The International Academy of Pathology
Hong Kong Division

HKIAP Scientific Congress 2026

Evolving Gastric Classification of Gastric Dysplasia and Polyps

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Definition of Dysplasia and evidence as a cancer precursor

"Unequivocally neoplastic epithelium that may be associated with or give rise to invasive adenocarcinoma."

40–100%

of early gastric cancers have adjacent high-grade dysplasia

5–80%

of advanced adenocarcinomas have adjacent high-grade dysplasia

- Shares predisposing conditions and many molecular alterations with adenocarcinoma

- Endoscopically detected GED carries **increased gastric cancer risk** on long-term follow-up
- Endoscopic removal of dysplasia **decreases subsequent cancer risk**
- **Two-tier system** (low / high grade) is more reproducible than the obsolete mild / moderate / severe scheme

IT IS NOW A BIT MORE COMPLICATED



PMID 17996792 · 18395075 · 10517922 · 9023391

6th Edition of the WHO Classification of Digestive System Tumours

- Gastric epithelial precursors are divided into several morphologic entities:

1. dysplastic lesions derived predominantly from the surface epithelium.
2. dysplastic lesions are predominantly present below the surface epithelium

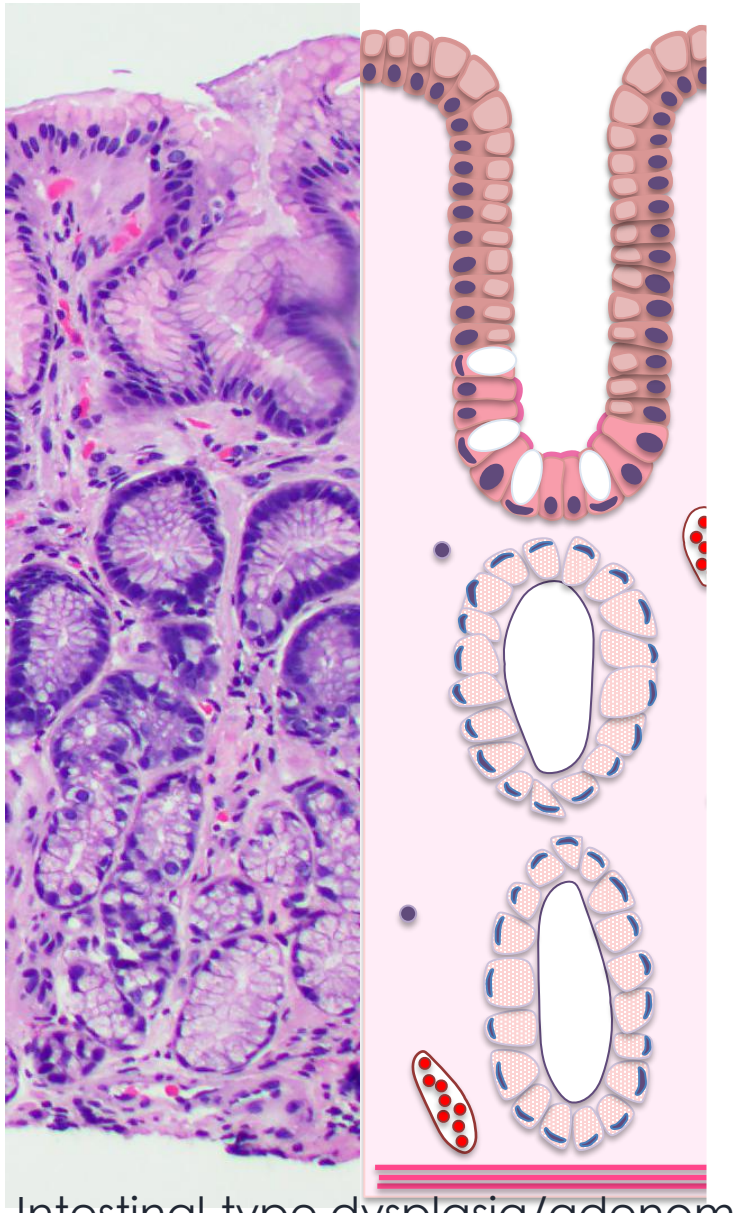
In this talk, the terms "dysplasia" and "adenoma" will be used interchangeably

A NEW LOOK AT GASTRIC DYSPLASIA

SURFACE EPITHELIUM-DERIVED

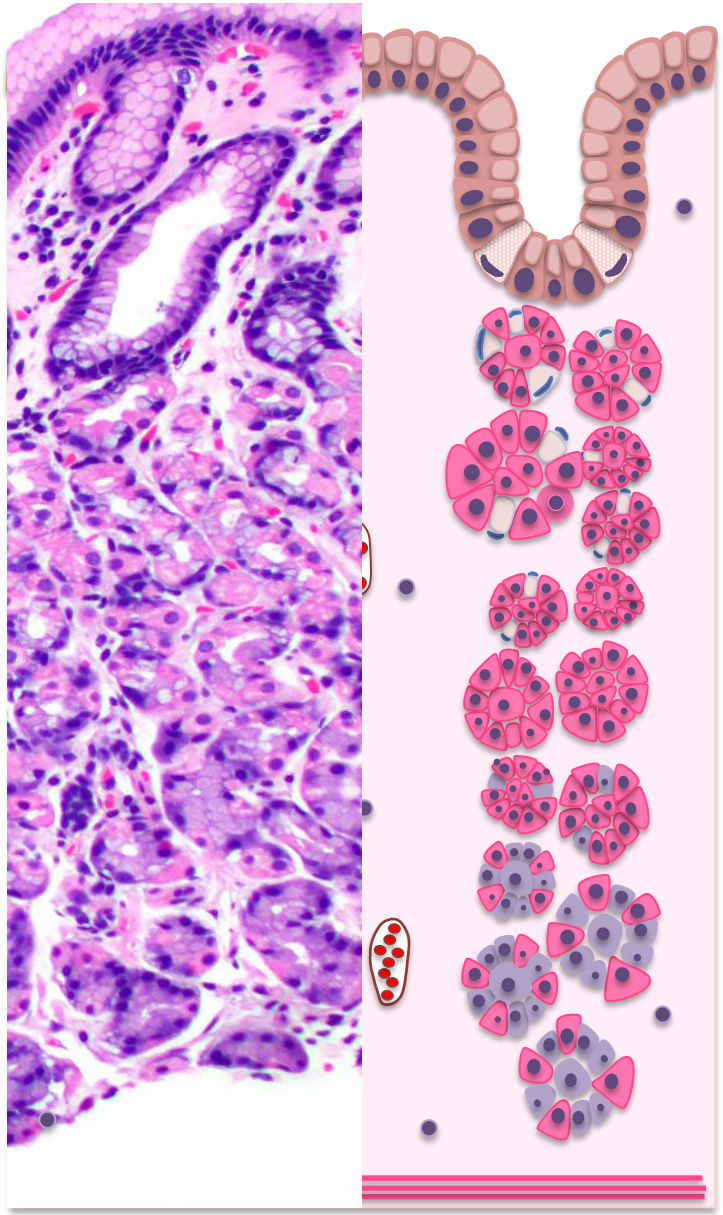
SUB-SURFACE-DERIVED

H. PYLORI POSITIVE



H. PYLORI NEGATIVE

- Intestinal-type dysplasia/adenoma
- Foveolar-type dysplasia/adenoma
- Serrated dysplasia/adenoma



H. PYLORI NEGATIVE

- Pyloric gland adenoma
- Oxyntic gland adenoma
- Pit/crypt dysplasia

Dysplasia Differs Morphologically and Prognostically

- Different dysplastic morphotypes have been recognized
- The probability and rate of progression to invasive carcinoma vary greatly by subtype and grade.
- Histologic interpretation guides the management strategy in differentiating indolent versus potentially more aggressive lesions.

Subtypes + Mucosal Background of Surface Derived GED

Subtype	Mucosal Background
Intestinal-type dysplasia/adenoma	**Atrophic / metaplastic mucosa**
Foveolar — flat-elevated type	**Non-atrophic oxyntic mucosa (sporadic, FAP/GAPPS)**
Foveolar — raspberry-type	**Non-atrophic oxyntic mucosa**
Foveolar — dysplasia in FGP	**FAP/GAPPS (rarely sporadic FGP)**
Foveolar — NOS / others	**Variable**
Serrated-type dysplasia/adenoma	Limited data

Clinical features of “classic” intestinal type dysplasia

9–20%

prevalence in high-risk areas (Colombia, China)

0.5–3.75%

prevalence in Western countries

6th–7th

decade of life at diagnosis

2.4–3.9 : 1

male-to-female ratio

Predisposing settings

- H. pylori, environment, population genetics
- FAP: 2–50%, antral, often multiple and polypoid
- Autoimmune gastritis: up to 40% with pernicious anemia; moderate excess cancer risk

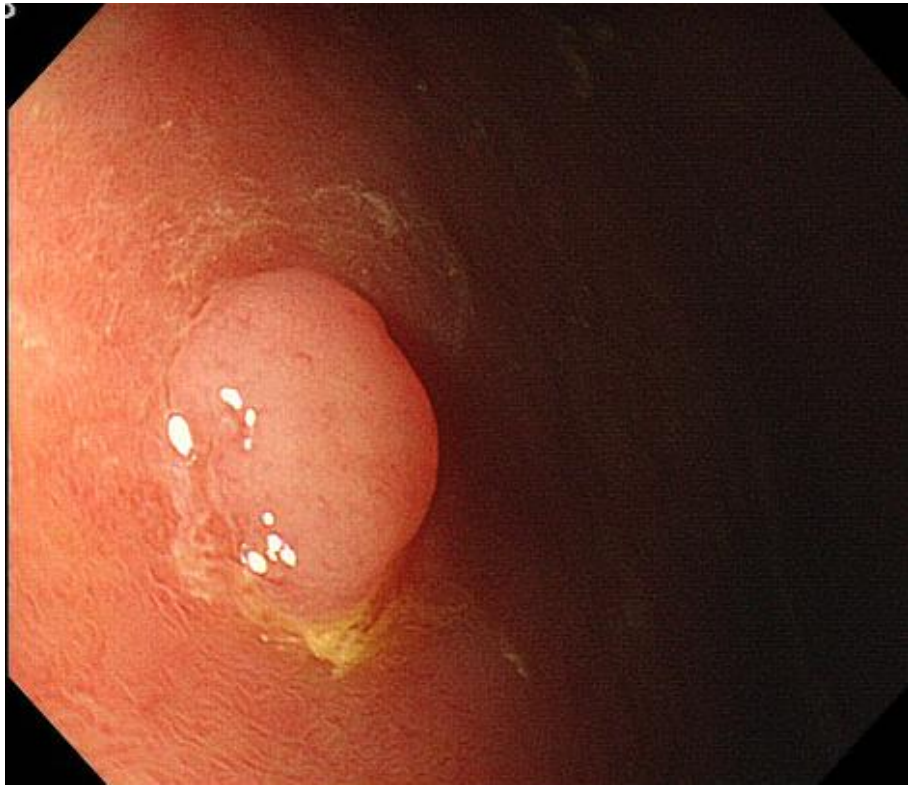
Endoscopic presentation

- Flat, elevated or polypoid (“adenoma”)
- Erosions or ulcers
- Irregular mucosa in atrophic background
- Previously: random biopsies without visible lesion

Location

- Anywhere in the stomach
- Most often lesser curvature: antrum and incisura angularis
- Frequently accompanied by intestinal metaplasia

Endoscopic Appearance Intestinal Type Dysplasia / Adenoma



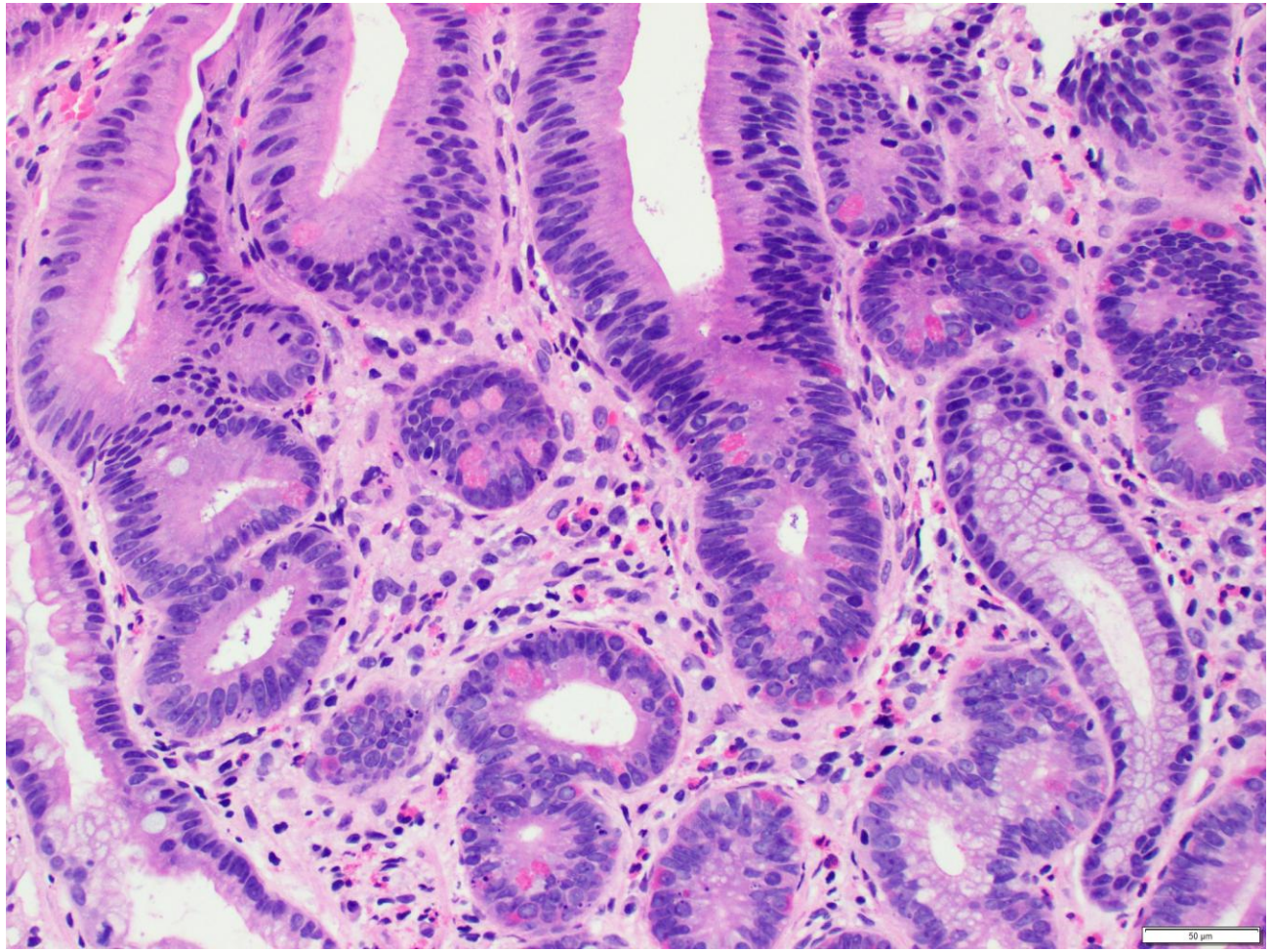
Protruded sessile 0-Is

1. **Location:** Antrum-predominant; solitary in 82% of cases; represents 1-10% of gastric polyps
2. **Morphology:** classic lesions flat/sessile, usually <20 mm with uniformly smooth surface and little or no change over time *('low grade')*.
3. **Features carrying higher risks of CA:** size >20 mm with villous architecture; Redness and depression.

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“Classic” intestinal-type dysplasia

- Adenomatous dysplasia or type I
- Crowded tubular glands
- Cells are columnar
- Nuclei: overlapping, pencillate, hyperchromatic
- Variable pseudostratification
- Nucleoli more or less conspicuous
- Associated with intest. metaplasia

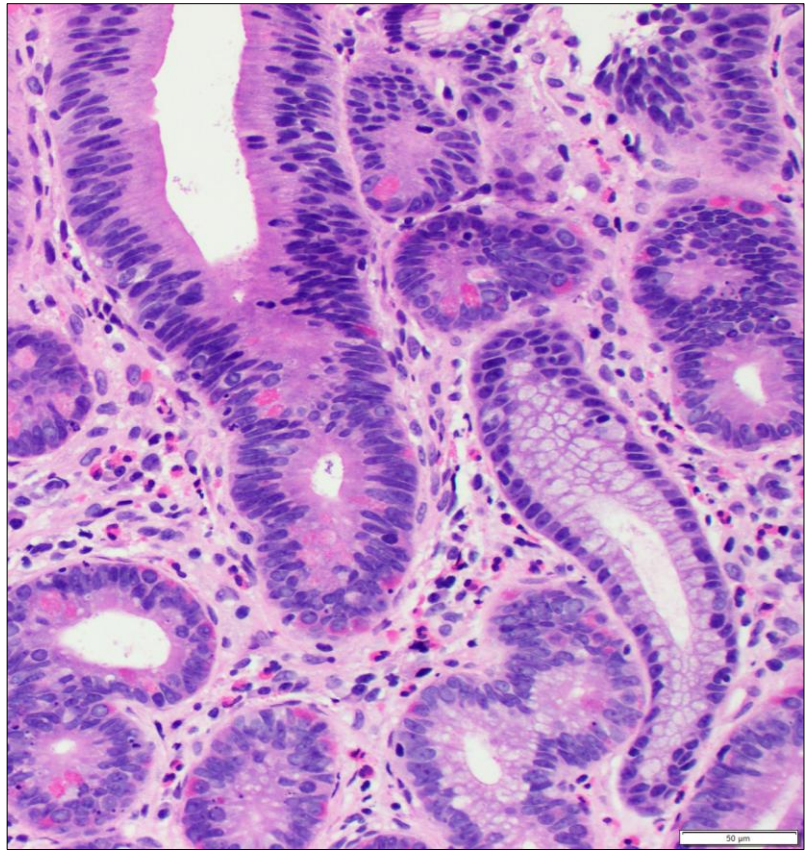


Most common phenotype — resembles colonic adenoma

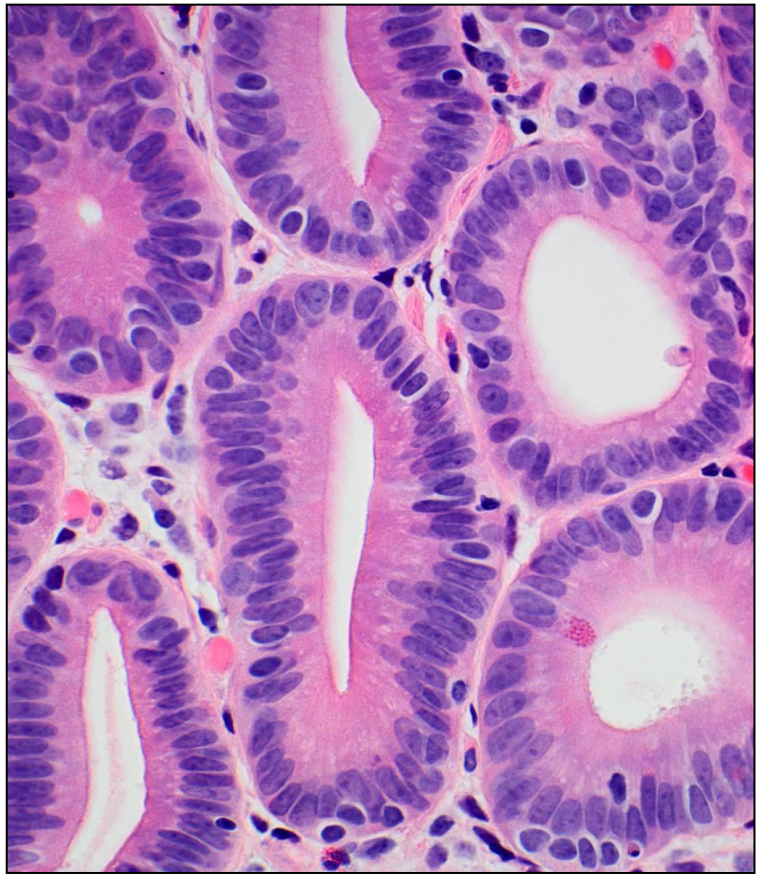
Distinguishing Low-Grade from High-Grade

	Low-Grade	High-Grade
Endoscopic	Pale, flat-elevated, smooth, <20 mm, stable over time	Redness, erosion, depression, nodular surface diameter >20 mm
Architecture	Minimal disarray, simple tubular glands, little branching/papillary pattern	Marked disarray, Irregular elevation/depression, papillary, branching/anastomosing or irregular tubular glands; gland crowding
Cytology	Cigar-shaped, uniform nuclei Lower N/C	Cuboidal to low-columnar; high N/C Rounded nuclei, prominent nucleoli, hyperchromatic / coarse chromatin
Nuclei/Mitoses	Mild–moderate atypia with retained polarity Limited mitoses	Round-oval, vesicular nuclei; prominent nucleoli Distinct loss of polarity Frequent mitoses / atypical forms
Differentiation	Small-intestinal (brush border, goblet, Paneth cells)	

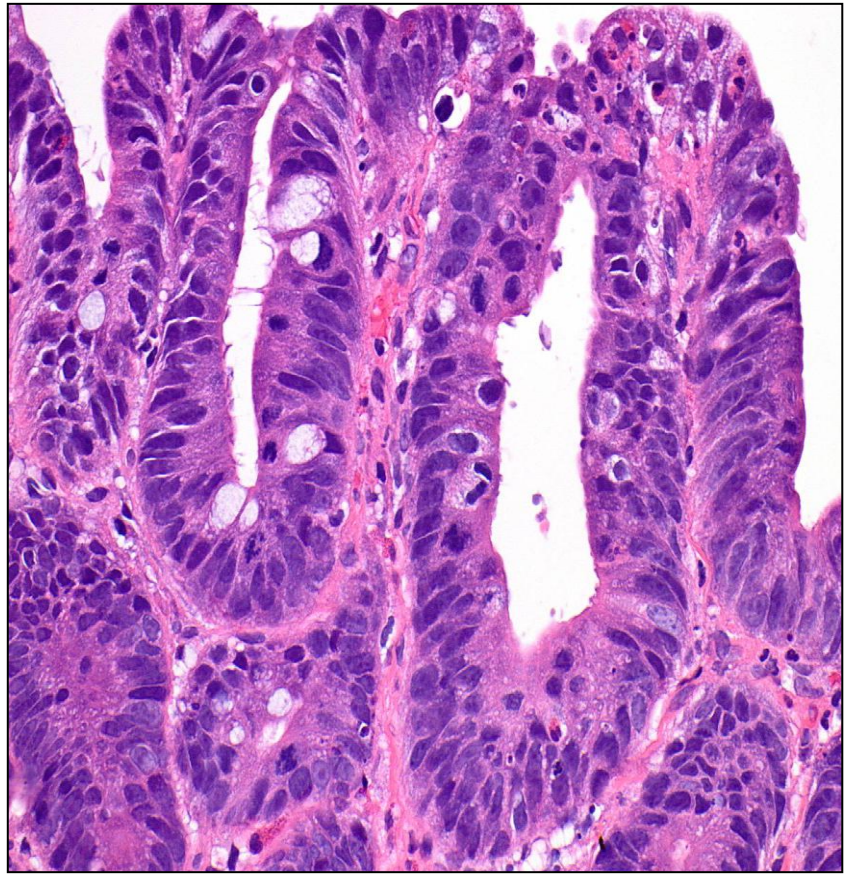
Intestinal type— Low- vs High-Grade Cytology



Pseudostratified columnar epith, pencil-shaped N, Absorptive and Paneth cells ; MUC2/CD10/CDX2+.

