Last updated: 6/1/2024

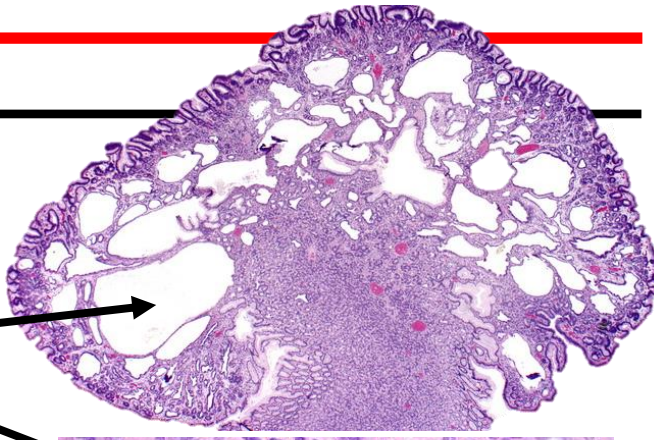
(Note: Mesenchymal tumors are discussed separately)

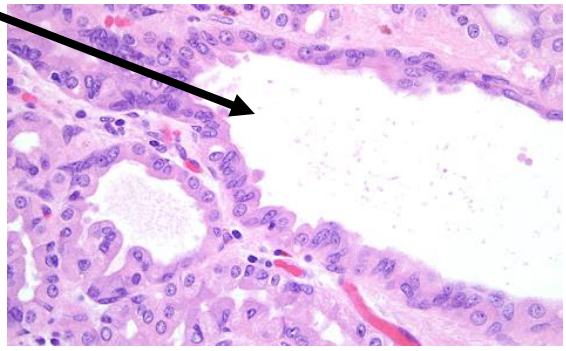
Prepared by Kurt Schaberg

Stomach Tumors

Polyps/Dysplastic lesions

Fundic Gland Polyps





Benign. Most common stomach polyp.

Hyperplastic expansion of deep oxyntic mucosa with cystically dilated oxyntic glands and foveolar hypoplasia.
Parietal cell hyperplasia

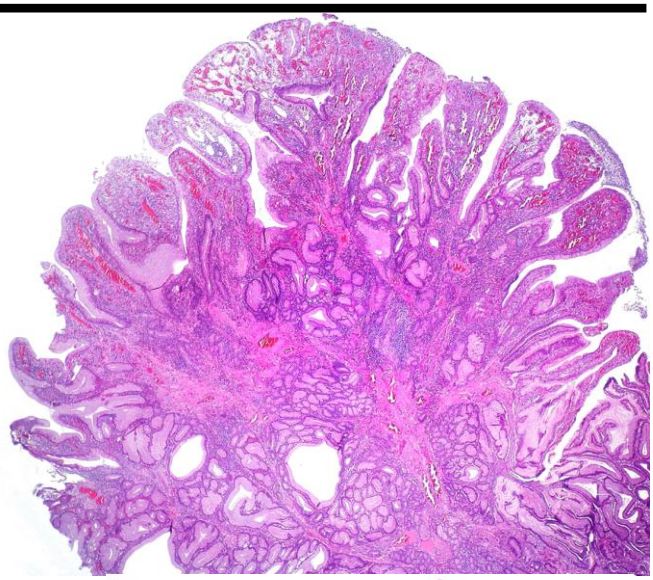
Usually asymptomatic and incidental.
Associated with PPI use (resemble PPI change)
Body/fundus (where oxyntic mucosa is).

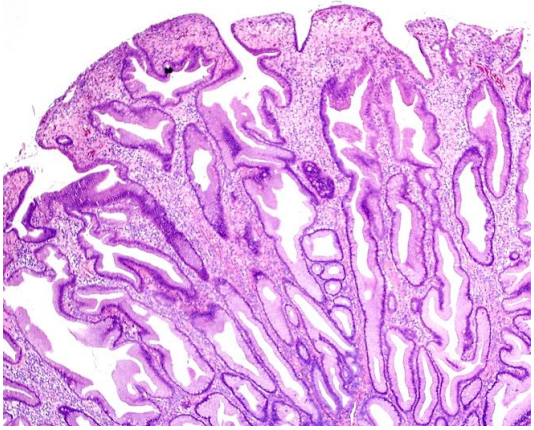
Can have CTNNB1 (β-catenin) mutations

If numerous (esp. >20) in a young patient, consider a polyposis syndrome, such as FAP or GAPP.

