

GASTRIC ADENOCARCINOMA

Morphologic patterns • etiopathogenesis • molecular subtypes • clinical behavior

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Learning objectives

- Distinguish intestinal-type from diffuse-type gastric adenocarcinoma.
- Trace environmental, hereditary, and molecular mechanisms of tumor development.
- Recognize gross and microscopic patterns and their mechanistic basis.
- Integrate clinical presentation, metastatic patterns, stage, and prognosis.

Adenocarcinoma dominates gastric malignancy

>90%

Of gastric cancers are adenocarcinomas account.

The core morphologic distinction is gland-forming intestinal type versus discohesive diffuse type.

Two principal patterns of gastric adenocarcinoma

Intestinal-type

- Usually forms a bulky or ulcerated tumor.
- Shows cohesive, gland-forming malignant epithelium.
- Often follows metaplasia and dysplasia.

Diffuse-type

- Infiltrates gastric wall without a dominant mass.
- Cells are poorly cohesive; Signet-ring forms are typical.
- Closely linked to defects of cell adhesion.

Why diagnosis may be delayed

- Early dyspepsia, dysphagia, and nausea overlap with benign gastric disease.
- Symptoms become more specific as tumor burden and wall involvement increase.
- Weight loss, anorexia, anemia, or gastrointestinal bleeding often signal advanced disease.
- Diffuse infiltration may produce early satiety without a conspicuous luminal mass.

Geographic variation is pronounced

Up to 20-fold

Higher gastric cancer incidence in selected high-risk regions.

Textbook examples: Japan, Chile, Costa Rica, and Eastern Europe versus several lower-incidence regions.

Population risk differs by geography

High-incidence settings

- Marked regional burden, including parts of East Asia.
- Endoscopic screening can identify early lesions.
- Intestinal-type cancers historically predominated.

Low-incidence settings

- Population screening is generally less cost-effective.
- Advanced stage at presentation is more frequent.
- Diffuse-type disease shows less geographic variation.

Screening changes stage at diagnosis

35%

Early cancers among newly detected cases in Japan, as reported.

Early gastric cancer is confined to mucosa or submucosa, regardless of nodal involvement.

Early detection remains uncommon in low-risk regions

<20%

Early gastric cancers detected in North America and northern Europe account.

This historical textbook comparison should not be treated as a current national surveillance estimate.

The long-term incidence decline has etiologic clues

- An 85% decline in U.S. Incidence since 1930.
- Decline is linked mainly to reduced H. Pylori infection and intestinal-type cancers.
- Changes in preserved foods and refrigeration are additional plausible contributors.
- The decline does not apply equally to every site and histologic subtype.

Environmental influences on intestinal-type disease

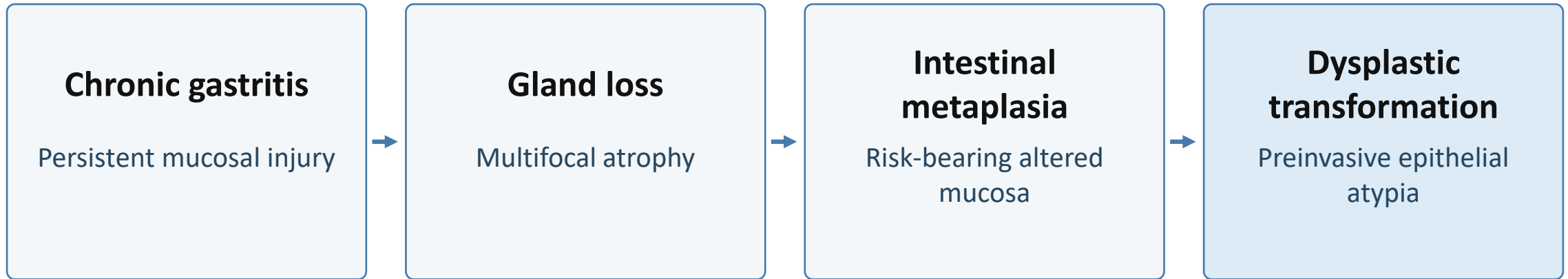


Conceptual progression: Not every infected or metaplastic stomach progresses to carcinoma.

Helicobacter pylori: The major infection association

- H. Pylori–associated gastritis is frequent in gastric cancer development.
- Host–bacterial interactions help determine whether atrophy develops.
- The falling prevalence of infection is linked to a decline in intestinal-type cancer.
- Carcinogenesis is multifactorial; Infection does not imply inevitable neoplasia.

