

Small Intestine and Colon

Adenocarcinoma

Pathogenesis • morphology • clinical correlation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Distinguish inherited predisposition, sporadic pathways, and precursor lesions.
- Explain how APC/Wnt signaling, mismatch repair deficiency, and CIMP promote colorectal cancer.
- Recognize the clinical implications of tumor location, invasion depth, nodal spread, and metastasis.
- Apply the pathologic distinctions between dysplasia, intramucosal carcinoma, and invasive carcinoma.

Colonic versus small-intestinal adenocarcinoma

Colon

Small intestine

- Colonic adenocarcinoma is the most common malignancy in the gastrointestinal tract.
- Small-intestinal malignant tumors are uncommon despite the organ's great length.
- Small-bowel adenocarcinoma and well-differentiated neuroendocrine tumors occur at roughly equal frequencies.
- The chapter's detailed molecular and morphologic discussion centers on colorectal carcinoma.

Why colorectal adenocarcinoma matters

- It contributes substantially to cancer-related mortality worldwide.
- Adenomas offer an identifiable, removable precursor for many sporadic tumors.
- Clinical symptoms may appear only after a prolonged period of occult growth.
- Pathologic stage strongly influences outcome.

Epidemiologic variation

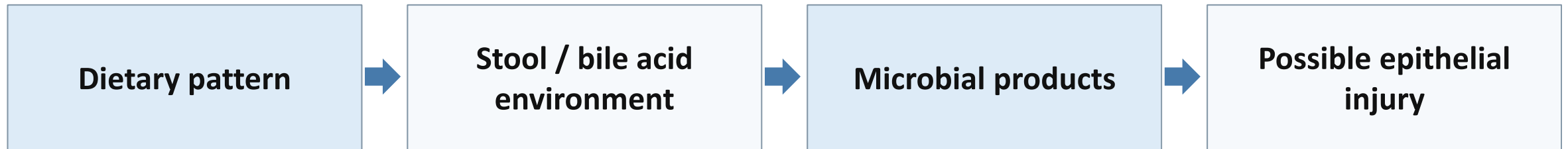
- Higher incidence in North America, Australia, New Zealand, Europe, and Japan.
- Incidence varies with geography, diet, and lifestyle; Rates change over time.
- Peak incidence occurs in later adulthood, classically during the seventh decade.
- The text notes increasing disease frequency in younger adults.

Dietary associations

- Low intake of unabsorbable vegetable fiber correlates with increased risk.
- High intake of refined carbohydrate and fat is also associated with risk.
- These are epidemiologic associations—not a proven single causal model.
- Mechanistic hypotheses involve stool bulk, microbial metabolism, and bile acids.

Proposed diet–microbiota mechanisms

Schematic



Hypothesized links—not an established obligatory sequence

- Reduced stool bulk may prolong contact between luminal products and epithelium.
- Microbial metabolism may generate oxidative or other potentially harmful products.
- High-fat diets may alter bile-acid production and microbial conversion products.
- Robbins explicitly regards these mechanisms as incompletely understood.

Inflammation-linked growth signaling

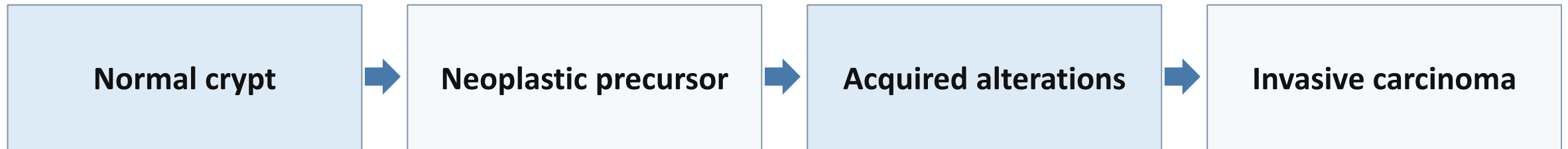
- Cyclooxygenase-2 (COX-2) is commonly expressed in colorectal neoplasia.
- COX-2 supports prostaglandin E₂ synthesis, which can encourage epithelial proliferation.
- TLR4 signaling can upregulate COX-2 expression.
- These observations help explain interest in anti-inflammatory chemoprevention.

NSAIDs and colorectal neoplasia

- Aspirin and other nonsteroidal anti-inflammatory drugs can have a protective effect.
- Some NSAIDs induce regression of residual rectal polyps in familial adenomatous polyposis.
- COX-2 inhibition is a plausible contributor to this effect.
- A mechanistic association is not a recommendation for unsupervised prophylaxis.

From normal epithelium to carcinoma

Schematic



- Colorectal neoplasia evolves through stepwise genetic and epigenetic alterations.
- The same invasive phenotype can arise through distinct molecular pathways.
- Tumor morphology may suggest—but does not definitively establish—molecular etiology.
- Dysplasia and invasion are different pathologic milestones.

Three major carcinogenic pathways

Schematic

APC / β -catenin

MMR deficiency / MSI

CpG methylation / CIMP

- APC/ β -catenin: Conventional adenoma–carcinoma progression.
- Mismatch repair deficiency: Microsatellite instability and mutation accumulation.
- CpG island methylator phenotype: Epigenetic gene silencing, often including MLH1.
- Pathways are not entirely mutually exclusive.

Sporadic and inherited disease

- Most colorectal cancers are sporadic, but hereditary syndromes reveal key pathogenic mechanisms.
- FAP is linked to germline APC disruption of Wnt control.
- Lynch syndrome reflects inherited mismatch repair deficiency susceptibility.
- MUTYH-associated polyposis follows a distinct autosomal recessive DNA repair defect.

FAP: Early APC pathway activation

- Individuals with FAP inherit an altered copy of APC.
- Acquisition of a second functional hit permits widespread adenoma formation.
- Untreated classic FAP has an exceptionally high colorectal cancer risk.
- APC biology also helps explain the common sporadic adenoma–carcinoma sequence.

