*Last updated: 6/2/2024*

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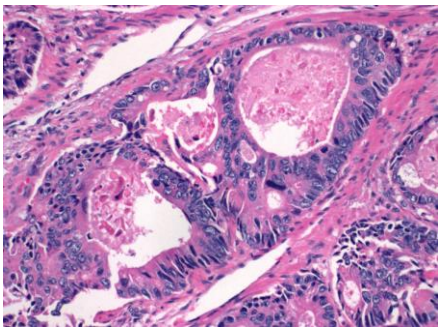
# Colorectal Cancer

## Adenocarcinoma, NOS



Classic "intestinal" morphology:

**Architectural complexity** ("cribriform growth")

Abundant **"dirty" necrosis**

Most arise through Adenoma → Carcinoma sequence

3rd most common cancer in U.S.

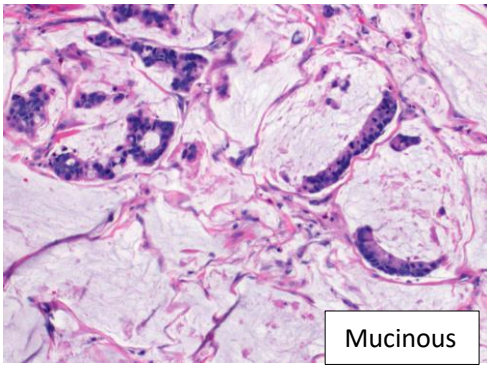
Associated with processed food, obesity, red meat, low-fiber diet, and alcohol

## Subtypes

Although most colorectal cancers (CRCs) are "NOS" (**N**ot **O**therwise **S**pecified), some subtypes exist, many of which have distinct morphology, clinical implications, and molecular alterations

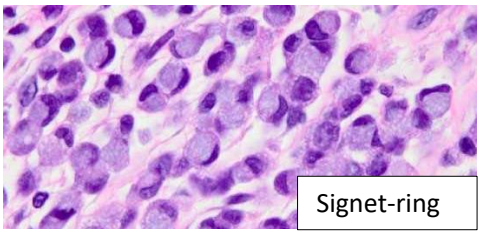
**Mucinous adenocarcinoma**

>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"



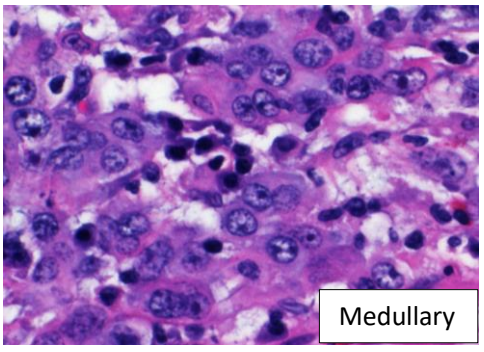

**Signet-ring cell carcinoma**

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




**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. CK20&CDX2(-/+)




**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**

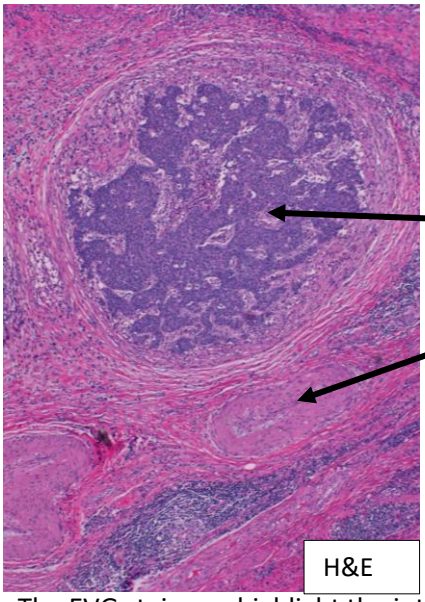
Based on gland formation in the least differentiated component. Don't include areas of tumor budding or poorly differentiated clusters (these are counted elsewhere).

