

WHO Classification of Tumors, 6th Edition

Key Changes, Reorganization, and New Entities

Gregory Y. Lauwers, MD

H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL, USA

Key Changes, Reorganization, and New Entities

- Restructuration around anatomical site for epithelial tumors.
- Neuroendocrine, mesenchymal, and hematolymphoid neoplasms now form dedicated, cross-aligned chapters.
- Grading is simplified to two-tier (low/high grade) systems across precursor lesions in the biliary tree and pancreas, with sharper criteria for neuroendocrine tumor grading.
- New entities: esophageal epidermoid metaplasia to sonic hedgehog hepatocellular adenoma — mostly driven by novel molecular insights (e.g. GLI1, INHBE fusions).
- Amphicrine-like carcinoma: distinguished from MiNEN, broadening how dual neuroendocrine–non-neuroendocrine differentiation is recognized and staged.
- Anal canal terminology is harmonized with HPV-related LAST nomenclature.
- Carcinoma of unknown primary gets its own section for the first time.

Lamarca et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

Reorganization of Chapters (vs 5th Edition)

Chapter	Tumour type / section	Nature of change
Esophagus	Carcinomas with combined squamoid/glandular components	Adenosquamous, mucoepidermoid, and adenoid cystic carcinoma grouped together for comparison
Stomach	Gastric tumor precursors	Gastric dysplasia, intestinal-type and gastric-type adenomas combined into one section
Stomach	Gastroblastoma	Moved to the mesenchymal chapter
Small bowel	All tumors	Split into duodenum/ampulla vs jejunum/ileum
Colorectum	Serrated polyps	Split into hyperplastic polyps, sessile serrated lesions (SSL), and traditional serrated adenomas (TSA)
Other tumours & metastases	Digestive metastases	Split into liver, peritoneal, and other-site metastases, plus a new CUP section
Genetic tumour syndromes	Serrated polyposis	Moved to colorectal chapter — acknowledges mostly non-germline origin

New Entities : Esophagus, Colon & Rectum, Liver

Site	New entity	Defining feature	Clinical relevance
Oesophagus	Epidermoid metaplasia	Keratinised, skin-like change from chronic injury	Precursor to squamous cell carcinoma
Colon & rectum	Intramucosal adenocarcinoma	Unequivocal infiltration confined to lamina propria	Flags pts at high risk for additional CRC; negligible nodal risk
Colon & rectum	Low-grade tubuloglandular carcinoma	Haphazard, well-differentiated glands, no desmoplasia	IBD-associated; easily under-recognised as invasive
Colon & rectum	Lymphoglandular complex-like adenocarcinoma	Lymphoglandular complexes with desmoplasia/necrosis	Formerly ‘dome/GALT carcinoma’; usually low stage, screen-detected
Liver	Sonic hedgehog HCA (SHH-HCA)	INHBE–GLI1 fusion in bland, small hepatocytes	5–10% of HCAs; high hemorrhage risk, low malignant potential

Lamarca et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

- dense granular layer overlying
- hyperorthokeratosis



700um

Esophageal epidermoid metaplasia

Esophageal Epidermoid Metaplasia: A Squamous Precursor Lesion

2014 · CLINICOPATHOLOGIC STUDY

Esophageal leukoplakia / epidermoid metaplasia: 18 patients

Modern Pathology 2014;27:38–43

18	56%	61%
patients	dysphagia	smokers

17% **Concurrent or subsequent high-grade squamous dysplasia and/or SCC (3 of 18 pts)**

Follow-up: 13 pts (mean 2.3 yrs) — **7/13** persistent disease; none developed dysplasia or SCC

Controls: 198 consecutive esophageal biopsies, 3 academic institutions over 6 months — no cases identified

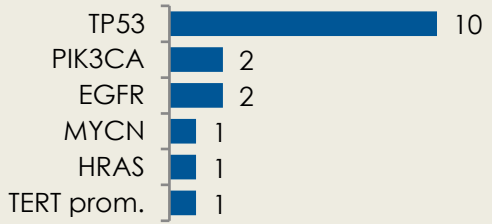
2017 · MOLECULAR STUDY

Targeted NGS supports epidermoid metaplasia as a precursor to esophageal squamous neoplasia

Modern Pathology 2017;30:1613–1621

Tested: matched normal squamous mucosa & EM (18 pts), plus synchronous / metachronous HGD/SCC (5 pts, 28%)

67%
of EM had alterations in SCC-associated genes

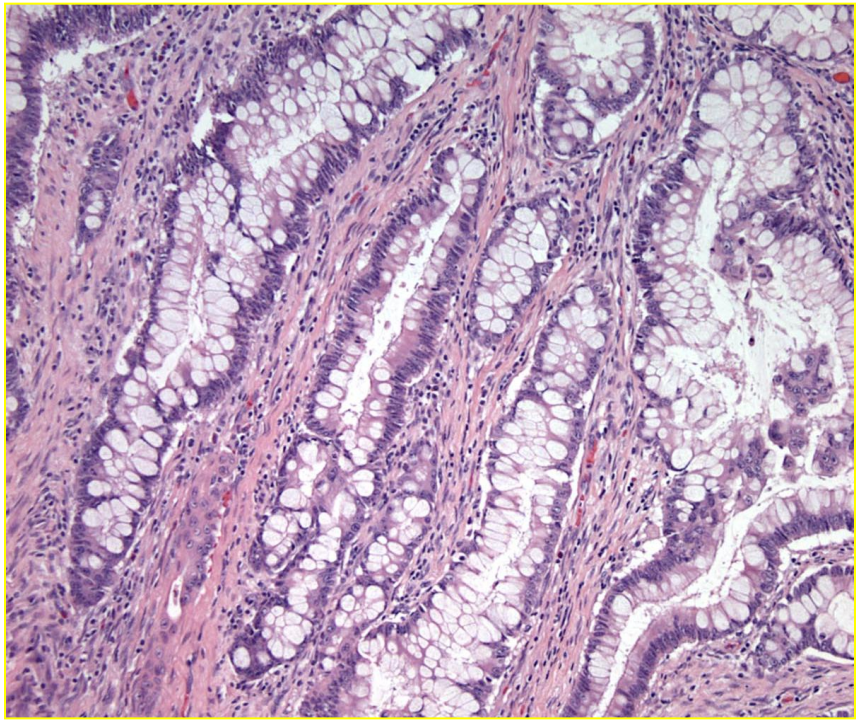


- **TP53 mutation correlated with concurrent or progression to HGD/SCC**
- **No genetic alterations in uninvolved mucosa**

Rare, but linked to HGD/SCC in ~1 in 6 patients and carries SCC-type mutations (esp. TP53) — report it.

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Low-grade tubuloglandular adenoCA

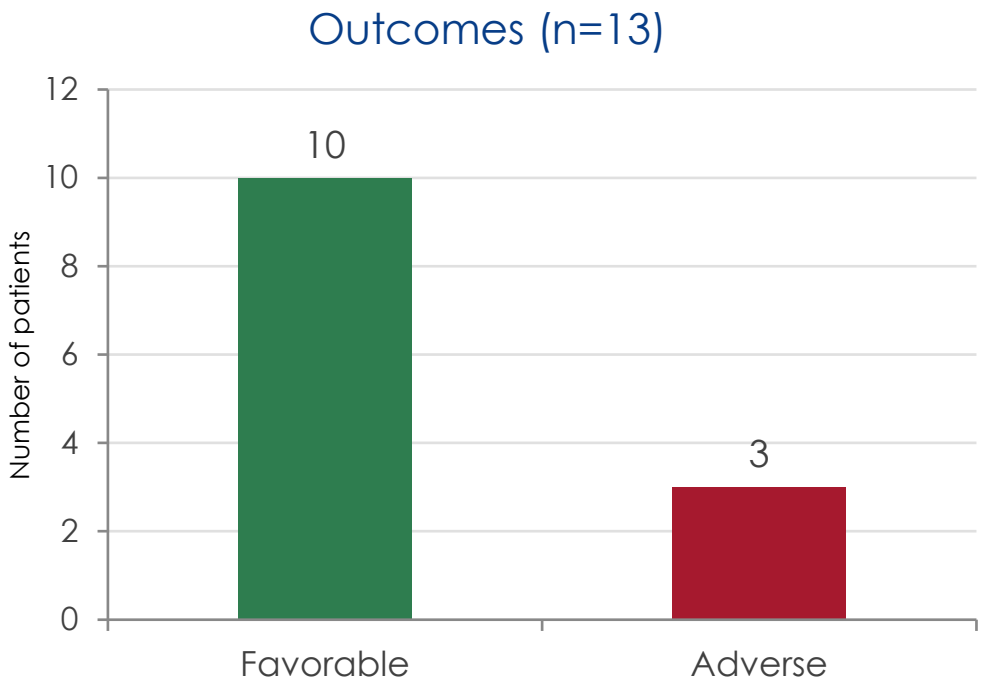


- The neoplastic glands infiltrate haphazardly without evidence of desmoplasia.
- Almost exclusively arises in patients w/ IBD (UC/CD).
- Can arise from low-grade conventional dysplasia or from non-conventional colitis-associated dysplasia

