

Neuroendocrine tumors

Gastrointestinal pathology

Morphology | Endocrine function | Clinical behavior

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Learning objectives

Recognize neuroendocrine differentiation and characteristic tumor architecture.

Explain endocrine secretion, hepatic first-pass metabolism, and carcinoid syndrome.

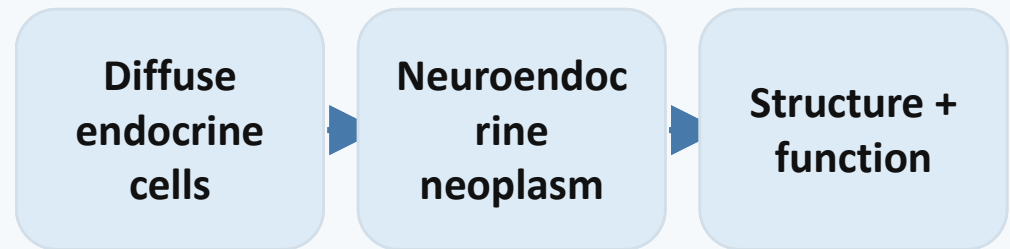
Relate differentiation, proliferation, size, and location to tumor behavior.

What constitutes a neuroendocrine tumor?

Neoplasms originate from diffusely distributed endocrine cells.

Gastrointestinal tumors often retain a recognizable organoid microscopic appearance.

Some tumors synthesize bioactive hormones;
Others are recognized incidentally.



Interpretation: Consider each step separately

Schematic (not a histologic specimen)

“Carcinoid” and modern terminology

Carcinoid is the historical term for many well-differentiated tumors.

Well-differentiated neuroendocrine tumor is the preferred descriptive term.

The word carcinoid remains in common use, especially for the clinical syndrome.

Historical term	Preferred framing
Carcinoid tumor	Well-differentiated NET
Carcinoid syndrome	Recognized clinical syndrome

NET and neuroendocrine carcinoma differ

A well-differentiated NET exhibits relatively uniform cells and organized patterns.

A poorly differentiated neuroendocrine carcinoma is high-grade by its nature.

Distinguishing these categories changes clinicopathologic interpretation.

Well-differentiated NET	Poorly differentiated NEC
Organoid growth	Poor differentiation
Typically bland cytology	Small-cell or large-cell type
Proliferation assessed	High mitotic/Ki-67 activity

Distribution is predominantly gastrointestinal

Most neuroendocrine tumors arise within the gastrointestinal tract.

More than 40% occur in the small intestine description.

The tracheobronchial tree and lung form the next most frequent site group.

Stomach

Small intestine

Appendix

Rectum

GI predominance • >40% small intestine

Schematic (not a histologic specimen)

Tumor location is biologically consequential

Primary site influences presenting symptoms and patterns of detection.

Stomach, small intestine, appendix, and rectum have different typical behaviors.

A diagnosis of NET is incomplete without its anatomic context.

Stomach

Small intestine

Appendix

Rectum

Site affects presentation and prognosis

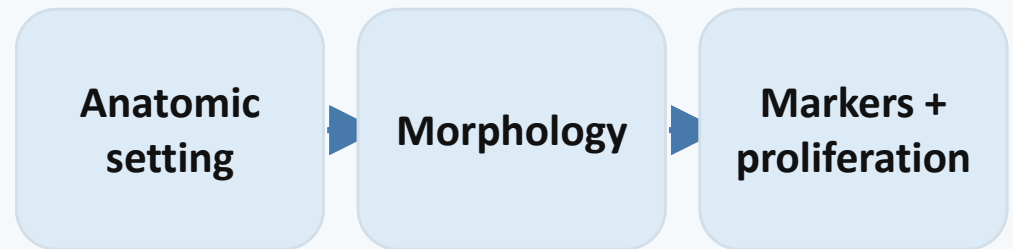
Schematic (not a histologic specimen)

A useful diagnostic triad

Recognize the location and depth of the lesion.

Assess architectural and cytologic differentiation.

Integrate immunophenotype with mitotic and Ki-67 findings.



Interpretation: Consider each step separately

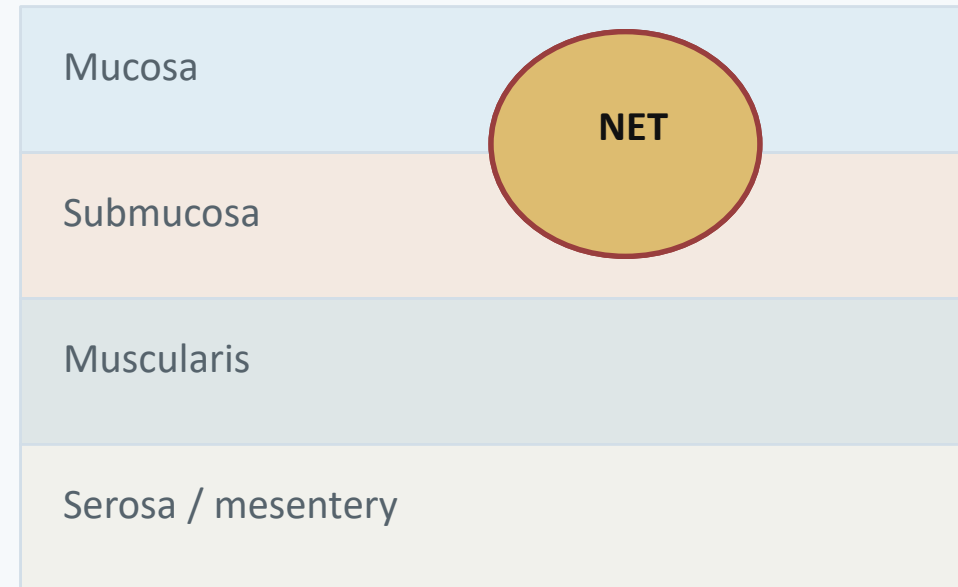
Schematic (not a histologic specimen)

Gastric tumors arise in an endocrine context

Gastric NETs often develop in the oxyntic mucosa.

Background endocrine-cell hyperplasia may accompany some lesions.

The underlying clinical setting helps interpret their likely behavior.



Gastric wall / oxyntic mucosa

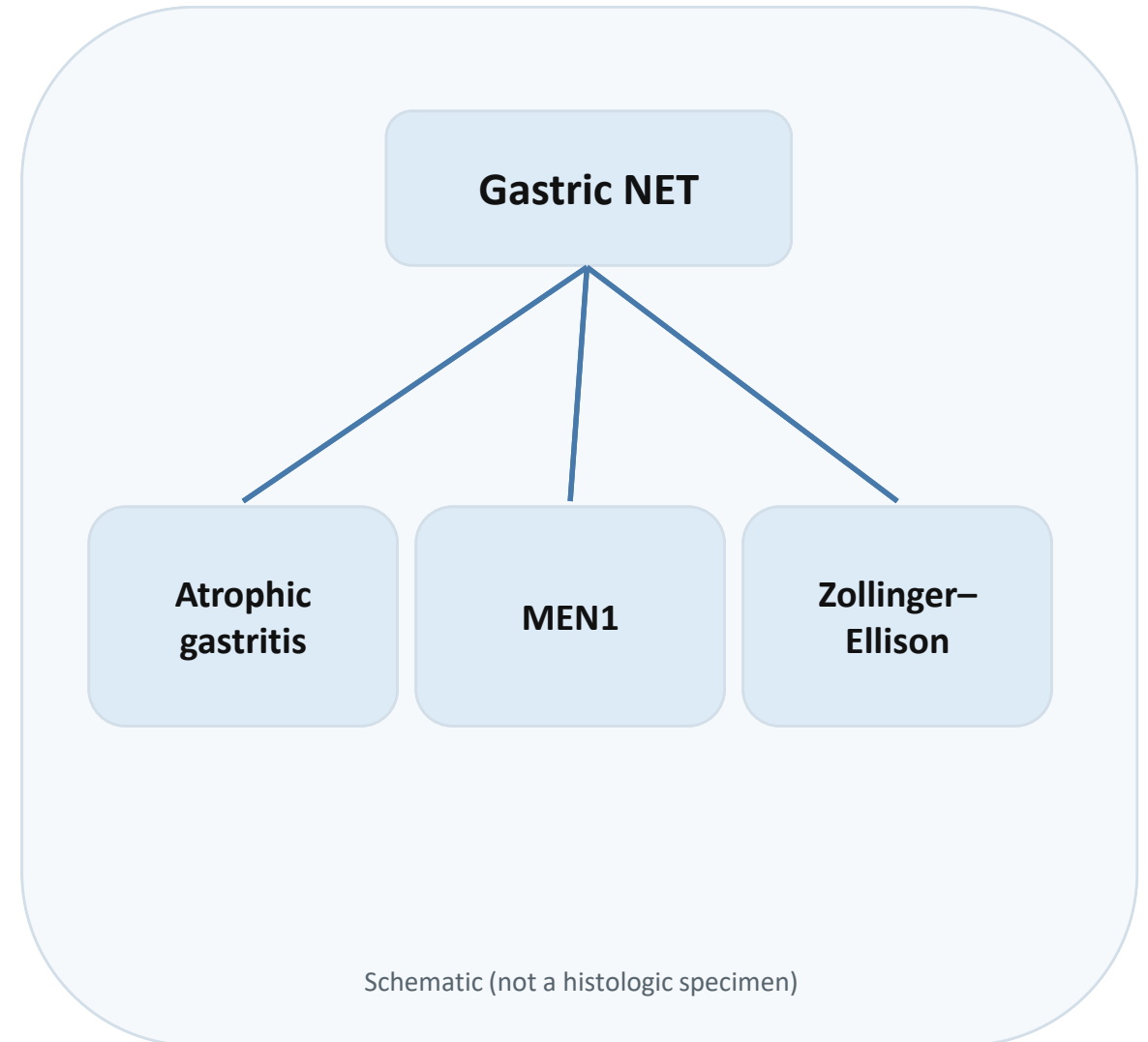
Schematic (not a histologic specimen)

Associated conditions in the stomach

Autoimmune chronic atrophic gastritis is a recognized association.

Multiple endocrine neoplasia type 1 (MEN1) is another association.

Zollinger–Ellison syndrome can accompany gastric neuroendocrine tumors.

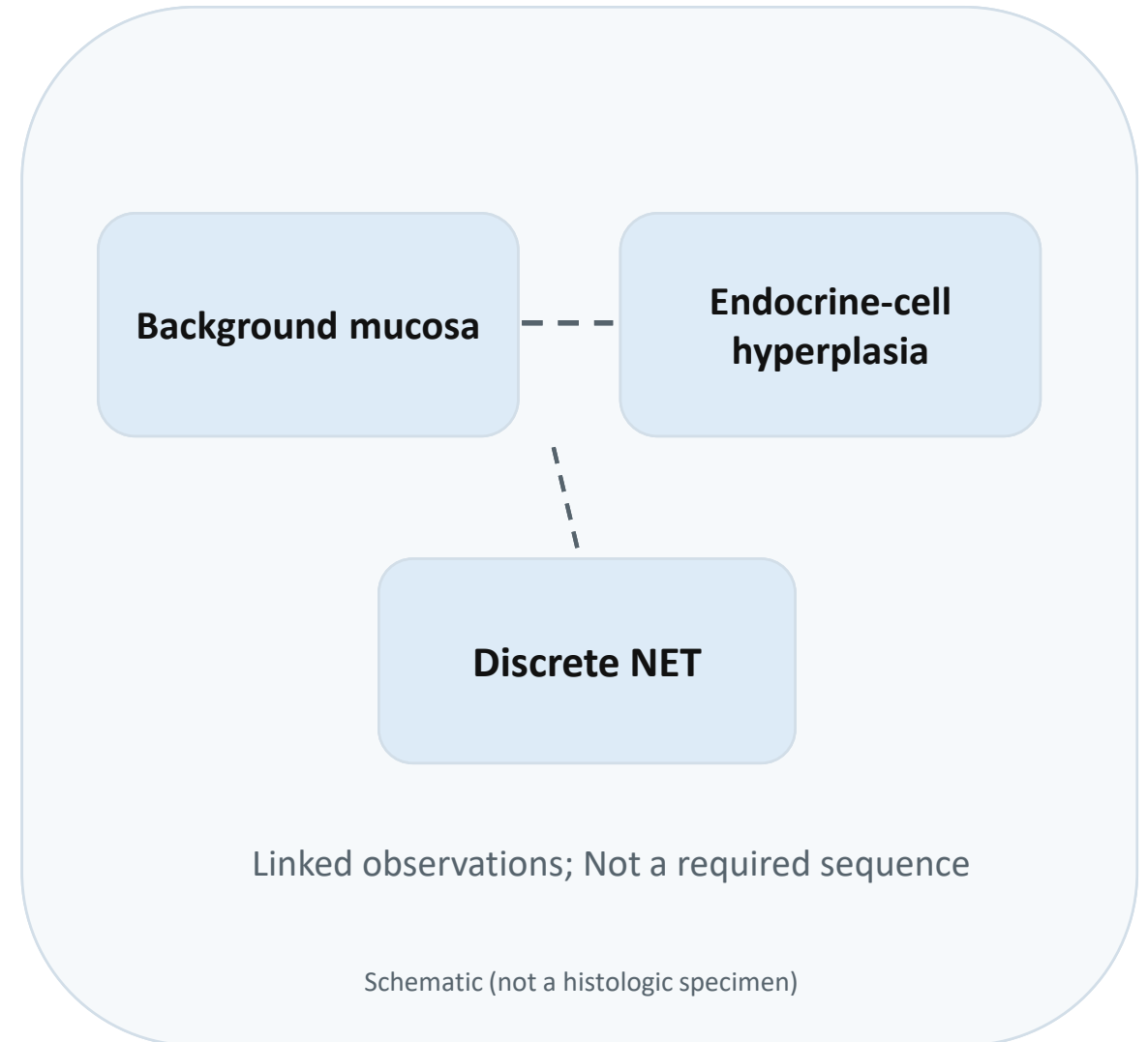


Endocrine-cell hyperplasia is a background clue

Hyperplasia and a discrete neoplasm are not synonymous diagnoses.

