

The International Academy of Pathology
Hong Kong Division

HKIAP Scientific Congress 2026

Amphicrine-Like Carcinomas (ALCs)

Gregory Y. Lauwers, MD

H. Lee Moffitt Cancer Center

MOFFITT CANCER CENTER

NENs develop throughout the G.I.T.

- NENs fall into two lineages:

Epithelial NENs · CK +

- Well-diff. neuroendocrine tumor (NET)
- Poorly diff. neuroendocrine CA (NEC)
- Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN)
- **Amphicrine-like carcinoma (ALC) — new category this edition**

Non-epithelial NENs · CK –

- Neuronal lineage;
- E.g, paraganglioma

NET and NEC are "pure" NENs

≥ 70%

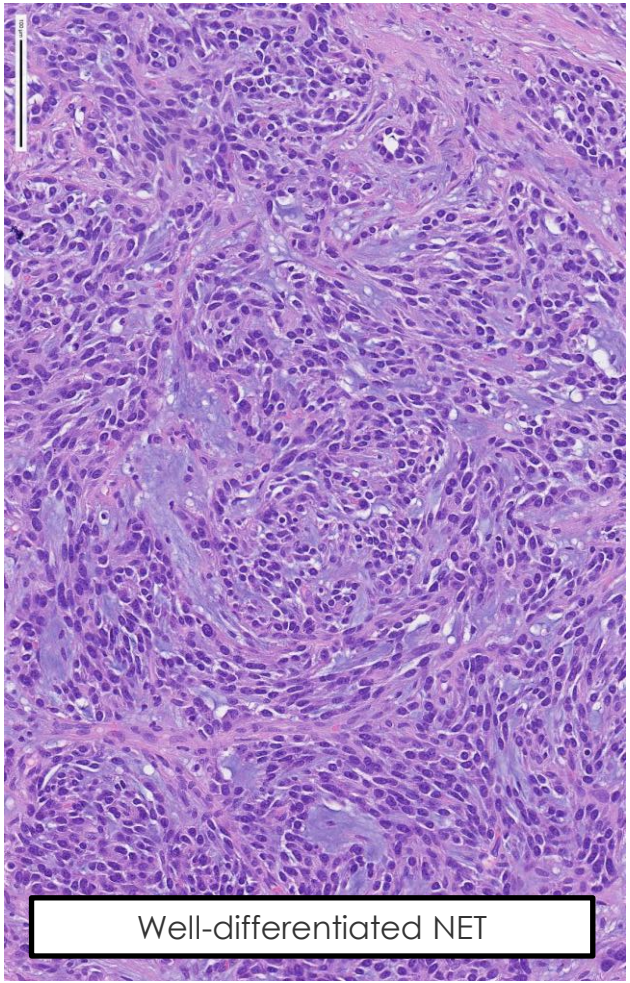
of tumor cells show neuroendocrine differentiation

Well-differentiated NET

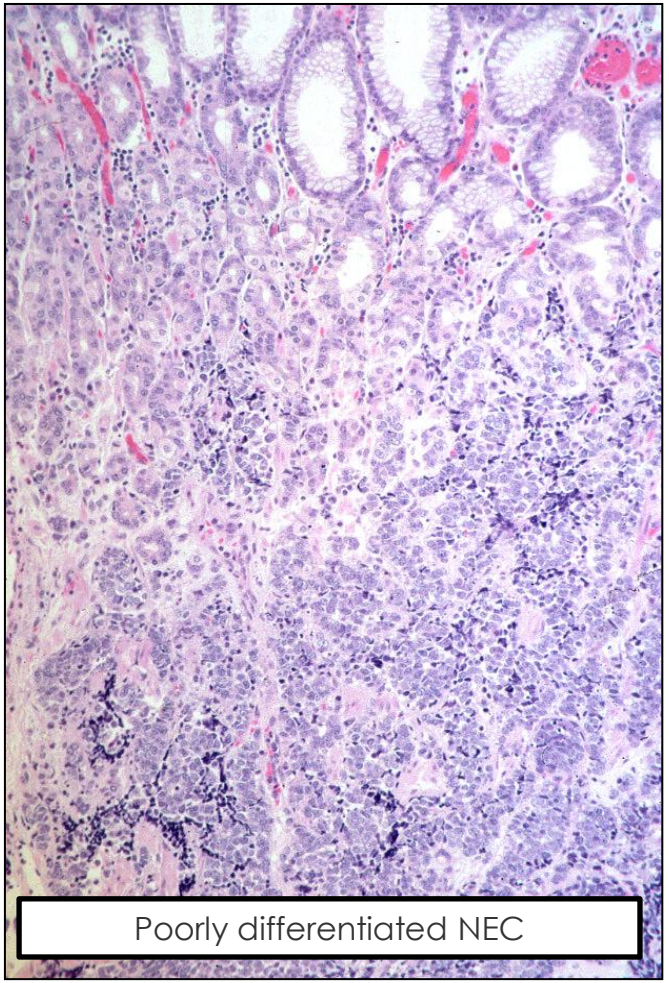
Pure NEN — composed exclusively (≥ 70%) of cells with NE differentiation