Am J Surg Pathol 2006;30:1022–1029

Low-Grade Tubuloglandular AdenoCA: Outcomes

13/17 patients (76% of cohort) — mean follow-up 4.0 years (range 0.75–9.0 y)



10 (77%)
Favorable outcomes

3 (23%)
Adverse outcomes

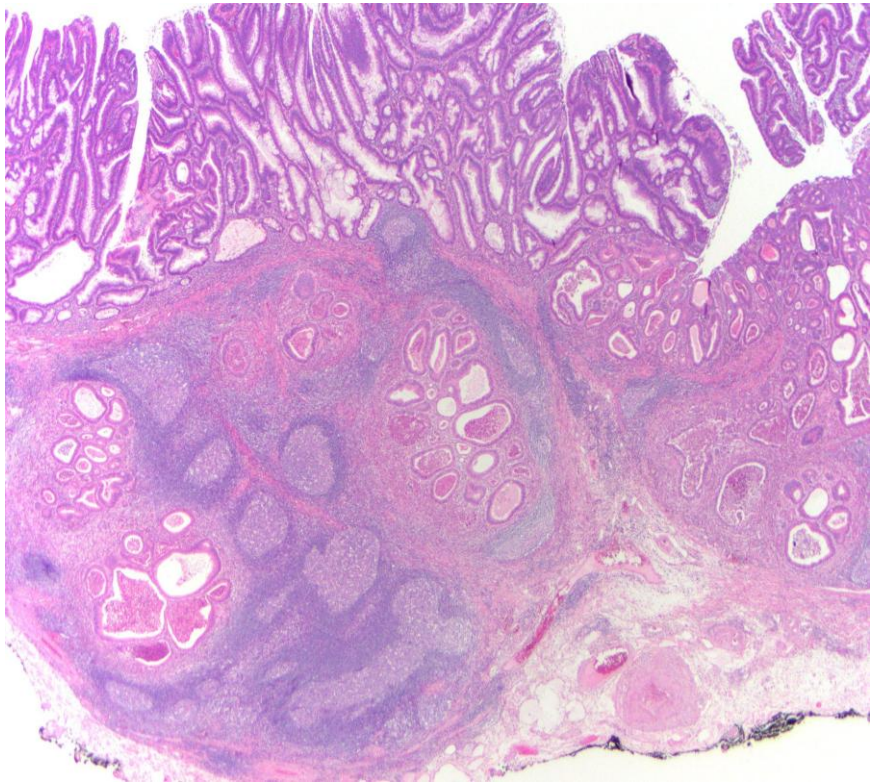
Adverse outcomes attributable to:

- 2 synchronous advanced-stage conventional cancers
- 1 progression from LGTGA to poorly differentiated adenocarcinoma

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Am J Surg Pathol 2006;30:1022–1029

Lymphoglandular Complex-Like CRC (LGCC)

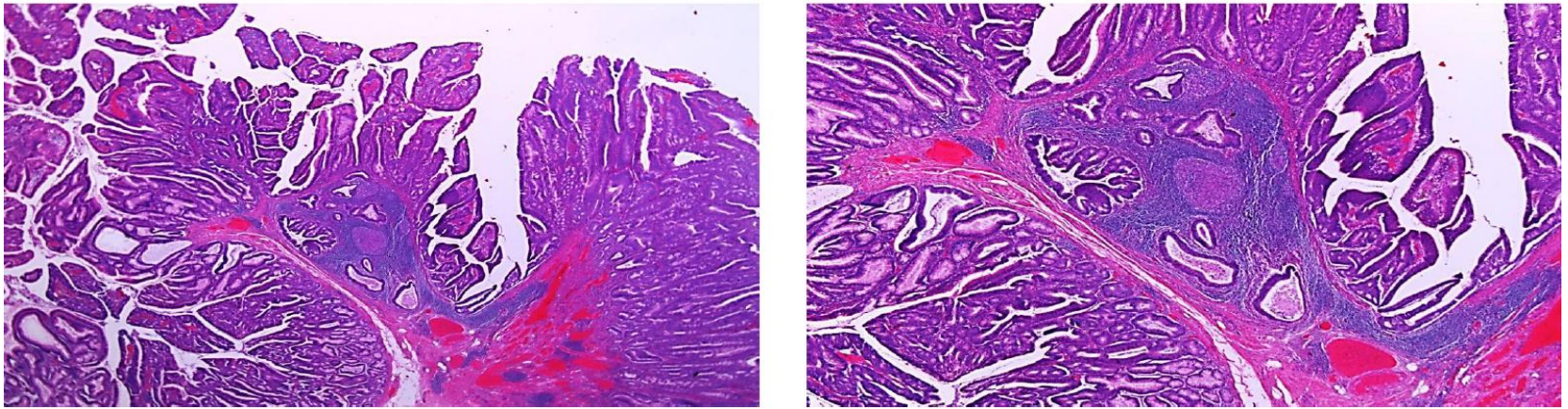


- Prominently associated w/ lymphoid tissue & reminiscent of lymphoglandular complexes.
- Rarely extends beyond submucosa (~10%)
- LN metastasis in 38% of resections, but overall prognosis is good w/ no recurrence or disease-specific mortality (20 cases / F-up 2–120 mo)
- Deficient MMR in 22% of tested cases

Am J Surg Pathol. 2024;48:70–79

Pitfall: Adenoma in a Lymphoglandular Complex

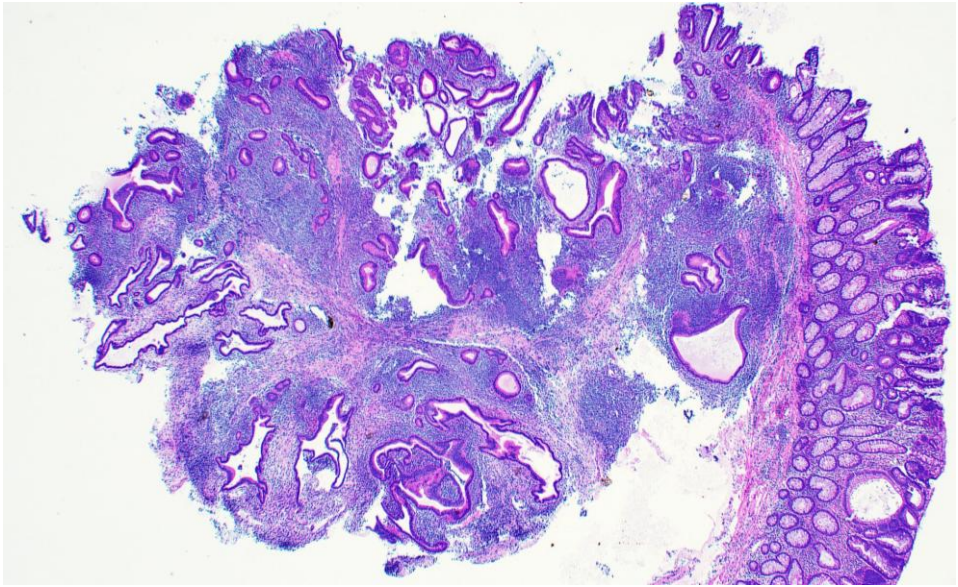
Adenoma in a lympho-glandular complex: much commoner in the right colon



