Dr. Shannon McCall
Neoplasms of the GI Tract

APPROVED

Assistant Professor

Department of Pathology

shannon.mccall@duke.edu

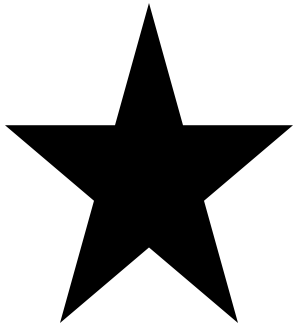
Benign malignant neoplasms in this lecture in any cell of origin are fair game

most important class of neoplasms; most like to go wrong:
- continuous turnover
- exposed to everything that we put inside our body (unique to GI epithelium)

GI Neoplasms

- Epithelium - adenomas, carcinomas
- Enterochromaffin cells - carcinoid tumors. (aka, “Neuroendocrine tumors”)
- Lymphocytes - lymphomas
- Mesenchymal cells - smooth muscle tumors, GIST

GI Neoplasms



Epithelium - adenomas, carcinomas

- ***Enterochromaffin cells - carcinoid tumors.***
- ***Lymphocytes - lymphoma***
- ***Mesenchymal cells - smooth muscle tumors***

GI Carcinomas

	New Cases per yr in US*	5 yr. Survival* (all stages)
Esophagus	16,640	17%
Stomach	21,000	26%
Colorectal	147,000	65%
Pancreas	43,000	6%

Less common for her in the GI clinic - we don't like to see these given their survival and fortunately we don't!

She most commonly deals with this day-to-day

***American Cancer Society 2010**

GI Tract Carcinomas
Pattern of Spread

- Local Invasion
- Lymphatic Spread - regional lymph nodes
- Distant Metastases (hematogenous)- lung, liver

starts with local invasion - T stage

N stage

M score for whether or not they have distant mets

Start at the top and move to the bottom

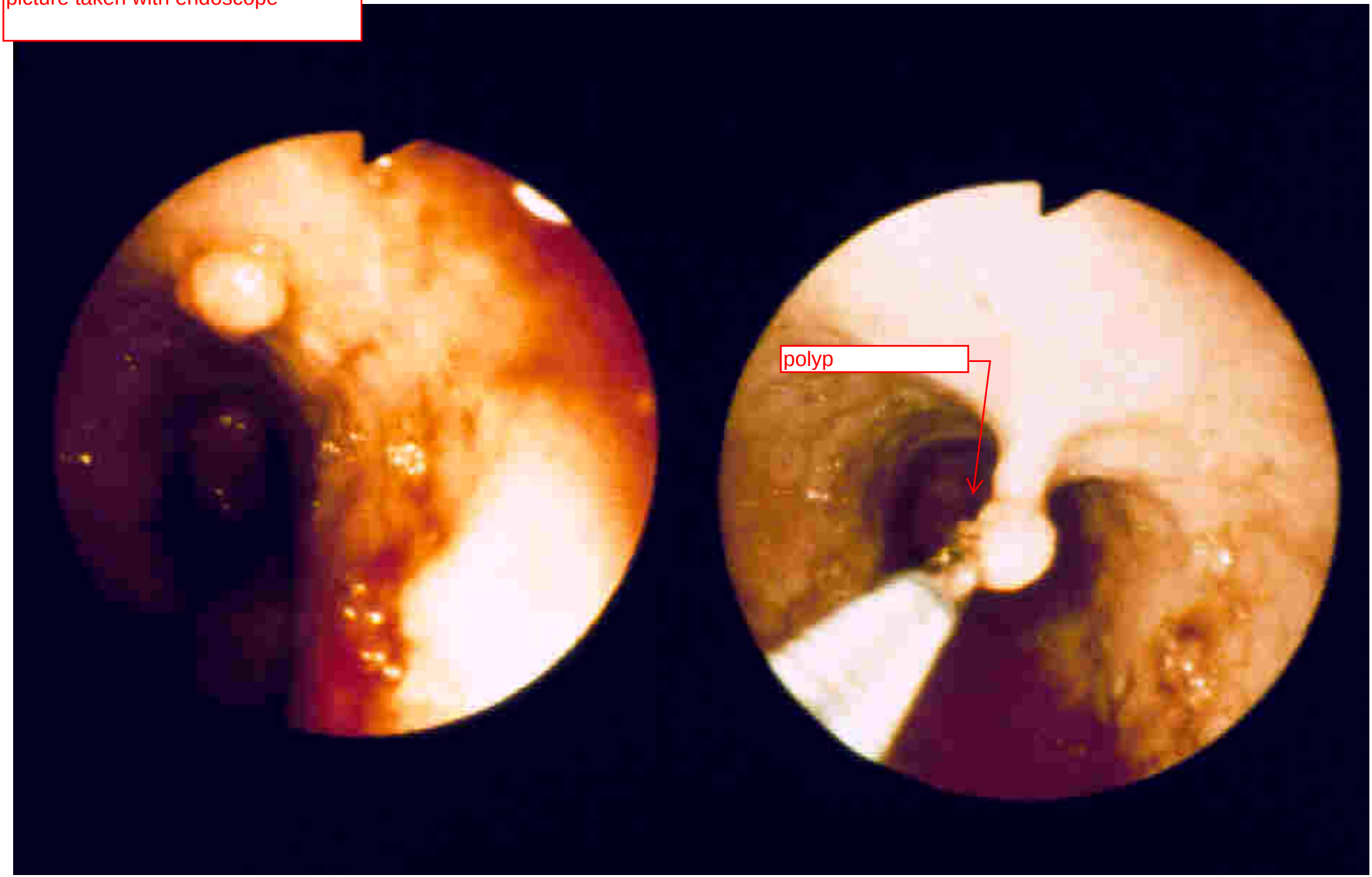
Esophagus

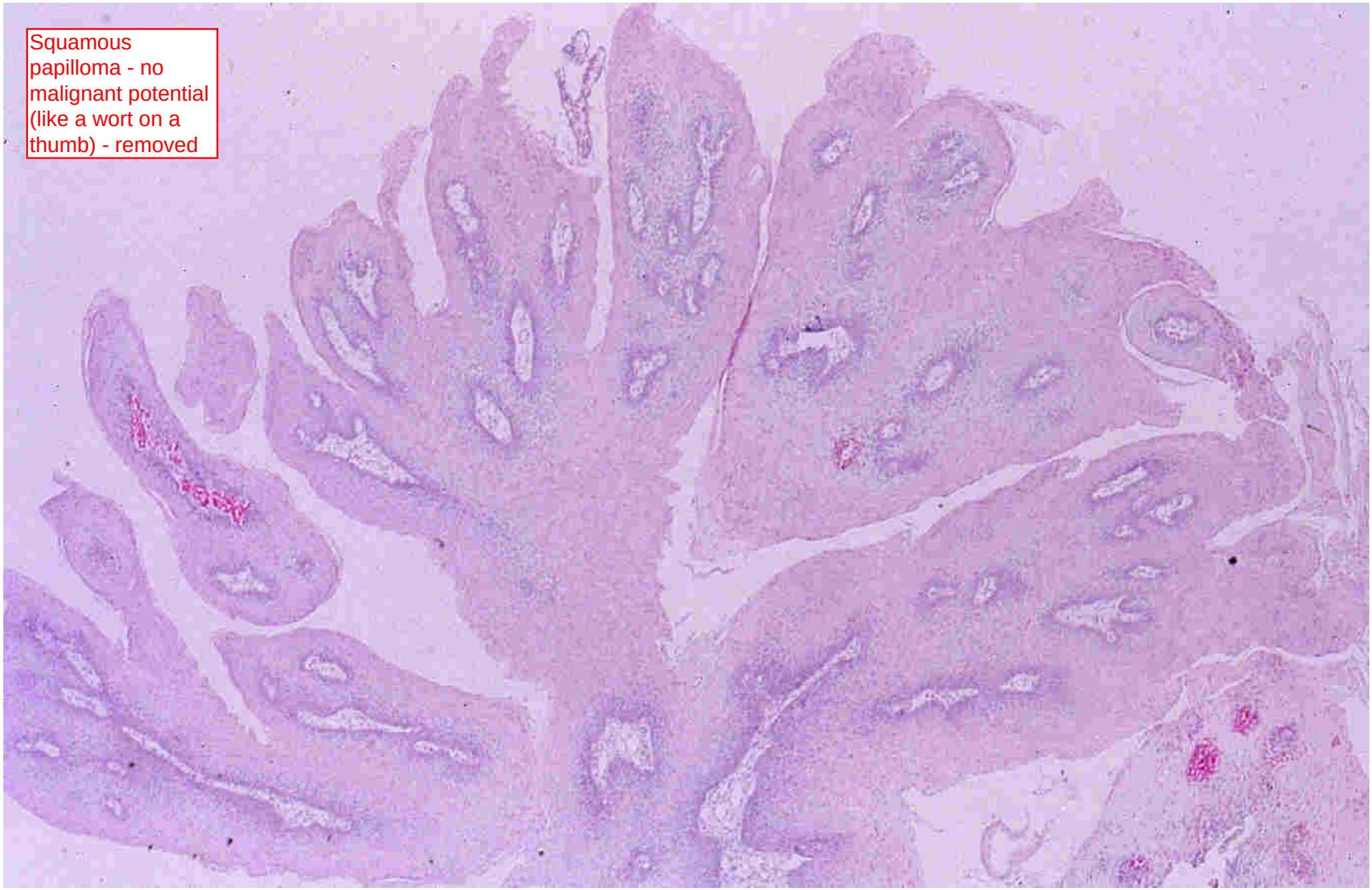
Squamous Papilloma (benign)

Squamous Cell Carcinoma

Adenocarcinoma

There are TONS of benign lesions but we'll focus on the malignant ones


picture taken with endoscope
polyp


Squamous papilloma - no malignant potential (like a wort on a thumb) - removed

malignant tumor of epithelial cells

Esophageal Carcinomas: Presentation

- Difficulty swallowing
- Pain
- Systemic effects of malignancy
  - Weight loss — because they cannot maintain nutritional status
  - Fatigue, malaise
  - Local effects of metastases

2 types of Esophageal Carcinomas

same presentation clinically for both types

- Squamous cell carcinoma
  - Remains the most common esophageal malignancy worldwide
  - Used to be most common in the US (comprised 90% of esophageal carcinomas in the 1960's)

overtaken by adenocarcinoma

- Adenocarcinoma
  - Now makes up >50% of esophageal carcinomas in the US and Western Europe

Squamous Cell Carcinoma

Has patches in the world where it is very high prevalence

- In most parts of the world 2.5 to 5 per 100,000
- In high risk areas as much as 100x this
  (China, Iran, South Africa)
- Male:Female is 3:1
- In U.S., African-American:Non is 5:1

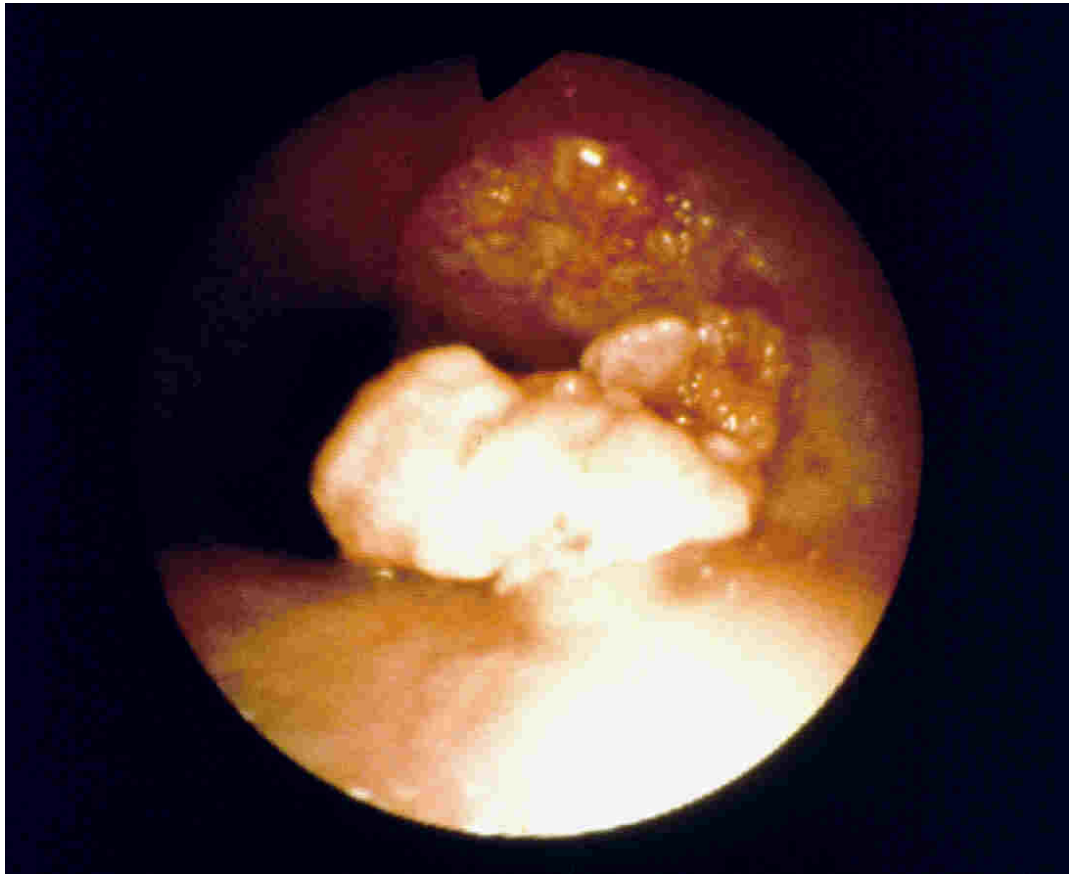
Risk Factors:
- cigarettes
- alcohol
- diet related factors (nitrates, nitrosamines, pickled foods, extremely hot beverages)

SCC - Risk Factors

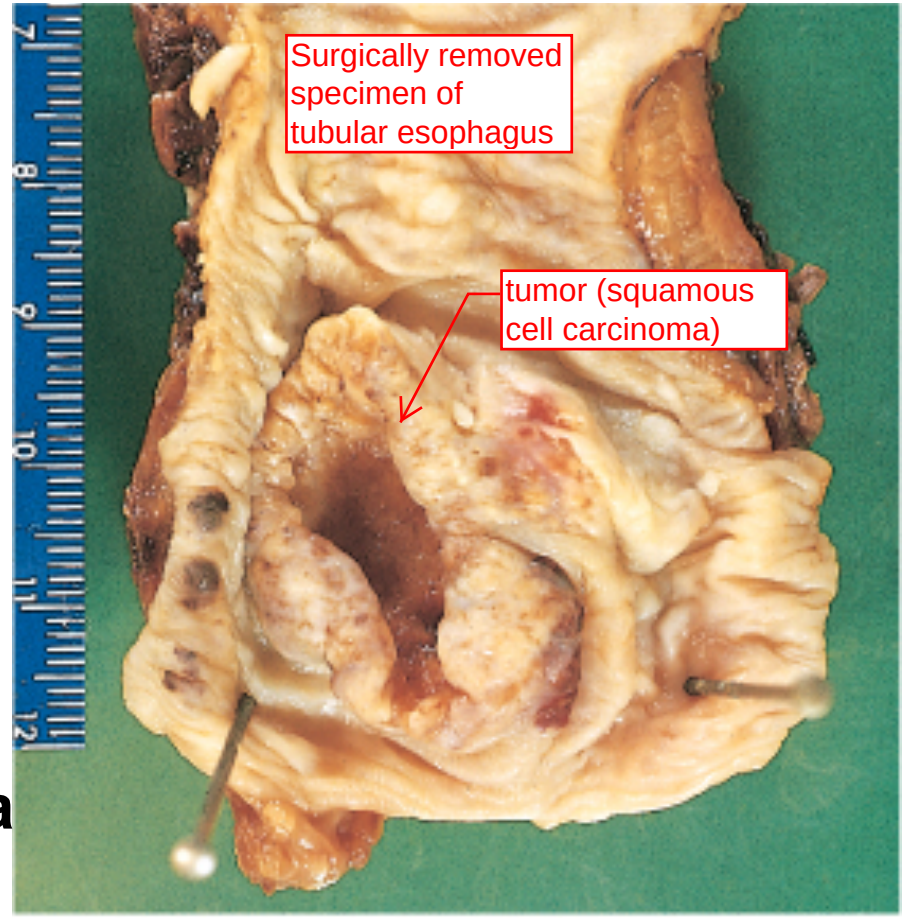
- Cigarette Smoking
- Alcohol
- Caustic injury, trauma, stricture

SCC - Risk Factors - Diet

- Deficiencies in vitamins or minerals
- Nitrate and Nitrosamine Consumption leading to chronic esophagitis
  - Pickled/smoked foods
  - Fungi in grains
- ?Thermal injury - Very hot tea



Squamous mucosa normally looks white/tan and pearly



Esophageal Squamous Cell Carcinoma

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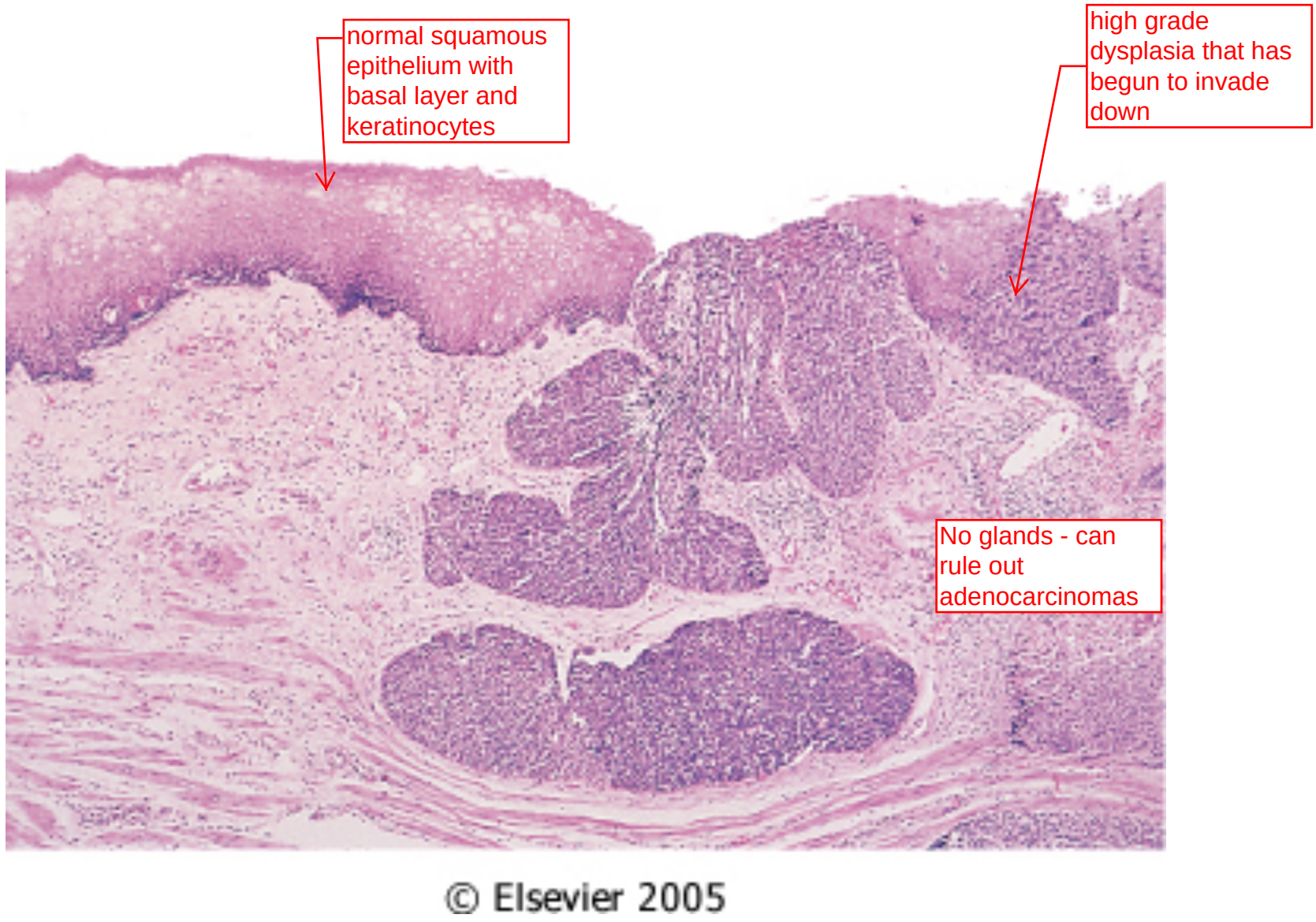

