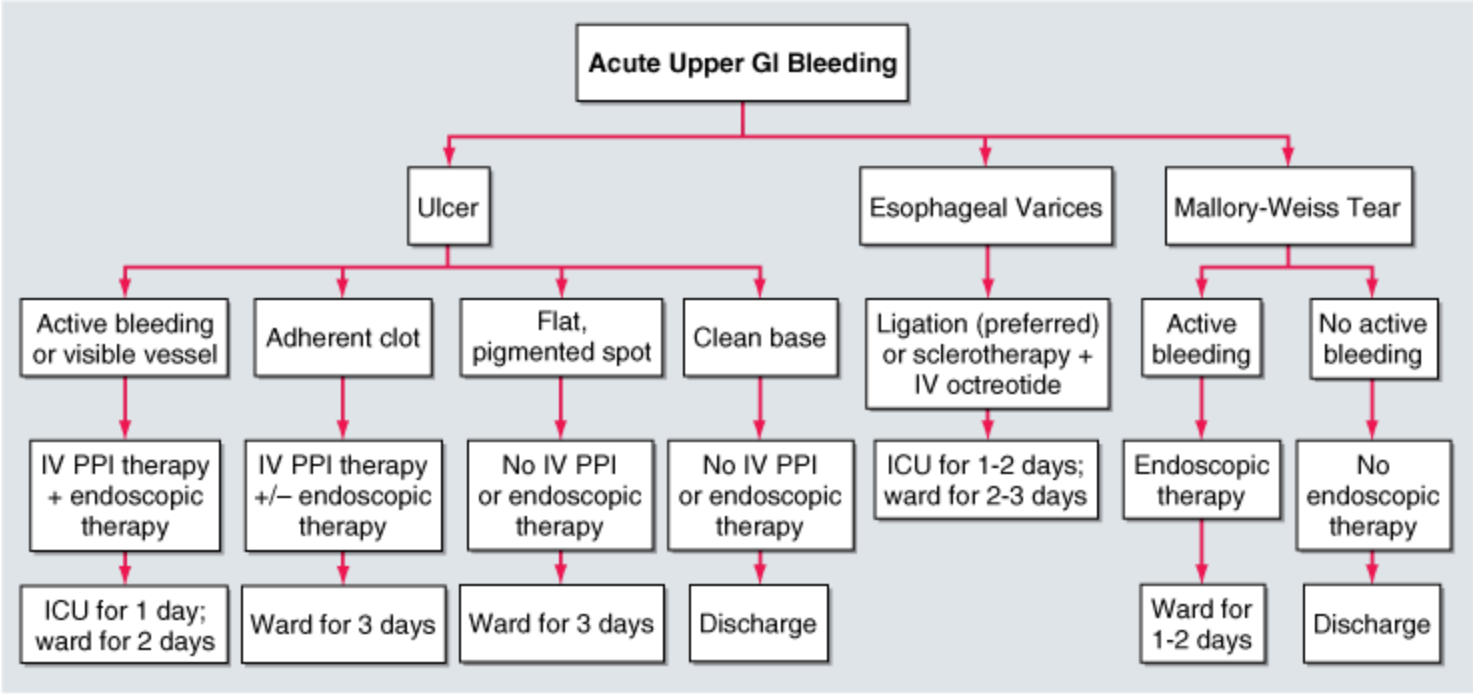


Fig. 42-1
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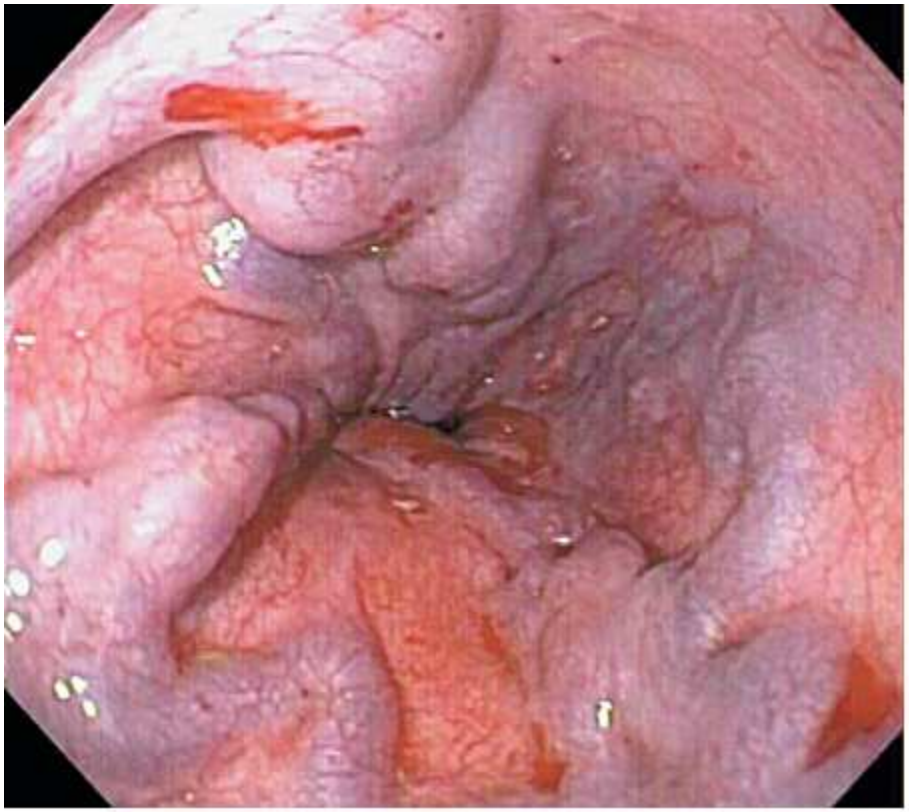
Esophageal varices