A hyperplastic endocrine-cell population may form a recognizable background.

Interpret the lesion together with the adjacent nonneoplastic mucosa.



Autoimmune atrophic gastritis: Clinical meaning

A tumor associated with autoimmune chronic atrophic gastritis differs from an unassociated sporadic gastric tumor.

The source identifies a generally favorable pattern for gastritis-associated gastric lesions.

Avoid transferring that prognosis automatically to all gastric NETs.

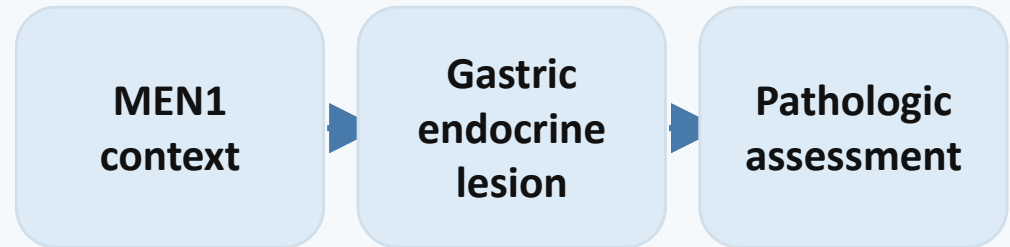
Gastritis-associated	No recognized predisposition
Often less aggressive	Often more aggressive
Background mucosal disease	No specific predisposing context
Site alone is insufficient	Biologic context matters

MEN1 is a predisposing clinical setting

MEN1 is listed among the associations of gastric NET.

Its presence should orient interpretation toward a syndromic context.

The topic excerpt does not supply site-specific surveillance or grading rules for MEN1.



Interpretation: Consider each step separately

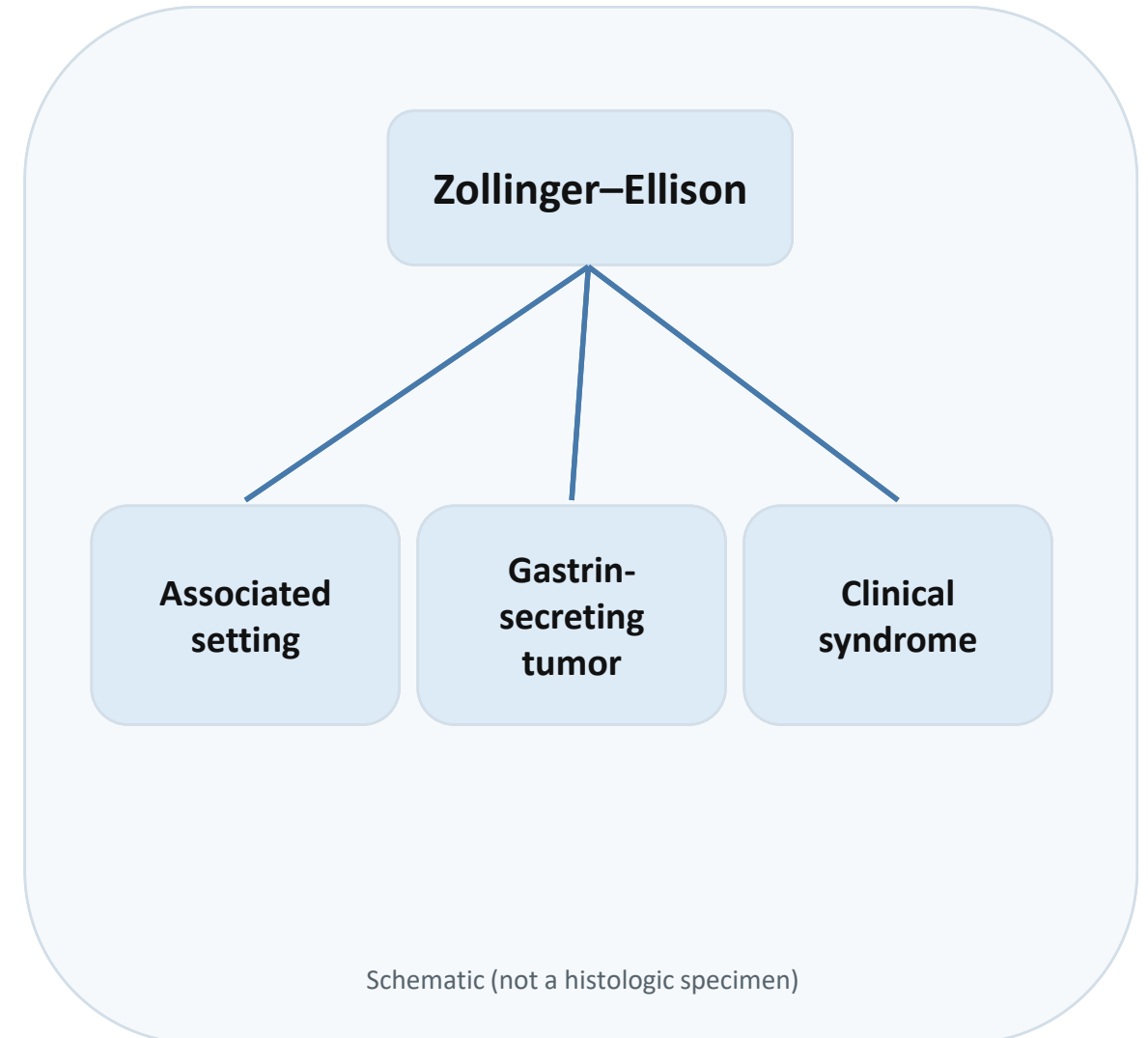
Schematic (not a histologic specimen)

Zollinger–Ellison: Two connections

Zollinger–Ellison syndrome is associated with some gastric NETs.

A NET that secretes gastrin may itself cause the syndrome.

Separate a syndrome-associated background from hormone production by the tumor.



Proton pump inhibitors: Avoid overstatement

PPI therapy is associated with endocrine and enterochromaffin-like cell hyperplasia.

Progression to neuroendocrine neoplasia in this setting as negligible.

Do not equate PPI-associated hyperplasia with a diagnosed gastric NET.

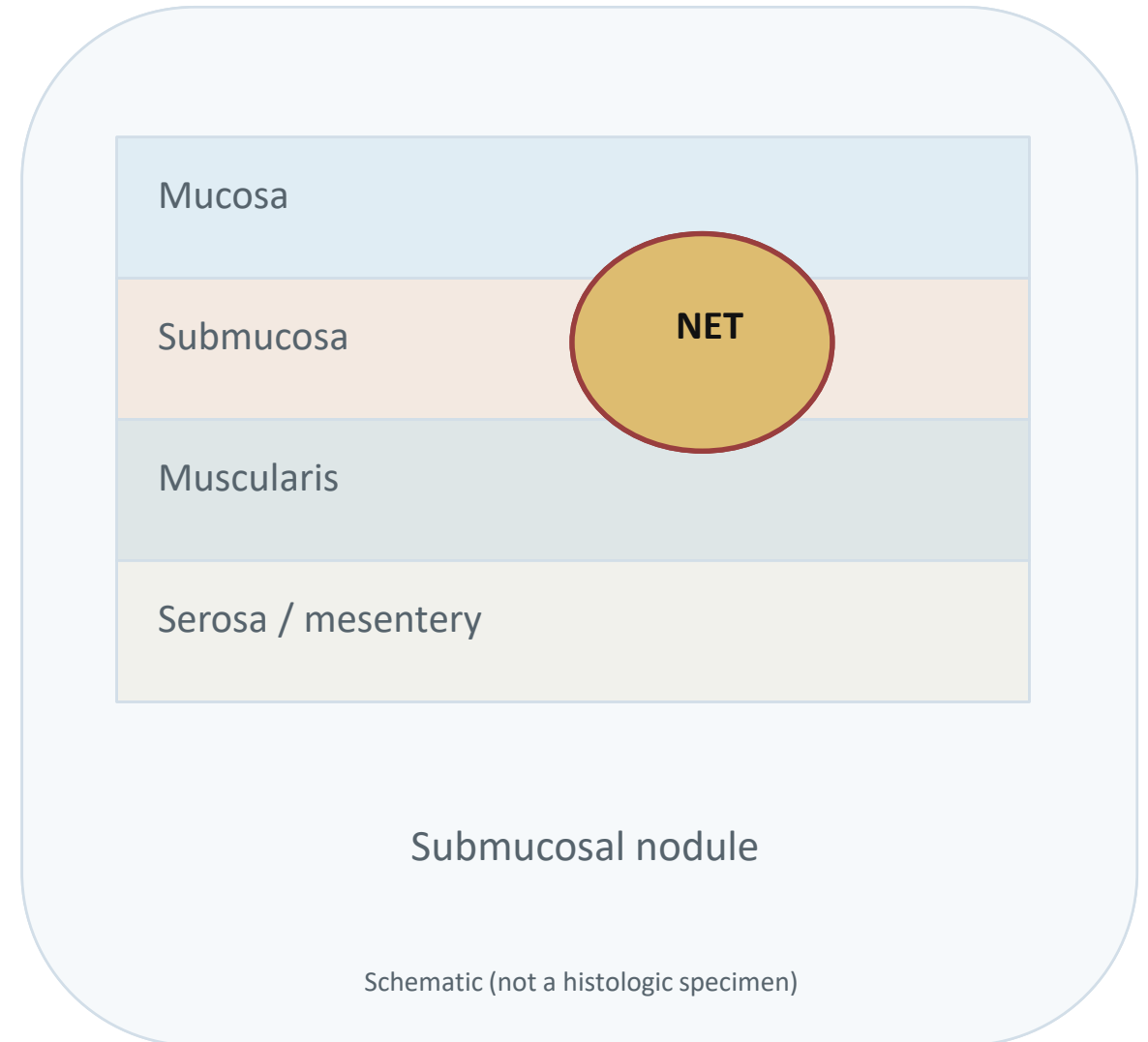
Supported association	Not a supported inference
Endocrine-cell hyperplasia	An inevitable neoplasm
PPI exposure context	Clinically meaningful NET risk by itself

A polypoid lesion can be submucosal

Gross tumors are typically intramural or submucosal masses.

The lesion may project beneath the surface as a polypoid bulge.

A gross mucosal appearance alone may underestimate its intramural component.



An intact surface does not exclude a tumor

The mucosa overlying the NET may remain intact.

Other lesions develop overlying ulceration.

Correlate the surface with the location of the principal tumor mass.

