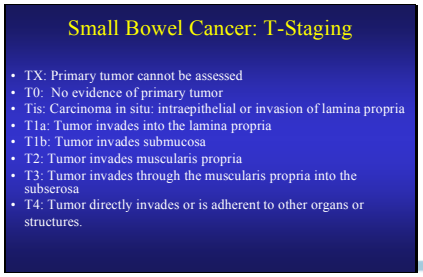
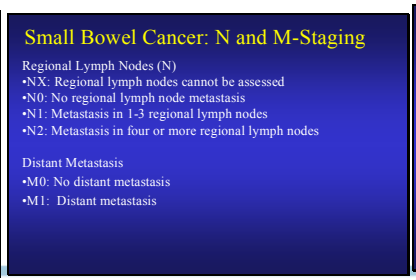
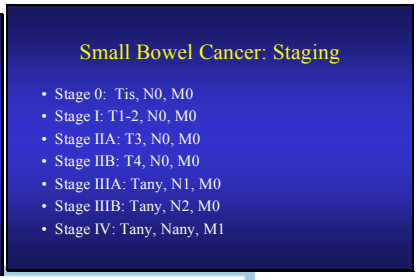
General

- Small Bowel Tumors
  - Epidemiology
    - Despite its great length and vast number of dividing cells SI tumors rare but why? Alkaline pH prevents formation of nitrosamines, rapid transit, sparse bacteria, abundant lymphatic tissue, detoxifying enzymes
    - SI cancer represents <5% of all GI cancers
  - S/S: ab pain (NB back pain suggests RP involvement), weight loss, GIB, perforation, obstructive jaundice if periampullar, obstruction from intussusception but often Sx are obscure and mild b/c they are generally mild b/c of the distensibility of the SI
  - Staging







  - Types
    - Benign (10x): adenoma, leiomyoma, lipoma, hemangioma, neurofibromas, desmoid tumor
      - Neurofibromatosis
        - involves the GI tract in ¼ of cases with neurofibromas forming in the stomach and jejunum, on rare occasion the neurofibromas can turn into neurofibromasarcomas
        - skin findings (café au lait spots, axillary/inguinal freckling, dermal neurofibromas, iris Lisch nodules)
        - can be associated w/ HNPCC
    - Malignant (1x)
      - Mets (more common than primaries, in order of incidence: melanoma, breast, lung, ovary, colon, stomach)
      - Ampullary AC (25%, ampullary) – refer
      - Non-Ampullary Adenocarcinoma (25%, proximal)
        - arise from pre-existing small/tubular/pedunculated adenomas (unlike ampullary AC)
        - RFs
          - Ethnicity: AA males, the Maori tribe of New Zealand
          - Diet: Alcohol/tobacco are not RFs but diet high in refined carbs, red meat, salted-cured-smoked meats
          - Prior Conditions: SI reconstruction eg. ileal conduit, ileostomy, etc, Celiac Sprue, Crohn's, all the inherited hamartomatous/adenomatous polyposis syndromes
      - Carcinoid (25%, distal SI)
      - Lymphoma (25%, distal SI)
      - Sarcoma (rare, entire SI)

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- Large Bowel Tumors
  - Appendiceal Cancers
    - Types
      - Mucinous AC (35%) = mucocele w/ mucin spreading throughout the peritoneal cavity w/ peritoneal mets creating "psuedomyxoma peritonei" aka "jell belly" (DDx: ovarian cancer)
      - Intestinal AC (25%)= mass
      - Signet Ring Cell AC (10%) = mass
      - Carcinoid (10%) = mass
    - S/S: acute appendicitis, ascites, complications from having jelly belly, 20% incidental finding
    - Tx: simple appendectomy if <submucosal vs right hemicolectomy if >submucosal
  - Adenocarcinoma (colorectal)
  - Hamartomas
  - Squamous Carcinoma Cell (anal)
  - NeuroEndocrine Tumors
  - Heme: Lymphoma
  - Sarcomas: GastroIntestinal Stromal Tumors, Kaposi, Leiomyosarcomas
    - In general location of GI sarcomas: stomach (50%), SI (30%), colorectal (15%), esophagus (5%)
    - Colorectal sarcomas represent <0.1% of all CRC