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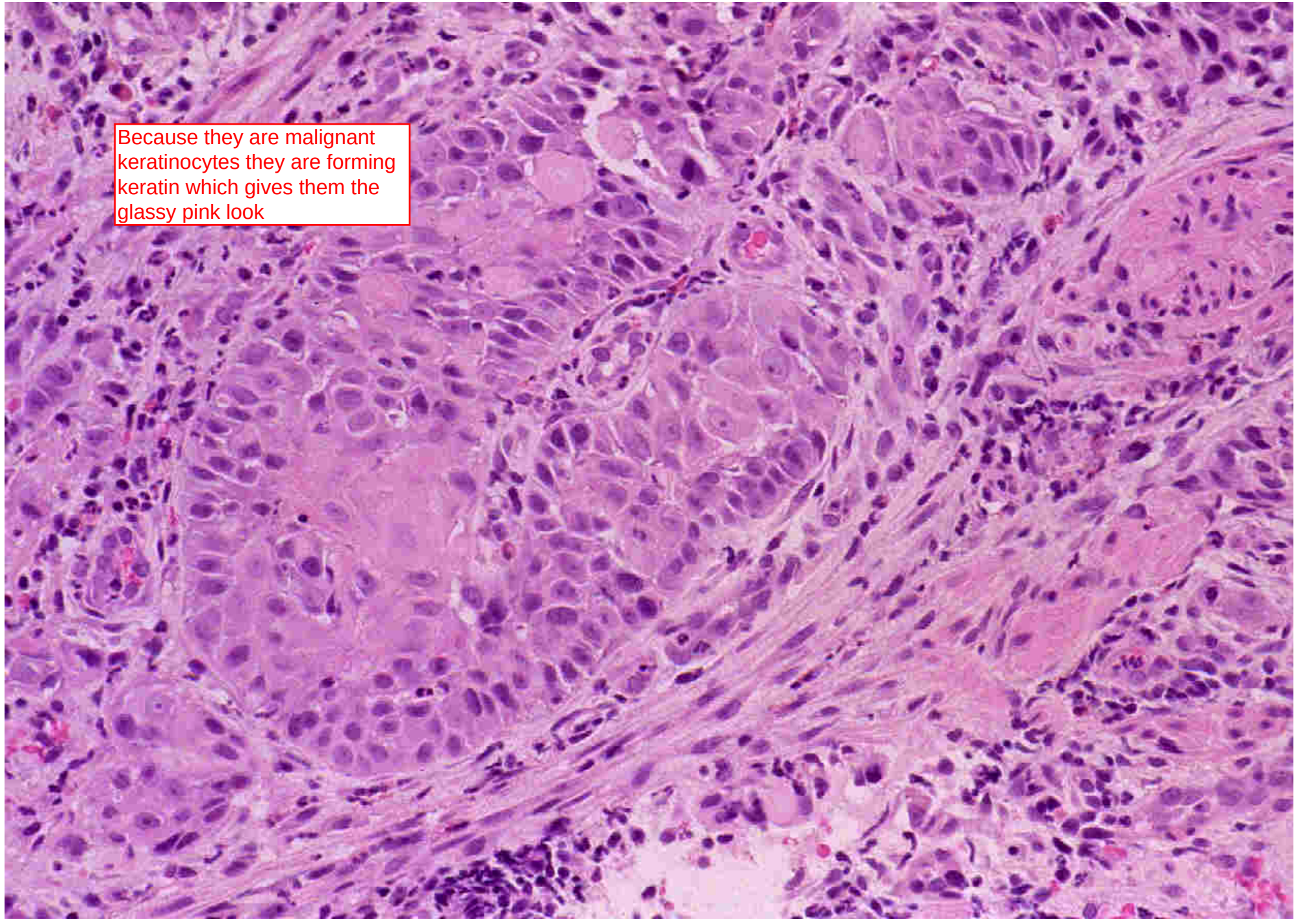

Because they are malignant keratinocytes they are forming keratin which gives them the glassy pink look

How do we get adenocarcinoma in squamous epithelium?
- Metaplasia (see next slide)

Esophageal Adenocarcinoma

Requires a larger explanation

The increasing incidence of adenocarcinoma in the distal esophagus may be related to increased reflux.

Obesity increases risk for reflux which increases risk for adenocarcinoma

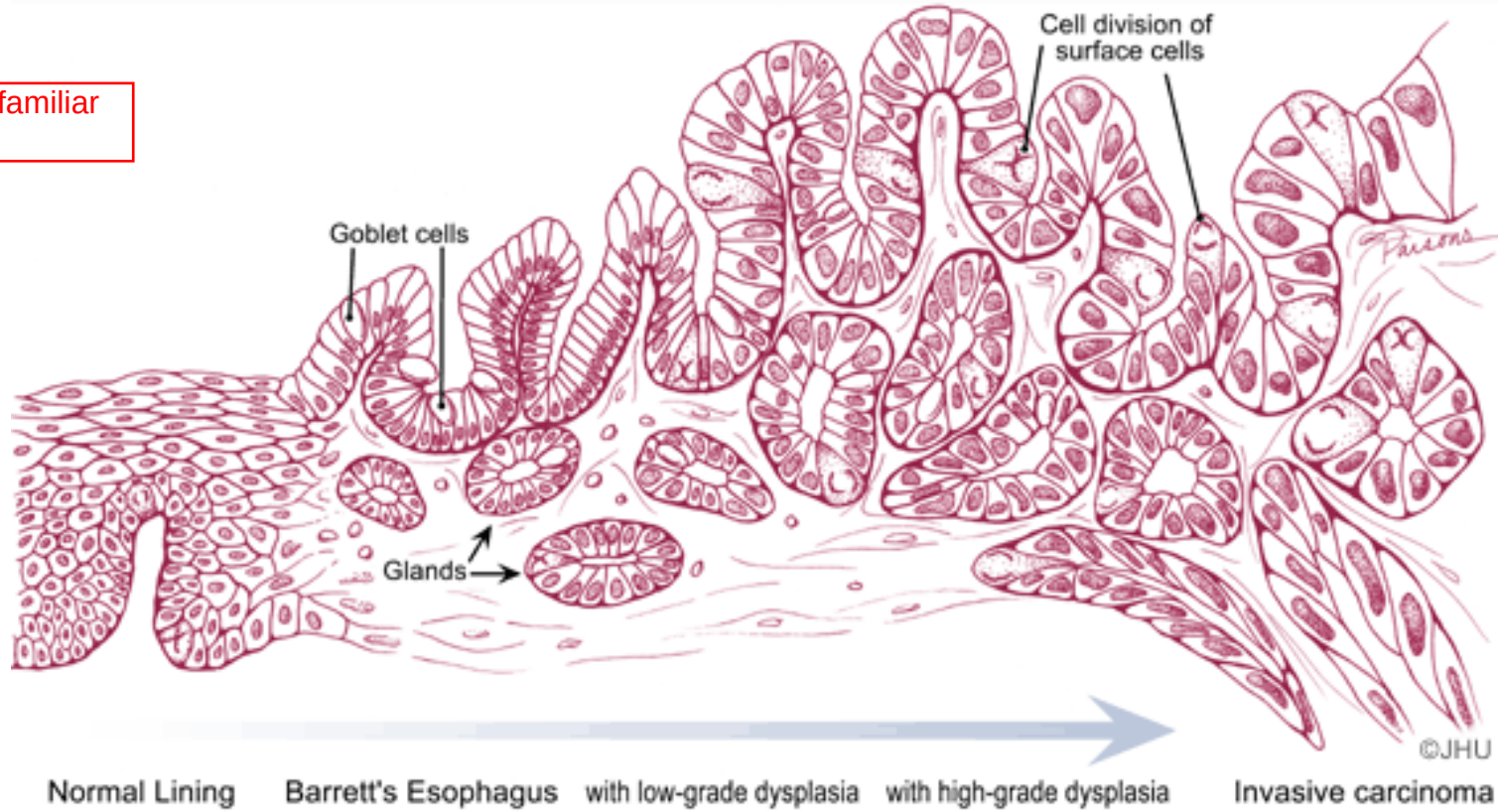
The demographics for esophageal adenocarcinoma are the same as those for Barrett's esophagus (Caucasian, older, male).

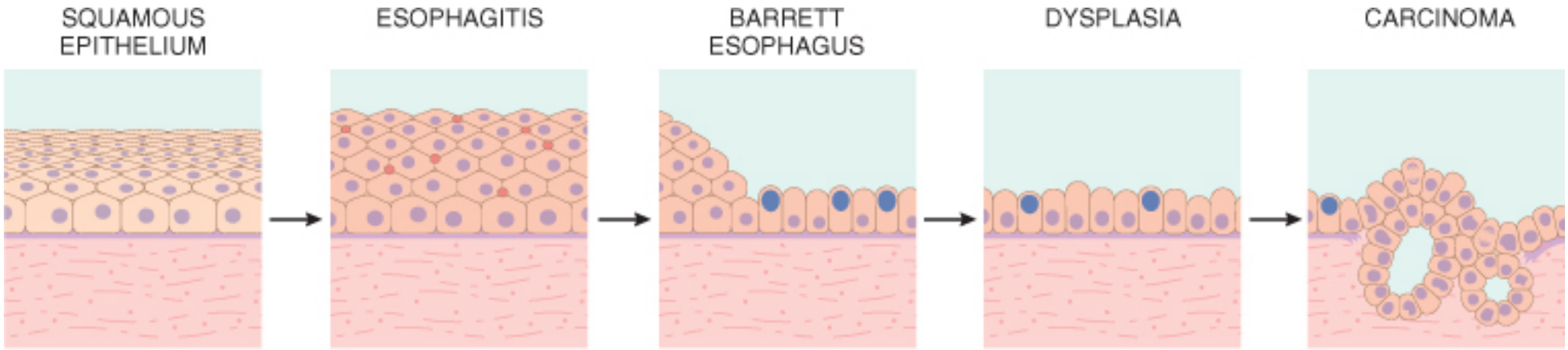
If you have consistent reflux or injury the squamous epithelium becomes metaplastic and recapitulates small intestinal epithelium (glandular or columnar) and you are then at increased risk for dysplasia and eventually carcinoma

Be familiar with this sequence of events (three slides on this one fact)

Reflux Esophagitis → Intestinal Metaplasia (Barrett's Esophagus) → Dysplasia → Invasive Adenocarcinoma

Again, be familiar with this





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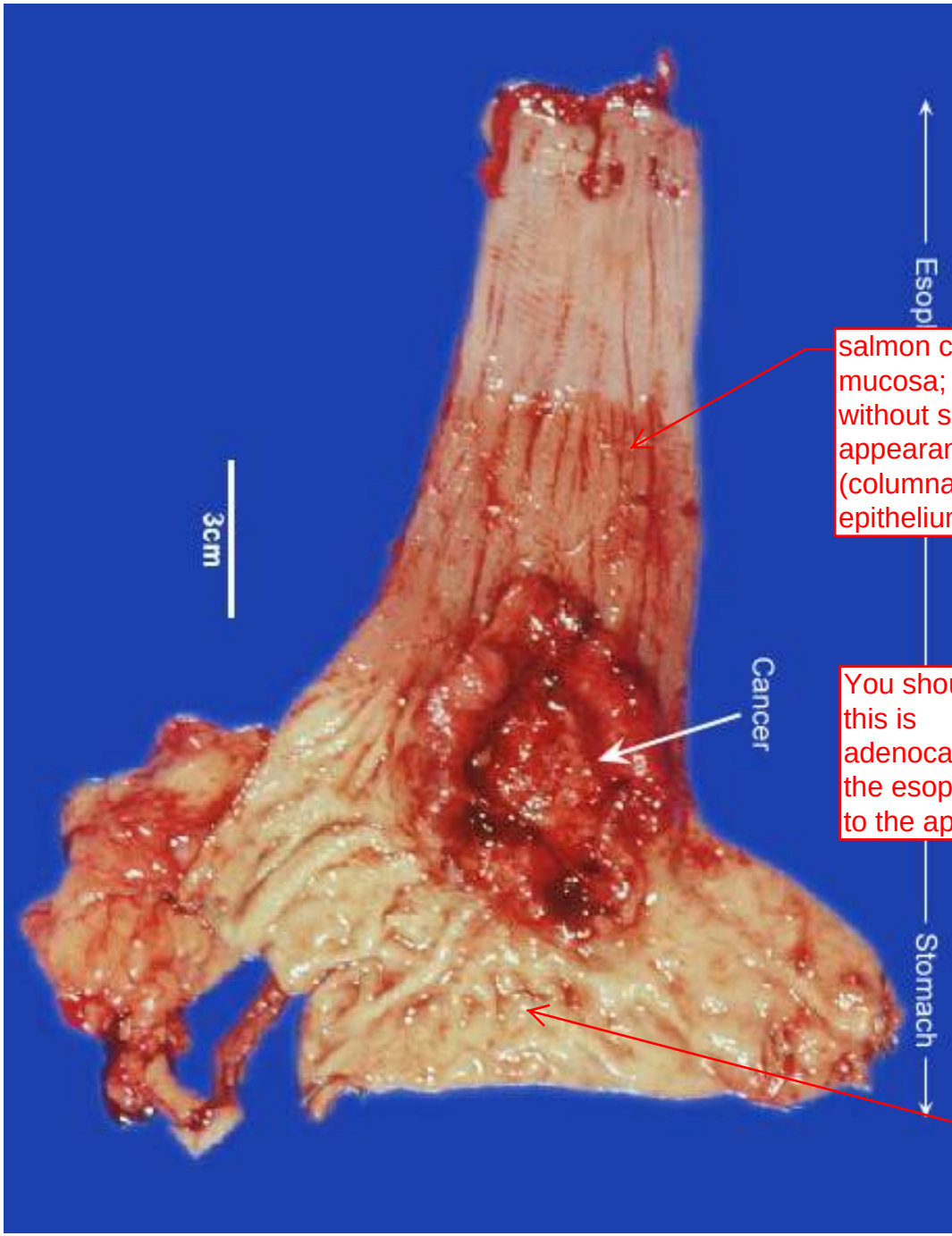
What Does Barrett’s Esophagus Look Like?



Main difference:
- for squamous cell it was light tan, squamous mucosa but this tumor is not arising in white tan

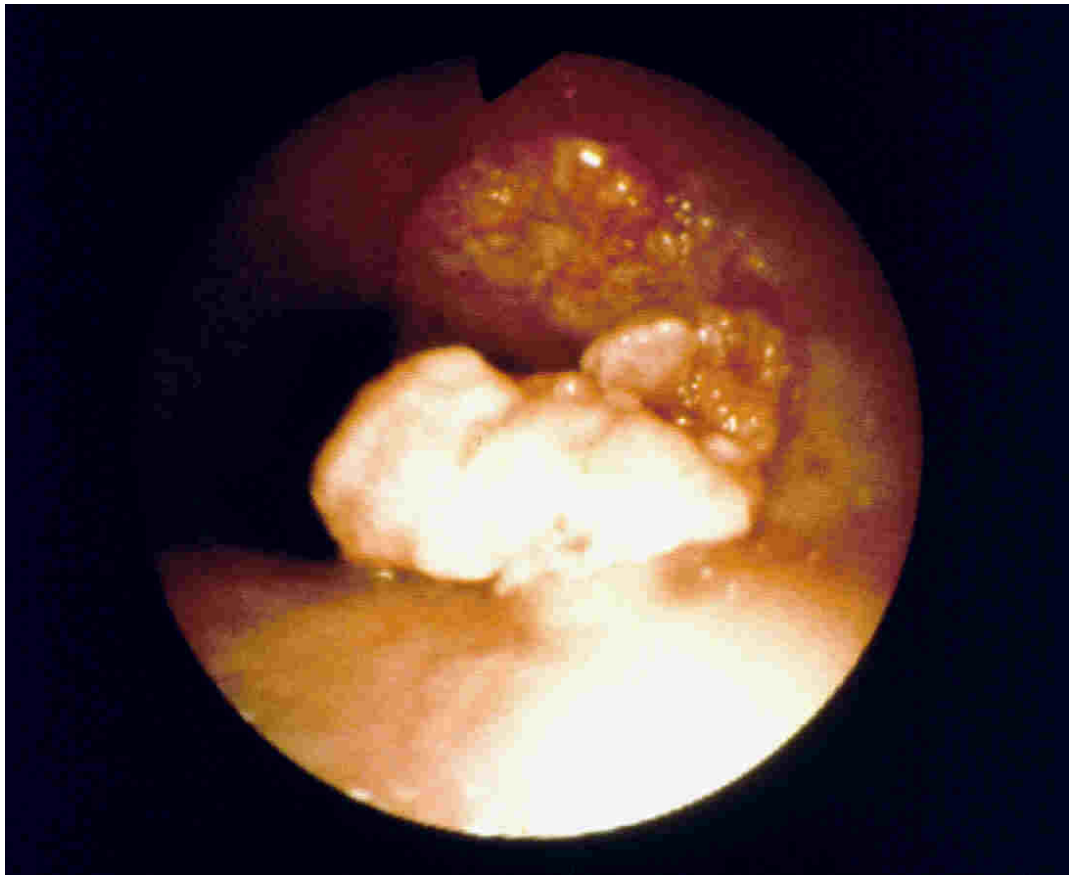
salmon colored mucosa; velvety without squamous appearance (columnar epithelium)

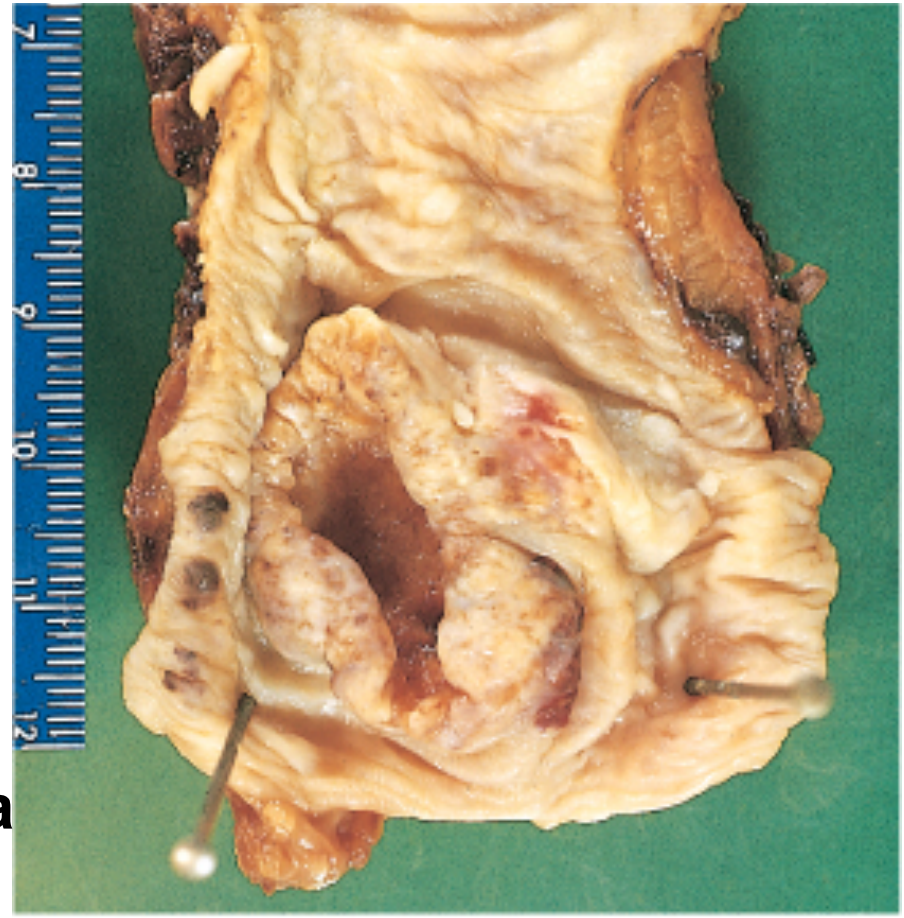
You should know this is adenocarcinoma of the esophagus due to the appearance

rugal folds

Invasive Adenocarcinoma arising in Barrett's Esophagus:

Can you spot the Barrett's?