Atrophy and intestinal metaplasia alter cancer risk

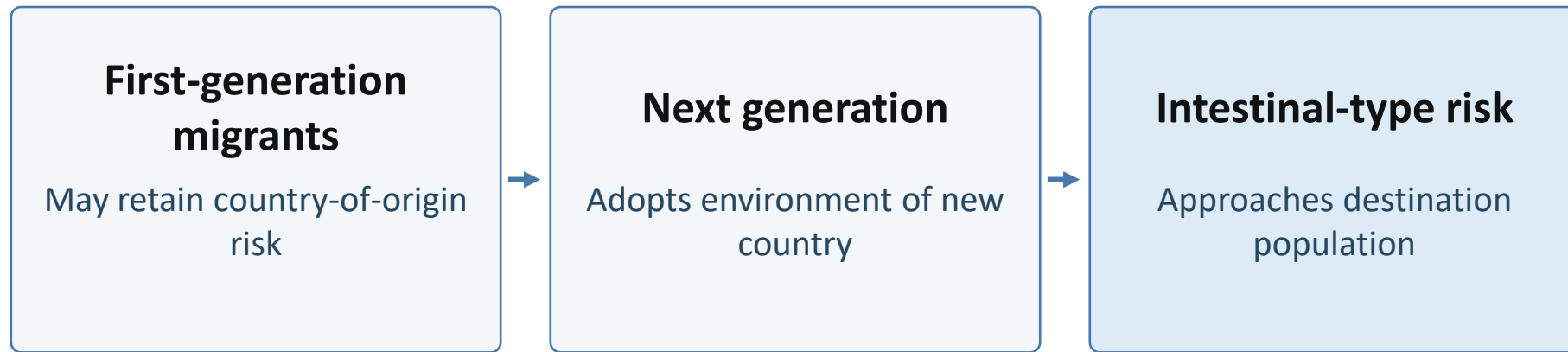


Precursor-associated pathway is characteristic of intestinal-type adenocarcinoma.

Environmental contributors extend beyond infection

- Dietary carcinogens cited include N-nitroso compounds and benzo[a]pyrene.
- Historic salt preservation and smoking of food increased relevant exposures.
- Greater refrigeration access contributed to changed food preservation practices.
- These associations support a substantial environmental contribution to risk.

Migrant populations support environmental causation



The generational change is difficult to explain by inherited variants alone.

Atrophic and metaplastic mucosa marks susceptibility

- Multifocal gastric mucosal atrophy is associated with increased cancer risk.
- Intestinal metaplasia is a background lesion linked to adenoma and carcinoma.
- Risk is not equivalent to a diagnosis of dysplasia or invasive carcinoma.
- Assessment must distinguish the background field from a focal neoplastic lesion.

Gastric adenomas as epithelial precursors

Background

- Most arise with atrophic gastritis and intestinal metaplasia.
- Hereditary APC- or MUTYH-associated lesions are exceptions.
- Usually located in the antrum.

Clinical importance

- Adenomas are dysplastic epithelial neoplasms.
- Carcinoma risk rises with increasing adenoma size.
- Large lesions require careful assessment for coexisting carcinoma.

Dysplasia is graded by cytology and architecture

Low-grade dysplasia

- Nuclear enlargement, elongation and hyperchromasia.
- Pseudostratified dysplastic epithelium.
- Architectural changes less severe than high-grade.

High-grade dysplasia

- Greater nuclear and architectural atypia.
- Gland budding and complex gland-in-gland structures.
- Cribriform arrangements may develop.

Size increases carcinoma risk in gastric adenoma

>2 cm

Adenomas of this size have particularly elevated carcinoma risk.

Up to 30% cancer risk among large gastric adenomas; Not a universal risk for all adenomas.

Peptic ulcer and post-gastrectomy risk are different

Peptic ulcer disease

- Reported association with reduced gastric carcinoma risk.
- Do not treat every benign gastric ulcer as premalignant.

Residual gastric stump

- Prior partial gastrectomy for ulcer disease increases later cancer risk.
- Potential mechanisms: Hypochlorhydria and bile reflux.

Cardia cancers do not follow every distal trend

- Rising gastric cardia adenocarcinoma despite declining overall incidence.
- Increasing reflux, Barrett esophagus, and obesity may contribute.
- Cardia and distal esophageal adenocarcinoma share clinicobiologic features.
- Avoid combining proximal and distal tumors uncritically in etiologic discussions.

Distal and cardia adenocarcinoma: Different contexts

Feature	Distal gastric site	Cardia / proximal site
Major association	H. Pylori / mucosal atrophy	GERD–Barrett-related context
Trend in textbook	Intestinal-type incidence declines	Incidence rising
Molecular overlap	Heterogeneous intestinal subtypes	Similarity to distal esophageal tumors
Interpretive caution	Background mucosal field matters	Precise anatomic classification matters

Contextual comparison; Not a formal clinicopathologic subclassification.

Intestinal-type and diffuse-type epidemiology

Intestinal type

- More frequent in high-incidence populations.
- Mean presentation age approximately 55 years.
- Male:female ratio approximately 2:1.

Diffuse type

- Incidence varies less between countries.
- Sporadic frequency similar between sexes.
- Germline CDH1-associated tumors may present around age 40.

Adenocarcinoma evolves through distinct mechanisms

Intestinal type

Inflammatory precursor field; Molecular heterogeneity.

Diffuse type

Disrupted epithelial adhesion and discohesive infiltration.

Chromosomal instability

Aneuploidy and signaling-pathway alterations.