Sporadic polyps→ no surveillance necessary
FAP-associated→ frequent dysplasia, usually low-grade; malignant transformation is rare→ surveil (no gastrectomy)

Hyperplastic Polyps





Benign. Second most common gastric polyp

Elongated, tortuous, **hyperplastic foveolar epithelium.**
Cystically dilated glands.
Inflammatory changes and edema.
Often eroded at surface.
Small, haphazardly distributed smooth muscle.

Hyperproliferative response to tissue injury.
Usually arise in setting of long-standing gastritis.
Resembles reactive (chemical) gastropathy.
Precursor lesion = polypoid foveolar hyperplasia.
Most common in Antrum.

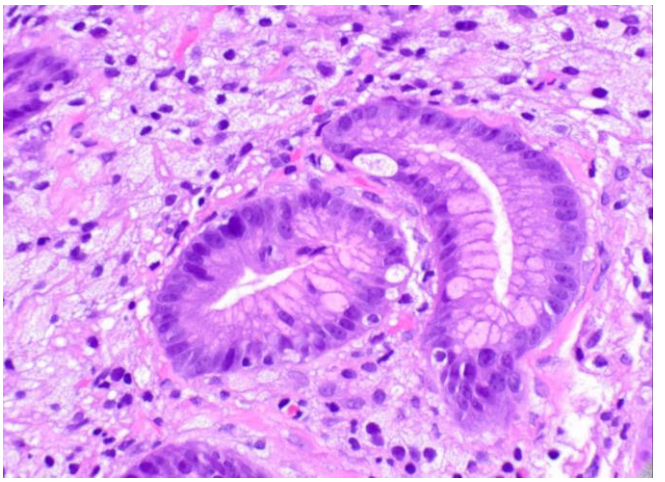
Risk of transformation/dysplasia is proportional to size, so often remove large ones

Hard to differentiate from hamartomatous polyps (see GI tumor syndrome notes)

If diffuse change involving whole stomach → consider Ménétrier's Disease

If there is a cystic dilation of glands extending into the submucosa→ consider Gastritis cystica profunda

Gastric Xanthoma

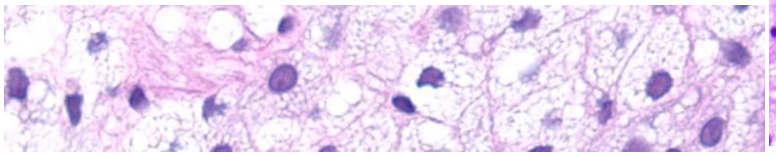


Non-neoplastic. Incidental finding.

Foamy lipid-laden histiocytes expanding lamina propria. Endoscopically **yellow/white nodule** or plaque.

Limited associated acute and chronic inflammation. Minimal disarray. No atypia or mitoses.

IHC: (+) CD68; (-) CK

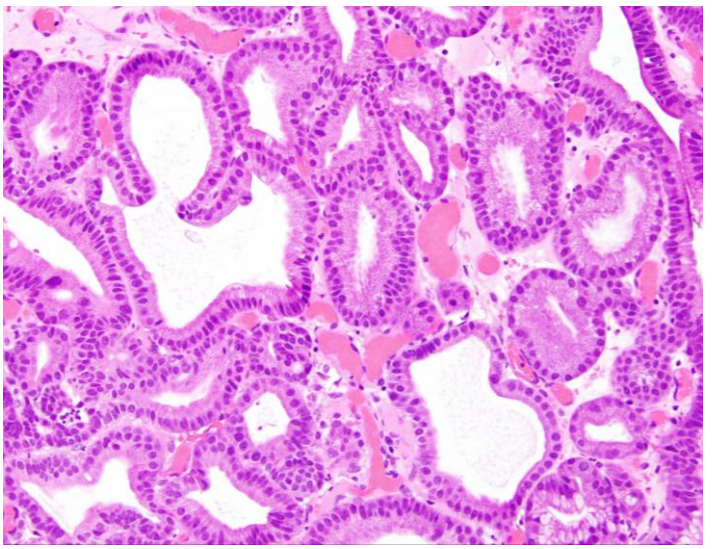


Important DDX: *(that you really don't want to miss!)*
Poorly-cohesive carcinoma: Look for destructive growth, atypia, and signet ring cells. Cytokeratin IHC +, PAS-d positive mucin.