- Carcinoid
- Mets: Melanoma, Breast, Ovary, Prostate, Lung, Stomach, Lymphoma

GastroEnteroPancreatic NeuroEndocrine Tumors (GEP-NETs)

- General
  - Neuroendocrine cells, as the name implies, refers to cells that communicate via neural impulses or hormones
  - Tumors of these cells aka NETs can occur in almost any organ
  - Very confusing tumors as classification schemes vary from organ to organ differing in terms and grading/staging criteria
  - Incidence is rising
  - Incidence is rare but prevalence is high b/c of their generally indolent behavior
  - Unlike other solid organ tumors GEP-NETs are slower growling BUT despite this they metastasize to LNs and liver much quicker than other solid organ tumors such that it is not uncommon to see liver/LNs mets with no apparent primary source!!!
- History
  - 1907: Orberndorfer (coined "carcinoid" to describe a carcinoma-like tumor that has tight nests of small uniform cells)
  - 1963: Sandler (divided carcinoids based on embryologic origin: foregut, midgut, hindgut)
  - 1995: Cappela (changed the term carcinoid to "neuroendocrine tumors")
  - 2010: WHO (divided NETs into well vs poorly differentiated NETs and well-differentiated NETs into tubular GI tract NETs and pancreatic NETs)
- Classification (grade based on mitotic count and Ki-67 index w/ Grade II cancers having a mitotic count of 2-20 HPF and Ki67 index of 3-20%, this is the current classification system but still evolving)
  - **Well Differentiated or Grade I-II NETs**
    - General
      - organoid arrangement of cells w/ regular nuclei and finely granular cytoplasm producing abundant neurosecretory granules
      - vary in their aggressiveness and even with mets these tumors can be relatively indolent
      - despite only 10% of carcinoids and 70% of PETs being functional, functional carcinoids are still more common than functional PETs
    - (1) **Carcinoids** (originate outside of the pancreas both GI and extra-GI (divided into foregut/midgut/hindgut), generally less aggressive and usually non-functioning)
      - Non-Functioning aka w/o Carcinoid Syndrome (90%)
      - Functioning aka w/ Carcinoid Syndrome (10%)
    - (2) **PETs** (originate from the Islets of Langerhans w/in the tail of the pancreas (rarely in duodenum), generally more aggressive and usually functioning)
      - Non-functioning (30%)
      - Functioning (70%)
      - Syndrome Associations
        - MEN-1 Syndrome aka Werner's Syndrome: PET esp insulinomas/gastrinomas/PPomas + PTH Hyperplasia + Pituitary Prolactinoma
        - Phacomatoses (Syndromes of skin and nervous system)
          - Von Hippel Lindau
          - Von Recklinghausen
          - Tuberous Sclerosis
    - NB the carcinoid and PET distinction is not clear as PETs can occur outside the pancreas hence it is not recommended to not use these terms anymore and just describe tumor based on grade and functionality (some tumors can stain for certain hormones but they are only considered "functional" if a clinical syndrome exists)
  - **Poorly Differentiated or Grade III NETs**
    - General
      - sheet like arrangement of cells w/ irregular nuclei and non-granular cytoplasm producing little neurosecretory granules
      - uniformly aggressive cancers
      - transformation of well differentiated NET to poorly differentiated NET has been reported but very rare
    - (1) **Small Cell Carcinoma**
    - (2) **Large Cell Carcinoma**
- General Dx
  - **Serum Chromogranin-A (CgA)**
    - Protein found in vesicles of all NETs and detectable in serum even in non-functioning NETs
    - + if >32 U/L w/ sensitivity of 75% and specificity of 85% if…
      - clinical suspicion AND
      - other conditions which can cause a False + are not present: PPI use (not H2B), renal/liver insufficiency, gastric atrophy, IBD, colon/breast/ovarian/prostate/lung cancer, trauma
    - Correlate w/ Tx response
    - Have prognostic value (higher the level the shorter overall survival times)