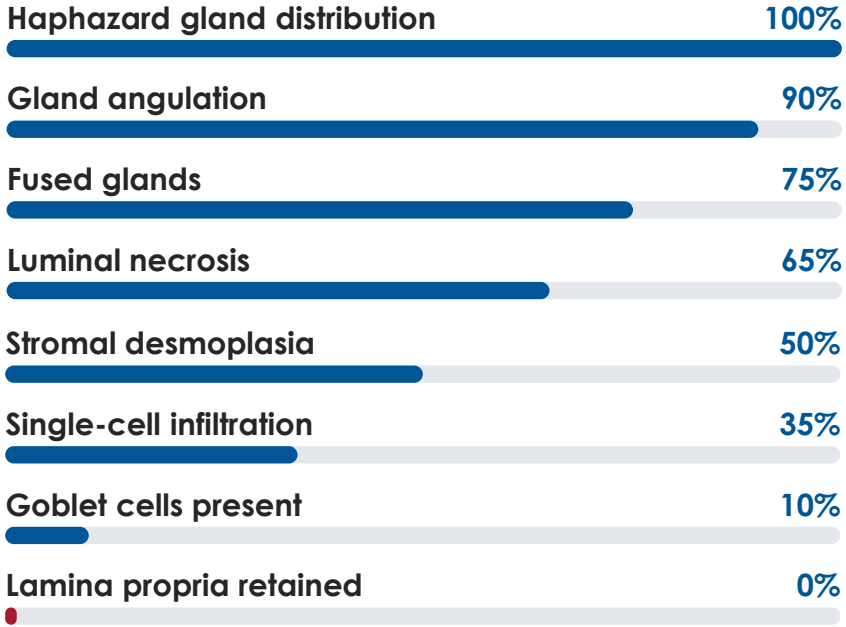
The Pathology of Bowel Cancer Screening. Prof. N.A. Shepherd. USCAP, Vancouver, BC, March 18, 2018

Adenomas can herniate through weak points in the muscularis mucosae into lymphoid agregates. These adenoma-in-LGC are well-rounded, retain lamina propria, and lack infiltrative features.

LGCC: Frequency of Invasive Features



Courtesy of Prof. P. Kumarasinghe, Univ. Western Australia



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Am J Surg Pathol. 2024;48:70–79

New Entities: Bile Ducts, Pancreas, Mesenchymal

Site	New entity	Defining feature	Clinical relevance
Bile ducts	Intraductal tubulopapillary neoplasm (ITPN)	High-grade dysplastic, back-to-back tubules, little mucin	High progression risk, but relatively good survival
Bile ducts	Intraductal oncocytic papillary neoplasm (IOPN)	Exophytic nodules, abundant eosinophilic cytoplasm	Rare; intermediate outcome once invasive
Pancreas	Simple mucinous cyst	Gastric-type epithelium, no papillae/ovarian stroma, >1 cm	Likely PDAC precursor (KRAS/BRAF/TP53/SMAD4 alterations); good outcome if non-dysplastic
Mesenchymal	SDH-deficient GIST	Loss of succinate dehydrogenase function	Distinct, strongly syndromic GIST subtype
Mesenchymal	NUT-rearranged sarcoma	NUTM1/NUTM2 gene rearrangement	Newly recognised in the GI tract; aggressive behaviour

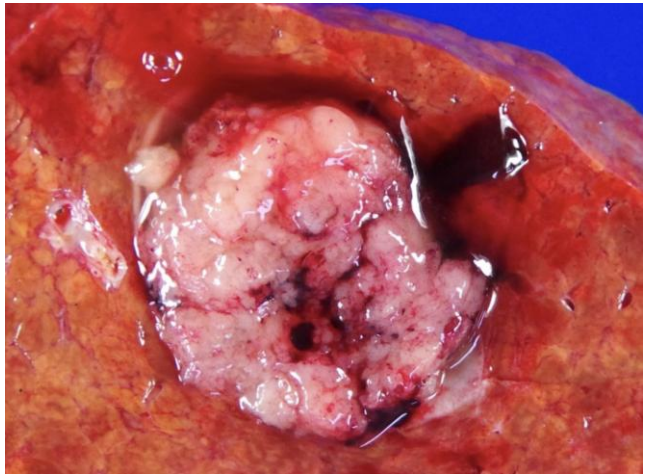
Arends et al. Changes in the 6th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

Intraductal Oncocytic Papillary Neoplasm (IOPN)

DEFINITION

Non-invasive, intraluminally growing epithelial tumour

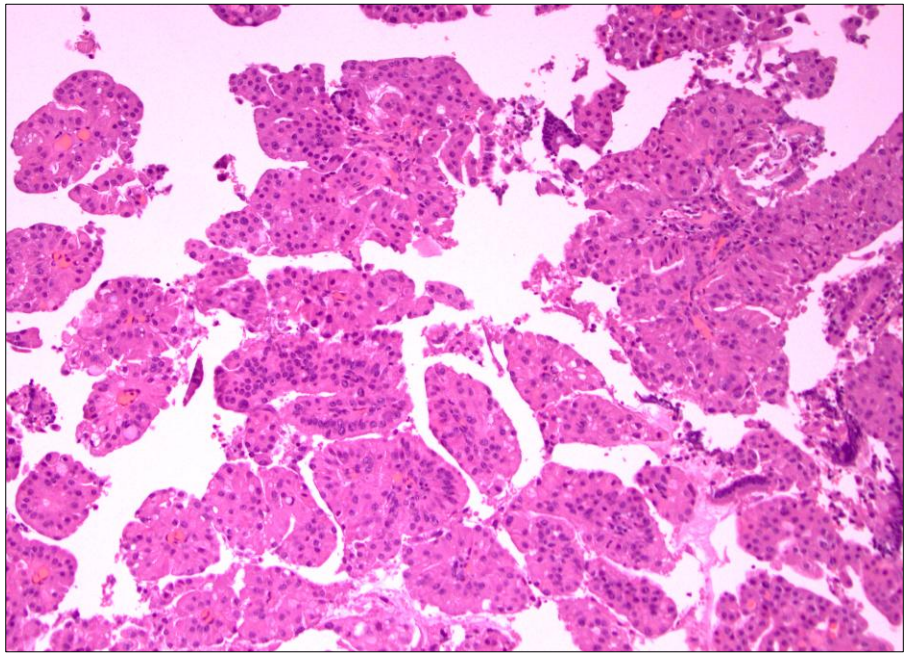
Exophytic nodular fronds lined by epithelium with **abundant eosinophilic cytoplasm**