Whipple disease: History of diarrhea and malabsorption, CNS symptoms. Foamy macrophages in small bowel too. PASd positive in histiocytes. Positive PCR for *Tropheryma whipplei.*

MAI infection: Immunosuppressed. AFB/FITE highlights organisms.

Pyloric gland adenoma



Polypoid proliferation of **pyloric-type gastric gland**s (cuboidal to columnar cells with foamy, ground-glass cytoplasm) and no well-formed apical mucin cap. Often dilated glands. Basal round nuclei.

Usually older individuals with **atrophic/metaplastic autoimmune gastritis** and/or *H. pylori*

Sometimes syndromic (e.g., FAP, GAPPs, etc…)

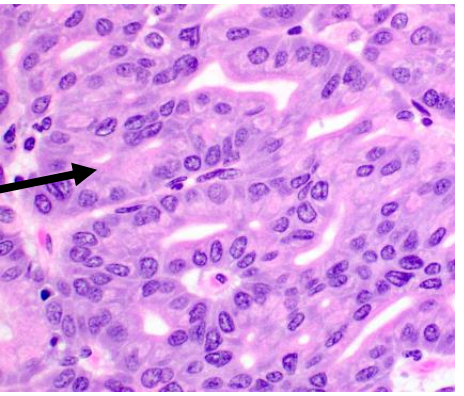
Activating GNAS and/or KRAS mutations and inactivating APC mutations.

Can develop high-grade dysplasia → carcinoma

Stain with MUC6

Rarer Polyps

Essentially, remember that every cell type can develop into a polyp. Intestinal are the most common adenoma, but if it looks different/weird, consider one of the "special" ones like pyloric, foveolar, or oxyntic.



Foveolar-type adenoma: Similar to foveolar dysplasia (discussed below), but localized, polypoid lesion. Usually syndrome-associated (FAP or GAPPs), with no background of inflammation (unlike intestinal-type adenomas). Low rate of progression.

Oxyntic gland adenoma: Neoplasm composed of columnar cells with mainly chief cell differentiation (pale basophilic cytoplasm) with mild nuclear atypia, mimicking oxyntic glands. High rate of progression to invasive adenocarcinoma.

Dysplasia *(Intraepithelial Neoplasia)*

Neoplastic change of gastric epithelium without stromal invasion.

Can be gastric/foveolar or intestinal-type (or mixed):
Intestinal-type dysplasia: looks like a colonic adenoma with tall columnar cells with hyperchromatic elongate ("cigar-shaped") nuclei. May see goblet cells or endocrine cells.

Gastric/Foveolar-type dysplasia: has tubulovillous or serrated fronds lined by cuboidal to columnar cells resembling gastric foveolar cells. Nuclei are round to oval. There is apical neutral mucin.

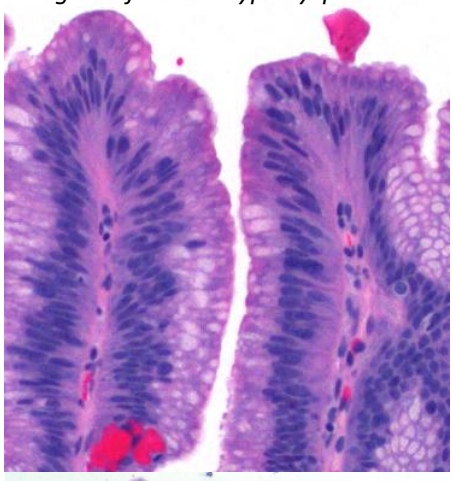
Rarely, can see serrated or pit/crypt dysplasia.