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        - Other non-specific non-functioning serum/tissue markers: CgB/C, neuron specific enolase, pancreatic polypeptide, beta-HCG, etc
        - Specific functioning serum/tissue markers: gastrin, insulin, etc
    - **Radiolabeled Octreotide Scintigraphy w/ SPECT aka Octreoscan**
        - Generally 90% of GEP-NETs (only 50% of insulinomas) have high [ ] of somatostatin receptors
        - Indium-111 labeled octreotide
        - Good for primary/metastatic lesions
        - Predictive of response to therapy with somatostatin analogues (if used then hold for >24hrs for short acting forms and >6wks for long acting forms if doing an Octreoscan to look for response and mets)
        - NB there is physiologic uptake in kidneys/spleen/bladder and false + in inflammation and in other tumors (image below shows pancreatic NET w/ diffuse liver mets)
- General Tx
    - Resection
        - Indication
            - Carcinoid (refer)
            - Pancreatic NETs
            - Poorly Differentiated NETs
        - Approach
            - All lesions should be resected varying from endoscopic approaches to extensive surgical approaches
            - Even metastatic lesions may require primary resection to manage local Sx if present
            - If liver involvement consider resection (if limited, nl liver fxn, no extrahepatic mets, can increase survival, transplant has been done in some cases aka Steve Jobs) or debulking (in which majority but not all of the dz is resected, can provide better quality of life) or if not a candidate then embolization, ablation (RFA/Cryo), chemoembolization
            - Long term management of metastatic dz can vary from watching and waiting to potentially life threatening potentially morbid interventions
    - Chemo
        - Indication (**not effective for carcinoids**)
            - Pancreatic NETs
            - Poorly Differentiated NETs
        - Approach
            - Cytotoxic Chemo: streptozocin (historical Tx standard but lots of toxicity), dacarbazine, oxalaplatin
            - Molecular Targeted Therapy: TK inhibitor (sunitinib), mTOR inhibitor (everolimus)
    - Octreotide
        - Indication
            - controlling Sx from hormone hypersecretion
            - early studies were conflicting as to whether octreotide had any effect on tumor burden but recent RDBPC trials demonstrated stabilization of tumor growth but not regression (Rinke A, et al. PROMID Trial. JCO. 2009;27:4656.) therefore consider its use even in asymptomatic pts who have high tumor burden and are octreotide avid
        - Approach
            - start w/ short acting octreotide w/ transition to long acting octreotide w/ short acting form for break through Sx
            - if Sx are not adequately controlled then consider the addition of IFN-alpha which has been found to control secretion of tumor products like octreotide and even have anti-tumor effects but, b/c of SEs, its use is limited to pts who have Sx despite octreotide
            - Radiolabeled octreotide and MIBG (norepinephrine-like protein that accumulates in neuroendocrine tumors) are being investigated
- Carcinoid
    - Pathophysiology
        - Certain neuroendocrine cells release serotonin and carcinoids are tumors of these cells
        - In carcinoid there is altered tryptophan metabolism
            - (1) normally 1% of tryptophan is converted to serotonin while in pts with carcinoid >75% of tryptophan is converted
            - (2) foregut carcinoids lack aromatic amino acid decarboxylase enzymes that converts 5-hydroxytryptophan (5-HT) to serotonin resulting in the formation of other substances: bioamines (neorepi, dopamine, histamine, et al) and non-bioamines (kallikrein, bradykinin, motilin, VIP, neuropeptide K, substance P, et al)
            - (3) hindgut carcinoid rarely secrete anything

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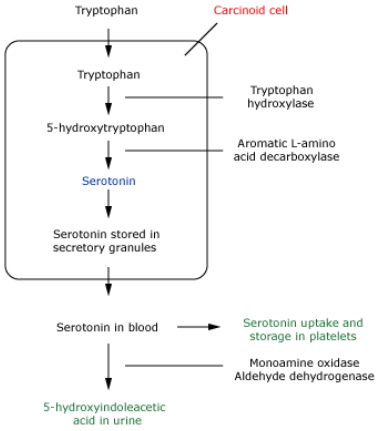

