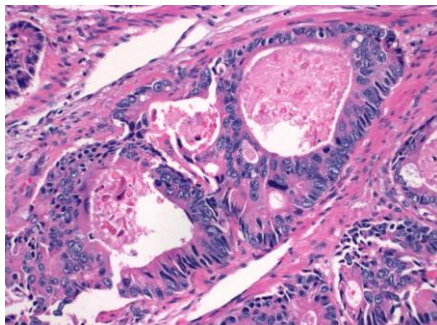


Colorectal Cancer

Adenocarcinoma, NOS



Characteristic morphology:

Architectural complexity (“cribriform growth”)
Abundant **“dirty” necrosis**

Most arise through Adenoma → Carcinoma sequence

3rd most common cancer in U.S.

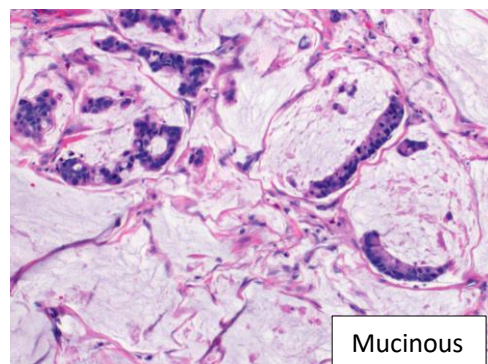
Associated with processed food, obesity, red meat, low-fiber diet, and alcohol

Subtypes

Although most colon cancers are “NOS” (Not Otherwise Specified), some subtypes exist, many of which have distinct morphology, clinical implications, and molecular alterations

Mucinous adenocarcinoma

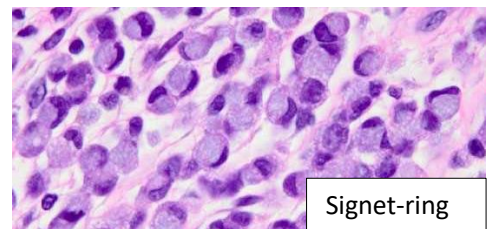
>50% of tumor composed of pools of extracellular mucin (most common subtype). No prognosis implications. Enriched for MSI-high tumors.
If <50% → “Mucinous features” or “mucinous component”



Mucinous

Signet-ring cell carcinoma

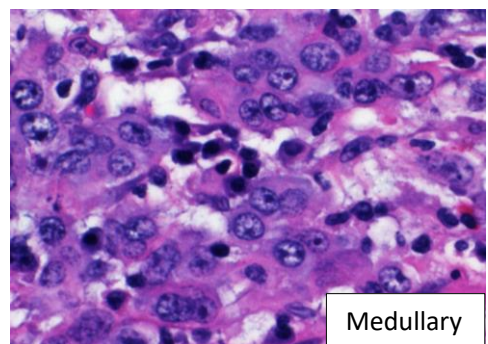
>50% of tumor cells have prominent intracytoplasmic mucin displacing the nucleus. Worse outcome. Associated with Lynch syndrome and MSI-high.



Signet-ring

Medullary carcinoma

Sheets of malignant cells with vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm, and a prominent inflammatory infiltrate. BRAF mutations → MSI-high. Better prognosis.



Medullary

Serrated adenocarcinoma

Morphologically similar to serrated polyps

Micropapillary adenocarcinoma

Small clusters of tumor cells with stromal retraction.
Worse outcome (like in all organs) with early metastasis to LN.

Adenoma-like adenocarcinoma

Pushing invasion with minimal desmoplasia. Hard to Dx on Bx. Good prognosis.

Adenosquamous carcinoma

Grading For “NOS” cancers

Based on gland formation in the least differentiated component. Don't include areas of tumor budding or poorly differentiated clusters (these are counted elsewhere).