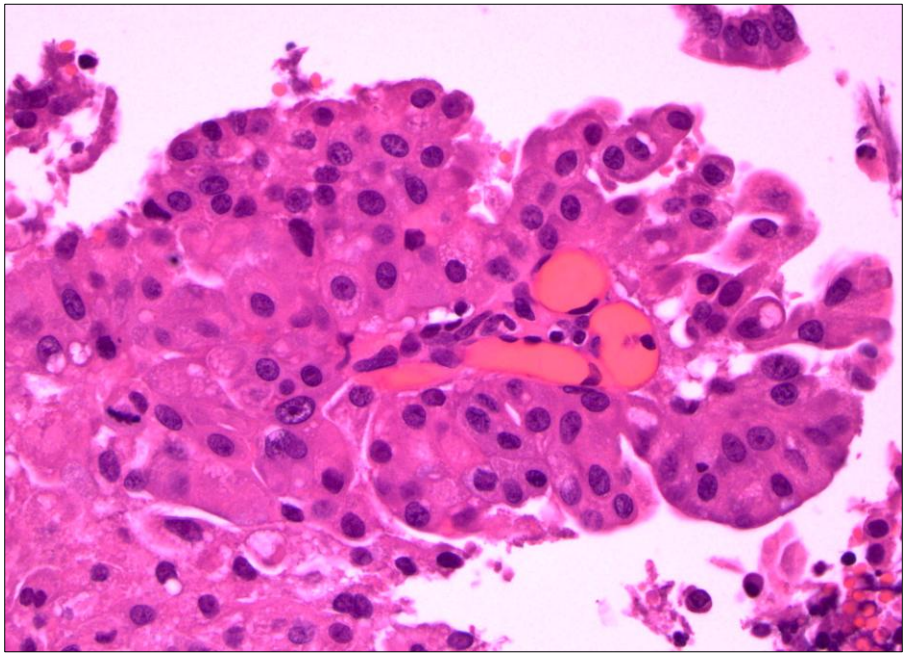


Intrahepatic 70%	Extra 15%	Diffuse 15%

Distribution of IOPN across the biliary tree

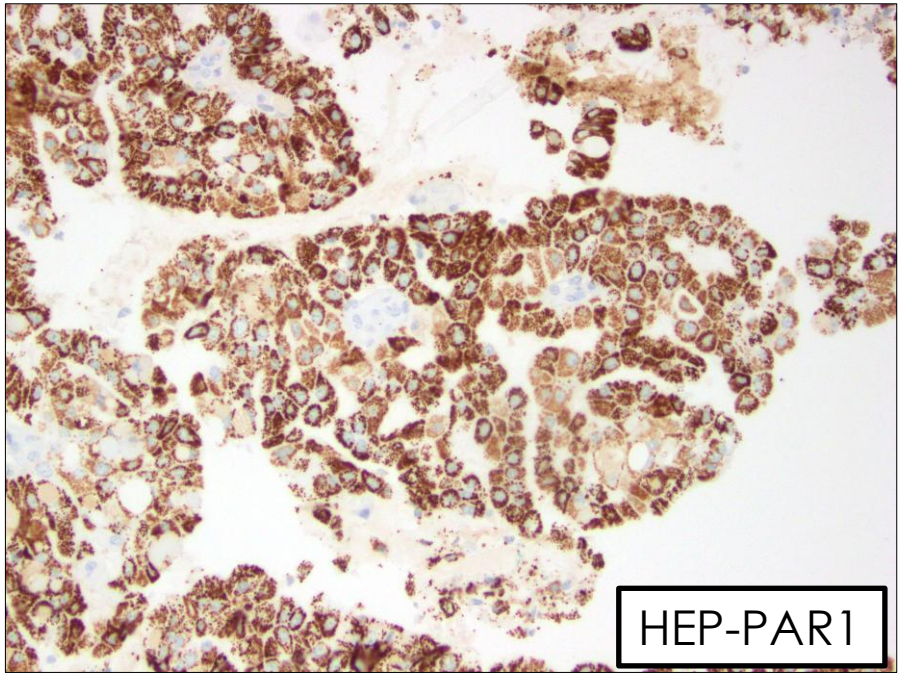
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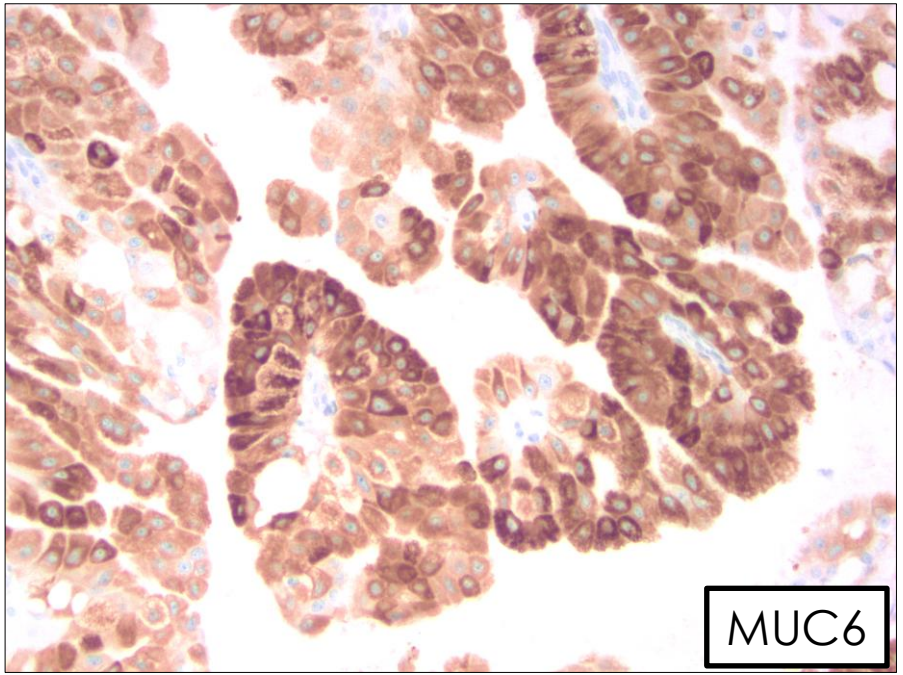




Thick & complex, arborizing fronds with delicate, myxoid, fibrovascular stroma.

The papillae are lined by cuboidal to columnar cells with abundant eosinophilic granular cytoplasm w/ large, round nucleus; and a prominent nucleolus.





(+) MUC5AC and MUC6 and focally label for MUC1. MUC2 expression is limited to goblet cells. Consistent immunoreactivity for HepPar1 / (CD117)

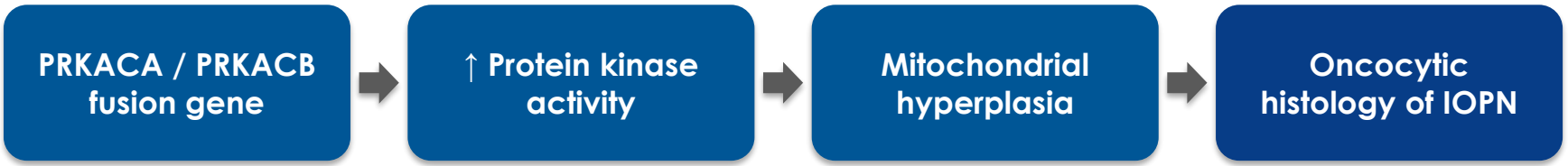
IOPN lacks the mutations that drive IPNB and cholangiocarcinoma

Gene	IPNB / cholangiocarcinoma	IOPN
KRAS	**Reported**	**Not observed**
BRAF	**Reported**	**Not observed**
GNAS	**Reported**	**Not observed**
RNF43	**Reported**	**Not observed**
PIK3CA	**Reported**	**Not observed**
SMAD4	**Reported**	**Not observed**
Overall genetic alterations	More numerous	Fewer

PMIDs 23828315; 31678302; 32100878; 36821179; 37871652

Recurrent PRKACA / PRKACB fusions characterize IOPN

Fusion gene	Genomic mechanism	Kinase gene	IOPN	Associated invasive ca.
ATP1B1::PRKACB	Translocation t(1;1)(p31;q24)	PRKACB	Common	Observed
ATP1B1::PRKACA	Translocation t(1;19)(q24;p13)	PRKACA	Common	Observed
DNAJB1::PRKACA	Single ~400 kb deletion, 19p	PRKACA	Common	Observed



PMIDs 31676785; 31678302; 36821179

New Entities III: NETs & Amphicrine-Like CA

New entity	Definition	Relevance
Type 4 ECL-cell NET	ATP4A inactivating mutation → impaired acid production	Severe hypergastrinemia, prominent parietal-cell hyperplasia, multiple gastric NETs
Type 5 ECL-cell NET	Long-term proton pump inhibitor (PPI) use	Moderate hypergastrinemia; often multifocal
Amphicrine-like carcinoma (ALC)	Neuroendocrine + non-neuroendocrine markers intimately admixed in the same/adjacent cells	Distinct from MiNEN (which shows separate morphologic zones); staged as a carcinoma, not a NET

MiNEN vs ALC: in MiNEN, neuroendocrine and non-neuroendocrine components form morphologically distinct zones or nodules. In ALC, the two lines of differentiation are intermixed throughout — the prototype is goblet cell adenocarcinoma of the appendix, with prognosis between NET and conventional adenocarcinoma.

