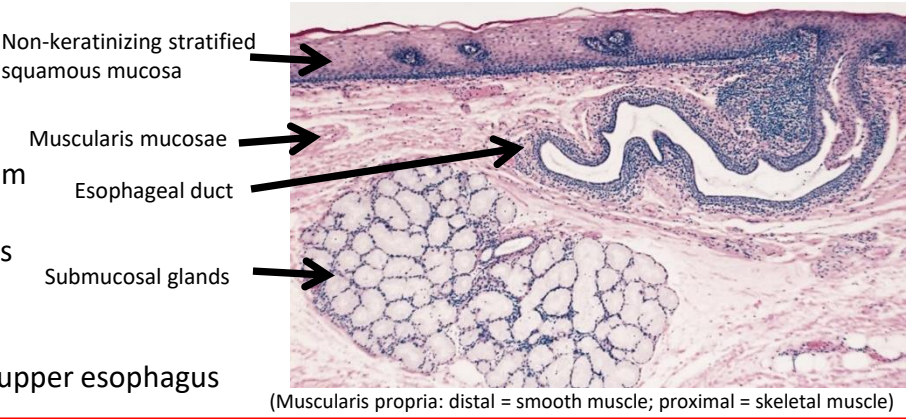# Esophagus Tumors

Normal

Benign Incidental Findings:

Pancreatic Heterotopia/Metaplasia

"Multilayered Epithelium"– Epithelium at transition between squamous and glandular mucosa with some features of BOTH. Looks like squamous metaplasia of the cervix.

Inlet Patch—Stomach epithelium in upper esophagus

Non-keratinizing stratified squamous mucosa

Muscularis mucosae

Esophageal duct

Submucosal glands

(Muscularis propria: distal = smooth muscle; proximal = skeletal muscle)

Glandular Lesions

Complete **Intestinal Metaplasia** Exact duplicate of intestinal mucosa with <u>absorptive cells</u> between goblet cells. Usually seen in stomach.

Incomplete **Intestinal Metaplasia** Goblet cells with intervening <u>foveolar cells</u>. More common at <u>GEJ.</u> Higher risk for dysplasia

Complete IM

"Barrett's Esophagus":

British (and Japanese) Columnar epithelium (regardless of goblet cells!) extending ≥1 cm above the gastric folds

AGA 2011 Columnar epithelium with goblet cells in the esophagus (No length requirement)

ACG 2016 Columnar epithelium with goblet cells extending ≥1 cm above the gastric folds

Incomplete IM

Risk factors: GERD, Obesity, Male gender, Smoking, H. pylori
Pathogenesis: Acid/Bile reflux→ Intestinal metaplasia → Mutations → Low-grade dysplasia → TP53 mutation → High-grade Dysplasia → DNA/Chromosomal instability → Cancer

Negative for Dysplasia　　*Should be most common Dx by far!*
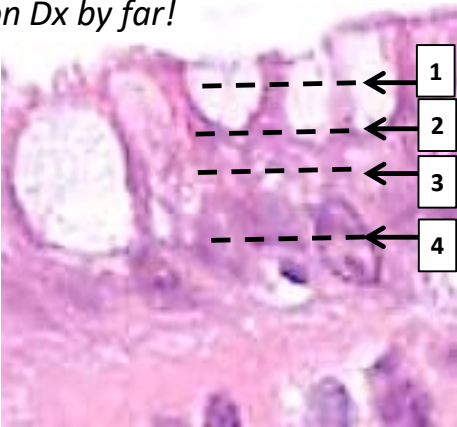
Surface maturation

"The Four Lines" (shows <u>preserved cell polarity</u>)
1- Apical mucin cap
2- Base of mucin cap
3- Cytoplasm (between mucin and nucleus)
4- Row of nuclei (maintained nuclear polarity)

"Wild-type" p53 staining

Management: Follow-up in 3-5 yrs

1
2
3
4

Indefinite for Dysplasia　*Used in cases where it is <u>unclear</u> if there is true dysplasia*

Often obscuring inflammation or partial maturation. Could consider getting p53 IHC.
Management: Treat for reflux (hoping things calm down) and repeat biopsy in 3-6 months