Grade	Differentiation	Gland formation
Low-grade	Well-differentiated	>95%
	Moderately-differentiated	50-95%
High-grade	Poorly-differentiated	<50%

Special Data to Report

Large Venous Invasion

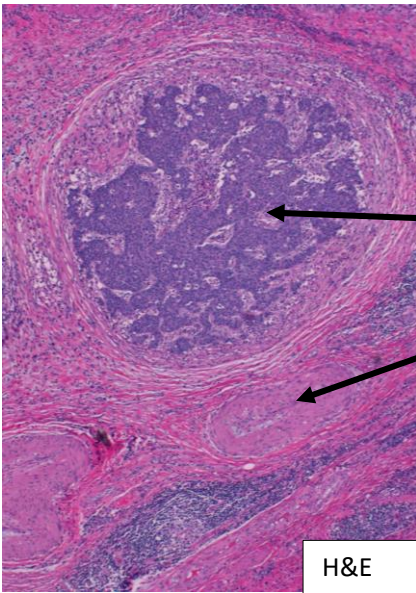
Tumor involving endothelium-lined spaces with an identifiable **smooth muscle layer** or **elastic lamina**

Extramural venous invasion (outside muscularis propria) is a risk factor for **liver metastasis**

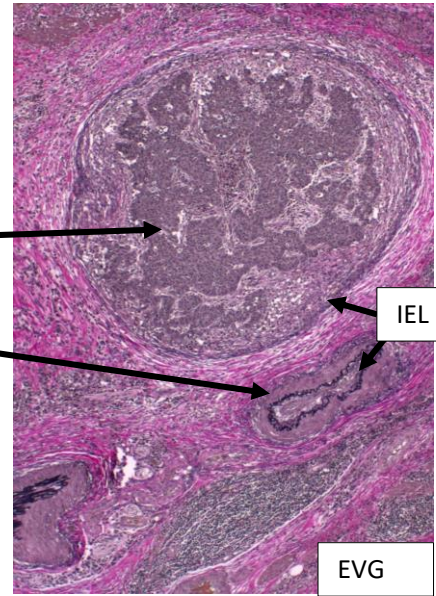
Tumor filling large vein (destroying lumen)

"orphan" artery (without its paired vein)

Sometimes you might just see the orphan artery and/or a large, rounded "Tongue" of tumor next to it



H&E



IEL

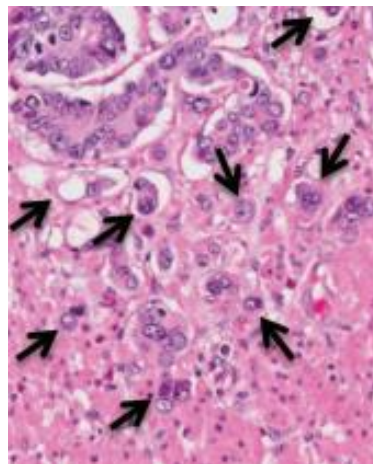
EVG

The EVG stain can highlight the internal elastic lamina of both the artery and vein. If you don't see large venous invasion, consider getting an EVG to look for it.

Tumor Budding

Single cells or small clusters of **<5 cells** at the advancing front of the tumor

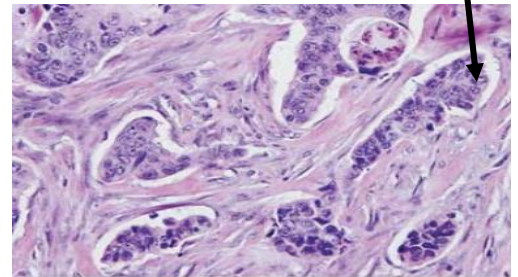
High tumor budding is a significant risk factor for nodal involvement/poor outcome. Represents "epithelial-mesenchymal transition"