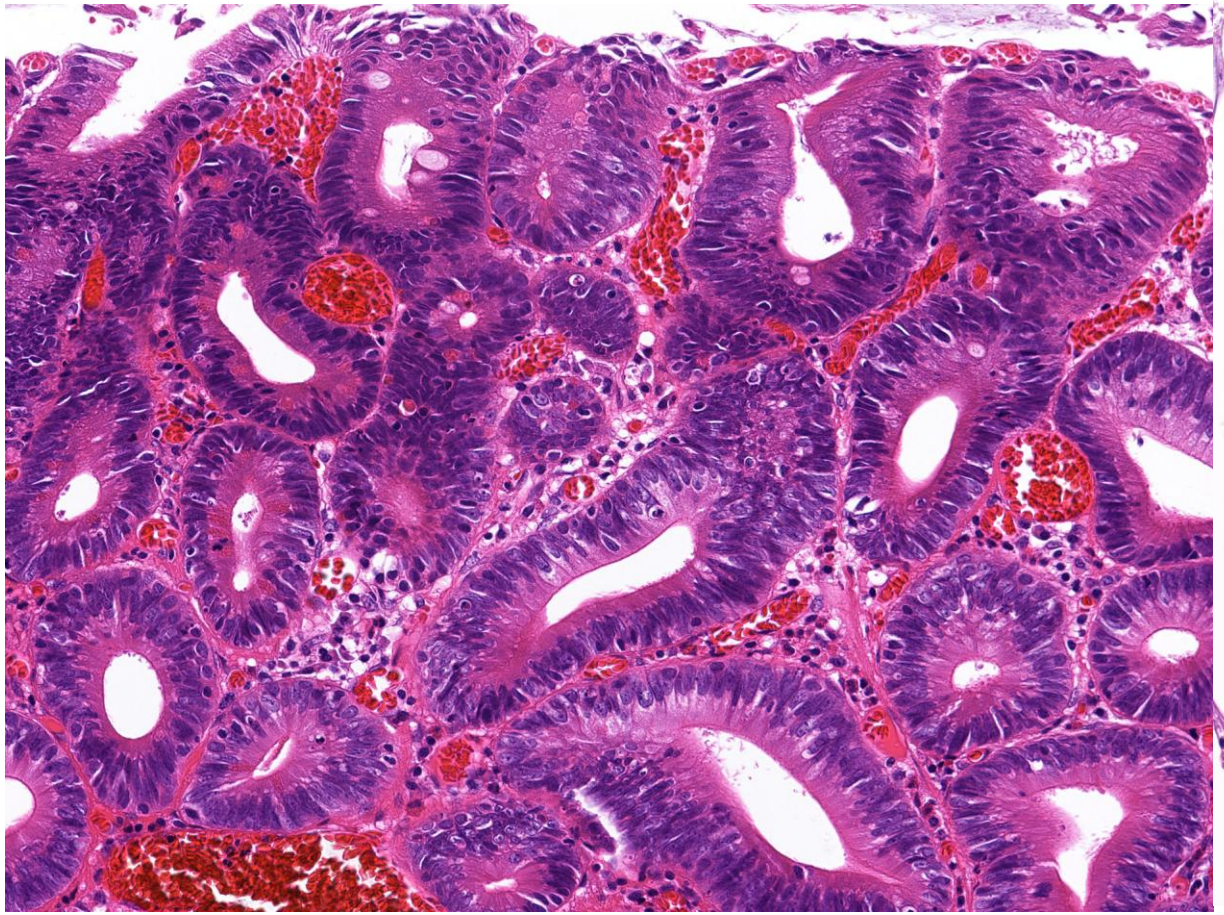


Low grade cytology

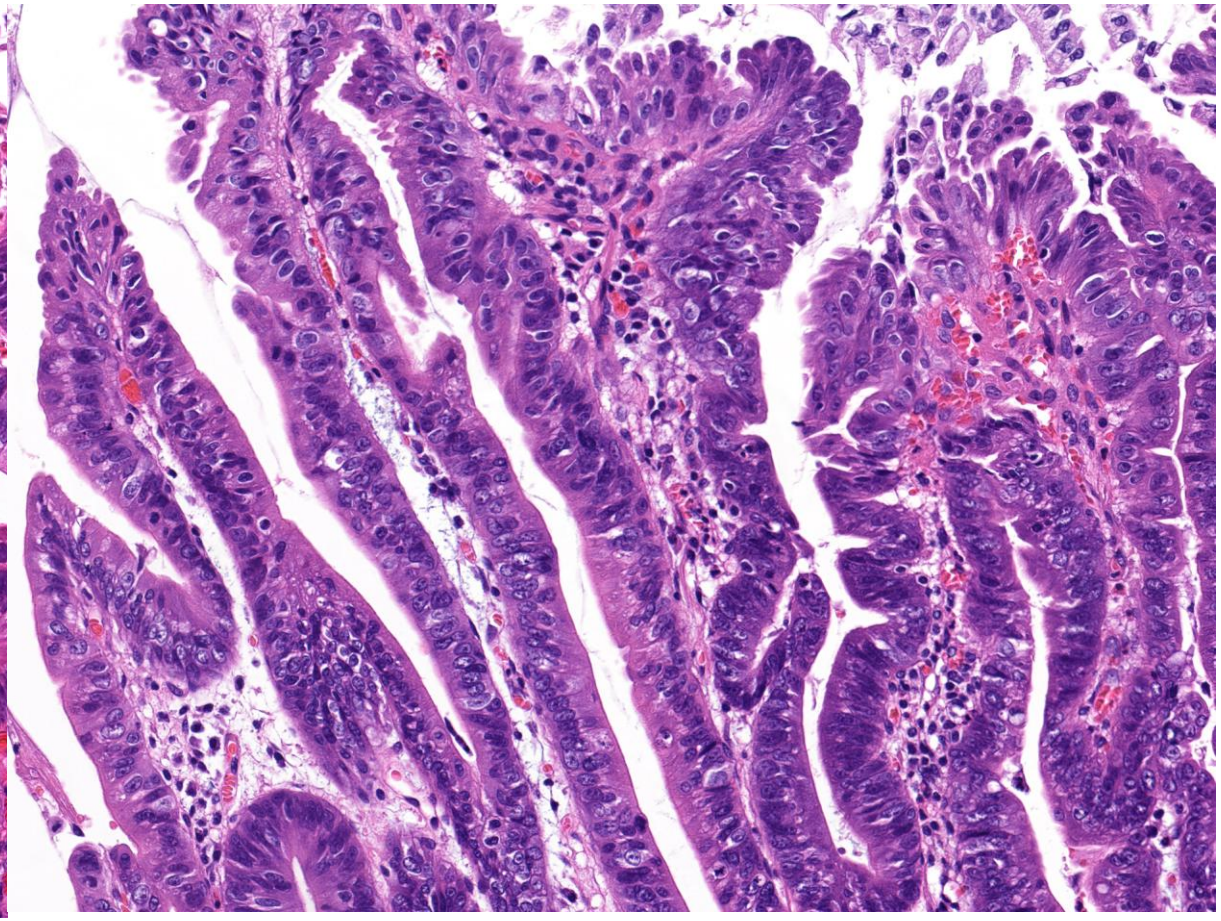


High grade cytology

Intestinal type— Low- vs High-Grade Cytology

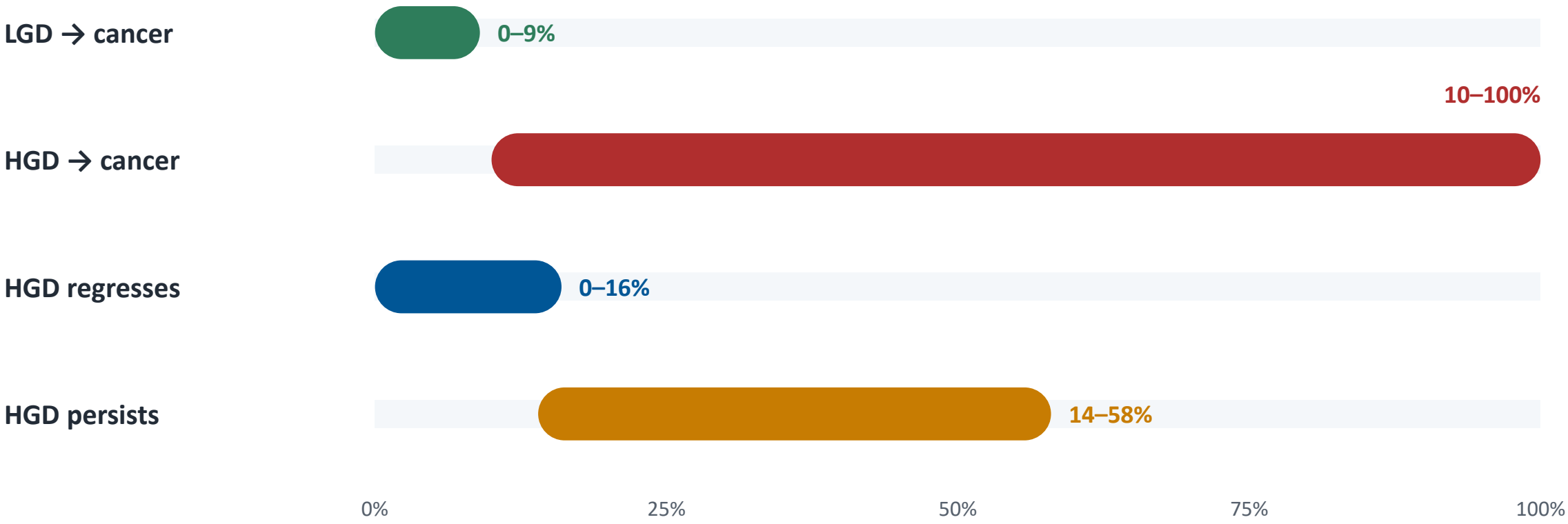


Low grade cytology



High grade cytology

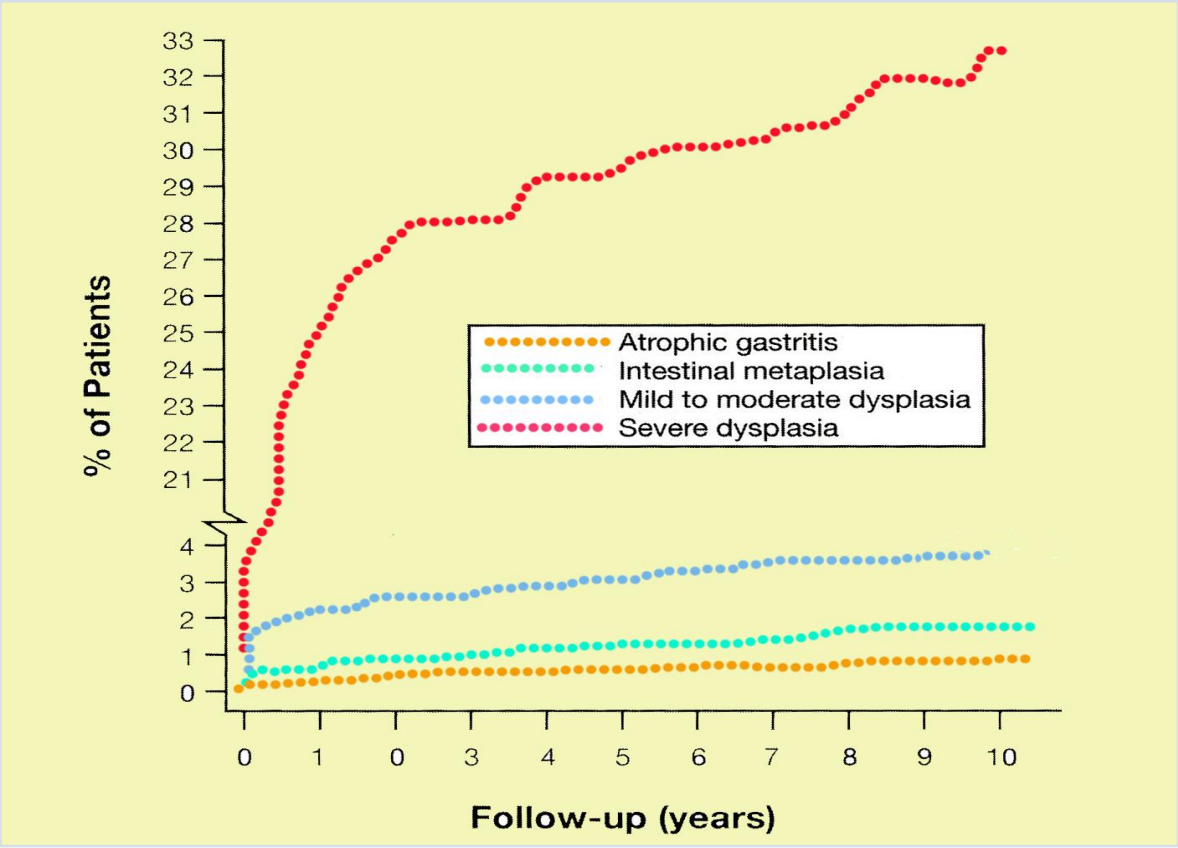
Natural history: outcomes by grade



Bars show the reported range across studies. Final step: intramucosal adenocarcinoma — may mimic HGD endoscopically.

Ushiku T; Lauwers GY; Gastroenterol Clin North Am. 2024 Mar;53(1):39-55

Progression of Dysplasia of Intestinal Type Dysplasia



Atrophic gastritis → IM → LGD → HGD

6% / 0.6%

annual GC incidence: HGD vs LGD

- HGD: 4.3% progressed after mean follow-up of 2.6 yrs
- LGD: 4.5% progressed after mean follow-up of 3.1 yrs
- Long-term follow-up: the 5-year cumulative incidence of carcinoma developing within an intestinal-type dysplasia was 34%; size ≥15 mm and depression were risk factors.

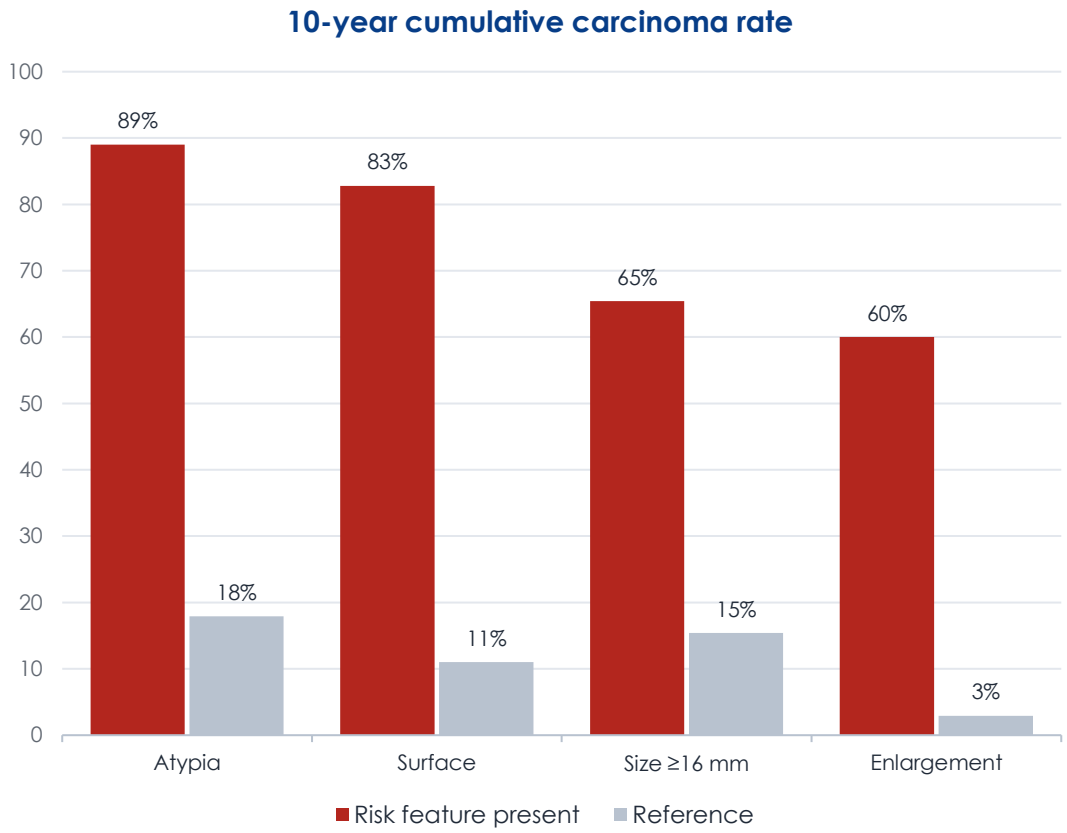
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Gastroenterology 2008;134 · Am J Gastroenterology 2016

Western Experience

Cumulative malignant transformation rate at 5 & 10 years [by initial feature]

Factor	n	5 y (%)	10 y (%)	p*
High grade dysplasia	12	56.0	89.0	**0.0001**
Mild / moderate atypia	95	0	17.9	
Irregular Nodular surface	25	16.1	82.8	**0.0004**
Other surface	82	5.1	11.0	
Size ≥16 mm	27	16.8	65.4	**0.015**
Size ≤15 mm	80	5.2	15.4	
Size ≥21 mm	11	20.0	65.7	**0.008**
Size ≤20 mm	96	5.9	21.0	
Erythema	11	11.1	60.5	0.086
Isochromatic / pale	96	7.7	26.0	
Enlarged in follow-up	28	18.4	60.0	**0.0001**
Unchanged / decreased	79	2.9	2.9	



Macroscopic type (IIa vs other) was not predictive: 25.8% vs 45.3% at 10 y, p=0.69

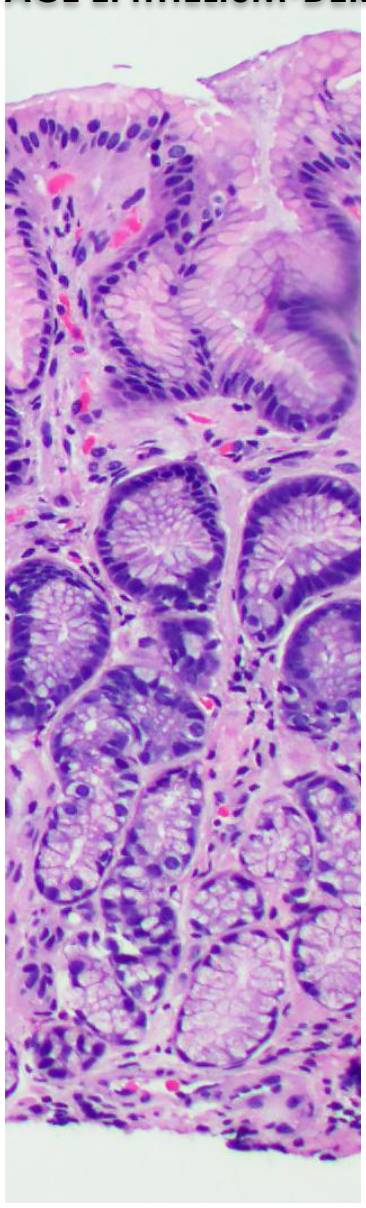
Nakamura S, Ito Cho 2003;38(10)

Eastern Experience

Hp Non-Infected vs Hp-infected Gastric Neoplasia: Different Diseases

SURFACE EPITHELIUM-DERIVED

H. PYLORI POSITIVE



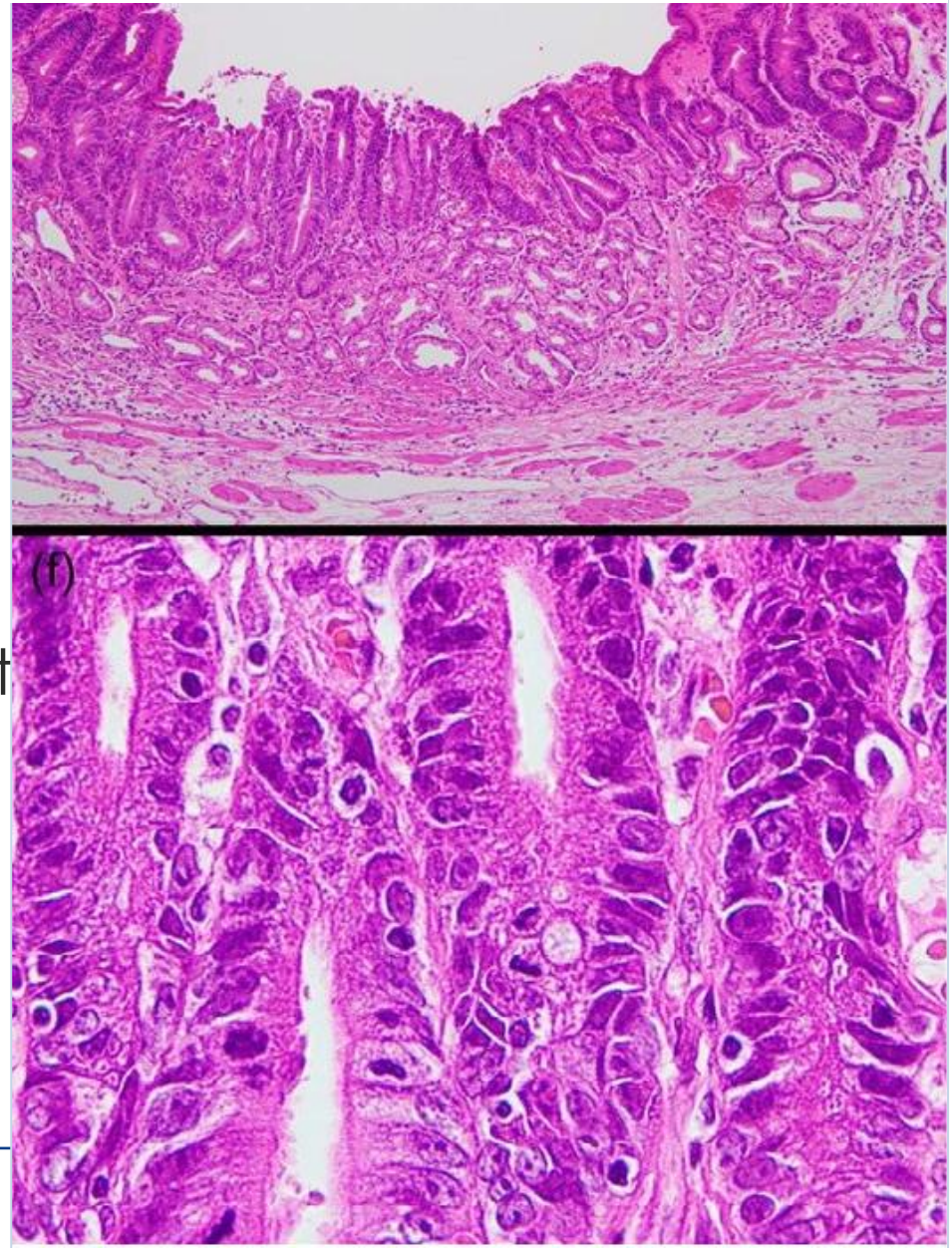
H. PYLORI NEGATIVE

	Hp-naïve (HpNeg GN)	Hp-infected (HpIntGN)
Background	*Non-atrophic mucosa, no IM*	Chronic gastritis → atrophy, IM
Age	*Mean age 59.5 y*	Mean age 71.8 y
Sex	*Female 40%*	Female 27%
Lifestyle	*~50% Smokers and drinkers >general population*	~50% Smokers and drinkers >general population
Phenotype	*Mostly gastric (IGD excepted)*	Gastric or intestinal
Location	*Fixed compartment per type*	Follows atrophy / IM
Behavior	*Low-grade, slow, rarely invasive*	Higher malignant potential