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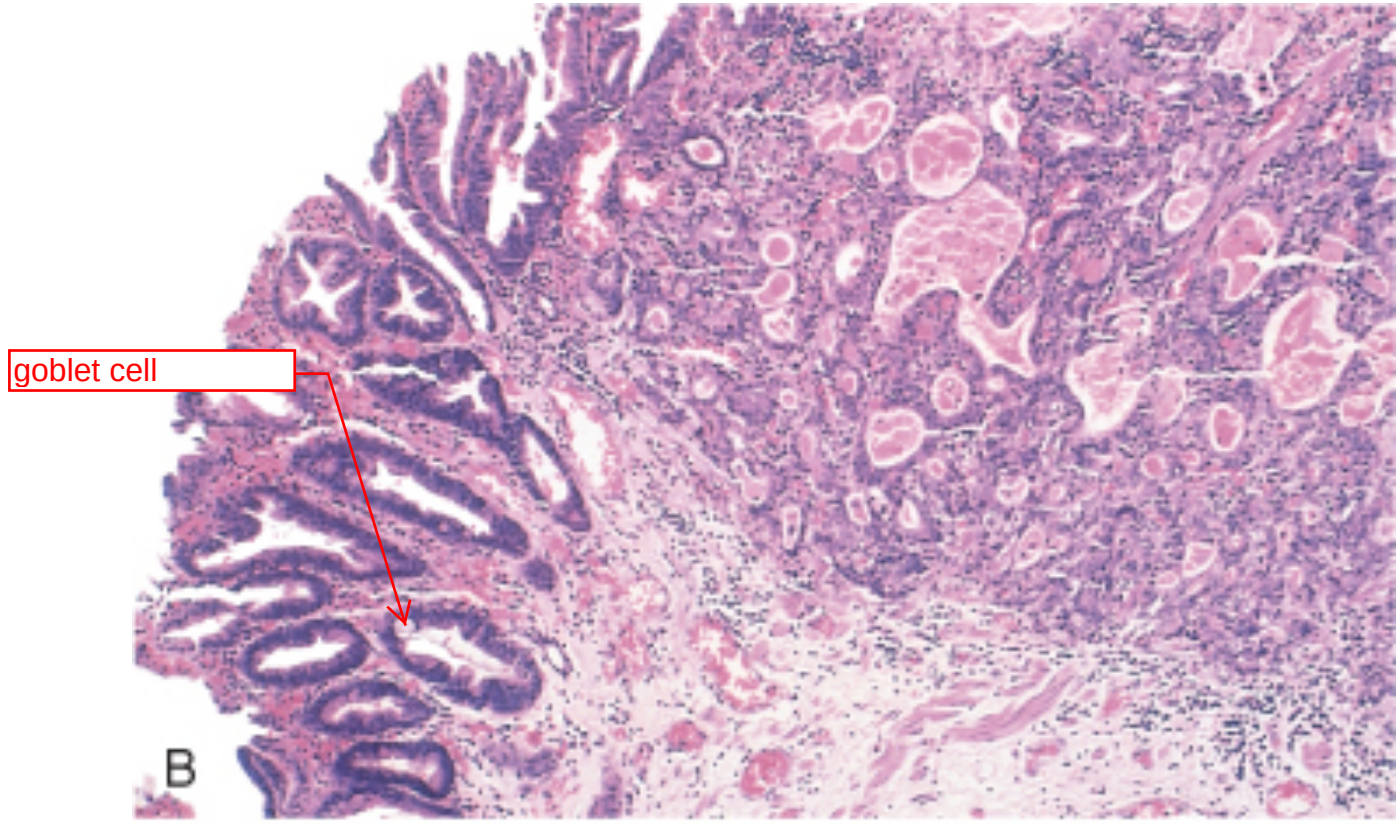
Esophageal Squamous Cell Carcinoma

Note: No Barrett's in Background



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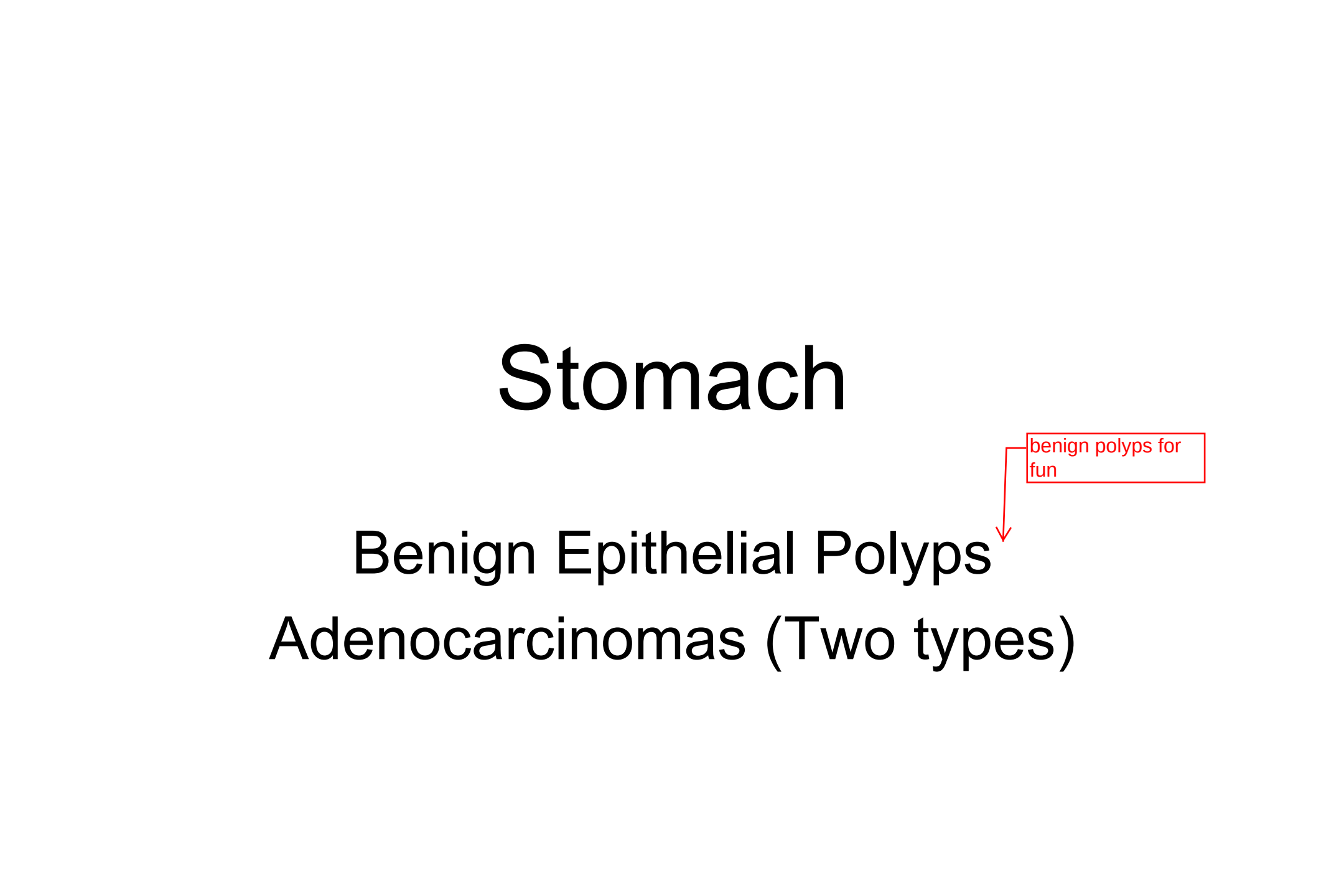
There is no way to even know that you are in the esophagus but once you know this you would see glandular mucosa with goblet cells and if this is truly esophagus then it must be Barrett's (you can argue about whether or not it is dysplastic)

Invasive Adenocarcinoma of the Esophagus, Arising in Barrett's Esophagus

Stomach



Benign Epithelial Polyps

Adenocarcinomas (Two types)

Two kinds of polyps with no clinical consequences

Hyperplastic polyps and Fundic-Gland Polyps

Reaction to injury with no malignant potential

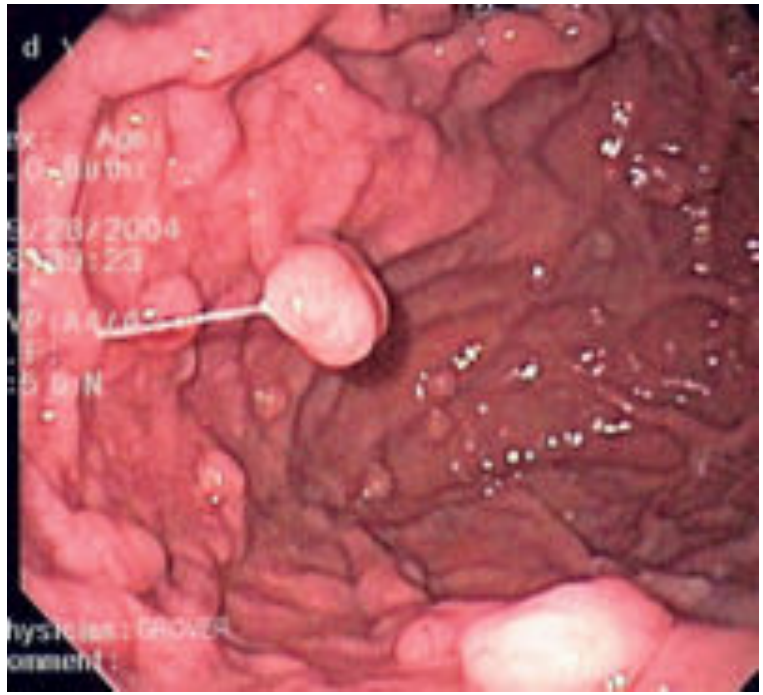
- Hyperplastic polyps are exceedingly common – risk factors are inflammatory and overlap with those for chronic gastritis

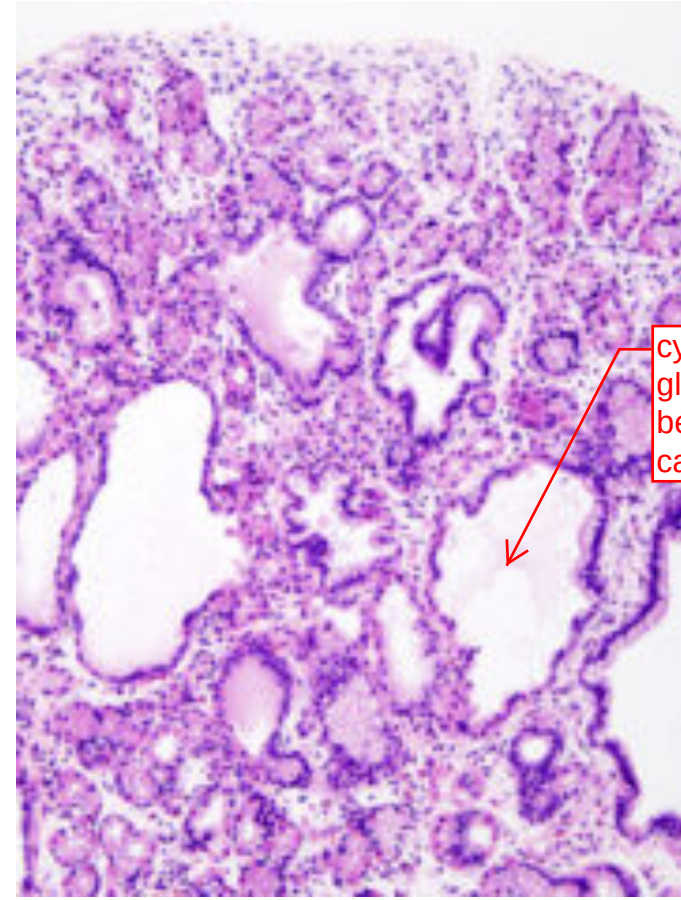
- Fundic-gland polyps are also very common – risk factor is parietal cell hyperplasia resulting from PPI's

PPIs turn off proton pumps and the body sends signals (needs more acid) and you get increased parietal cell mass in stomach making them develop cystic dilation (polyps)

Very low risk of becoming malignant - still being worked out whether this is possible

Fundic Gland Polyp





Stomach

Adenocarcinoma:

Two main types

There are a lot of malignant tumors of the stomach but we will focus on these

Gastric Adenocarcinoma, Intestinal Type

More common type

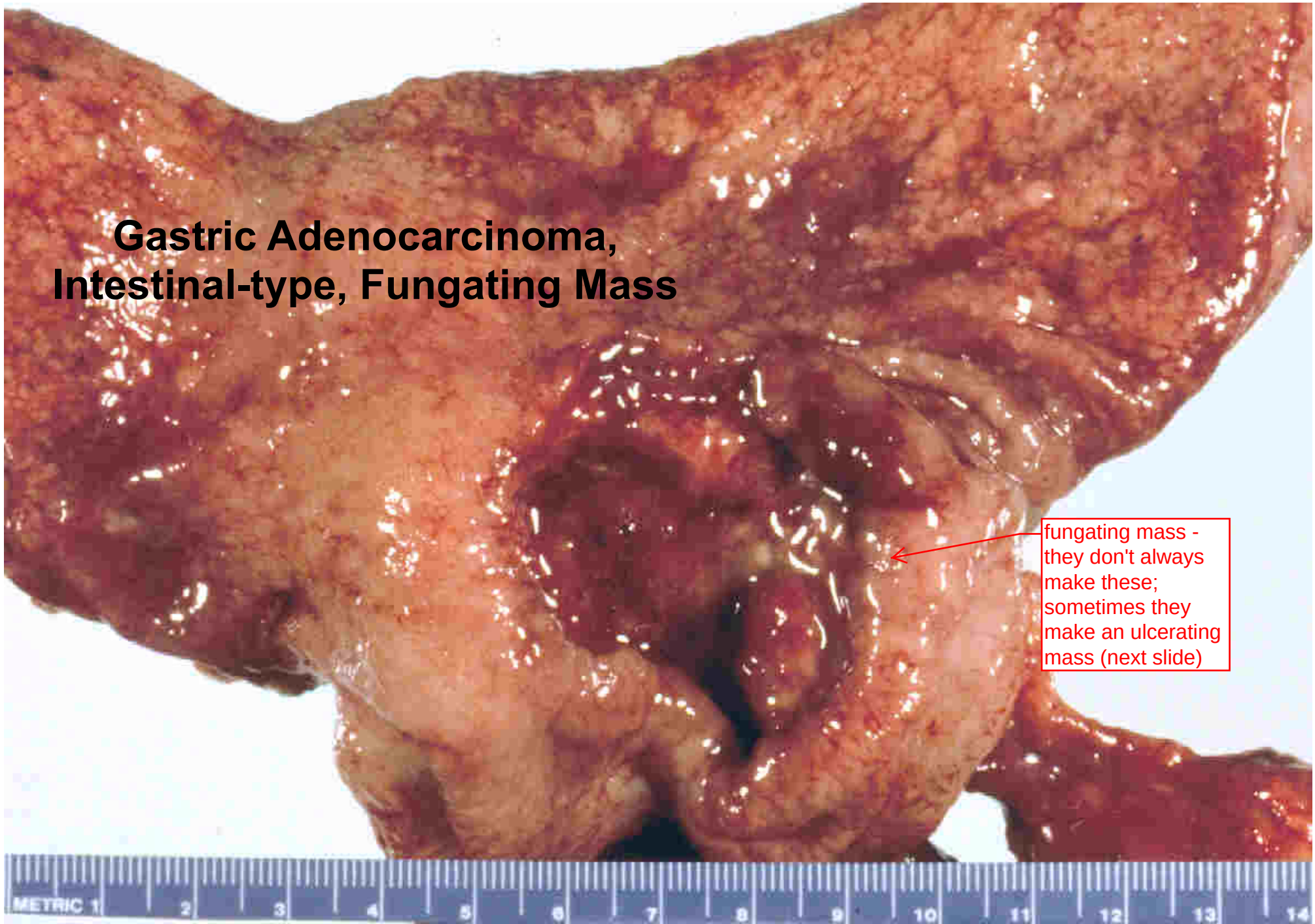
- Risk Factors
  - Diet
  - Previous Gastrectomy