Dilated submucosal veins in distal esophagus and proximal stomach

Fig. e25-16
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Esophageal varices

- The upper two thirds of the esophagus drain into the azygos vein and into the superior vena cava
- Esophageal veins from the lower third of the esophagus empty into left gastric vein and into the portal vein
- Portal hypertension leads to enlargement of submucosal venous plexes in the distal esophagous and proximal stomach
- Venous channels directly beneath the esophageal epithelium may also become massively dilated.
- They collapse in the absence of blood flow
- Those without splenomegaly or thrombocytopenia are at lowest risk for having varices.

Esophageal varices

- Portal pressure >12 mmHg defines portal hypertension
- Variceal rupture results in hemorrhage into the lumen or the esophageal wall
- The overlying mucosa appears ulcerated and necrotic.
- If rupture has occurred in the past, venous thrombosis, inflammation, and fibrosis are present.
- 33% die at time of first bleed
- 70% recurrent bleeding in first year.
- High risk for infections.

Therapy of esophageal varices

- Screening endoscopy yearly
- β-blockers and nitrates decrease portal pressures; β-blockers reduce rate of first bleed
- Intravenous octreotide stops variceal bleeding in 80% of cases.
- Endoscopic ligation.
- Intrahepatic portal shunt if ligation fails

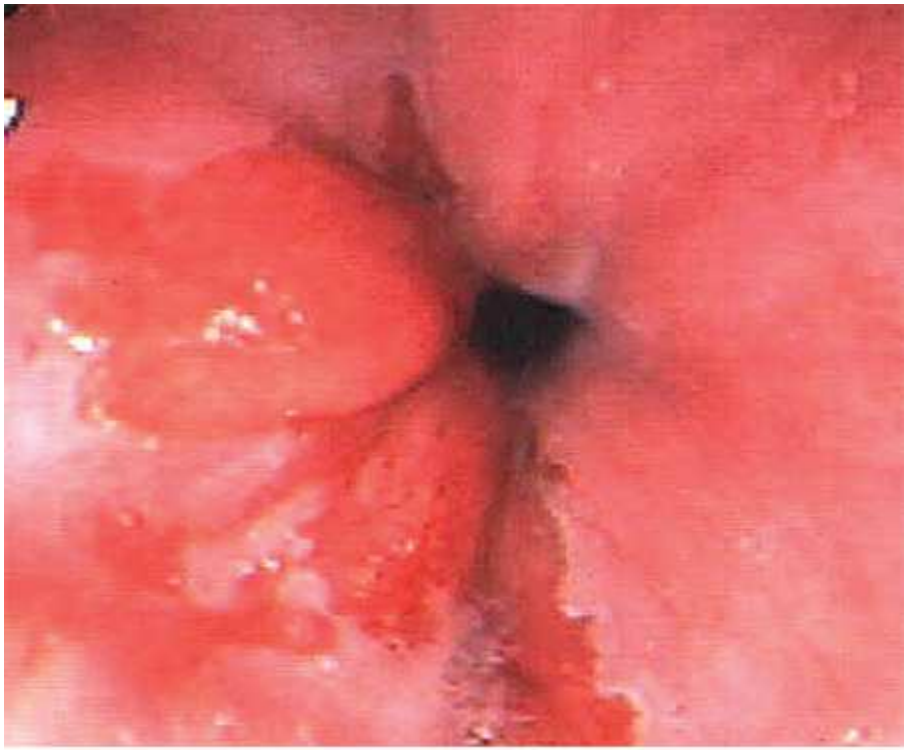
Barrett esophagus

- 40-50 years of age.
- A complication of long-standing gastro-esophageal reflux.
- Resistant to proton pump therapy.
- Up to 10% of patients with symptomatic gastro-esophageal reflux disease (GERD).
- Red, velvety appearance on endoscopy.
- This metaplastic mucosa of distal esophagous alternates with residual smooth, pale squamous (esophageal) mucosa and interfaces with light-brown columnar (gastric) mucosa distally
- May reflect abnormality in stem cell maturation.

Barrett esophagus

- It is the single most important risk factor for development of esophageal adenocarcinoma.
- Divided into short (<3cm) and long (>3cm) segment disease depending upon length of mucosal abnormality.
- Risk related to extent of disease.
- Multifocal dysplasia treated as if it were intramucosal carcinoma.
- Intramucosal carcinoma is characterized by invasion of the lamina propria.

Barrett esophagus



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Endoscopic view. Metaplastic change.