| 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**

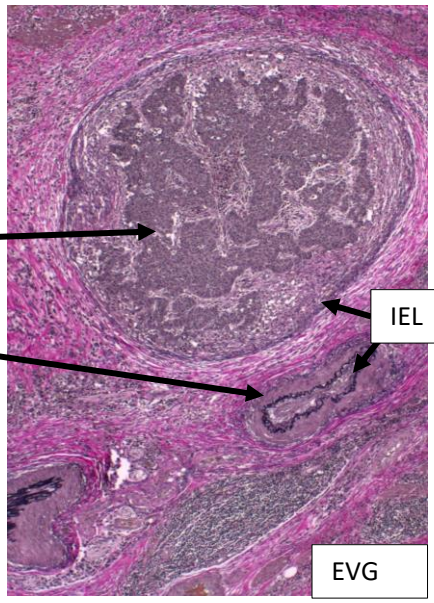



Extramural venous invasion (outside muscularis propria) is a risk factor for **liver metastasis**

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

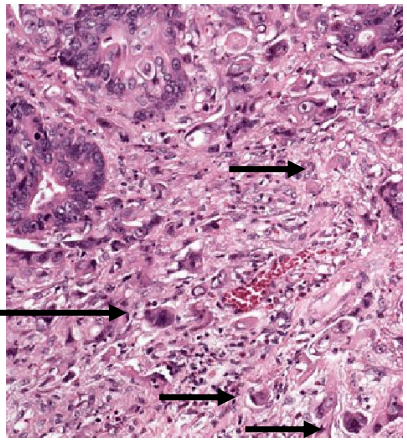



The EVG stain can highlight the internal elastic lamina of both the artery and vein. If you don't see large venous invasion, consider getting an EVG to look for it. I tend to get it on at least 2 blocks to exclude large venous invasion.

## 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"

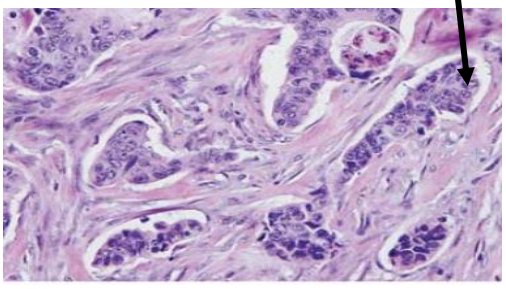


Count in "Hot spot."

## Poorly differentiated clusters

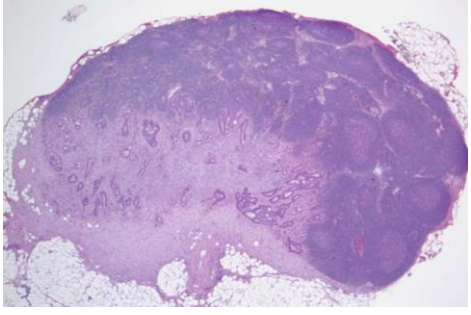
Clusters of **≥5 cells <u>without gland formation</u>**

Associated with worse outcome



## Lymph Node Metastases

Must have residual lymphoid tissue. Usually rounded contour.

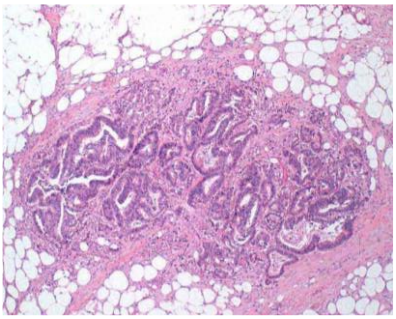


## Tumor Deposits

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

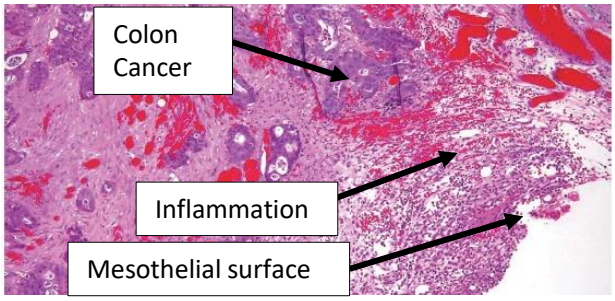
Often irregular contours.