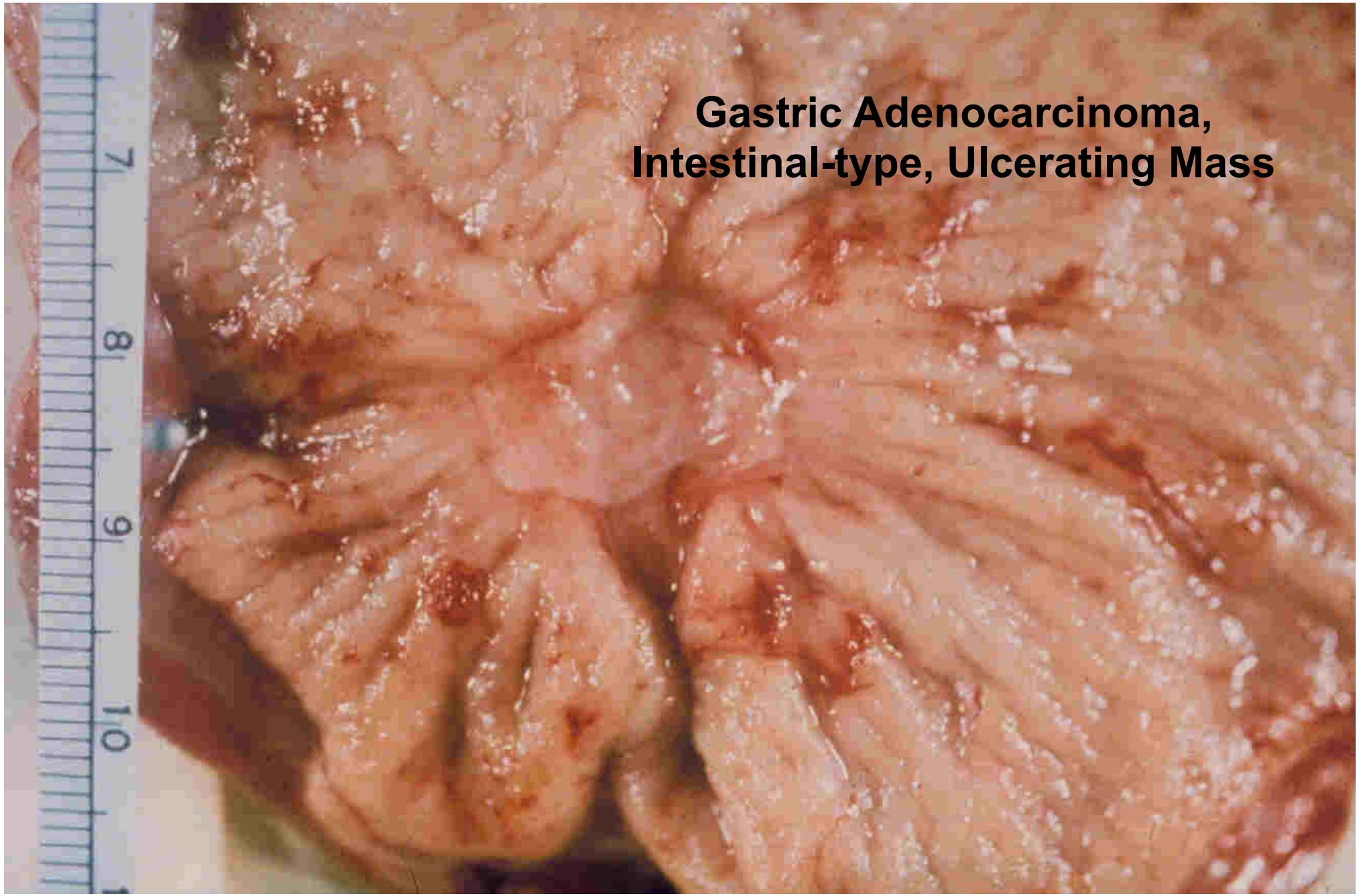
alters hormone balance

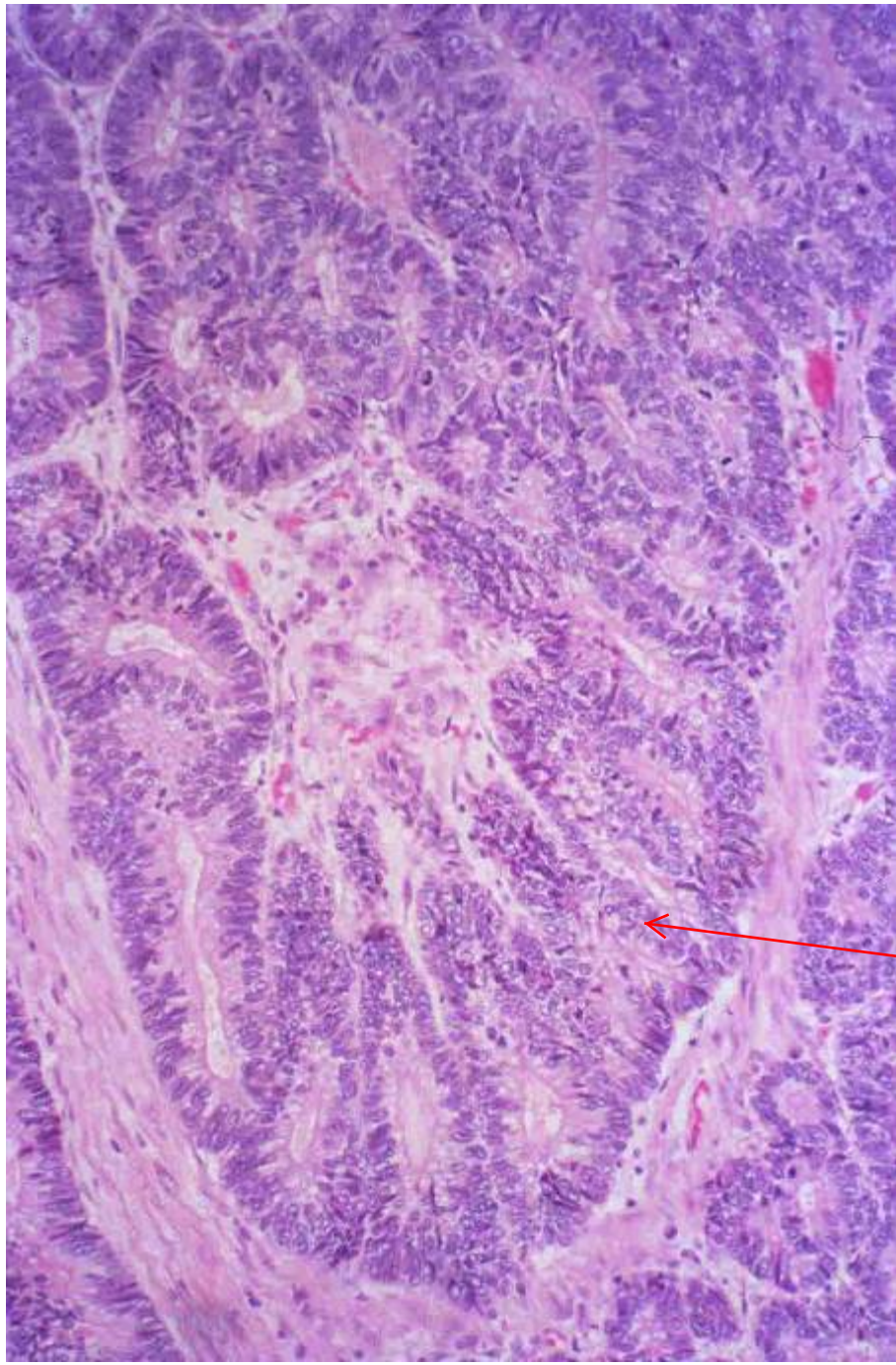
  - Atrophic Gastritis (Intestinal Metaplasia)
- Decreasing in Incidence, paralleling decline in *H. pylori* infection

similar to intestinal metaplasia of the esophagus - can be the result of *H. pylori* infection or autoimmune etiology

WHO maintains list of possible/probable and Class I carcinogens. They put cell phones on the list of possible carcinogens with things like dirt and automobile exhaust. H. pylori is on the list of Class I carcinogens (along with cigarettes and tanning beds)


Gastric Adenocarcinoma,
Intestinal-type, Fungating Mass
fungating mass - they don't always make these; sometimes they make an ulcerating mass (next slide)
METRIC 1 2 3 4 5 6 7 8 9 10 11 12 13 14


Gastric Adenocarcinoma,
Intestinal-type, Ulcerating Mass



Gastric Adenocarcinoma, Intestinal-type

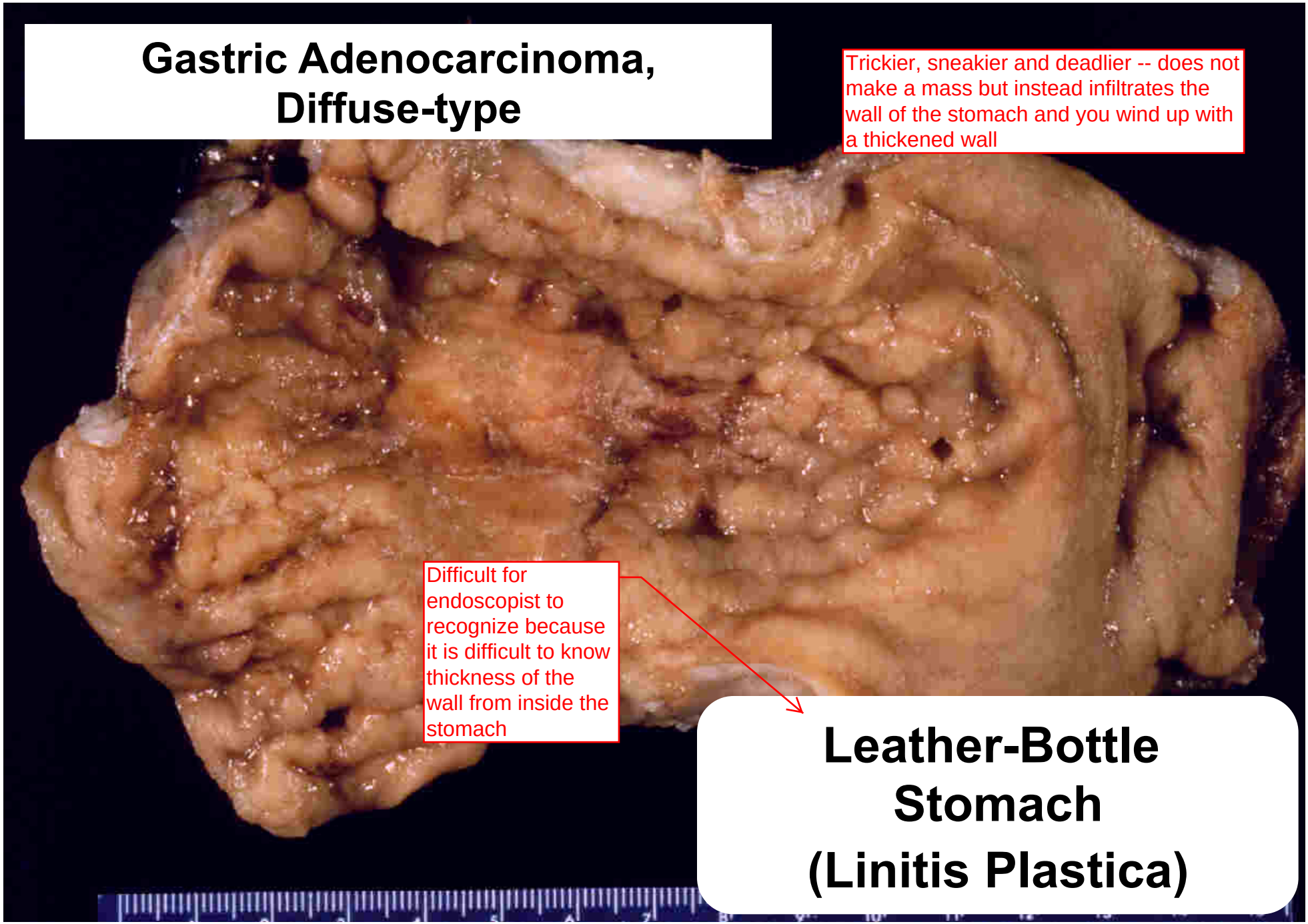
Gastric Adenocarcinoma, Diffuse Type

- Increasing in frequency
- More common in younger patients
- Risk factors are being elucidated *(not chronic gastritis/IM/dysplasia)*

Less common with a less well understood mechanism

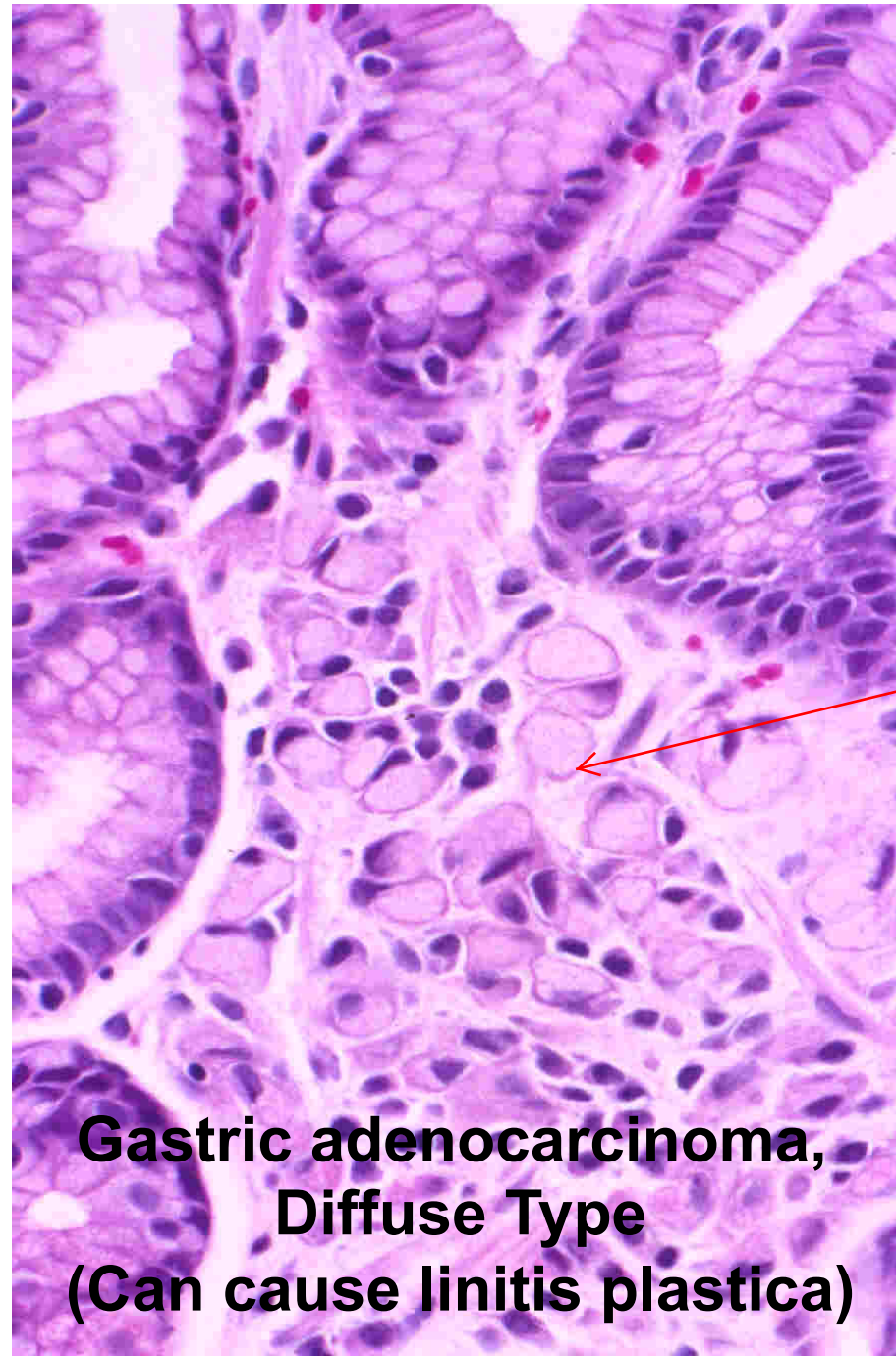
Gastric Adenocarcinoma, Diffuse-type

Trickier, sneakier and deadlier -- does not make a mass but instead infiltrates the wall of the stomach and you wind up with a thickened wall



Difficult for endoscopist to recognize because it is difficult to know thickness of the wall from inside the stomach

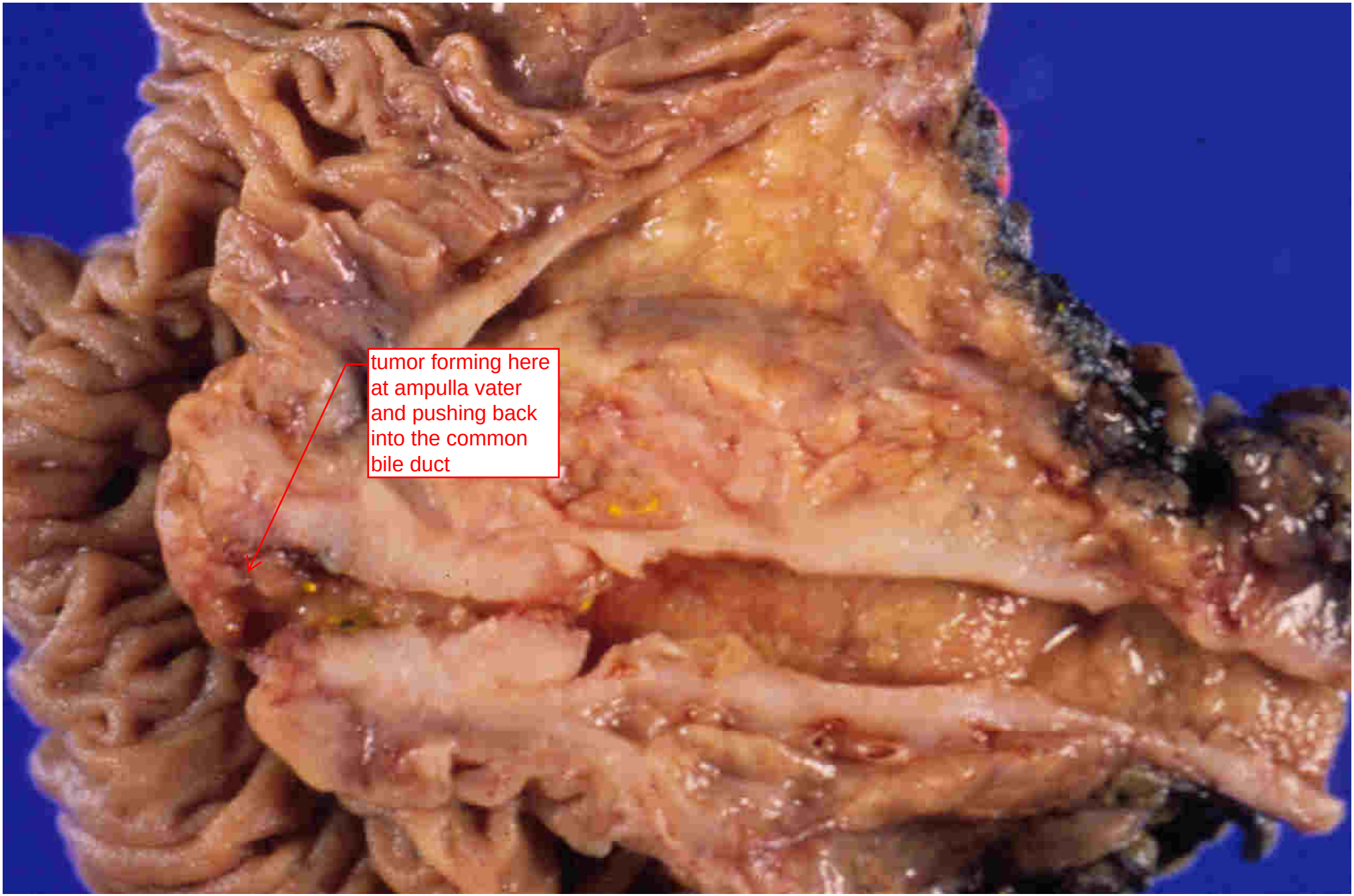
Leather-Bottle Stomach (Linitis Plastica)


Tumor (signet ring carcinoma a.k.a. diffuse type adenocarcinoma) - these cells have lost their cell-cell adhesion; makes mucin internally (hence is an adenocarcinoma) > each droplet is a mucin droplet
Gastric adenocarcinoma, Diffuse Type (Can cause linitis plastica)

Two big things to remember for the rest of your life (not necessarily for test on Monday):
- SI is enormous! always turning over and we dump a bunch of "stuff" from stomach into the SI but we don't get too many tumors of the SI (mystery! -- how is it protected?)
- the exception is the proximal duodenum where the ampulla of vater opens > this is the only area where we see cancer form (very very rare in the distal intestine)

Small Intestine

Ampulla of Vater


tumor forming here
at ampulla vater
and pushing back
into the common
bile duct

Colonic Epithelial Neoplasms

Adenoma (= Polyp with Low-Grade Dysplasia)
Adenocarcinoma

Adenoma → Carcinoma

usually a polypoid lesion in the colon that is pre-malignant (related to downstream development of cancer)

- Residual adenoma is often found adjacent to an adenocarcinoma
- Adenomas are more common in colons with carcinomas than in other colons
- The age related rise in frequency of colon adenomas precedes that of adenocarcinomas by 5-10 year

Lots of supporting evidence that adenoma led to carcinoma

Adenoma ⟶ Carcinoma

- Removing colon polyps seems to reduce the incidence of colon carcinoma

  (Colon polyp/cancer surveillance)

  – **Initial screening colonoscopy**

  – **Removal of polyps**

  – **Repeat colonoscopy at interval dictated by endoscopic and pathologic findings**

Set guidelines based on what is seen endoscopically tells them when to bring the pt back for another endoscopy (are there multiple adenomas? is there high grade metaplasia? ...)