Poorly differentiated NEC

Pure NEN — same ≥ 70% threshold; categories unchanged from the 5th edition



Well-differentiated NET



Poorly differentiated NEC

How the mixed-neoplasm concept has evolved

1

4th edition

MANEC

Mixed adenocarcinoma–neuroendocrine carcinoma

2

5th edition

MiNEN

Broadened: some mixed tumours are low-grade, so not all are NECs

3

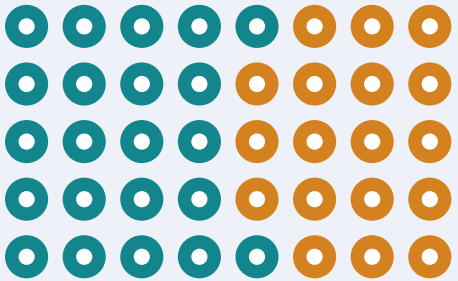
Current edition

ALC

Amphicrine neoplasia revisited for subtle, intermixed NE differentiation

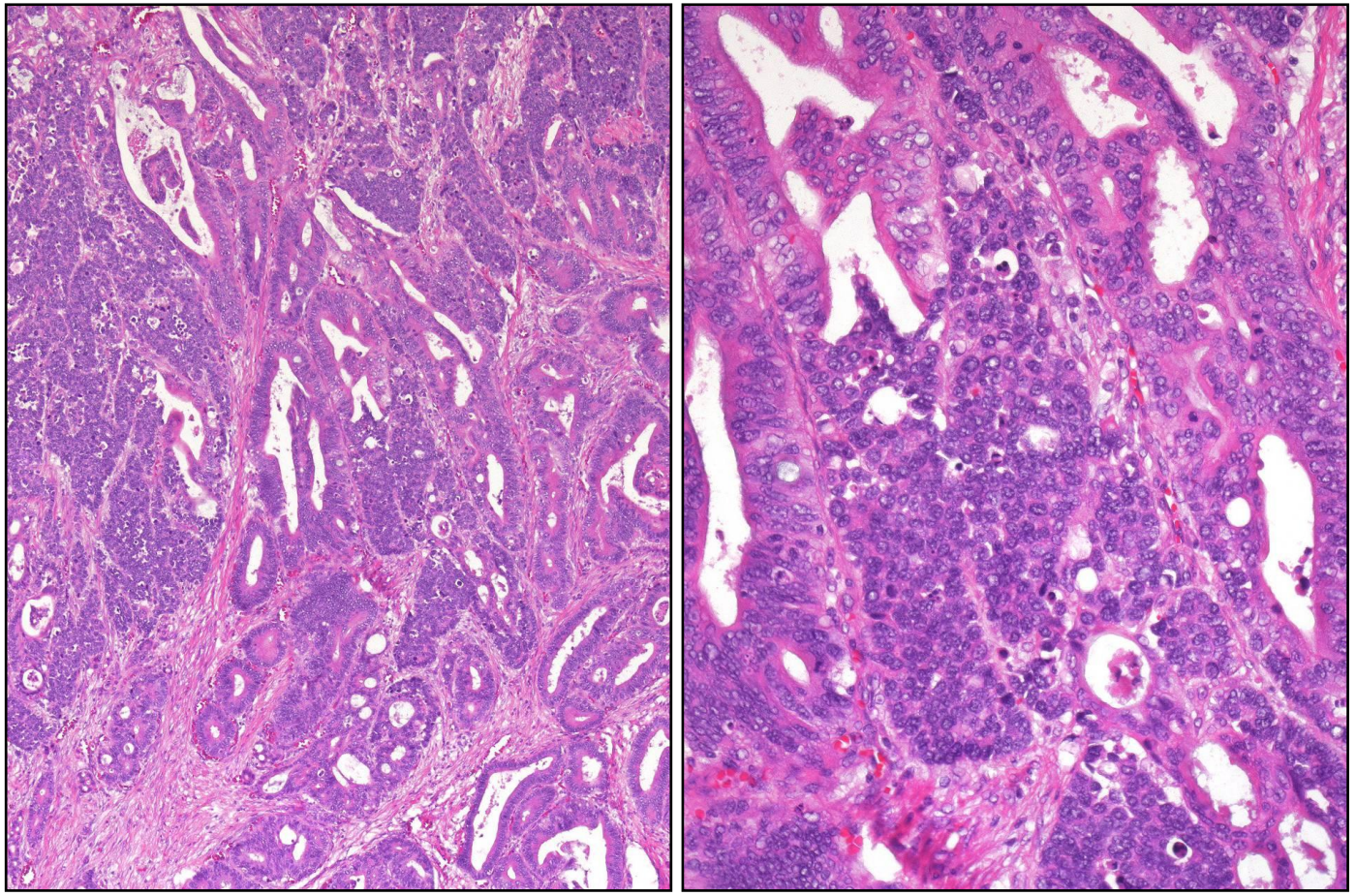
MiNEN — what it covers

- A category of neoplasia, not a specific diagnosis
- Two morphologically distinct regions of different differentiation
- One region neuroendocrine, the other non-neuroendocrine



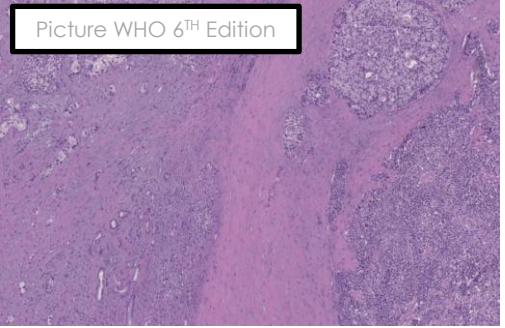
MiNEN: two separate regions

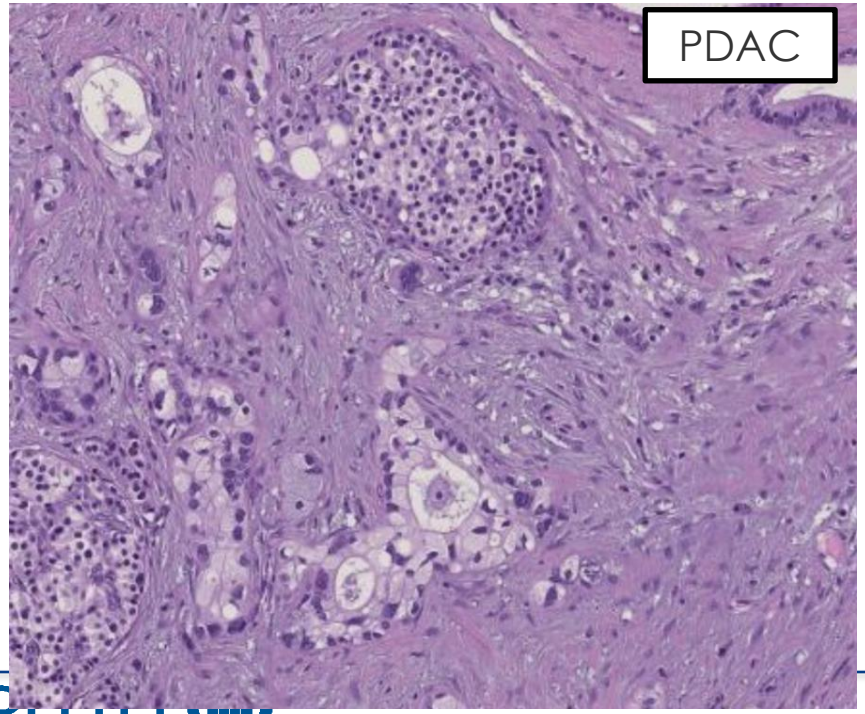
Non-NE (e.g., mucin) Neuroendocrine markers

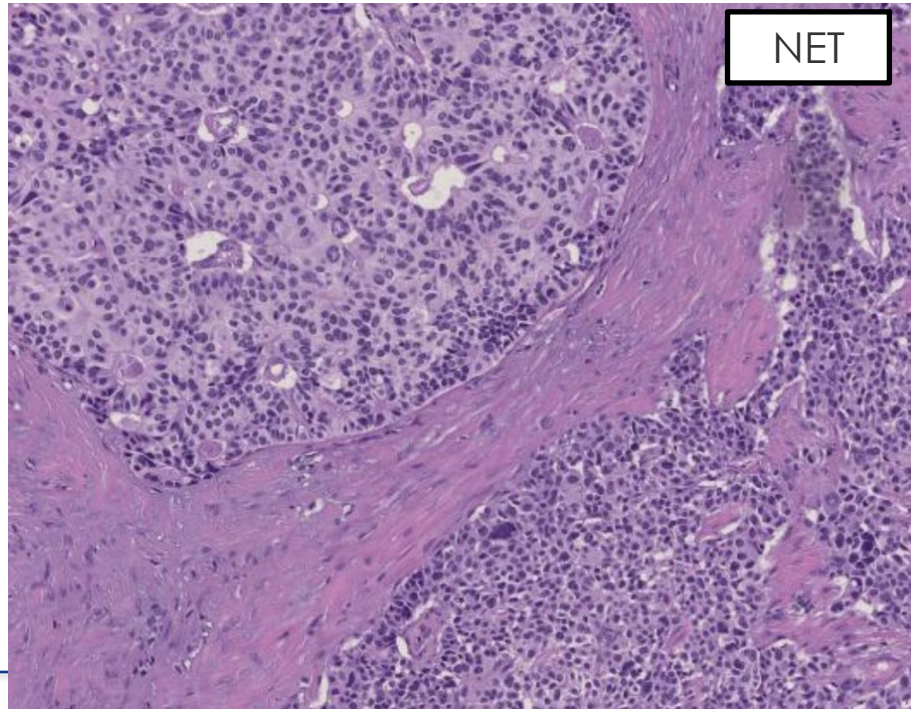


GASTRIC MINEN

PANCREATIC MINEN

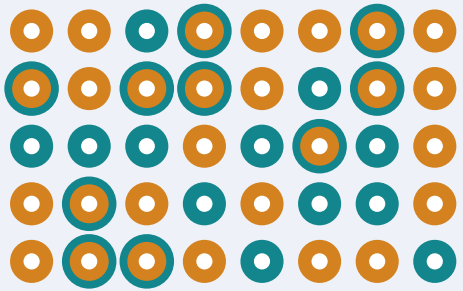






What MINEN does not cover

- CAs where NE differentiation is intermixed rather than in obvious separate areas
- Termed "amphicrine" in the literature — invariably carcinomas
- Reported at almost every site in the GIT