Rindi G, et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

2026 WHO classification: five gastric NET subtypes

TYPE 1
Atrophic gastritis
Gastrin-dependent

TYPE 2
ZES / MEN1
Gastrin-dependent

TYPE 3
Sporadic
Sporadic,Aggressive

TYPE 4 NEW
Endogenous proton-pump dysfunction
Gastrin-dependent · very rare

TYPE 5 NEW
PPI-induced
Gastrin-dependent ·rising

Colorectum: Serrated Polyps & ACA Grading

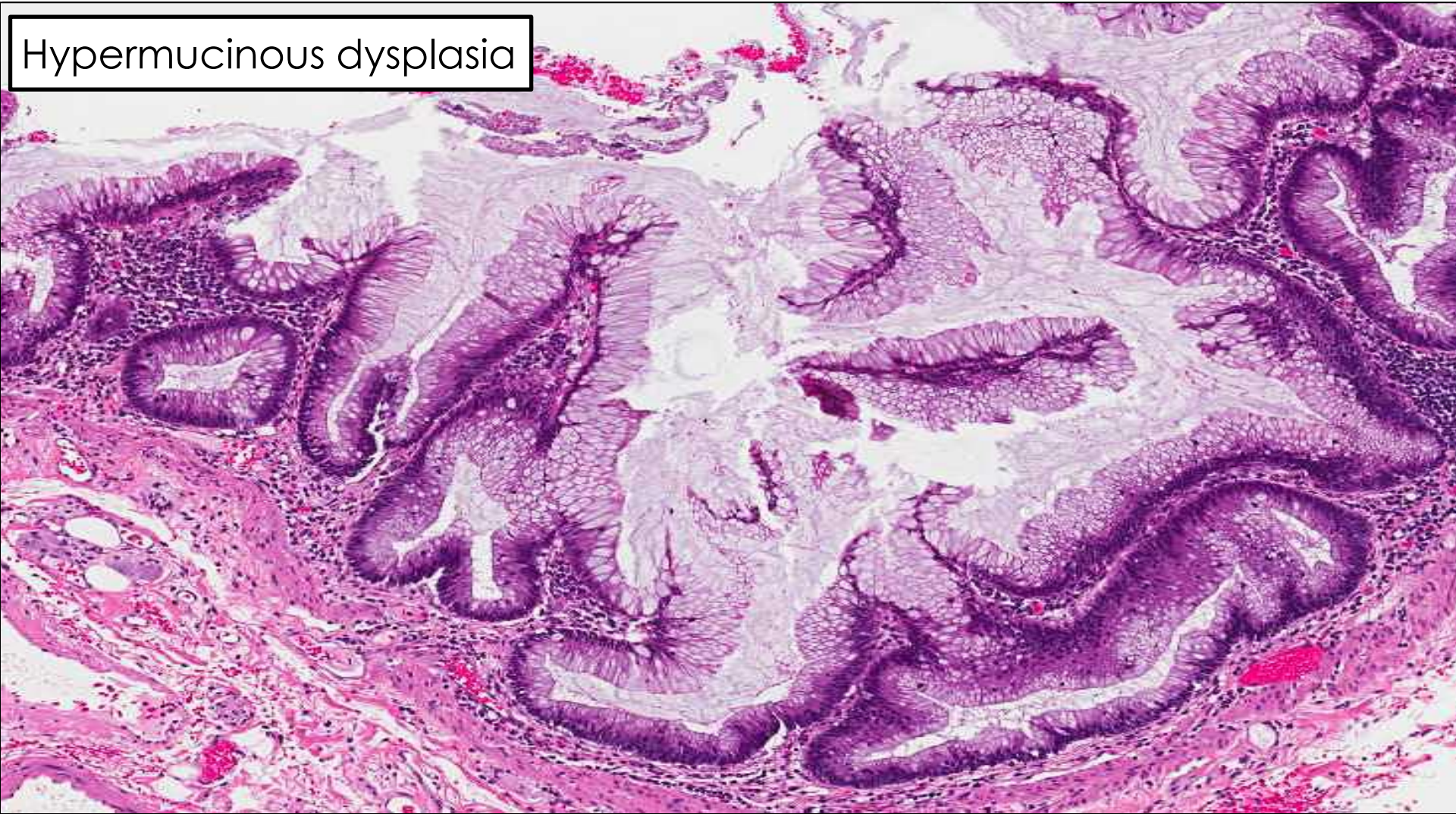
Topic	6th edition refinement
Serrated polyp subtypes	Hyperplastic polyp, sessile serrated lesion (SSL), traditional serrated adenoma (TSA) — now clearly separated
TSA with conventional dysplasia	Newly recognised distinct progression pathway; graded as TSA with low- or high-grade dysplasia by nuclear cytology
Grading basis	Based on gland formation (not cytology) in the least-differentiated component
High-grade threshold	≥ 1 focus lacking gland formation in one high-power field → high grade; otherwise low grade
Excluded from grading	Tumor budding / poorly diff. clusters at the invasive front (reported separately); cribriform pattern still counts as glandular differentiation

Lamarca et al. Changes in the 6th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