(Courtesy of Klaus Monkemuller, MD, UAB, Birmingham, AL)

Fig. 14-16
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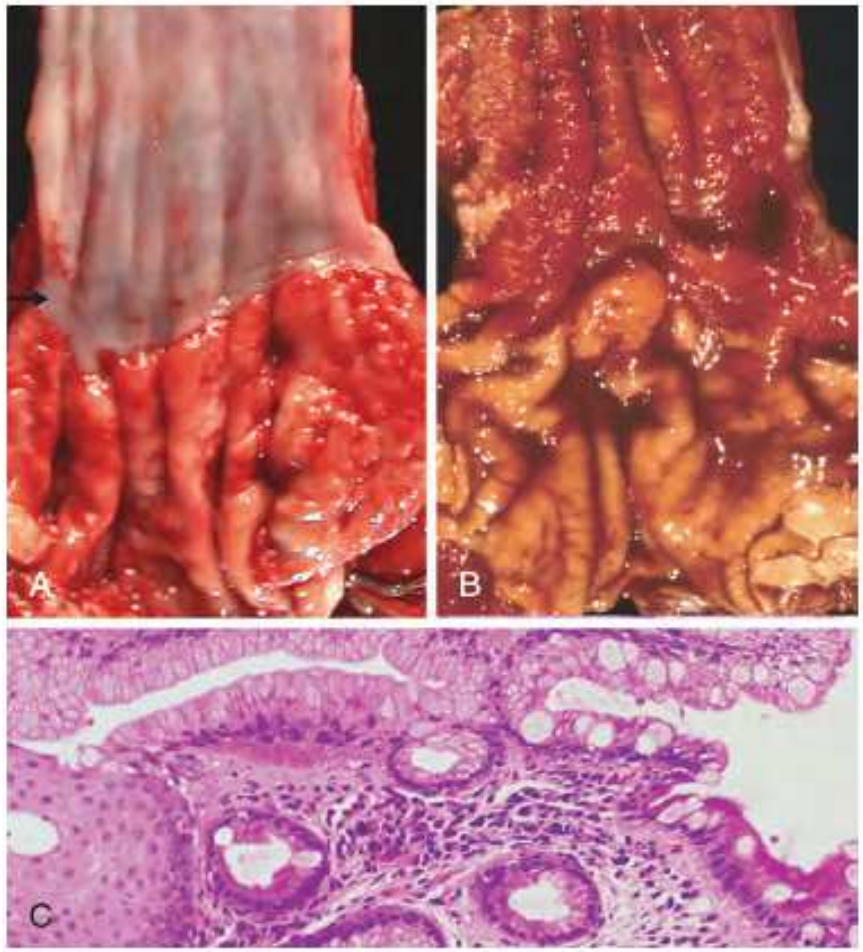


Figure 17-7 Barrett esophagus. **A,** Normal gastroesophageal junction. **B,** Barrett esophagus. Note the small islands of residual pale squamous mucosa within the Barrett mucosa. **C,** Histologic appearance of the gastroesophageal junction in Barrett esophagus. Note the transition between esophageal squamous mucosa (left) and Barrett metaplasia, with abundant metaplastic goblet cells (right).

Barrett esophagus

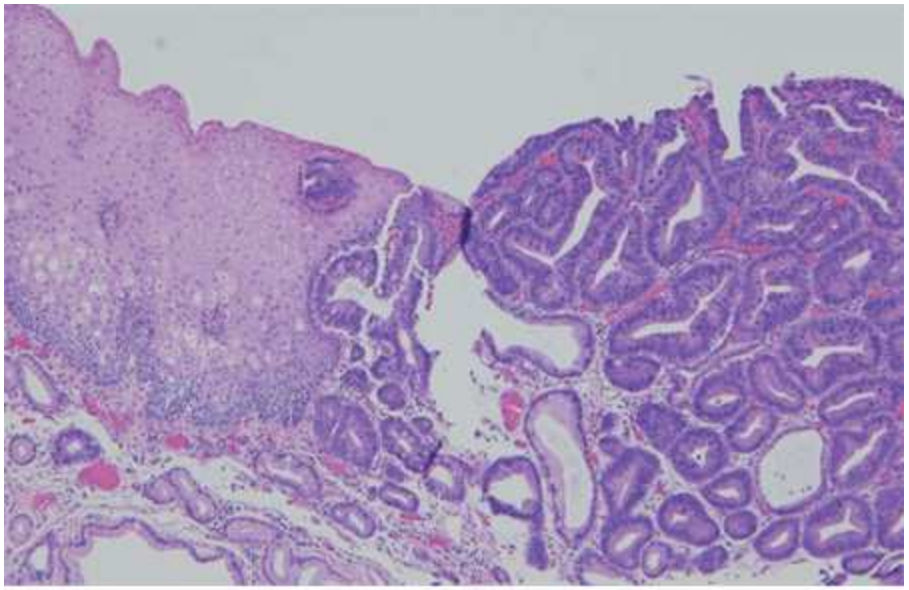


Fig.14-17 Accessed 04/01/2010

Microscopically, intestinal-type metaplasia
is seen as replacement of the squamous esophageal epithelium with goblet cells. These are diagnostic of Barrett esophagus,
and have distinct mucous vacuoles that stain pale blue by H&E and impart the shape of a wine goblet
to the remaining cytoplasm. Non-goblet columnar cells, such as gastric type foveolar cells, may also be present.