Poorly differentiated clusters

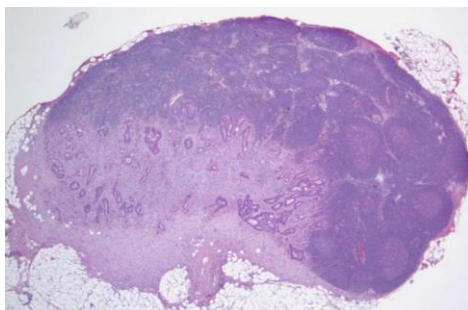
Clusters of **≥5 cells** **without gland formation**

Associated with worse outcome



Lymph Node Metastases

Must have residual lymphoid tissue
Usually rounded contour

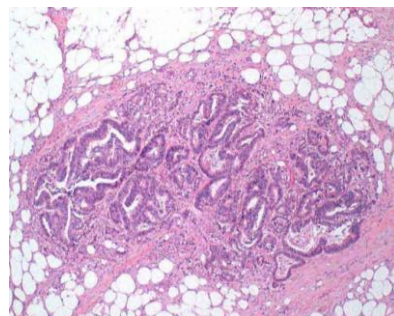


Tumor Deposits

A tumor focus in the fat, but without identifiable lymph node tissue, nerve, or vascular structure → Staged as **pN1c**

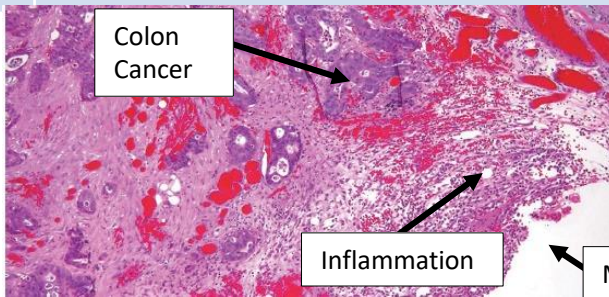
Often irregular contours.

Unpaired artery or elastic lamina? → Large venous invasion!



Stage

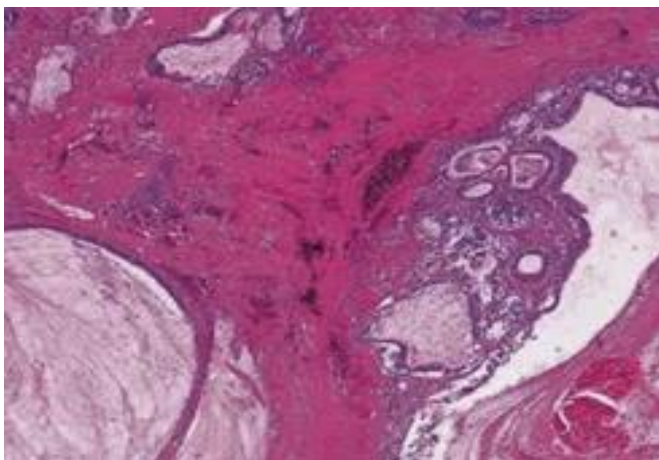
Stage	Criteria
pT0	No evidence of primary tumor
pTis	Carcinoma in situ (High-grade dysplasia), intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae) → Few lymphatics → low risk of mets
pT1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria) → Usually elicits a desmoplastic response
pT2	Tumor invades the muscularis propria
pT3	Tumor invades <u>through</u> the muscularis propria into pericolorectal tissues
pT4a	Tumor invades through the <u>visceral peritoneum</u> (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
pT4b	Tumor directly invades or adheres to adjacent organs or structures



In this example, even though the tumor isn't "at the surface," because it is continuous with the surface through inflammation, it is pT4a