- Epidemiology
  - ~60yo, slight M>F, W=AA except, incidence of 4/100,000 and rising probably due to increased detection on imaging/endoscopy
- Location
  - GI tract (65%)
    - Foregut: esophagus, 4° stomach (three types), duodenum
      - Type 1 (75%): chronic atrophic gastritis → chronic gastric achlorhydria → chronic high gastrin → neuroendocrine hyperplasia → INDOLENT small multifocal carcinoids
        - NB some animal (not human) studies indicate that chronic PPI use may lead to Type I/II gastric carcinoids
      - Type 2 (5%): gastrinoma → INDOLENT small multifocal carcinoids
      - Type 3 (20%): sporadic w/ normal gastrin levels → AGGRESSIVE unifocal carcinoid
    - Midgut: jejunum, 1° ileum esp near ICV, 3° appendix, ascending colon
      - NB appendiceal carcinoids used to be the most common site ~40% but over the past few decades now becoming rare like 2%
      - NB 25% of midgut carcinoids are multifocal, usually functional and are generally more aggressive EXCEPT appendiceal carcinoids
    - Hindgut: transverse colon, descending colon, sigmoid colon, 2° rectum
  - Airway (25%, most dramatic Sx)
  - Other: ovary/testis, liver/gallbladder, thymus, spleen, breast, etc (10%)
- S/S
  - Tryptophan Deficiency (Pellagra) & Protein Wasting
  - Local Tumor Bulk & Mets (usually asymptomatic found incidentally during surgery/endoscopy/imaging)
    - Gastric (bleeding, dyspepsia)
    - SI (pain, obstruction, bleeding)
      - Pain 2/2 intussusception or mesenteric ischemia from local fibrosis and mesenteric vascular invasion
      - Obstruction 2/2 intussusception, intraluminal tumor burden or mesenteric distortion from desmoplastic response and LN mets
    - Appendix (acute appendicitis)
    - Colon (pain, change in bowel habits, bleeding)
    - Rectal (bleeding, change in bowel habits)
  - Carcinoid Syndrome
    - General
      - Exact S/S based on various type of bioamines
      - Syndrome requires the presence of liver metastasis allowing for bypass of hepatic metabolism of bioamines
      - also can be seen in non-GI carcinoid like lung, kidney, gonad b/c they secrete bioamines directly into systemic circulation
      - mainly seen w/ midgut carcinoids and extraintestinal carcinoids (foregut and hindgut rarely secrete bioamines)
    - S/S
      - Flushing (Non-Serotonin Substances) 75%
        - Episodic face/neck/chest flushing/edema/warmth w/ pruritus/burning
        - Menopausal hot flashes (wet) vs carcinoid flushing (dry)
        - sudden onset, lasting 30sec-30min, usually spontaneous but can be triggered by eating/alcohol/defecation/stress

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        - after repeated episodes nose/malar/upper lip telengectasias can form
    - Diarrhea (Serotonin) 75%
        - watery D and ab cramping
        - serotonin which stimulates intestinal secretion/motility and inhibits absorption
    - Heart Disease (Serotonin) 40%
        - Occurs with more extensive dz
        - T&P R/S 2/2 R sided peri/endocardial fibrosis w/ retraction creating regurg and fixation creating stenosis
        - Most common is TR
        - serotonin is metabolized by lungs hence only L sided dz therefore R sided dz can occur if R-to-L shunt is present
        - anorectic agents like FenFen cause similar dz b/c they increase serotonin
        - b/c of the indolent nature of carcinoid tumors it is reasonable for pts to undergo surgical repair if valve dz is causing significant morbidity
    - Wheezing (Serotonin) 20%
        - bronchospasm
        - beta agonist actually make Sx worse
    - Other Fibrosis: mesentery, ureters, urethra
- "Carcinoid Crisis"
    - Life threatening release of overwhelming amount of active hormones
    - Hemodynamic instability and AMS along w/ severe Sx above
    - Triggered by tumor manipulation (Bx, surgery, even significant bedside palpation), anesthesia, chemotherapy, embolizatuon, radionuclide therapy
    - Seen mainly in pts with extensive tumor burden
    - Px: octreotide 300mg SC x1
    - Tx: HDIS refractors to IVF and catecholamines may promote further release of hormones therefore Tx w/ plasma and octreotide gtt