(*Courtesy of Dr. Stephen May, MD, and Dr. Asif Rashid, MD, UTMDACC, Department of Pathology, Houston, TX*)

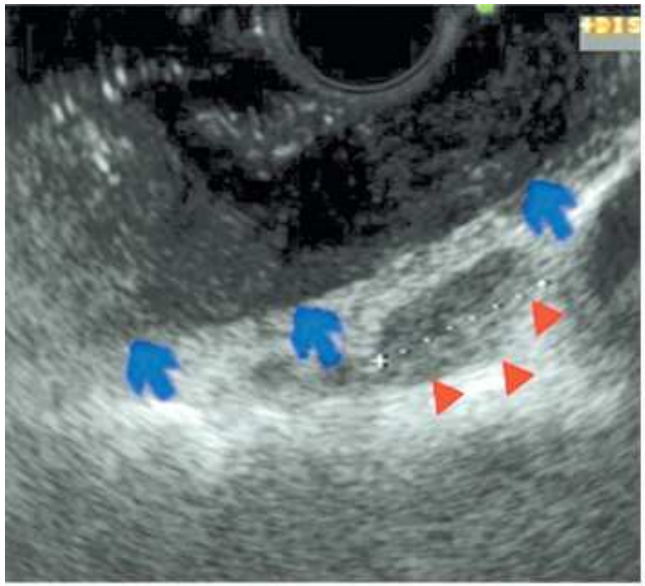
Benign esophageal tumor

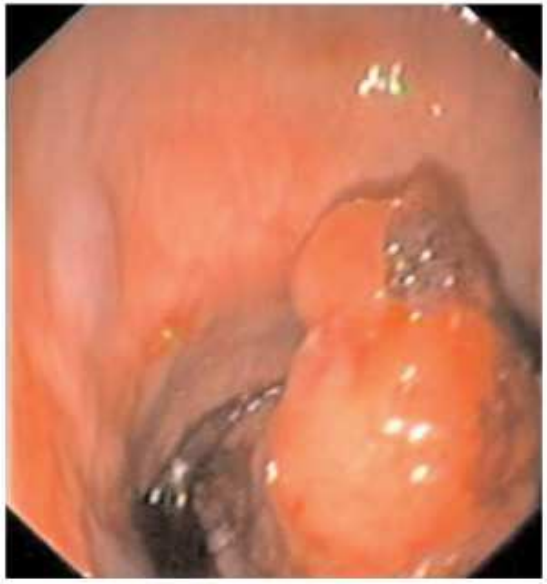
- Leiomyoma (tumor of smooth muscle) is the most common benign tumor of the esophagus.
- May interfere with swallowing.
- Resect

Esophageal cancer

- Endoscopy with biopsy is the primary test for the diagnosis of esophageal cancer.
- Endoscopic ultrasound (EUS) is important in the initial local staging.
- CT of the chest and abdomen is recommended for staging and assessing tumor resectability.
- MRI provides better assessment of vascular structures than does CT.