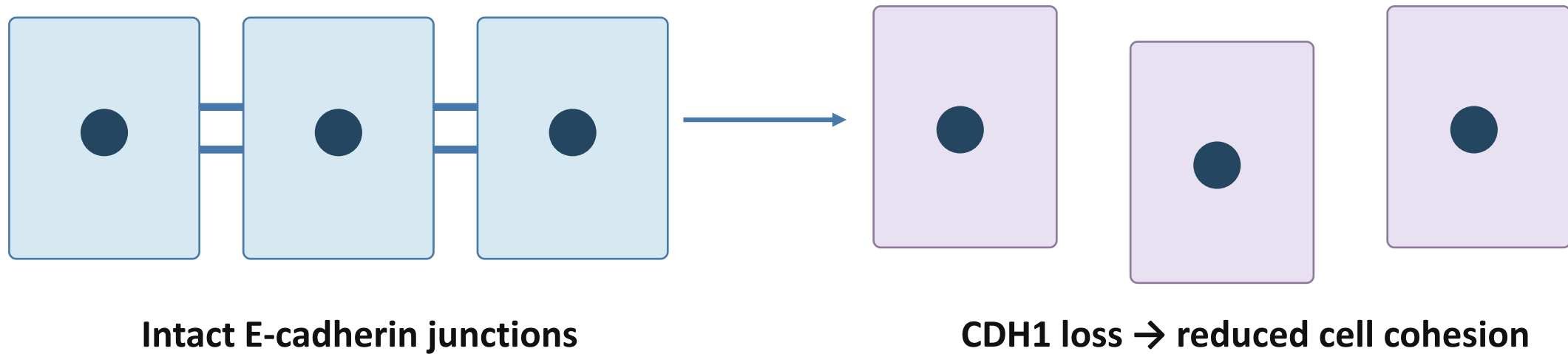
Microsatellite instability

Mismatch-repair dysfunction, often via MLH1 silencing.

EBV-associated cancer

Epigenetic alterations and immune-associated phenotype.

E-cadherin loss creates the diffuse growth phenotype



Adhesion failure explains single-cell infiltration and the absence of cohesive glands.

CDH1 encodes the adhesion protein E-cadherin

- E-cadherin is an adherens-junction component maintaining epithelial cohesion.
- Loss of function permits individual cells and small clusters to infiltrate.
- A noncohesive growth pattern explains the diffuse histologic phenotype.
- CDH1 alteration is central in hereditary and many sporadic diffuse cancers.

Hereditary diffuse gastric cancer: CDH1

CDH1

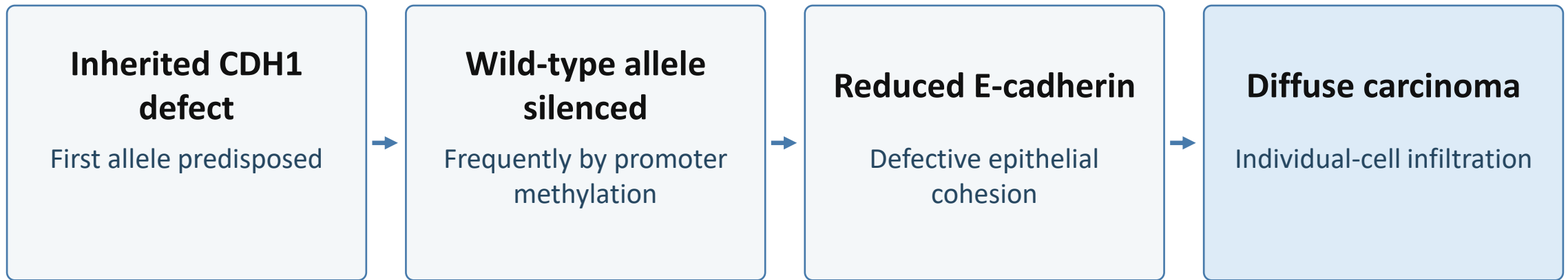
A major inherited susceptibility gene for hereditary diffuse gastric cancer.

Other heritable mechanisms exist, including CTNNA1; Genetic heterogeneity matters.

Two routes to E-cadherin loss in diffuse carcinoma

- Germline CDH1 loss-of-function variants predispose to hereditary disease.
- Somatic CDH1 mutations occur in approximately half of sporadic diffuse tumors.
- Promoter hypermethylation may silence CDH1 when sequence variants are absent.
- Epigenetic silencing may also affect the remaining normal allele in hereditary cases.

Hereditary CDH1 tumor development



This is a mechanism schematic; Individual patients may have differing second-hit mechanisms.

CTNNA1 adds another hereditary adhesion pathway

- CTNNA1 encodes α -catenin, an adherens-junction component.
- α -Catenin links the E-cadherin/ β -catenin complex with actin organization.
- Germline CTNNA1 alterations also occur in hereditary diffuse gastric cancer.
- Different inherited defects converge on loss of organized epithelial adhesion.

Additional sporadic diffuse cancer alterations

RHOA

- RHOA mutation is associated with sporadic diffuse gastric cancer.
- Contributes to altered cell behavior in this adhesion-related subtype.

CLDN18::ARHGAP26

- Fusion is associated with sporadic diffuse gastric cancer.
- RHOA mutations and this fusion are reported as mutually exclusive.

Diffuse cancers may be relatively genomically stable

- Many diffuse gastric cancers carry fewer mutations than intestinal cancers.
- Genomic stability does not mean biologically indolent behavior.
- Discohesive infiltration and wall stiffening can be extensive.
- Morphologic aggressiveness and total mutation burden are different concepts.

Three intestinal-type molecular patterns

CIN

Chromosomal instability, aneuploidy, signaling activation.