- Dx
    - Gross: well circumscribed solid round yellow (if fatty) vs red (if vascular) submucosal lesion w/ surrounding kink b/c of intense desmoplastic response
    - 24hr Urine 5-HIAA
        - nl <10 w/ + >100 mg/d w/ 90% sens and spec if…
            - clinical suspicion AND
            - other conditions which can cause a False + are not present: malabsorptive syndrome and eating foods/drugs high in tryptophan/serotonin (eg avocado, pineapple, kiwi, plums, eggplants, walnuts, pecans, bananas, tomatoes) and (eg. Tylenol, mesalamine, cumeric, caffeine) = these generally generate levels b/t 10-100
        - NB falsely normal in foregut/hindgut carcinoids and pts taking aspirin/levodopa
        - b/c of the 24hr collection most people monitor disease with serum chromogranin-A (CgA)
- Staging
    - each GI location has its own AJCC TNM staging system
    - Mets (mainly seen in midgut tumors): 1° Liver, 2° Mesentery, LNs, Peritoneum, 3° Bone, Gonads, Breasts
- Prognosis
    - 60-80% 5yr survival depending on location (best for midgut vs worst for foregut/hindgut), grade/differentiation, size and stage
    - relapse often occurs especially for gastric/small intestine carcinoids therefore surveillance w/ CT/MRI, urine 5-HIAA, serum CgA Q6mo x2yrs then Q1yr x4yrs then Q1yr x10yrs (not needed for small appendiceal/rectal carcinoids)
- Tx (refer above) Endoscopic to Surgical Resection
    - Stomach
        - Type 1/2: EMR/ESD w/ close surveillance b/c pt will continue to form carcinoids based on etiology (unclear what to do if large and/or many, some recommend surgery, some say just follow b/c they are indolent, some do antrectomy for Type I)
        - Type 3: partial/total gastrectomy w/ LN dissection (? EMR/ESD in small tumors)
    - Small Intestine
        - All: en bloc resection w/ removal of mesentery for ANY size b/c potential to metastasize does not correlate w/ size unlike other locations (? EMR/ESD for small tumors)
    - Appendix
        - <2cm: appendectomy
        - >2cm: hemicolectomy
    - Colon
        - <2cm: EMR/ESD
        - >2cm: partial colectomy
    - Rectum

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- <2cm/shallow: EMR/ESD
- >2cm/deeper: LAR/APR based on distance from anal verge