Lynch syndrome: Mismatch repair predisposition

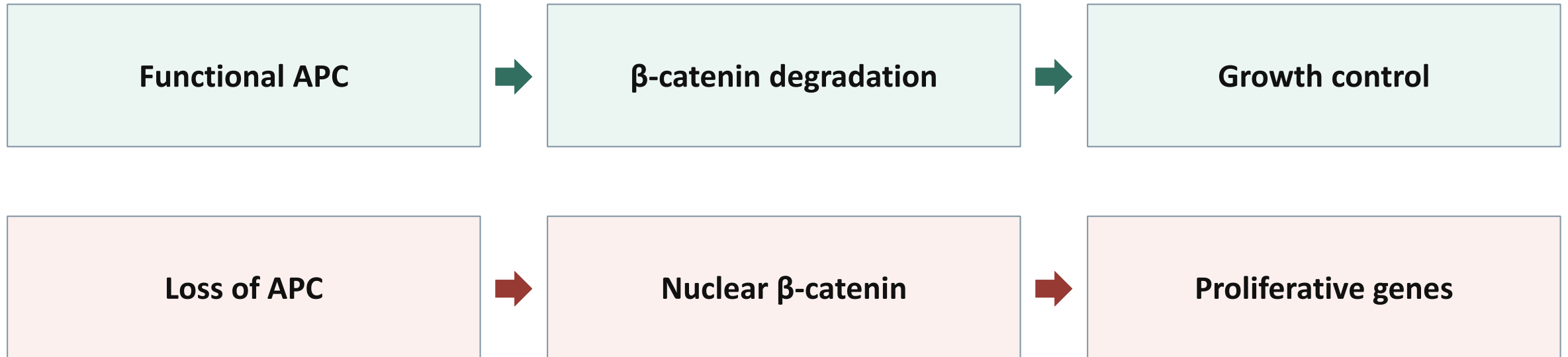
- Inherited pathogenic variants affect DNA mismatch repair genes, especially MLH1 or MSH2.
- A somatic second hit eliminates remaining repair function in susceptible epithelium.
- Mutation accumulation and microsatellite instability accelerate neoplastic evolution.
- Associated malignancies extend beyond the colorectum.

MUTYH-associated polyposis

- Biallelic MUTYH alterations impair base-excision DNA repair.
- The syndrome is autosomal recessive, unlike classic FAP and Lynch syndrome.
- Polyp burden and timing differ from classic FAP.
- Do not confuse MUTYH-mediated base-excision repair with mismatch repair.

APC acts as a β -catenin regulator

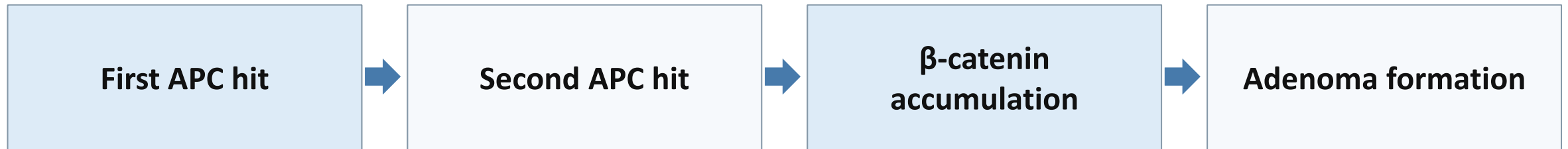
Schematic



- Functional APC helps target β -catenin for degradation.
- This limits β -catenin accumulation and transcriptional Wnt outputs.
- When APC is lost, β -catenin accumulates and can enter the nucleus.
- Nuclear β -catenin with TCF promotes growth-associated transcription.

The APC two-hit principle

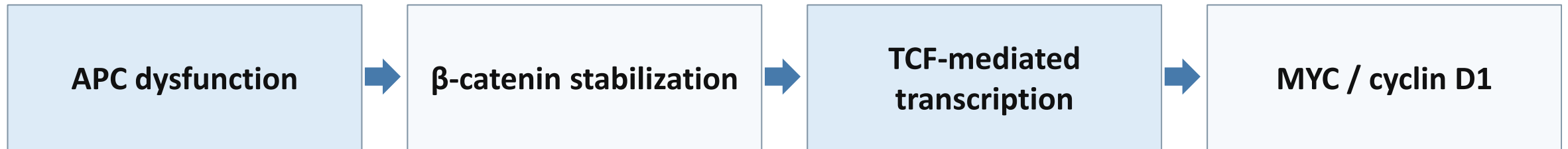
Schematic



- Inactivation of both functional APC copies permits conventional adenoma development.
- In FAP, one hit is inherited and the second is acquired.
- In sporadic neoplasia, both hits arise in somatic cells.
- Epigenetic silencing may also contribute to loss of tumor suppressor function.

β -catenin connects Wnt to proliferation

Schematic



- APC loss stabilizes β -catenin in the cytoplasm and nucleus.
- β -catenin binds TCF-family transcriptional factors.
- Transcription of genes including MYC and cyclin D1 is increased.
- Some APC-intact neoplasms instead harbor β -catenin alterations that prevent degradation.

Why APC disruption is an early event

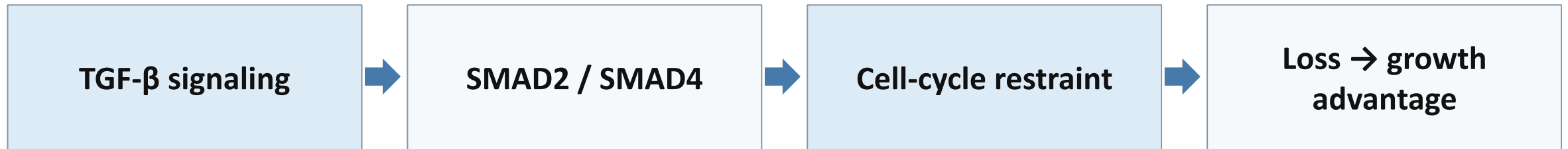
- Wnt dysregulation promotes a proliferating dysplastic epithelial clone.
- Later acquired alterations allow further clonal expansion and malignant conversion.
- Early APC loss does not, by itself, explain invasive behavior.
- This separation underlies the stepwise adenoma–carcinoma model.