Modified from Shibagaki K et al. *Pathology International* 2024;74:423–437

A Distinctive H. pylori-Naïve Variant with intestinal phenotype

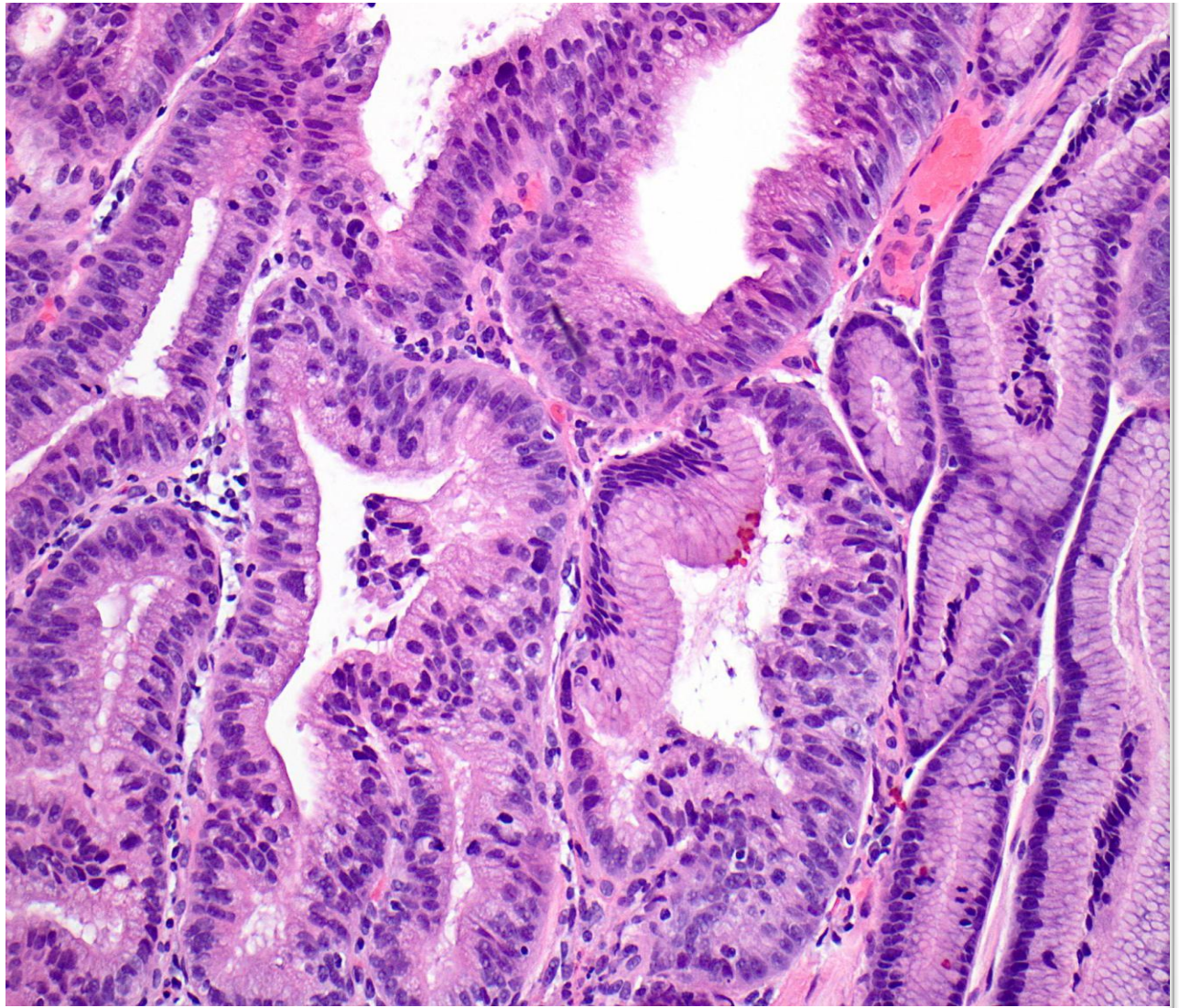
- Non-atrophic antrum/prepyloric region +++
- Small — typically 7–9 mm;
- Superficial depressed++; 30% multiple
- IM in 40% of cases.
- (??) Duodenogastric reflux contributing (??).
- CDX2+ w/ MUC2 / CD10 ± gastric mucins → intest
- P53 overexpressed in 90% of cases (VS 38–54% Hp-infected gastric neoplasms)

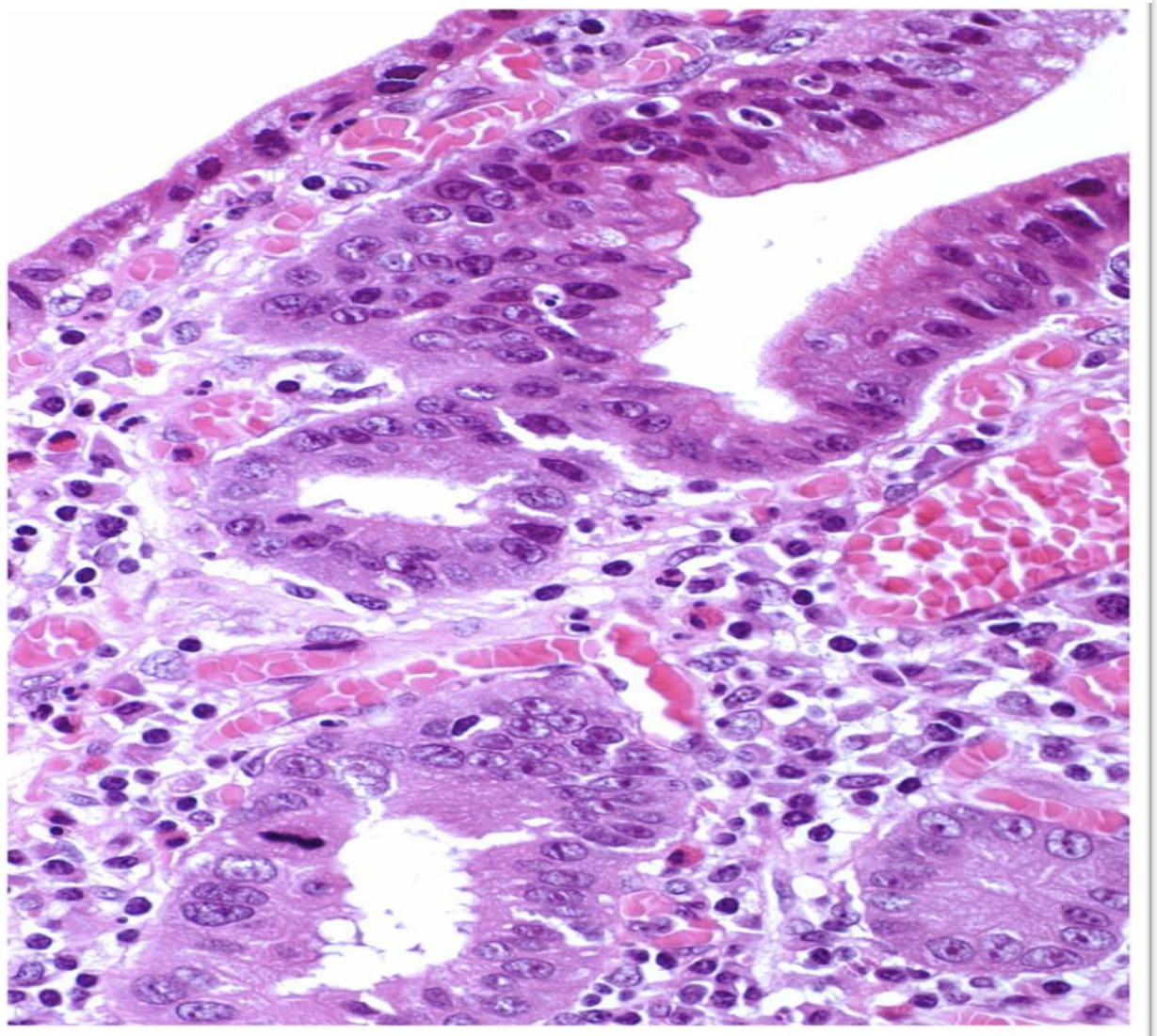


Shibagaki K et al. *Pathology International* 2024;74:423–437 ·

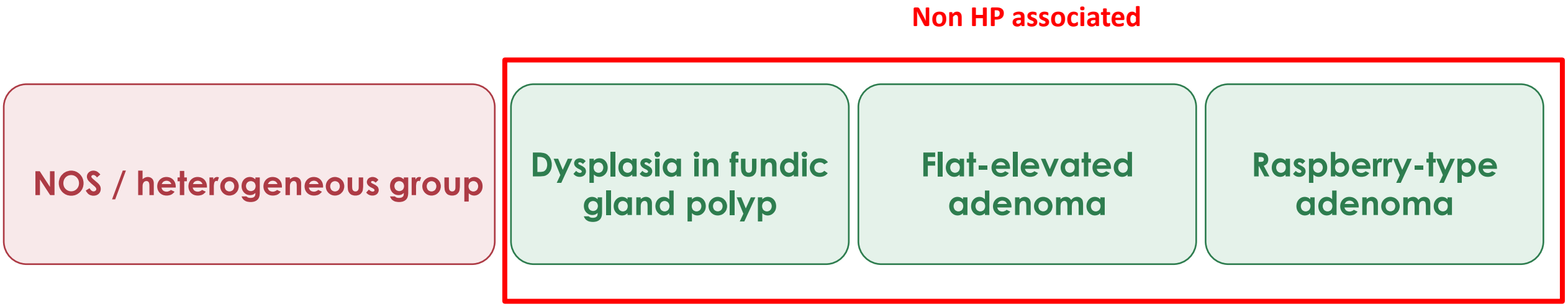
Type 2 Foveolar dysplasia

Tall columnar cells w/ apical neutral mucin, variable nuclear stratification, MUC5AC expression. Brush border, goblet cells, and Paneth cells are usually absent.



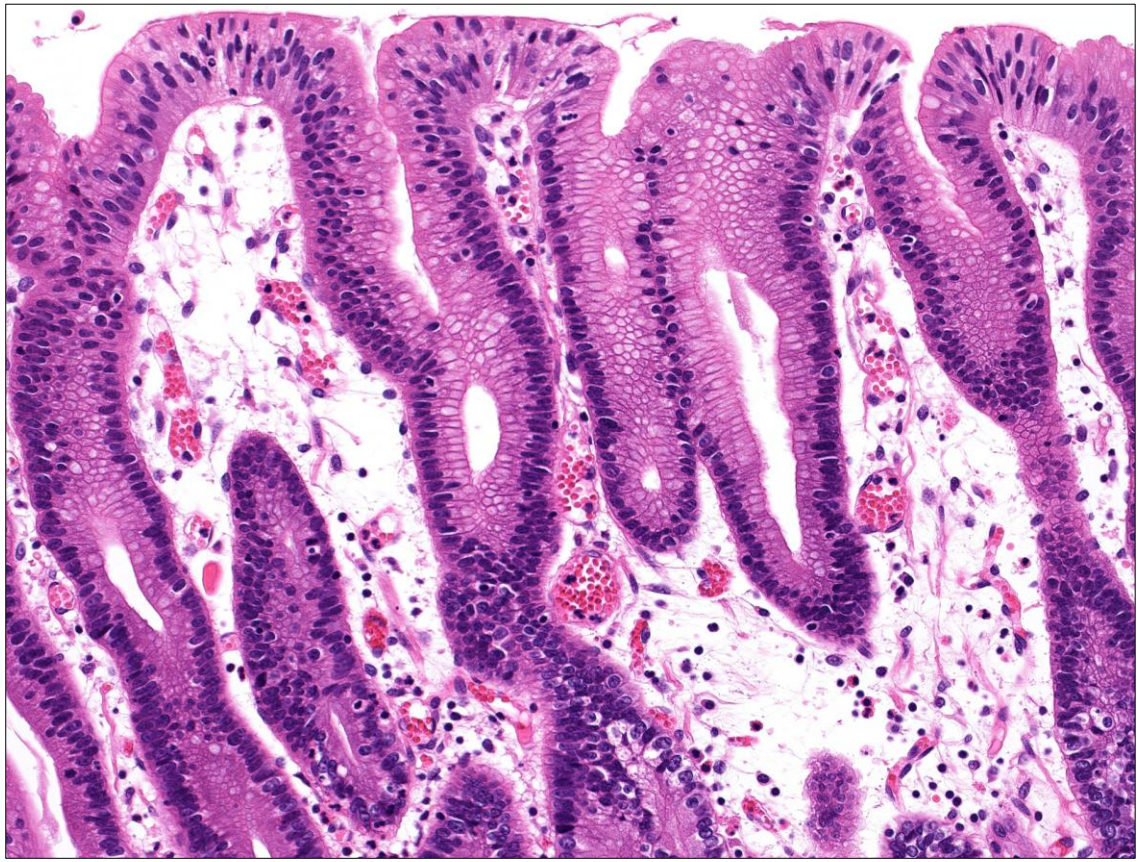


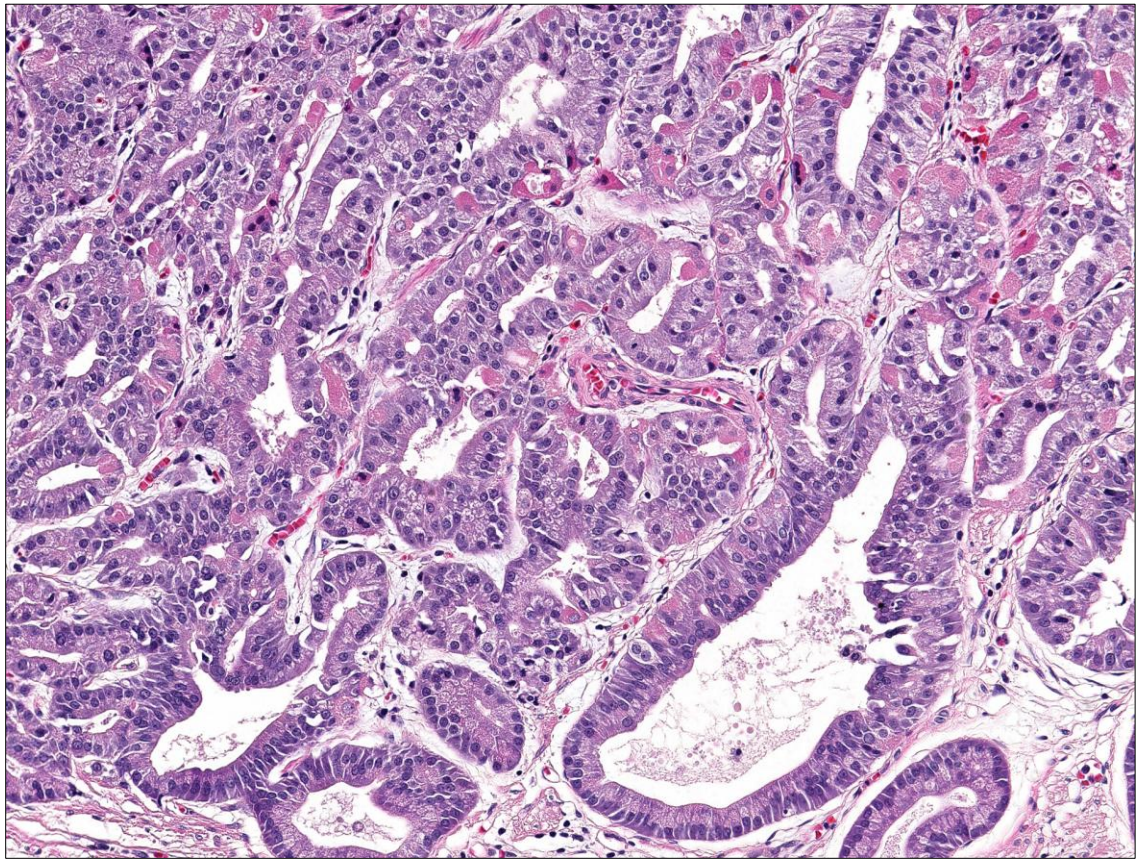
Foveolar type dysplasia is a differentiation pattern rather than a single entity



- Lesions differ markedly in setting, architecture, molecular pathogenesis, and malignant potential

Foveolar type dysplasia, NOS





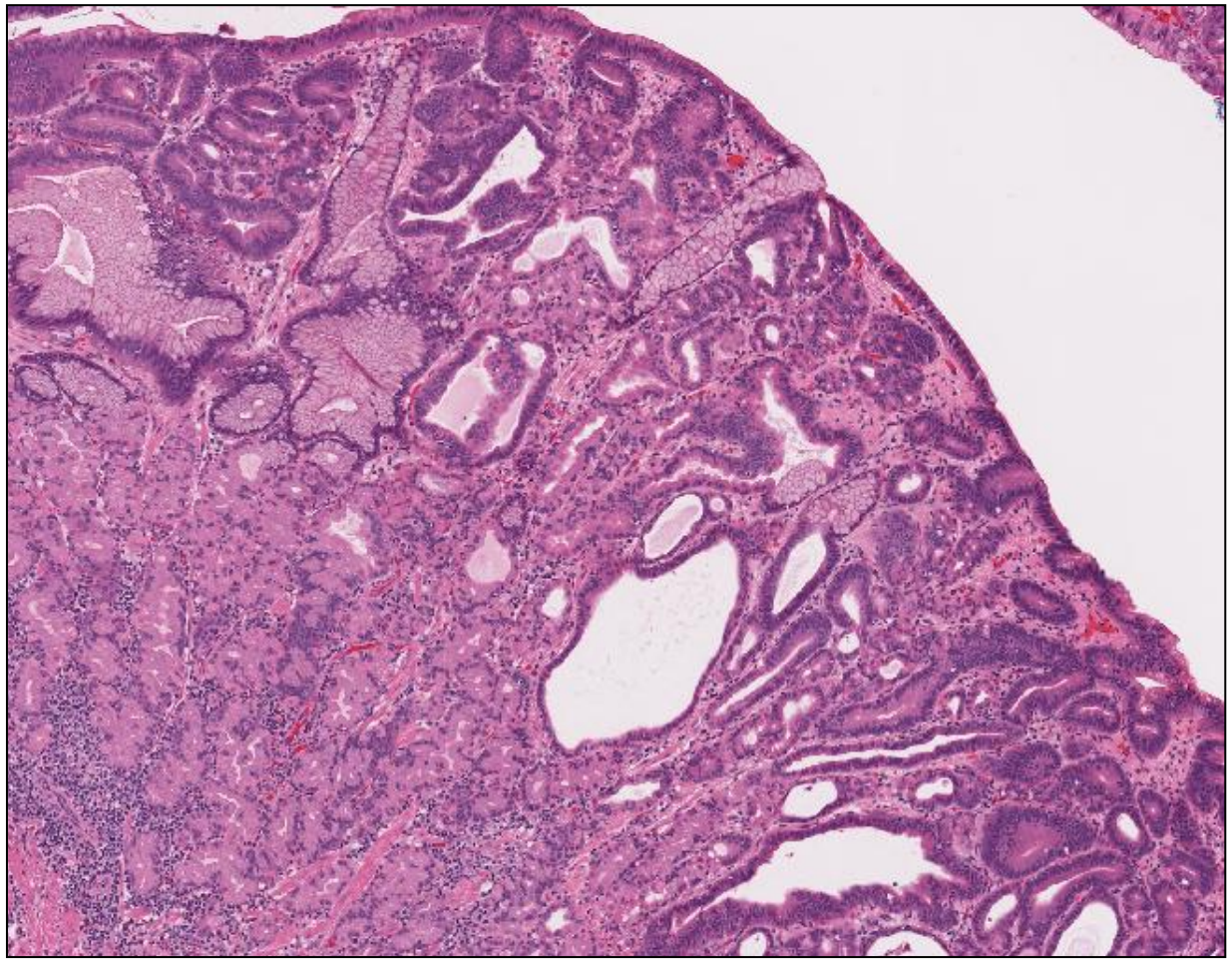
75% arise in *H.pylori* infected stomach

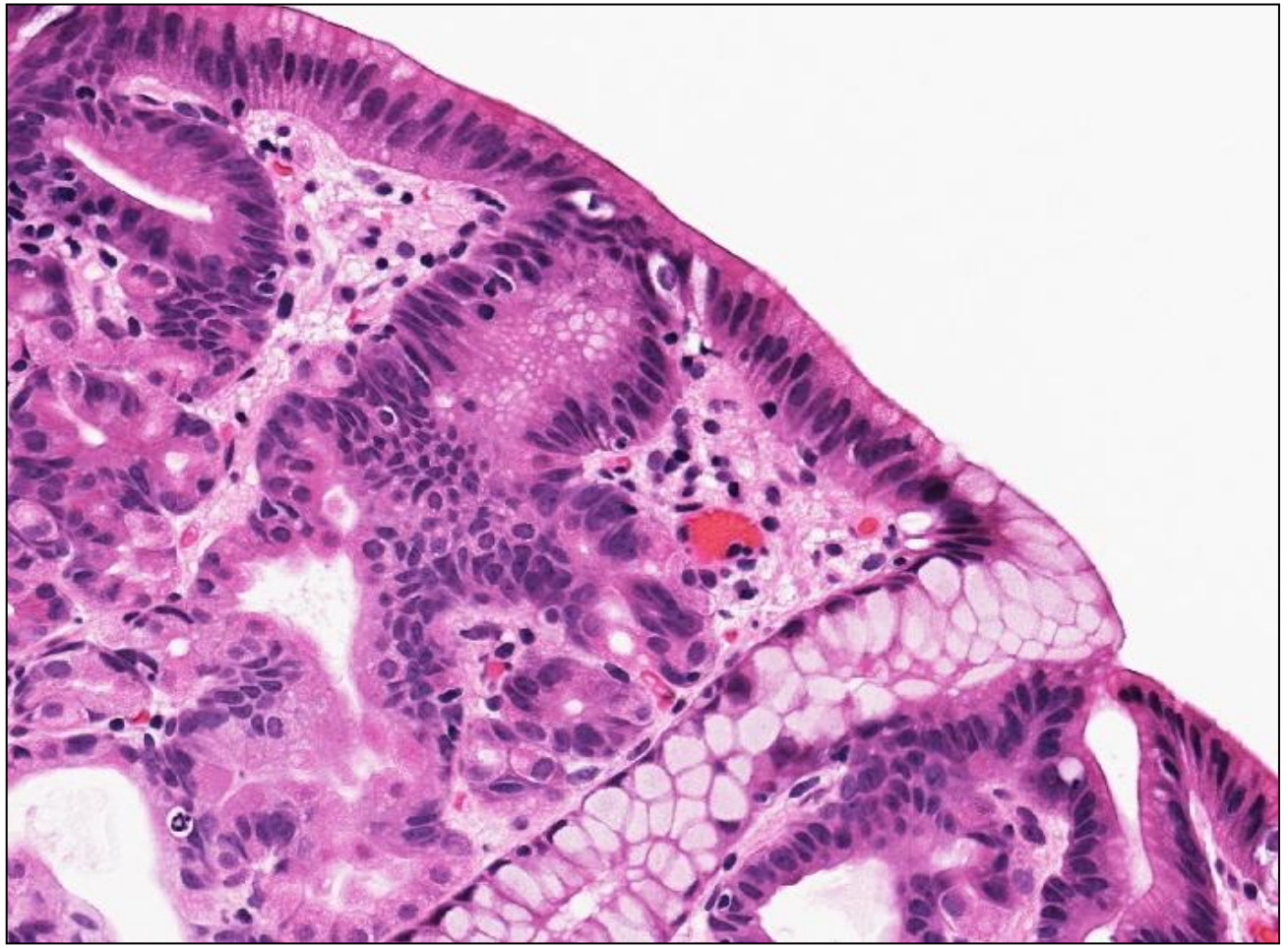
75% are located in the antrum

36% are high-grade

- Differs from the subtypes that develop in H. pylori-naïve oxyntic mucosa and are usually low-grade.