MSI

MLH1 promoter silencing and mismatch-repair dysfunction.

EBV-associated

Extensive promoter methylation, PIK3CA changes, PD-L1/2 upregulation.

Chromosomal instability defines a major molecular subset

- CIN tumors exhibit aneuploidy and chromosomal copy-number abnormalities.
- Receptor tyrosine kinase–RAS signaling is frequently altered.
- ERBB2 (HER2), EGFR, MET, KRAS, and VEGFA are implicated in the source account.
- CIN tumors are particularly associated with the antrum and pyloric channel.

CIN: Interacting signaling pathways

Receptor/RAS network

ERBB2 (HER2), EGFR, MET, KRAS and VEGFA-related signaling.

Wnt pathway

APC and CTNNB1 alterations are prevalent.

TGF- β pathway

SMAD2 and SMAD4 may be altered.

Genome integrity

TP53 alterations also occur frequently.

HER2 in the molecular context of gastric cancer

- ERBB2 encodes the HER2 receptor, part of oncogenic growth signaling.
- ERBB2 among frequently altered CIN-associated genes.
- Molecular subtype, morphologic subtype, and actionable biomarkers are distinct axes.
- Do not infer HER2 positivity from intestinal-type morphology alone.

MSI tumors often silence MLH1

- Microsatellite instability reflects defective DNA mismatch repair.
- The source describes MLH1 silencing within CpG-island hypermethylation (CIMP).
- MSI cancers more commonly involve the gastric body.
- This mechanism differs from the copy-number–driven CIN pathway.

MSI and CIN differ in their typical mutation pattern

MSI-associated findings

- MLH1 promoter silencing / mismatch-repair deficiency.
- BRAF and mitosis-regulating gene changes are described.
- TP53 and KRAS changes are comparatively uncommon.

CIN-associated findings

- Aneuploidy and receptor/RAS pathway changes.
- Alterations involving Wnt, TGF- β and TP53.
- Often located toward the antrum and pylorus.

EBV-associated cancers form a smaller subset

<10%

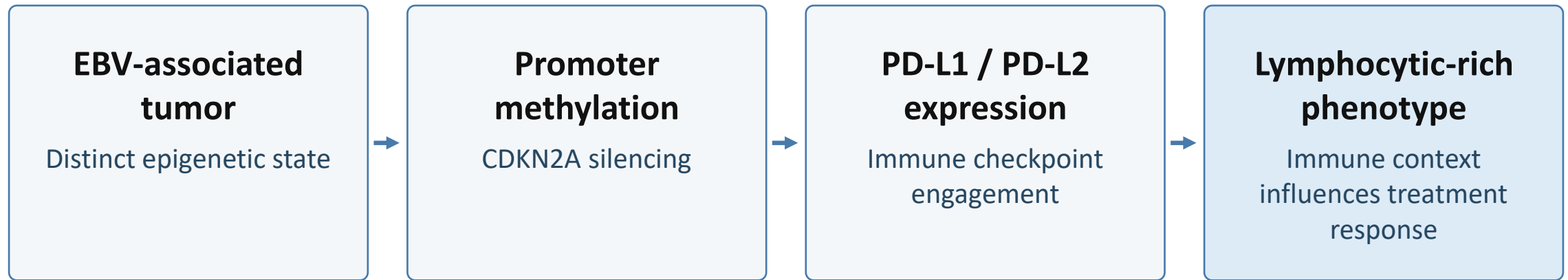
Gastric carcinomas associated with Epstein–Barr virus.

They often arise in the fundus or proximal gastric body.

EBV-associated gastric cancer has a distinct epigenome

- More extensive promoter hypermethylation is described than in MSI tumors.
- CDKN2A may be epigenetically silenced, without corresponding MLH1 silencing.
- PIK3CA mutations are frequent account.
- Increased PD-L1/2 expression helps explain the immune-associated phenotype.

EBV tumor biology links genetics to host response



PD-L1/2 expression to lymphocytic infiltrates and checkpoint-inhibitor sensitivity.

Molecular subtype comparison

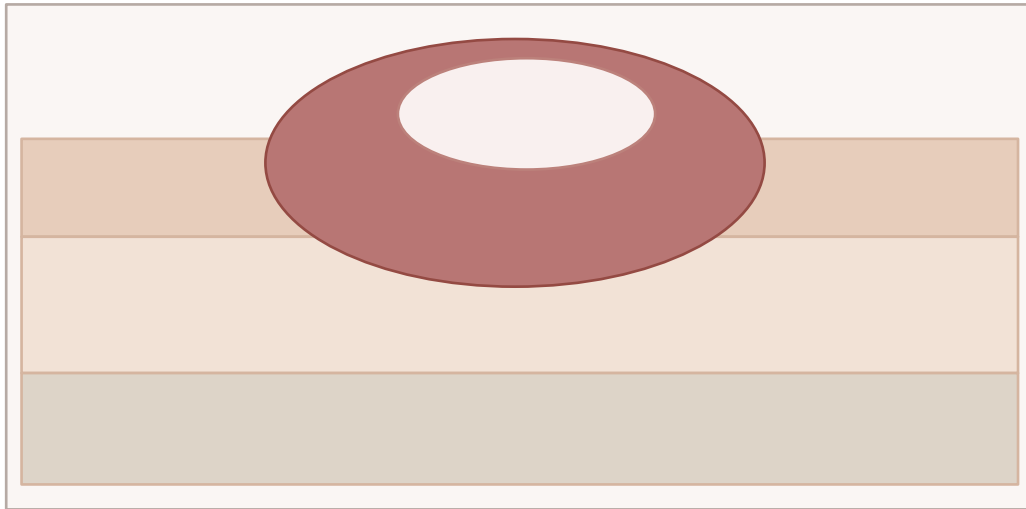
Axis	Typical abnormalities	Pattern emphasized
CIN	Aneuploidy; RTK/RAS; TP53	Antrum / pyloric channel
MSI	MLH1 silencing, CIMP	Gastric body
EBV-associated	CDKN2A methylation, PIK3CA, PD-L1/2	Fundus / proximal body
Diffuse-associated stable	CDH1; RHOA or CLDN18::ARHGAP26	Discohesive growth