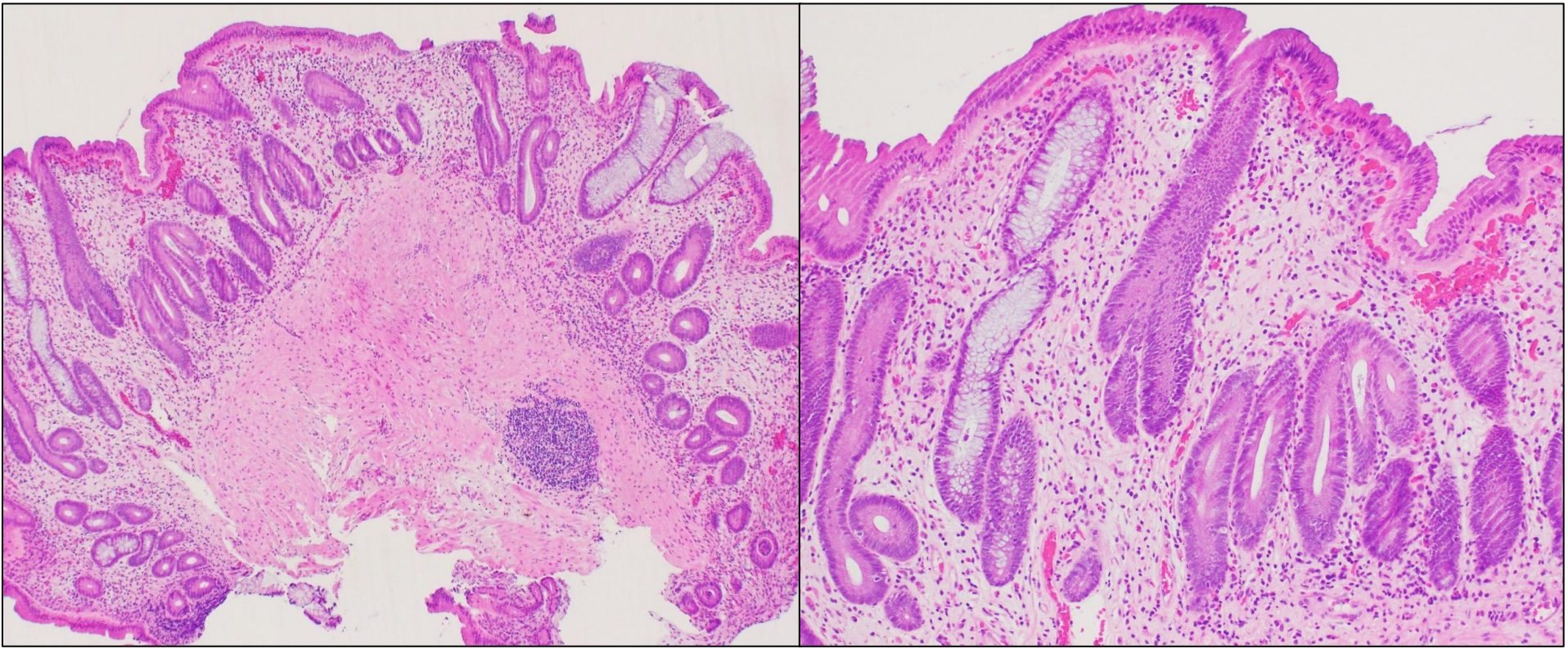
Non-Conventional Dysplasia in IBD

Pattern	Architecture	Cytology / differentiation	Diagnostic key
Hypermucinous	Tubulovillous / villous; plaque-like	Tall columnar cells, multilayered mucin vacuoles (acidic or gastric/foveolar)	Mild atypia, worst in lower crypts
Goblet cell–deficient	Tubular architecture	Enterocyte-like eosinophilic cytoplasm; goblet cells absent/near-absent	Eosinophilic cytoplasm, not just mucin loss
Crypt cell	No significant architectural change	Mildly enlarged, hyperchromatic, round–oval, non-stratified nuclei; terminal differentiation	Not the same as basal crypt dysplasia
Serrated	SSL-like, TSA-like, or complex serrated (NOS)	Varying atypia; may coexist with adenomatous dysplasia	Spectrum mirrors sporadic lesions
Paneth cell–rich	Any of the above	Prominent Paneth cells	A feature, not a separate pattern