Low-Grade Dysplasia

Adenoma-like (Truly dysplastic appearing)
  (in typical "<u>intestinal type</u>")
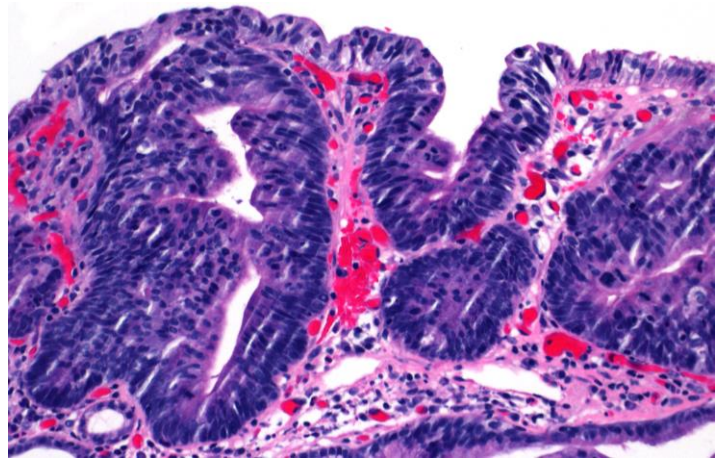Penicillate, hyperchromatic nuclei

Extends to <u>surface</u> epithelium
Often **abrupt transition** from reactive to neoplastic
Loss of "the 4 lines," but retained basal nuclei
Hyperchromatic nuclei

Management: Mucosal ablation

High-Grade Dysplasia

Nuclear Hyperchromasia and pleomorphism
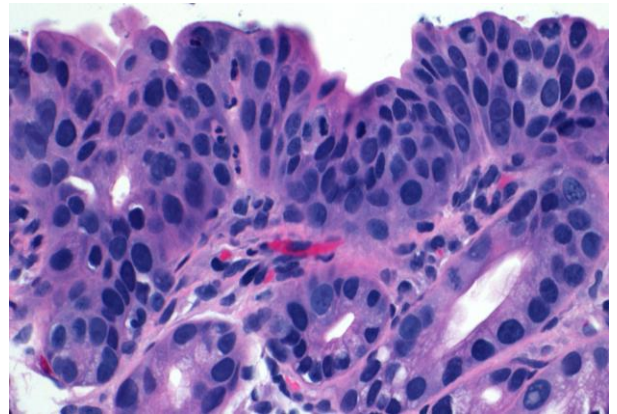<u>Loss of cell and nuclear polarity</u>
No surface maturation
Rounded, irregular nuclei
Complex architecture

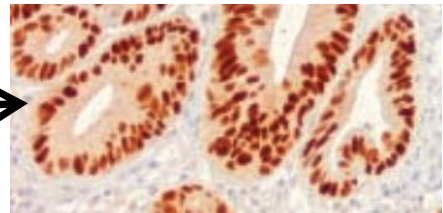**Management:** Mucosal ablation if flat
EMR if mucosal irregularity (to rule out carcinoma)

P53 IHC:
Considered indicative of dysplasia/neoplasia if:
1) Overexpressed (every nucleus, strong) or
2) "Null" phenotype (tumor cells all negative)

Other types of Glandular Dysplasia *(other than "Intestinal")*

Foveolar Type
  Few, if any, goblet cells (may arise independently)
  <u>Prominent cytoplasmic mucin</u>
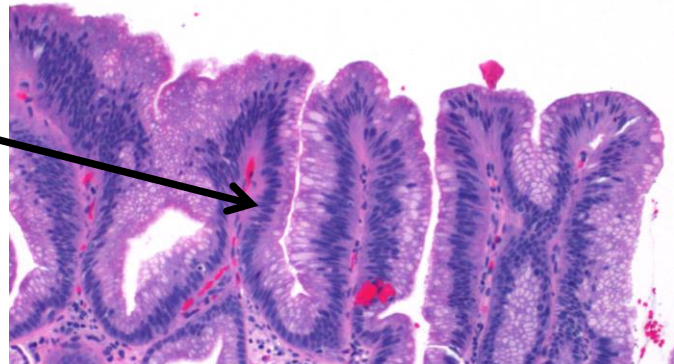 <u>Hyperchromatic</u>, slightly enlarged nuclei
  Possible pseudo-stratification

Basal Crypt Dysplasia
   Dysplasia at the <u>base of the crypt</u> that <u>matures</u> at the surface