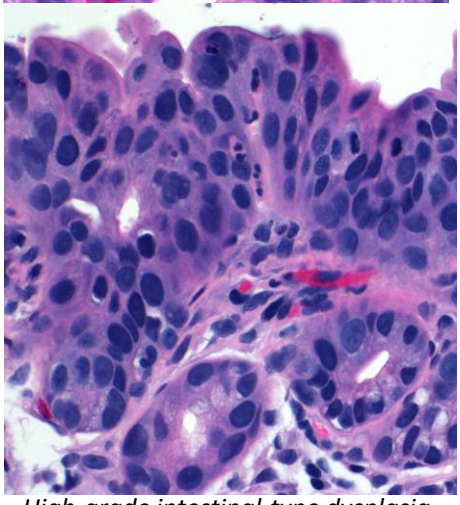
Regardless of type, graded as high vs low:
Low-grade dysplasia: preserved polarization (basal nuclei), relatively preserved architecture. Only mild to moderate atypia.

High-grade dysplasia: Prominent cytologic atypia with enlarged nuclei, high N:C ratios, sometimes prominent nucleoli. Loss of polarity. Complex architecture. Frequent p53 overexpression by IHC.

Indefinite for dysplasia: Not a biologic entity. Used when there are questions as to if a lesion is neoplastic or reactive. Often very inflamed. Often managed by "treat and repeat" (treat inflammation and repeat scope & biopsy).

Low-grade foveolar-type dysplasia





High-grade intestinal-type dysplasia

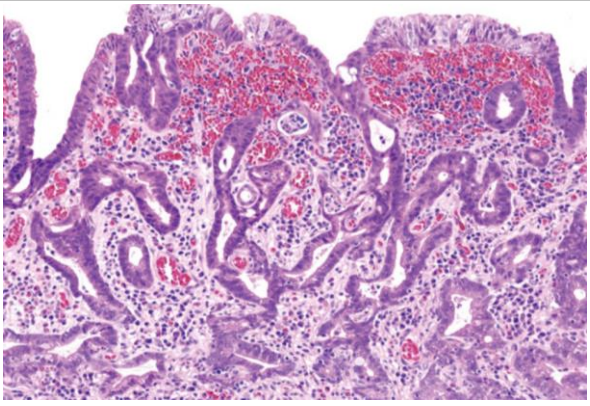
Intramucosal adenocarcinoma

Invasion into lamina propria

Characterized by gland crowding, excessive branching/anastomosing, and budding "spiky" growth. Irrespective of desmoplasia.

Can see: Single cell infiltration, trabecular growth, intraglandular necrotic debris, and irregular gland fusion.

Can treat endoscopically potentially.



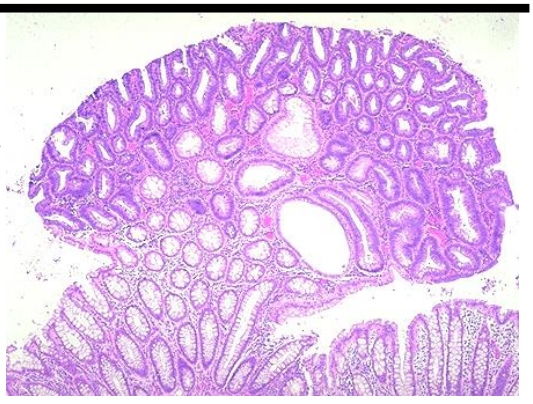
Intestinal-type Adenoma

Localized, polypoid lesion (whereas dysplasia can be flat and multifocal/non-localized) with dysplastic intestinalized epithelium.

Third-most common type of gastric polyp.

Any cause of gastric intestinalization is a risk factor (e.g., H. pylori, autoimmune gastritis, etc…)

Look **similar to colorectal adenomas** and have similar genetics.



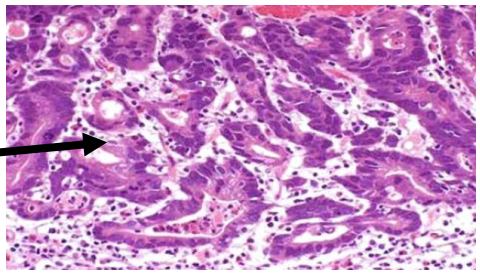
Malignant Tumors

Gastric Adenocarcinoma

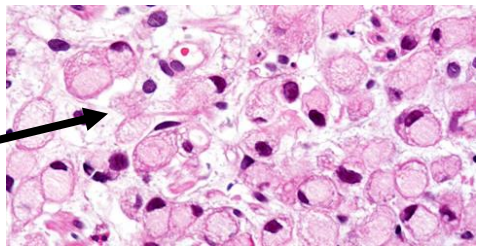
Malignant epithelial neoplasm with invasion of lamina propria (or beyond) by neoplastic glandular cells.