Molecular and histologic classification systems overlap; They are not exact synonyms.

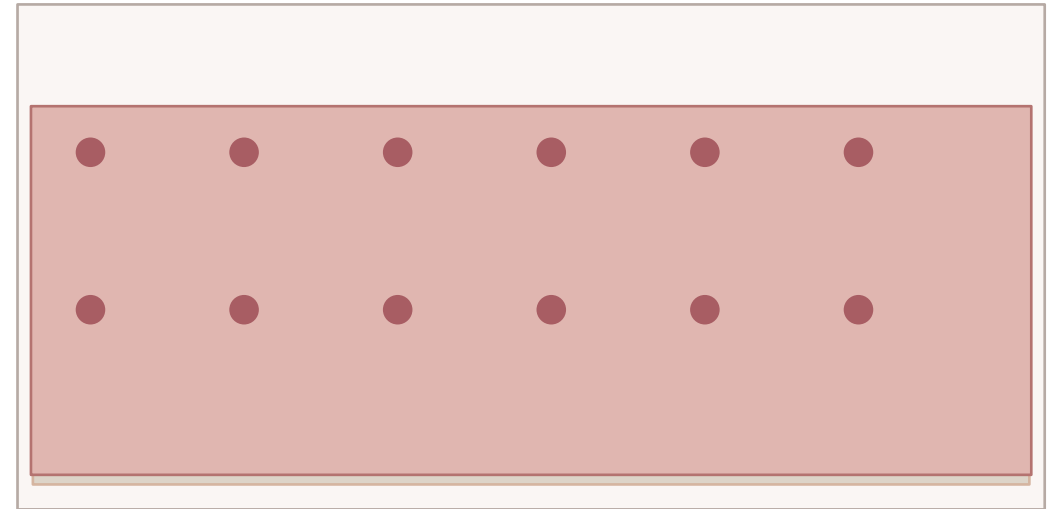
Anatomic setting of distal gastric adenocarcinoma

- Most distal adenocarcinomas arise in the antrum.
- The lesser curvature is affected more often than the greater curvature.
- Location and architecture both contribute to morphologic classification.
- Location alone cannot establish intestinal or diffuse histologic type.

Gross growth pattern: Mass versus infiltrative wall



Intestinal: Localized mass or ulcer



Diffuse: Circumferential wall infiltration

Conceptual wall cross-section — not gross pathology photographs

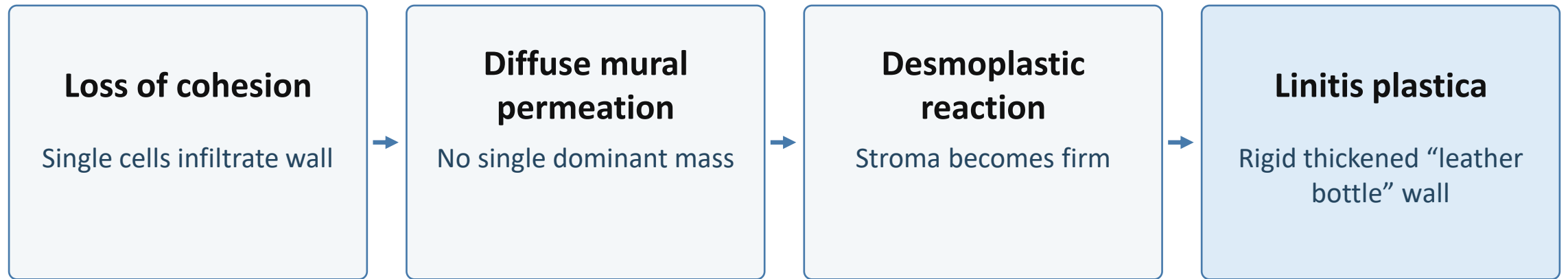
Intestinal-type tumors form cohesive masses

- An elevated mass with heaped-up borders may have central ulceration.
- Some tumors form ulcerated infiltrative lesions rather than exophytic masses.
- The invasive front is often broad and relatively cohesive.
- Gross ulceration is not by itself proof of invasive adenocarcinoma.