Dysplasia in a Fundic Gland Polyp





FAP patient

Dysplasia in a Fundic Gland Polyp

- Confined to the surface foveolar epithelium and cytologic atypia is usually low-grade,

SPORADIC (NON-FAP)

Dysplasia / adenocarcinoma risk: exceedingly low (~1%), but reported

Recommended work-up:

Exhaustive endoscopy and exclusion of concurrent risk factors *(H. pylori; atrophic gastritis / intestinal metaplasia)*

~1%

Estimated lifetime risk of dysplastic transformation

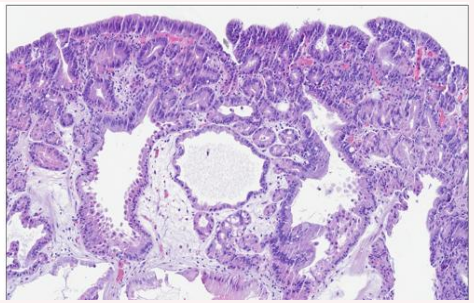
PMID: 27833394

FAP-ASSOCIATED

Dysplasia in ~25–46% of FAP-FGP

LGD > HGD (0–12%); average age 31 · 5-yr cumulative incidence of dysplasia ~36%

Progression risk: 4% rate of progression from LGD to HGD/adenocarcinoma (mean follow-up 6 yrs)





- Risk is higher with mucosal carpeting by polyps or polyps >1 cm
- Patients with GAPPS are also at high risk of developing GC

Histopathology 2014;65:353-62 · Am J Gastroenterol 2022;117:1246–1254

Hp Negative Foveolar-type adenoma: two different tumors

	Flat type	Raspberry type
Setting	Syndromic (FAP, GAPPS) and sporadic	Sporadic, Hp-naïve;
Size	Large: median 37–51 mm	Small: mean ~3 mm; 20.6% multiple
Endoscopy	Whitish, flat, laterally spreading	Bright red, well-demarcated polyp
Architecture	Long papillae, thin stroma; cystic fundic glands below	Irregular papillae, broad vascular stroma
IHC	MUC5AC+ upper, MUC6+ lower; nuclear β-catenin	MUC5AC+ diffuse; MUC6 −/basal; Ki-67 high; p53 wild-type
Genetics	APC + KRAS (± GNAS → pyloric gland adenoma)	KLF4 c.A1322C SNV

Both: gastric phenotype (MUC2, CD10, CDX2 negative) and rare progression to invasive carcinoma

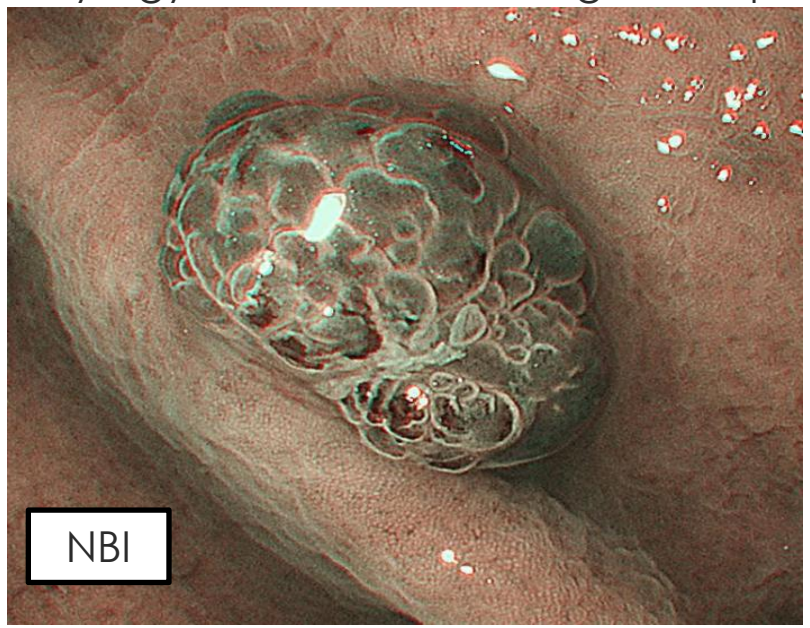
Raspberry-Type Foveolar Adenoma

- Bright red, sharply demarcated



K. Yamamoto, M.D. (Hokkaido Univer. /Moffitt Cancer Ctr)

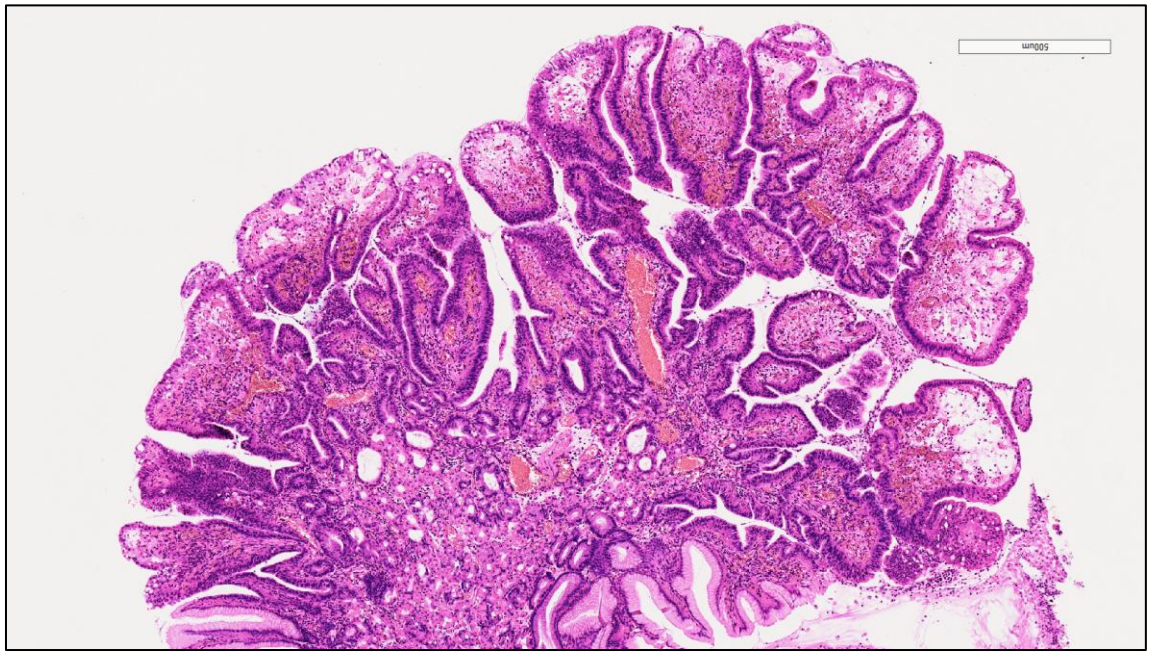
- Papillary / gyrus-like surface, irregular capillaries



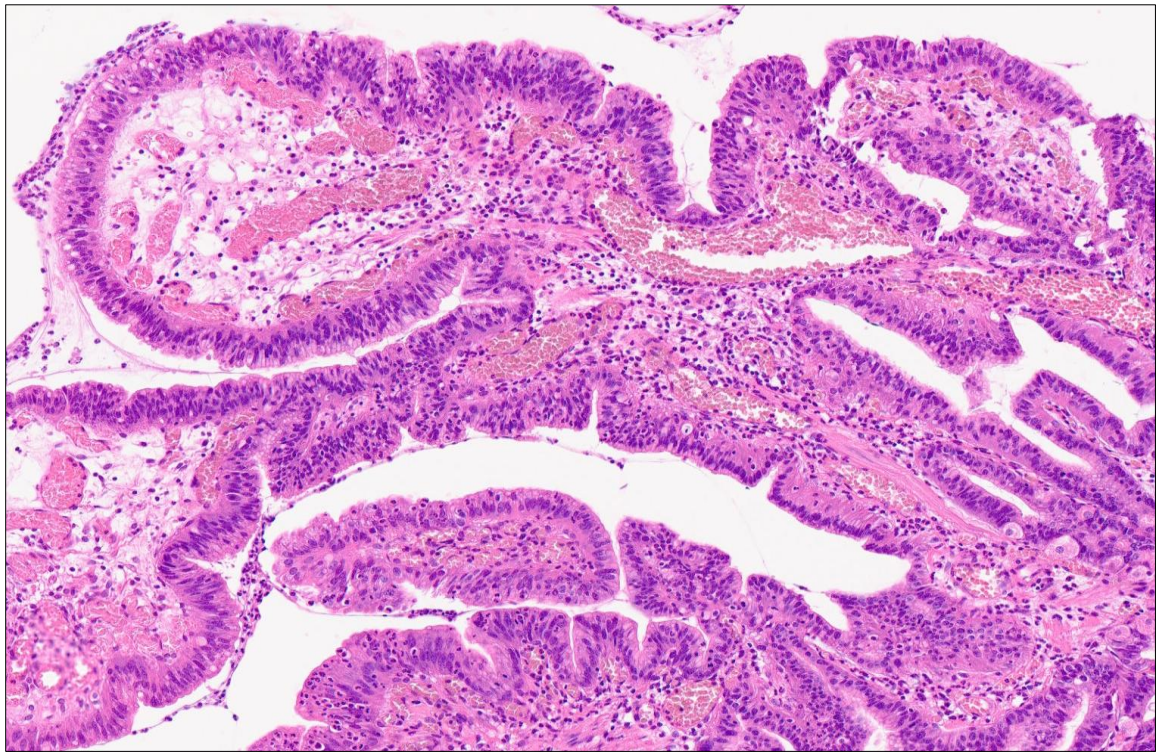
K. Yamamoto, M.D. (Hokkaido Univer. /Moffitt Cancer Ctr)

- Arises in non-atrophic oxyntic mucosa.
- Increasingly encountered during screening — Prevalence 0.26-0.42%;
- size 2–10 mm; associated with FGP
- No convincing progression to invasive carcinoma documented (to date).

Raspberry-Type Foveolar Adenoma



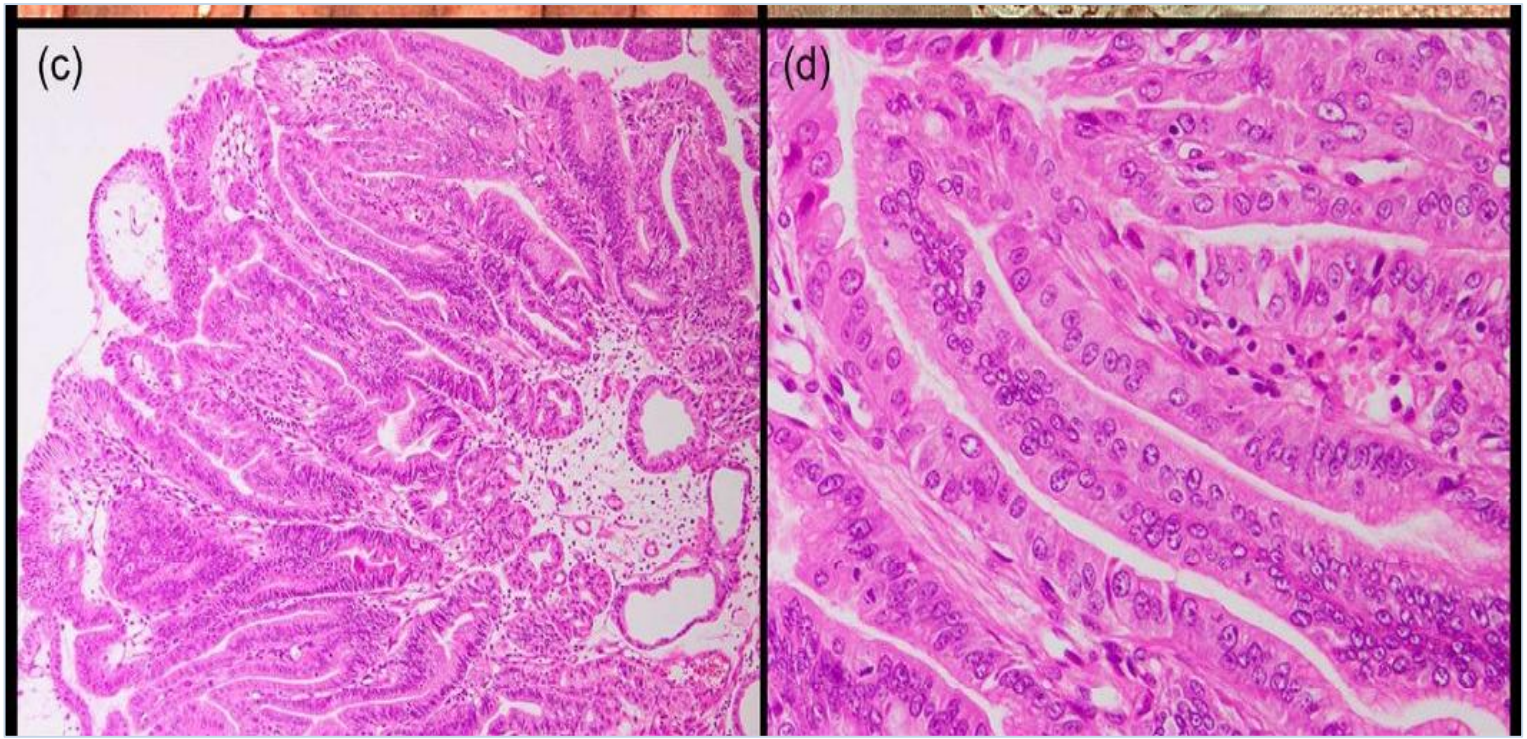
Tubulo-papillary structure with vascularized broad stroma



Papillae with broad, capillary-rich stroma; low-grade cytologic dysplasia

- MUC5AC diffuse; MUC6 −/basal; MUC2, CD10

Raspberry-Type Foveolar Adenoma



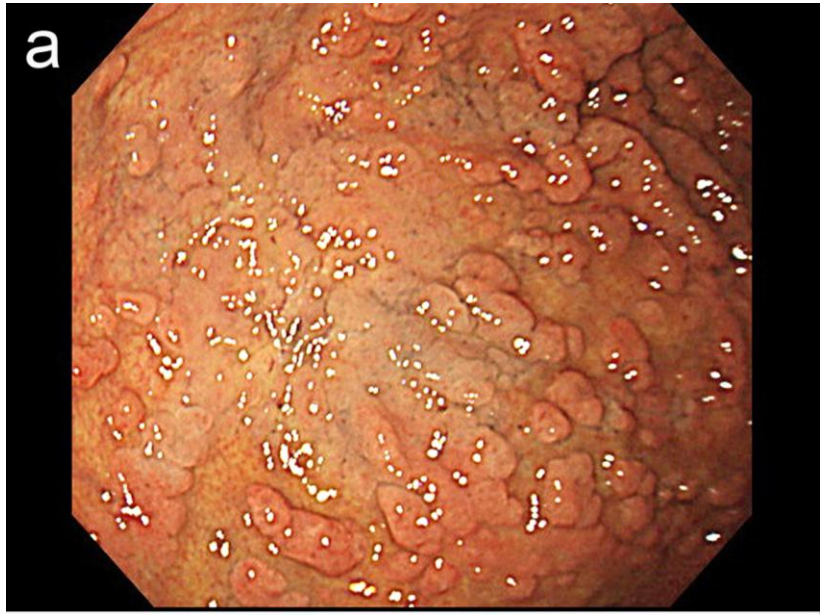
- **Low grade: 63%** preserved architecture, basal slightly stratified nuclei, distinct mucin cap
- **High grade i**rregular architecture, stratification with loss of polarity, indistinct cap

- **KLF4 c.A1322C** — Never detected in gastric carcinoma or any other cancer type,

Shibagaki K et al. *Pathology International* 2024;74:423–437 ·

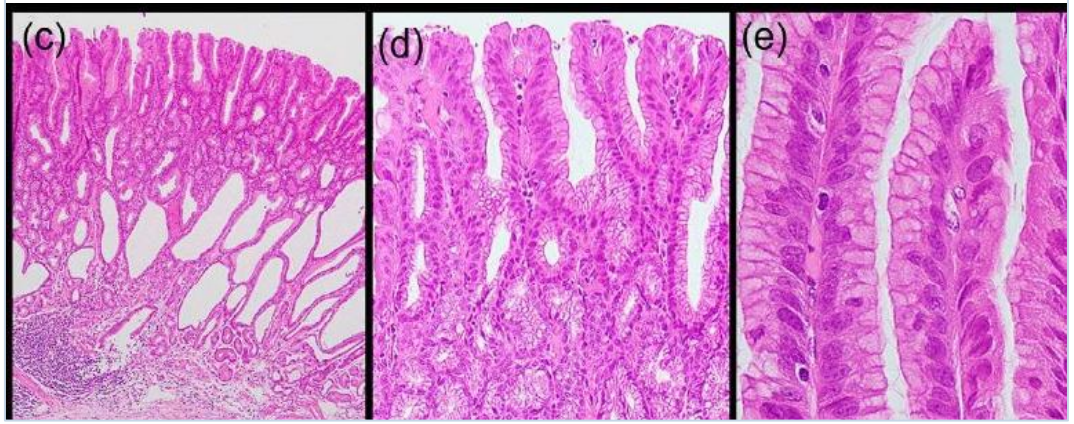
Flat-Elevated Type Foveolar Adenoma

- Occurs sporadically and in association with FAP or GAPPS.
- Sporadic and syndromic cases share the same essential characteristics.
- Arises in non-atrophic/non-metaplastic oxyntic mucosa;

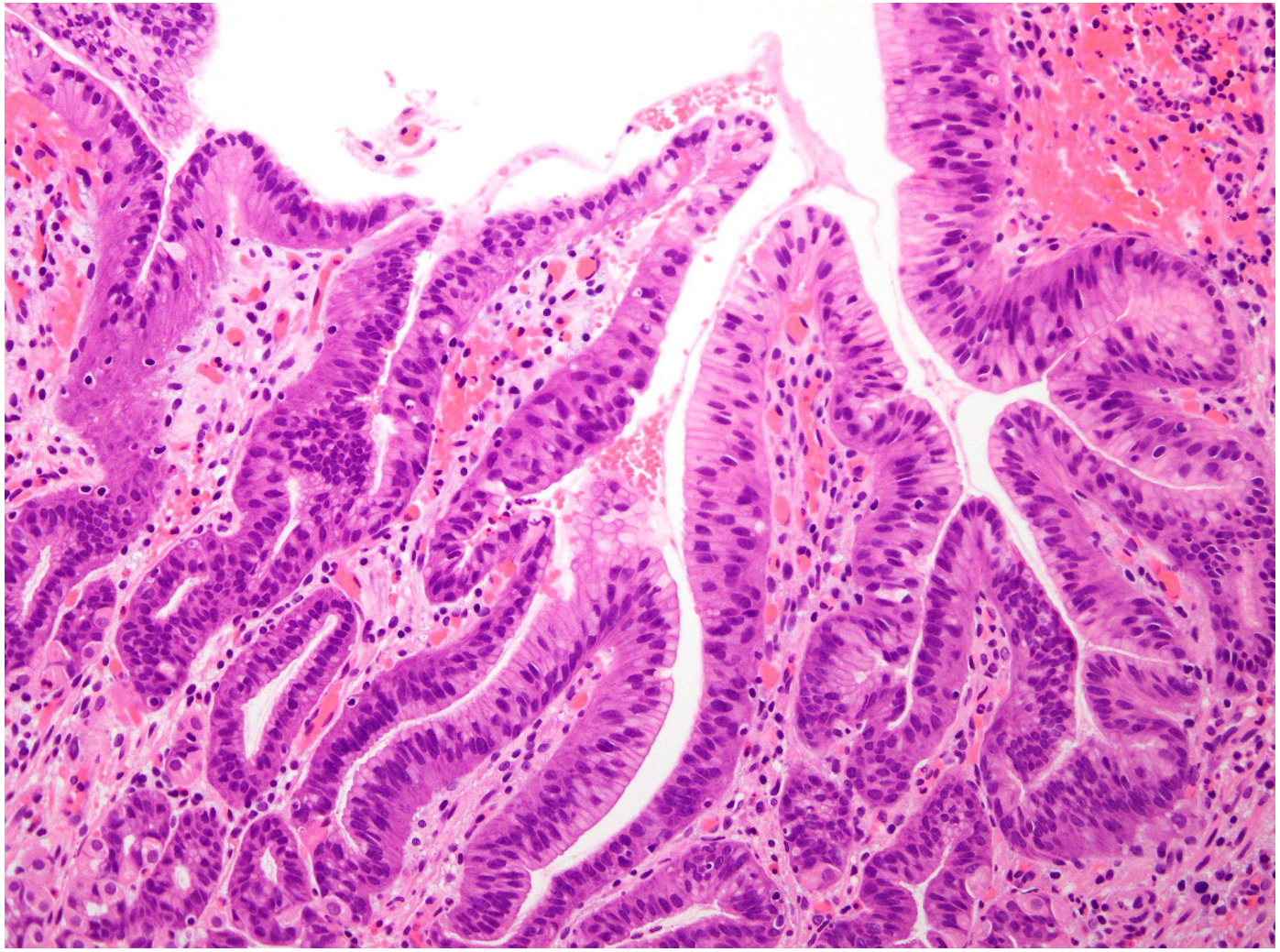


- Endoscopy: flat or slightly elevated lesions. Size varies. Measuring 11–87 mm (mean 52 mm) in one series.

Flat-type FGA: histology

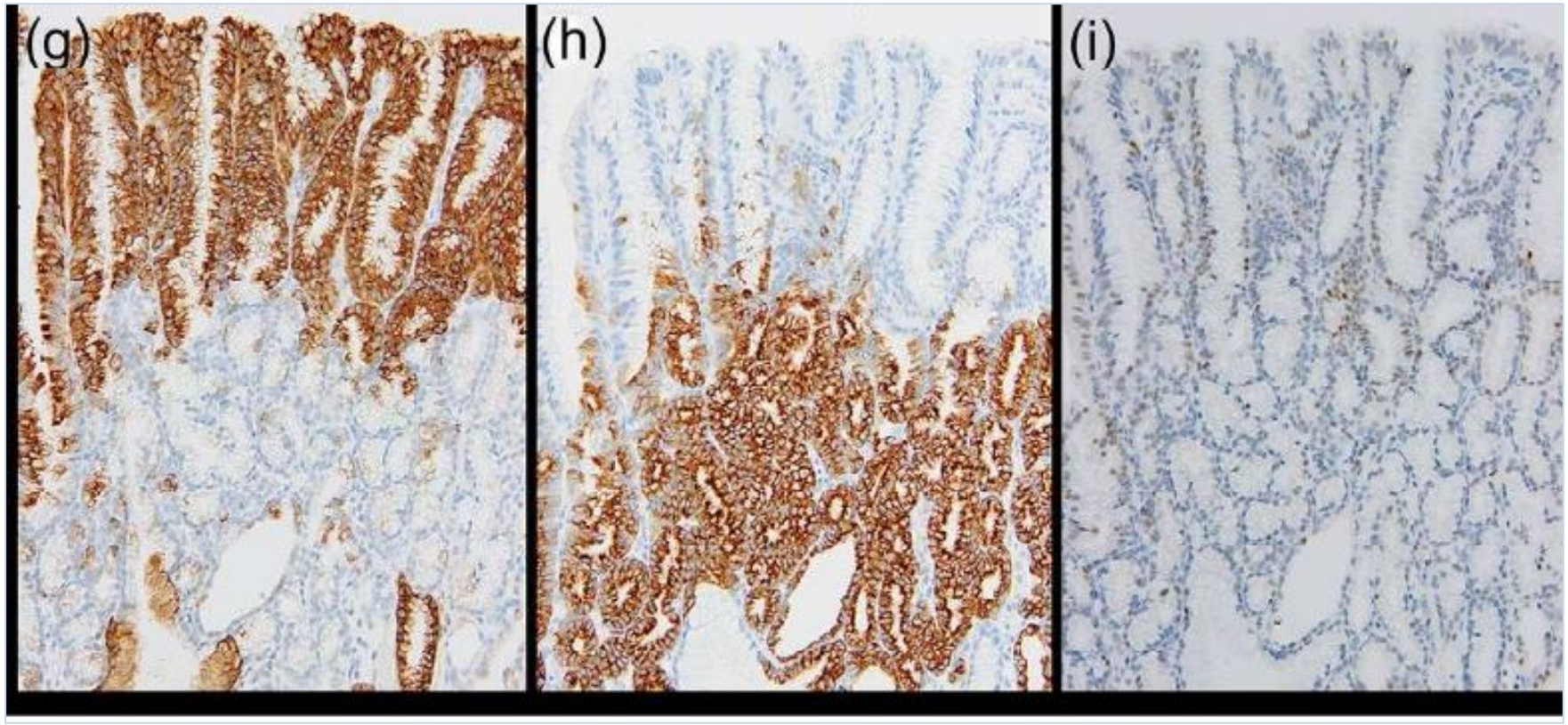


- deeper glands resemble mucous neck or pyloric gland cells.
- Commonly harbor APC and KRAS mutations — a shared tumorigenic mechanism.