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 |



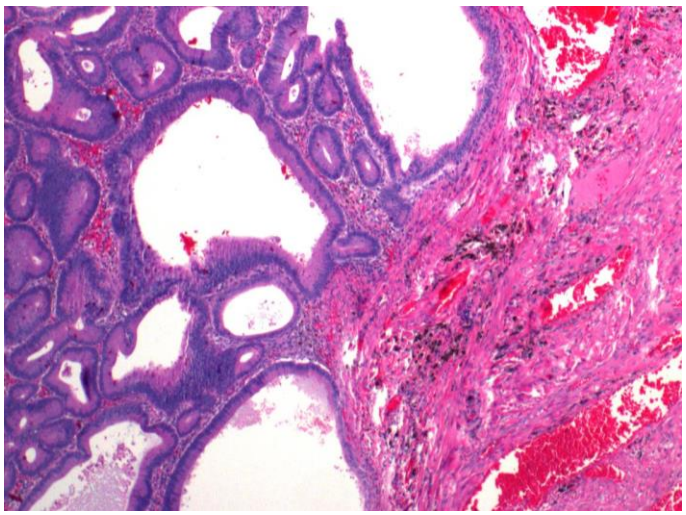

*In this example, even though the tumor isn't "at the surface," because it is continuous with the surface through inflammation, it is pT4a.*

*The significance of tumors that are < 1mm (but not quite at) the surface is unclear with some (but not all) studies indicating a higher risk of peritoneal recurrence.*

*When in doubt → get levels and more sections.*

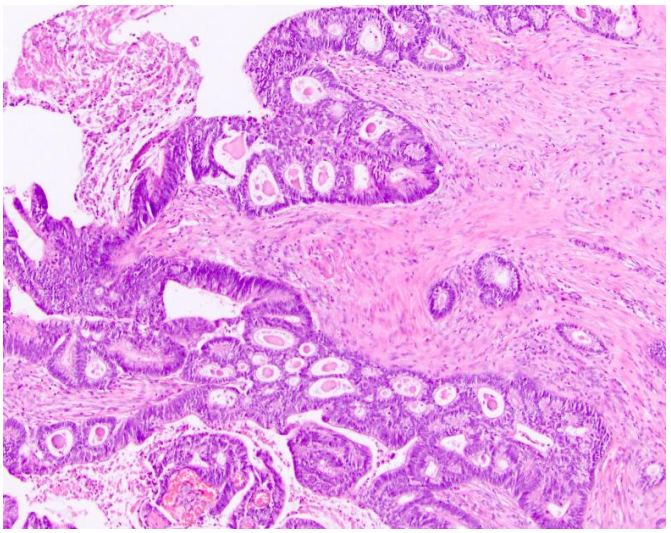
## "Pseudo-Invasion"

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

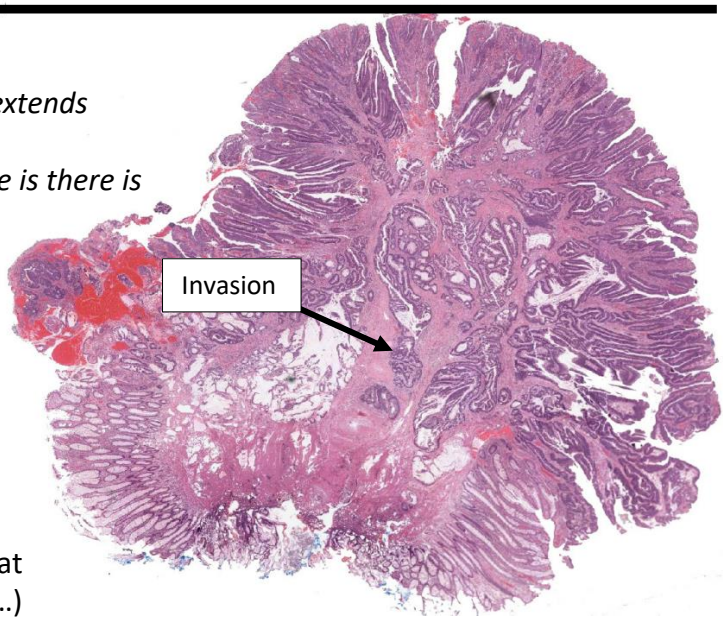


## (True) Invasion

Cytologic or architectural atypia
<u>Desmoplastic</u> stroma
<u>Infiltrative/irregular</u> growth
NOT accompanied by lamina propria
Anywhere in colon