Small Cell Pattern
   Proliferation of numerous tiny, monotonous glands with loss of polarity and nuclear hyperchromasia

Adenocarcinoma

Nearly all occur near GE junction due to Barrett's esophagus.
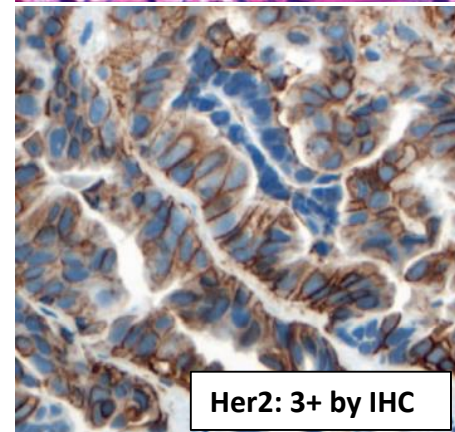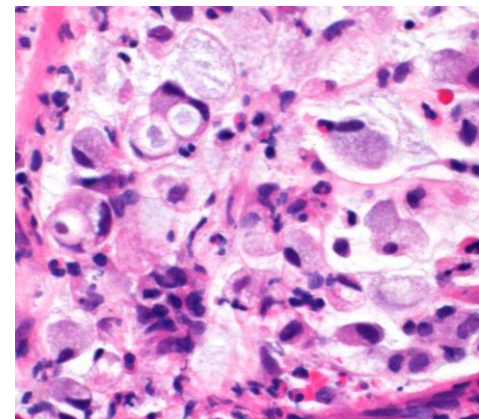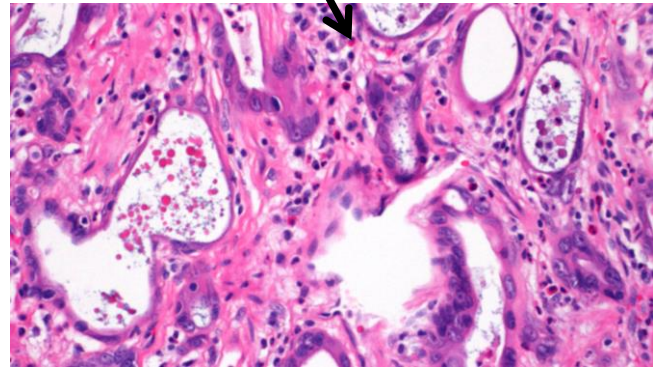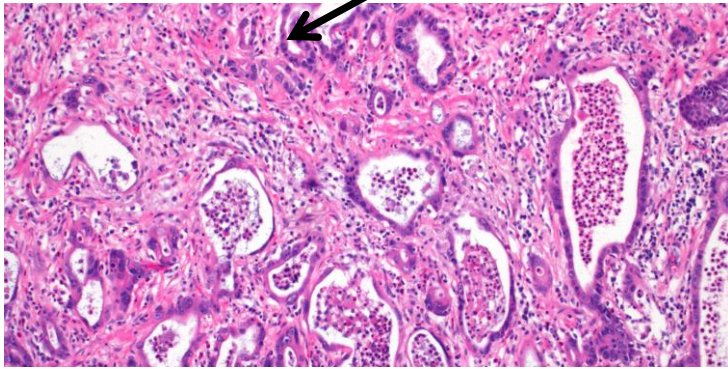
Often present with dysphagia

Invasion across the basement membrane
→ **Lamina propria overrun by glands**
→ May see single infiltrating cells, or expansively growing glands without intervening lamina propria

Features associated with <u>EARLY</u> invasion: Luminal necrosis, Prominent nucleoli, glands growing parallel to the surface.

Features associated with <u>DEEP</u> invasion: Angulated glands, Prominent desmoplasia (at least into submucosa likely), Pagetoid spread of malignant cells in squamous epithelium.

Her2: 3+ by IHC

Classification: Shows a mixed gastric/intestinal lineage.

<u>Patterns of growth</u>: Tubular (most common, see above), papillary, mucinous, and signet-ring cell patterns (worse prognosis, see figure to the left ←). Often a mixture of patterns is seen.