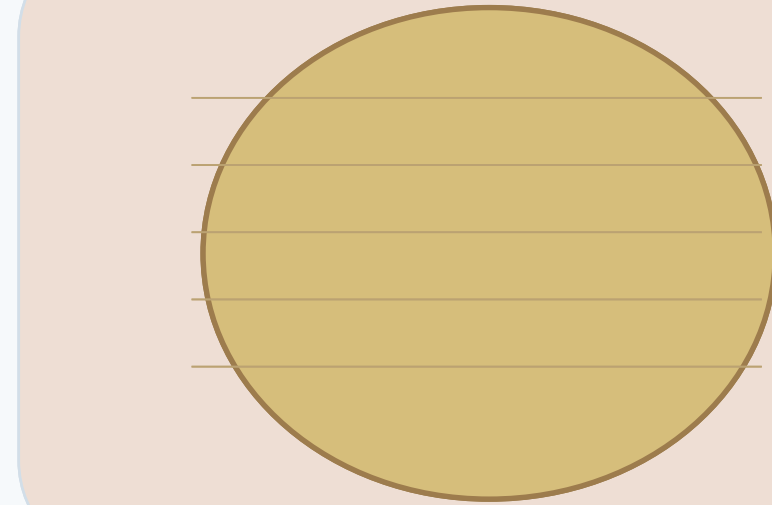
Intact overlying mucosa	Ulcerated overlying mucosa
Submucosal mass possible	Submucosal mass possible
Surface can appear preserved	Mucosal defect is present

The gross cut surface is distinctive

Neuroendocrine tumors tend to have a yellow-to-tan appearance.

The tumors may be unusually firm.

Marked fibrosis contributes substantially to that consistency.



Yellow–tan, firm nodule (gross schematic)

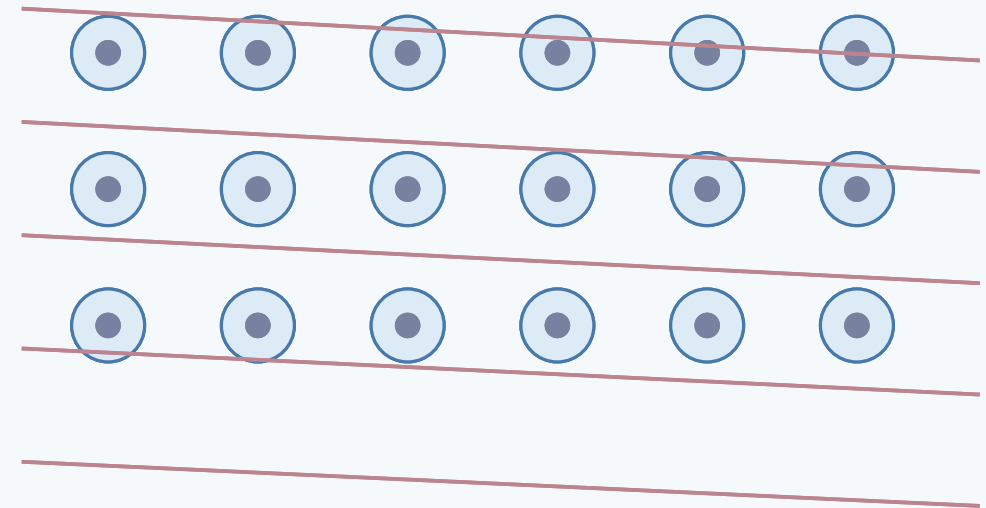
Schematic (not a histologic specimen)

Desmoplasia is not an incidental finding

Intense desmoplastic reaction surrounds or accompanies some lesions.

Fibrous tissue contributes to the stiff, retracted tumor mass.

In the small bowel, fibrosis may produce clinically important distortion.



Tumor groups + fibrous stroma

Schematic (not a histologic specimen)

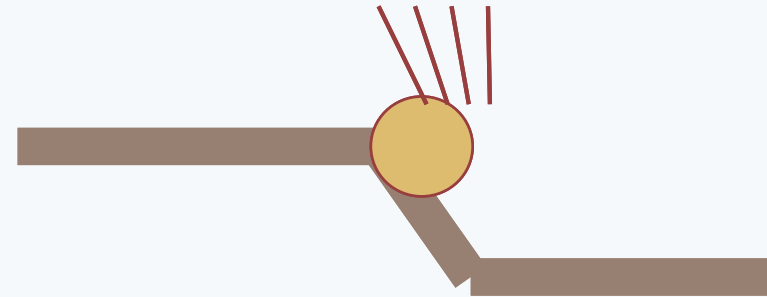
Why a small bowel lesion causes obstruction

A firm tumor may evoke mesenteric or mural desmoplasia.

Fibrosis can kink the bowel and change its normal course.

Mechanical obstruction can follow from this distortion.

Fibrotic traction can distort the bowel



NET + desmoplasia

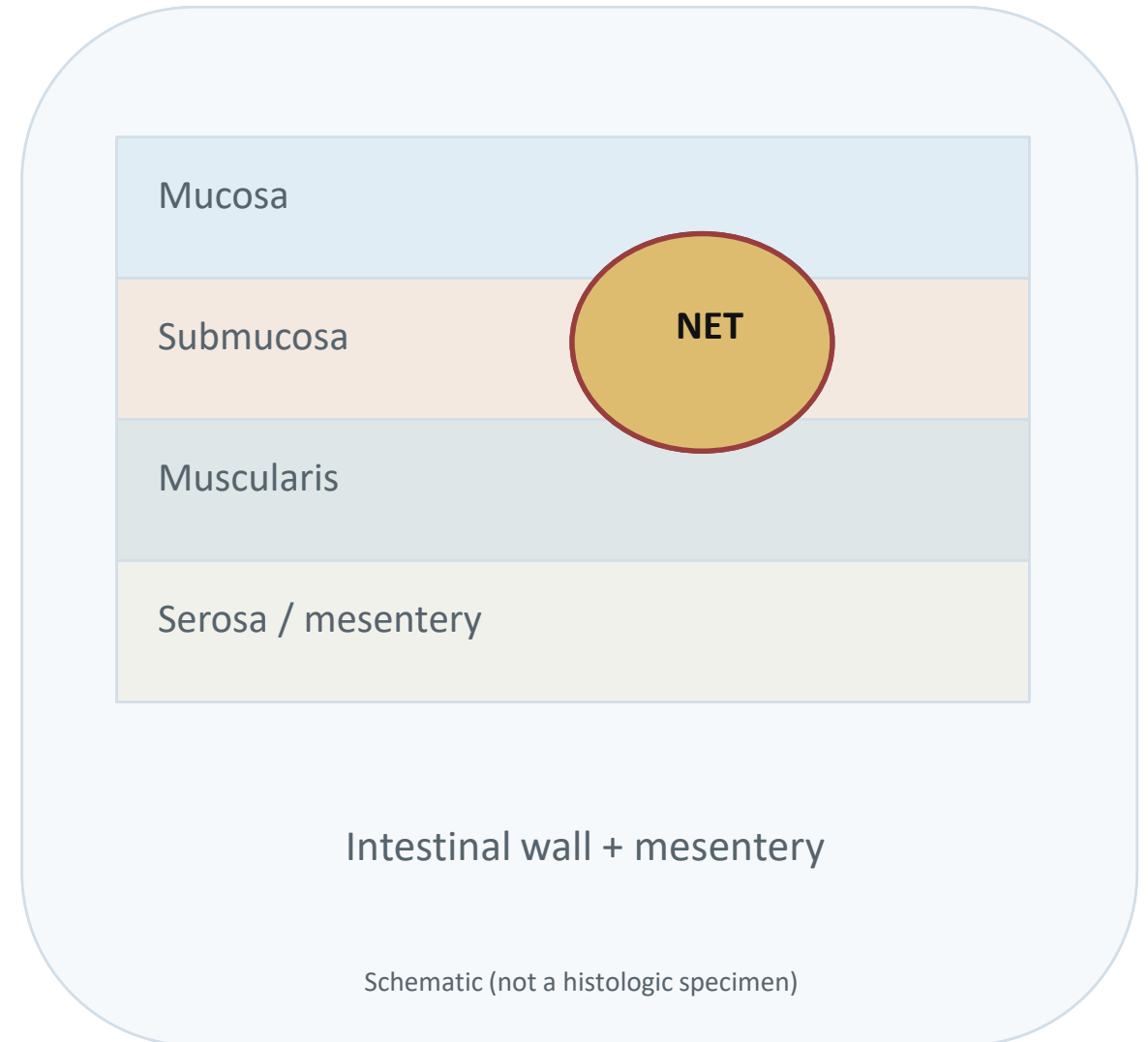
Schematic (not a histologic specimen)

Small bowel tumors can extend into mesentery

Intestinal lesions may invade deeply through the wall.

Mesenteric involvement can be extensive even when the mucosal lesion is modest.

Gross depth and local spread should be considered separately from surface size.



Gross-to-microscopic correspondence

The polypoid bulge reflects underlying wall expansion.

Firmness corresponds to a prominent fibrous stromal response.

Cytologic blandness cannot establish the absence of deep invasion.

**Submucosal
mass**



**Tumor +
dense
stroma**



**Local
extension
possible**

Interpretation: Consider each step separately

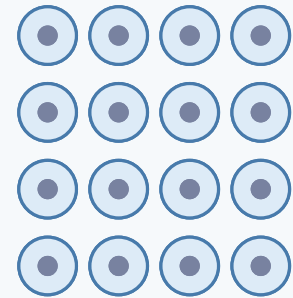
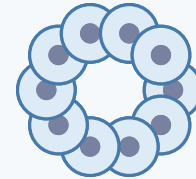
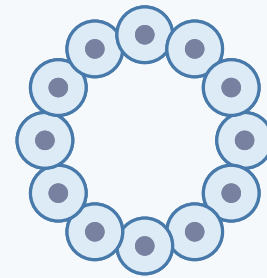
Schematic (not a histologic specimen)

NETs form recognizable organoid arrangements

Islands and nests are common growth patterns.

Trabeculae and cords may create a branching architecture.

Gland-like structures and sheets can also be present.



Gland-like, nested, and sheet-like patterns

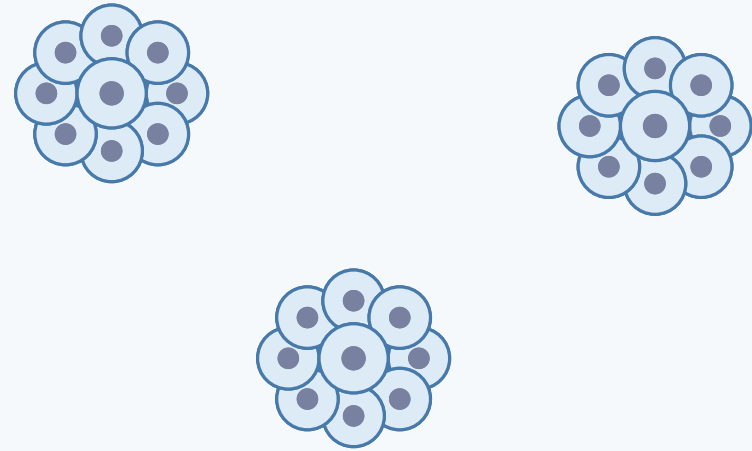
Schematic (not a histologic specimen)

Nests and islands: An architectural pattern

Uniform tumor-cell groups form discrete rounded islands.

Fibrous tissue may separate the cellular groups.

Architecture is useful in identifying neuroendocrine differentiation.



Separate nests / islands of tumor cells

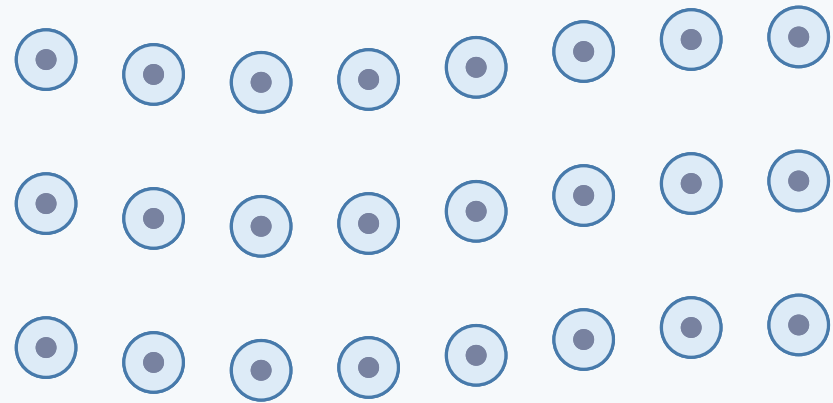
Schematic (not a histologic specimen)

Trabeculae and strands

Cells may align in elongated cords or slender trabeculae.

Different patterns can coexist within a single tumor.

Growth pattern should be assessed alongside nuclear features.