## "Malignant Polyps"




*Adenomas containing invasive adenocarcinoma that extends through the muscularis mucosa into the submucosa.*
*(CIS and intramucosal carcinoma are excluded as there is there is minimal metastatic risk)*

Polypectomy and local excisions (e.g., ESD) for early CRC may suffice as the definitive treatment of early colorectal carcinoma (pT1 tumors).

Proper assessment of the specimens is needed to assess the risk of residual carcinoma and adverse outcomes (nodal or distant metastasis).

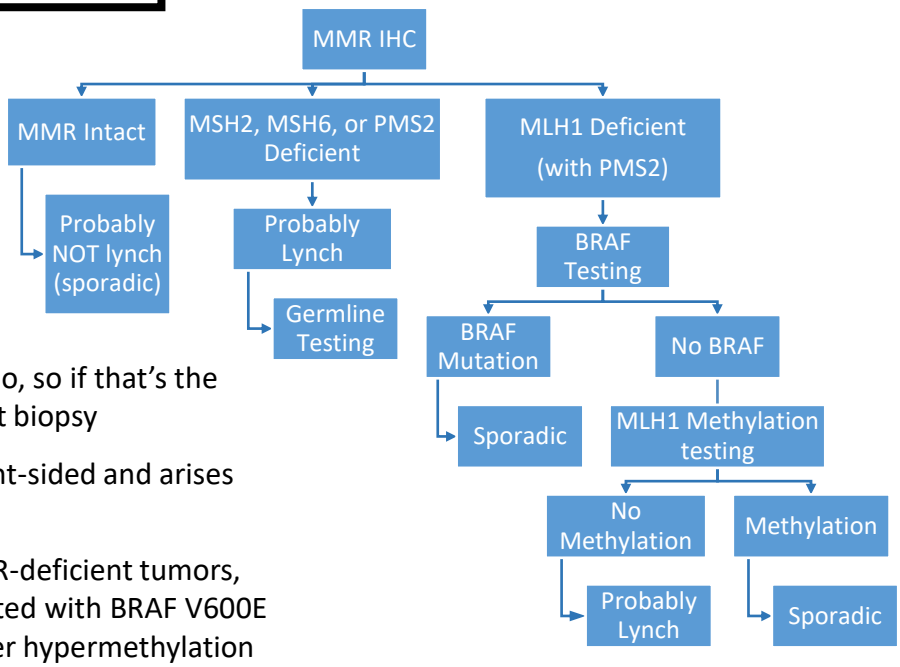
<u>High risk findings</u> (for which additional therapy, likely at least colectomy, is necessary to get lymph nodes, etc…)

- High-grade carcinoma
- Tumor less than 1mm from resection magin
- Lymphatic/venous invasion
- High-grade tumor budding
- Deep submucosal invasion (usually >2mm)
- Broad invasion (>4mm)

## Mismatch Repair Enzyme Testing

**Universal screening of all new CRC.**
Do IHC first (see algorithm), can also do MSI testing by PCR.

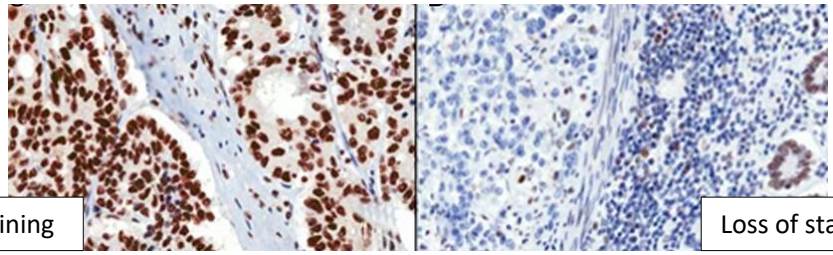
Looking for LOSS of staining.
Normal is intact staining of all 4 MMR enzymes.