Staging Challenges: Often in Barrett's esophagus the muscularis mucosae can be **duplicated** and/or distorted, which can make determining the depth of invasion challenging, particularly on EMR.
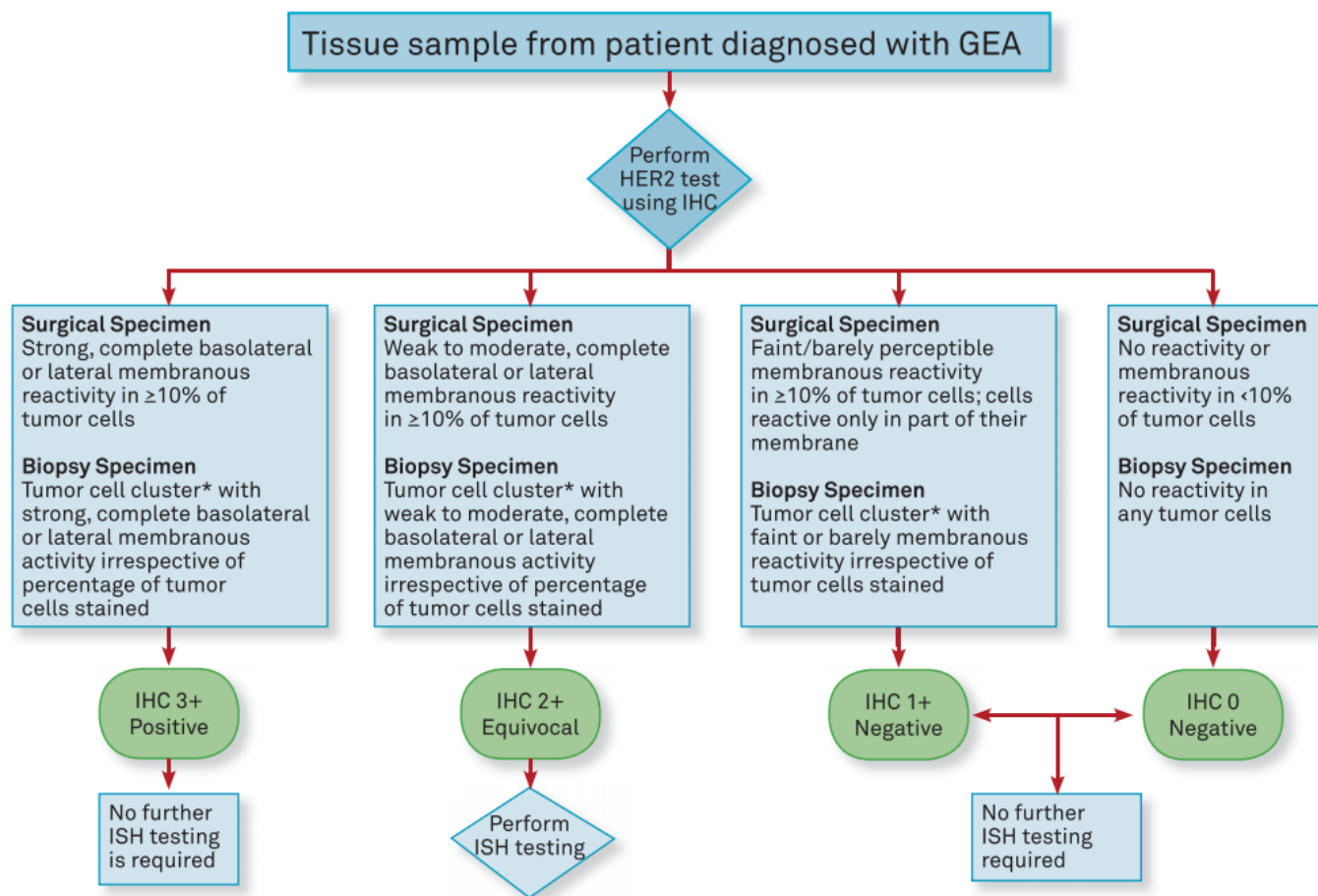
HER2: If amplified → approved for treatment with Trastuzumab First, start with IHC, if equivocal (2+), then do FISH
(See next page for full grading and algorithm)

Management: If seems low stage clinically (i.e., just intramucosal) → EMR & Ablation

If advanced stage (Into the submucosa, or more) → Esophagectomy (if not too advanced), possibly after chemo and radiation.