Papillary fronds of foveolar-type cells with slender fibrovascular cores

Flat-type FGA: Immunophenotype



(g) MUC5AC · (h) MUC6 · (i) p53 ·

- p53 wild-type; nuclear β-catenin usual (APC)
- Link to Pyloric gland adenoma: shared APC/KRAS, plus GNAS in the PGA component

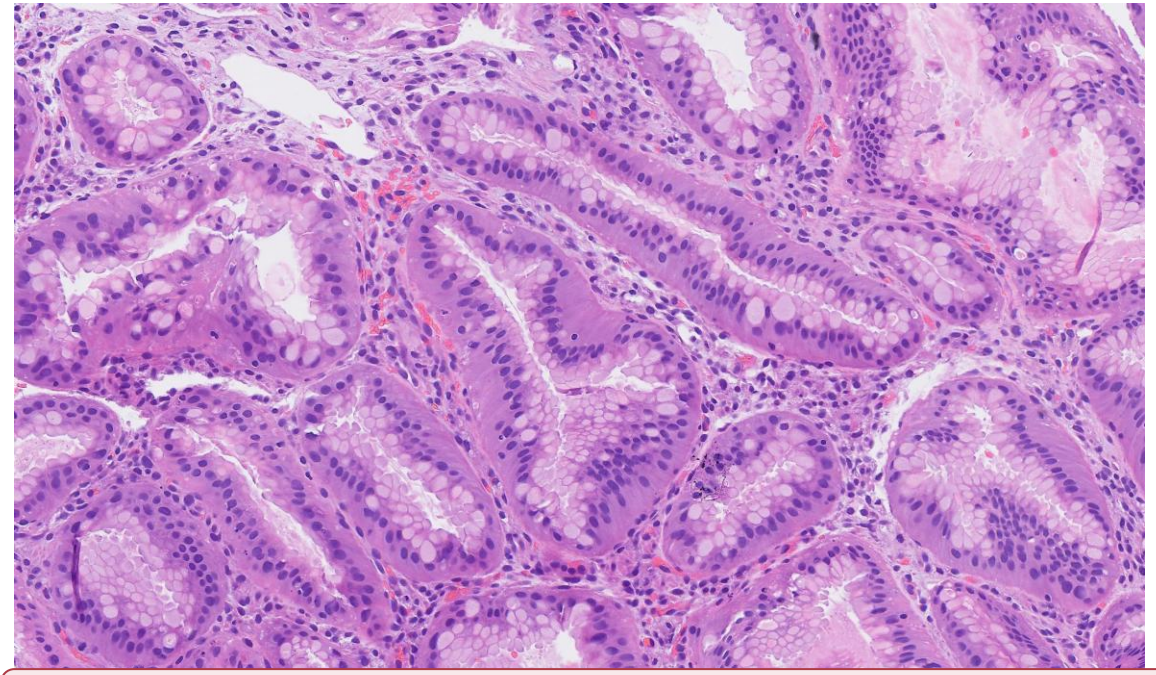
Shibagaki K et al. *Pathology International* 2024;74:423–437 ·

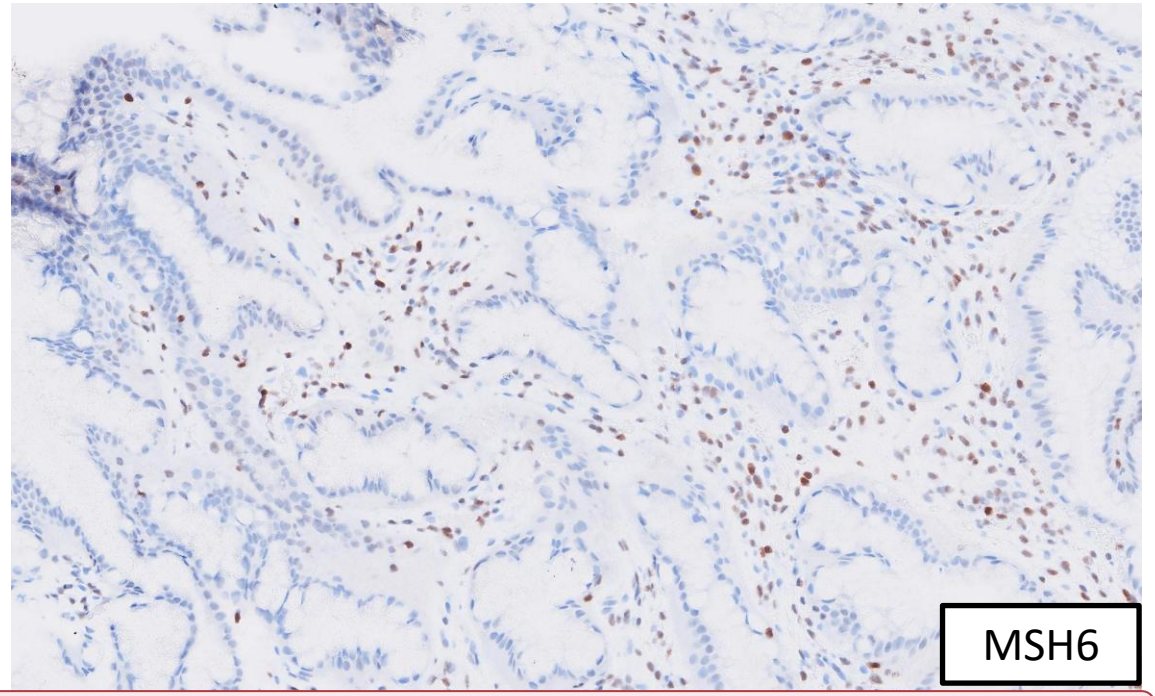
H. Pylori Negative Dysplasia-Summary

1 A distinct disease	Hp Neg. Gastric Neoplasms are rising, occur in younger patients and more women, and carry few genetic and epigenetic hits.
2 Location predicts type	Each lesion has its own compartment. IGD is prepyloric; FGA and OGA/GA-FG are in fundic mucosa.
3 Fov. Adenoma is two tumors	Flat (APC/KRAS, large, whitish) vs raspberry (KLF4 SNV, tiny red polyp).
4 Intestinal subtype is an outlier	Intestinal phenotype and p53 overexpression — closest to Hp-infected cancer; possible multistep path.

Low grade foveolar morphology in dMMR pathway

- MSI has been reported in foveolar-phenotype gastric neoplasms, including early lesions.
- Some precursor lesions of MSI gastric carcinoma show the histologic features of low-grade foveolar-type dysplasia.





These lesions can progress to MSI-H carcinoma and should be completely resected.
In a suspicious foveolar lesion showing intraepithelial lymphocytosis, MMR IHC should be ordered.

American Journal of Pathology, Vol. 157, 2000

An Epstein–Barr Virus Pathway

- EBV-associated gastric neoplasia may present with low-grade foveolar dysplasia contiguous with EBV-positive adenocarcinoma.
- In a suspicious foveolar lesion showing intraepithelial lymphocytosis, EBER ISH shall be tested.
- As with the MSI pathway, bland low-grade morphology does not guarantee indolent behavior — background clues (lymphocytosis, contiguity with carcinoma) matter.

Virchows Archiv (2022) 480:939–944
https://doi.org/10.1007/s00428-021-03206-2

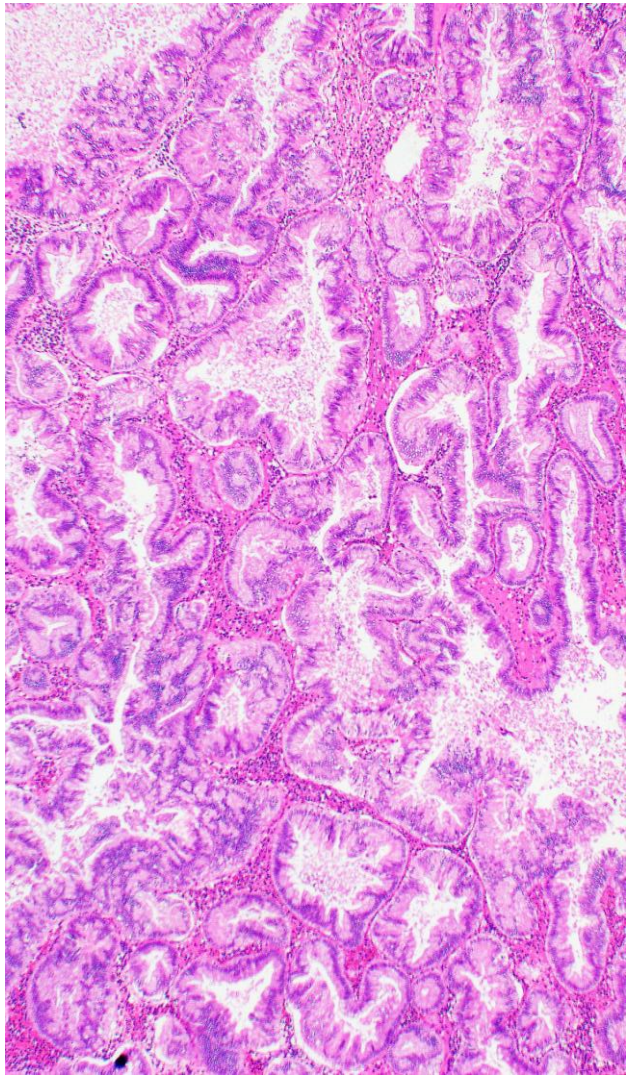
BRIEF REPORT

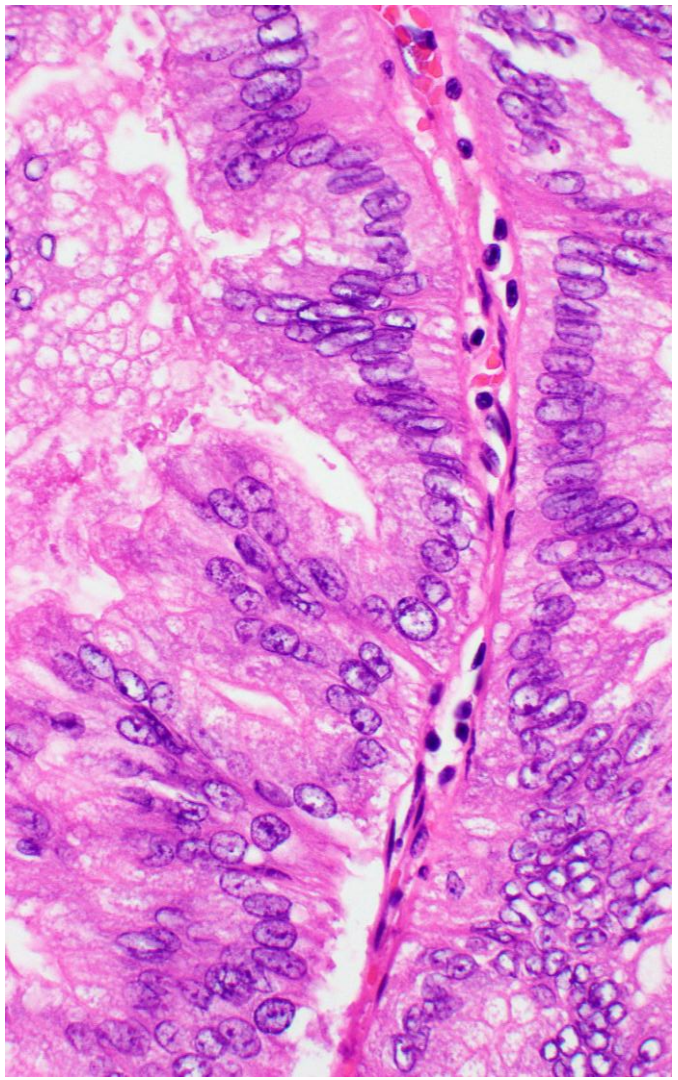
Check for updates

Epstein-Barr virus associated gastric dysplasia: a new rare entity?

Serrated Dysplasia

- Rare (few series in 2001 and thereafter)
- Pure (>80% of tumor) or mixed w/ conventional adenoma
- Foveolar differentiation, >60% express MUC5AC.
- High risk lesion, 75% associated with invasive adenocarcinoma.





- Elongated glands w/ a serrated, saw-toothed contour.

J Clin Pathol 2016;69:1-5. J Clin Pathol 2001;54:849-53.

Take Away Message

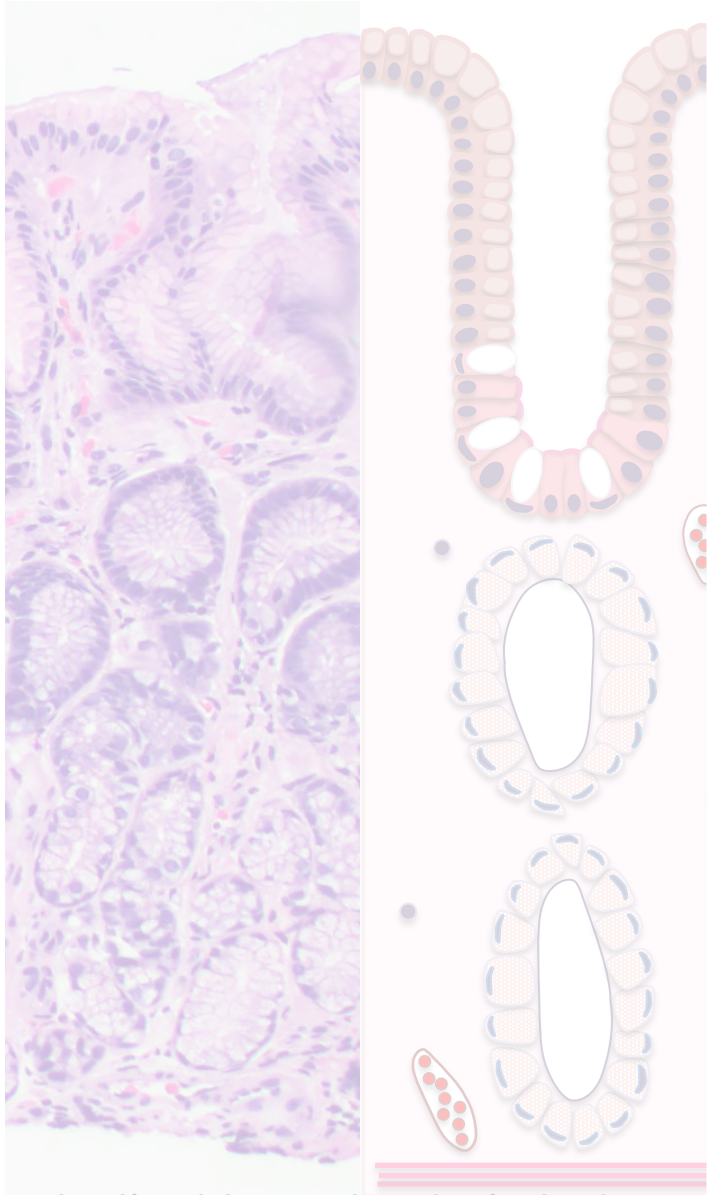
- Surface epithelium-derived dysplasia divides broadly into intestinal-type and foveolar-type (including serrated-type) — but each category contains heterogeneous subgroups.
- Endoscopic appearances, background mucosae, histologic patterns, and molecular alterations are increasingly characterized.

LOWER RISK	VARIABLE	HIGHER RISK
▪ Typical low-grade intestinal-type dysplasia/adenoma ▪ Flat-elevated foveolar adenoma ▪ Raspberry-type adenoma · ▪ Dysplasia in fundic gland polyp	▪ Intestinal-type in H. pylori-naïve stomach (p53 overexpression) ▪ Lesions with atypical endoscopic features	▪ Serrated dysplasia/adenoma · ▪ Foveolar-type NOS · ▪ MSI- and EBV-associated precursors ▪ Any high-grade lesion

Evolving characterization and precise prediction of progression of each lesion is not yet possible in every case. Best practice: recognize the distinctive entities, identify features suggesting an unsampled high-grade/carcinoma component, and integrate pathology with endoscopic and clinical context.

SURFACE EPITHELIUM-DERIVED

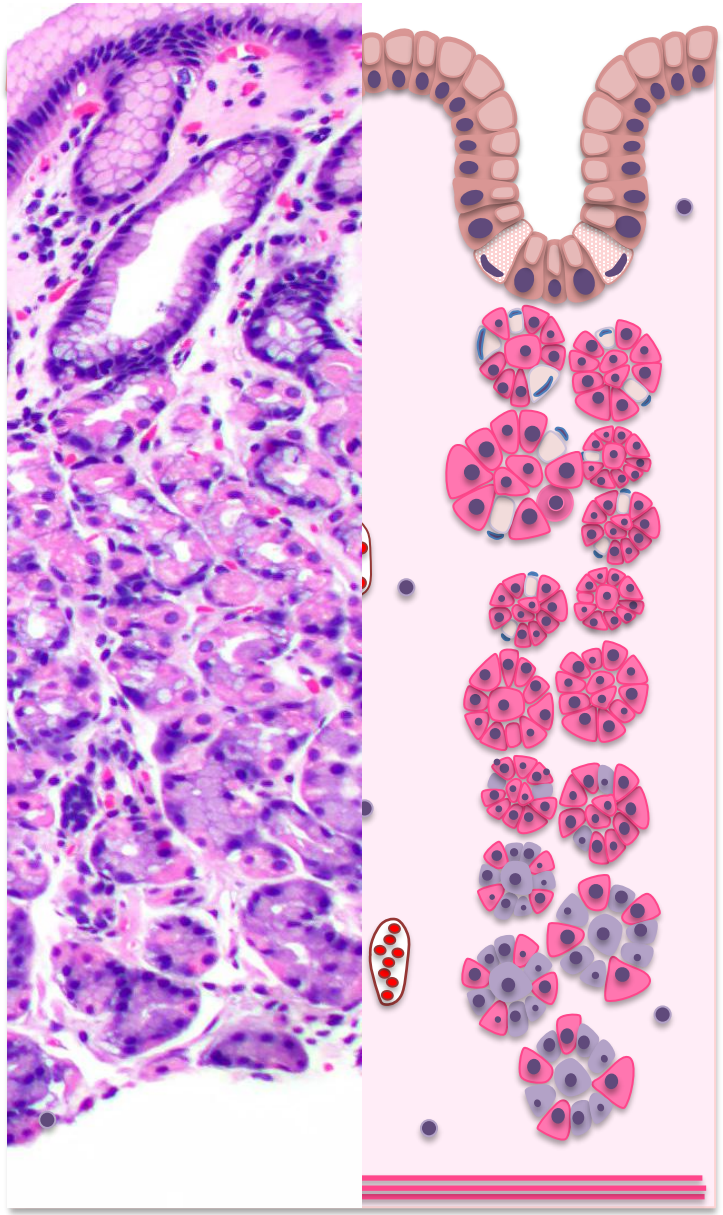
H. PYLORI POSITIVE



H. PYLORI NEGATIVE

- Intestinal-type dysplasia/adenoma
- Foveolar-type dysplasia/adenoma
- Serrated dysplasia/adenoma

SUB-SURFACE-DERIVED



H. PYLORI NEGATIVE

- Pyloric gland adenoma
- Oxyntic gland adenoma
- Pit/crypt dysplasia

PGA: a rare neoplasm of injured mucosa

<3%
of all gastric polyps

6%
of FAP patients develop PGA

Lynch syndrome
PGAs described; malignant transformation reported

Background settings

- **Atrophic gastritis** — *H. pylori* or autoimmune
- **FAP** — alongside fundic gland polyps and foveolar-type adenomas
- **Lynch syndrome**

Pathogenesis

- Unknown; arises in areas of **pyloric gland metaplasia** related to chronic mucosal injury
- Presumed result of repeated injury and repair

Clinical and gross features of PGA

Corpus

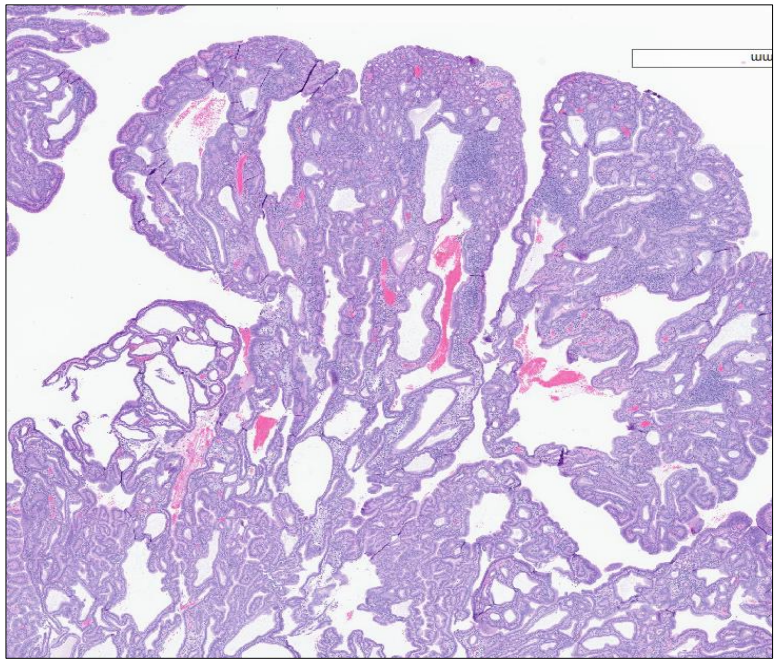
most common gastric site, but can occur anywhere

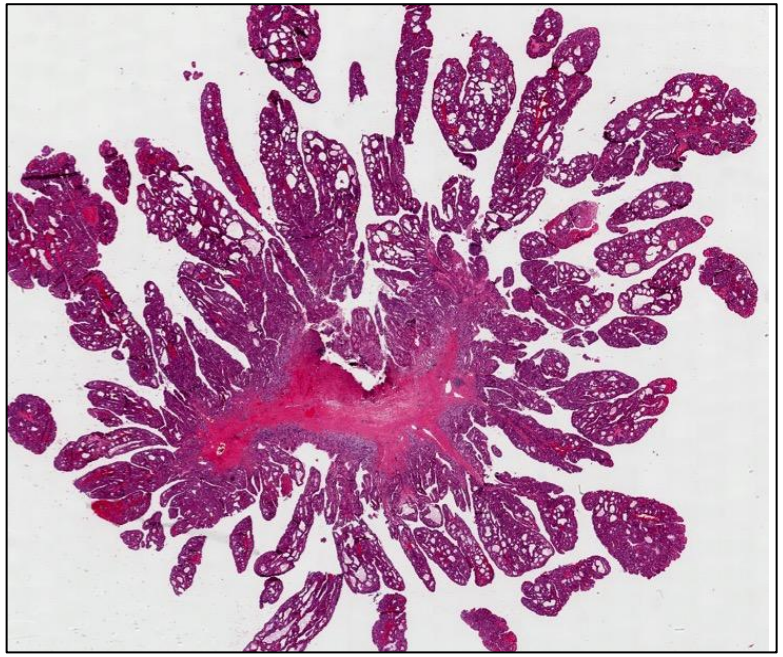
1.7 cm

median diameter

75 years

average age; elderly women predominate





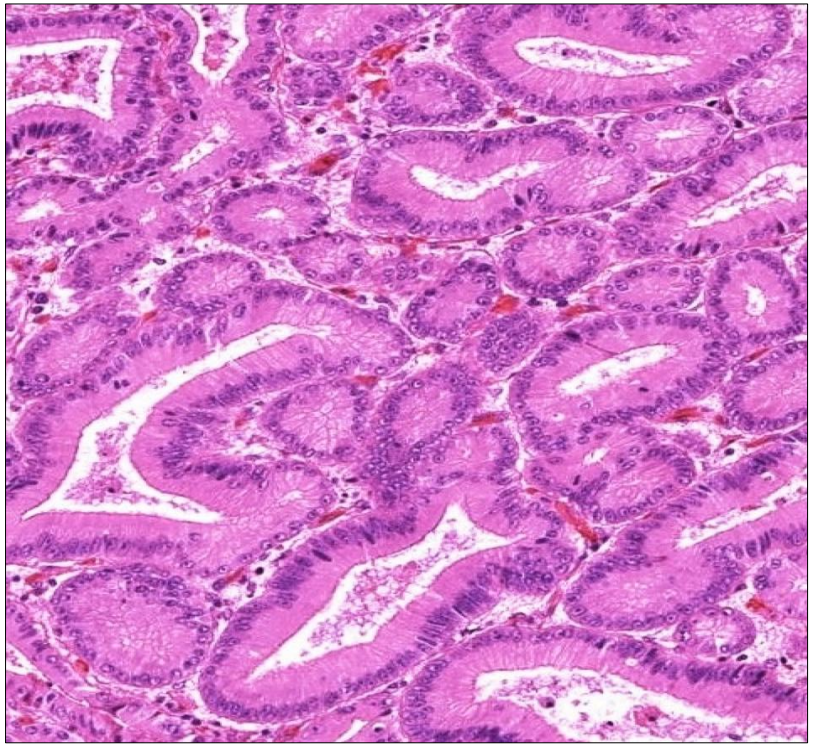
Presentation

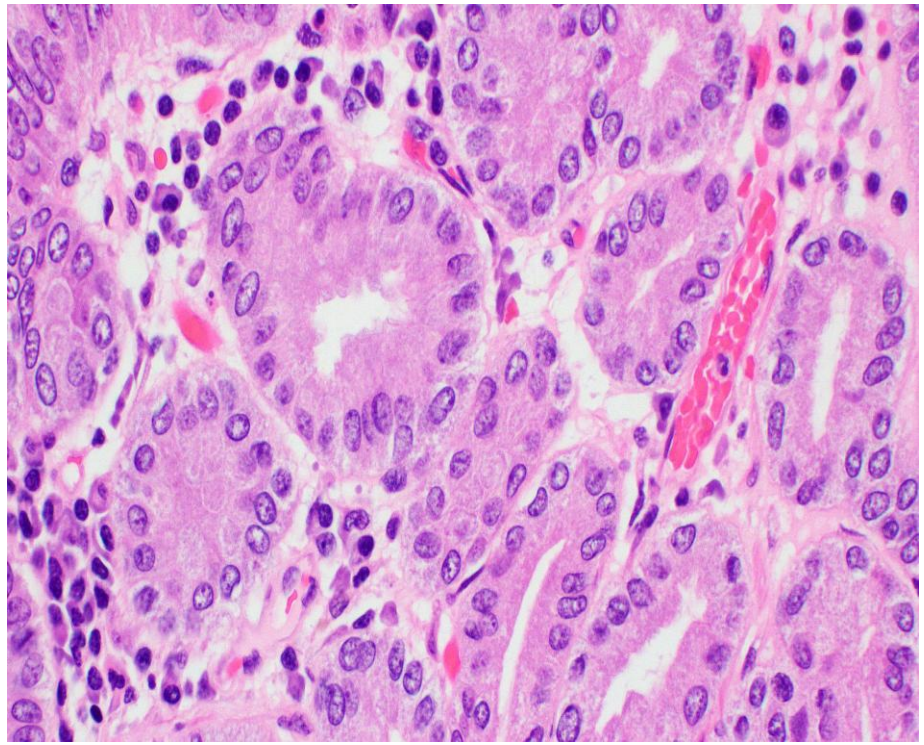
- Usually asymptomatic
- Found secondary to symptoms of underlying gastritis