Elongated strands and trabeculae

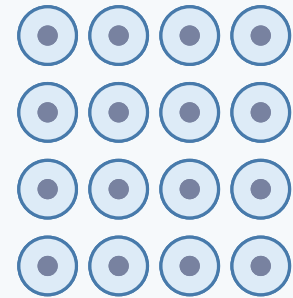
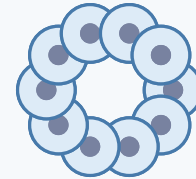
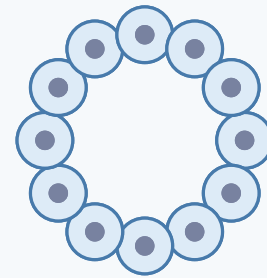
Schematic (not a histologic specimen)

Gland-like and sheet-like patterns

Well-differentiated tumors can contain gland-like formations.

Solid sheets may also occur.

One pattern in isolation is not a complete diagnostic criterion.



Gland-like, nested, and sheet-like patterns

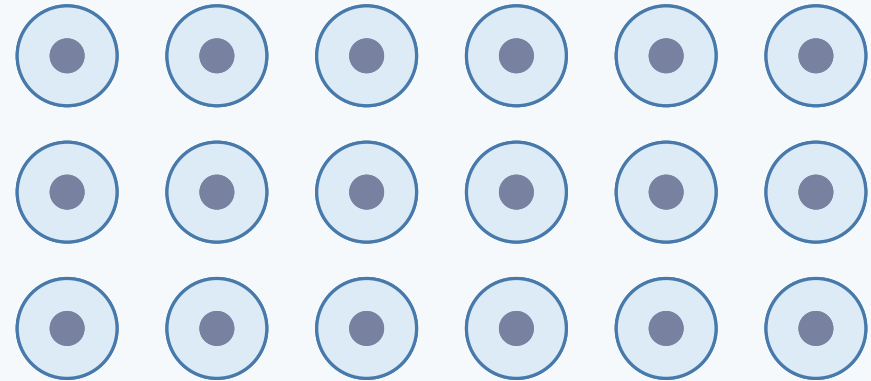
Schematic (not a histologic specimen)

The typical cell population is uniform

The constituent cells are comparatively monotonous.

Nuclei are round or oval.

Cytologic uniformity supports well differentiation but does not define stage.



Uniform round–oval nuclei; Granular cytoplasm

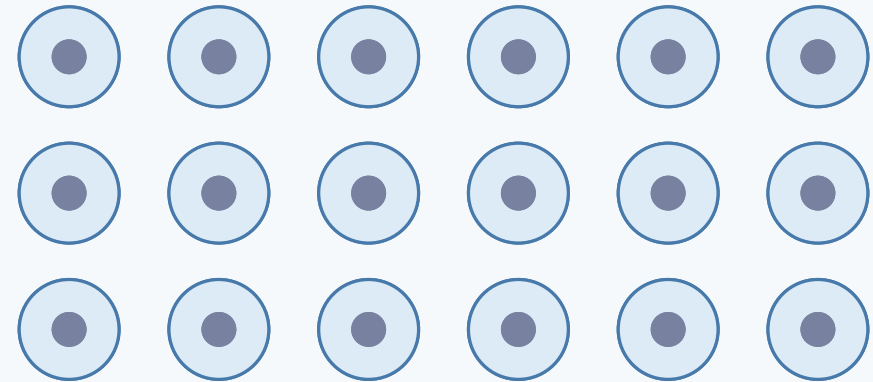
Schematic (not a histologic specimen)

Cytoplasm is often granular and eosinophilic

The cytoplasm may be scant, pink, and finely granular.

This appearance complements the characteristic nuclear pattern.

Routine H&E evaluation should still be integrated with IHC.



Uniform round–oval nuclei; Granular cytoplasm

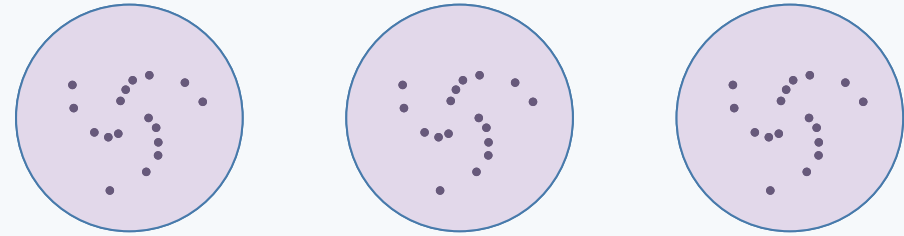
Schematic (not a histologic specimen)

“Salt-and-pepper” chromatin

Nuclear chromatin shows fine and coarser dispersed clumps.

The distribution produces the characteristic speckled appearance.

The pattern is descriptive rather than a stand-alone specific test.



Dispersed fine + coarse chromatin clumps

Schematic (not a histologic specimen)

Bland nuclei do not guarantee indolence

A tumor may be cytologically bland yet invade deeply.

Lymphatic permeation can occur in morphologically differentiated lesions.

Proliferation and anatomic extension are essential additional assessments.

Bland cytology

Vs

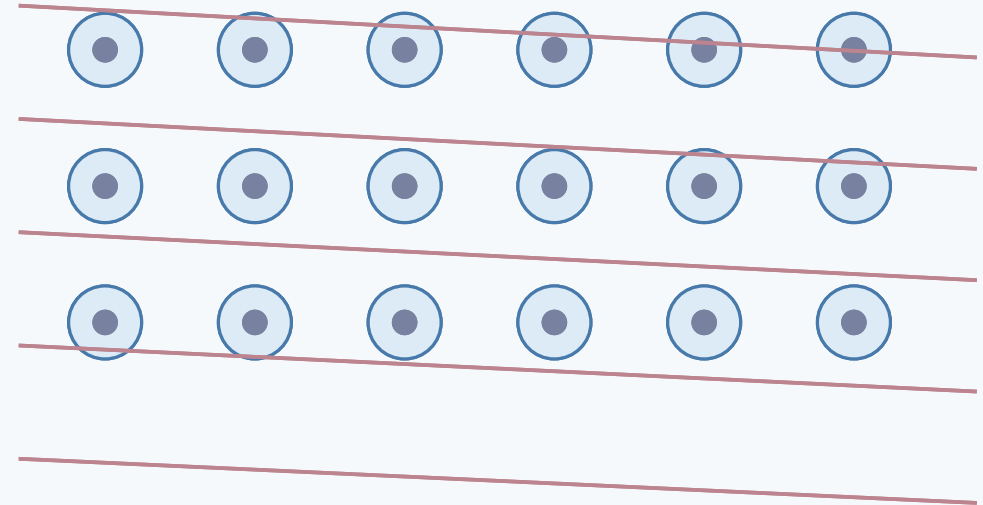
**Invasion may
coexist**

Dense fibrous tissue surrounds tumor groups

The textbook figure describes tumor cells embedded in dense fibrosis.

Fibrosis is a structural correlate of the gross firmness.

The tumor–stroma interface can be visually prominent.



Tumor groups + fibrous stroma

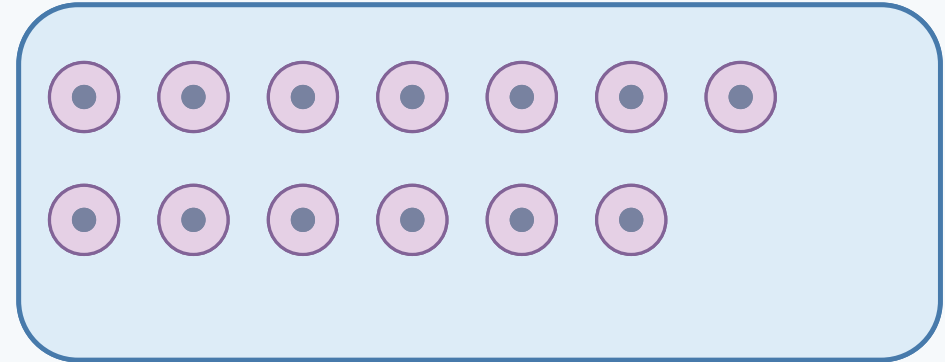
Schematic (not a histologic specimen)

Lymphatic channel involvement

Tumor groups may permeate mucosal lymphatic channels.

Lymphatic spread represents an invasive feature.

This finding cannot be inferred from cytologic appearance alone.



NET cells within a lymphatic lumen

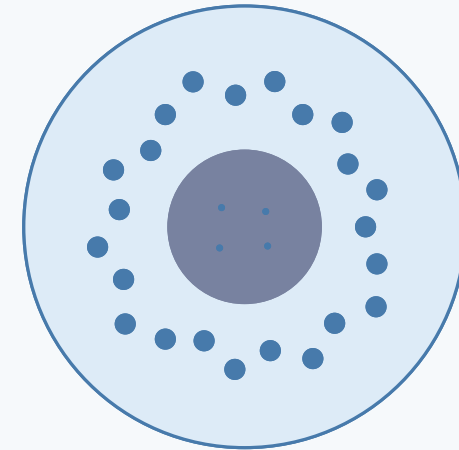
Schematic (not a histologic specimen)

Dense-core granules and secretory identity

Ultrastructural neurosecretory granules are a characteristic feature.

They provide a morphologic correlate of endocrine secretory differentiation.

Routine diagnosis generally relies on histology and IHC rather than electron microscopy.



Dense-core secretory granules (conceptual)

Schematic (not a histologic specimen)

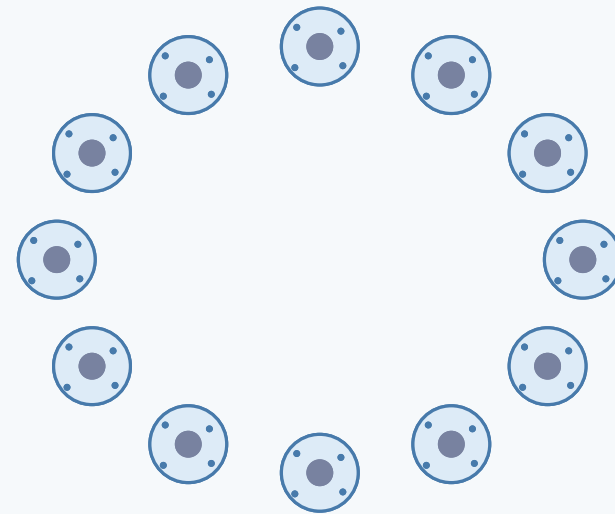
Synaptophysin identifies neuroendocrine lineage

Synaptophysin is an endocrine granule-associated immunohistochemical marker.

Positive staining supports neuroendocrine differentiation.

Interpret the stain with the histologic architecture and cytology.

Synaptophysin



Neuroendocrine granule-associated marker

Schematic (not a histologic specimen)

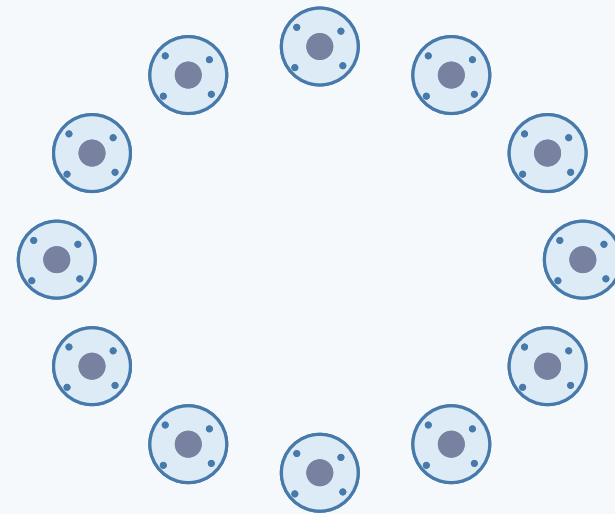
Chromogranin A is a complementary marker

Chromogranin A is another neuroendocrine granule-associated marker.

Its expression supports secretory differentiation.

A positive marker should not replace classification by morphology.

Chromogranin A



Neuroendocrine granule-associated marker

Schematic (not a histologic specimen)

A combined diagnostic synthesis

Tumor architecture suggests an organoid neuroendocrine lesion.

Nuclear chromatin and cytoplasmic granularity strengthen the impression.

Synaptophysin and chromogranin A provide immunophenotypic support.

**Organoid
pattern**

**Salt-and-
pepper
nuclei**

**Neuroendoc
rine IHC**

Interpretation: Consider each step separately

Schematic (not a histologic specimen)

Morphology and proliferation answer different questions

Differentiation describes the nature of the tumor morphology.

Mitoses and Ki-67 convey proliferative activity.

Both dimensions are important for prognostication.

Morphologic axis	Proliferative axis
Well versus poor differentiation	Mitotic activity
Architectural/cytologic phenotype	Ki-67 labeling index
Classification context	Prognostic context

Poorly differentiated neuroendocrine carcinoma

Poorly differentiated neuroendocrine neoplasms are classified as carcinomas.