Hypermucinous dysplasia

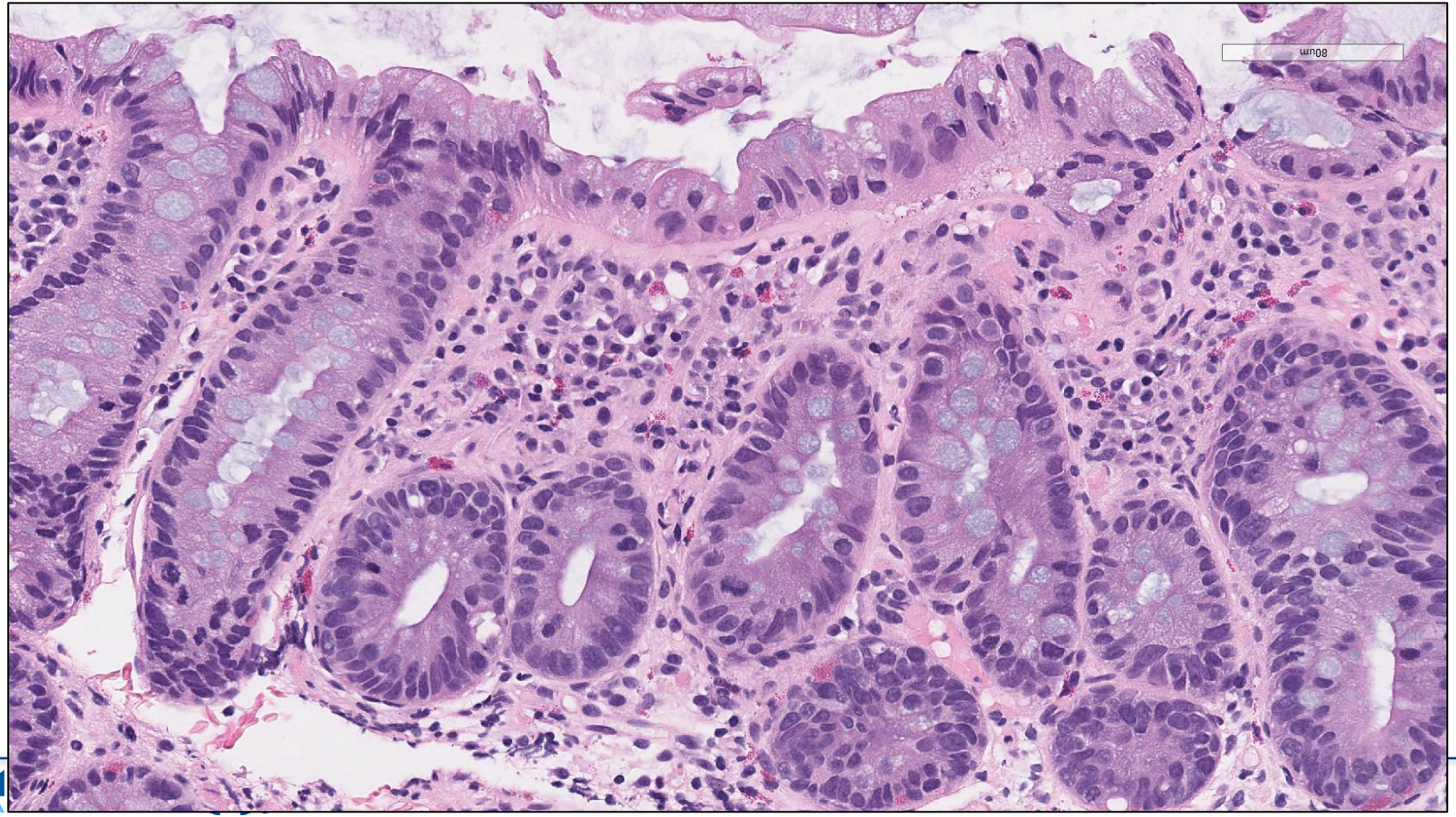


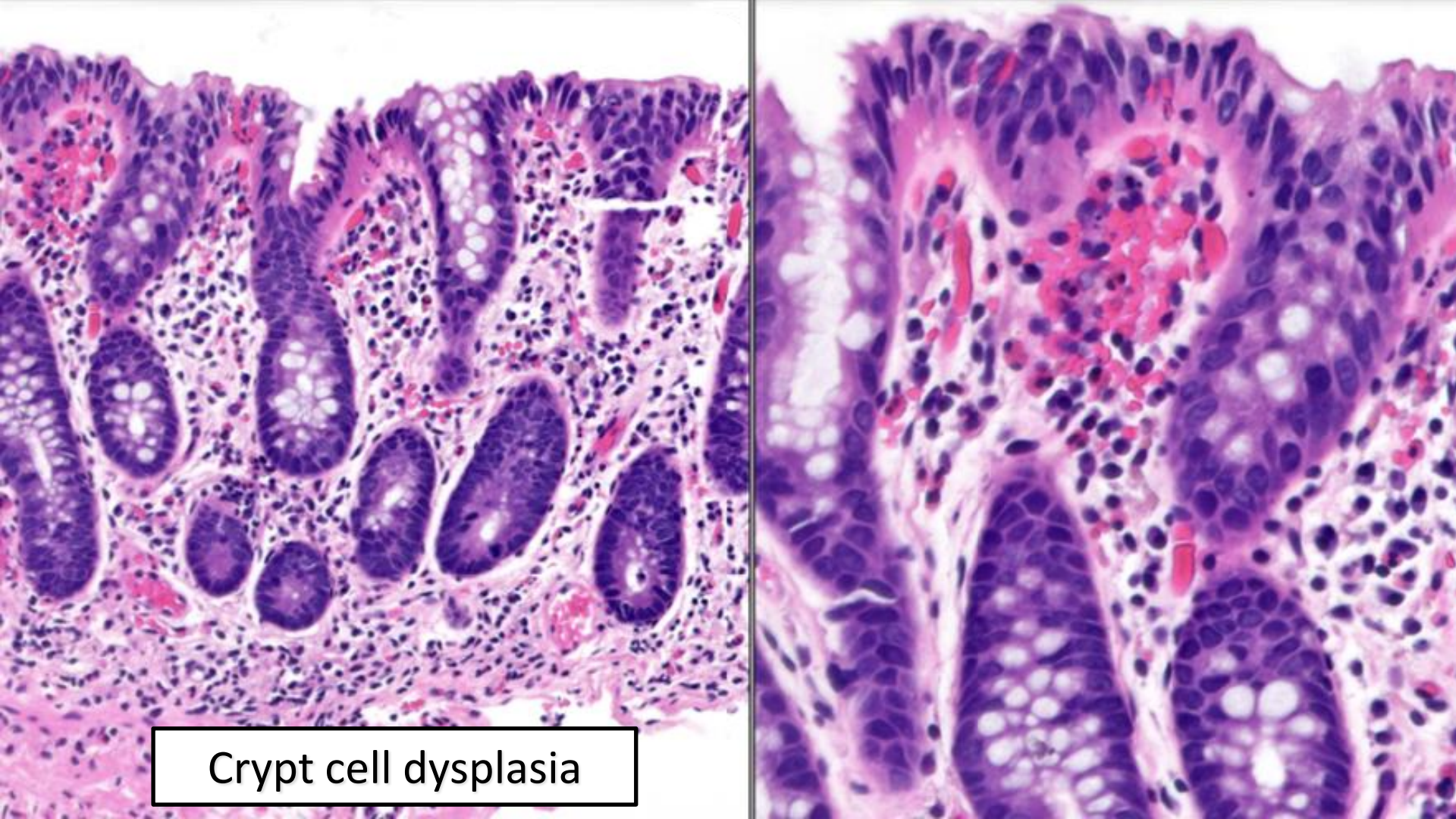
goblet cell deficient dysplasia



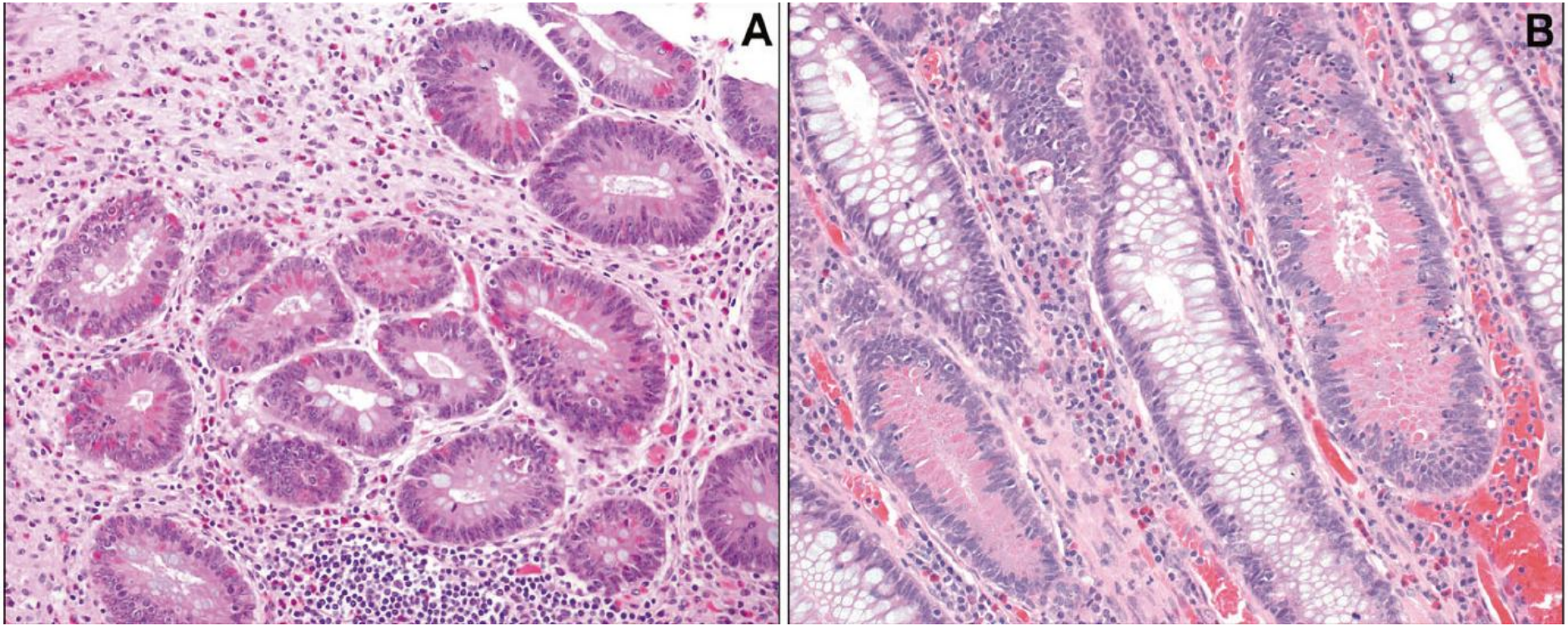
Tubular growth pattern; Non-crowded crypts.