Esophageal cancer

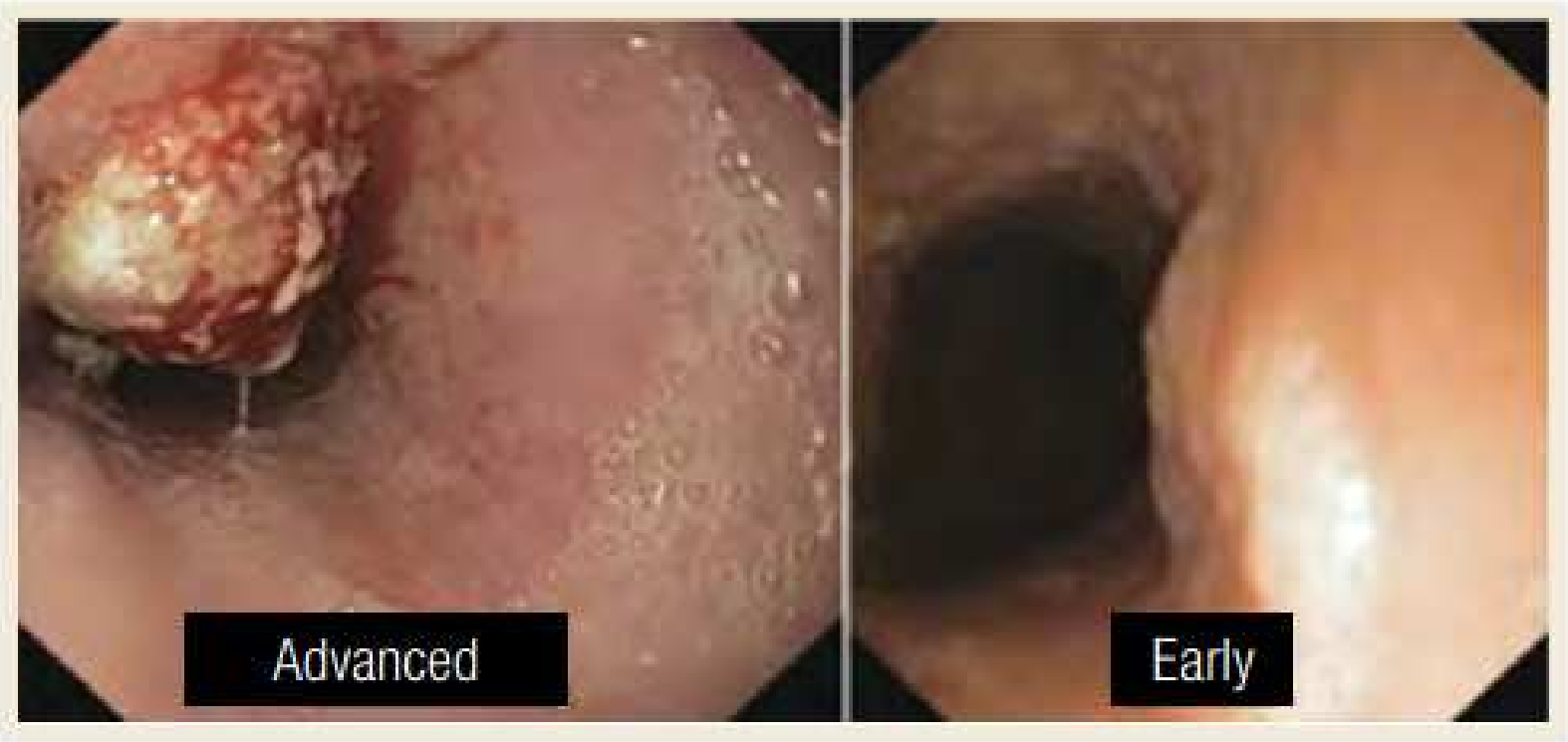


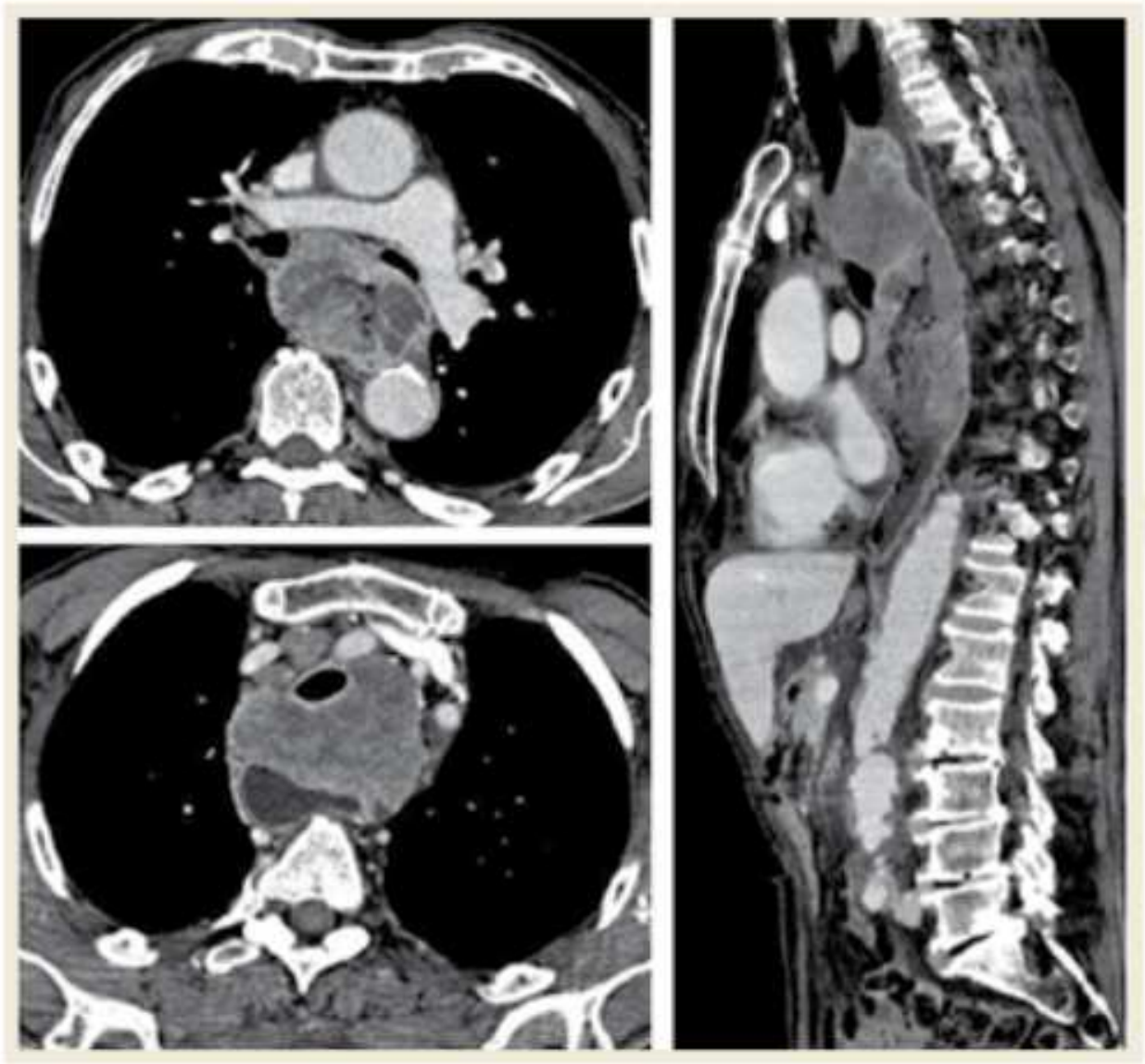


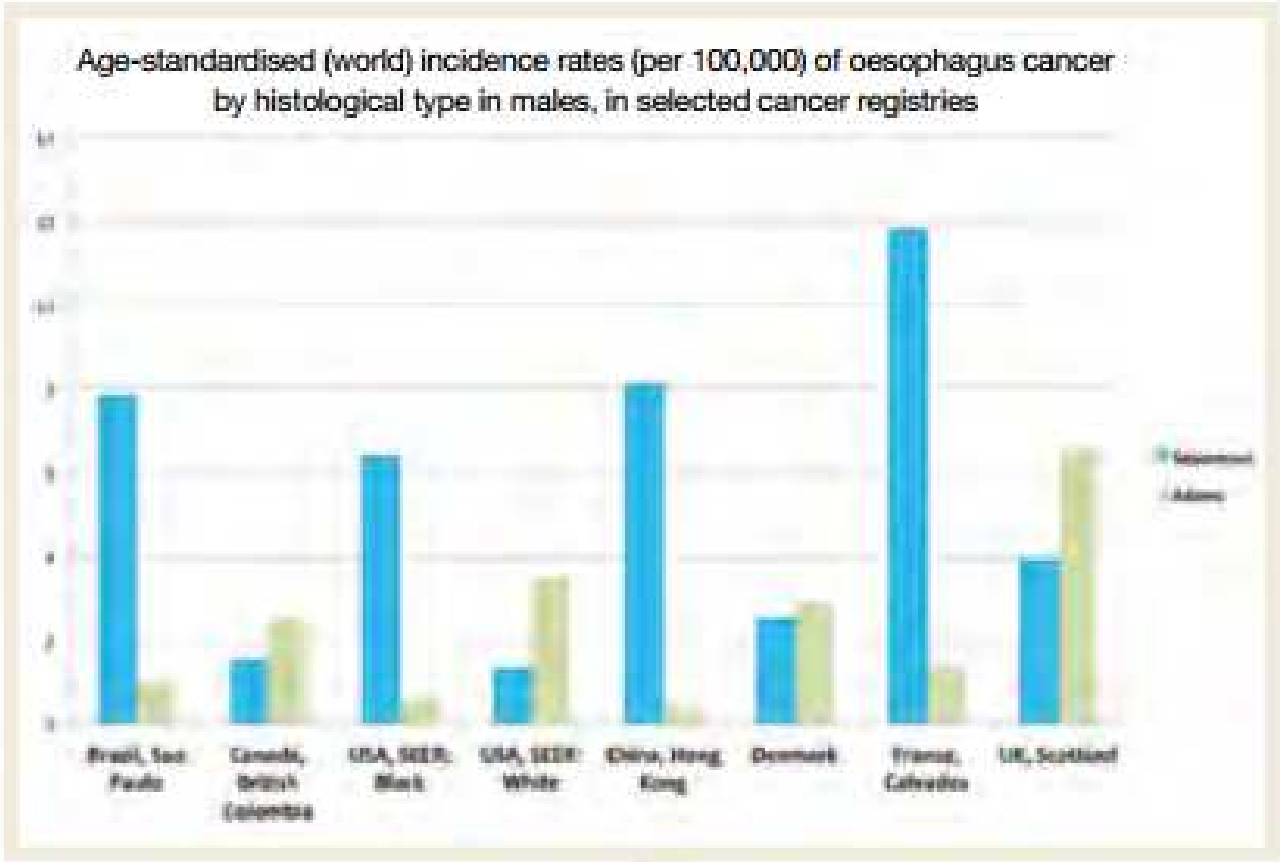
Endoscopic ultrasound and endoscopic view demonstrating polypoid mass.

(Courtesy of Adrian Saftiou, MD, University of Medicine and Pharmacy Craiova, Romania.)

Fig. 14-20 Accessed 04/01/2010


Advanced
Early




Age-standardised (world) incidence rates (per 100,000) of oesophagus cancer by histological type in males, in selected cancer registries

FACTORS	OSCC	OAC	
	INCREASES RISK	DECREASES RISK	INCREASES RISK
Tobacco	Smoking (mainly in Western population)		Smoking
Dietary factors	Low fruit intake Low vegetable intake High alcohol intake (mainly in Western population) High intake of processed meat		Low fruit intake Low vegetable intake Low vitamin C intake Low carotene intake High intake of processed meat
Infectious agents		*H. pylori* infection	
Hot beverages	Coffee, tea, mate		Coffee, tea, mate
Body mass index			Obesity
Other	Tooth loss and poor oral hygiene (in Asian populations)		Gastro-oesophageal reflux disease Barrett's oesophagus Some drugs (beta-blockers, aminophyllines, anticholinergics) that relax the sphincter

OAC, Oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Adenocarcinoma

- Adenocarcinoma now represents up to half of all esophageal cancers reported in the United States.
- The majority of cases arise from the Barrett mucosa.
- Occur in the distal third of the esophagus.
- May invade adjacent gastric cardia.
- Tobacco use also a risk factor.
- In rare instances, adenocarcinoma originates from heterotopic gastric mucosa or submucosal glands.

Adenocarcinoma

- Morphologic patterns
- Barrett esophagus is frequently present adjacent to the tumor.
- Tumors most commonly resemble mucin producing colon adenocarcinoma
- Less frequently, resemble diffusively infiltrative adenocarcinoma (with signet ring cells) as in the stomach
- Rarely, resemble poorly differentiated small cell carcinoma as in the lung.

Adenocarcinoma

- The more common genetic and epigenetic alteration is the inactivation of CDKN2A (p16/INK4a)
- Bi-allelic loss or hypermethylation of CDKN2A
- Patients with LOH in TP53 are 16 times more likely to progress to adenocarcinoma
- Overexpression of p53
- Predominantly G:C to A:T transitions at CpG dinucleotides
- These changes are seen both in Barrett's as well as in adenocarcinoma of the cardia

Adenocarcinoma

- In high-grade dysplasia, chromosome 4 amplification is generally present.
- When the dysplastic epithelium develops into adenocarcinoma, additional genetic changes, including nuclear translocation of β-catenin and amplification of *c*-ERB-B2, are present.
- MET as well as Cyclin D1 and E amplifications are also noted.
- TNF as well as NF-kB upregulated.

Molecular relationships

- Esophageal squamous cell carcinoma resembles squamous cell carcinoma of other organs
- Esophageal adenocarcinoma strongly resembles the chromosomally unstable variant of gastric adenocarcinoma:
- The EAC-like group
- High copy number amplification and increased protein expression of ERBB2 and EGFR
- The gastric adenocarcinoma located at the fundus or body of the stomach–like group
- Activated phosphoinositide 3-kinase–AKT signaling with decreased expression of ERBB2.

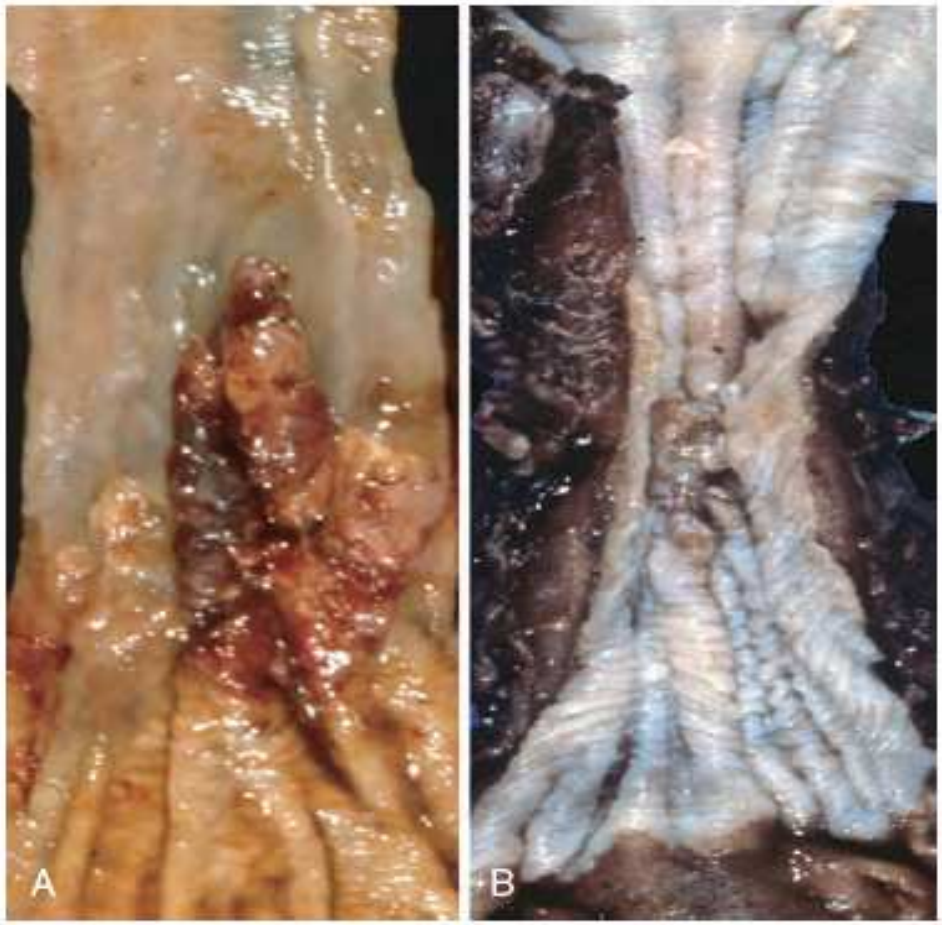


Figure 17-9 Esophageal cancer. **A,** Adenocarcinoma usually occurs distally and, as in this case, often involves the gastric cardia. **B,** Squamous cell carcinoma is most frequently found in the mid-esophagus, where it commonly causes strictures.

Squamous cell carcinoma

- Dysphagia and pain on swallowing are the usual presenting symptoms
- Most squamous cell carcinomas occur in adults over age 50.
- Iran, central China, Hong Kong, Brazil, South Africa are regions of highest incidence
- More common in rural and undeveloped areas
- Those of African descent in the US are at significantly higher risk for squamous cell carcinoma
- Likelier in males.
- This may reflect tobacco and alcohol use.

Squamous cell carcinoma

- Other risk factors
- Polycyclic hydrocarbon exposure
- Nitrosamines in food
- Nutritional deficiencies
- Aflatoxin
- HPV
- Associated with consumption of a fermented acetaldehyde containing milk (mursik) in Western Kenya

Squamous cell carcinoma

- GWAS studies in Asian populations showed a significant increase of squamous cell carcinoma risk associated with:
- 2q33 (CASP8, ALS2CR12, TRAK2
- ALDH2 and ADH1B locus in alcohol drinkers
- 10q23 (PLCE1, C20orf54)
- 5q31.2 (TMEM173)
- 17p13.1 (ATP1B2).

Squamous cell carcinoma

- Generally occur in middle-third of esophagous
- May either be polypoid or exophytic and protrude into esophageal lumen
- May be diffusely infiltrative in submucosa and wall
- May extend to surrounding structures such as aorta, lung, mediastinum, or pericardium
- Lymph node involvement for cancers in the upper-third of the esophagous are cervical;
- For the middle-third of the esophagous, mediastinal, paratracheal, or tracheobronchial;
- For the lower-third of the esophagous, gastric and celiac nodes

Esophageal squamous carcinoma

- Loss of function early change in squamous cancer.
- Transversion G:C to T:A occurred preferentially at known sites of adduct formation on DNA.
- A spectrum of p53 point mutations are present in over half of squamous cell esophageal cancers.
- Mutations common in area that affects adduct formation.

Squamous cell carcinoma

- Other genetic alterations, such as mutations in p16INK4, and amplification of Cyclin D1, C-MYC, and epithelial growth factor receptor (EGFR), are prevalent in these cancers as well.
- Notably rare in esophageal squamous cell carcinomas are KRAS and APC mutations

Treatment strategy for cancer

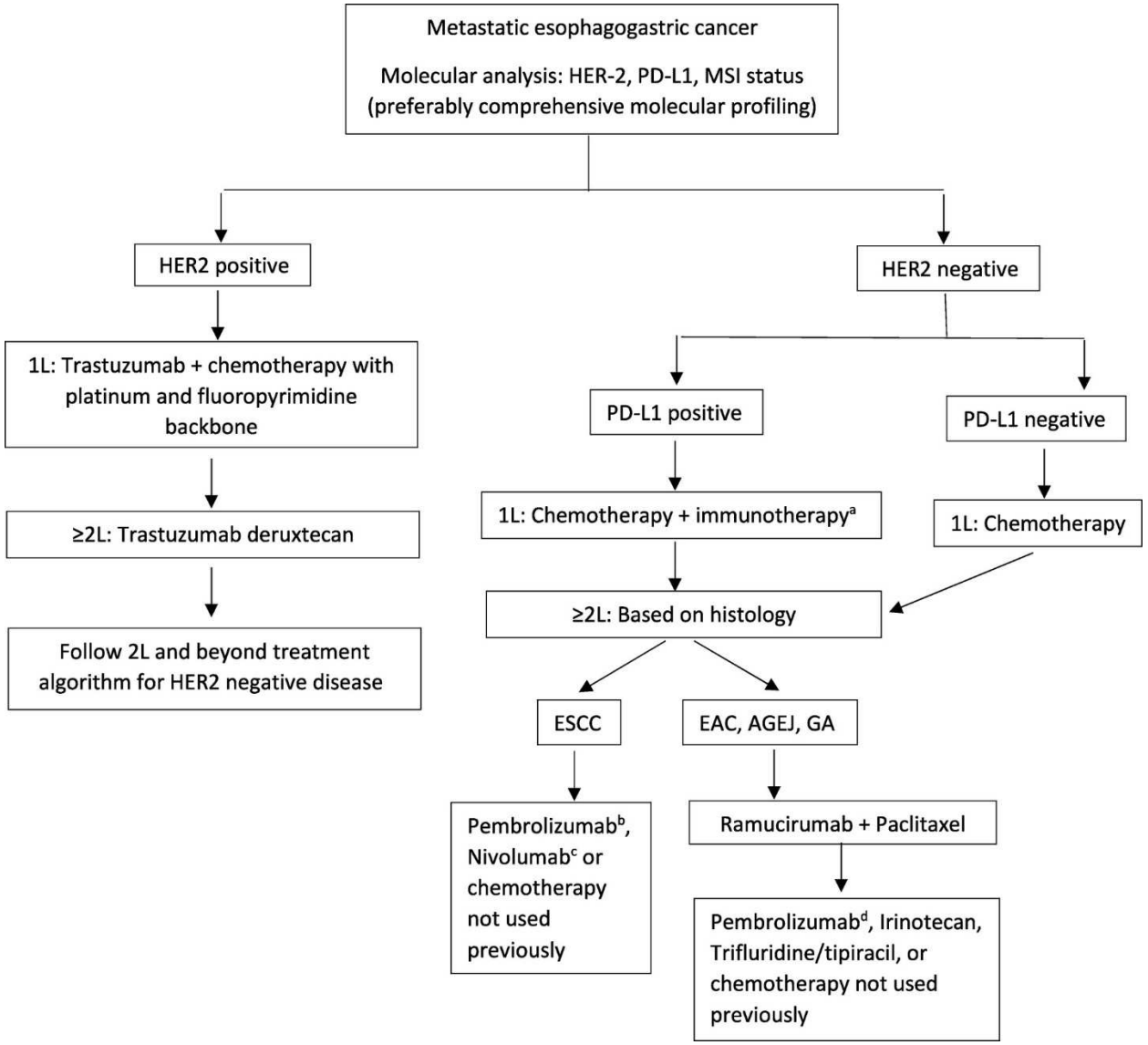
- Endoscopic ultrasound is the optimal technique for local regional staging.
- MRI provides better assessment of vascular structures than does CT.
- Thoracic esophageal tumors above the aortic arch as well as T4 or N1 tumors are not resectable.

Treatment strategy for cancer

- Tis and T1a tumors are potentially curable with endoscopic mucosal resection.
- Stage I and II cancers are treated with en bloc resection of the esophagus and lymphadenectomy of the cervical and superior mediastinum in Japan
- OR
- By transhiatal esophagectomy with cervical anastamosis (avoiding thoracotomy).

Treatment strategy

- Much longer survival (40% vs 27% at 5 years) but much higher morbidity is noted with the Japanese approach.
- Chemotherapy with cisplatin and 5FU and Pembrizolumab (PDL-1 target) is administered as definitive therapy in stage III esophageal cancer, irrespective of HER2 status.
- Trastuzumab induces antibody dependent cellular phagocytosis, allowing uptake of tumor by antigen processing cells. May also be used if HER2+.
- Stents may be placed in advanced lesions.



Mamdani, H, and Jalal, SL, "Where to Start and What to Do Next: The Sequencing of Treatments in Metastatic Esophagogastric Cancer," American Society of Clinical Oncology Educational Book 41 (March 25, 2021) 170-185. DOI: 10.1200/EDBK_321243 Figure 1