Gross

- Polypoid, dome-shaped polyp
- Larger lesions may form a fungating mass

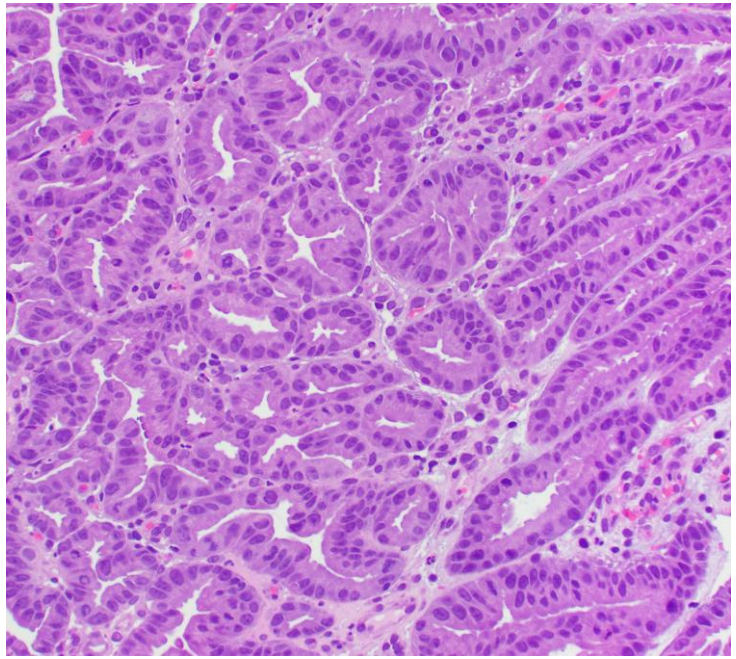
PGA with low-grade dysplasia

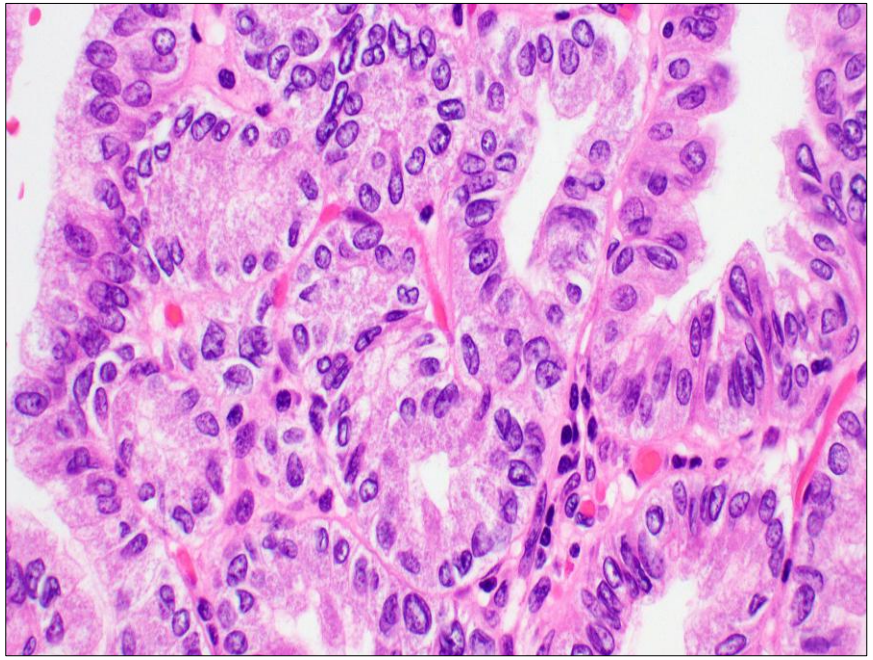




- **55%** LGD (avg. 1.7 cm)
- Packed tubules; irregularly shaped, cystically dilated glands may be seen; rarely broad villous projections
- Single layer of low columnar to cuboidal cells
- Distinctly pale eosinophilic cytoplasm with a ground-glass quality
- Basally located round nuclei

PGA with high-grade dysplasia





37% HGD (avg. 3.4 cm)

TVA more commonly associated with HGD (52%) than LGD

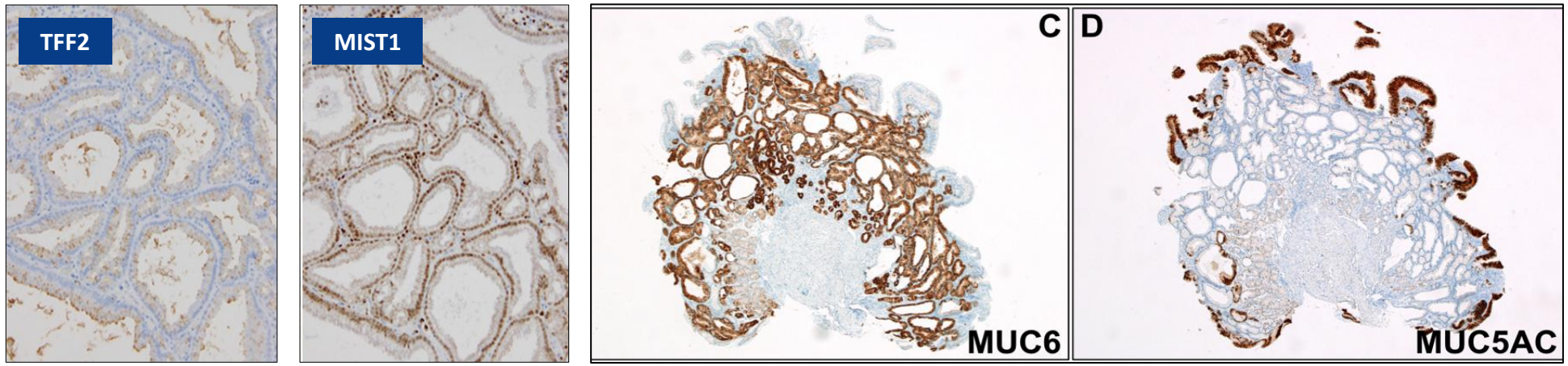
High-grade features

- Varied cytoarchitectural anomalies: back-to-back glands, cribriforming
- Hyperchromasia, high N/C ratio, loss of nuclear polarity, enlarged nucleoli

Ushiku T, Lauwers GY. Gastroenterol Clin North Am 2024;53:39–55

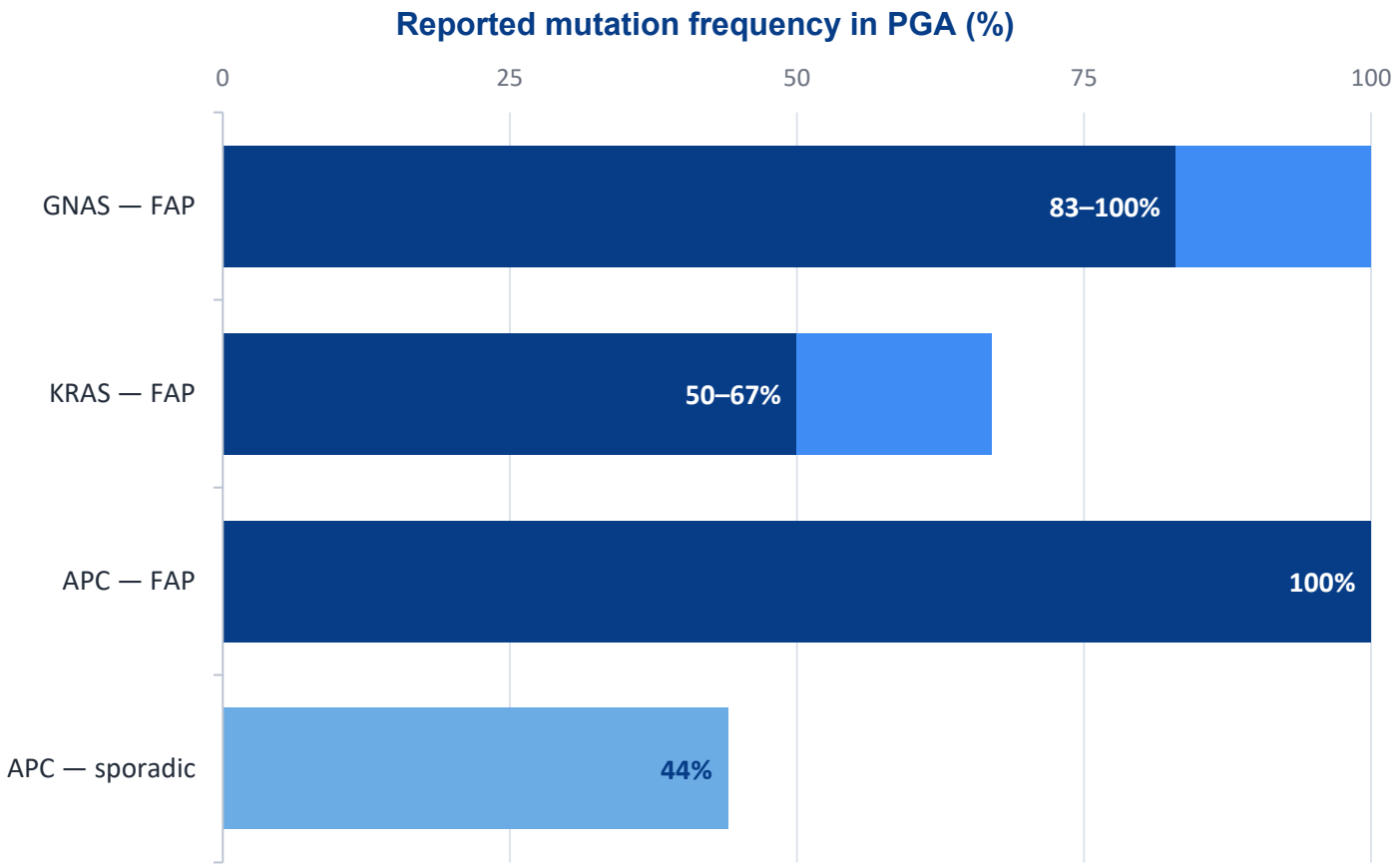
Immunohistochemical profile of PGA

Marker	Expression in PGA	Pattern / significance
MUC6	Positive	Always at the base; may involve the entire lesion incl. surface
MUC5AC	Positive (variable)	Varies case to case; co-expression with MUC6 throughout
TFF2	Diffusely positive	In keeping with pyloric gland phenotype
MIST1 / Pepsinogen I	Focal	Chief cell / mucous neck cell differentiation in some cases
MUC2	Rare	Only in areas of intestinal metaplasia
CDX2	Rare	Only in intestinal metaplasia, often adjacent mucosa



Choi WT et al. Histopathology 2018

Molecular features: GNAS, KRAS and APC



Light segment = reported range. APC: somatic truncating mutations.

Shared genotype

FAP-associated and sporadic PGAs share morphology and GNAS, KRAS and APC mutations

Lynch syndrome

Unlike sporadic PGAs, Lynch-associated PGAs are MSI

Common pathogenesis with OGA

Oxyntic gland adenomas share these alterations

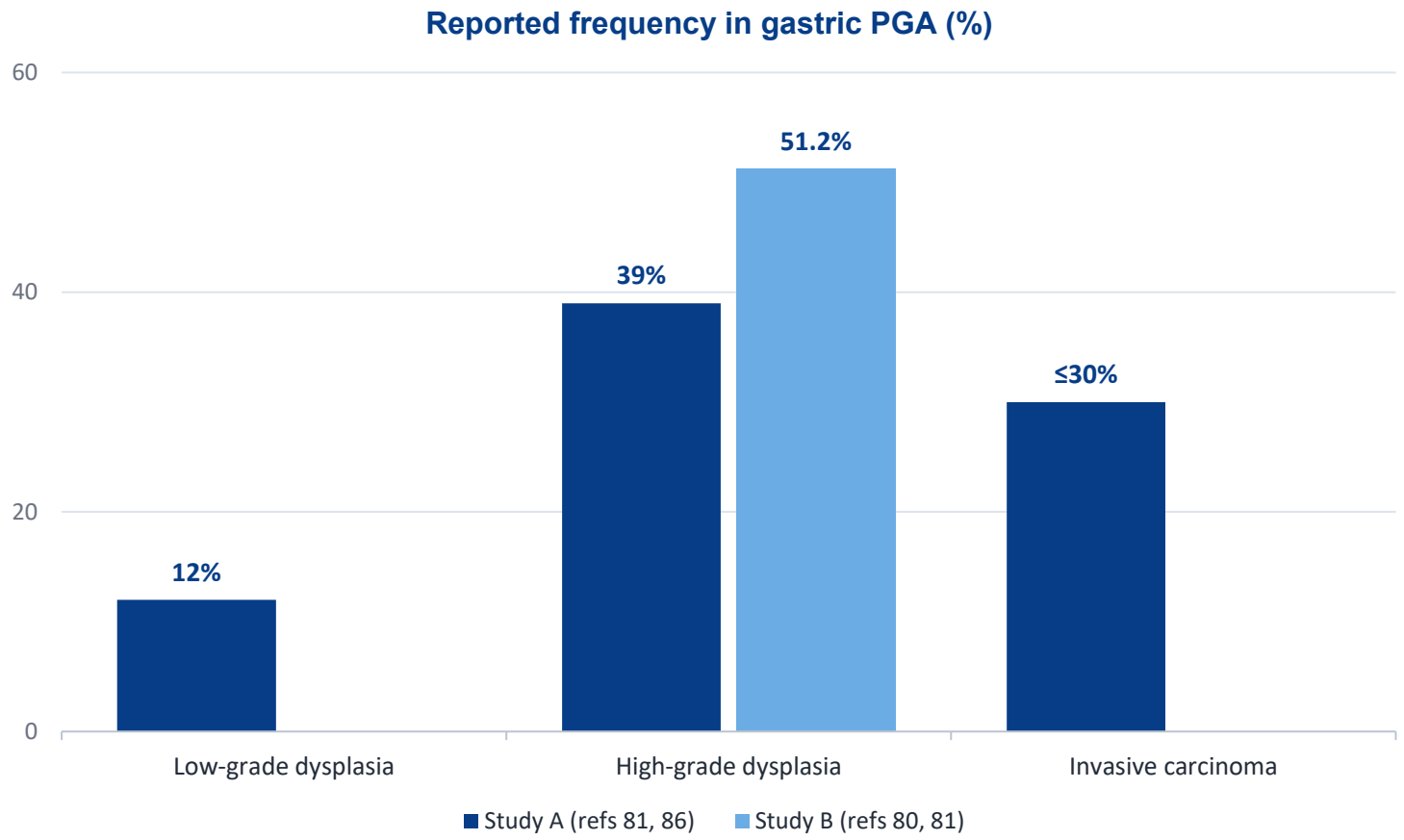
Differential: PGA vs foveolar adenoma

Feature	Pyloric gland adenoma	Foveolar-type adenoma
Apical mucin cap	Not well formed	Well-formed
MUC5AC	**Positive**	**Positive**
MUC6	**Positive**	**Negative**
PAS / Alcian blue	Granular cytoplasmic staining	Bright red, uniform mucin staining
Parietal cells	Scattered to abundant in FAP-associated PGA	Not commonly seen (sporadic)

Discriminating stain
MUC6 positivity favors PGA; foveolar-type adenoma is MUC5AC+ / MUC6−

Also consider
Oxyntic gland adenoma — morphologic overlap and shared GNAS/KRAS/APC alterations

PGA are frequently progressive



~25%

of HGD cases in Study B also had invasive carcinoma

Bottom line

Despite bland histology, PGAs can — and often do — evolve into invasive adenocarcinoma with pyloric gland differentiation

Oxyntic gland neoplasms: adenoma and adenocarcinoma of fundic gland type

- Arise from the oxyntic mucosa with a **multilineage phenotype** — differentiation toward chief cells, parietal cells and mucous neck cells
- Biologic behavior ranges from benign (*oxyntic gland adenoma*) to malignant (*adenocarcinoma of fundic gland type*)
- Novel unifying nomenclature proposed: **“oxyntic gland neoplasm”**

66 yrs
mean age

3 : 1
male : female

3–40 mm
most in upper third of the stomach

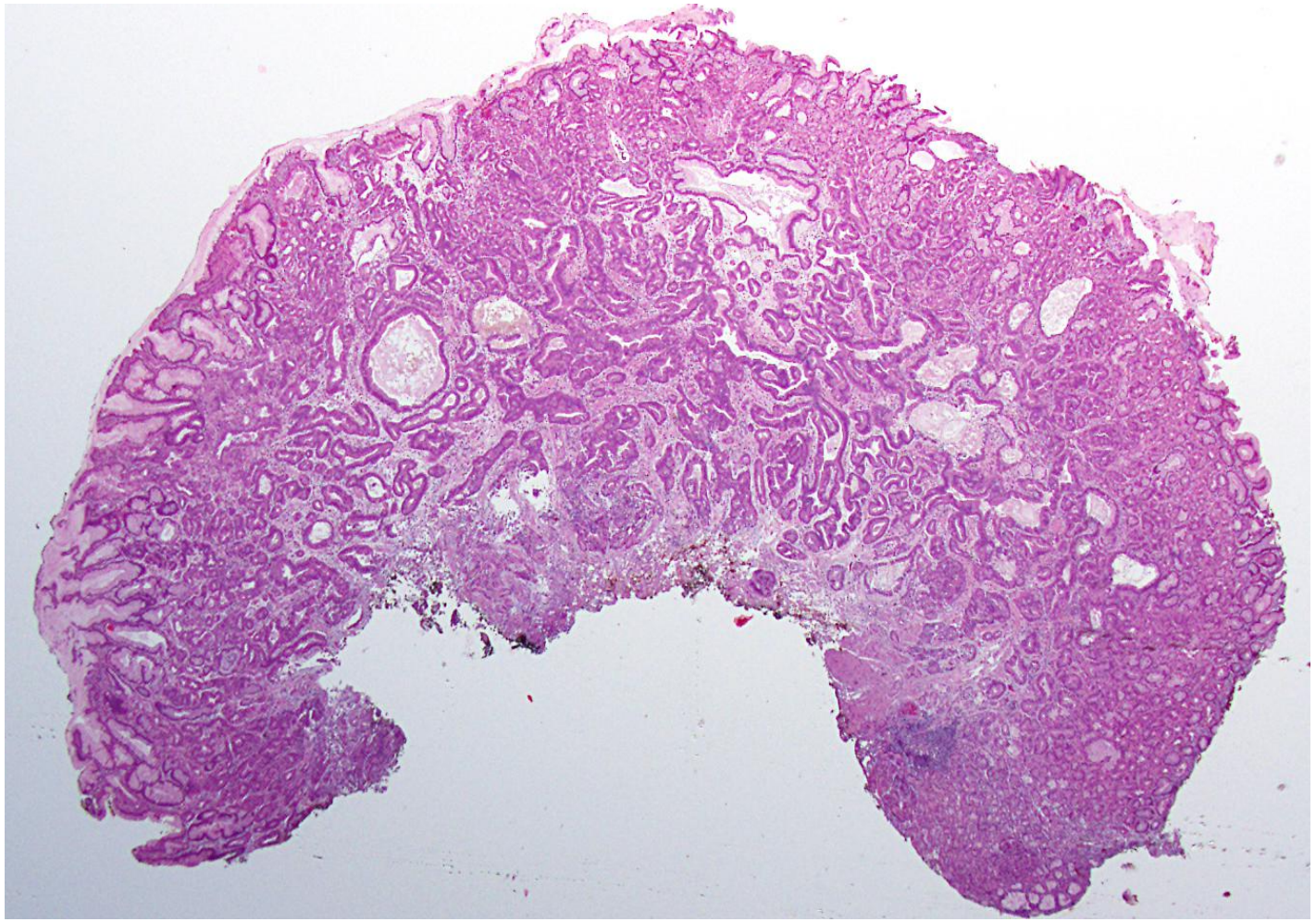
50%
of cases with PPI use

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Ushiku T, Lauwers GY. Gastroenterol Clin North Am 2024;53:39–55

Gastric adenocarcinoma of fundic gland type

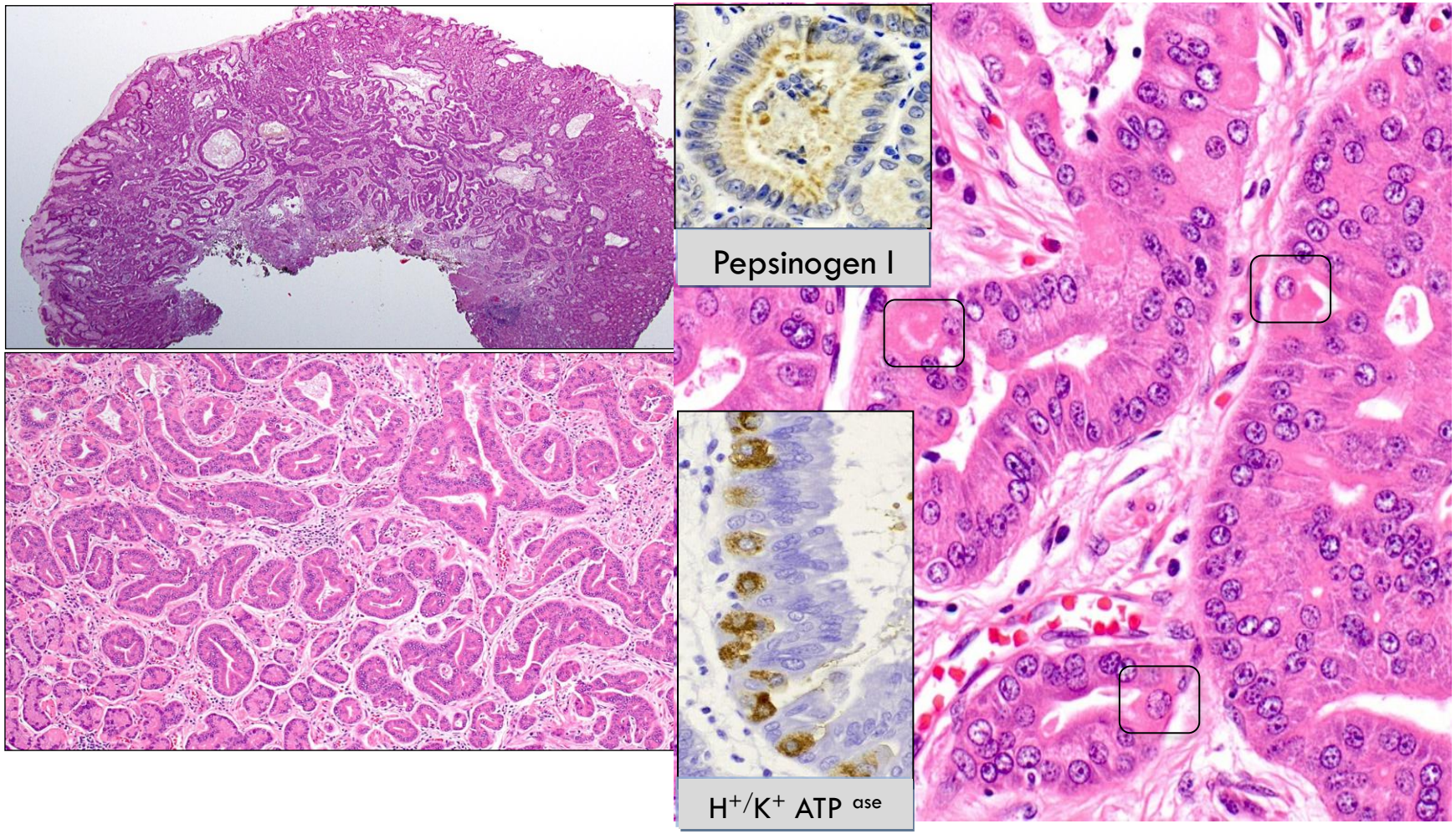
(chief cell predominant type) *a new entity (2010)*