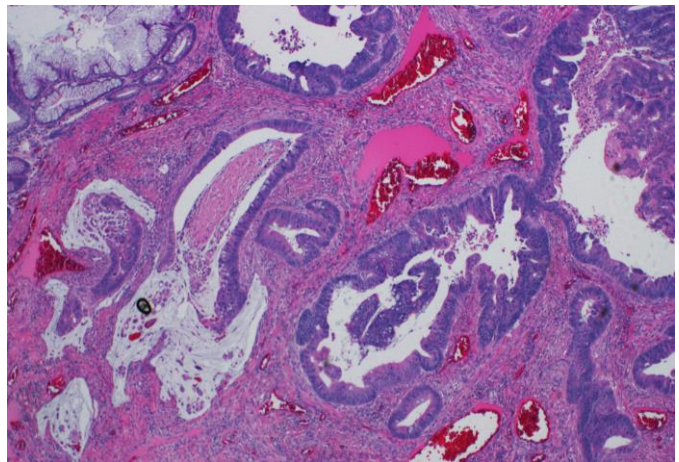
"Pseudo-Invasion"

Usually NO/little cytologic or architectural atypia
 Inflamed/fibrotic stroma
Hemosiderin-laden macrophages
 Glands accompanied by lamina propria
Rounded/well-circumscribed
 Mostly left colon



(True) Invasion

Usually cytologic or architectural atypia
Desmoplastic stroma
Infiltrative/irregular growth
 NOT accompanied by lamina propria
 Anywhere in colon



Some Molecular

Chromosomal Instability Pathway (Non-hypermuted Pathway): ~85% CRC.

Adenoma → Carcinoma sequence. Large chromosome arm gains/losses.

Common mutations: APC (early, starts adenoma → activates WNT pathway), KRAS, and P53.

RAS mutations (~50% of tumors) → Resistant to anti-EGFR therapy (used to treat metastatic CRC)

Microsatellite Instability (MSI) Pathway (Hypermuted Pathway): ~15% of CRC.

Sporadic: BRAF mutation → MLH1 promoter hypermethylation → Inactivation of mismatch repair (MMR) enzymes → Serrated polyp → Carcinoma

Lynch-associated: Germline mutations in MMR proteins → loss of heterozygosity → Adenoma → Carcinoma

→ Lots of mutations → more immunogenic → more inflammatory response to tumor → better outcome. Also, response to check point inhibitors (e.g., anti-PD-L1 drugs)

Ultramutated Pathway: ~3% of CRC.

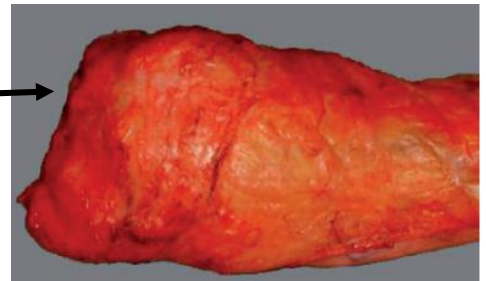
POLE (DNA replication enzyme) mutation → lots of mistakes with DNA replication → Ultramutated tumor

Rectal Cancers Stuff

For RECTAL cancers: The quality of the surgical technique is a key determinant of local recurrence and long-term survival. **Grossly**, assess the completeness of the non-peritonealized mesorectal excision. Score according to **worst** area.

Complete:

Intact, bulky mesorectum with a smooth surface.
No visible muscle, only very minor irregularities (<5mm)
No "Coning" (where the specimen tapers dramatically distally)

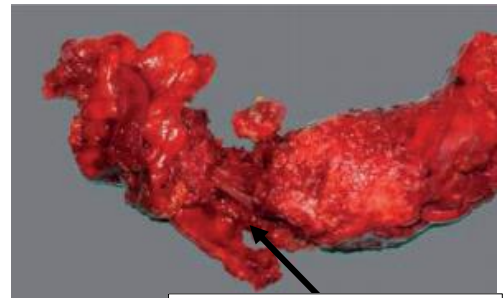


Nearly Complete:

Moderately bulky mesorectum
Minor irregularities (>5mm), but no visible muscle

Incomplete:

Little bulk to mesorectum
Muscularis propria visible



"Coning"
And visible muscle

Circumferential Resection Margin: Considered positive if tumor is microscopically <1mm from inked circumferential margin (non-peritonealized)