High mitotic activity and high Ki-67 are characteristic.

These tumors warrant distinction from well-differentiated NET.

**Well-
differentiated NET**

Vs

**Poorly
differentiated NEC**

Small-cell and large-cell NEC

Poorly differentiated NEC into small-cell and large-cell types.

The distinction is part of morphologic tumor classification.

Neither label should be assigned from an IHC result alone.

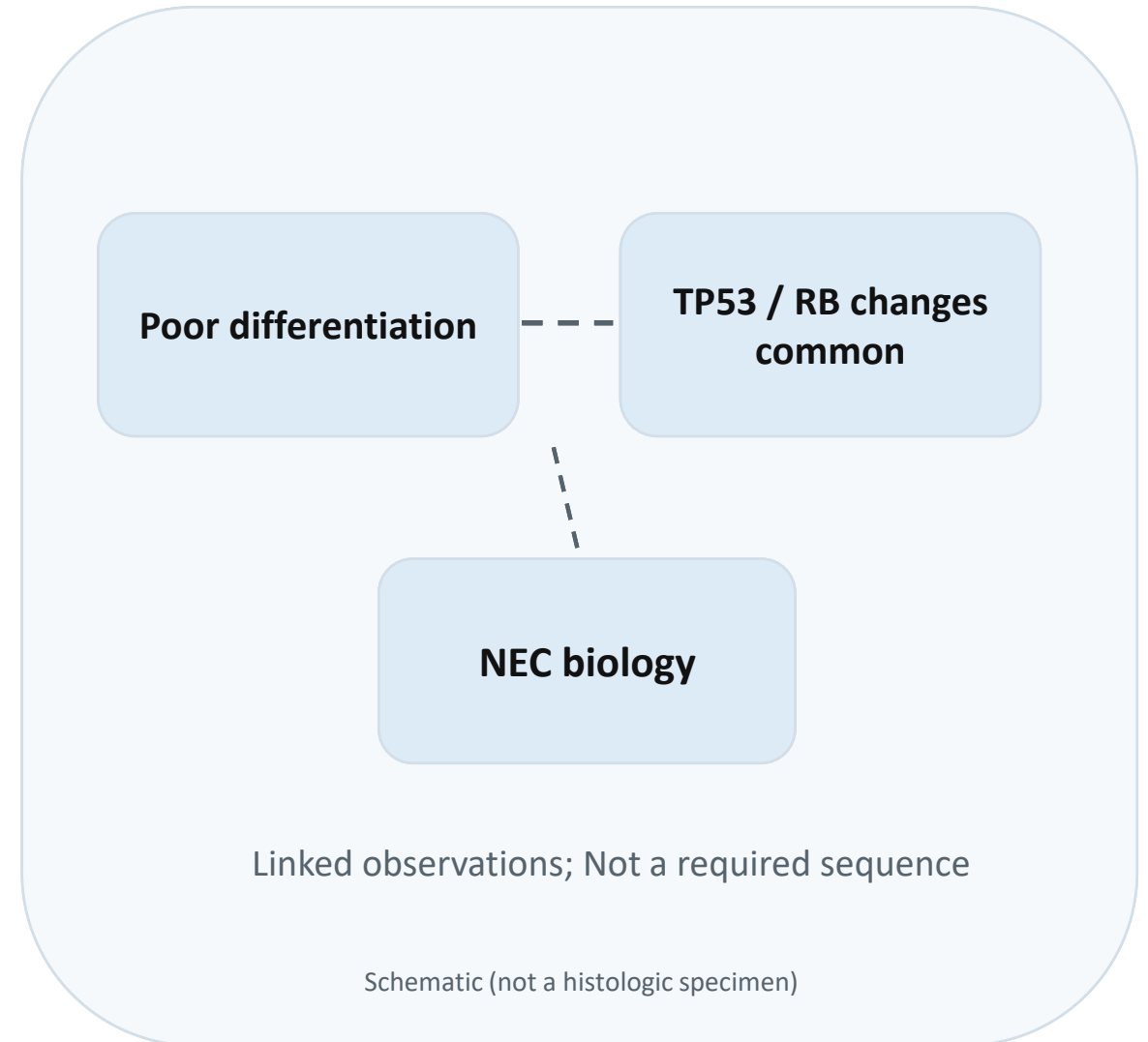
Small-cell NEC	Large-cell NEC
Poorly differentiated	Poorly differentiated
High proliferative activity	High proliferative activity
Morphologic subtype	Morphologic subtype

TP53 and RB alterations in NEC

Alterations of TP53 and RB are common in poorly differentiated NEC.

The textbook draws a parallel with neuroendocrine carcinomas at extraintestinal sites.

These molecular observations do not replace tissue-level diagnosis.



Mitoses reflect active cell division

A mitotic count samples proliferative behavior morphologically.

Mitotic rate as a major prognostic factor.

Mitotic rate should not be confused with architectural differentiation.

Morphology

Mitoses

Ki-67

Complementary information; No source cutoffs assumed

Ki-67 measures proliferative fraction

Ki-67 immunolabeling estimates the fraction of cycling tumor cells.

The index is explicitly identified as a major prognostic factor.

The supplied excerpt does not specify grading cutoffs; None are assumed here.

Morphology

Mitoses

Ki-67

Complementary information; No source cutoffs assumed

No universal site-independent staging rule

Size and location modify expected behavior.

GI neuroendocrine tumor staging is region specific.

Avoid applying an identical staging framework to every bowel segment.

Stomach

Small intestine

Appendix

Rectum

Site affects presentation and prognosis

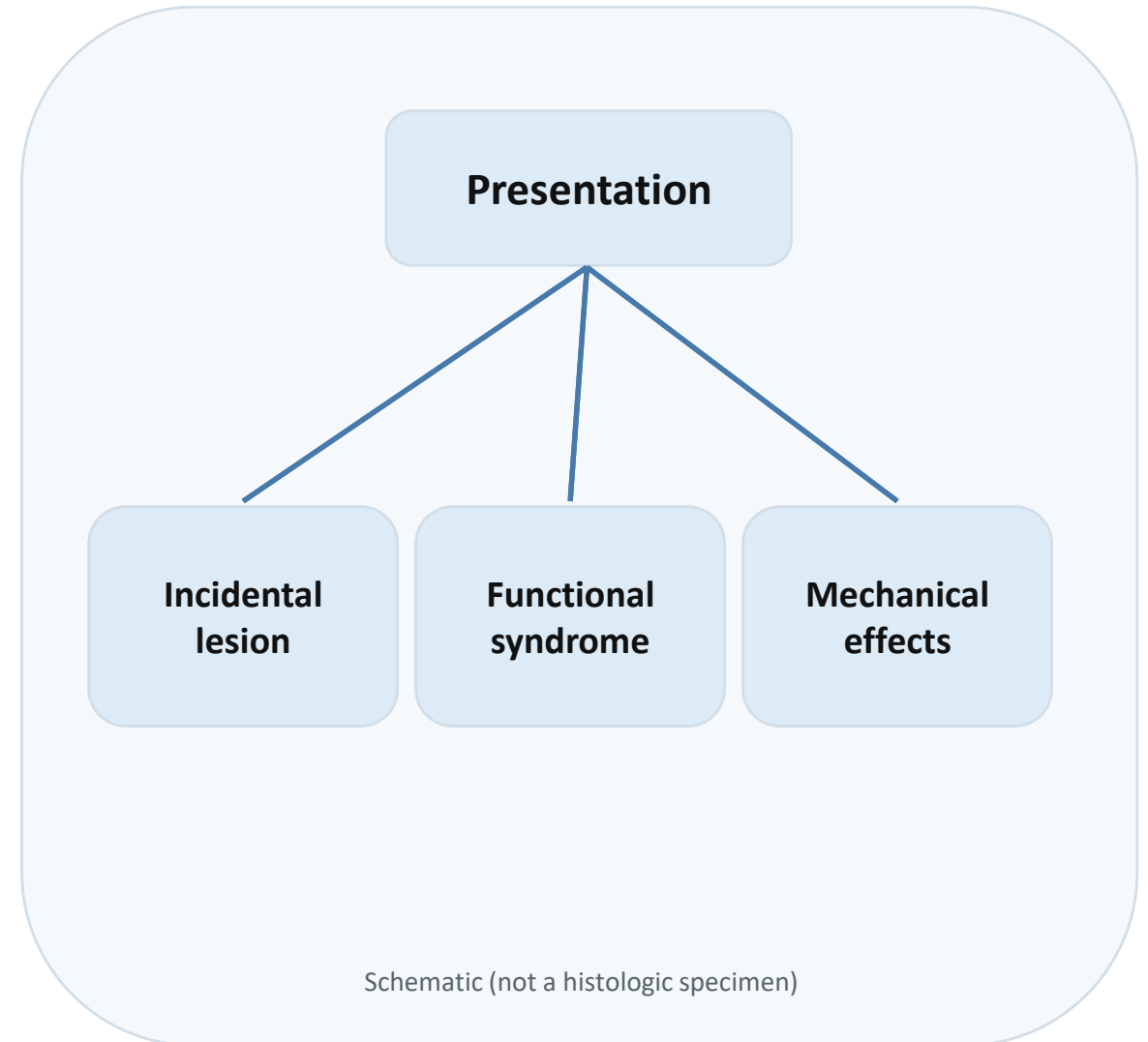
Schematic (not a histologic specimen)

Presentation spans incidental and functional disease

Some tumors are detected incidentally.

Others produce symptoms from hormone secretion.

Local fibrosis and bowel obstruction form an additional mechanical pathway.



When in life do GI NETs present?

Peak incidence in the source is in the sixth decade.

Presentation can occur at any age.

Age alone does not rule out the diagnosis.

Possible at any age

Peak: Sixth decade

Hormone production explains some symptoms

Certain tumors synthesize and release bioactive products.

The specific hormone determines the clinical syndrome.

A tumor can be present without a conspicuous systemic syndrome.



Interpretation: Consider each step separately

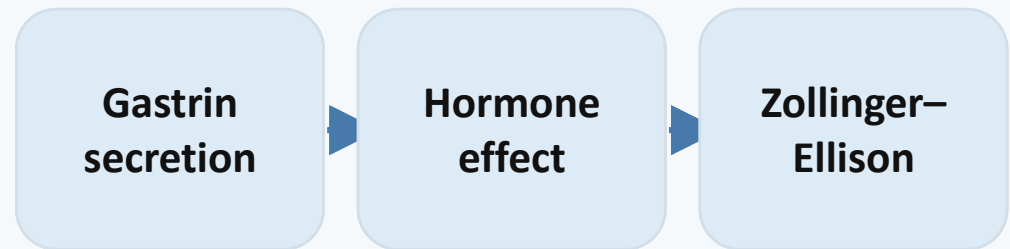
Schematic (not a histologic specimen)

Gastrin-producing tumors

Tumoral gastrin secretion may cause Zollinger–Ellison syndrome.

This example links endocrine product to recognizable clinical effects.

A functional syndrome and the tumor location are distinct descriptors.