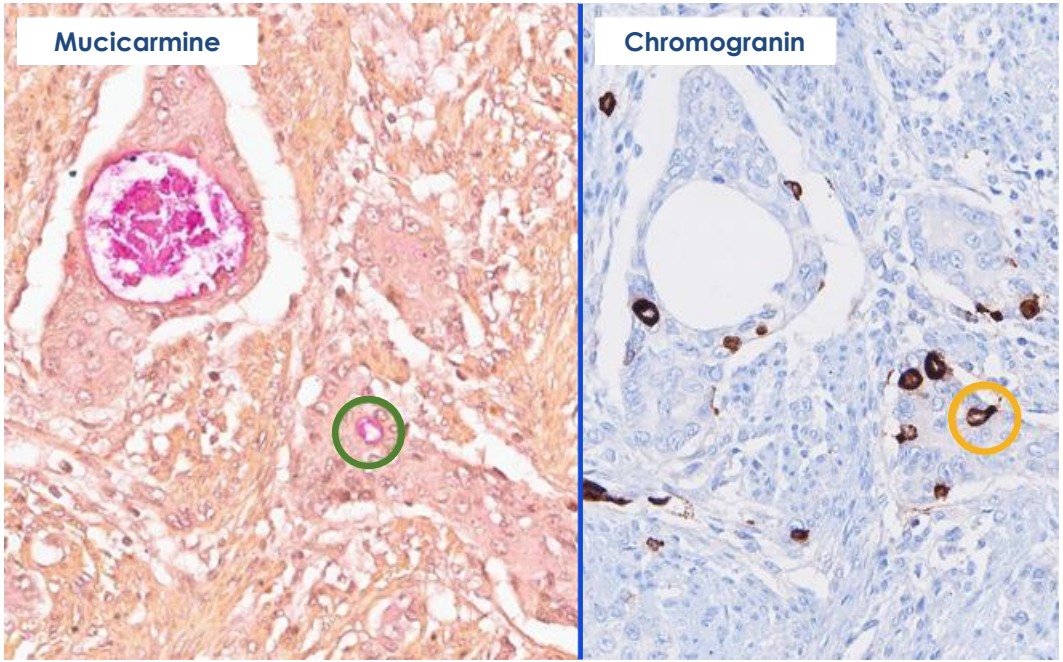


Amphicrine: intermixed; some cells show both

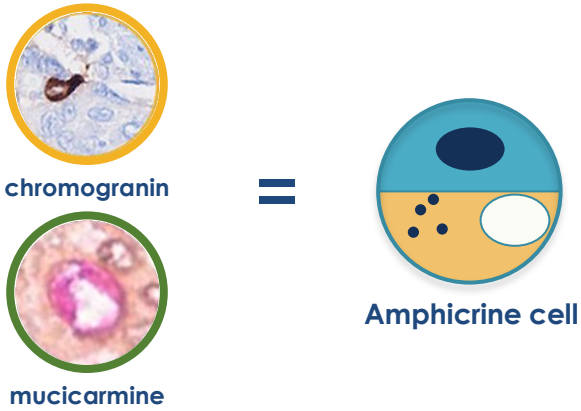
Non-NE (e.g., mucin) Neuroendocrine markers Co-expression

The Amphicrine Cell

One neoplastic cell, two lineages: neuroendocrine and mucinous



Chromogranin granules rim an intracytoplasmic mucin vacuole: both lineages in one cell



Compare:



NE, neuroendocrine. Same field: mucicarmine (left), chromogranin (right). A single neoplastic cell can co-express both lineages, reflecting a shared progenitor with divergent differentiation.

Patterns of amphicrine-like differentiation

MOST COMMON

Intimate admixture of different cells



Morphologically similar cells; some express NE markers, others express non-NE markers such as mucin (a third population will express both)

LESS COMMON

Dual differentiation in the same cell



Both classes of marker expressed in the same neoplastic cells

HOW TO NAME IT

ALC is a family, not a diagnosis.

Name the carcinoma type:

✓ **Amphicrine-like adenocarcinoma**

✓ **Amphicrine-like squamous cell carcinoma**

✗ **"ALC" alone**

Non-NE (e.g., mucin) Neuroendocrine markers Co-expression

Like MiNEN, ALC is an umbrella term: the diagnosis must state the underlying carcinoma type.

Amphicrine Like Carcinoma: WHO 6th ed. criteria

≥30%

of neoplastic cells

show morphological evidence of neuroendocrine differentiation

+

≥2

neuroendocrine markers

expressed by immunohistochemistry to confirm the morphology

ACKNOWLEDGED CHALLENGES

- Separation from other carcinomas may be controversial
- Recognition in practice may be difficult