Risk factors:
H. pylori—very strong risk factor. Chronic infection→ chronic inflammation → intestinal metaplasia → dysplasia → carcinoma.
Also—**smoking**, EBV-infection, and dietary factors

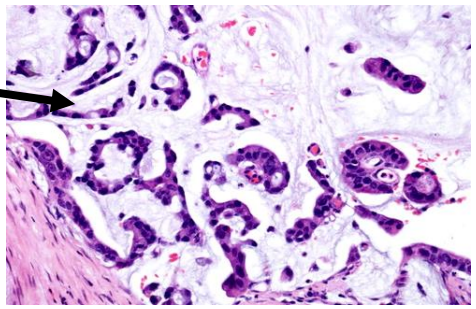
Morphological subtypes:



Tubular—Most common subtype. Branching tubules of variable diameter. Solid growth with barely recognized tubules is included in this group.

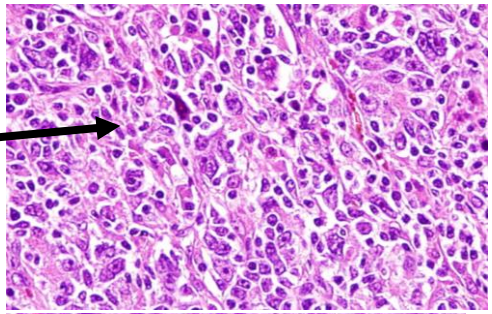


Poorly cohesive (including signet ring)—Second most common. Neoplastic cells are isolated or arranged in small aggregates without well-formed glands. Can be signet-ring cells, histiocytoid, etc… Signet-ring cell type is composed predominantly or exclusively of signet ring cells, which are characterized by a central, optically clear, globoid droplet of cytoplasmic mucin with an eccentric nucleus.

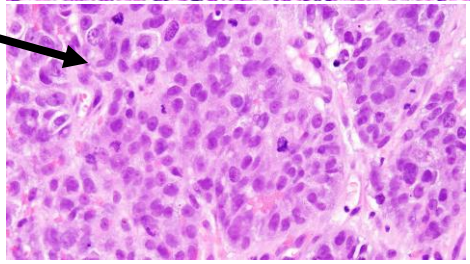


Mucinous—malignant epithelium in extracellular mucin pools. Must be >50% of tumor. Tumor cells may be in glands or single cells.

Papillary—Relatively rare. Exophytic growth with elongated finger-like processes lined by cuboidal to columnar cells supported by fibrovascular cores. Well-differentiated with pushing invasion, but nevertheless has a worse prognosis.



Gastric (adeno)carcinoma with lymphoid stroma—(aka "lymphoepithelial-like carcinoma" or "medullary carcinoma") Syncytial growth of irregular sheets and tubules of polygonal tumor cells with rich lymphocytic infiltrate. Often EBV-associated. A separate subset are MMR-deficient (so get EBV ISH and MMR IHC on any case you are considering for this).



Hepatoid carcinoma—resemble liver (large polygonal eosinophilic cells). May stain with Hepar-1 and/or AFP. Usually Arginase-1 negative.

Micropapillary adenocarcinoma—small clusters of tumor cells without fibrovascular cores protruding into clear spaces. Worse prognosis (like micropapillary carcinomas in other organs).

Fundic-gland type—develop from oxyntic gland adenomas. Very rare!

Mixed—contain two or more subtypes. Often worse prognosis.

Molecular subtypes of Gastric Cancer

Chromosomally unstable: Most common subtype. Predominantly intestinal type morphology with extensive DNA copy number variations. Frequent TP53 mutations. Often older men in the setting of intestinal metaplasia. Helicobacter association. Frequent HER2 amplifications. Frequent LN metastasis. (~50% of stomach cancers)

Genomically stable: Predominantly diffuse (signet-ring) morphology. Fewer genetic alterations. Frequent CDH1 and RHOA alterations/mutations. Younger patients with rapid progression and worse prognosis. (~30%)

Microsatellite instability (MSI): Mutations or promoter methylation of mismatch repair enzymes (often MLH1). Better prognosis. Diverse histology (intestinal, lymphoid stroma, mucinous). (~15%)