Risk Factors for Colon CA

any colon cancer

- Western diet (high meat, low fiber)
- Family history of colon carcinoma
- Ulcerative Colitis (Less Crohn's Dz)
- Hereditary syndromes
  - Familial Adenomatous Polyposis Syndrome (FAP)
  - Hereditary Nonpolyposis Colorectal Cancer Syndrome (HNPCC)

Low residue diets - theory: by the time food stream gets to colon there is not a lot of fiber left and the toxins are more concentrated so there is exposure factor that we discussed

RF if you have colonic involvement

All colon cancers can be divided into two main groups of how they got colon cancer

Molecular Events of Colorectal Carcinogenesis

multiple-hit hypothesis (loss of APC gene happens first)

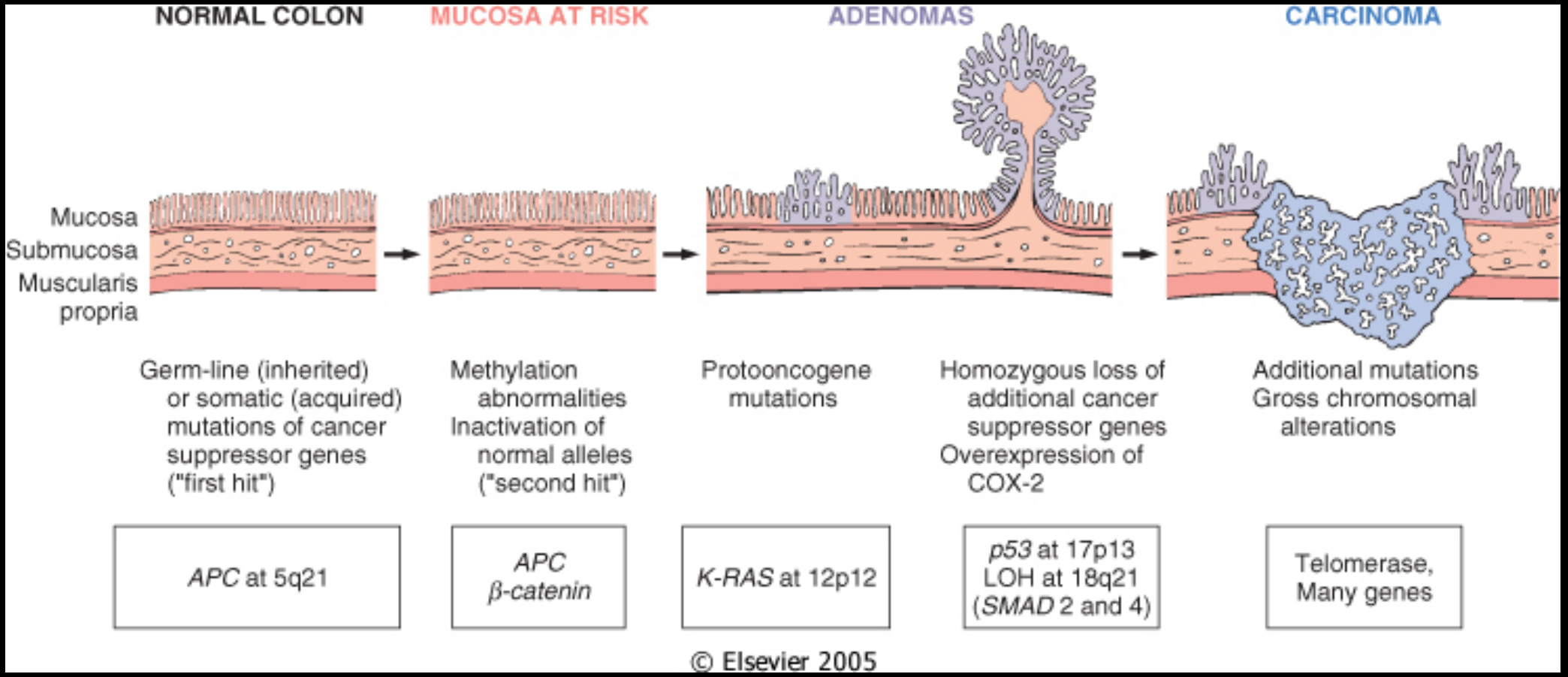
- Chromosomal instability – 85% colon cancer
  - Loss of the APC gene (5q) is one of earliest events in sporadic cancers assoc. w/ chromosomal instability
  - APC is also the gene mutated in Familial Adenomatous Polyposis, FAP

FAP pts are born with first hit to APC gene and it does not take long to get second hit (they get it by their teens whereas normal individuals get it by 50s/60s.

- Microsatellite instability – 15% colon cancer
  - Methylation of MLH1 promoter in sporadic cases
  - Hereditary Nonpolyposis Colorectal Cancer Syndrome: HNPCC cases show Microsatellite Instability

If born with mutation in one of these proteins you have one hit already. Proteins:
MLH1
MSH2
MSH6
PMS2

4 important genes that make DNA mismatch repair proteins that come behind the polymerase and make checks for error and repair those errors. If these proteins do not function normally you accumulate more hits. By 60 you can methylate MLH1 protein and you develop microsatellite instability pathway to colorectal carcinogenesis



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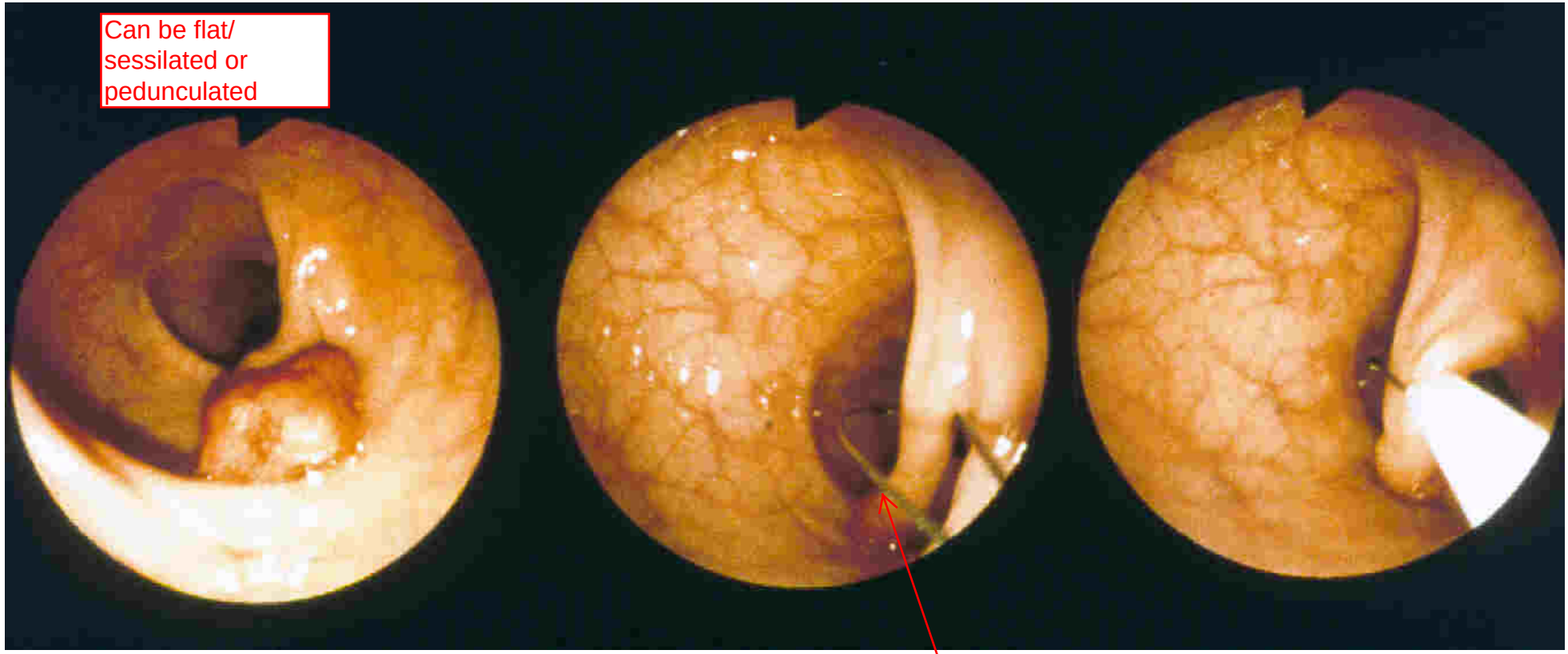
Adenomas = Polyps with Low Grade Dysplasia

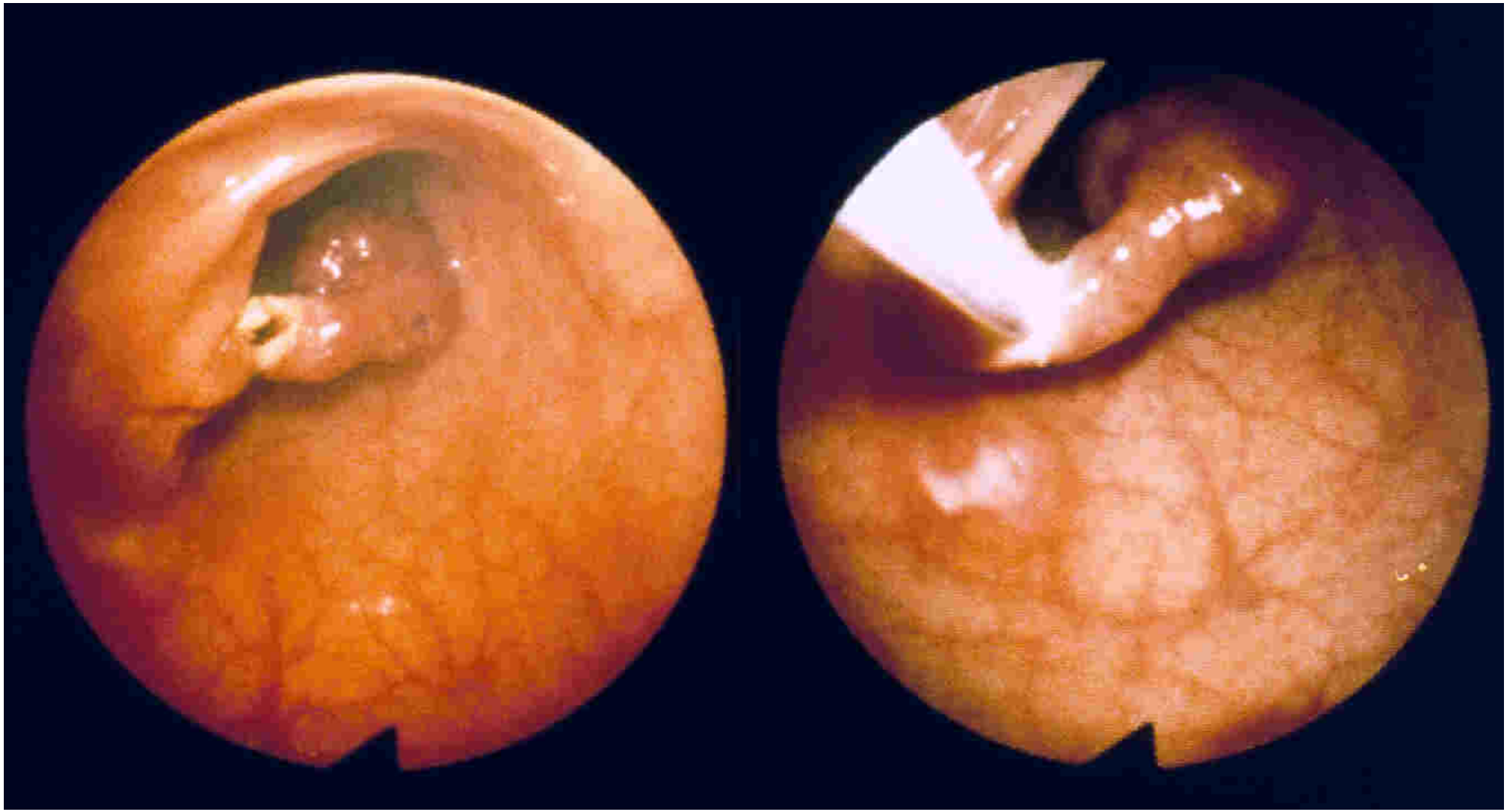
Architecture:

- Tubular adenoma
- Tubulovillous adenoma
- Villous adenoma

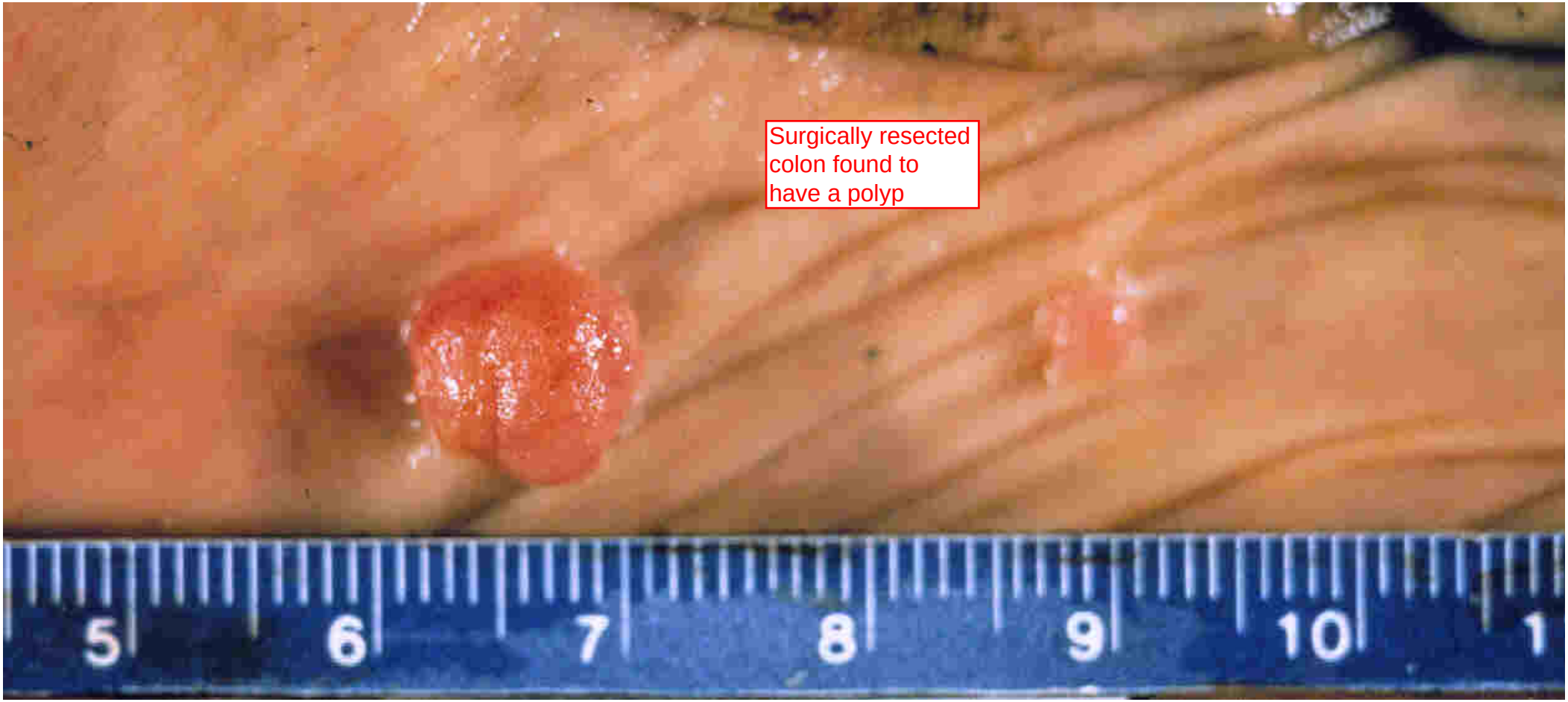
Progression to…

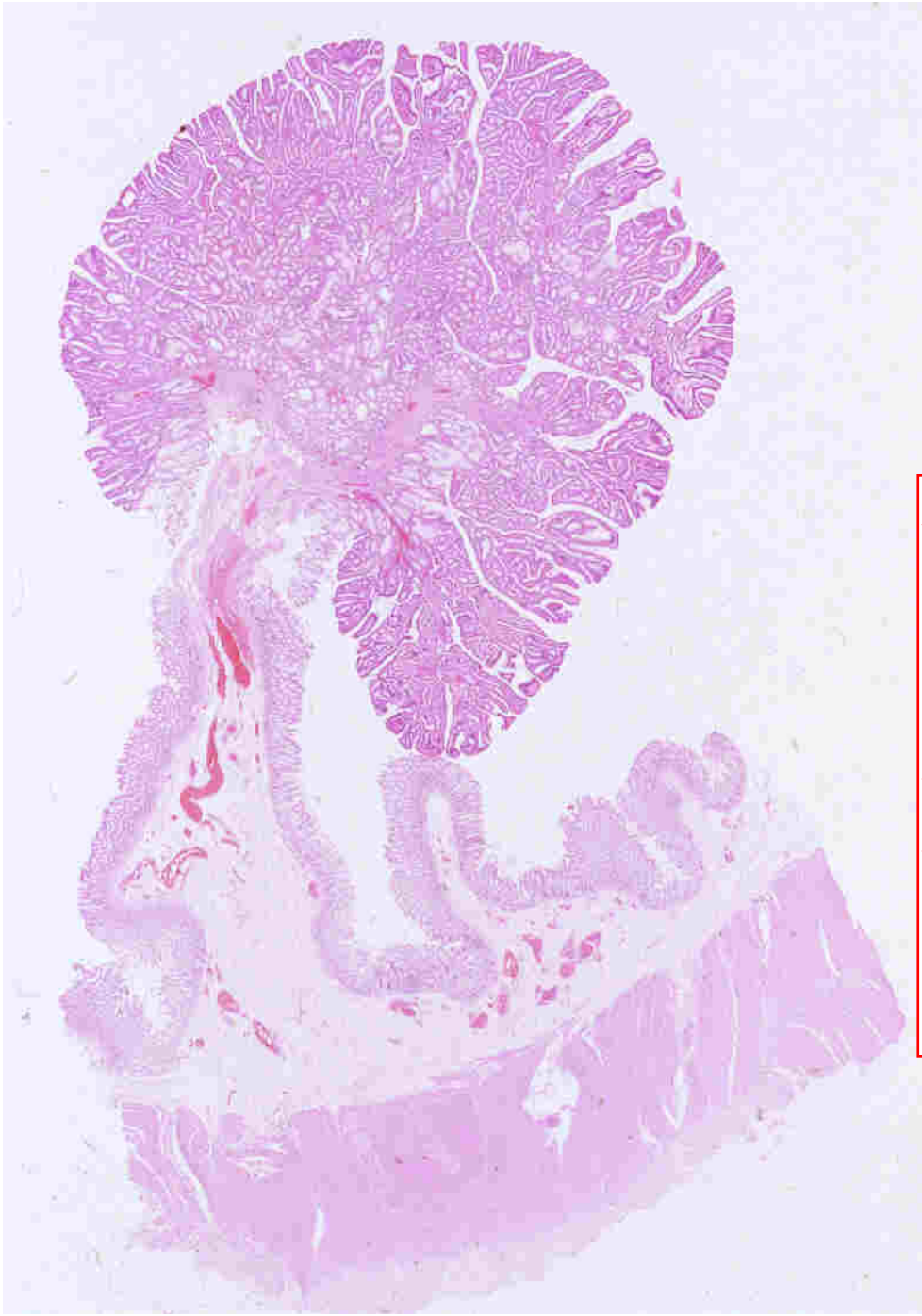
- High grade dysplasia
- Intramucosal adenocarcinoma


Can be flat/ sessilated or pedunculated
wire loop can be used for snare polypectomy that is wrapped around stalk, put electric current through loop and burn it!