Diffuse-type tumors may conceal their extent

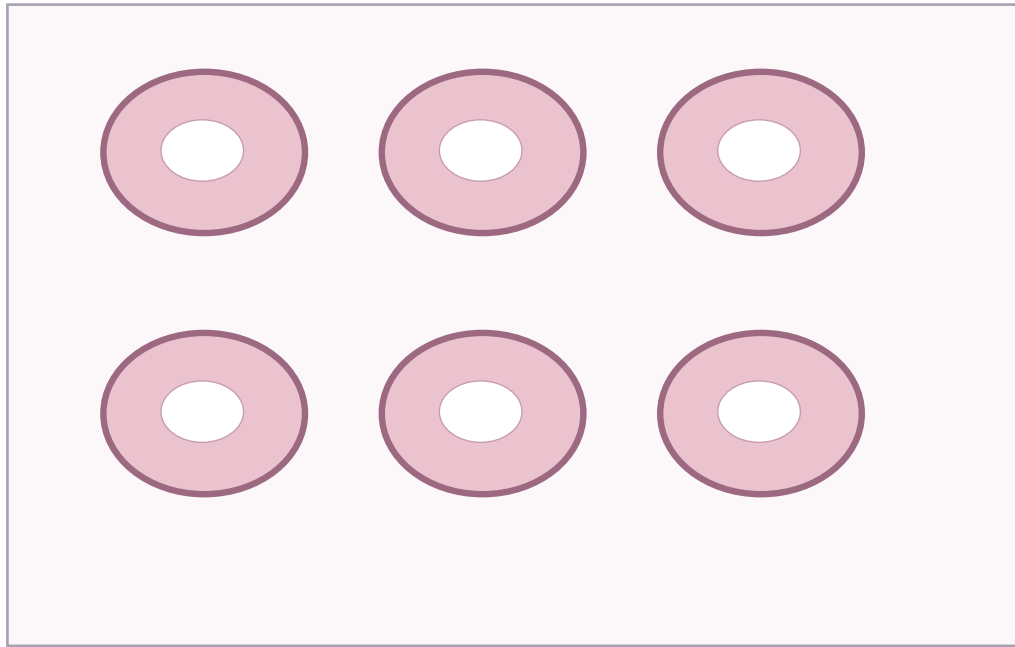
- Discohesive neoplastic cells permeate the gastric wall.
- The stomach may become thickened without a circumscribed tumor mass.
- Desmoplastic stromal reaction contributes to rigidity.
- Flattening of rugal folds reflects broad mural involvement.

How diffuse infiltration produces linitis plastica

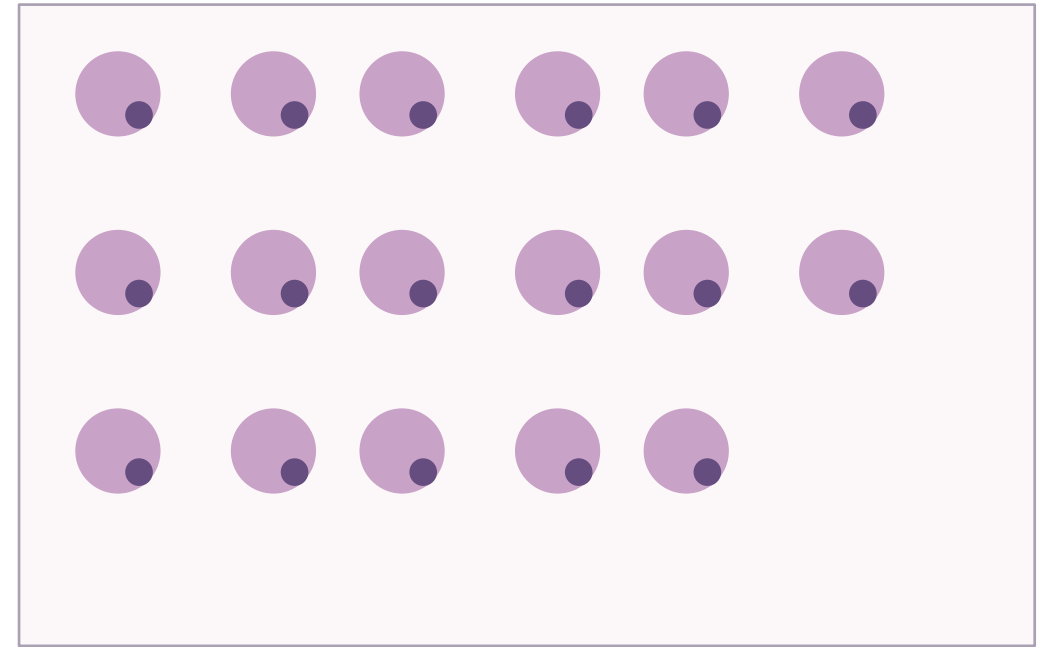


Linitis plastica is a gross morphologic pattern, not a separate genetic subtype.

Histologic architecture: Glands versus separate cells



Gland-forming intestinal pattern



Discohesive diffuse pattern

Schematic representation — not histology images

Intestinal-type histology is gland-forming

- Neoplastic epithelial cells form irregular infiltrative glands.
- Glands traverse a reactive, often desmoplastic stroma.
- Apical mucin vacuoles may be visible in the malignant cells.
- Mucin may accumulate within neoplastic gland lumina.