1 **Morphology**
NE features in ≥30% of tumour cells

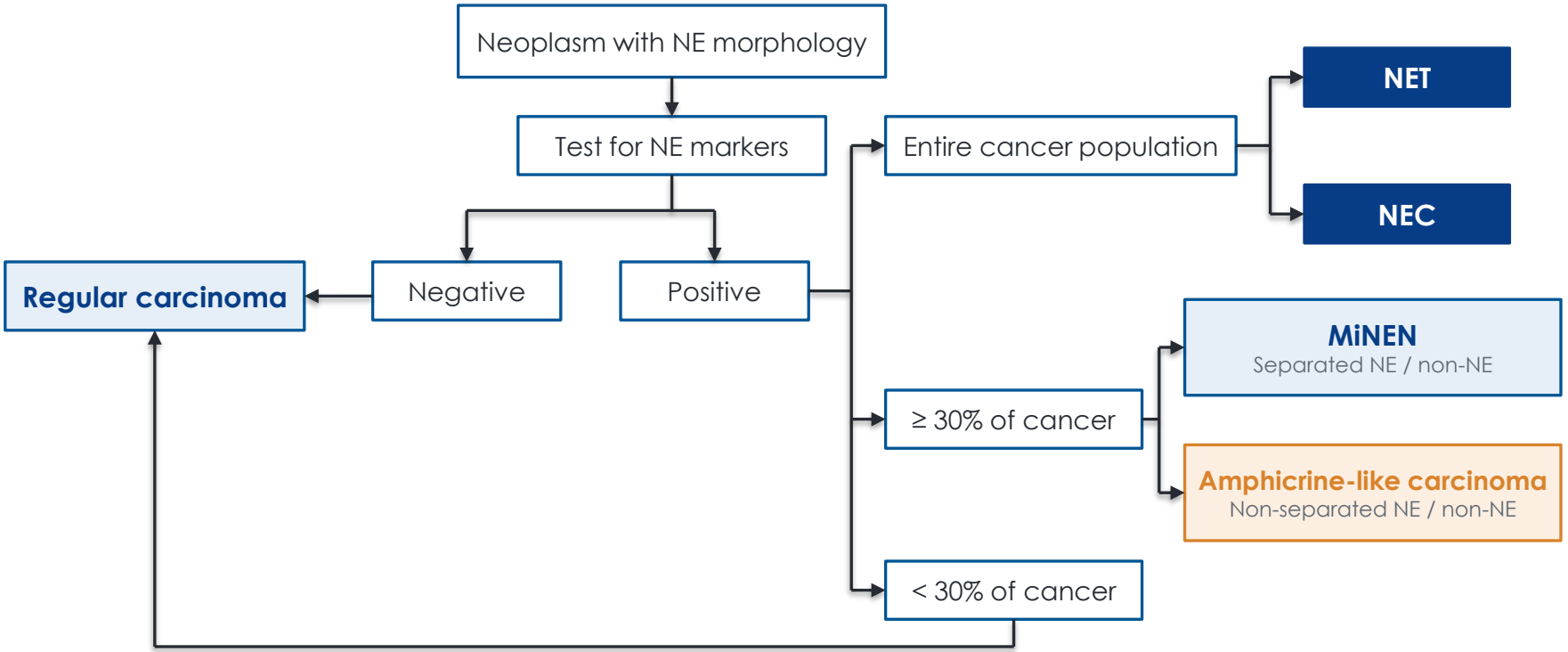
→

2 **IHC**
≥2 NE markers expressed

→

3 **Classify**
Amphicrine-like + carcinoma type

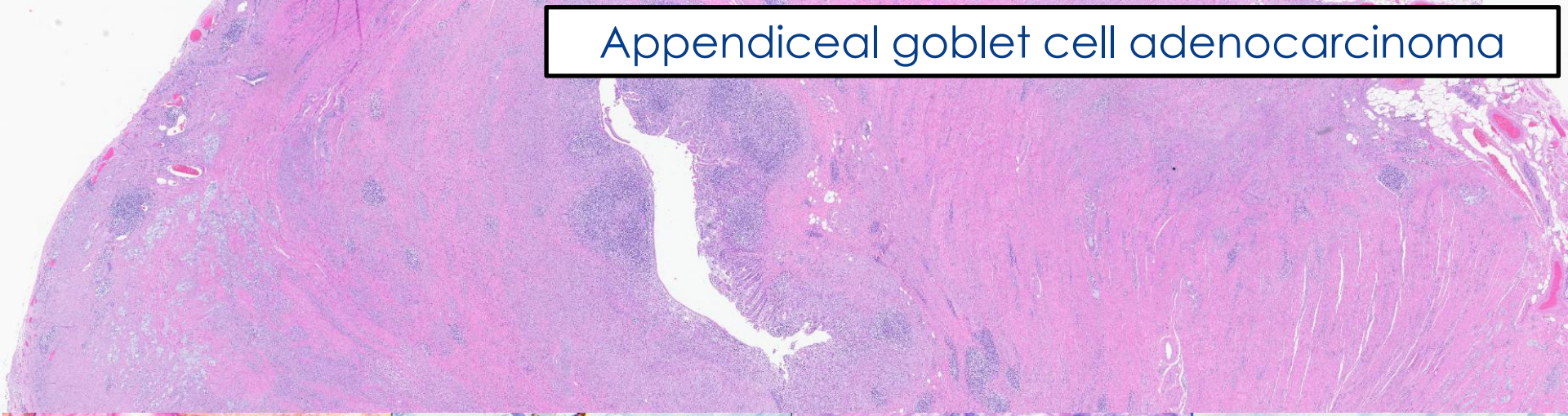
Diagnostic algorithm

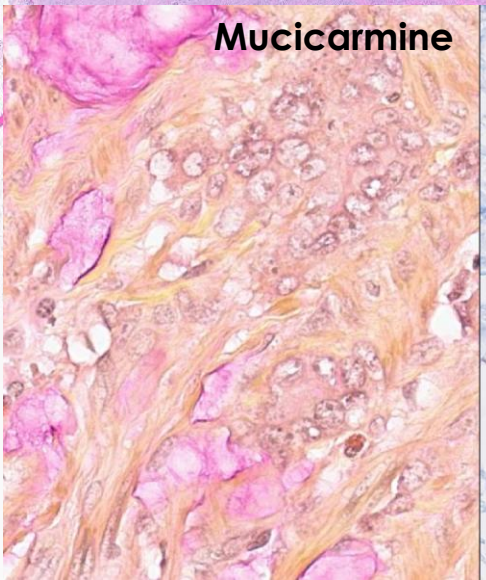


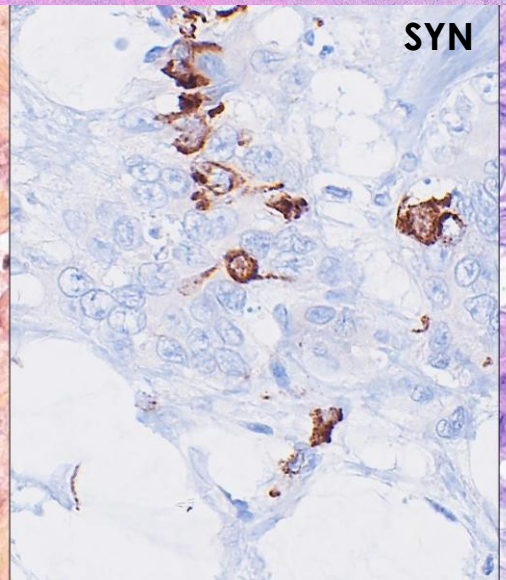
Comparison MiNEN vs ALC

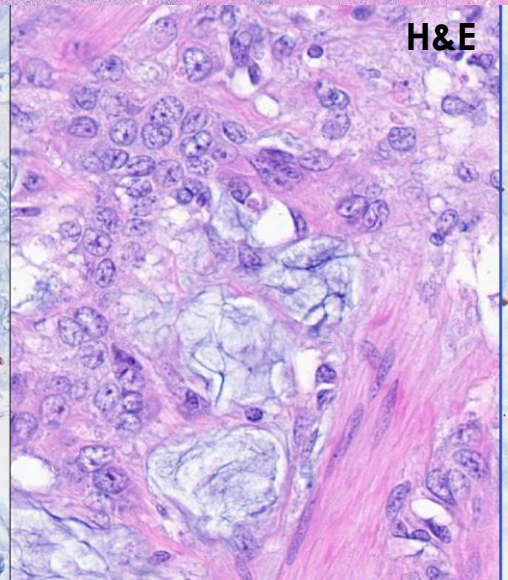
	MiNEN	Amphicrine-like carcinoma
Pattern	Morphologically distinct zones of NE and non-NE differentiation. Each zone displays a line of differentiation	NE and non-NE are intimately intermixed with no distinct zones. The cells are similar looking
Dominant component	Either component	Always a non-NE carcinoma (usually adenocarcinoma; rarely SCC)
NE evidence required	Morphology + IHC	Morphology + IHC: ≥30% NE cells, ≥2 NE markers
Diagnostic Status	Category of tumors, not a specific diagnosis	Category of tumors, not a specific diagnosis
Small biopsies	May be difficult to diagnose	May be difficult to diagnose
Staging	As a carcinoma (carcinoma TNM)	As a carcinoma (carcinoma TNM), not as a NET