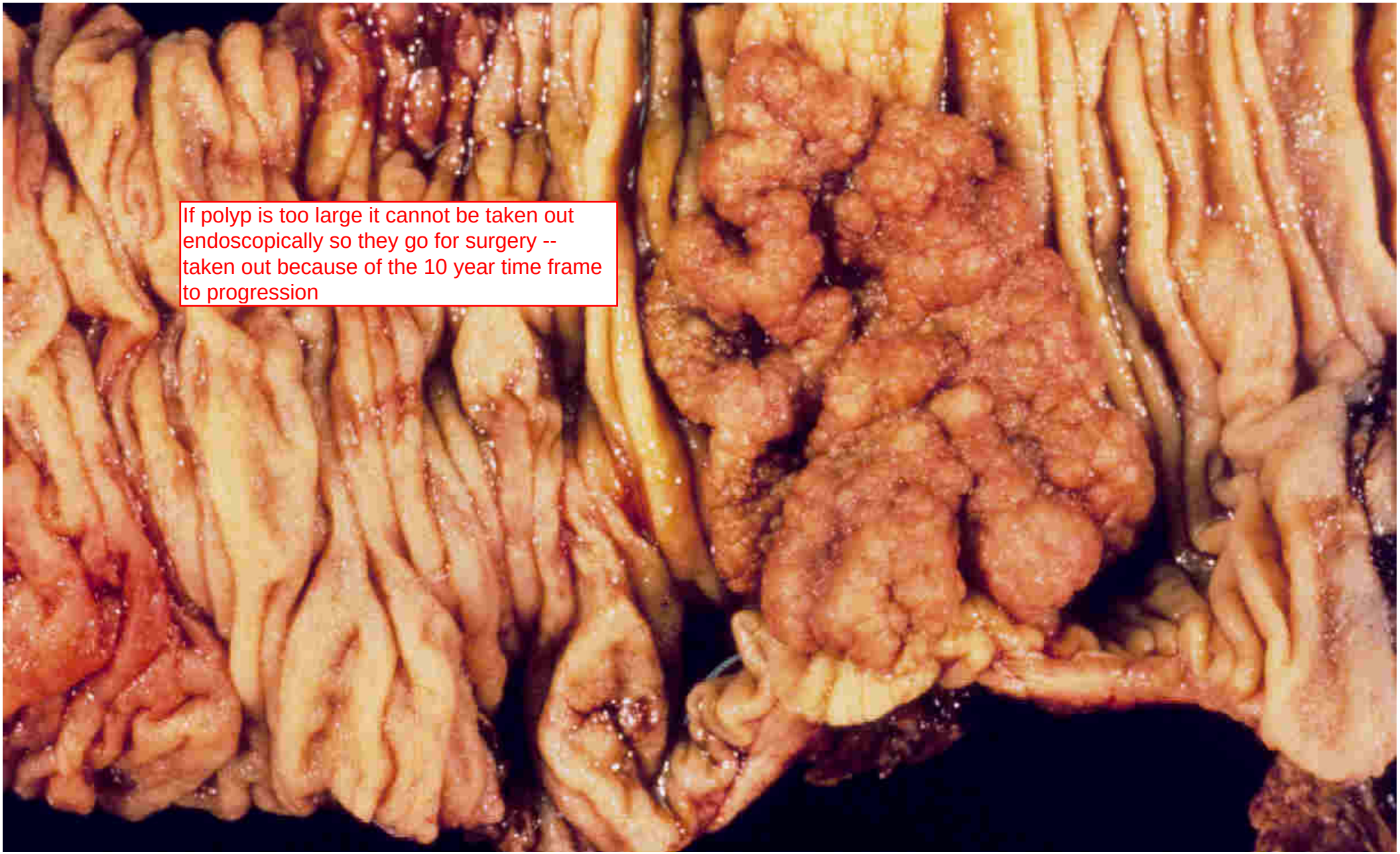


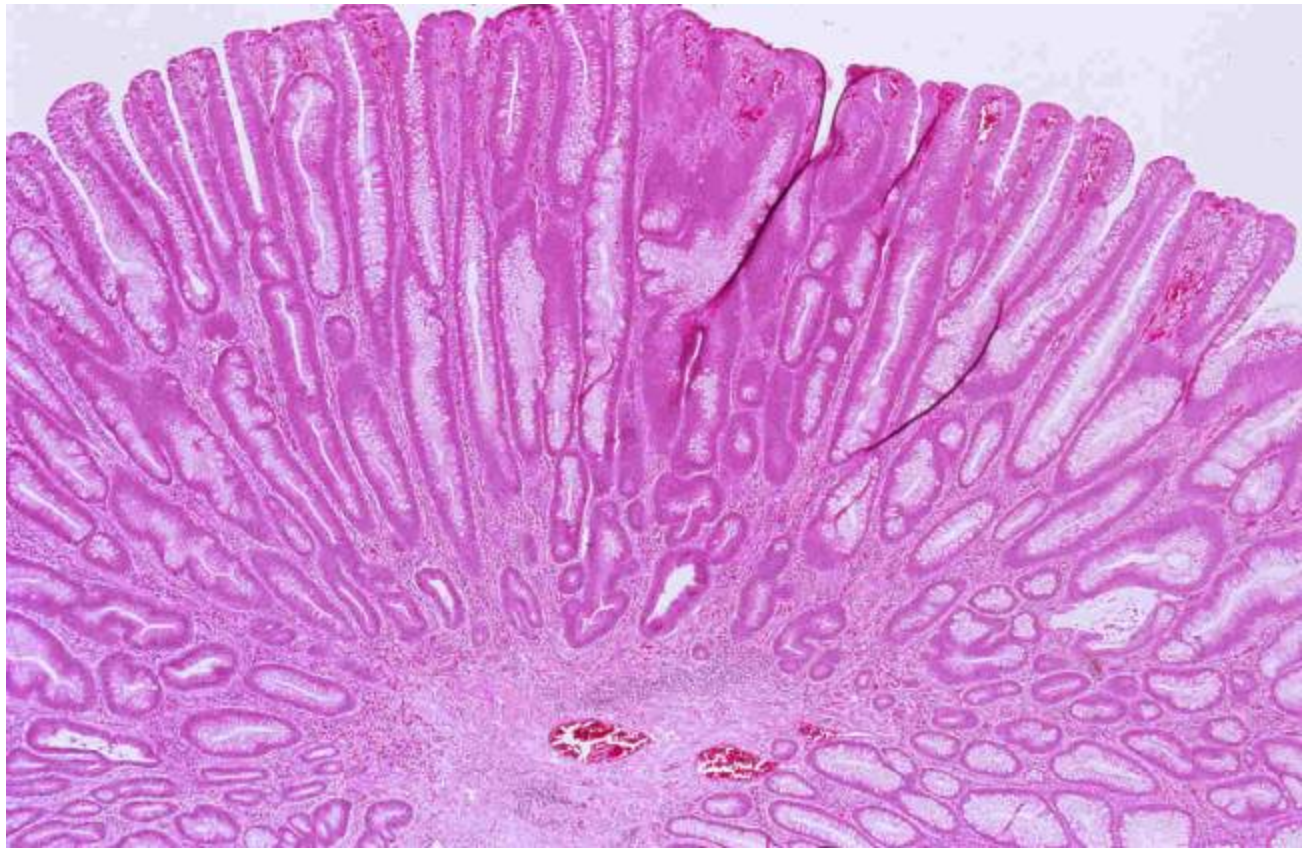
Tubular Adenoma

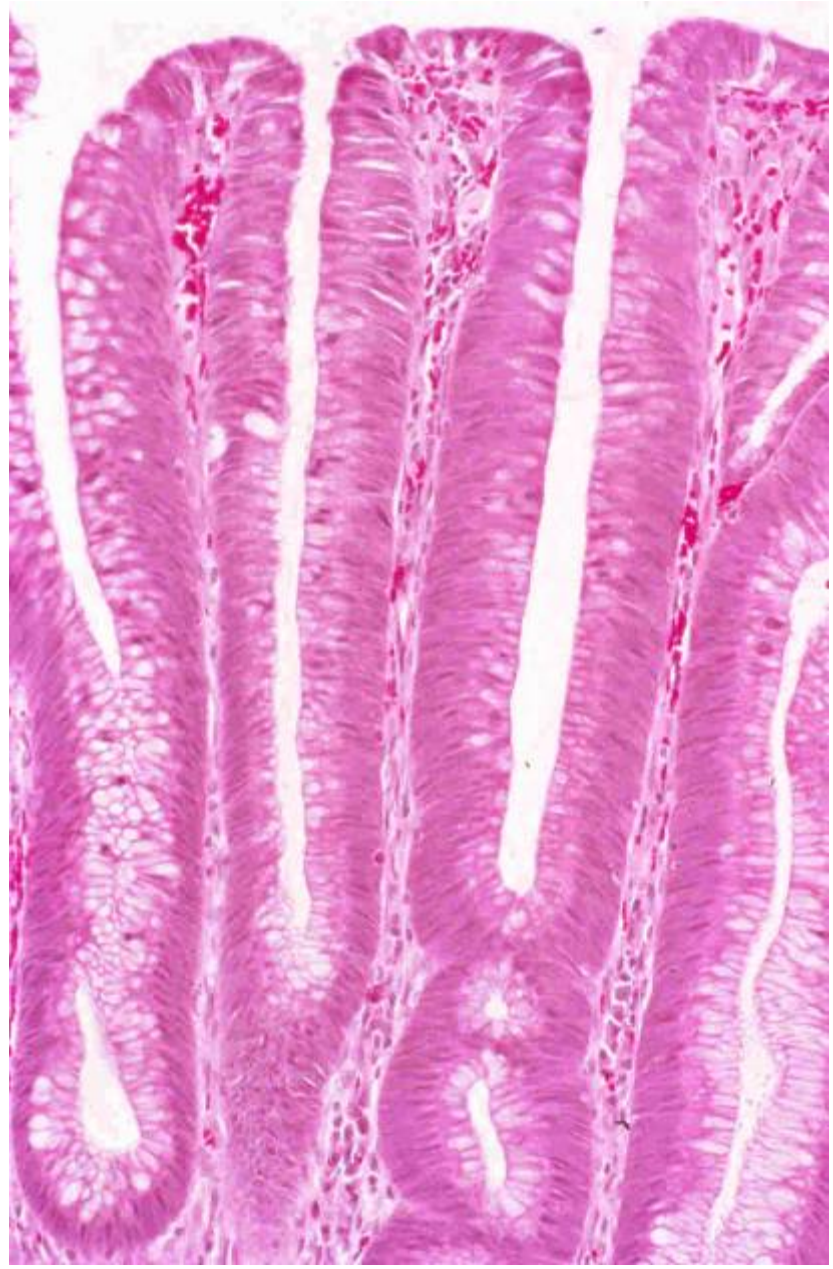




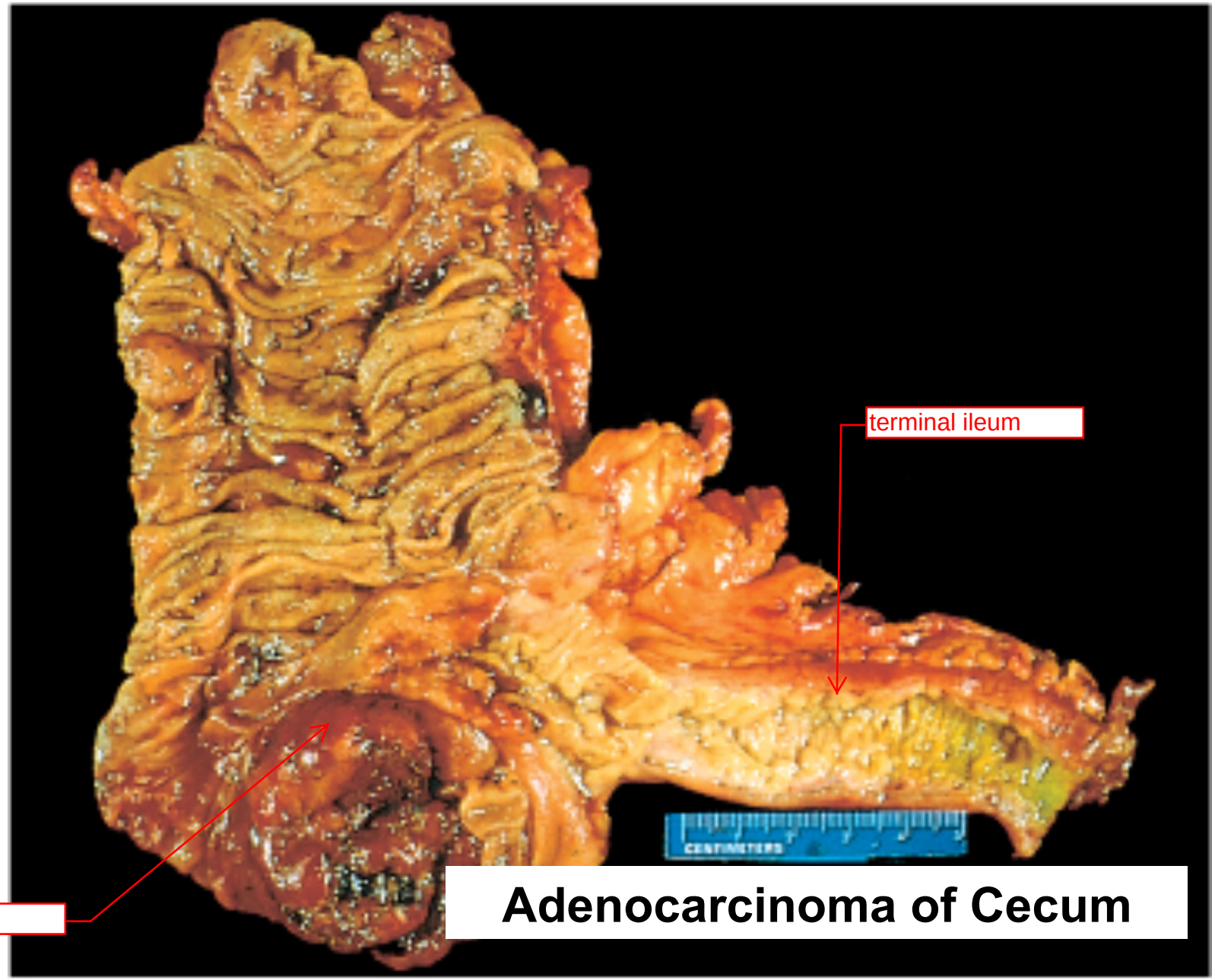
In normal colon you have basally located nuclei but in adenomatous mucosa they are all squeezed in, cigar-shaped because there are too many of them per unit area giving them a blue appearance. They still have a bit of polarity (still somewhat basally oriented)


If polyp is too large it cannot be taken out endoscopically so they go for surgery -- taken out because of the 10 year time frame to progression