Interpretation: Consider each step separately

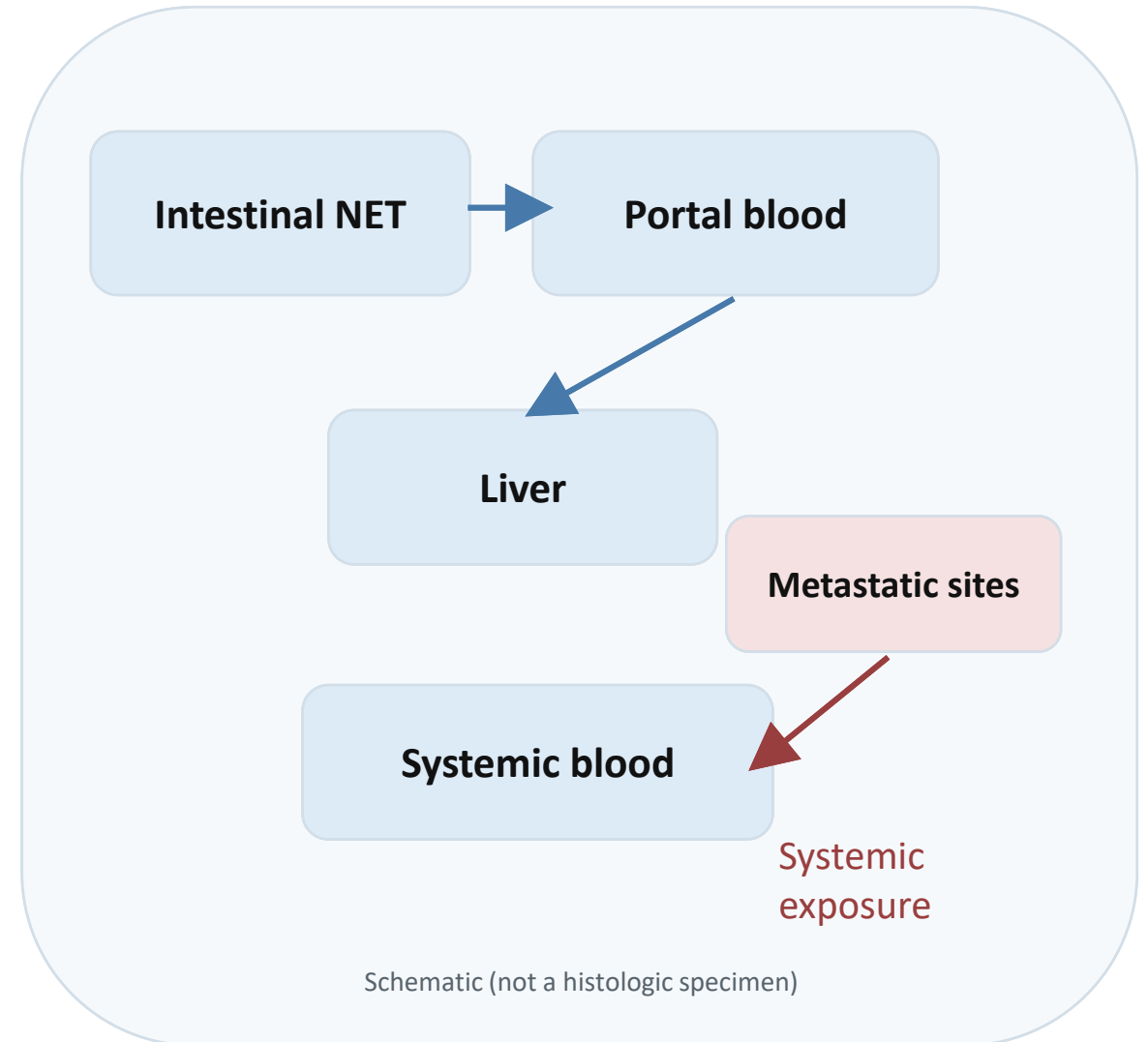
Schematic (not a histologic specimen)

What is carcinoid syndrome?

A systemic syndrome caused by circulating vasoactive substances from NETs.

It in fewer than 10% of affected patients.

It is strongly associated with metastatic spread enabling hepatic bypass.

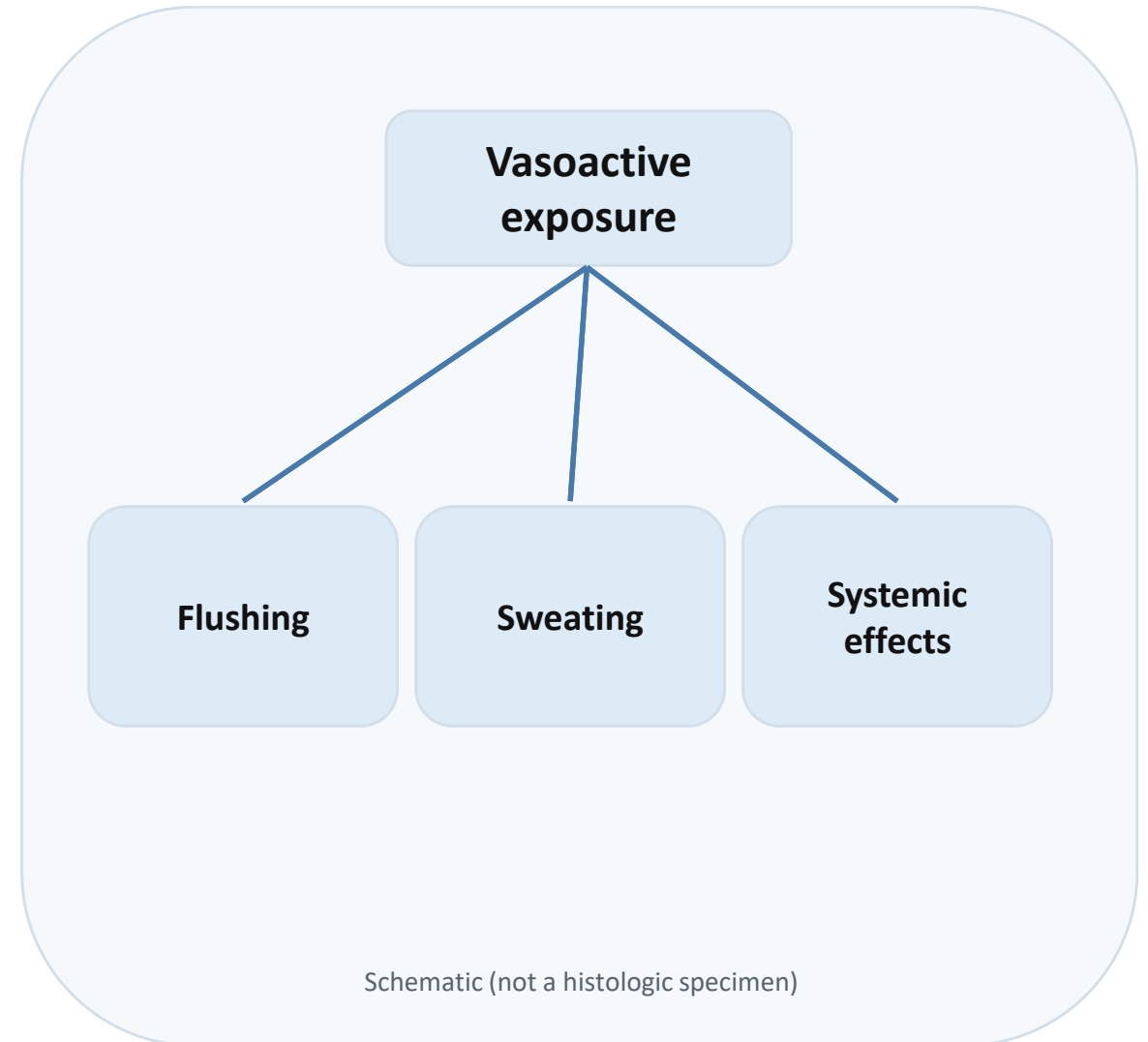


Cutaneous and autonomic symptoms

Flushing is a characteristic clinical manifestation.

Sweating can accompany episodes.

These features reflect systemic exposure to secreted vasoactive agents.

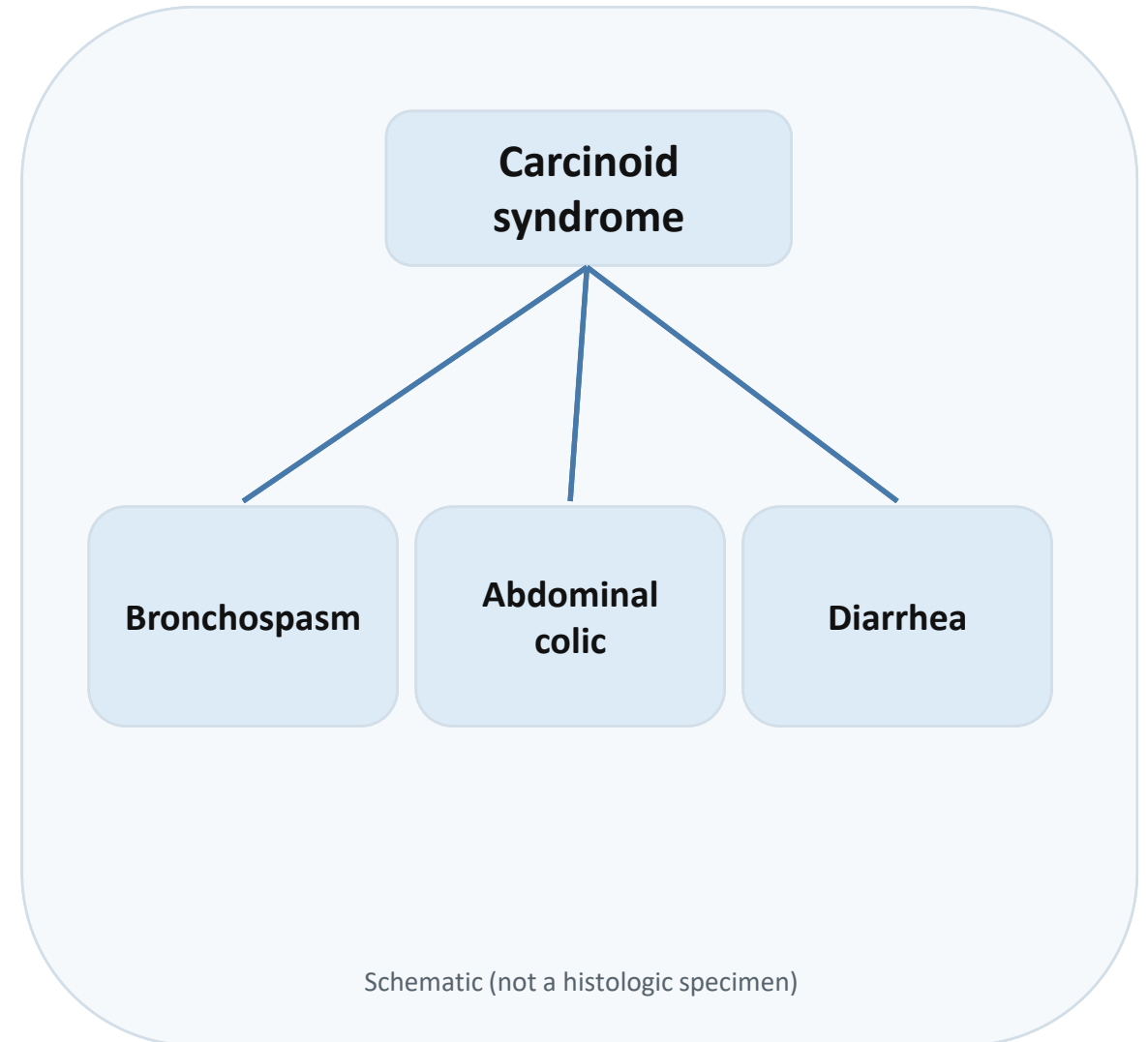


Respiratory and abdominal manifestations

Bronchospasm is a recognized component of the syndrome.

Colicky abdominal pain and diarrhea may occur.

Symptoms must be interpreted in the setting of tumor hormone secretion.

