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Neoplasms of the GI Tract
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GI Neoplasms

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

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.
- *Lymphocytes* - lymphoma
- *Mesenchymal cells* - smooth muscle tumors
# GI Carcinomas

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>New Cases per yr in US*</th>
<th>5 yr. Survival* (all stages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>16,640</td>
<td>17%</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,000</td>
<td>26%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>147,000</td>
<td>65%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,000</td>
<td>6%</td>
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*American Cancer Society 2010

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!
GI Tract Carcinomas
Pattern of Spread

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

Squamous Papilloma (benign)
Squamous Cell Carcinoma
Adenocarcinoma

There are TONS of benign lesions but we'll focus on the malignant ones
Squamous papilloma - no malignant potential (like a wort on a thumb) - removed
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

• **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)

• **Adenocarcinoma**
  – Now makes up >50% of esophageal carcinomas in the US and Western Europe
Squamous Cell Carcinoma

- 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
Esophageal Squamous Cell Carcinoma

Squamous mucosa normally looks white/tan and pearly

Surgically removed specimen of tubular esophagus

tumor (squamous cell carcinoma)
normal squamous epithelium with basal layer and keratinocytes

high grade dysplasia that has begun to invade down

No glands - can rule out adenocarcinomas
Because they are malignant keratinocytes they are forming keratin which gives them the glassy pink look.
Esophageal Adenocarcinoma

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

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

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.
Reflux Esophagitis → Intestinal Metaplasia (Barrett’s Esophagus) → Dysplasia → Invasive Adenocarcinoma
Again, be familiar with this
What Does Barrett’s Esophagus Look Like?
Invasive Adenocarcinoma arising in Barrett’s Esophagus:

Can you spot the Barrett’s?

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
Esophageal Squamous Cell Carcinoma

Note: No Barrett’s in Background
Invasive Adenocarcinoma of the Esophagus, Arising in Barrett’s Esophagus
Stomach

Benign Epithelial Polyps
Adenocarcinomas (Two types)
Hyperplastic polyps and Fundic-Gland Polyps

- 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.

Two kinds of polyps with no clinical consequences.

Reaction to injury with no malignant potential.

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

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).
Fundic Gland Polyp

cystically dilated glands - totally benign in 99% of cases
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

• Risk Factors
  – Diet
  – Previous Gastrectomy
  – Atrophic Gastritis (Intestinal Metaplasia)

• Decreasing in Incidence, paralleling decline in *H. pylori* infection

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)
Gastric Adenocarcinoma, Intestinal-type, Ulcerating Mass
Gastric Adenocarcinoma, Intestinal-type

pretty typical adenocarcinoma; Infiltrating, Malignant Glands
Gastric Adenocarcinoma, Diffuse Type

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

Leather-Bottle Stomach (Linitis Plastica)

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.
Gastric adenocarcinoma, Diffuse Type
(\(\text{Can cause linitis plastica}\))
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 $\rightarrow$ Carcinoma

- 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 years
• 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

- 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

any colon cancer
Molecular Events of Colorectal Carcinogenesis

- 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

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

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

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

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.)

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
NORMAL COLON

MUCOSA AT RISK

ADENOMAS

CARCINOMA

Mucosa
Submucosa
Muscularis propria

Germ-line (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")

APC at 5q21

APC β-catenin

Methylation abnormalities Inactivation of normal alleles ("second hit")

Protooncogene mutations

K-RAS at 12p12

Homozygous loss of additional cancer suppressor genes Overexpression of COX-2

p53 at 17p13 LOH at 18q21 (SMAD 2 and 4)

Additional mutations Gross chromosomal alterations

Telomerase, Many genes

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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

Surgically resected colon found to have a polyp
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
Spread through the colon wall

patient here would have T stage (wall infiltration) on path report

muscularis propria layer is obliterated by the tumor mass to its right
resemble intestinal type adenocarcinoma seen in esophagus and stomach
Colon CA - Spread

- Local invasion
- Lymphatic spread
- Distant metastases - liver
GI Neoplasms

- Epithelium - adenomas, carcinomas
- Enterochromaffin cells - carcinoid tumors
- Lymphocytes - lymphomas
- Mesenchymal cells - smooth muscle tumors
Neuroendocrine (Carcinoid) Tumors

- Ileum
- Appendix
- Stomach
- Rectum

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

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

Common place to find them
Neuroendocrine Tumors

- 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

• 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
GI Neoplasms

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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
Esophageal Leiomyoma
Malignant Submucosal Gastric tumor

DDx:
Leiomyomyosarcoma
Vs. GI Stromal Tumor

Hard to tell that this is not an adenocarcinoma -- you would have to cut it open and you would see spindle cells (with atypia, high N:C ratio, mitotic figures) rather than glands under the microscope.
Smooth Muscle Tumors
Benign (leiomyoma) vs. Malignant (leiomyosarcoma)