KRAS contributes to adenoma growth

- Activating KRAS mutations enhance growth and cell survival.
- KRAS alteration later than APC loss in many conventional adenomas.
- KRAS alterations are more common in larger than in very small adenomas.
- The sequence is a biological model, not an invariant genotype for every tumor.

TGF- β growth inhibition can be lost

Schematic



- The TGF- β pathway normally restrains epithelial cell-cycle progression.
- SMAD2 and SMAD4 transduce growth-inhibitory signaling.
- Mutation or deletion of pathway components removes a proliferative brake.
- SMAD disruption can cooperate with APC and KRAS abnormalities.

TP53 in late progression

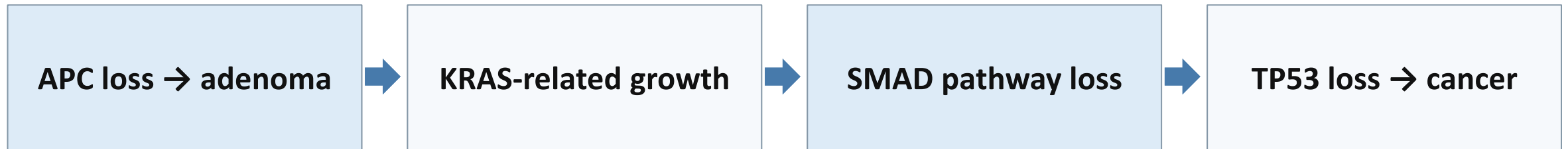
- TP53 alteration is common in colorectal carcinoma but relatively infrequent in adenomas.
- This distribution supports a later role in conventional tumor progression.
- TP53 loss weakens stress responses to abnormal proliferation and genomic injury.
- Mutations often coexist with chromosomal losses.

Chromosomal instability and epigenetics

- The APC/ β -catenin route often includes chromosomal deletions and allelic losses.
- Loss of tumor suppressor alleles contributes to progression.
- Promoter CpG methylation can also silence growth-regulatory genes.
- Genetic and epigenetic events can cooperate within the same neoplasm.

Conventional adenoma–carcinoma sequence

Schematic



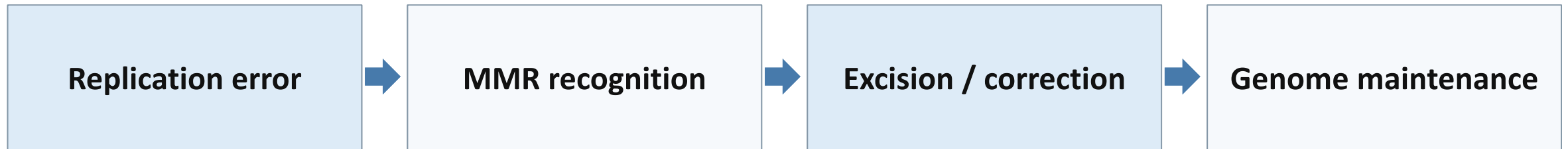
- The sequence is initiated by loss of APC-mediated growth regulation.
- KRAS activation can support adenoma enlargement.
- Loss of TGF- β -mediated suppression and later TP53 dysfunction favor progression.
- Only a minority of adenomas ultimately become invasive cancer.

Adenoma progression is not inevitable

- Adenomas are precursors, but most do not progress to invasive adenocarcinoma.
- Adenoma size and architecture correlate with risk but do not perfectly predict fate.
- The practical preventive strategy is identification and endoscopic removal.
- Removing a precursor interrupts its opportunity for progression.

Mismatch repair: The normal function

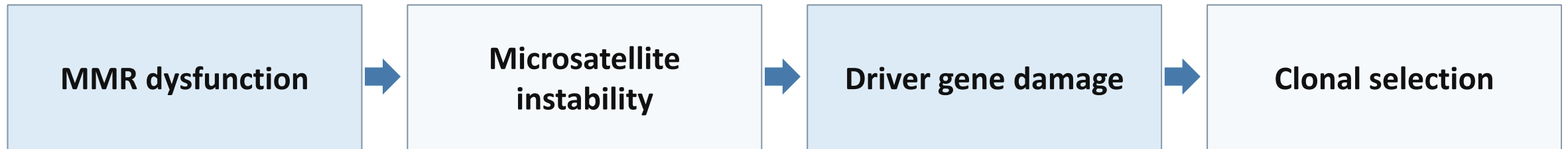
Schematic



- Mismatch repair detects and corrects DNA replication errors.
- Microsatellite repeats are especially prone to slippage during copying.
- Loss of repair function allows unstable repeat lengths to accumulate.
- Such instability is a molecular signature rather than a microscopic diagnosis.

Mismatch repair deficiency and MSI

Schematic



- Inactivated MLH1, MSH2, or related proteins compromise mismatch repair.
- Uncorrected replication errors accumulate, often within repetitive microsatellites.
- MSI-high carcinomas arise when mutations affect critical proliferation and survival genes.
- MMR deficiency can be inherited or sporadically acquired.

MSI target: TGFBR2

- Some coding microsatellite mutations affect TGFBR2.
- The encoded receptor participates in growth-inhibitory TGF- β signaling.
- Receptor loss reduces the epithelial response to this inhibitory signal.
- This provides a mechanistic link between MSI and proliferative advantage.

MSI target: BAX

- BAX is involved in apoptosis of damaged cells.
- Microsatellite mutations affecting BAX can impair pro-apoptotic signaling.
- Abnormally surviving clones may then persist and acquire further alterations.
- Mutation accumulation has consequences only when biologically relevant targets are affected.