Villous Adenoma



Adenocarcinoma of Cecum

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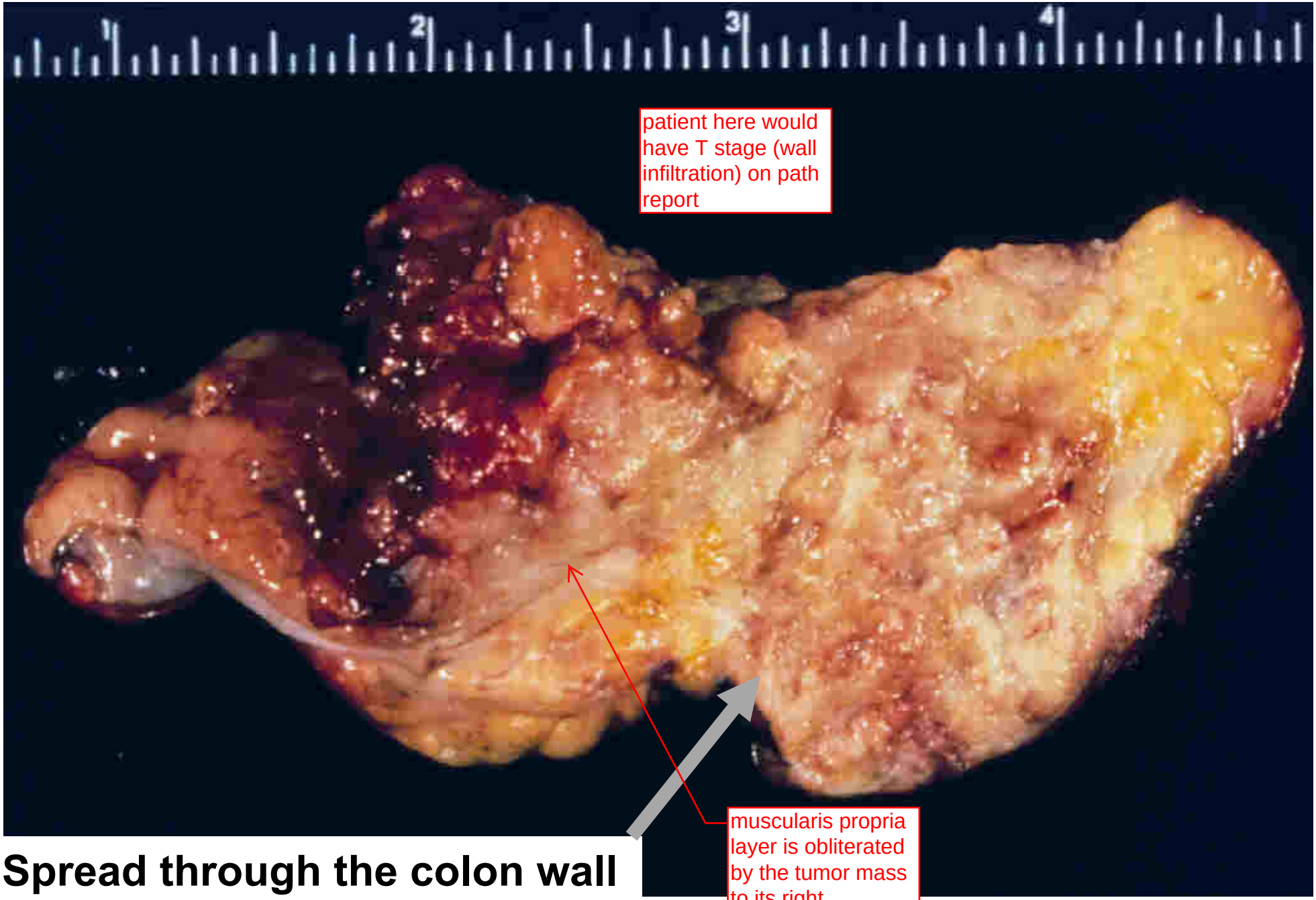
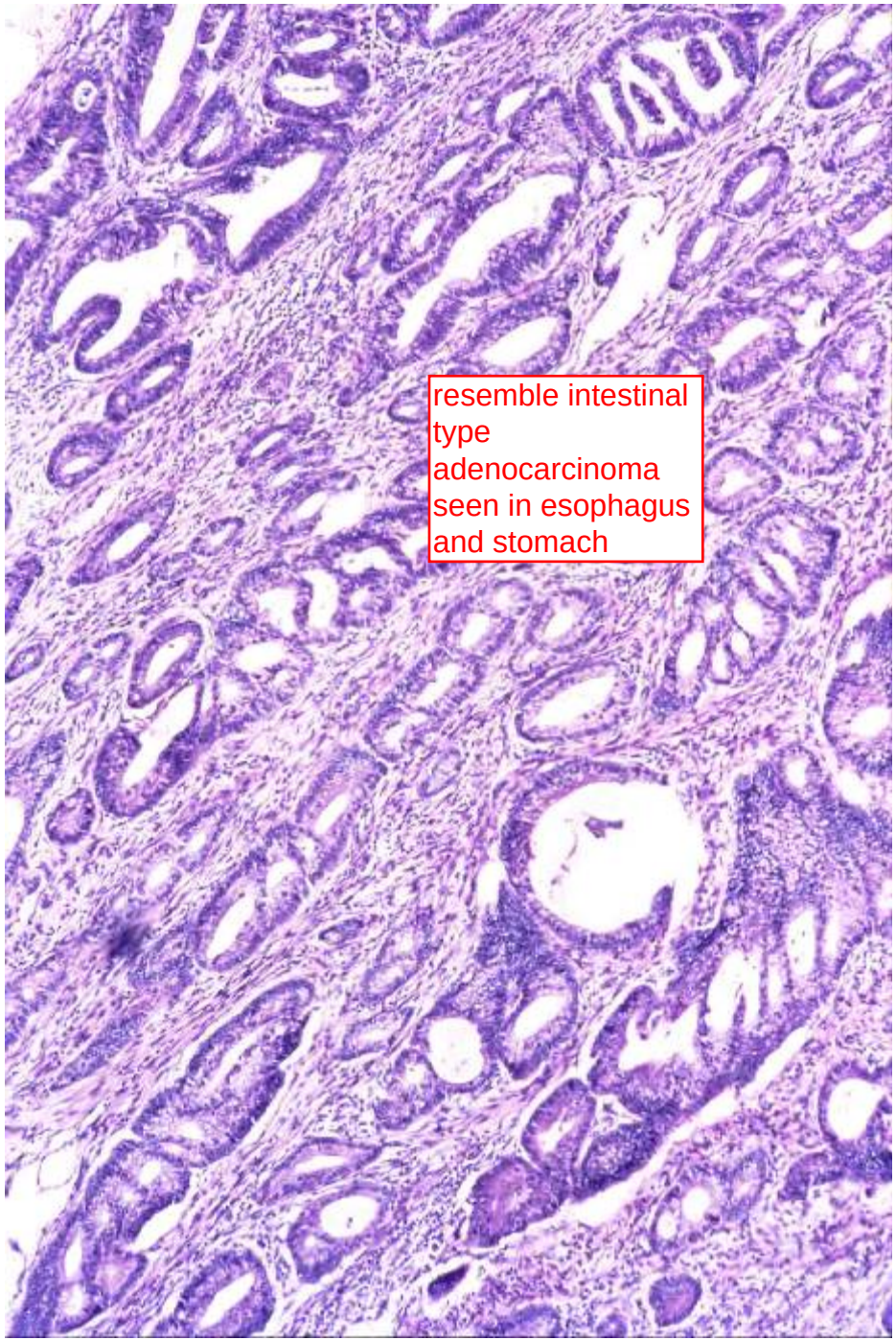
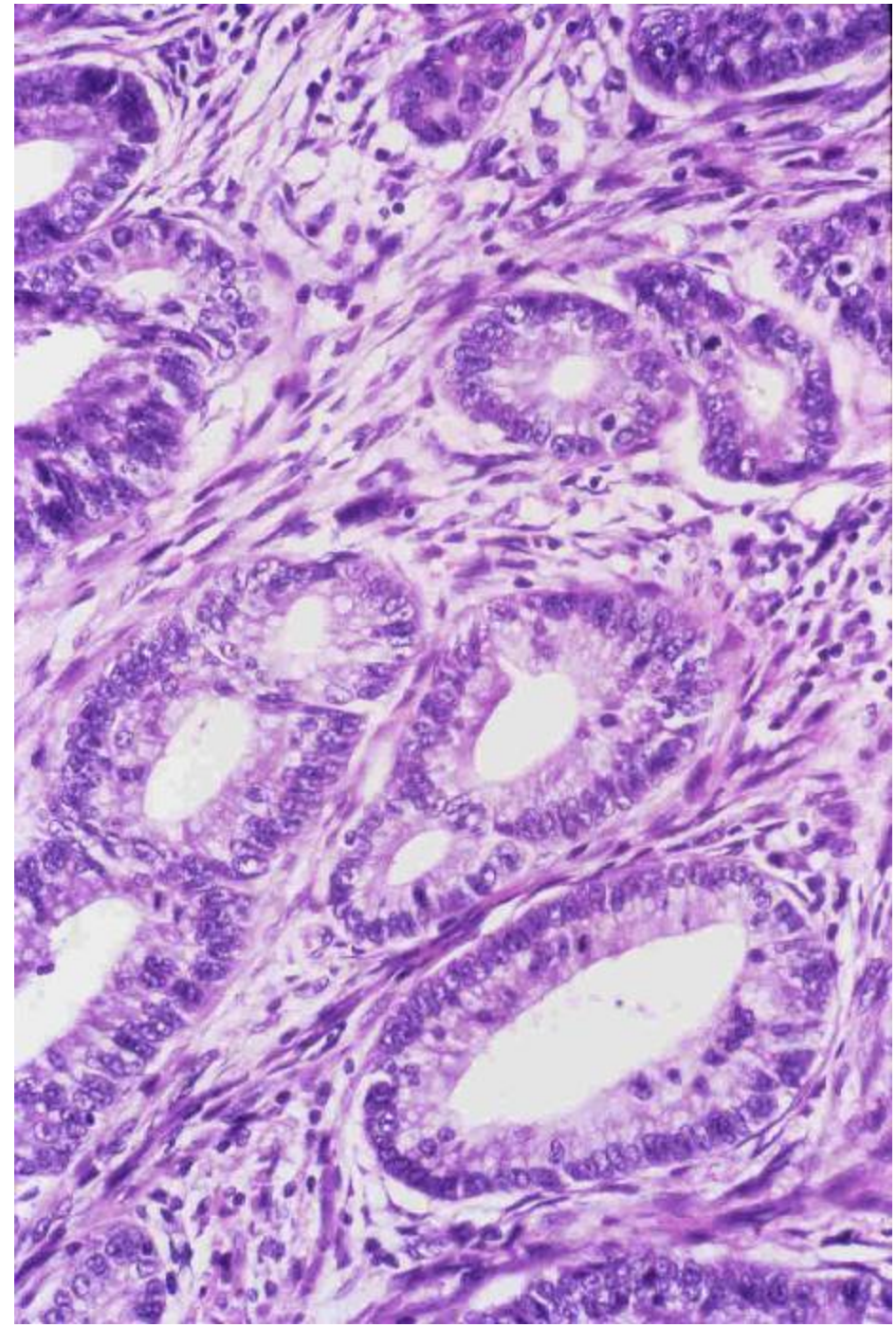
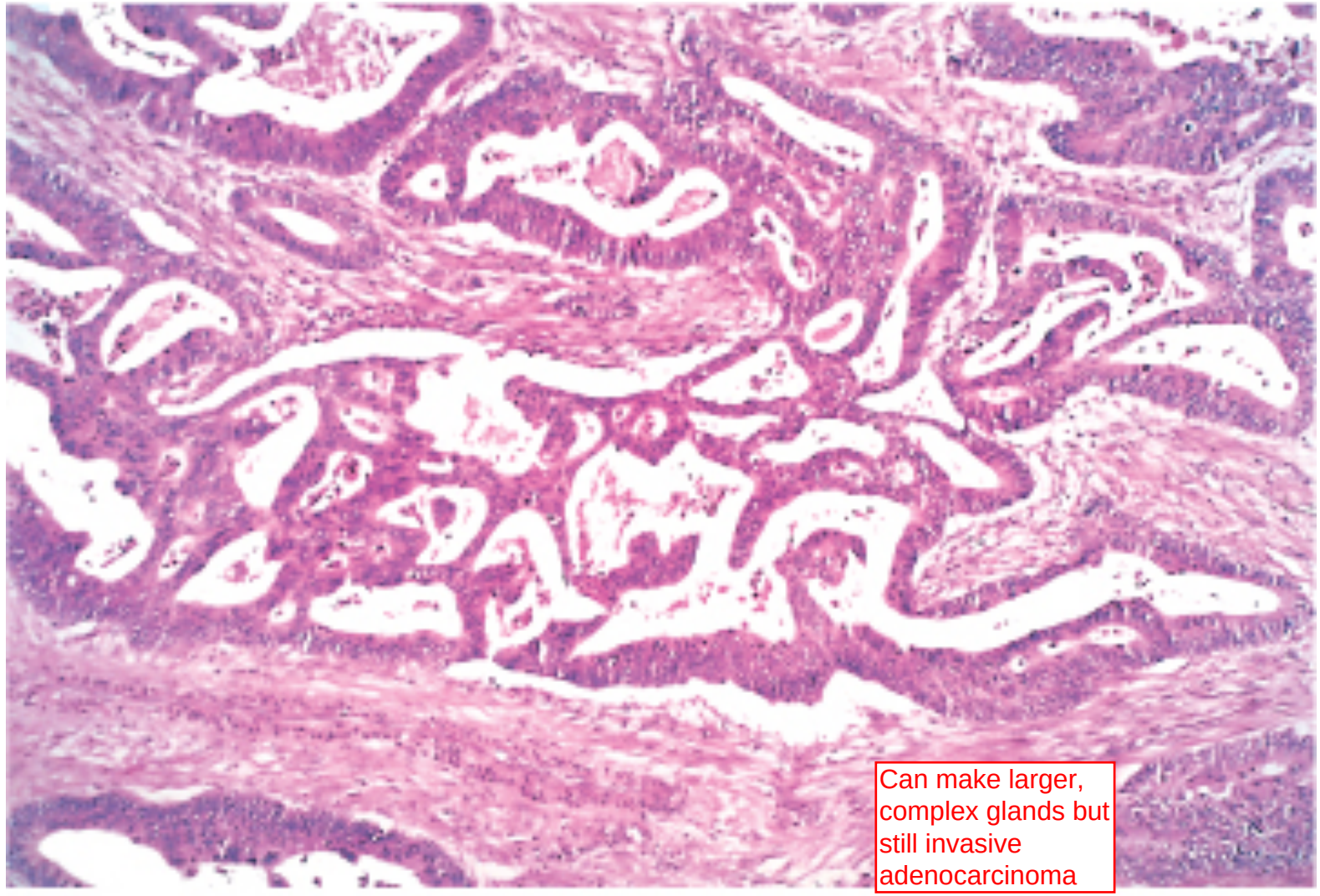


Spread through the colon wall


resemble intestinal type adenocarcinoma seen in esophagus and stomach





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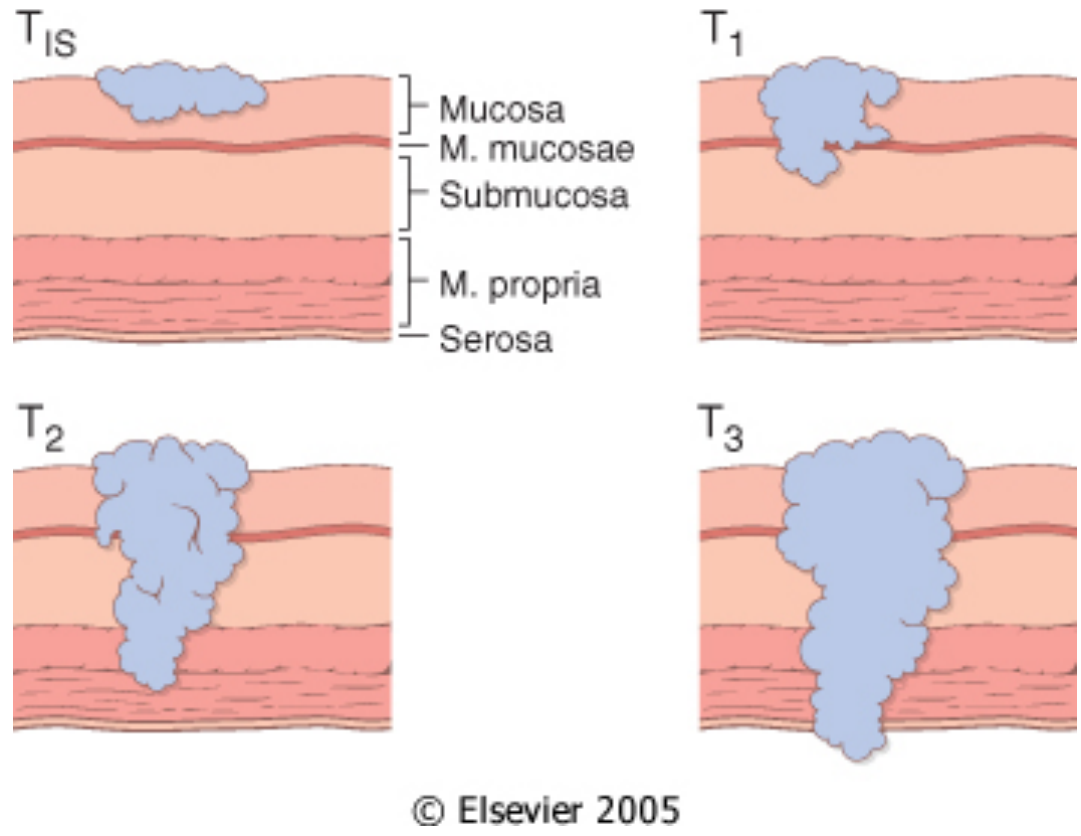
Colon CA - Spread

- Local invasion
- Lymphatic spread
- Distant metastases - liver



Based on this you can get HACC cancer staging manual and see people's 5 yr prognosis fairly accurately

GI Neoplasms

- Epithelium - adenomas, carcinomas
- Enterochromaffin cells - carcinoid tumors
- Lymphocytes - lymphomas
- Mesenchymal cells - smooth muscle tumors

Neuroendocrine neoplasms

Neuroendocrine (Carcinoid) Tumors

- Ileum
- Appendix
- Stomach
- Rectum

Distal/terminal ileum -- no carcinomas of ileum but still get carcinoids

Common place to find them

Confusing name because it is very different from carcinoma. Carcinoid means well-differentiated neuroendocrine tumor.

NeuroendocrineTumors

- Amines
  - Serotonin
  - Histamine
- Polypeptides
  - Gastrin (Zollinger-Ellison)

Clonal proliferation of neuroendocrine cells -- tumors generally just make one hormone and sometimes the patient will have syndrome associated with that hormone but most of the time they do not and it is not very interesting (we have no idea what the hormone is)

If a carcinoid tumor makes gastrin they will have increased acid production and they get multiple peptic ulcers and we call it Zollinger-Ellison.