Potential pitfall: ↓MSH6 post-chemo, so if that's the case, consider testing pre-treatment biopsy

Lynch-related CRC is more often right-sided and arises from adenomas

Compared to sporadic tumors, MMR-deficient tumors, that come from SSP/A's, are associated with BRAF V600E mutations and then MLH-1 promoter hypermethylation and MLH1 loss of expression



## Some Molecular

**<u>Chromosomal Instability Pathway (Non-hypermutated Pathway)</u>:** ~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)

**<u>Microsatellite Instability (MSI) Pathway (Hypermutated Pathway)</u>:** ~15% of CRC.
<u>Sporadic:</u> BRAF mutation→ MLH1 promoter hypermethylation → Inactivation of mismatch repair (MMR) enzymes → Serrated polyp → Carcinoma

<u>Lynch-associated:</u> Germline mutations in MMR proteins→ loss of heterozygosity→ Adenoma → Carcinoma. Lots of mutations → more immunogenic → more inflammatory response to tumor → better outcome. Also, responds to check point inhibitors (e.g., anti-PD-L1 drugs)

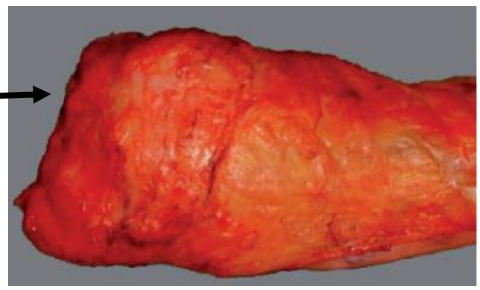
**<u>Ultramutated Pathway</u>:** ~3% of CRC.
*POLE* (DNA replication enzyme) mutation → lots of mistakes with DNA replication → Ultramutated tumor. Better prognosis and response to anti-PD-L1.

## Rectal Cancers Stuff

Rectal cancers are unique among colon cancers in that they are often treated preoperatively with chemoradiation (unless they are very early).

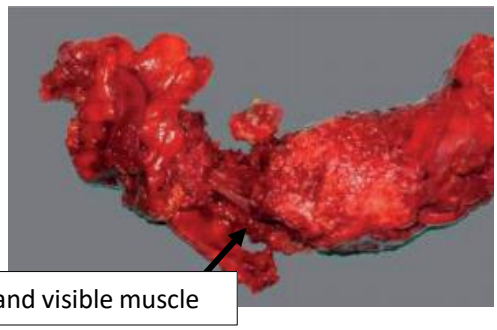
The quality of the surgical technique (LAR or APR) is a key determinant of local recurrence and long-term survival. ***<u>Grossly</u>***, asses the completeness of the non-peritonealized mesorectal excision. Score according to **worst** area.

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



**<u>Nearly Complete:</u>**
Moderately bulky mesorectum
<u>Minor irregularities</u> (>5mm), but no visible muscle

**<u>Incomplete:</u>**
Little bulk to mesorectum. Irregular surface.
*<u>Muscularis propria visible</u>*




**Circumferential (non-peritonealized) Resection Margin:**
Considered <u>positive</u> if tumor is microscopically <u><1mm</u> from inked circumferential margin (high risk of recurrence)

| | Mesorectum | Defects | Coning | Circumferential Resection Martin |
|---|---|---|---|---|
| **Complete** | Intact, smooth | Not deeper than 5mm | None | Smooth, regular |
| **Nearly Complete** | Moderate bulk, irregular | No visible muscularis propria | Moderate | Irregular |
| **Incomplete** | Little bulk | Down to muscularis propria | Moderate/ marked | Irregular |

*Modified from: AJCC staging Cancer Staging Manual. 8th Edition.*