MSI-associated morphologic clues

- MSI-associated carcinomas are often right-sided.
- Some show abundant extracellular mucin or mucinous differentiation.
- Prominent peritumoral lymphocytes can accompany these tumors.
- None of these morphologic clues replaces direct molecular or immunohistochemical assessment.

How MMR deficiency is assessed

Schematic

MMR immunohistochemistry

Microsatellite analysis

Hereditary-risk interpretation

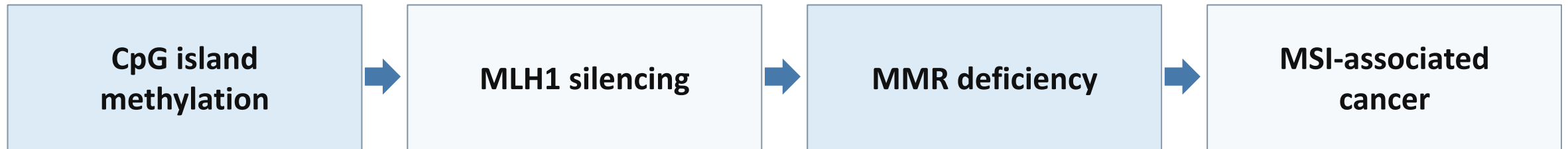
- Immunohistochemistry can demonstrate loss of expression of mismatch repair proteins.
- Molecular analysis can assess instability of microsatellite sequences.
- Morphology helps prompt testing but is insufficient to determine MMR status.
- An abnormal result may warrant evaluation for inherited predisposition.

Consequences of detecting MMR deficiency

- MMR/MSI status can influence therapeutic decision-making.
- Greater responsiveness of these tumors to immune checkpoint inhibitors.
- A germline cause has implications for the patient and relatives.
- A molecular result is not automatically evidence of Lynch syndrome.

CIMP: Gene silencing by methylation

Schematic



- The CpG island methylator phenotype is marked by extensive promoter-region methylation.
- Silencing of MLH1 may cause secondary mismatch repair deficiency.
- This pathway often occurs without inherited mismatch repair gene mutation.
- The methylation event changes gene expression without changing the base sequence.

BRAF and the methylator pathway

- Activating BRAF mutations are common in the MLH1-methylated CIMP pathway.
- The characteristic combination is BRAF alteration, gene methylation, and sometimes MSI.
- KRAS and TP53 are often intact in this particular subset.
- Molecular combinations are useful for classification but vary across tumors.

CIMP without microsatellite instability

- Some carcinomas have increased CpG island methylation but remain microsatellite stable.
- Frequent KRAS alterations in this subgroup.
- BRAF and TP53 alterations are less common in that described subset.
- CIMP and MSI should not be treated as synonymous terms.

Integrated molecular-pathway comparison

Pathway	Central defect	Typical associations
Conventional APC route	APC / β -catenin regulation	Conventional adenoma; chromosomal instability
MMR / MSI route	Replication-error repair lost	MSI; sometimes right-sided, mucinous, lymphocytic
CIMP route	CpG promoter hypermethylation	MLH1 silencing; often BRAF alteration

Precursor lesions: Terminology

- Conventional adenomas contain epithelial dysplasia.
- Sessile serrated lesions can be premalignant without classic cytologic dysplasia.
- Adenomas and serrated lesions support different, partly overlapping routes to cancer.
- Pathology reports should distinguish architecture, dysplasia, and invasion.

What epithelial dysplasia looks like

- Colorectal adenomas display elongated, hyperchromatic, stratified nuclei.
- Nucleoli may be conspicuous and goblet cell numbers reduced.
- The abnormality is epithelial; The degree of invasion is a separate question.
- Dysplasia is not synonymous with invasion through the muscularis mucosae.

Serrated lesions and malignancy risk

- Sessile serrated polyps are often right-sided.
- Distorted crypt bases, dilation, and lateral crypt growth separate them from many hyperplastic polyps.
- Typical conventional adenomatous cytologic dysplasia may be absent.
- Molecular correlations include CIMP and mismatch-repair-related neoplasia.

The anatomic boundary that defines invasion

Mucosa (epithelium + lamina propria)	Intramucosal Minimal metastatic risk
Muscularis mucosae	
Submucosa	Submucosal invasion Metastatic risk emerges
Muscularis propria	
Pericorectal soft tissue	

The muscularis mucosae separates intramucosal from invasive colorectal carcinoma.

Intramucosal carcinoma in a polyp

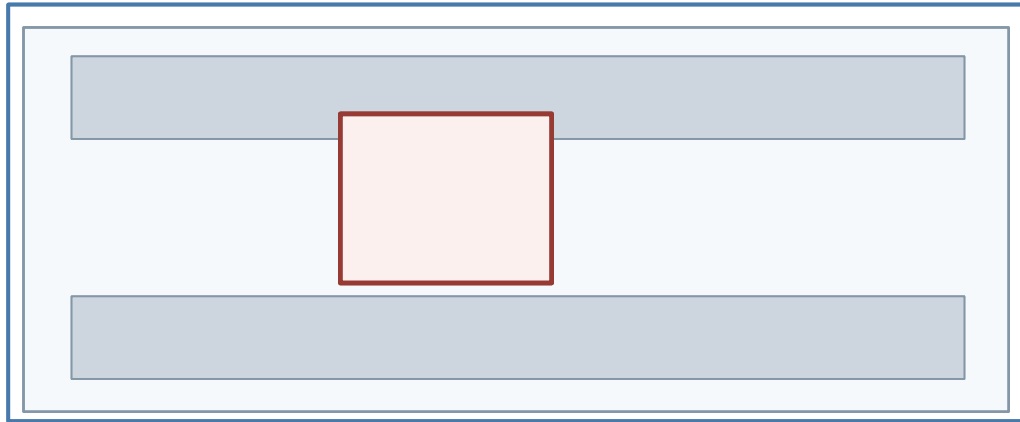
- Dysplastic cells breach the basement membrane and enter the lamina propria.
- They may extend into, but not beyond, the muscularis mucosae.
- Functional mucosal lymphatic channels are absent in this setting, explaining negligible metastatic risk.
- Complete excision is generally curative when invasion remains intramucosal.