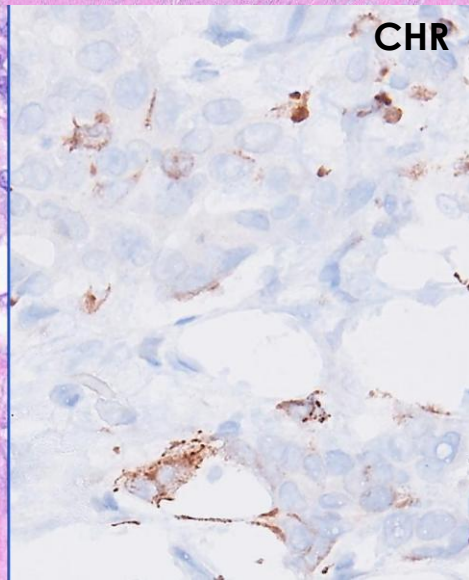
Appendiceal goblet cell adenocarcinoma



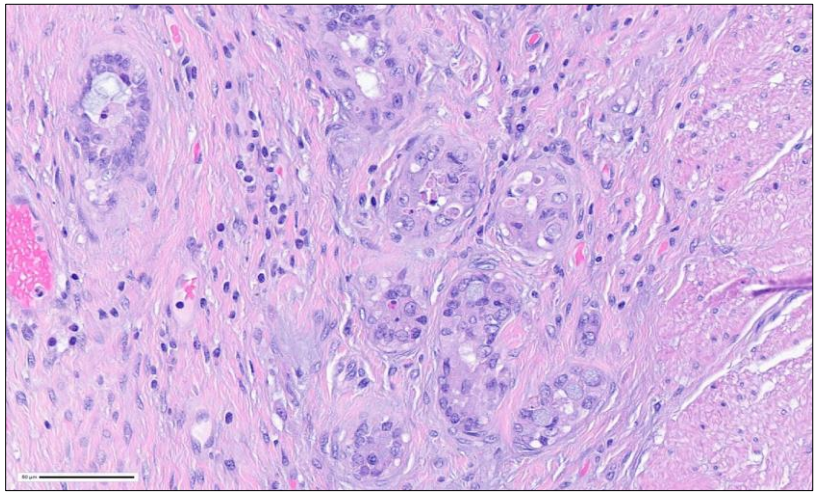








Goblet cell adenocarcinoma: prototype ALC



Classified and Staged as	GCC in appendix – CA elsewhere, not NET (carcinoma TNM)
Natural history	Distinct from both NET and conventional adenocarcinoma of the appendix

PROGNOSIS IN THE APPENDIX

Neuroendocrine tumour (NET)