Why mucin can be abundant in gland-forming tumors

- Malignant glandular cells retain variable secretory differentiation.
- Intracellular apical mucin produces epithelial vacuolation.
- Luminal mucin supports the gland-forming morphologic phenotype.
- Mucin location must be distinguished from stromal extracellular pools.

Diffuse carcinoma infiltrates as single cells

- Cells appear singly or in small poorly cohesive clusters.
- Well-formed glands are absent in the classic diffuse pattern.
- Infiltrative cells may spread widely beyond grossly obvious lesions.
- Discohesion follows loss of the adhesion apparatus, especially E-cadherin.

Signet-ring morphology is produced by mucin

- Large intracellular mucin vacuoles expand the cytoplasm.
- The nucleus is displaced to one side of the cell.
- The compressed peripheral nucleus gives a signet-ring appearance.
- The signet-ring cell is a morphologic finding, not a standalone site-of-origin diagnosis.

Low-power diffuse carcinoma can be missed

- Scattered poorly cohesive tumor cells may resemble inflammatory cells.
- Attention to atypical nuclei and intracellular mucin is important.
- A gland-free infiltrate does not exclude epithelial malignancy.
- The distinction between inflammation and carcinoma requires full morphologic assessment.

Extracellular mucin pools occur in either type

- Extracellular mucin may escape into the surrounding tissue.
- Large mucin lakes can dissect stromal planes.
- The finding is not exclusive to intestinal-type or diffuse-type tumors.
- Record extracellular pools separately from intracellular signet-ring mucin.

Desmoplasia explains a crucial gross feature

- Invasive tumor stimulates a fibrous stromal response.
- Desmoplasia contributes to wall firmness and diffuse thickening.
- Extensive involvement may flatten the gastric mucosal rugae.
- A stiff wall can have advanced infiltration despite no bulky exophytic lesion.

Intestinal and diffuse type: Morphologic contrasts

Feature	Intestinal type	Diffuse type
Growth pattern	Mass-forming or ulceroinfiltrative	Widespread mural permeation
Cell cohesion	Relatively cohesive	Poorly cohesive
Histology	Neoplastic glands	Single cells / small clusters
Mucin	Apical / luminal; Sometimes extracellular	Intracellular signet-ring; Sometimes extracellular
Stromal change	Desmoplasia can surround glands	Desmoplasia stiffens the wall

Precursors distinguish the principal morphologic types

Intestinal-type pathway

- Background atrophy and intestinal metaplasia.
- Flat dysplasia and gastric adenomas as recognized precursors.
- More strongly influenced by population-level exposures.

Diffuse-type pathway

- No identified precursor lesions.
- Cell-adhesion abnormalities often precede the phenotype.
- Familial risk can exist without an endoscopically obvious precursor.

Do not conflate dysplasia and invasive cancer

Gastric dysplasia

- Neoplastic epithelial atypia and altered architecture.
- Adenoma shows dysplasia but is not automatically invasive carcinoma.
- Grade describes the degree of intraepithelial atypia.

Invasive adenocarcinoma

- Malignant gland-forming or discohesive cells invade tissue.
- Tumor depth and spread directly affect prognosis.
- The question is invasion, not simply cytologic severity.

Histologic interpretation integrates site and invasion

- Document whether tumor forms glands or diffusely infiltrates as separate cells.
- Describe intracellular and extracellular mucin appropriately.
- Assess depth of tissue invasion in available material.
- Do not infer the entire wall extent from a limited mucosal biopsy.

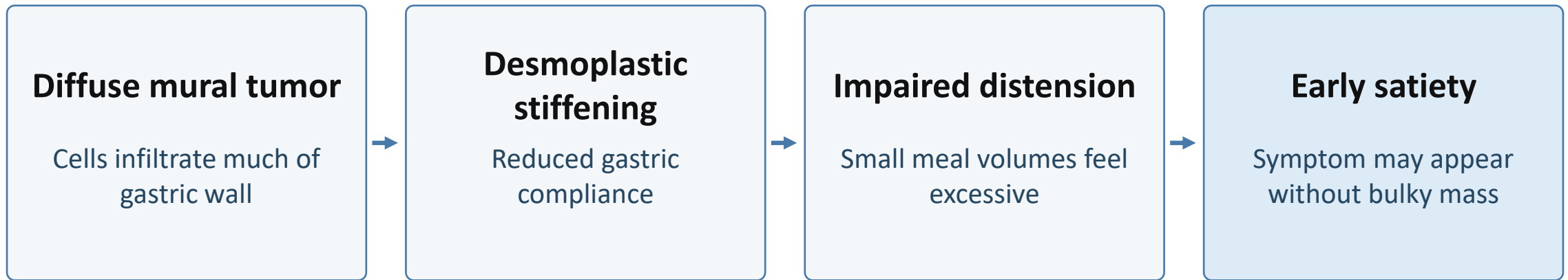
Early complaints are often nonspecific

- Dyspepsia is a common initial symptom account.
- Dysphagia and nausea may also occur.
- Overlap with gastritis and peptic ulcer disease lowers symptom specificity.
- Persistent symptoms alone cannot determine morphology or stage.

Advanced disease changes the symptom pattern

- Weight loss and anorexia may reflect established tumor burden.
- Anemia and gastrointestinal hemorrhage can follow mucosal ulceration.
- Early satiety is particularly associated with diffuse wall infiltration.
- Clinical manifestations depend on local extent and metastatic spread.