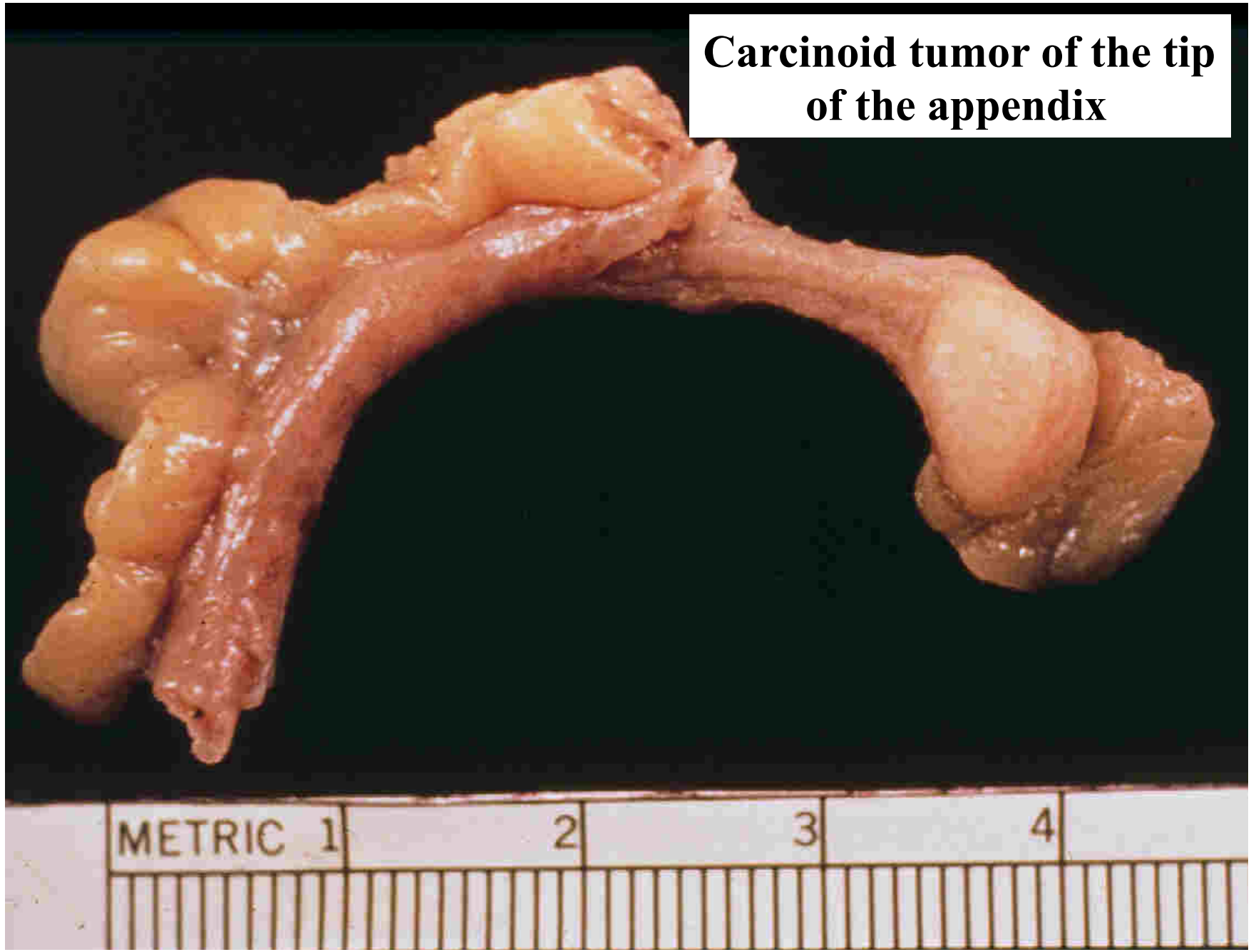
Carcinoid Tumors - Spread

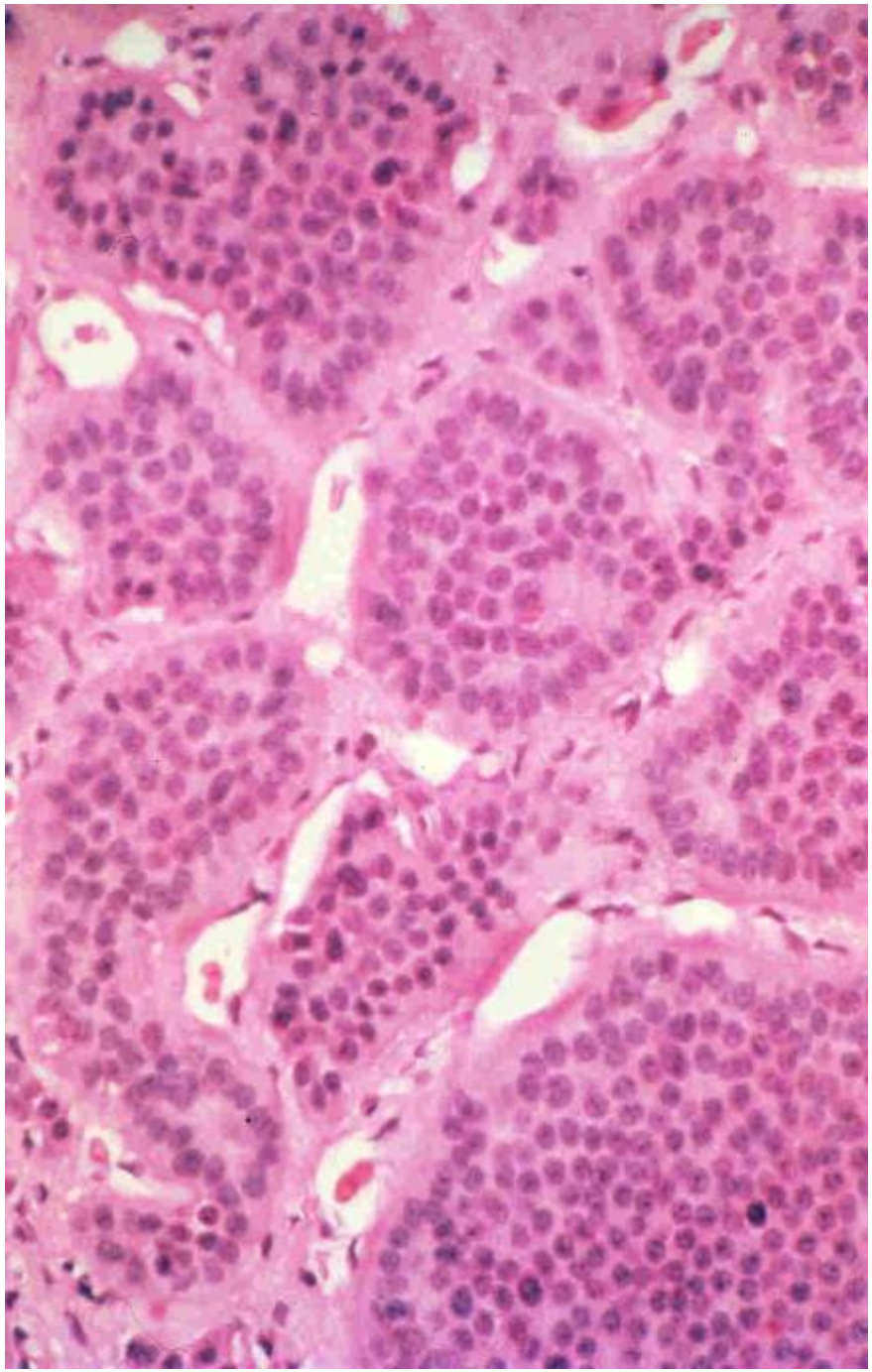
- Incidence of metastases is roughly related to size (<1cm rarely metastasize)
- Pattern of spread is similar to carcinomas, but usually with a more indolent course

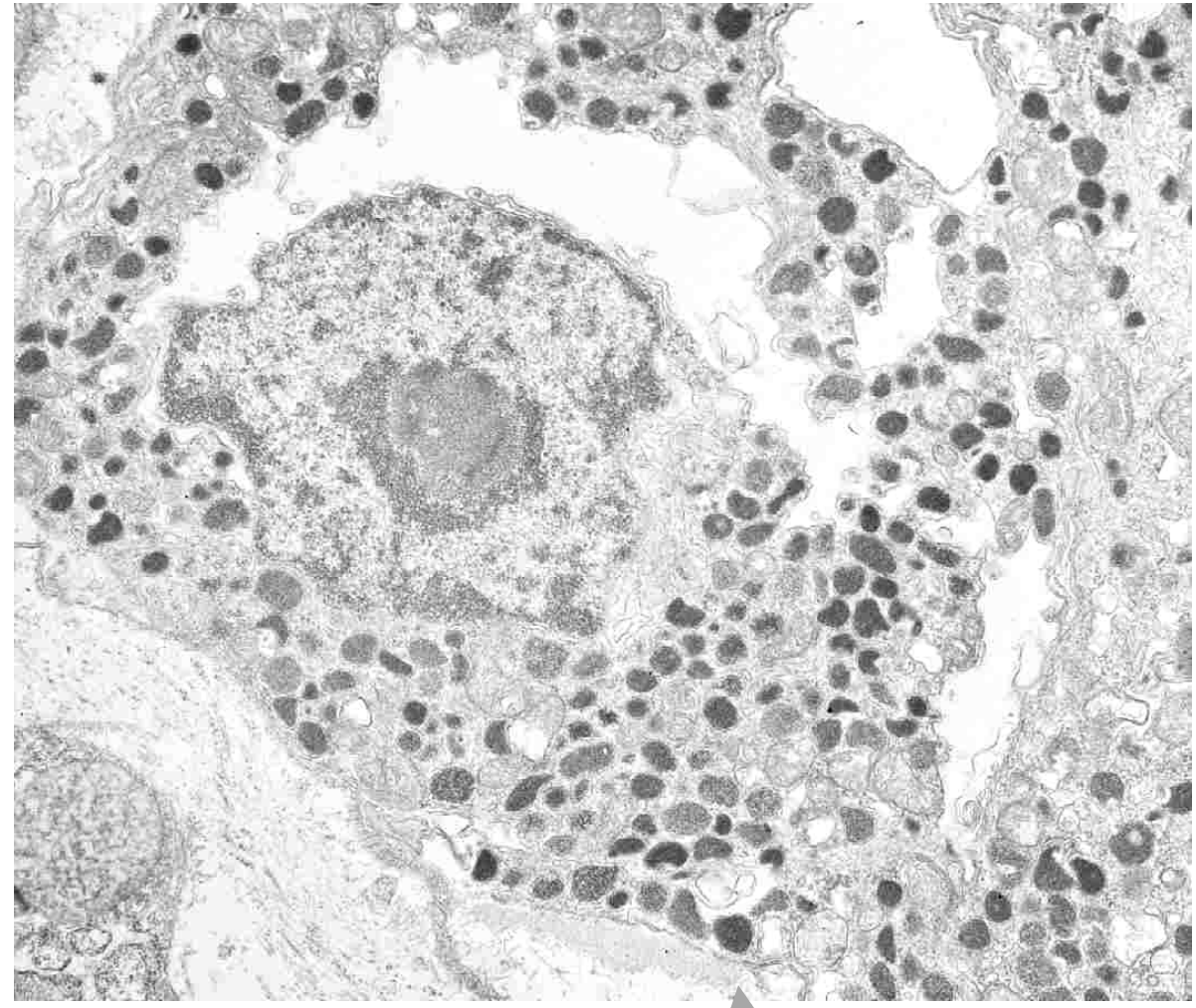
Clinically Evident Secretory Products

Class carcinoid syndrome is when the pt has too much serotonin.

- Carcinoid syndrome (serotonin) is most common in large tumors with liver metastases
  - Diarrhea
  - Flushing
  - Bronchospasm
- Zollinger Ellison Syndrome - gastrin. Increased acid production results in multiple peptic ulcers.


Carcinoid tumor of the tip of the appendix
METRIC 1
2
3
4





Neurosecretory Granules

GI Neoplasms

- *Epithelium - adenomas, carcinomas*
- *Enterochromaffin cells - carcinoid tumors.*
- *Lymphocytes - lymphomas*

skipping lymphocytes because we get it from other lectures. GI tract is lined by mucosa associated lymphoid tissue (peyer's patches) and you can get lymphomas directly from that tissue. You can get secondary involvement of the GI tract from for instance mantle cell lymphoma showing as colon polyp. Don't have time to cover.

- Mesenchymal cells - smooth muscle tumors, other

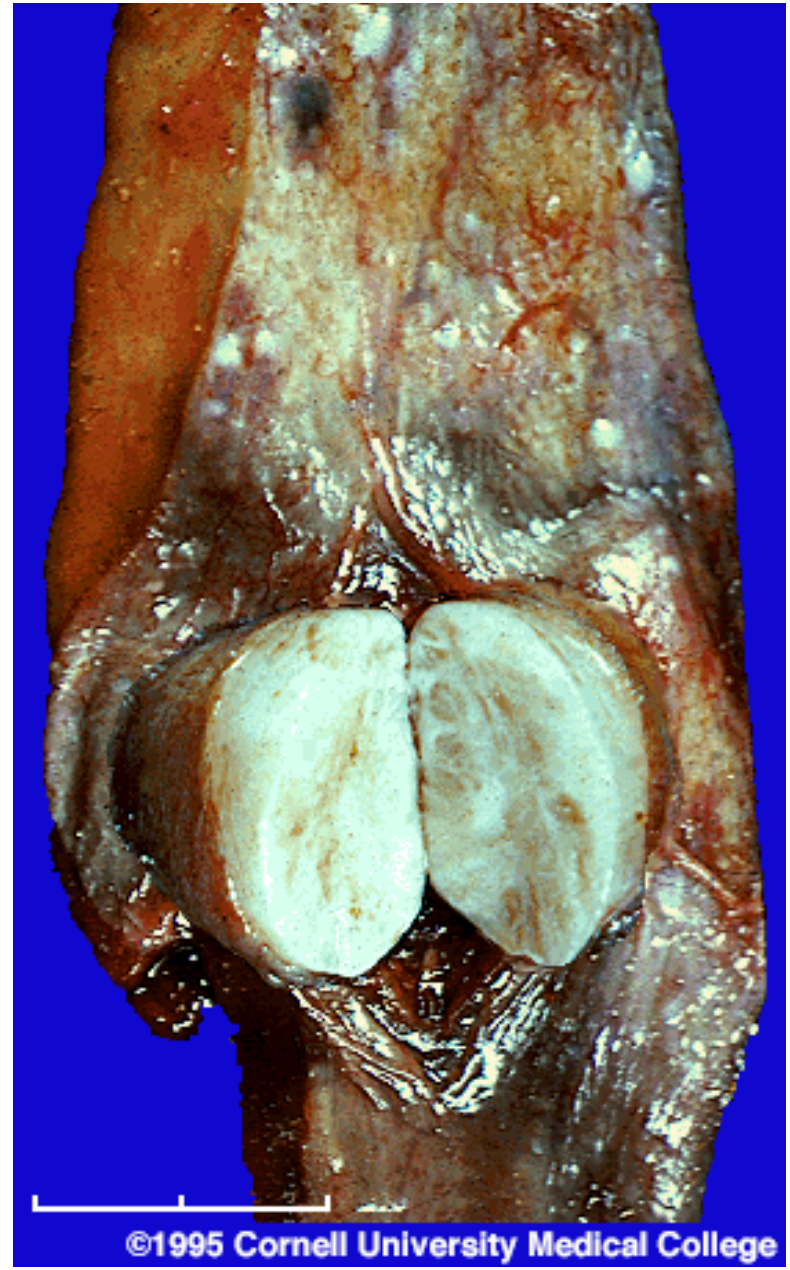
Mesenchymal Tumors

- Usual types as in other parts of the body, usually benign in GI tract
  - Smooth muscle cells (leiomyoma)
  - Adipose tissue (lipoma)
  - Vascular channels (hemangiomas)
- GI Stromal tumors
  - Interstitial Cells of Cajal
  - Behavior variable
  - KIT mutations, responsive to imatinib

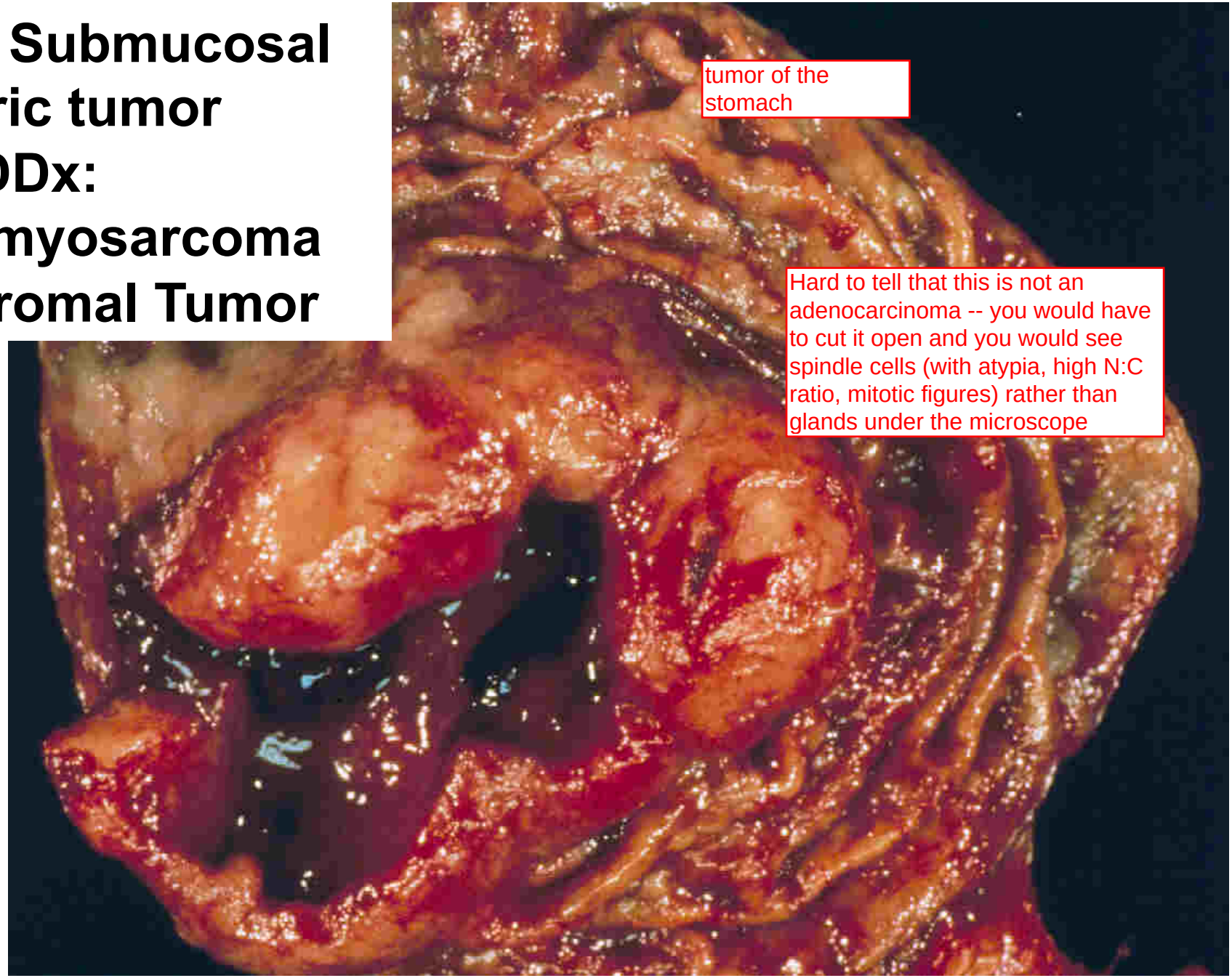
We have talked about these in other parts of the body

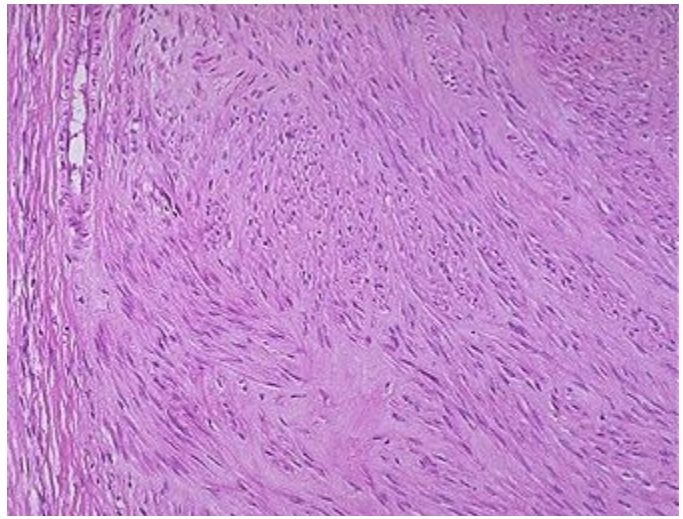
Interesting because this cell type is the go-between between nervous system and smooth muscle of the GI tract (regulates peristalsis and hence is called pacemaker cell). GI stromal tumors (GIST) are characterized by mutations in CD117 (c-KIT) and we have medication for this that works for a while! (until they become resistant)

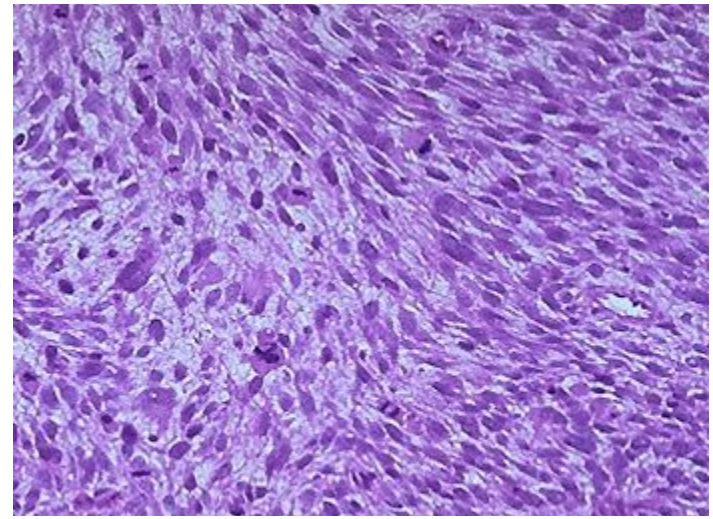
Esophageal Leiomyoma



Malignant Submucosal Gastric tumor
DDx:
Leiomyomyosarcoma
Vs. GI Stromal Tumor







Smooth Muscle Tumors

Benign (leiomyoma) vs. Malignant (leiomyosarcoma)