MOFFITT CANCER CENTER

Ueyama H et al. Am J Surg Pathol 2010;34:609–619

Chief and parietal cell differentiation:
pepsinogen I and H+/K+-ATPase



Pepsinogen I
chief cell component

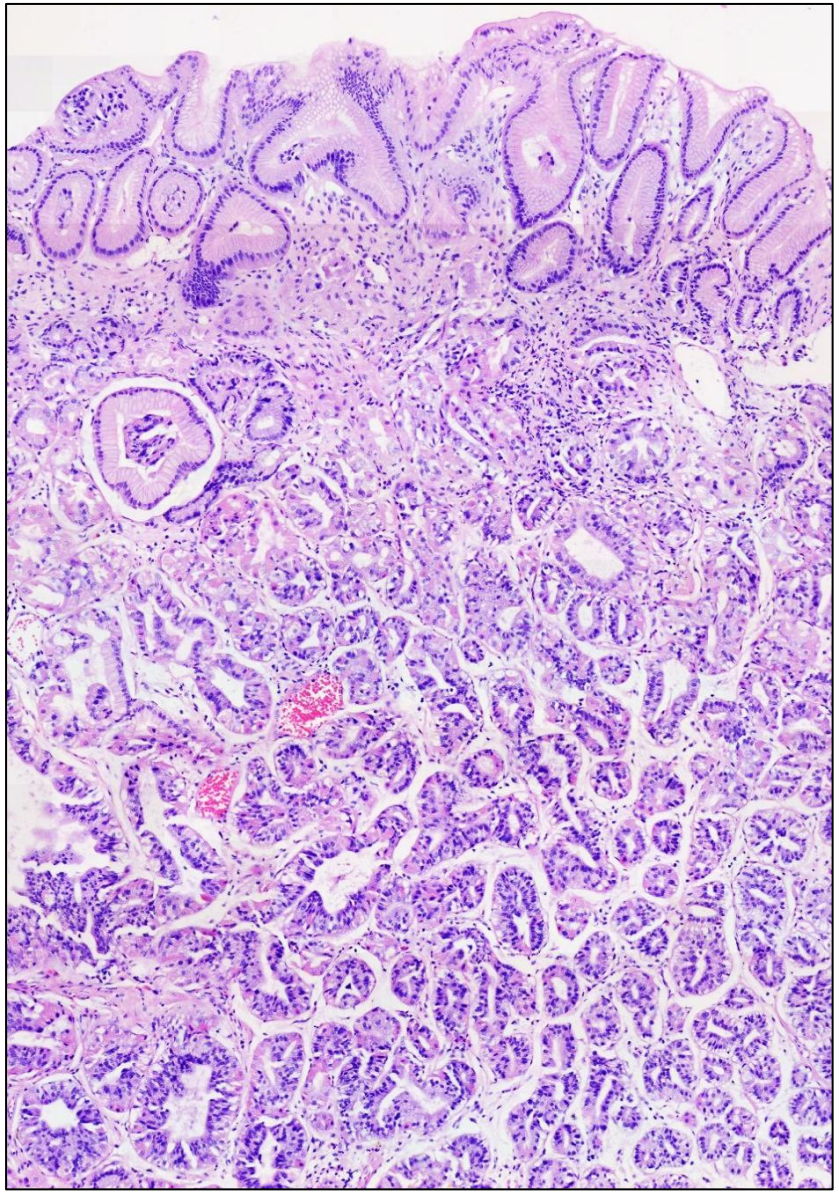
H+/K+-ATPase
parietal cell component

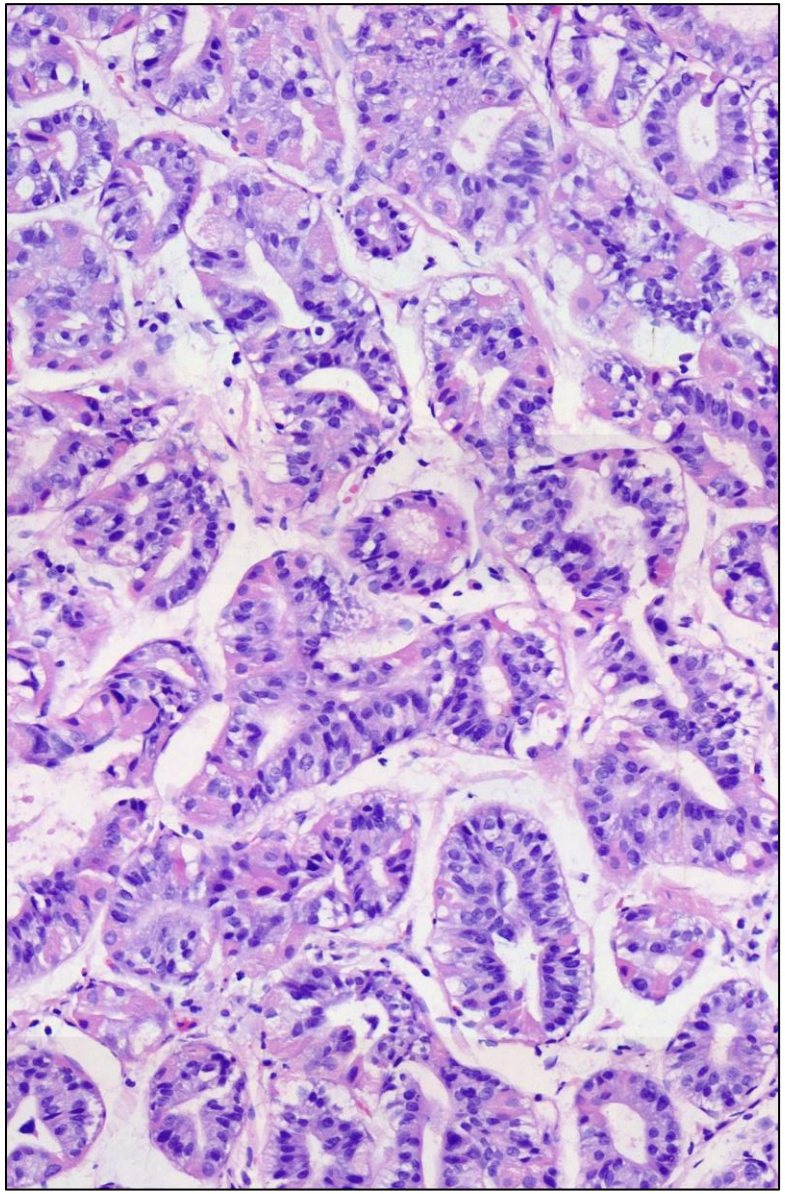
Lymphovascular invasion & nodal metastases

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Ueyama H et al. Am J Surg Pathol 2010;34:609–619

Reclassification as oxyntic gland polyp/adenoma





Am J Surg Pathol 2012;36:1030–1035

Oxyntic gland adenoma (OGA): clinical profile

1. **Demographics**
   Mean age ~66 years

2. **Etiology**
   Not associated with H. pylori, intestinal metaplasia or atrophic gastritis

3. **Molecular**
   Wnt/β-catenin alterations (CTNNB1, AXIN, APC, GNAS) in ~50% of cases

4. **Spectrum**
   Part of a spectrum with PGA — chief/parietal-predominant tumors are OGAs; hybrids occur

0.01–0.07%
reported incidence

~66 yrs
mean age

50%
of patients used PPIs

Ushiku T., Lauwers GY Gastroentol Clin North Am, 2024;53:39-55

OGA: gross and endoscopic features

1. **Location**

   Oyntic mucosa of the gastric body and fundus

2. **Size**

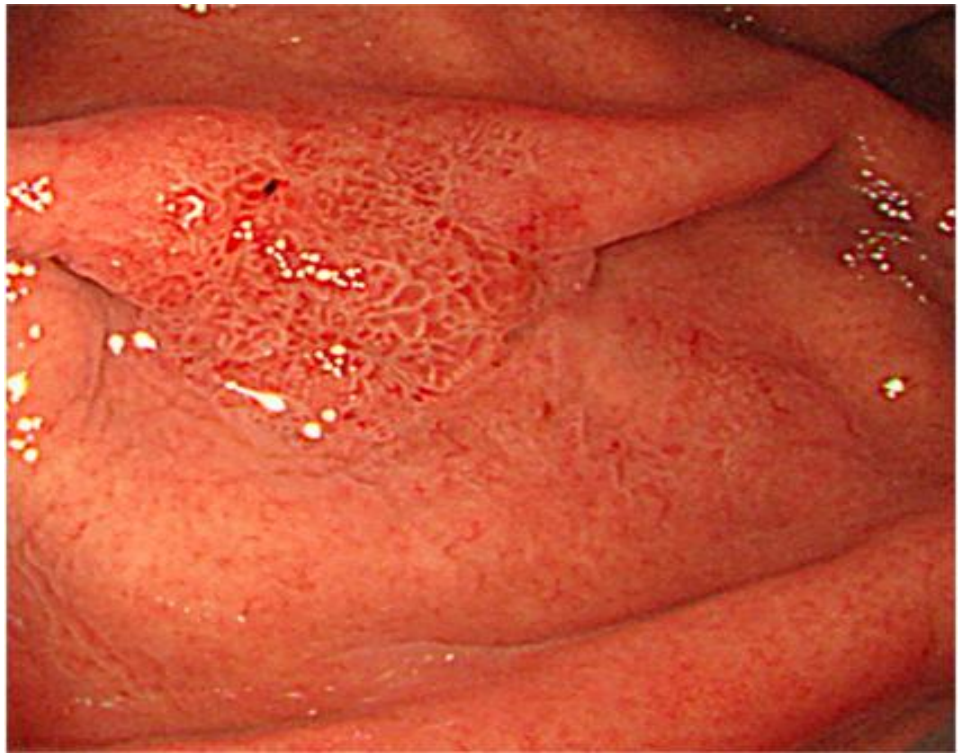
   Small, 4–20 mm; most <10 mm; typically solitary

3. **Configuration**

   Usually superficially elevated (polypoid or raised-flat); may also appear depressed

4. **Background**

   Endoscopically normal or near-normal mucosa

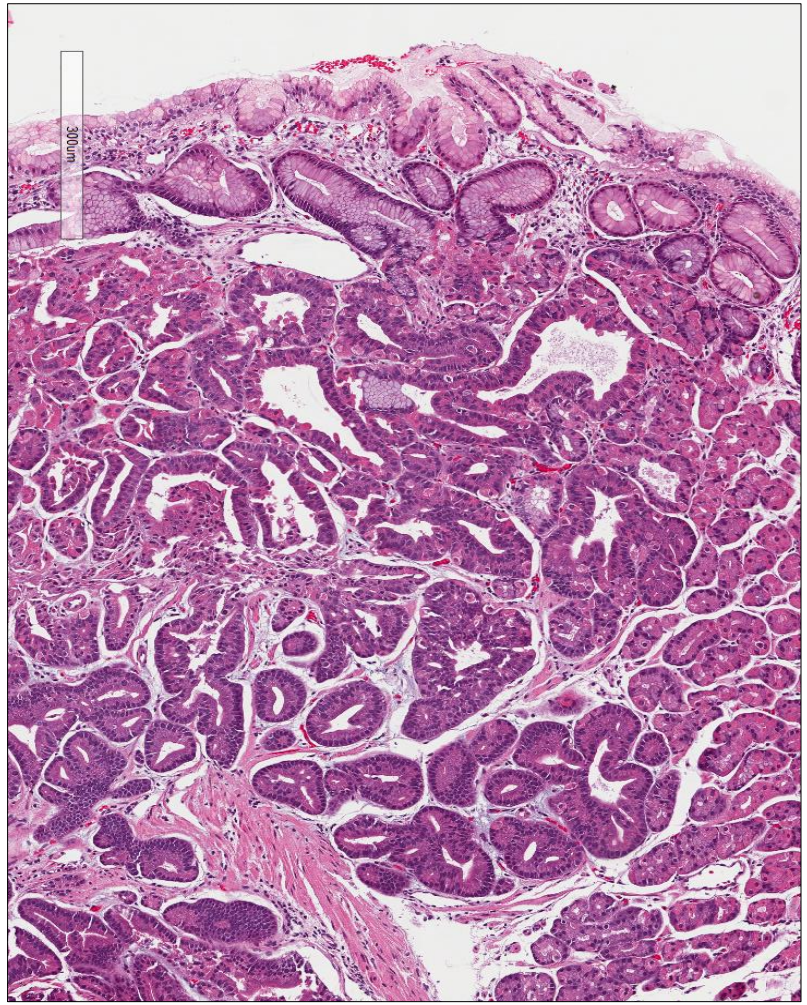


Elevated, polypoid gastric-body lesion with a finely nodular, corrugated surface arising from otherwise unremarkable mucosa.

Ushiku T., Lauwers,GY Gastroentol Clin North Am, 2024;53:39-55

OGA: Architectural patterns

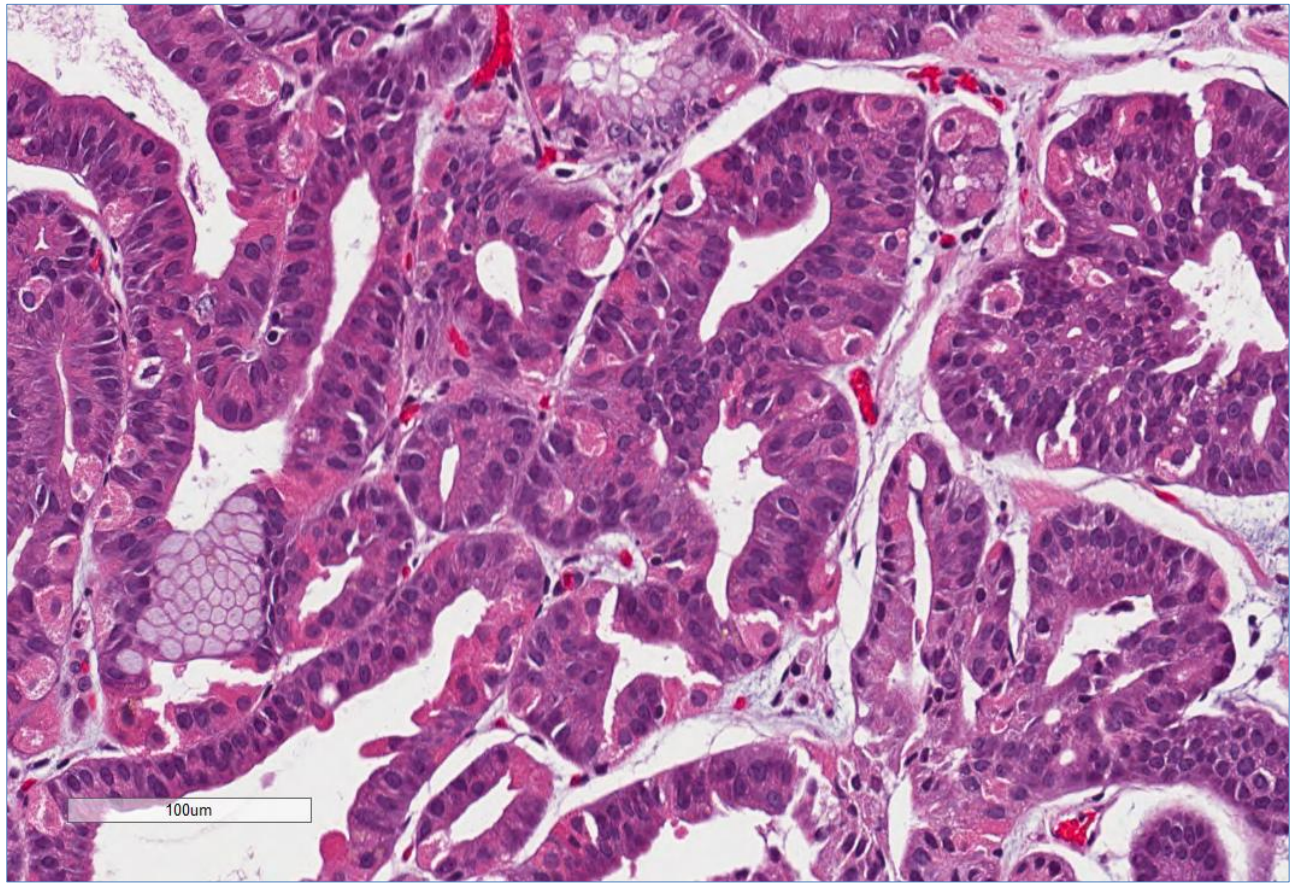
- Packed tubules/trabeculae; chief-cell-predominant, mixed chief/parietal, or mucous-neck/foveolar patterns
- Solid glands.
- Anastomosing cords
- **Key pitfall:** Herniation through the muscularis mucosae should not be mistaken for invasive carcinoma absent desmoplastic changes



OGA: Morphologic Spectrum

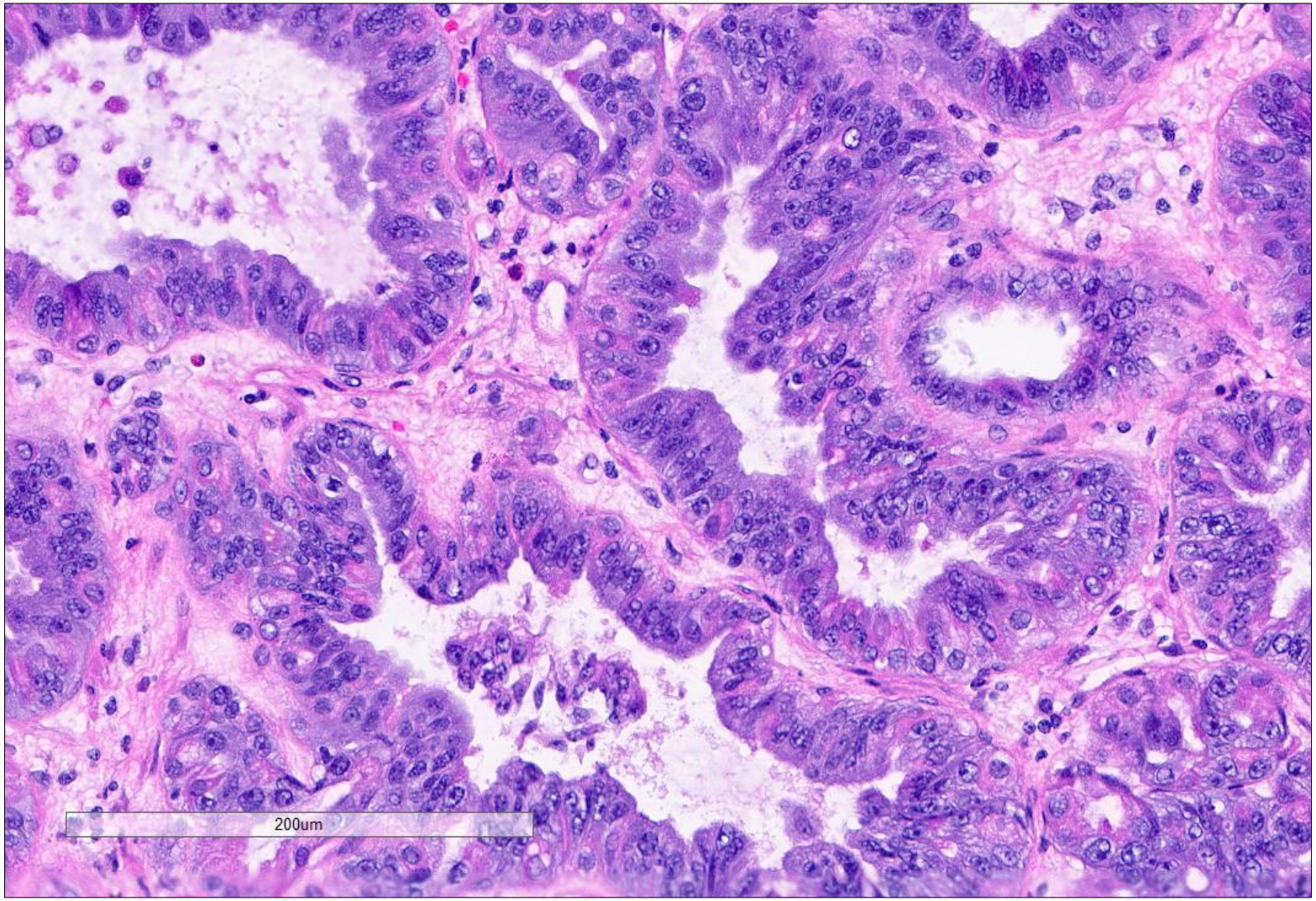
- Dilated glands ± luminal infolding
- Complex glds

  w/ multiple cell layers
- Cribriform glands



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- NO PNI - NO LVI -NO Submucosal involvement



>50% mild atypia anisonucleosis; Increased N:C ratio

8% necrosis

Chan K et al. Histopathology 2016;68:825–833

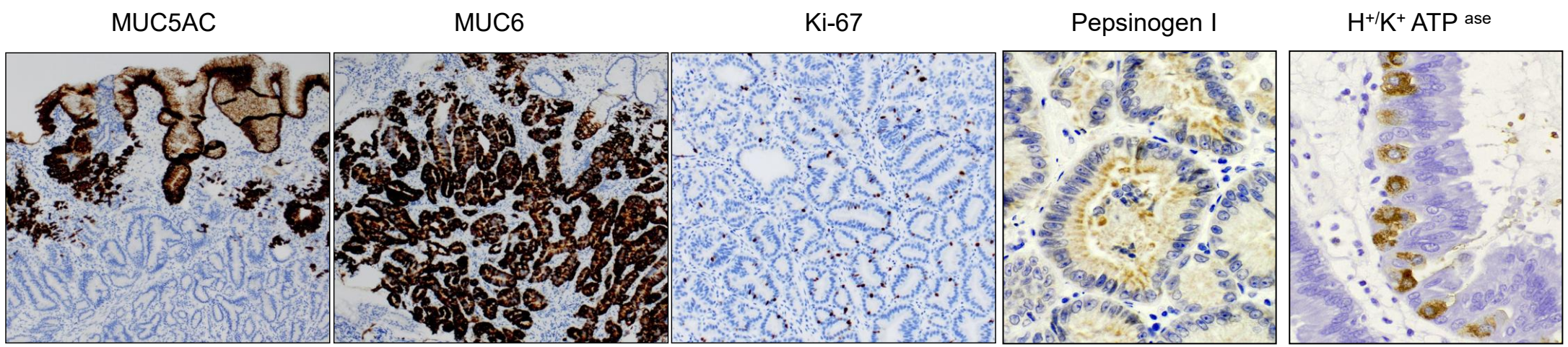
Immunophenotype

Marker	Result	Interpretation
MUC6	**Positive**	Gastric (pyloric / neck-cell) mucin
Pepsinogen-I	**Positive**	Chief cell differentiation
MUC5AC	**Negative**	No foveolar differentiation
MUC2	**Negative**	No intestinal differentiation
CD10	**Negative**	No intestinal brush border

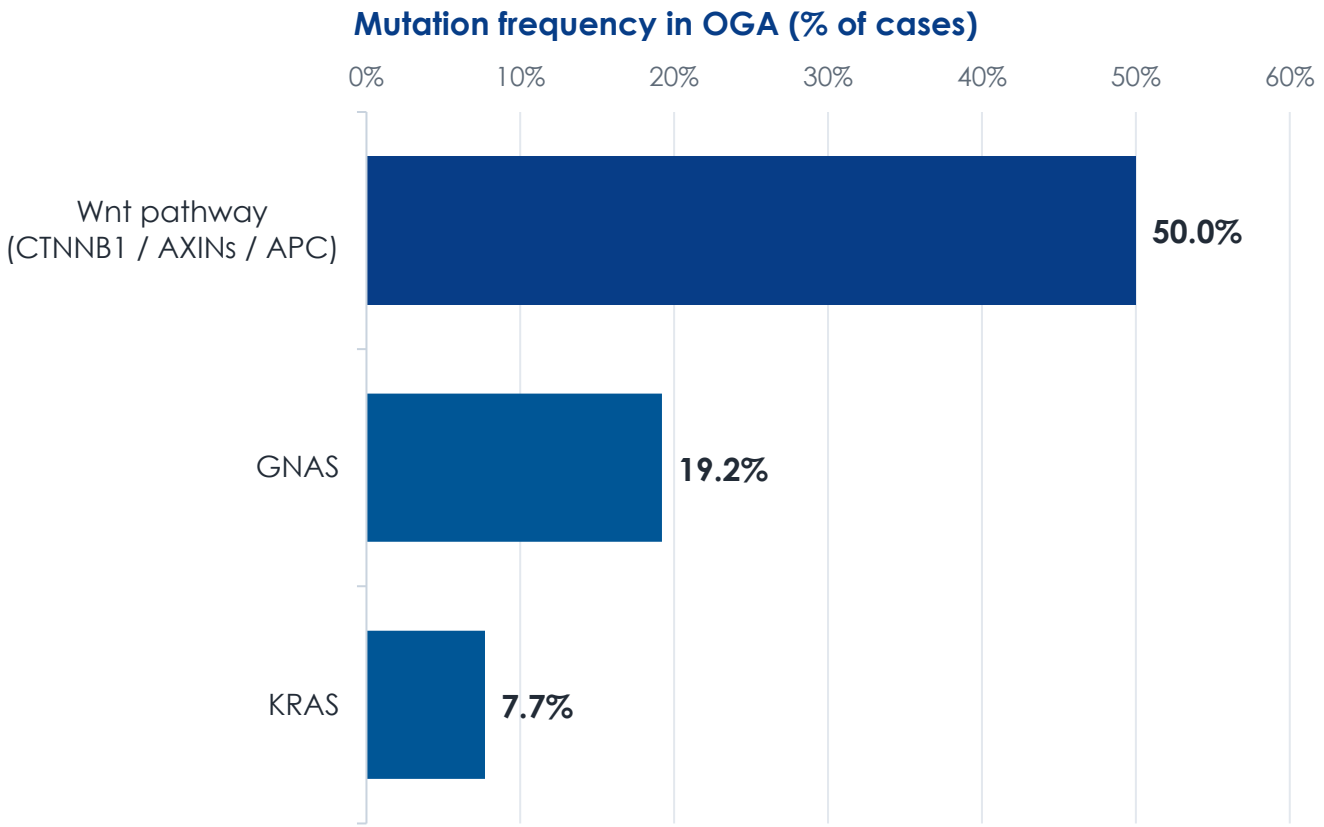
Gastric phenotype

MUC6+ / pepsinogen-I+
MUC5AC− / MUC2− / CD10−

MUC5AC negativity helps separate OGA from fundic gland polyp, whose foveolar epithelium is MUC5AC-positive.