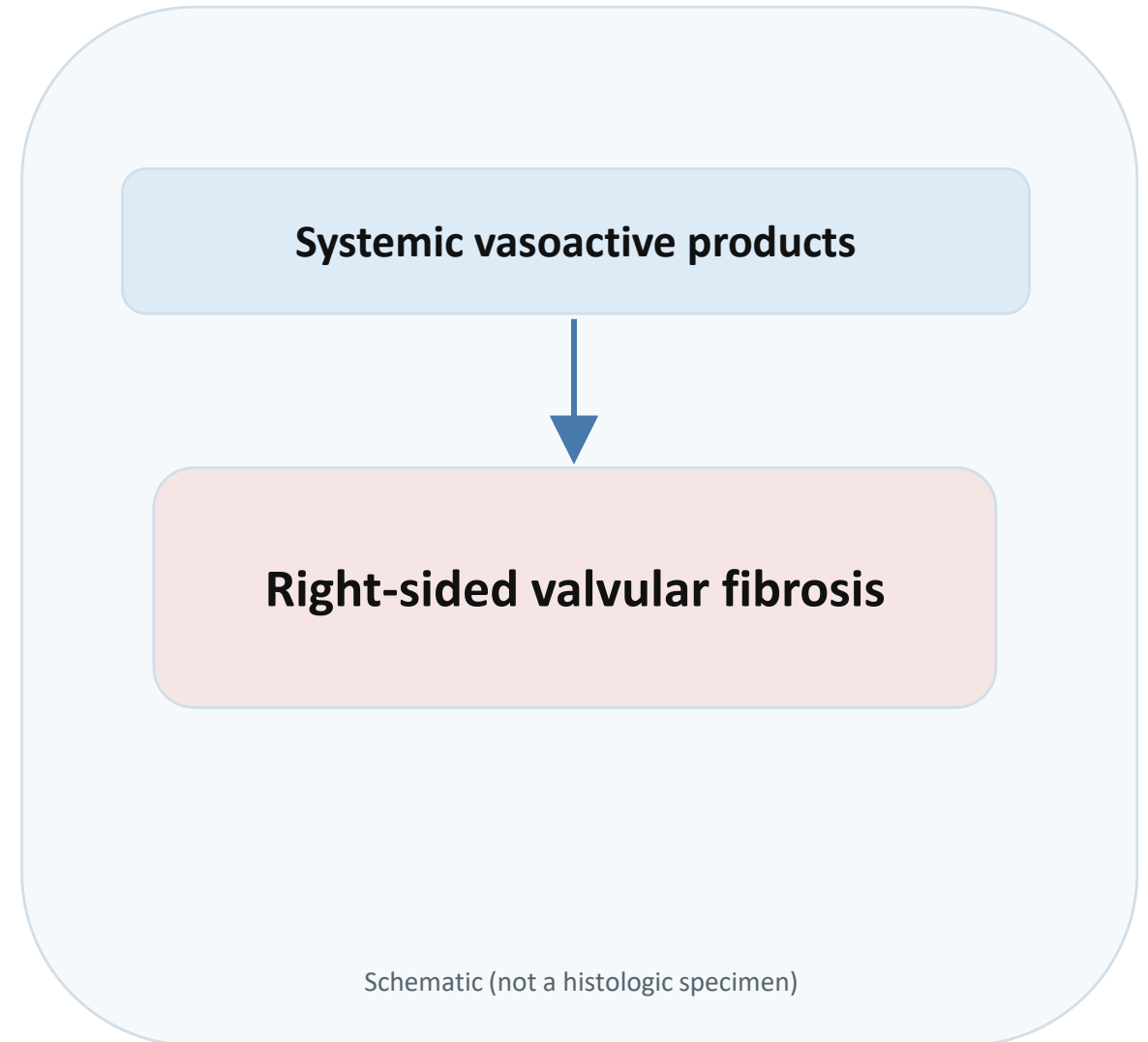


Right-sided cardiac valvular fibrosis

Right-sided cardiac valvular fibrosis is a major classic manifestation.

The cardiac lesion is part of the systemic endocrine effect.

The syndrome should not be reduced to flushing and diarrhea alone.

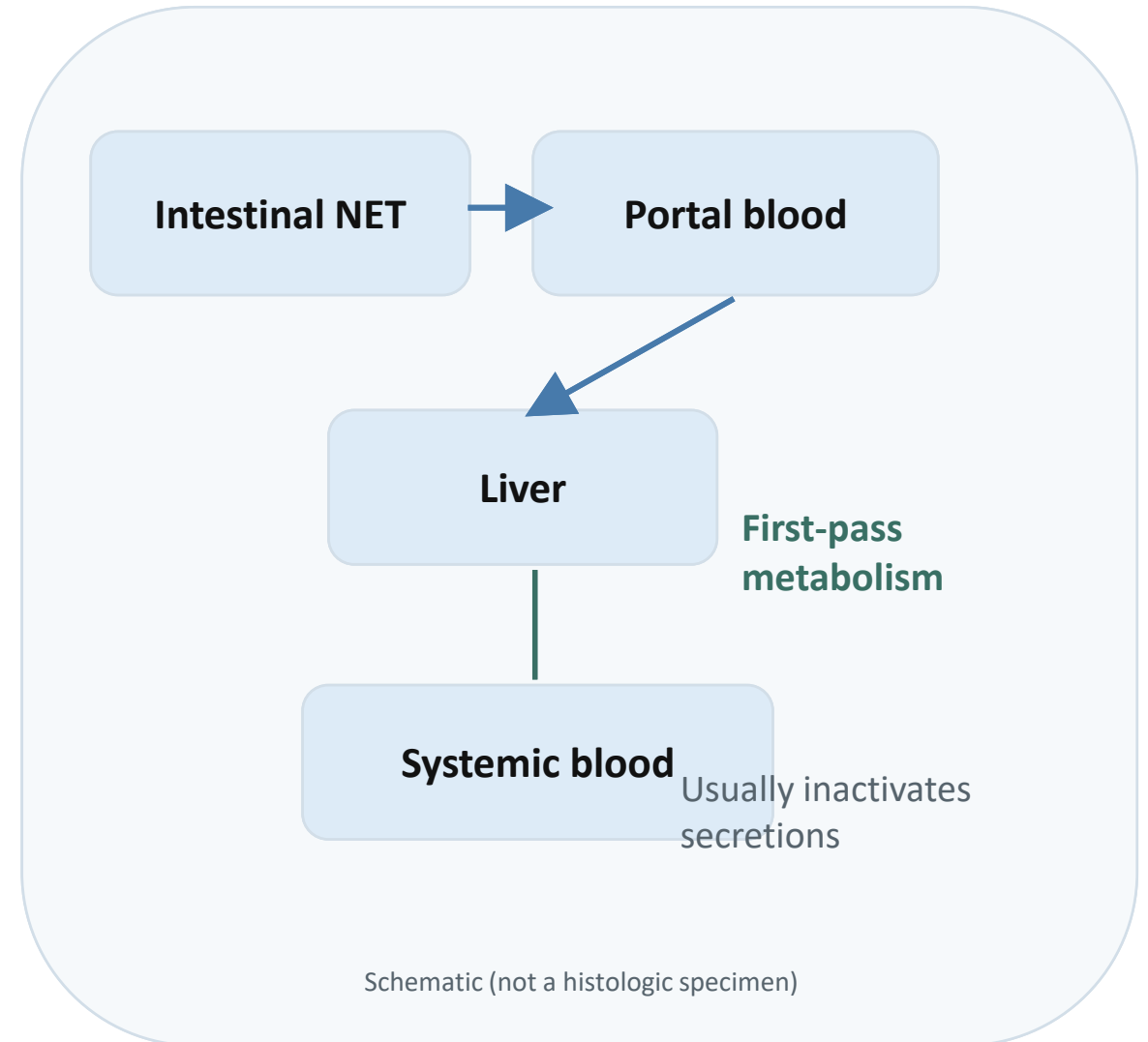


Hepatic first-pass metabolism is protective

Products draining from intestinal lesions enter the portal circulation.

The liver usually metabolizes vasoactive substances to inactive forms.

Consequently, a confined intestinal tumor may not produce carcinoid syndrome.

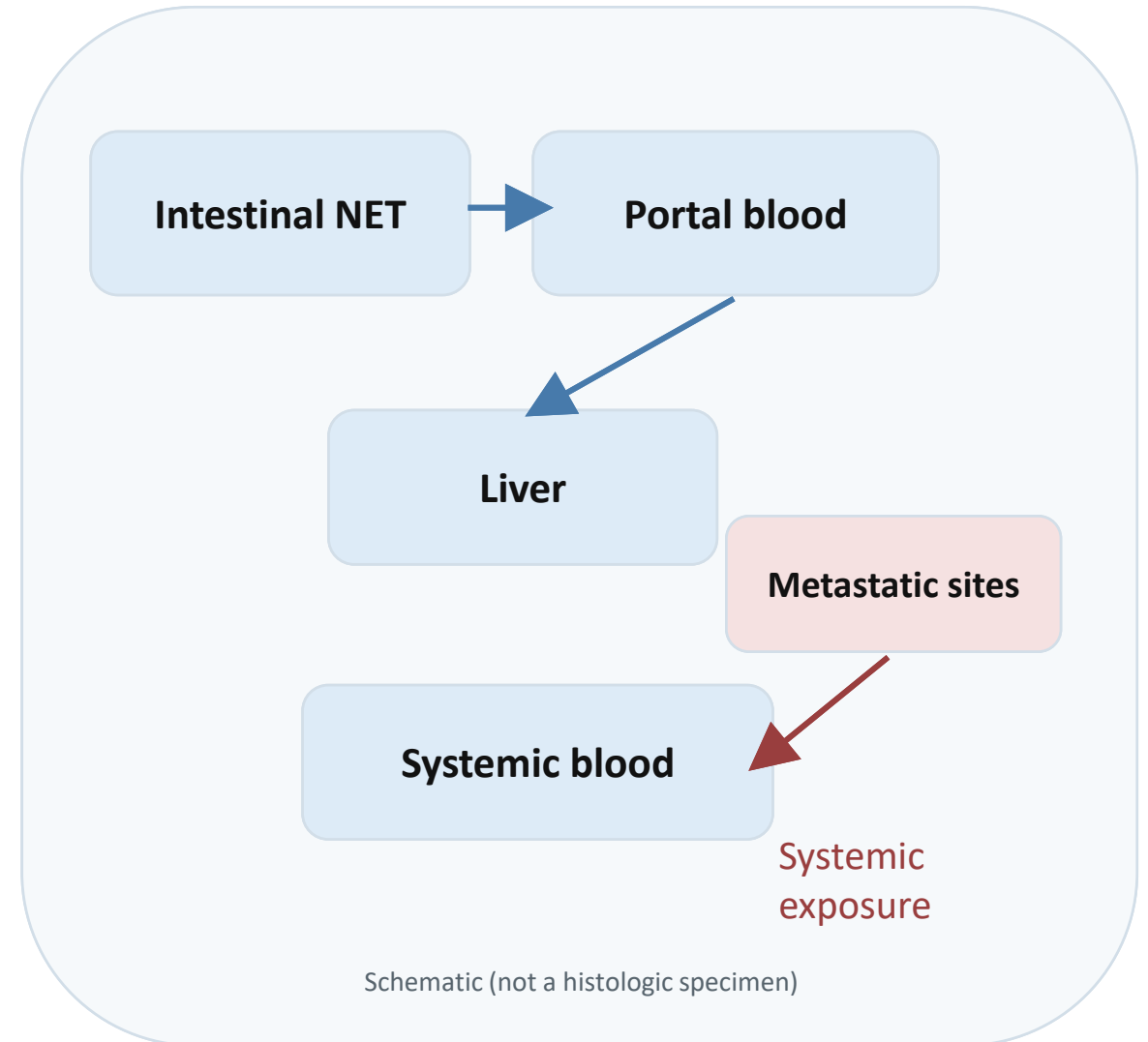


Why metastases enable carcinoid syndrome

Metastatic disease can permit vasoactive products to reach systemic blood.

This bypasses or exceeds normal hepatic first-pass inactivation.

Syndrome occurrence therefore signals the need to consider disease distribution.

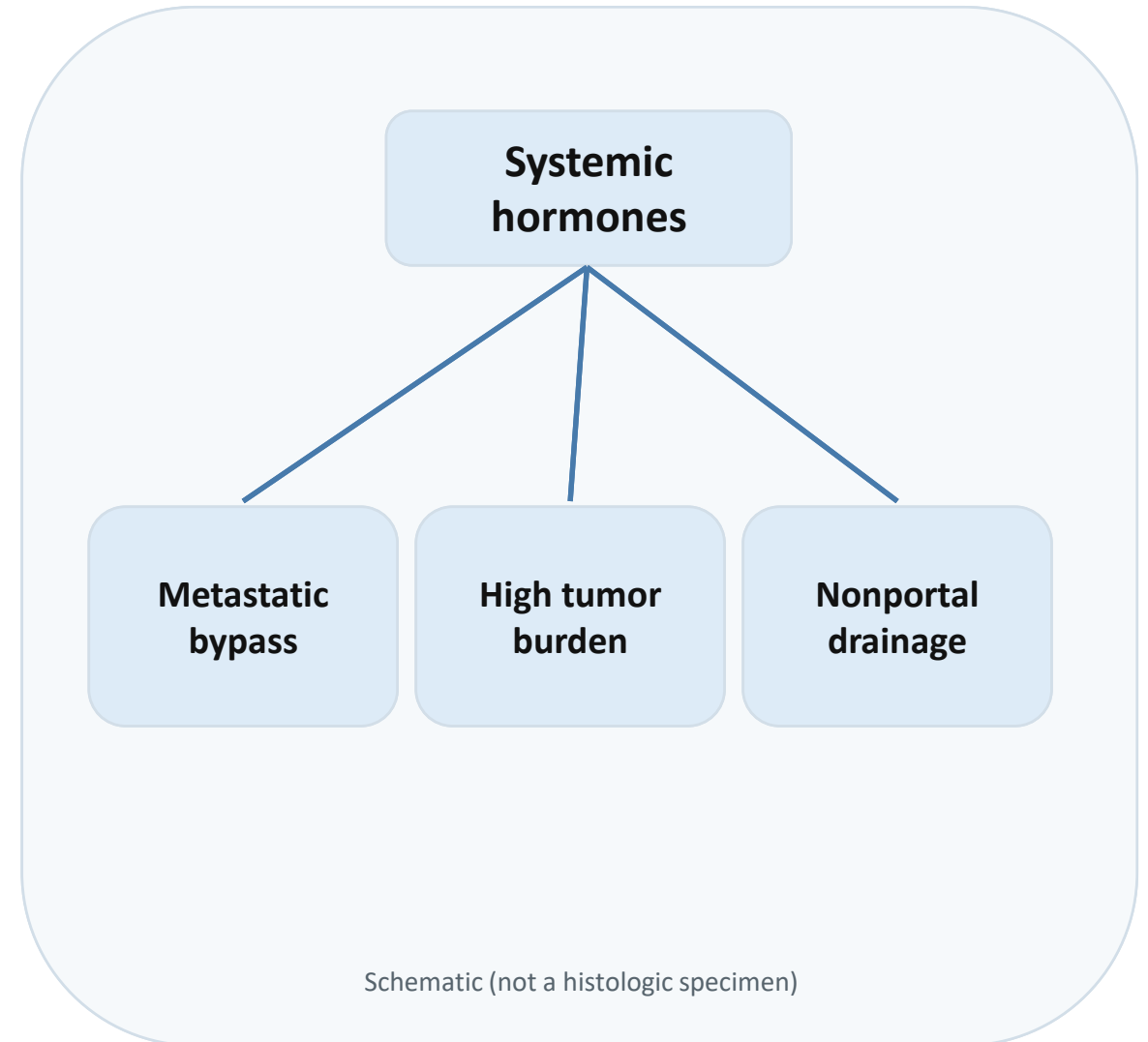


Not every systemic syndrome requires liver metastasis

Large tumor burden may overcome hepatic metabolic capacity.