Submucosal invasion changes risk

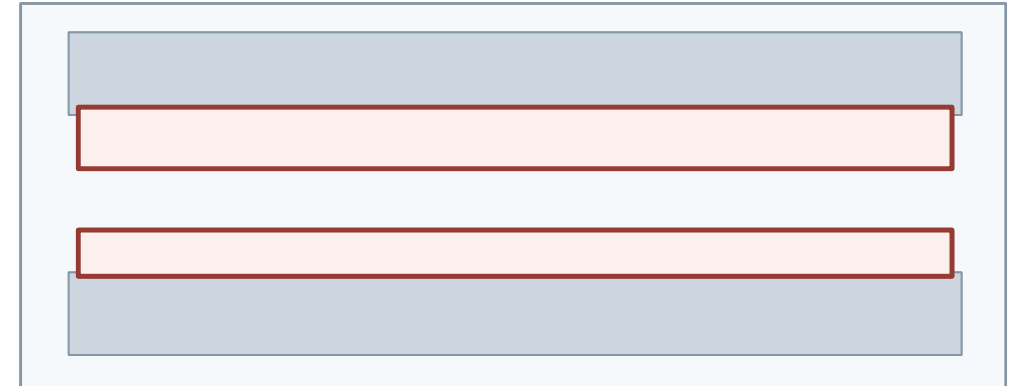
- Tumor below the muscularis mucosae constitutes invasive adenocarcinoma.
- An invasive focus can occur within the stalk of a pedunculated polyp.
- Grade, lymphovascular invasion, and resection-margin proximity influence further management.
- A superficially small lesion may therefore require more than endoscopic removal.

How right-sided carcinomas grow

Gross schematic



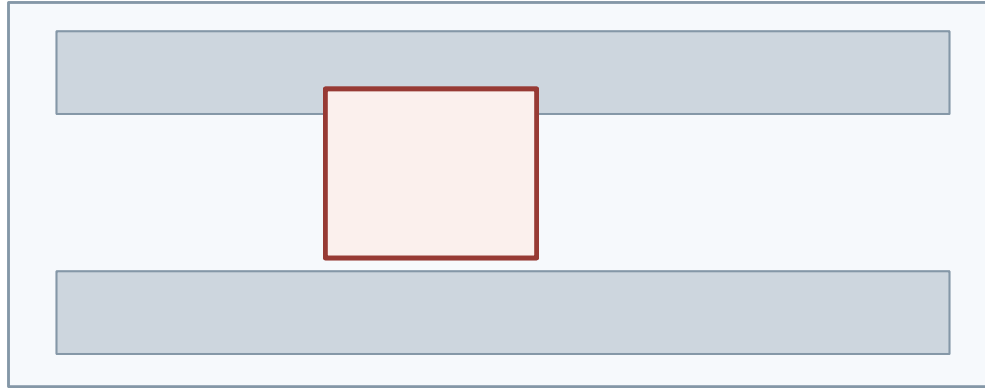
Exophytic / polypoid



Annular / constricting

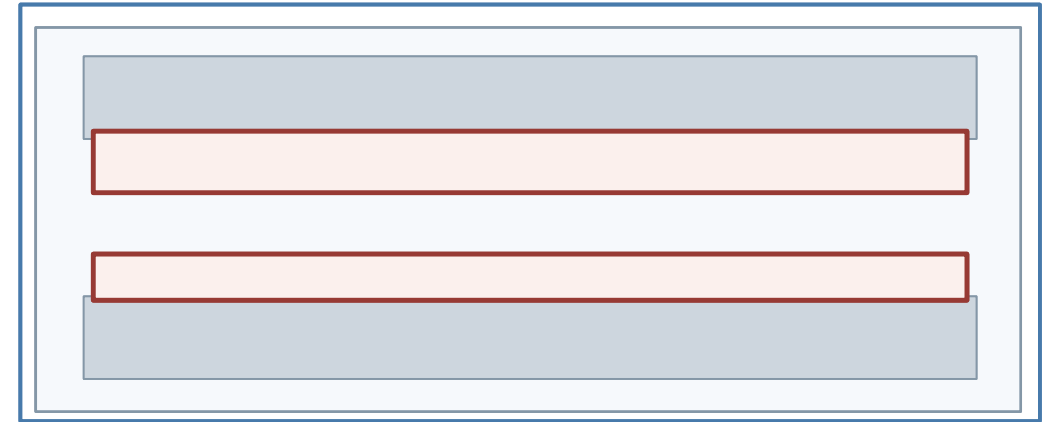
- Proximal colonic carcinomas often form exophytic, polypoid masses.
- The relatively wide bowel lumen allows substantial growth without early obstruction.
- Chronic occult bleeding may be the dominant early clinical effect.
- Gross configuration helps explain presentation but does not establish molecular class.