EBV-positive: Usually histologically gastric carcinoma with lymphoid stroma. PIK3CA and ARID1A mutations. Often PD-L1 amplified. Better prognosis. (~5%)

Grading & Staging

Grading: Primarily for tubular and papillary types. Use binary system.
Low-grade: well-formed glands (well to moderately-differentiated)
High-grade: poorly-formed glands, solid growth, or individual cells (poorly differentiated)

Staging: Tumors with an epicenter within 2 cm of the GE junction should be staged as *esophageal* cancers. All tumors in the stomach that do not cross the GE junction (or have an epicenter in the stomach >2 cm from the GE junction) should be staged as gastric

Stage	Finding
Tis	Carcinoma in situ = High-grade dysplasia
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosae
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa
T4a	Tumor perforates serosa
T4b	Tumor invades adjacent structures

Predictive biomarkers

Anti-**HER2 (ERBB2)** therapy is used in patients with unresectable or metastatic tumors. (see esophageal guide for grading scheme)

EBV and MSI: tumors that are EBV-positive or MSI-high are better prognosis and can often be treated with PD-L1 inhibitors.

Some institutions do all of the following on all new gastric carcinoma cases:
HER2, EBV ISH, MMR, PD-L1

Well-Differentiated Neuroendocrine Tumors *"NET"*

Proliferation of cells with round nuclei, "salt and pepper" (speckled) chromatin and abundant eosinophilic cytoplasm, arranged in nests, acini, trabeculae, and ribbons. (Old name = "carcinoid")

Express neuroendocrine (NE) markers: Synaptophysin, Chromogranin, INSM1

3 main clinical settings/types (see chart below):

Type 1: Associated with autoimmune gastritis→ destruction of parietal cells→ decreased stomach acid → compensatory hyperplasia of antral G-cells (to try to signal to make more acid)→ secrete gastrin → ECL cell hyperplasia and NET formation

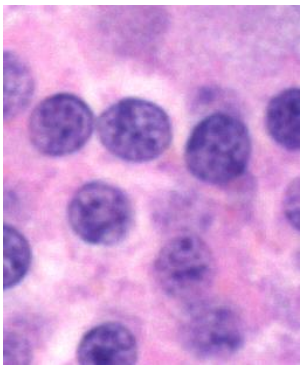
Type 2: Zollinger-Ellison syndrome with a duodenal or pancreatic gastrin-secreting NET, which stimulates ECL cell hyperplasia and stomach NET formation

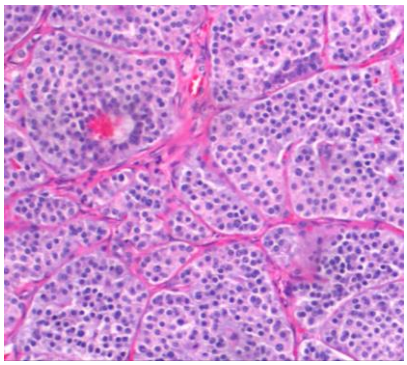
Type 3: Sporadic, often higher stage and more aggressive.

Size Requirements: (this can vary a little by source, but generally…)
NE cell **hyperplasia**: collections of >5 NE cells. Can be linear (chain) or micronodular (clusters), <0.15mm
NE cell **dysplasia**: nodules > 0.15 mm, fused nodules, or infiltrative nodules (pTis)
Micro-NET: cellular proliferation filling lamina propria. Nodule >0.15mm, but < 0.5mm (pTis)
NET: >0.5mm or invasion into submucosa

Grading: Ki67 Proliferation index based on evaluation of ≥ 500 cells in a "hot spot." Mitotic count based on evaluating 50 Hpfs, but reported per 10 Hpfs.

Grade	Ki67 Proliferation Index	Mitotic index
Grade 1	<3%	<2
Grade 2	3-20%	2-20
Grade 3	>20%	>20