Most favourable

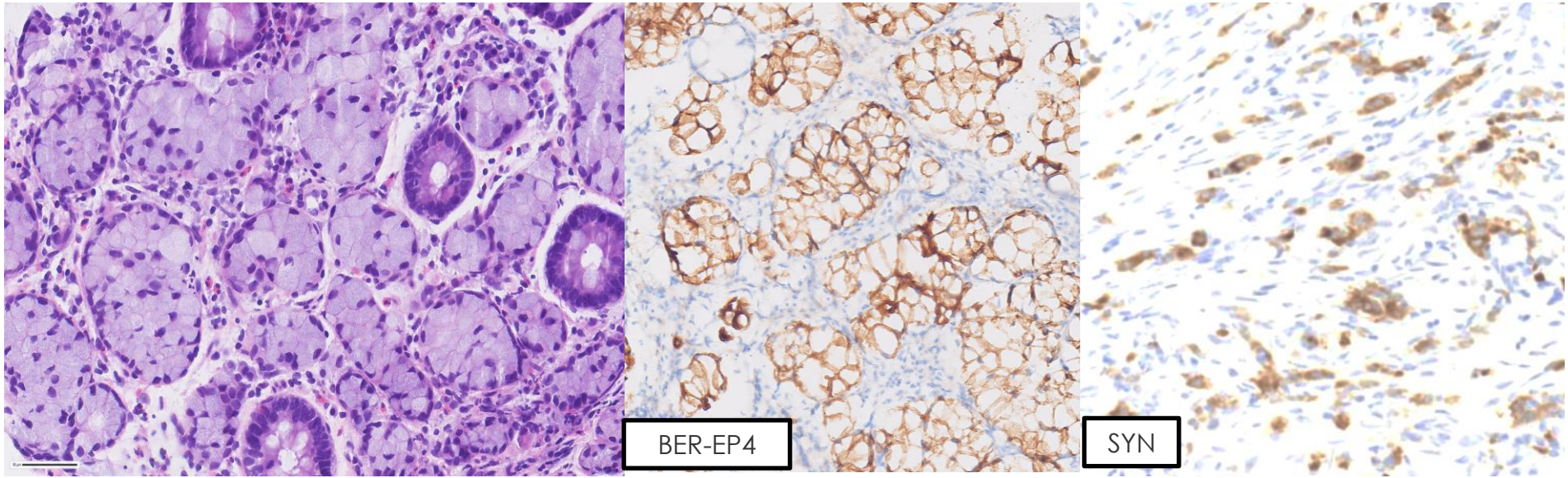
Goblet cell adenocarcinoma

Significantly worse than NET

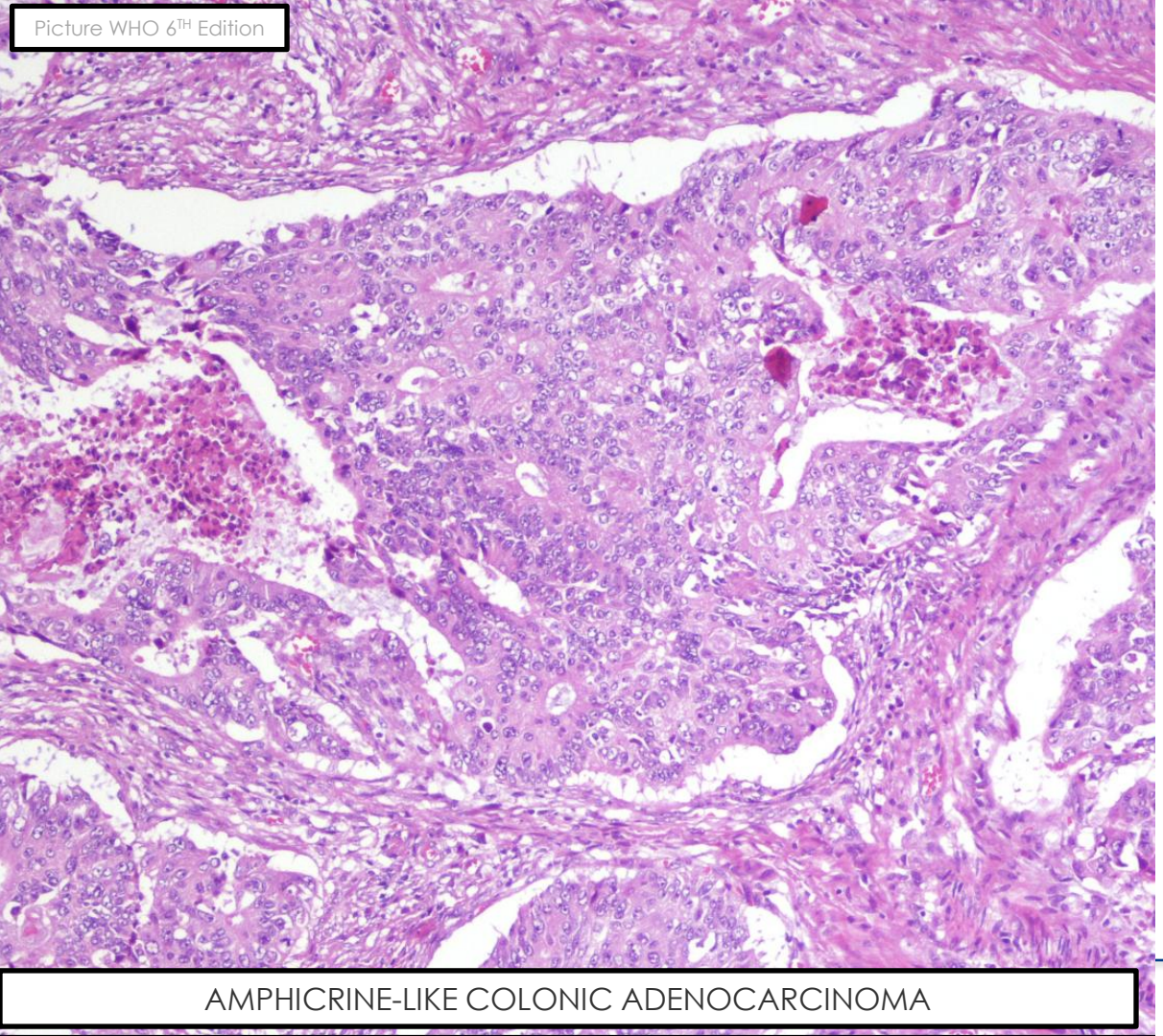
Conventional adenocarcinoma

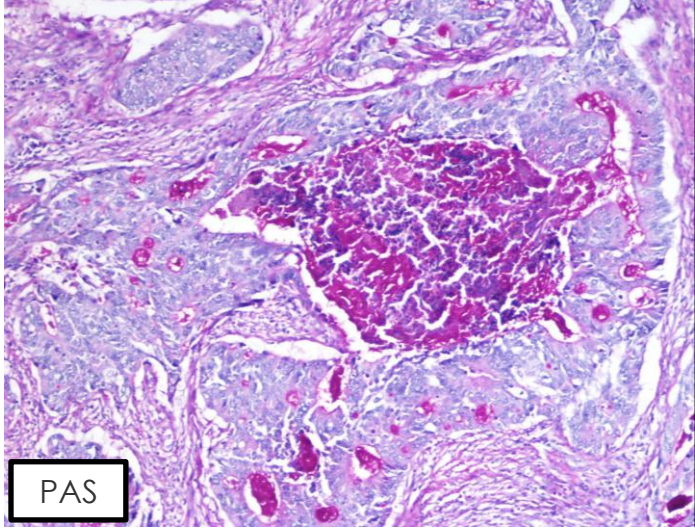
(Slightly) worse than GCA

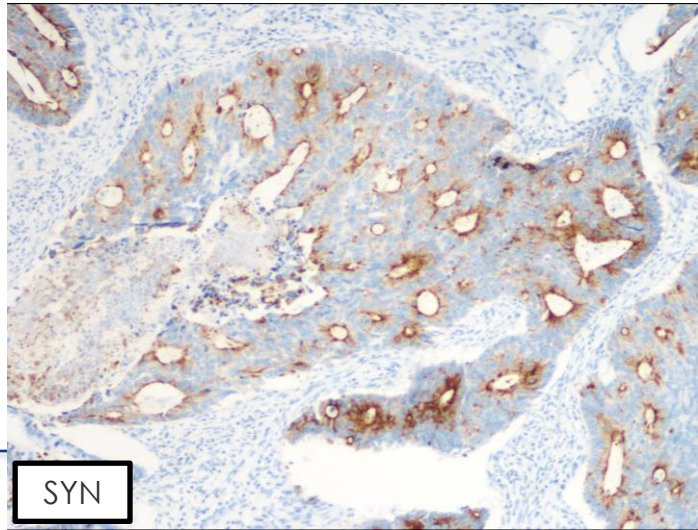
Arrow: increasingly unfavourable outcome (qualitative)