How left-sided carcinomas grow



Exophytic / polypoid

Gross schematic



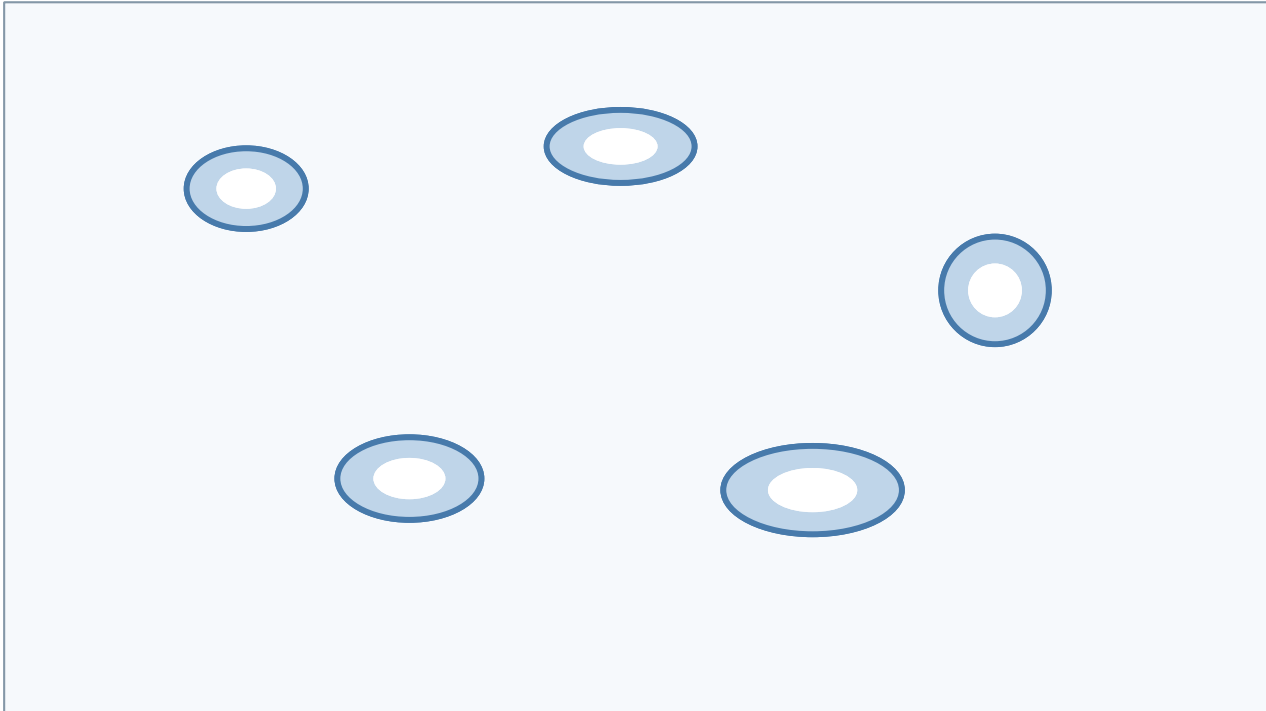
Annular / constricting

- Distal colonic tumors often form circumferential, annular lesions.
- The resulting “napkin-ring” narrowing can impede fecal transit.
- Obstruction, cramping, and altered bowel habits are clinically important consequences.
- Both proximal and distal tumors ultimately infiltrate the bowel wall.

Proximal versus distal: Clinicopathologic contrast

Feature	Proximal / right colon	Distal / left colon
Common gross pattern	Exophytic, polypoid	Annular, constricting
Luminal effect	Obstruction less common	Narrowing and obstruction
Typical symptom clue	Occult bleeding, iron deficiency	Visible bleeding, altered habits
Microscopic phenotype	Not reliably site-specific	Not reliably site-specific

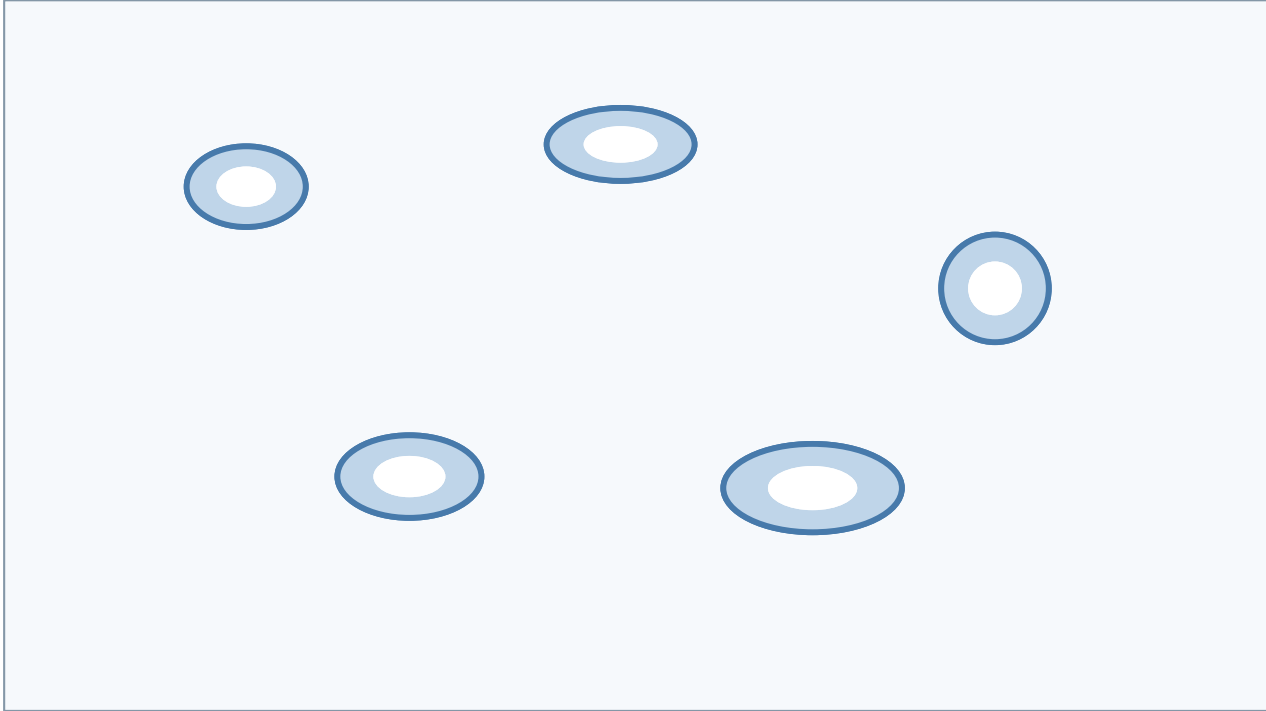
Typical colorectal adenocarcinoma histology



Schematic of infiltrative irregular gland profiles

- Infiltrating atypical glands are commonly composed of columnar tumor cells.
- Nuclei are elongated and hyperchromatic, resembling neoplastic adenomatous epithelium.
- Tumor gland lumina often contain necrotic cellular debris.
- An infiltrative pattern and stromal reaction support invasion.