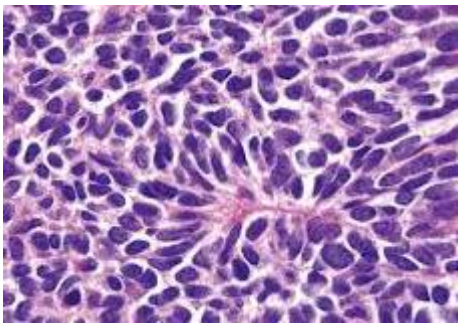


	Type 1	Type 2	Type 3
Cause	Autoimmune gastritis	Zollinger-Ellison syndrome, often MEN1	Sporadic
Focality	Multifocal	Multifocal	Unifocal
Cell of origin	ECL (body/fundus)	ECL (body/fundus)	D,G, ECL, and EC-cells
% of Gastric NET's	~85%	~5%	~10%
Hypergastrinemia	Yes (secondary)	Yes (primary)	No
ECL-cell proliferation	Yes	Yes	No
Acid secretion	Low	High	Normal
Background mucosa	Atrophic gastritis	Parietal cell hyperplasia	Normal
Stage at Dx:	Low (Tx = EMR)	Low (usually)	Often advanced
5-year survival	~100%	~75%	<50%

Neuroendocrine Carcinoma

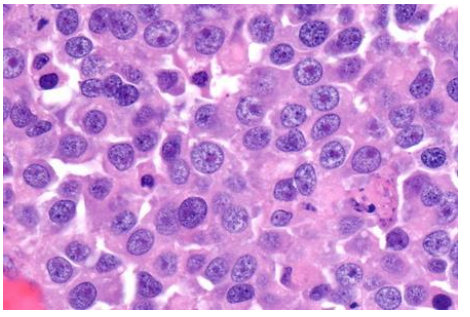
Often arise from non-neuroendocrine tumors (and subsequently *develop* neuroendocrine differentiation.
Sheet-like growth
Not Graded. Ki67/Mitotic index >20% (often much higher).
Malignant! Very metabolically active/**rapidly growing**
→ see on normal FDG-PET scan

Molecular: p53, RB1 (and other carcinoma-associated mutations)
Treatment: Platinum-containing chemotherapy



Small Cell Neuroendocrine Carcinoma

Morphology: Fusiform nuclei, **finely granular chromatin**, **scant cytoplasm**, and nuclear molding. Extensive necrosis.
Tons of mitoses. Ki67 almost 100%.



Large Cell Neuroendocrine Carcinoma

Morphology: Large, round nuclei, with **prominent nucleoli**, and moderate amounts of cytoplasm. Sheet-like to nested growth.
Ki67 often in 60-80% range.

Other Malignancies

Lymphoma

The GI tract is the most common site of extranodal lymphomas and the stomach is the most commonly involved site. The two most common are DLBCL and extranodal marginal zone lymphoma.

Diffuse Large B-Cell Lymphoma (DLBCL)—Diffuse infiltrate of atypical large lymphoid cells that show immunoreactivity to B cell markers (CD20, PAX5, CD19, CD79a) and are negative for EBV. Most cells resemble centroblasts. Tend to localize to one anatomical site and are less aggressive than their nodal counterpart. However, like nodal disease, must still do full work-up to classify as Germinal center (GCB) or Activated B Cell (ABC) subtypes and look for MYC and BCL2 alterations.

Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue ("MALT lymphoma")—Often associated with *H. pylori* infection. Diffuse to perifollicular infiltrate of small centrocyte-like to monocytoid lymphocytes. Positive for B-cell markers (CD20, PAX5). CD43 and MNDA1±. Negative for mantle cell markers (CD5, SOX11, and CyclinD1), CLL/SLL markers (CD5, CD23, LEF1), and Follicular Lymphoma markers (CD10, BCL6). Indolent course. Often cured by eradication *H. pylori.*

Squamous cell carcinoma—carcinoma with exclusively squamous differentiation, with keratinocyte-cells with intercellular bridges and/or keratinization. Very rare.

Adenosquamous carcinoma—carcinoma with both glandular and squamous differentiation (with each at least 25%).

Undifferentiated carcinoma—carcinoma composed of anaplastic cells without histologic or immunophenotypic evidence of differentiation. Diffuse malignant cells. Often patchy keratin. Freqeuent mutations in SWI/SNF pathway (e.g., SMARCB1 or SMARCA4). Dx of exclusion—must rule out lymphoma, melanoma, EBV-associated gastric carcinoma, etc…

Gastroblastoma—Often young men. Biphasic tumor of gastric muscularis propria with spindled cells and nests of epithelial cells. MALAT1-GLI1 gene fusion. IHC: (+)CD56; (+/-) CK, CD10, S100, Cyclin D1