Molecular Features



≈50% of cases harbor at least one Wnt-component mutation. Data per ref 99.

Convergent mechanism

CTNNB1 / AXINs / APC mutation

GNAS mutation

Constitutive Wnt/β-catenin activation
β-catenin accumulation

GNAS mutations act as an alternative route to the same pathway; activating KRAS mutations occur in a minority.



OGA
Benign end of spectrum

Adenocarcinoma, fundic gland (chief cell) type

Modern Pathology
https://doi.org/10.1038/s41379-019-0338-1

ARTICLE

Oxyntic gland neoplasm of the stomach: expanding the spectrum and proposal of terminology

Tumors with typical morphology (chief cell predominant)

- mucosal or submucosal
- mild or focal moderate nuclear atypia

OXYNTIC GLAND ADENOMA

Tumors with atypical features (= submucosal invasion)

- morphologic component (chief mucus neck cells/ foveolar)
- marked atypical proliferation
- larger 26.8 mm average (5/6x)
- 50% had LVI
- One case with *K-ras* mutation in addition to *GNAS*

ADENOCARCINOMA OF FUNDIC GLAND TYPE

Ushiku T, et al. Mod Pathol 2019 · Ueyama H, et al. J Gastroenterol 2021;56:814–828

https://doi.org/10.1007/s00535-021-01813-z

Gastric epithelial neoplasm of fundic-gland mucosa lineage: proposal for a new classification in association with gastric adenocarcinoma of fundic-gland type

Type	MUC5AC	MUC6	PG-I and/or H^+/K^+-ATPase	Defining feature	n	Grade*
Oxyntic gland adenoma (OGA)	–	+ / –	+	Fundic-gland–like cells; confined to mucosa	20	**Low**
GA-FG (fundic-gland type)	–	+ / –	+	Same cells; submucosal invasion	55	**Low**
GA-FGM (fundic-gland mucosa type)	+	+	+	Mixed fundic-gland–like and foveolar-like cells	25	**High**

MUC5AC is the switch: tumoral MUC5AC expression separates GA-FGM from OGA/GA-FG. OGA and GA-FG are usually covered by non-neoplastic foveolar mucosa (exposed tumor <10%); they differ only in depth of invasion.

*Authors' designation: low- vs high-grade epithelial neoplasm

Ueyama H, et al. J Gastroenterol 2021;56:814–828

Two frameworks, converging names

Ushiku 2019 — depth + atypical features		Ueyama 2021 — IHC lineage + architecture
Group A · intramucosal "Oxyntic gland adenoma"		**OGA · intramucosal** OGA (n = 20) — "intramucosal phase of GA-FG"
Group B · submucosal, typical "Oxyntic gland adenoma"		**GA-FG · submucosal** GA-FG (n = 55) — MUC5AC−, MUC6±, PG-I and/or H+/K+
Group C · submucosal, atypical features "Adenocarcinoma of fundic gland mucosa type"		**GA-FGM** GA-FGM (n = 25) — MUC5AC+ foveolar plus fundic lineage; Types 1–3

Ushiku T, et al. Mod Pathol 2019 · Ueyama H, et al. J Gastroenterol 2021;56:814–828

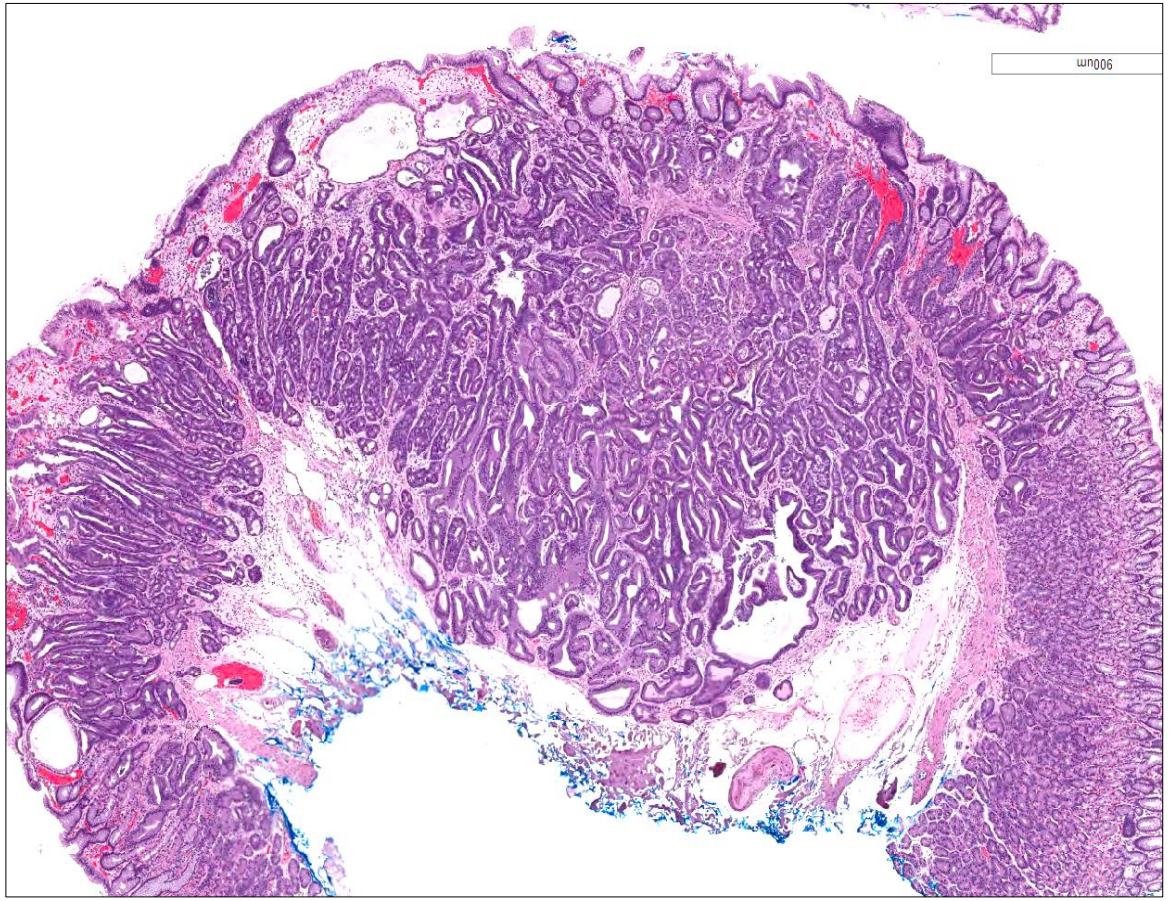
OGA vs GA-FG vs GA-FGM

Feature	OGA (n = 20)	GA-FG (n = 55)	GA-FGM (n = 25)	p
Mean size, mm	7.1	8.4	20.8	**<0.01**
Mean SM depth, µm	NA	251.5	1212.5	**<0.01**
Lymphatic invasion	0%	0%	24% (6/25)	**<0.01**
Venous invasion	0%	1.8% (1/55)	20% (5/25)	**<0.05**
MUC5AC	0%	0%	100%	**<0.01**
p53 overexpression	0%	2.0%	21.1%	**<0.05**

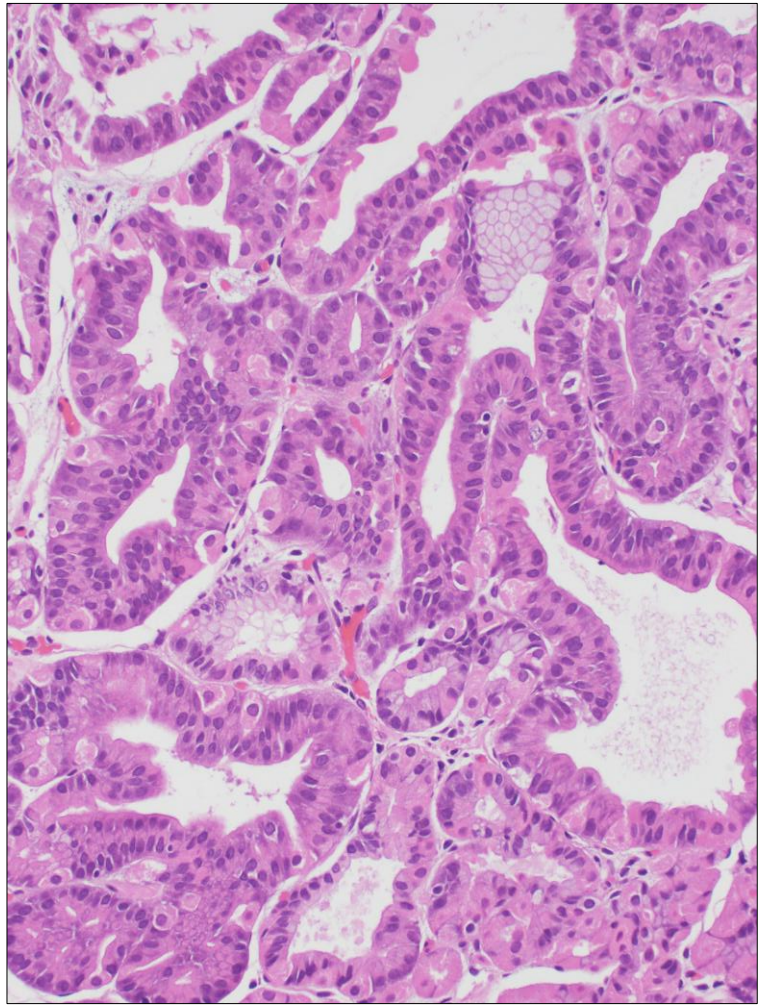
- GA-FGM is ~2.5× larger and invades ~5× deeper than GA-FG
- Lymphovascular invasion essentially confined to GA-FGM
- OGA and GA-FG differ only in depth of invasion
- No recurrence or tumor-related death in any group
- MUC5AC is the only discriminating lineage marker
- p53 overexpression and higher Ki-67 track with GA-FGM
- GNAS mutated in all three types → shared lineage

Modified from Ueyama et al. 2021

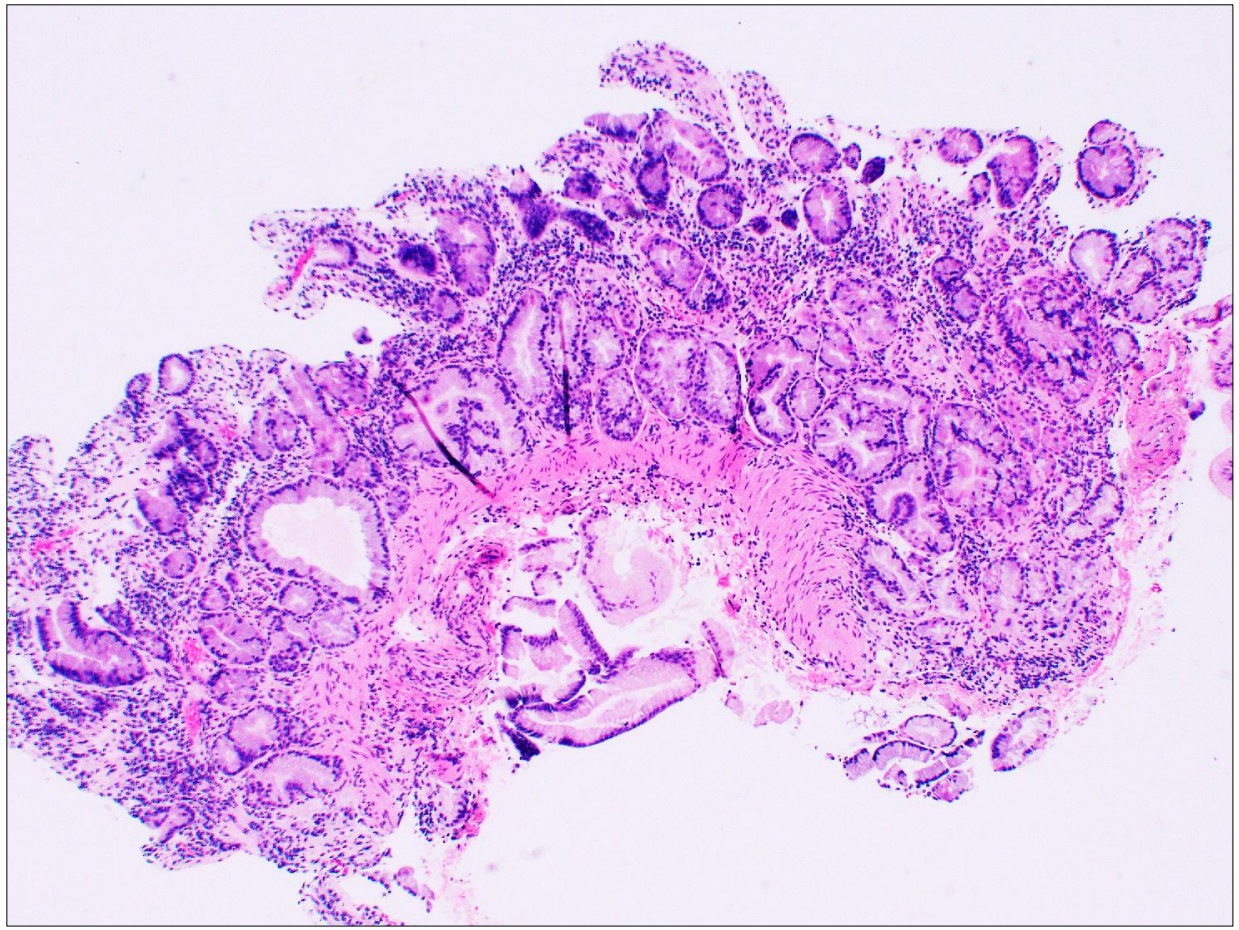
Spectrum: OGA to ACA, fundic gland (chief cell) type

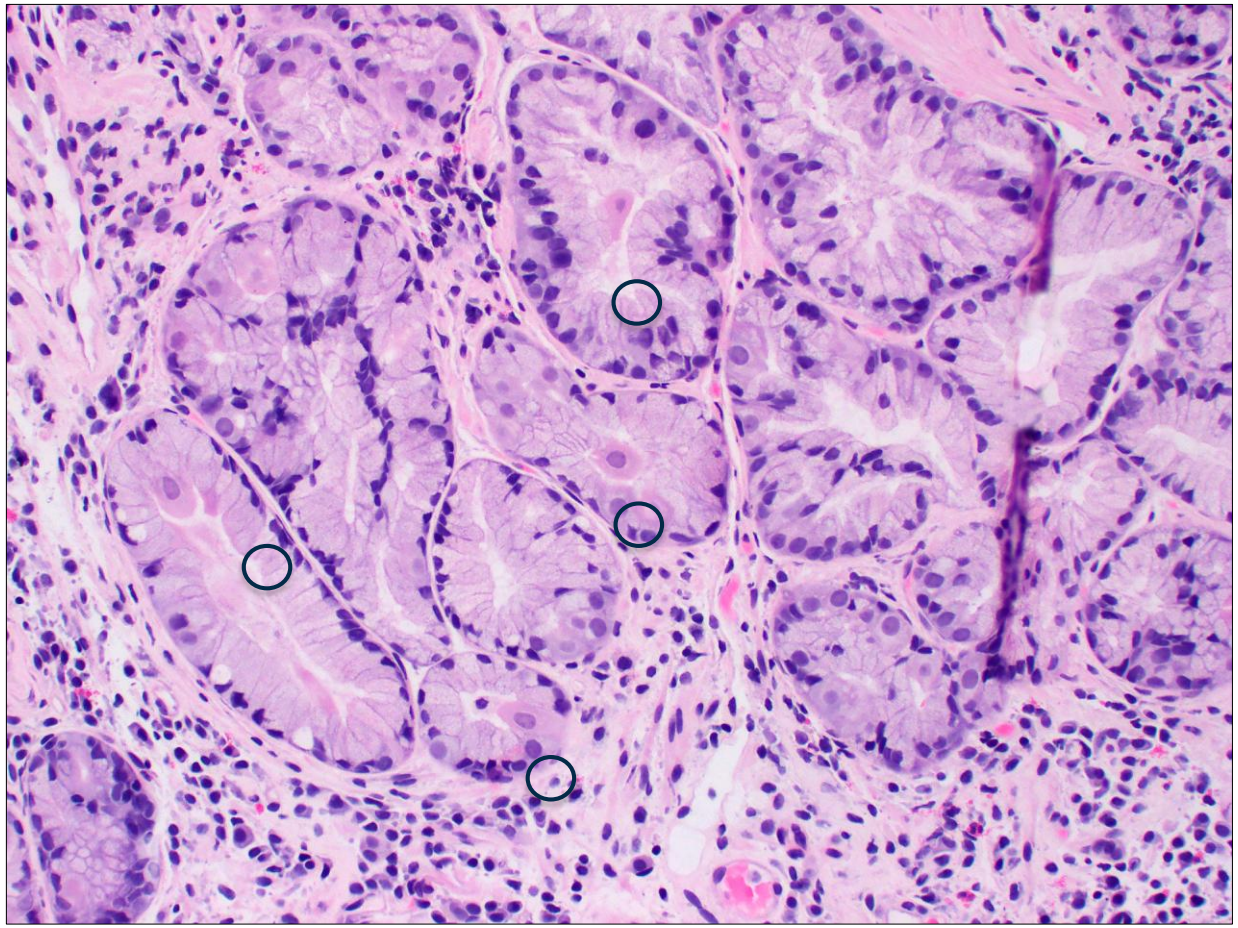


Complex & branching glands w/ pushing interface



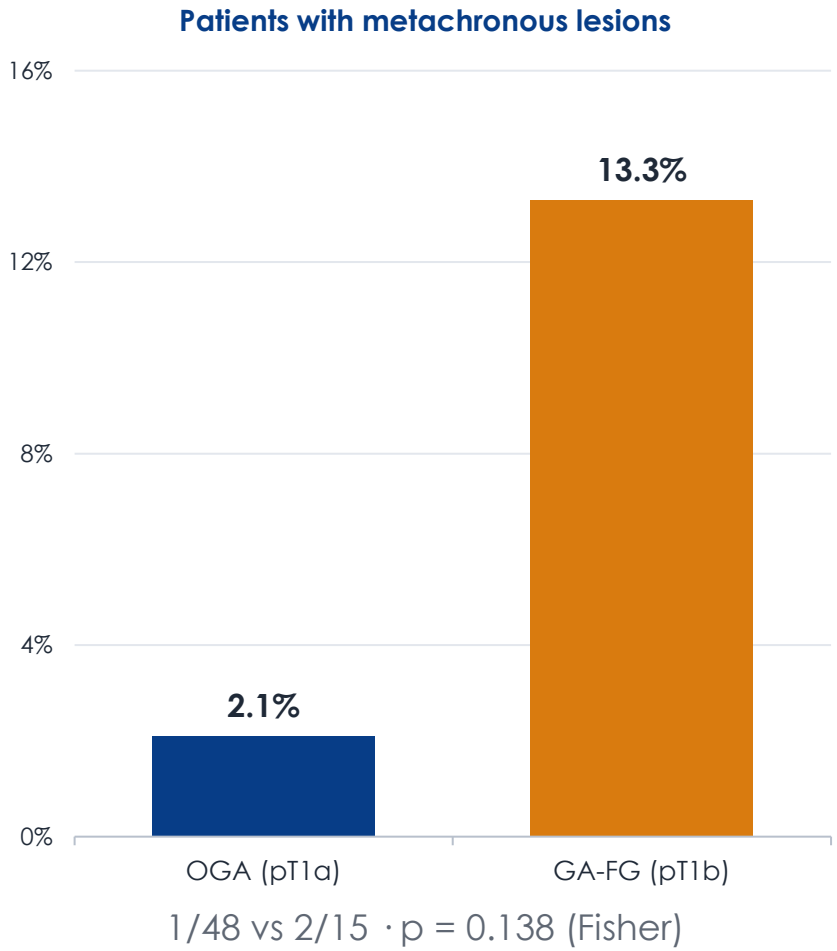
OGA, mucous neck cell type (mucous neck cell adenoma)





Slightly basophilic cytoplasm may suggest mucous neck cells

OGA vs GA-FG: similar outcome but excess of metachronous lesions in GA-FG



	OGA	GA-FG	p
Patients (lesions)	53 (54)	16 (19)	
Male	36	12	0.760
Median age, y	68	68	0.395
ESD / EMR	49 / 5	18 / 1	1.000
Mean clinical f/u, mo	70	64	0.530
Mean endoscopic f/u, mo	67	61	0.476
Local recurrence	**0**	**0**	1.000
Metachronous lesions (4.5%)	**1**	**2**	0.132
Disease-specific death	**0**	**0**	1.000
Death, other causes	2	1	0.553

Yoshikawa T, Iwamuro M, et al. Sci Rep 2026;16:26914

Take Away Message – Part 2

- Sub-surface epithelium-derived dysplasia divides broadly into pyloric gland adenoma, oxyntic gland neoplasms and pit/gland dysplasia.
- Histologic patterns, prognostic features and molecular alterations are increasingly characterized.

LOWER RISK	VARIABLE	HIGHER RISK
▪ Oxyntic Gland Adenoma ▪ Low grade Pyloric Gland Adenoma	▪ High grade Pyloric gland adenoma (small) ▪ Gastric adenocarcinoma Fundic Gland type	▪ High grade Pyloric Gland adenoma (large) ▪ Gastric adenocarcinoma Fundic Gland Mucosa type