Why invasive cancer feels firm



Schematic of infiltrative irregular gland profiles

- Invasive tumor frequently elicits a dense fibrous stromal response: Desmoplasia.
- Desmoplastic stroma surrounds irregular infiltrating malignant glands.
- This response contributes to the characteristic firmness of invasive colorectal carcinoma.
- Stromal reaction must be interpreted with gland location and architecture.

Poorly differentiated carcinoma

- Some colorectal carcinomas form very few recognizable glands.
- Infiltrating nests and poorly differentiated tumor cells may predominate.
- Reduced gland formation can complicate recognition of an adenocarcinoma origin.
- Histologic grade is important, although stage dominates prognosis.

Mucinous differentiation

- Some tumors produce large quantities of extracellular mucin.
- Mucin may accumulate within the bowel wall around tumor cells.
- Extensive mucinous morphology with adverse prognosis.
- Mucinous morphology is also seen in some mismatch-repair-deficient cancers.

Signet-ring cell morphology

- Rare colorectal carcinomas contain signet-ring tumor cells.
- Intracellular mucin displaces the nucleus toward the cell periphery.
- The resulting pattern resembles signet-ring carcinoma elsewhere in the gastrointestinal tract.
- The feature should be distinguished from pools of extracellular mucin.

Morphology does not uniquely encode genotype

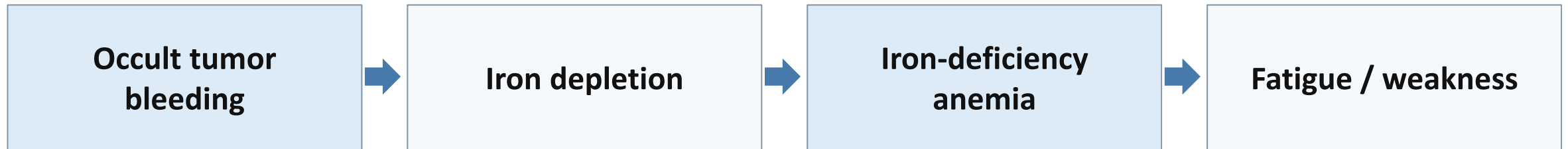
- Right-sided location, mucin, and lymphocytes may point toward MSI-related disease.
- Conventional gland-forming morphology does not prove APC mutation.
- Molecular and immunohistochemical tests resolve clinically relevant uncertainty.
- Describe what is observed separately from etiologic interpretation.

Clinical detection is often delayed

- Colorectal cancer may develop and enlarge over a long asymptomatic interval.
- Early occult bleeding may be overlooked until anemia develops.
- Obstruction or altered bowel habits may emerge as a mass narrows the lumen.
- This delayed symptom onset supports preventive endoscopic screening.

Right-sided cancer and iron deficiency

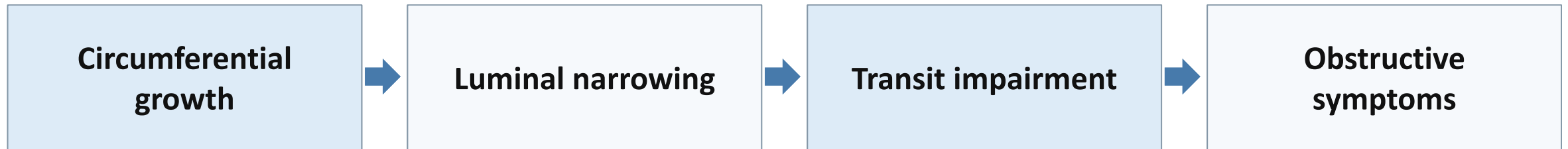
Schematic



- Blood loss may be chronic and not visibly apparent in the stool.
- Iron depletion causes fatigue and reduced exercise tolerance.
- In an older adult, unexplained iron deficiency requires evaluation for gastrointestinal blood loss.
- The clinical symptom reflects bleeding from the lesion, not merely its histologic subtype.

Left-sided cancer and obstruction

Schematic



- Annular growth reduces luminal caliber.
- Symptoms may include cramping, altered stool pattern, and visible rectal bleeding.
- Progressive constriction can produce bowel obstruction.
- Similar presenting symptoms can arise from nonmalignant bowel disease.

How colorectal carcinoma spreads

Schematic

Direct local invasion

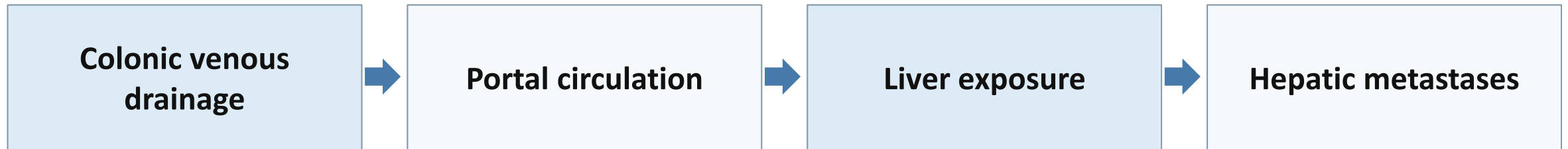
Lymphatic spread

**Hematogenous / peritoneal
spread**

- Direct extension proceeds through successive bowel-wall layers.
- Regional lymph nodes may receive metastatic disease.
- Hematogenous dissemination can reach the liver and other organs.
- Peritoneal involvement is a separate route relevant to advanced disease.

Why the liver is a frequent metastatic site

Schematic



- Much of the colonic venous outflow enters the portal circulation.
- Tumor cells may travel through the portal system to hepatic sinusoids.
- Liver metastases are therefore common in advanced colorectal carcinoma.
- Lung, bone, and other sites may also be involved.