Crypt cell dysplasia

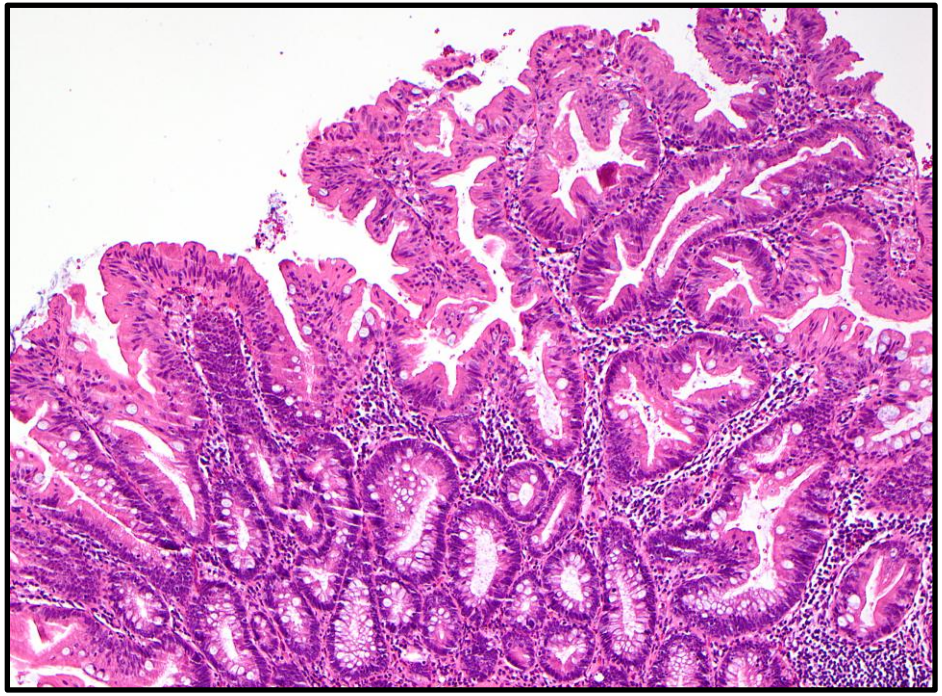


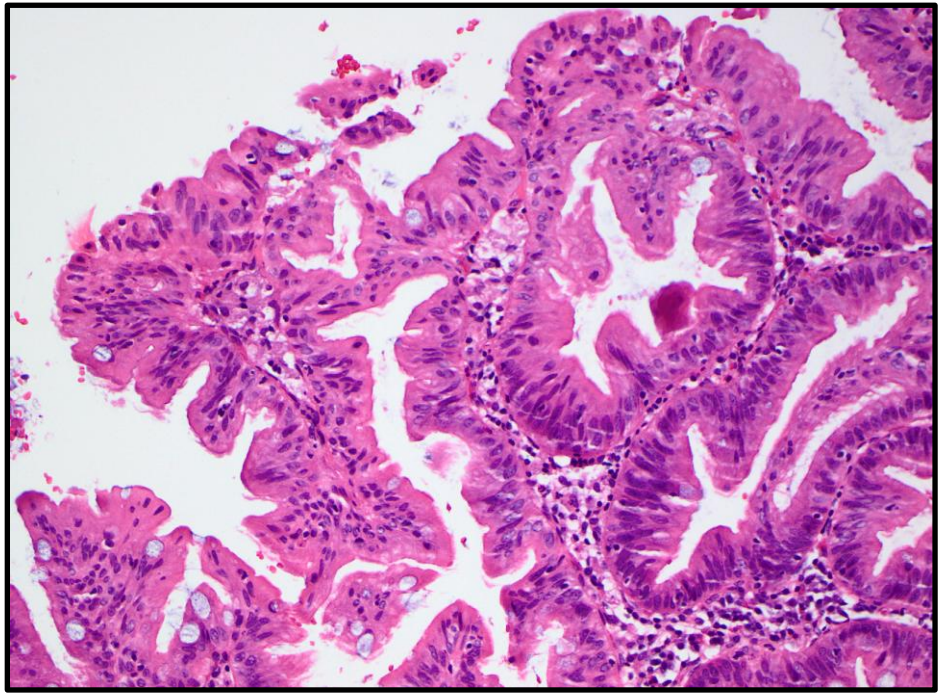

Crypt cell dysplasia

Paneth cell rich dysplasia



Serrated dysplasia





Molecular and immunohistochemical profile

Pattern	Aberrant p53	Aneuploidy	Mutations	Grade / other notes
Hypermucinous	33–50%	Up to 80%	KRAS 61%	Often adjacent to mucinous adenocarcinoma
Goblet cell–deficient	29–44%	—	PIK3CA 56%; KRAS 22%	High-grade features in 31–40%
Crypt cell	—	—	—	Not well defined
Conventional	Early TP53 events	—	TP53	Mutant p53 common even in LGD

p53 caveat: wild-type staining does not exclude dysplasia when morphology is diagnostic; aberrant p53 can rarely occur in non-dysplastic epithelium.

— = not reported in the WHO text. Key PMIDs 31111543; 31801800; 34232295; 33155325; 10517904; 37884500

Selected Improvements Across Chapters

Topic	Change
Undifferentiated carcinoma	Now includes a SWI/SNF-deficient subset (ARID1A, SMARCA2/4, SMARCB1)
Oxyntic gland adenoma	Clarified: chief-cell predominant, CyclinD1-positive, pushing interface
Ampullary adenomas	Separated from flat dysplasia; gives rise to ampullary-duct carcinoma
Anal canal (AIN)	Aligned with LAST; subclassified as TP53-mutant or TP53-wild type

Topic	Change
Intrahepatic cholangioCA	Split into small-duct (SD-ICCA) and large-duct (LD-ICCA) types
Gallbladder / bile ducts	Intracholecystic neoplasms (ICN) graded two-tier; ICPN vs ICTN subtypes
Pancreatic NET	Grade 2 optionally split into 2A (Ki67 3–<10%) and 2B (10–20%)
CA of unknown primary	Subcategorized into favorable vs unfavorable groups

Edwards et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

Anal Canal Neoplasia: Terminology Aligned w/ LAST

6th edition term	Includes / replaces	Key marker note
Low-grade SIL (LSIL)	Mild dysplasia, AIN I, anal SIL (ASIL), condyloma acuminatum	p16 usually negative or patchy
High-grade SIL (HSIL)	Moderate/severe dysplasia, AIN II/III, carcinoma in situ, Bowen's disease, Bowenoid papulosis	p16 diffusely positive — distinguishes HSIL from reactive change
TP53-mutant / TP53-wild type AIN	New: HPV-independent subsets, analogous to vulvar intraepithelial neoplasia	Arise independently of HPV infection

Anal condylomas should be sampled thoroughly, as both LSIL and HSIL can coexist due to infection with multiple HPV subtypes.

Edwards et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

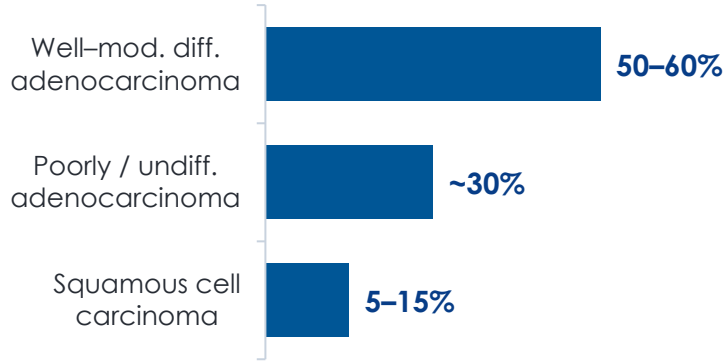
Metastases and CA of Unknown Primary

Category	Definition / key feature	Notes
Liver metastases	Digestive system's most common metastatic site	—
Peritoneal metastases — non-appendiceal	Metastatic tumours not of appendiceal origin	Differential diagnosis discussed vs appendiceal disease
Peritoneal metastases — appendiceal (AMN)	LAMN and HAMN are the leading cause of pseudomyxoma peritonei	Mucinous carcinoma peritonei (MCP) is the invasive histological counterpart
Metastases to other digestive sites	Non-liver, non-peritoneal digestive metastases	—
CUP — favourable group	Colon-like subtype: CDX2+/CK20+, CK7−, or matching colorectal molecular profile	Benefits from site-specific therapy
CUP — unfavourable group	Profile does not match a specific site-directed pathway	Optimal therapy not yet defined

Lewis et al. Changes in the 5th edition of the WHO classification of tumours of the digestive system. Histopathology 2026;88:1295–1314.

Pathogenesis and IHC work-up

HISTOLOGIC TYPES



Excluded from CUP: sarcoma, melanoma, germ cell tumour, NET, haematological malignancy

MINIMAL PANEL FOR ADENOCARCINOMA

CK7 **CK20** **CDX2** **TTF1**

All patients: MSI/MMR testing

WOMEN — EXCLUDE BREAST

ER · PR · ERBB2 (HER2) · GATA3 · SOX10

MEN — EXCLUDE PROSTATE

PSA · NKX3-1

<2%

MSI/dMMR

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PMIDs 29571084 · 33219618 · 36563965

Favourable vs. unfavourable CUP

~20%

FAVOURABLE — 7 subtypes with clear benefit from site-specific therapy

Only GI-type: colon-like CUP

CK7 − **CK20 +** **CDX2 +**

Also consider when CK20 − but MSI/dMMR, otherwise fitting colon-like criteria

~80%

UNFAVOURABLE — all remaining CUP; optimal treatment undefined

The majority are of likely GI tract origin or show a gastrointestinal profile

PMID 36563965

Clinical and pathological features	Subtype of CUP
Single metastatic deposit or oligometastatic disease amenable to local ablative treatment	Single-site or oligometastatic CUP[a]
Female patient with isolated axillary lymph node metastases	Breast-like CUP
Female patient with peritoneal carcinomatosis of a serous papillary adenocarcinoma	Ovary-like CUP
Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes	Head and neck–like CUP
Male patient with blastic bone metastases and/or immunohistochemistry or serum PSA expression	Prostate-like CUP
Adenocarcinoma with colorectal immunohistochemistry (CK7-negative, CK20-positive, CDX2-positive) or molecular profile	Colon-like CUP
Carcinoma with renal cell histological and immunohistochemical profile	Renal-like CUP

Two complementary molecular approaches

1 Tissue-of-origin classifiers

- Gene expression profiling / molecular cancer classifiers
- Most often suggested origins: pancreaticobiliary and gastro-oesophageal

2 NGS for actionable events

- DNA/RNA panels: mutations, rearrangements, high TMB — treat regardless of putative site
- Up to ⅓ harbour potentially targetable alterations; may flag a hereditary syndrome

Reclassification: highly specific events may change the diagnosis — e.g. **FGFR2 rearrangement or IDH mutation** → small duct intrahepatic cholangiocarcinoma, in the right clinical setting

PMIDs 39068945 · 23032625 · 30653423 · 33039710 · 39231374 · 39096924 · 36563965