May be hard to distinguish Adenocarcinoma from SCC, requiring stains. **Undifferentiated carcinoma** should be considered if the IHC pattern is equivocal or if there are no definite morphologic features

Adenocarcinoma	Squamous cell carcinoma
CK7+	CK7- (usually)
p63, p40, CK5/6 -	p63, p40, CK5/6 +
PAS/mucin stain +	PAS/mucin stain -

Figure 2. Algorithm for pathologists. *Tumor cell cluster is defined as a cluster of 5 or more tumor cells. Additional recommendations: Pathologists should ensure that biopsy or resection specimens used for HER2 testing are rapidly placed in fixative, ideally within 1 hour (cold ischemic time) and are fixed in 10% neutral buffered formalin for 6 to 72 hours. Routine histology processing and HER2 testing should be performed according to analytically validated protocols. Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in the GEA specimen for subsequent scoring when ISH is required. Abbreviations: GEA, gastroesophageal adenocarcinoma; IHC, immunohistochemistry; ISH, in situ hybridization.

Table 4. Scoring Guidelines for Interpretation of HER2 IHC in Gastric Carcinoma[a]

Surgical Specimen–Staining Pattern	Biopsy Specimen–Staining Pattern	Score	HER2 Expression Assessment
No reactivity or membranous reactivity in <10% of tumor cells	No reactivity or no membranous reactivity in any tumor cell	0	Negative
Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster[b] with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	1+	Negative
Weak to moderate, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster[b] with a weak to moderate, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	2+	Equivocal
Strong, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster[b] with a strong, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	3+	Positive

Abbreviation: IHC, immunohistochemistry.

[a] Reprinted with permission from Hofmann et al.[13]

[b] Tumor cell cluster (≥5 neoplastic cells).

From: Bartley et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma. Arch Pathol Lab Med—Vol 140, December 2016

Squamous Lesions

Squamous Papilloma

Papillary **proliferation of squamous epithelium** with **fibrovascular core** of lamina propria. **Benign**.

May contain koilocytes, but more dysplasia is rare.
Usually exophytic, but can be flat or endophytic.

Result from mucosal irritation stimulating a hyperregenerative response. Common irritations include: **HPV**, GERD, trauma, etc..
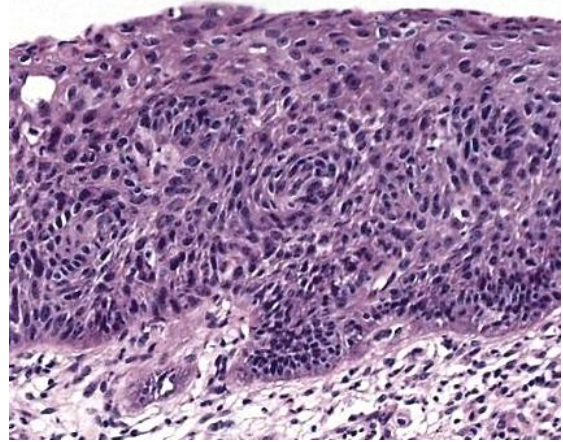
Squamous Dysplasia

Cytologic atypia: Nuclear enlargement, pleomorphism, hyperchromasia, loss of polarity, and nuclear overlap.

Architectural Atypia: Abnormal maturation

Low-grade dysplasia: Involvement of the lower ½ of the epithelium only, with mild atypia

High-grade dysplasia: Involvement of more than ½ of the epithelium OR severe cytologic atypia

Squamous Cell Carcinoma

Malignant epithelial neoplasm showing squamous differentiation With keratinocyte-type cells with **intercellular bridges and/or keratinization**

Risk factors: Tobacco, Alcohol, very hot beverages, achalasia, caustic ingestion, etc.. Most prevalent in Asia

HPV is thought to NOT contribute significantly. Although it is present in many cases, it not integrated or transcriptionally active.

Often presents with dysphagia.
Genetics: Complex cytogenetics, frequent TP53 mutations

Subtypes: **Verrucous**—often in setting of chronic irritation, exceedingly well-differentiated with minimal atypia, papillary surface, broad pushing invasion with associated inflammation

Spindle cell—polypoid growth with high-grade spindle cell component.

Basaloid—Solid or nested growth of basaloid cells. No HPV association (unlike basaloid SCC in oropharynx)