The essential pathologic report questions

- How deeply does the tumor invade the bowel wall?
- Are regional lymph nodes involved?
- Is distant or peritoneal metastatic disease present?
- Are histologic differentiation and relevant adverse invasion features documented?

Tumor depth: The T categories

Depth categories

Tis — mucosa

T1 — submucosa

T2 — muscularis propria

T3 — beyond muscularis propria

T4 — serosa / adjacent structures

Mucosa (epithelium + lamina propria)

Muscularis mucosae

Submucosa

Muscularis propria

Pericorectal soft tissue

T category depends on the deepest anatomically verified extent of tumor.

T4a and T4b have different boundaries

- T4a: Tumor penetrates the visceral peritoneal surface.
- T4b: Direct extension into or adherence to other organs or structures.
- Precise anatomic documentation is critical to correct staging.
- The staging summary here follows the AJCC 2023 classification reproduced.

Regional nodal categories

Category	Nodal disease	Interpretation
N0	No regional positive nodes	Node-negative
N1	1–3 positive nodes	Limited regional spread
N1c	Tumor deposits, no positive nodes	Separate deposit-based group
N2	≥4 positive nodes	More extensive nodal spread

Regional tumor deposits are evaluated separately from positive lymph-node counts (N1c).

Distant metastasis categories

- M0: No distant metastasis evident by the methods used.
- M1a: Metastasis to one site or organ without peritoneal metastasis.
- M1b: Two or more organs/sites, without peritoneal metastasis.
- M1c: Peritoneal metastasis, with or without other distant sites.

Grade versus stage

Grade: Tumor phenotype

Stage: Anatomic extent

- Grade describes morphologic differentiation of the tumor.
- Stage integrates depth of invasion, nodal involvement, and distant spread.
- Poor differentiation and mucinous features may be adverse morphologic findings.
- Depth of invasion and lymph node involvement as the strongest prognostic factors.

Depth and lymph nodes drive prognosis

- Invasion into the muscularis propria is an important adverse event.
- Regional lymph node metastasis reduces expected survival further.
- The familiar TNM framework formalizes these observed prognostic relationships.
- A patient's prognosis also depends on disease extent and clinical context.

Clinical prevention: The precursor window

- Most conventional colorectal cancers arise from pre-existing adenomas.
- Endoscopic detection and polypectomy can remove precancerous lesions.
- Screening works even though clinicians cannot predict which single adenoma would progress.
- Screening and surveillance schedules depend on patient risk and current guidance.

Case 1: Occult right-sided tumor

- A 68-year-old reports progressive fatigue without obvious rectal bleeding.
- Laboratory assessment demonstrates iron-deficiency anemia.
- Colonoscopy reveals a large exophytic cecal mass.
- Question: Which aspects of gross growth explain this presentation?

Case 1: Clinicopathologic reasoning

- A right-sided exophytic tumor can enlarge within a relatively capacious lumen.
- Chronic microscopic bleeding may precede obstructive symptoms.
- Iron deficiency produces the fatigue even without visible stool blood.
- Biopsy establishes histology; Extent of invasion requires appropriate staging.

Case 2: Adenoma with malignant focus

- A polypectomy specimen contains dysplastic glands and a small invasive focus.
- The key question is whether glands have crossed the muscularis mucosae.
- If invasion reaches submucosa, assess grade, lymphovascular invasion, and margin.
- Question: Why does an intramucosal-only focus differ from submucosal invasion?

Case 2: The invasion threshold

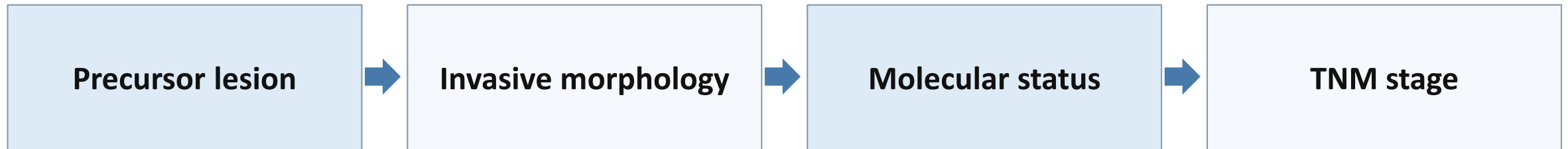
- Intramucosal invasion has little or no metastatic potential in colorectal mucosa.
- Submucosal invasion permits clinically relevant lymphovascular spread.
- Polyp size alone cannot substitute for histologic depth assessment.
- Accurate specimen orientation and margin evaluation are consequential.

Case 3: Molecular interpretation

- A right-sided carcinoma shows abundant mucin and prominent lymphocytes.
- The pattern raises suspicion for MSI-related neoplasia.
- Mismatch repair IHC or molecular MSI testing is needed for confirmation.
- An abnormal screening result requires separate evaluation for sporadic versus inherited causes.

Integrating molecular and morphologic evidence

Schematic



- The precursor identifies a plausible progression route.
- Histology establishes gland differentiation, invasion, and local tissue response.
- Molecular tests characterize MMR/MSI or selected driver/epigenetic pathways.
- TNM records spread and supplies core prognostic information.

Ten concepts to retain

- APC loss is a frequent early conventional event; KRAS, SMAD, and TP53 alterations can accumulate.
- MMR deficiency produces MSI; MLH1 methylation can cause sporadic MMR loss.
- Right-sided and left-sided cancers often present differently because they grow differently.
- Submucosal invasion changes metastatic risk; T, N, and M define anatomic stage.

References and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 17, pp. 738–744.
- Primary adenocarcinoma section: printed pp. 741–744; adjacent adenoma and hereditary predisposition material provides context.
- TNM definitions reproduce the AJCC (2023) staging table as printed in Robbins.
- Conceptual diagrams in this lecture are original editable schematics; no textbook histology plates were reproduced.