Why diffuse disease produces early satiety



Mechanistic explanation of the association reported.

Bleeding and anemia are clinicopathologic consequences

- Ulcerated tumors can expose vessels and produce hemorrhage.
- Chronic blood loss can contribute to anemia.
- The severity of anemia does not independently define depth of invasion.
- The bleeding presentation may resemble benign peptic ulcer disease.

Characteristic metastatic sites to recognize

Left supraclavicular node

Virchow node.

Periumbilical region

Sister Mary Joseph nodule.

Ovaries

Krukenberg tumor.

Additional locations

Left axillary nodes and pouch of Douglas are listed.

Krukenberg tumor identifies ovarian spread

- The ovaries are a characteristic metastatic destination of gastric carcinoma.
- Krukenberg tumor designates a characteristic metastatic ovarian tumor pattern.
- Its recognition should prompt consideration of an extraovarian primary.
- This metastatic association does not establish a particular gastric molecular subtype.

Local extension adds to clinical burden

- Adjacent duodenum, pancreas, and retroperitoneum can be invaded.
- Extensive local invasion may preclude curative surgical treatment.
- Nodal and distant metastatic deposits frequently coexist at diagnosis.
- Anatomic disease distribution determines management feasibility.

Depth of invasion is prognostically central

Mucosa



Submucosa



Muscularis propria



Serosa / outer surface

Depth through gastric wall layers is a key determinant of outcome; Schematic progression only.

Early gastric cancer is anatomically defined

- Early gastric adenocarcinoma is confined to mucosa or submucosa.
- The definition does not require absence of regional nodal metastases.
- Stage and prognosis depend on both local tumor extent and spread.
- Endoscopic early detection is important in high-incidence screening programs.

Early resected cancers have favorable survival

>90%

Five-year survival after surgical resection of early cancer.

The source states this can hold even when lymph-node metastases are present.

Advanced gastric cancer has poor outcomes

<20%

Five-year survival reported for advanced gastric cancer.

Historical textbook figure; Prognosis varies with stage, tumor biology, and treatment context.

Depth and metastatic extent dominate prognosis

- Depth of invasion is a major prognostic factor.
- Regional nodal burden and distant metastases are also critical.
- Morphologic subtype helps explain behavior but does not replace staging.
- The stage distribution at diagnosis strongly influences population survival.

Treatment context follows anatomic extent

Potentially resectable disease

- Surgery is a preferred option when feasible in the source account.
- Earlier detection improves the possibility of curative management.

Extensively invasive disease

- Local extension and metastasis can limit surgery.
- Systemic treatment, radiation, and palliation may become major components.

Case: An ulcerated antral mass

A 58-year-old man presents with dyspepsia and anemia. Endoscopy identifies an elevated antral lesion with central ulceration. The biopsy shows infiltrative, irregular malignant glands in desmoplastic stroma.

Which major morphologic type best fits this description?

- A. Intestinal-type adenocarcinoma
- B. Diffuse-type adenocarcinoma

Case analysis: Ulcerated antral mass

- Antral location, a bulky ulcerated lesion, and gland formation favor intestinal type.
- Desmoplastic stroma supports the invasive character of the biopsy.
- Clinical anemia is compatible with tumor-associated gastrointestinal bleeding.
- Further assessment is needed to establish local depth and nodal extent.

Case: A rigid stomach without a mass

A younger patient has early satiety and weight loss. Imaging/endoscopy identifies diffuse wall thickening with flattened folds. Histology demonstrates isolated mucin-filled cells with peripheral nuclei.

What mechanism best explains the infiltrative pattern?

- A. Disruption of epithelial cell adhesion
- B. Increased benign foveolar cell proliferation

Case analysis: Diffuse rigid stomach

- Signet-ring cells and mural infiltration support diffuse-type carcinoma.
- Loss of epithelial cohesion, commonly involving E-cadherin, is central.
- The stiff, thickened wall corresponds to linitis plastica.
- In a younger patient, family history may suggest inherited susceptibility.

Integrated classification: Four separate questions

Classification axis	Question it answers	Representative categories
Morphology	How does it grow?	Intestinal; Diffuse
Site	Where does it arise?	Distal/antral; Cardia/proximal
Molecular	Which tumor biology?	CIN; MSI; EBV; Adhesion-related stable
Extent	How far has it spread?	Mucosal/submucosal vs deeper; Nodes/metastases

Five pathology principles to retain

- Intestinal tumors are gland-forming; Diffuse tumors infiltrate as discohesive cells.
- Atrophy, intestinal metaplasia, and dysplasia mark the principal intestinal pathway.
- CDH1/E-cadherin dysfunction explains diffuse morphology and hereditary predisposition.
- CIN, MSI, and EBV are overlapping molecular rather than purely histologic groups.
- Invasion depth and metastatic spread are the strongest prognostic determinants.

Principal reference and evidentiary limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 17, Gastric Adenocarcinoma, pp. 705–707.
- Adjacent Robbins sections on chronic gastritis and gastric adenoma provide the precursor context.
- All morphology visuals in this lecture are original editable schematics, not authentic micrographs.
- Textbook epidemiologic and survival figures are reproduced as historical source statements, not current estimates.