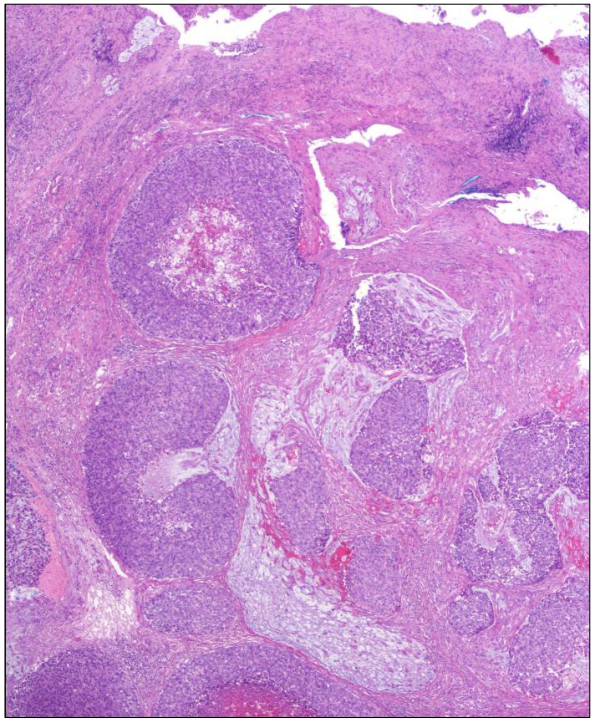
AMPHICRINE-LIKE RECTAL ADENOCARCINOMA

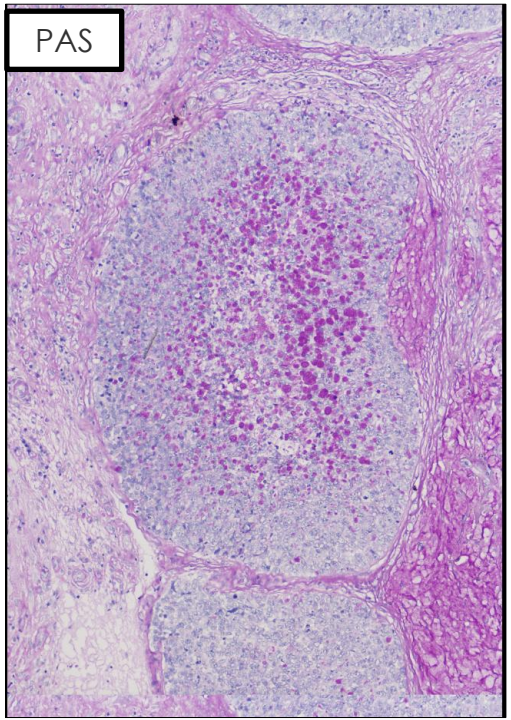


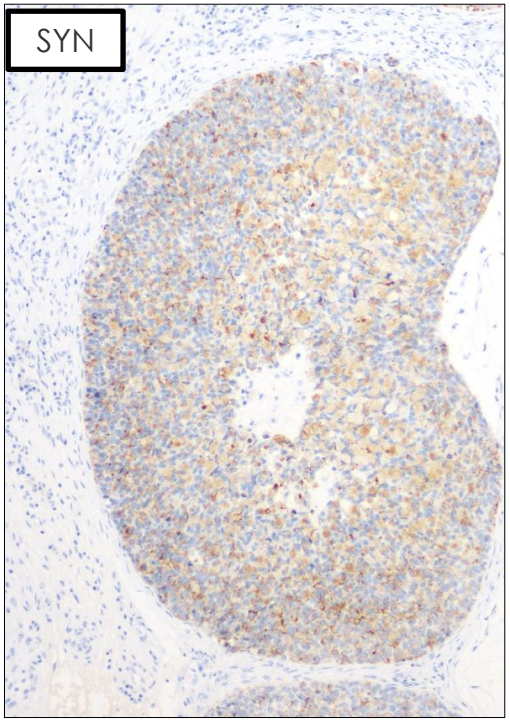




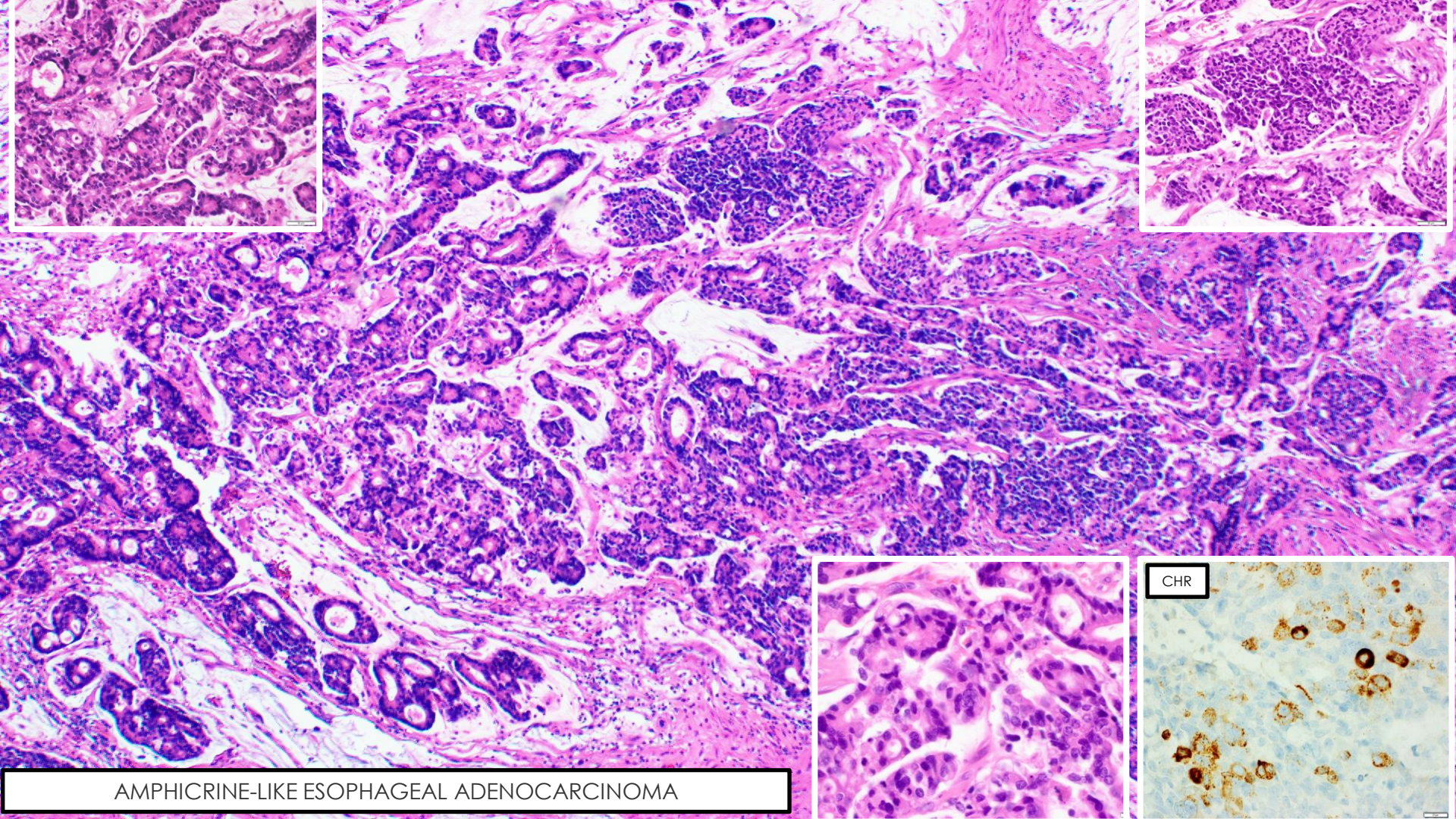
AMPHICRINE-LIKE COLONIC ADENOCARCINOMA



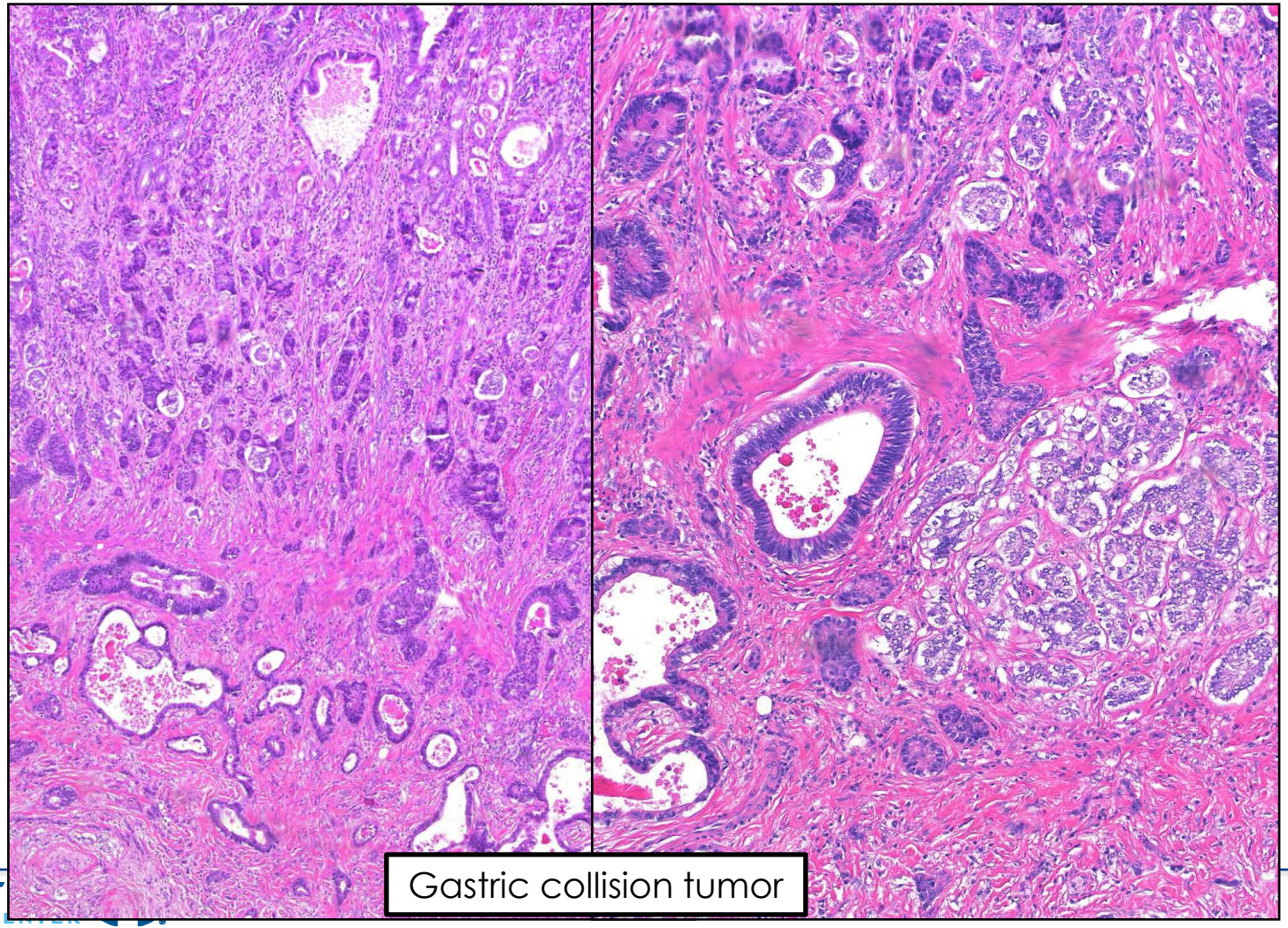




AMPHICRINE-LIKE ANAL SQUAMOUS CELL CARCINOMA



AMPHICRINE-LIKE ESOPHAGEAL ADENOCARCINOMA



Gastric collision tumor

ALCs in a Nutshell

ALCs are carcinomas: stage them with the TNM system for carcinomas of that site, not the NET system

1

Intermixed, not compartmentalised

ALC cells of both lineages are intimately intermixed; Morphological + IHC evidence of NE differentiation

MiNEN has distinct zones

2

Name the carcinoma type

e.g., amphicrine-like adenocarcinoma; never "ALC" alone

3

Apply the WHO thresholds

≥30% NE morphology, confirmed by ≥2 NE markers on IHC.