PETs (produce no hormone OR produce hormones that cause no syndrome (eg. neurotensin) OR produce hormones but no apparent clinical Sx OR a clinical syndrome is present)	**Gastrinoma**	**Insulinoma**	**Glucagonoma**	**Somatostatinoma**	**Vasoactive Intestinal Peptide (VIPoma)** Verner-Morrison Syndrome WDHA – Watery Diarrhea Hypokalemia Hypochlorhydria Syndrome Pancreatic Cholera Syndrome
Cell Type	?	B	α Cells (Pancreas) L Cells (Ileum)	Δ	Δ
Pancreatic Localization	60%	97%	95%	55%	90%
Incidence	Common	Common	Rare	Rare	Rare
Malignancy w/ Liver Mets	80%	10%	60%	70%	60%
Syndromes	25%	10%	10%	50%	5%
Symptoms (Local Tumor Bulk, Liver Mets, Syndrome)	Zollinger-Ellison Syndrome (ZES): tumor at any point within "Passaro's Triangle" (jxn cystic duct and CHD, junction of 2nd and 3rd part of duodenum and jxn of neck and body of pancreas, w/ most common sites: D1 duodenum (50%) and pancreas (25%)) • PUD (2/2 increased production of gastric acid, represents 0.1% of all PUD but suspect in pt with recurrent multiple ulcers in weird places esp post-bulbar along with severe GERD, resistant to standard therapy, when you see a duodenal bulb ulcer in the absence of NSAIDs or H. pylori then it is almost always ZES) • Diarrhea (2/2 massive acid hypersecretion and destruction of digestive enzyme) • Large Gastric Folds (2/2 trophic effect of gastrin) • Gastrin stimulates the growth of also ECL cells leading to carcinoids	"Whipple's Triad" (refer) occurring during times of fasting (normally glu does not drop <70 while fasting)	"The D's" • Dermatitis: **Necrotizing Migratory Erythema** (transient cycles of a painful red rash w/ serpiginous border occurring around orifices, fingers, and flexural regions w/ blisters, erosions, scaling along w/ stomatitis and glossitis) • Diabetes • DVT • Depression • Diarrhea • Dyslipidemia • Drop in Weight • Drop in Hct • Glossitis	• Nausea • Ab Pain • Weight Loss • Somatostatin Syndrome (DM, Cholelithiasias, Steatorrhea)	• Diarrhea (watery, profuse >3L/d, nocturnal/fasting b/c secretory) • NAGMA, Hypokalemia • Ab Pain • Hypercalcemia • Hyperglycemia
Diagnosis	• Fasting Gastrin Levels (>1200pg/mL) but not specific as seen in pernicious anemia, chronic atrophic gastritis, CKD, etc must stop PPI x7d • Basal Acid Output (BAO) to distinguish primary vs secondary hypergastrinemia • "Secretin Injection Test" normally somatostatin cells tonically restrain gastrin secretion, secretin stimulates G-cells directly but concurrently indirectly inhibits G-cells by stimulating somatostatin secretion which occurs to a greater degree hence gastrin is not stimulated but gastrinoma are NOT coupled w/ somatostatin cells thus the effect on secretin is solely stimulation	• "72 Hour Fast Test" (refer)	• Serum Glucagon >150pg/ml	• Serum Somatostatin >150pg/mL	• Serum VIP >150pg/mL

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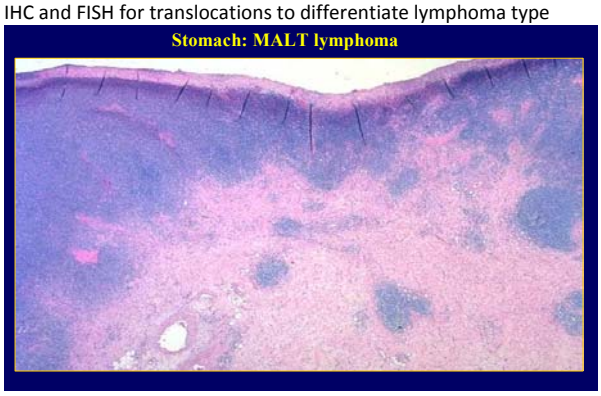
	of gastrin secretion from the tumor hence a paradoxic increase in gastrin (Nl 100 pg/mL w/ ZES having 200-1000 pg/mL)				
Treatment Surgery Chemo Octroetide + Specific Tx to the right	• High Dose H2B/PPI	• NB 50% do not have somatostatin receptors hence octreotide is not helpful • General (timed feedings Q6hrs, restrict fast acting carbs which stimulate insulin release, continuous IV glucose infusion) • Potassium supplementation • Diazoxide/Everolimus inhibits insulin release and stimulates glycogenolysis	• Spontaneous remissions often occur but if Tx is needed then use insulin and lifelong AC		• Steroids • Clonidine • Indomethacin • Lithium