Hormone release into nonportal venous drainage can also bypass the liver.

These exceptions are explicit in the source and prevent an absolute rule.



A functional syndrome is not a tumor grade

Endocrine activity describes biochemical function.

Differentiation and proliferation describe tumor biology.

Functional status alone cannot predict histologic grade.

Function	Histologic behavior
Secreted hormones	Degree of differentiation
Symptoms / syndrome	Mitotic rate + Ki-67
May be present or absent	Anatomic stage also matters

Core prognostic factors

Degree of histologic differentiation is central.

Mitotic rate and Ki-67 index provide proliferation information.

Location and tumor size further modify risk.

Differentiation
n

Mitotic rate

Ki-67 index

Modifiers: Size and anatomic site

Stomach and duodenum: Usually favorable

Tumors in these sites rarely metastasize
summary.

Most are generally curable by resection.

The outlook is particularly favorable for
gastritis-associated gastric NETs.

Stomach

Small intestine

Appendix

Rectum

Site affects presentation and prognosis

Schematic (not a histologic specimen)

Gastric background changes expected behavior

Gastric lesions linked to atrophic gastritis are commonly indolent.

Gastric lesions without recognized predisposing factors may be more aggressive.

Do not treat all gastric NETs as prognostically equivalent.

Associated with atrophy	Unassociated gastric lesion
Often favorable course	Often more aggressive
Background is informative	More cautious assessment
Site plus context	Site alone insufficient

Jejunal and ileal tumors deserve attention

Jejunal and ileal NETs are often multiple.

They tend to behave more aggressively than many gastric/duodenal tumors.

Depth of invasion and mesenteric desmoplasia are important correlates.

Stomach

Small intestine

Appendix

Rectum

Site affects presentation and prognosis

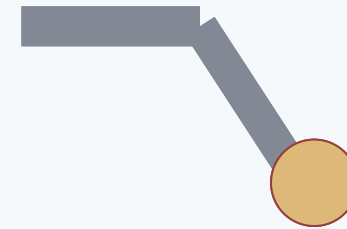
Schematic (not a histologic specimen)

Appendiceal NET: Frequently incidental

Appendiceal lesions may be discovered incidentally.

They are generally located at the appendix tip.

The source describes most as small and usually exhibiting favorable behavior.



Tip-predominant lesion

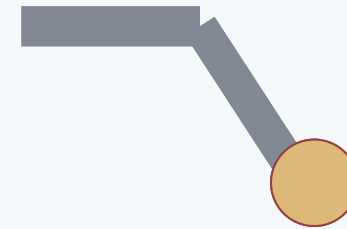
Schematic (not a histologic specimen)

Appendiceal size is a context clue

These lesions are rarely larger than 2 cm.

It describes appendiceal tumors as almost always benign in typical presentations.

This wording is source-specific; No modern risk algorithm is asserted.



Tip-predominant lesion

Schematic (not a histologic specimen)

Rectal NET: Often recognized while small

Rectal tumors are commonly found incidentally.

The source notes that metastasis is uncommon because many are detected at small size.

Location and observed size remain critical for interpretation.

Stomach

Small intestine

Appendix

Rectum

Site affects presentation and prognosis

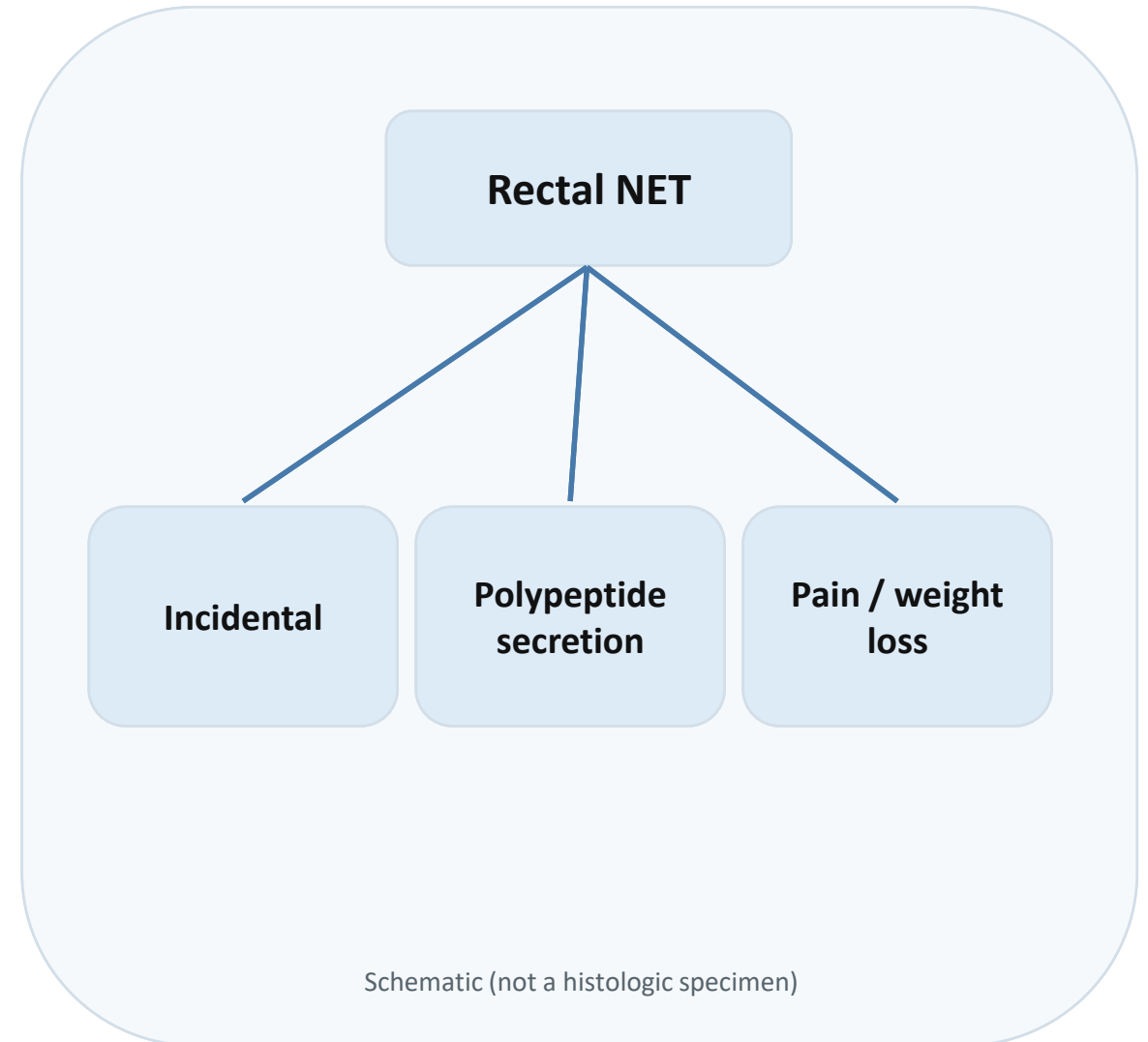
Schematic (not a histologic specimen)

Rectal hormone-related presentations

Rectal NETs may produce polypeptide hormones.

When symptomatic, abdominal pain and weight loss may occur.

Symptoms are not required to recognize a rectal NET.



Site-specific profiles side by side

Location modifies the expected natural history.

Compare common presenting patterns rather than imposing one rule.

Site	Typical source description
Stomach/duodenum	Usually favorable; resection often curative
Jejunum/ileum	Often multiple; relatively aggressive
Appendix	Incidental; often tip / small
Rectum	Incidental; metastasis uncommon if small

Case: Incidental gastric mucosal lesion

A small gastric polypoid lesion is found in a patient with chronic atrophic gastritis.

A biopsy shows uniform nests with salt-and-pepper nuclei.

Question: Which background feature supports a comparatively favorable course?

Clinical reasoning

Discuss the pathologic mechanism before revealing the answer.

Answer is documented in presenter notes

Case: An ileal lesion with bowel kinking

A firm ileal wall lesion is associated with pronounced mesenteric retraction.

Histology shows an organoid tumor with a dense fibrous response.

Question: What explains the mechanical symptom?

Clinical reasoning

Discuss the pathologic mechanism before revealing the answer.

Answer is documented in presenter notes

Case: Flushing and systemic tumor products

A patient with an intestinal NET develops episodic flushing, diarrhea, and wheezing.

The known tumor history includes metastatic spread.

Question: Why may a systemic syndrome appear after dissemination?

Clinical reasoning

Discuss the pathologic mechanism before revealing the answer.

Answer is documented in presenter notes

Case: A markedly proliferative neoplasm

A gastrointestinal tumor expresses neuroendocrine markers but shows poor differentiation.

Mitotic activity and Ki-67 are high.

Question: What major category should be considered?

Clinical reasoning

Discuss the pathologic mechanism before revealing the answer.

Answer is documented in presenter notes

Four interpretation pitfalls

Bland cytology does not exclude lymphatic invasion or deep spread.

Neuroendocrine marker positivity does not by itself determine differentiation.

Functional symptoms do not replace mitotic/Ki-67 assessment.

Gastric, ileal, appendiceal, and rectal sites do not share a uniform risk profile.

**Interpret each dimension
independently**

Morphology

Function

Proliferation

Site

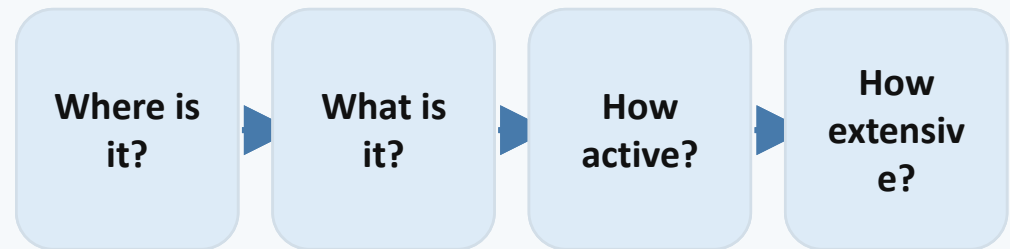
Integrating diagnosis and prognosis

Start with lesion site and gross depth.

Identify organoid morphology and neuroendocrine immunophenotype.

Evaluate differentiation, mitoses, and Ki-67.

Interpret clinical secretion and site-specific behavior alongside stage.



Interpretation: Consider each step separately

Schematic (not a histologic specimen)

Essential clinicopathologic conclusions

GI NETs combine distinct microscopic morphology with possible endocrine function.

Small-bowel desmoplasia and carcinoid syndrome have different mechanistic origins.

Differentiation, proliferation, size, and location are central prognostic dimensions.

Morphology

Functional status

Proliferation

Site + extent

Schematic (not a histologic specimen)

Primary source

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition.

Neuroendocrine Tumors, within The Gastrointestinal Tract.

Conceptual diagrams are editable schematics; no diagnostic histology is represented as a real specimen.