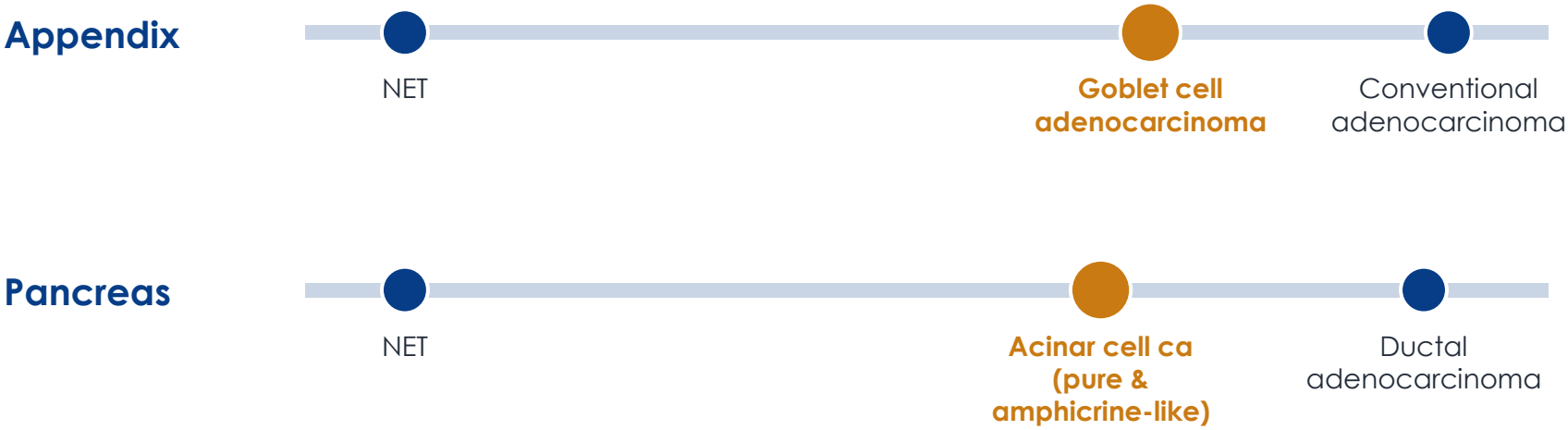
Common in poorly differentiated carcinomas at many sites — not enough for ALC

?

Open question

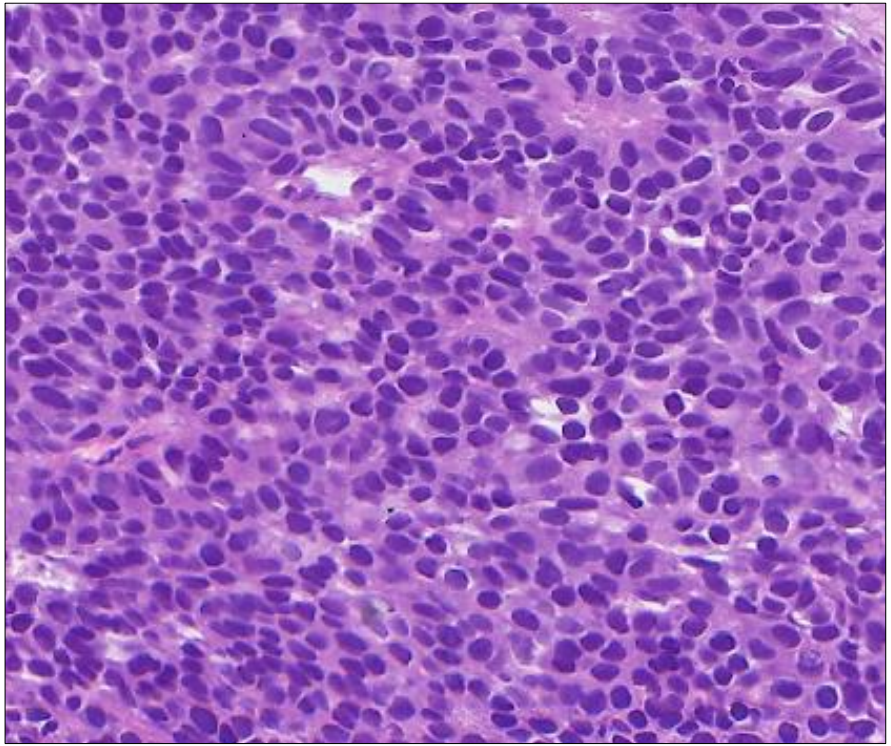
Do ALCs outside the appendix and pancreas have distinctive natural histories? More data are needed; the new classification should help collect them

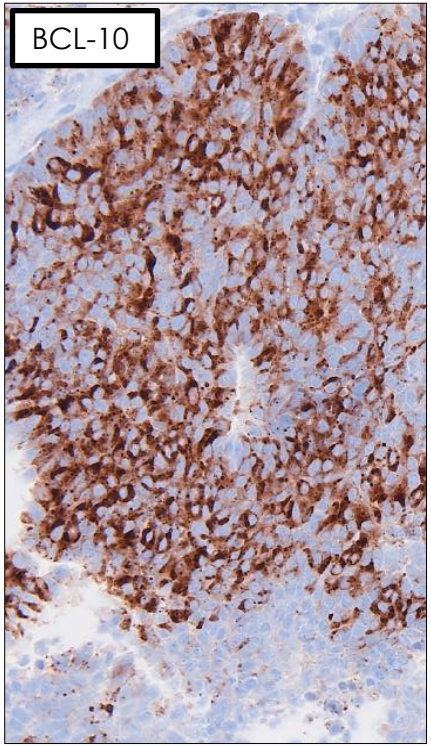
ALCs on the prognostic spectrum

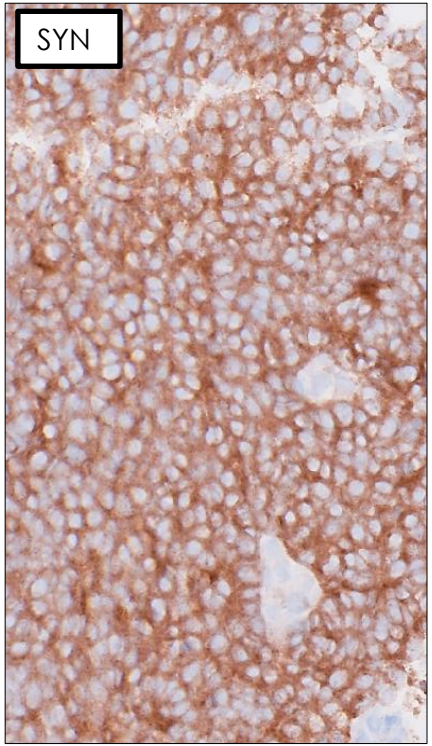


Amphicrine-like acinar cell carcinoma behaves like pure acinar cell carcinoma: intermediate between NET and PDAC, but closer to adenocarcinoma. Positions are qualitative, not survival data.

Amphicrine-like acinar cell carcinoma







ALC is a family — report the specific diagnosis

Once a tumour is placed in the ALC group, name it by its exocrine component:

✗ **Not acceptable**

"Amphicrine-like carcinoma" as the sole diagnosis

✓ **Report as**

Amphicrine-like adenocarcinoma
Amphicrine-like squamous cell carcinoma

Exception: goblet cell adenocarcinoma (appendix)

The most common ALC of the appendix. Because it is so well recognized and clinically distinct, it may be reported simply as goblet cell adenocarcinoma, without stating ALC-family membership.

ALCs are carcinomas: stage them with the TNM system for carcinomas of that site, not the NET system

WHO Classification & Grading of Digestive NENs

Definition		Differentiation	Grading			Tumour necrosis
			Grade	Mitotic count[a]	Ki67 index[b]	
Pure NEN	NET	Well differentiated	G1	<2	<3	Present/absent
			G2	2–20	3–20	
			G3	>20	>20	
	NEC	Poorly differentiated	High[c]	>20	>20	Not required
Nonpure NEN	MiNEN	Variable	Variable			Present/absent
	Amphicrine-like carcinoma	Carcinoma	Variable			Not required

[a] *Mitoses per 2 mm²* [b] *Ki67 % in hotspots* [c] *NEC are high grade by definition and not formally graded*
MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour