Gastrointestinal Pathology
Esophagus and Stomach

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Esophagus

- Anatomy
- Congenital anomalies
- Motor dysfunction
- Esophageal varices
- Inflammatory conditions
- Neoplasms
Anatomy

• between C6 and Th11-12
• Length:
  - 10 cm in the newborn
  - 25 cm in adults
  - by endoscopy: between 15 and 40 cm from the incisor teeth
• Areas of luminal narrowing
  - at the cricoid cartilage
  - at the anterior crossing of the left main bronchus and left atrium
  - at the diaphragm
Anatomy

Mucosa
- squamous epithelium

Submucosa
- glands, vessels, lymphatic vessels
- and follicles, veins!!!

Tunica musc propria

Adventitia

(No serosa)
**ESOPHAGUS**

**Esophagus atresia:** not or only partially developed esophagus

in 90% of cases simultaneous ösophagotracheale Fistule complication: Polyhydramnion (because of intrauterine defect of swallowing)

**Dysphagia lusoria:** abnormally positioned aortic arch or arteria lusoria (atypical a. subcl.)

Compression: stenosis of the esophagus

Dysphagia: disturbed act of swallowing
Physiology of swallowing

Oral Phase

Pharyngeal Phase

A

B

C

Bolus
Tongue
Soft palate
Epiglottis
Esophagus
Physiology of swallowing

Pharyngeal and esophageal phase:

Figure 4 A-E. Pharyngeal phase of swallowing.
Fiberoptical endoscopy investigation of disturbed act of swallowing
Congenital anomalies

- **Ectopic tissues:** gastric, pancreatic
- **Congenital cysts:**
  - duplication cysts in the lower esophagus
- **Diaphragmal hernia:**
  - abdominal viscera in the thorax (not to confuse with hiatal hernia → see later)
- **Atresia:**
  - a segment of the esophagus is a thin cord, the proximal part communicates generally with the upper respiratory tract by a *fistula* - the distal pouch may also be connected to the trachea
- **Mucosal webs:**
  - semicircumferential protrusion of the mucosa into the lumen of the upper esophagus
- **Mucosal rings:**
  - mucosa, submucosa and sometimes hypertrophied muscle protruding into the lumen of the lower esophagus in a concentric fashion (A ring, B or Schatzki ring)
Esophageal atresia and tracheoesophageal fistula
Motor dysfunction associated lesions I.

- **Achalasia**: failure to relax
  - degenerative changes in motor innervation
  - Chagas disease (Treponema cruzi infection)
  - polio, surgery, malignancies, amyloidosis
  - mostly of unknown etiology
  - aperistalsis
  - incomplete relaxation of the LES
    - (lower esophageal sphincter)
  - increased tone of the LES

*Gross*: progressive dilation of the esophagus above LES

*Micr*: inflammation, ulceration, fibrosis

*Sy*: dysphagia in young adult or childhood, nocturnal regurgitation

*Complications*: aspiration, candidiasis
Motor dysfunction associated lesions II.

- **Hiatal hernia**
  - **Axial or sliding** hernia: 95% of the cases
    - protrusion of the stomach above the diaphragm
  - **Paraesophageal or rolling** hernia: a portion of the stomach along the greater curvature enters the thorax

SY: heartburns, regurgitation

**Complications**: associated reflux esophagitis, ulceration, bleeding, perforation,
Motor dysfunction associated lesions III. (congenital disorder)

- **Diverticula**: dilatation
  - **true** - contains all layers of the esophagus
    - Zenker diverticulum (pulsion-craniohypoglossal),
    - Traction
    - Epiphrenic

- **false** - mucosa/submucosa (no muscular layer)

- Complications: diverticulitis, perforation, ulceration, mediastinitis, fistula
Motor dysfunction associated lesions IV. (Lacerations, perforations)

- **Mallory-Weiss syndrome**
  - Longitudinal lacerations and tears at the esophagogastric junction
  - Cause: alcoholism, chronic vomiting, hiatal hernia, reflux
  - Symptoms: hemorrhage, hematemesis, melaena

- **Boerhaave syndrome**
  - Esophageal rupture due to laceration and vomiting
Esophageal varicosity

- in portal hypertension
- cirrhosis (alcoholism)
- ~ rupture → massive hematemesis
- therapy:
  - balloon tamponade and sclerotherapy
Esophageal varices
ESOPHAGUS

Changes of the Lumen:

**Achalasie:** missing opening of the cardiasphincter
Retention of the food, Megaesophagus,
“Wineglassform”
Metaplasia, Karcinoma, Perforation
in South-Amerika: Achalasie might be the complication of Chagas diseases (Myositis - Trypanosoma cruzi).

**Stenosis:** inherited or caused by Tumors, Struma, Sklerodermia. It might come to Megaesophagus

**Diverticles:**

**Varices:**
Cricopharyngeal Achalasia

Figure 16. Radiographic image of cricopharyngeal dysfunction.
Figure 23. Endoscopic (A) and radiographic (B) findings in achalasia.
Figure 11. Esophageal stricture showing obstruction of food bolus with corresponding barium swallow.
Diffuse spasm of the esophagus

Figure 22. Barium swallow x-ray showing diffuse esophageal stricture (A) with corresponding manometric tracing (B).
Motoric Dysfunction associated lesions

- **Hiatus Hernia**
  - *Axial or sliding* herniation: 95% of cases
    - Protrusion of the stomach across diaphragm
  - *Paraesophageal or „rolling”* herniation:
    part of the stomach along major curvature enters thorax.

SYMPTOMS: heartburn, Regurgitation

**Complications**: associated reflux esophagitis,
Ulceration, bleeding,
Perforation: Mediastinitis
Motoric Dysfunction associated lesions

**Diverticles:** inherited or acquired outpouching

real (all layers of the wall) or Pseudodiverticle (mucosa only). Dysphagia, trigger for coughing, Regurgitation

**Pulsionsdiverticle:** inherited or acquired weakness of the wall by increased intraluminal pressure

**Zenker Diverticle:** 70 % of all Esophagusdiverticles-Pseudodiverticle, in upper third

**Epiphrenic Diverticle:** 10 %, Pseudodiverticle

**Tractionsdiverticle:** 20 %, mostly asymptomatic, traction of parabronchial sacs in the heights of bifurcation
• **Diverticle:** Dilation
  - **Real** (all layers of the wall) Zenker Divertikulum (Pulsion-cranio-pharyngeal),
    - Traction
    - Epiphrenic

  - **False** - Mucosa/submucosa only: **Pseudodiverticle** (the mucosa only, no muscle layer)

  – Complications: Diverticulitis, Perforation, Ulceration, Mediastinitis, Fistule
Zenker’s Diverticle

Figure 17. Zenker’s diverticulum (A) with corresponding barium x-ray (B).
Zenker’s Diverticle
Cervical rip disease
Hiatus herniation: content of the abdominal cavity is positioned in the thorax

sliding herniation: Cardia and Fundus, mostly asymptomatic

Paraesophageale Herniation: the position of the Cardia is normal, Regurgitation, Heartburns

Varices:
  inherited: weakness of the wall
  acquired: by portal Hypertension, mostly in the lower third of the Esophagus
Lower esophagus sphincter

- Normally blocks the regurgitation of the gastric juice
- It relaxes by swallowing
- Pressure: 15-30 mmHg

Untere oosphageale Sphincter
http://www.becomehealthynow.com/article/body digestive/727/
GERD

- **Symptoms**
  - Heartburn
  - Regurgitation
  - Nausea
- **Reflux**
  - LES is weak
  - Missing closing ability
    - it remains open

LES mit GERD

(Jackson Gastroenterology, 2004)
Esophagitis

- **Reflux esophagitis** *(Gastroesophageal reflux disease-GERD)*
  - due to a sliding hernia
  - delayed gastric emptying
  SY: dysphagia, heartburn, severe chest pain (mimicking AMI)

**Gross**: hyperemia, ulcerations, stricture
  (depending on severity)

**Micr**: inflammatory cells within squamous epithelium, elongation of lamina propria connective tissue papillae with dilated vessels showing marked congestion
Chemical and physical injury induced esophagitis

- **Causes**
  - alcohol
  - acids, alkalia (suicide)
  - cytotoxic therapy
  - irradiation

**Complications:** ulceration, mucosal necrosis, necrosis of the wall, stricture, fibrosis
Esophagitis of infectious origin

- **Candidiasis**: in antibiotic therapy, immunosuppression

- **Herpes simplex and CMV**: ulcerations with intranuclear inclusions
Fungal micella
• Barrett esophagus
  • with longstanding reflux
  • salmon coloured mucosa above the gastroesophageal junction
  • presence of metaplastic columnar epithelium (goblet cells)-diagnostic criterium (?)
  • long segment Barrett esophagus ($\geq$ 3 cm) or short segment Barrett esophagus (<3 cm)
  • $\sim$→dysplastic epithelium→→adenocarcinoma
...esophagus lined with **columnar epithelium** (rather than the usual squamous epithelium) due to a congenitally shortened esophagus leading to a tubular portion of stomach being trapped in the chest.
3. Definition of Barrett’s esophagus (BE)

In Japan (Japan Esophageal Society) and the UK (British Society of Gastroenterology), BE is defined simply as metaplastic CLE that is recognizable macroscopically.

i.e.; Barrett’s esophagus = CLE

In Germany and the USA, however, BE is defined as the metaplastic replacement of any length of the esophageal epithelium that can be recognized at endoscopy and that is confirmed by biopsy of the tubular esophagus to show intestinal metaplasia, excluding intestinal metaplasia of the gastric cardia.

i.e.; Barrett’s esophagus = CLE + goblet cells


The ingredients for a correct diagnosis of BE

1. **endoscopic** evidence that columnar mucosa extends above the gastroesophageal junction and lines the distal esophagus

2. **biopsy** confirming the presence of columnar intestinal metaplasia
Transverse section of the lower esophagus

Large vessels (100-200 μm in this tissue section, arrows) are evident more frequently in the lamina propria mucosae than in the submucosa in the esophageal lower sphincter.
VELVET MUCOSA ON ENDOSCOPY BECOMES BARRETT'S EPITHELIUM WHEN HISTOLOGY FEATURES COLUMNAR METAPLASIA
Palisade vessels are always seen within the esophagus (De Carvalho. Acta Anat 1966, Hoshihara et al. Gastroenterol Endosc 1986). These vessels are observed in the lower esophageal sphincter. The EGJ is defined endoscopically in Japan as the lower limit of the palisade vessels (by the Japan Esophageal Society 2000, Takubo et al. Esophagus 2003, Arch Pathol Lab Med 2005).

Palisade longitudinal vessels in the columnar-lined esophagus (CLE).
Palisade vessels are seen in both the squamous-lined and columnar-lined esophagus. In this case, a diagnosis of CLE can be made by endoscopy alone.
In Western countries, the definition of the EGJ is the “upper limit of gastric folds”.

Endoscopic appearance of the upper end of the gastric mucosal folds at the EGJ in a patient with Barrett’s esophagus.

The upper limit shows considerable up and down movement, depending on the volume of air in the esophagus.

When a small volume of air is present in the esophagus, the upper end of the mucosal folds (arrows) extends up to or beyond the level of the lower end (arrowheads) of the squamous epithelium.

Native epithelium → Metaplastic changes → Dysplastic lesions → Adenocarcinoma

Multi-step cascades

Oesophagus Barrett
Stomach Correa
BARRETT’S CASCADE

N  BM  LG-IEN  HG-IEN  BAc
Length of Barrett's esophagus and cancer risk: Implications from a population based study

H Pohl, O Pech, H Arash, M Stolte, H Manner, A May, K Kraywinkel, A Sonnenberg, C Ell

<table>
<thead>
<tr>
<th>BM Length at recruitment</th>
<th>Annual Transition to Barrett-Cancer</th>
<th>Patients who would need to undergo EGDS to find one BC/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>Ultra-Short</td>
<td>0.01 %</td>
</tr>
<tr>
<td>24%</td>
<td>Short</td>
<td>0.03 %</td>
</tr>
<tr>
<td>56%</td>
<td>Long</td>
<td>0.22 %</td>
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</tbody>
</table>
Endoscopic surveillance

- No dysplasia
  - Endoscopy every 3-5 yr

- LGD
  - Endoscopy every 6-12 mo or eradication therapy

- HGD
  - Endoscopic eradication therapy

...the clinical impact

P16 loss, MYC gain, and aneuploidy (centromeric probes for CEP7/CEP17, as surrogate marker for DNA ploidy change) measured by FISH (brush cytology) is an independent predictor of progression in non-dysplastic BE.

A prediction model including this Abnormal Marker Count is advantageous over a clinical model using only age and BE length for long-term risk stratification.
Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis.

Only TP53 and SMAD4 mutations occurred in a stage-specific manner, confined to HGD and EAC, respectively.

Weaver JM, et al – Nat Genet 2014
HER2 is overexpressed and amplified in dysplastic lesions

(KW: p < 0.001)

Fassan M, Rugge M et al - Histopathology 2012
Neoplasms

• **Benign tumors:**
  - leiomyomas
  - lipomas
  - fibromas
  - squamous papillomas
  - condyloma
  - inflammatory polyp
Malignant tumors

- Squamous cell carcinoma
- Adenocarcinoma
Squamous cell carcinoma

• over 50 yr, geographical differences
• male predominance
• Etiology:
  - **dietary** (deficiency of vitamin A, C, high nitrite content of water, fungal contaminated food)
  - **lifestyle** (hot beverages and food, alcohol, smoking)
  - **esophageal disease** (long standing esophagitis, achalasia),
  - **genetic predisposition**
• 20% upper third, 50% midportion, 30% lower third
• **Macr:**
  - exophytic
  - excavated (ulcerated)
  - flat
• **Micr:** mostly moderately and well differentiated
  - variants: verrucous, basaloid, spindle cell
• **Metastases:**
  - to regional lymph nodes
• **Local extension:**
  - to mediastinum, respiratory tree, aortic wall
Perforation
Well differentiated squamous cell carcinoma
Grade III.
Adenocarcinoma

- Barrett mucosa associated
- distal esophagus, male predominance
- Symptomes:
  - difficulty in swallowing, bleeding, vomiting, pain, weight loss
- Gross:
  - flat patches, sometimes large nodular masses
- Micr:
  - intestinal type adenocarcinoma (in majority)
- poor prognosis
esophagus

stomach
Adenocarcinoma

Barrett metaplasia
TNM classification

T1 Lamina propria, submucosa, „early”

T2 Muscularis propria

T3 Adventitia

T4 surrounding tissues

N1 regional lymph nodes

M1 distant metastases
**Primary tumor (T)**
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor invades lamina propria or submucosa
- T2: Tumor invades muscularis propria
- T3: Tumor invades adventitia
- T4: Tumor invades adjacent structures

**Regional lymph nodes (N)**
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

**Distant metastasis (M)**
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
  - Tumors of the lower thoracic esophagus:
    - M1a: Metastasis in celiac lymph nodes
    - M1b: Other distant metastasis
  - Tumors of the midthoracic esophagus:
    - M1a: Not applicable
    - M1b: Nonregional lymph nodes and/or other distant metastasis
  - Tumors of the upper thoracic esophagus:
    - M1a: Metastasis in cervical nodes
    - M1b: Other distant metastasis
AJCC stage groupings

**Stage 0**
- Tis, N0, M0

**Stage I**
- T1, N0, M0

**Stage IIA**
- T2, N0, M0
- T3, N0, M0

**Stage IIB**
- T1, N1, M0
- T2, N1, M0

**Stage III**
- T3, N1, M0
- T4, any N, M0

**Stage IV**
- Any T, any N, M1

**Stage IVA**
- Any T, any N, M1a

**Stage IVB**
- Any T, any N, M1b
Pathological determinants of survival in node negative esophageal cancer

219 N0 Plattenepithelkarzinom oder Adenokarzinom Ösophagustumoren, Untersuchte Faktoren: Alter, Geschlecht, Histologie, Resketionsoberfläche, Stádium, Grade, vaskulare und perineuralissche Invasion, Barett Metaplasie – Überleben.

Ein parametrische und mehrparametrische Analyse:

Schlechte Prognose war mit höheren T Stadium, mit Adenokarzinom Diagnose und niedrige Differentiation (höheres Grade)

TNM allein kann die Prognose nicht pünktlich voraussagen.
Esophageal carcinoma: Prognostic differences between squamous cell carcinoma and adenocarcinoma

742 kurative OP in 20 Jahren.


5 Jahre Überleben nach R0 Resektion in Plattenepithelkarzinom Patienten war 46%, sofern in Adenokarzinom Patienten 45%.

5 Jahre Überleben der T1 N0 oder Stadium I Adenokarzinom Patienten war in Adenokarzinom Patienten signifikant besser.
Gastrointestinal stromal tumor
STOMACH
Histology I.

- **foveolar compartment**
  - uniform in the whole stomach
  - consists of foveolar epithelial cells lining the surface and pits

- **glandular compartment**
  - major differences in composition:
    - cardia glands
    - fundic glands (oxyntic or corpus)
    - Pyloric (antral and pyloric) glands
Histology II.

- **Mucous cells**
- **Parietal cells:**
  - oxyphyl (mitochondria)
  - proton pump ($H^+, K^+ - \text{ATP-ase}$)
  - Intrinsic factor
- **Chief cells:**
  - basophilia (RER, prominent Golgi)
  - Pepsinogen I and II production
- **Endocrine cells:**
  - scattered triangular cells with brightly eosinophilic granules
  - $G$ cells, $D$ cells, $X$ cells
Gastric diseases

- Congenital anomalies
- Gastritis
- Peptic Ulcer Disease
- Miscellaneous Conditions
- Neoplasms
Congenital diseases

- Heterotopia: pancreas
- Diaphragmatic hernia
- Congenital hypertrophic pyloric stenosis
  - male predominance
  - Turner sy, trisomy 18, esophagus atresia
  - vomiting, regurgitation in 2-3 weeks old baby
  - palpable mass in the pyloric region
  - Th: surgery (muscle splitting)
**GASTRITIS**

- **ACUTE GASTRITIS**
  - **Etiology**
    - NSAIDs
    - alcohol, smoking
    - cytotoxic drugs
    - stress (surgery, burns, trauma)
    - ischemia, shock
    - uremia
    - systemic bacterial or viral infection
    - distal gastrectomy
Acute gastritis

- **Symptoms:**
  - pain, vomiting, nausea, hematemesis, melaena, severe blood loss

- **Gross:** hyperemia
  - in acute erosive hemorrhagic gastritis
    - **erosions** (mucosal defect not deeper than the muscularis mucosae)

- **Micr:** congestion and edema of the lamina propria
  - neutrophils within surface and glandular epithelium ("activity")
  - in acute erosive hemorrhagic gastritis- surface necrosis with hemorrhage
Acute hemorrhagic erosive gastritis
Chronic gastritis

• Signs of chronic inflammation
  - lymphocytes, plasma cells mainly within the gastric mucosa, potentially leading to atrophy and intestinal metaplasia

• Etiology:
  - *Helicobacter pylori*
  - autoimmune (with pernicious anemia)
  - alcohol, smoking
  - distal gastrectomy
  - uremia
  - Crohn disease
  - irradiation
  - motor dysfunction
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H. pylori

- 1983. *Campylobacter pylori*
- Gram neg rods
- urease production - diagnostic testing!
- Associated with
  - chr. gastritis,
  - peptic ulcer disease,
  - gastric carcinoma,
  - gastric MALT lymphoma
- Antibiotic therapy and proton pump inhibitors
H. pylori

The Nobel Prize in Physiology or Medicine 2005 was awarded jointly to Barry J. Marshall and J. Robin Warren “for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease”
H. Pylori by immunohistochemistry

H.pylori-Giemsa
Importance of fixation—Helico FISH

Overfixed

Properly fixed
Autoimmune gastritis

• 10% of chronic gastritis
• diffuse damage of corpus, antral inflammation less pronounced
• autoantibodies to parietal cells → gland destruction → mucosal atrophy → loss of acid production and intrinsic factor production leading to pernicious anemia
• associated with other autoimmune diseases (Hashimoto thyreoiditis, Addison disease, DM type I)
• increased risk of gastric cancer and carcinoid development
Thank you for Your Attention !!!

“Mr. Osborne, may I be excused? My brain is full.”