- **Lymphoma**
  - General
    - Primary = main bulk of dz in GI tract w/ or w/o contiguous LN involvement (2% of lymphomas, 2% of GI cancers) vs Secondary = mainly nodal dz w/ extra-nodal GI mets (20% of lymphoma)
      - The most common extra-nodal site is the GI
      - The most common GI site is gastric
      - Generally primary and secondary GI lymphomas are managed similarly
      - HL rarely involves the GI tract rather NHL is the main lymphoma
      - r/o lymphoma w/ IBD Tx is controversial
  - Mechanism: chronic inflammation → acquisition of MALT (in tissue normally devoid of MALT) → neoplastic transformation occurs w/in MALT as lymphocytes become autonomous (they are no longer dependent on the immunologic stimulus provided by the inflammation)
  - S/S: non-specific GI Sx (usually ab pain, weight loss, anorexia, nausea, bleeding w/ other specific Sx depending on location)
    - NB classic B symptoms are generally rare
  - Histology
    - Cell morphology has varying degrees of atypia (small = low grade vs large = high grade)
    - Lymphocyte infiltration can result in follicle formation or lymphoepithelial lesions (lymphocyte invasion/destruction of epithelium/glands)
    - Usually B-cell except in EATL
    - Florid chronic gastritis can look quite similar!!!
    - Southern Blotting or PCR for Ig heavy chain rearrangement to document monoclonality
    - IHC and FISH for translocations to differentiate lymphoma type



  - Dx
    - Modalities
      - EGD: variable depending on type and location but importantly some lesions can be submucosal thus biopsies may miss dz requiring other approaches including tunnel Bx and EUS guided approaches

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- EUS: instrumental in demonstrating depth of wall involvement aka T-staging (usually hypoechoic lesion, unlike carcinoma lymphoma tends to infiltrate horizontally vs growing vertically) and peri-LAD aka N-staging
- Pan-CT: assess distant LAD, + PET if high grade lesions
- BMBx: assess BM
- Labs: LDH and β2-microglobulin WNL

▪ Staging: **Ann Arbor Classification** is inadequate for GI lymphomas since it does not incorporate information on the depth of tumor invasion which is known to affect prognosis thus other systems have been developed with the most common one being the **Lugano Staging System**

▪ The International Prognostic Index (IPI)
- Based on age (≥60yo), Ann Arbor Stage (≥III-IV), ECOG Performance Status (≥2), Extranodal Dz (≥2), LDH (≥2xULN)
- Low (0-1), Int-Low (2), Int-High (3), High (4-5)

o Types based on immunodeficiency state and organ site

▪ Immunodeficient
- **EBV induced Post Transplant Lymphoproliferative Disorder (PTLDs)** (refer to immunology notes)
- **HIV Associated NHL** (refer to HIV notes)

▪ Gastric (5% of gastric malignancy, the most common extranodal site for secondary lymphoma, most common site for primary GI lymphoma 65%)
- **Marginal Zone B Cell Lymphoma of MALT Type aka MALTomas (45%)**
  - o Type: low grade lymphoma w/ small less-atypical lymphocytes
  - o Mech: arise from MALT that…
    - ▪ (1) has been acquired in sites of inflammation (eg. *Helicobacter pylori* infection – 90% however not all chronic HP gastritis develop lymphoma suggesting unknown environmental, microbial, genetic factors) or
    - ▪ (2) exists under normal physiologic circumstances (eg. rare Peyer's Patch – 10%)
  - o Epidemiology
    - ▪ incidence correlates w/ the incidence of HP infection
    - ▪ ~60yo
    - ▪ 1M:1F
  - o Gross
    - ▪ variable in number (½ single vs ½ multiple)
    - ▪ variable in appearance (1° mucosa/submucosal infiltration, 2° eroded/ulcerated mass, no findings suggest lymphoma vs carcinoma)
    - ▪ variable in location (localized vs diffuse, most commonly in antrum)
    - ▪ always obtain separate normal antral Bx for HP staining and to characterize extent and multifocality
  - o S/S: dyspepsia, anorexia, early satiety, weight loss, N/V (bleeding, obstruction and B-Sx are rare)
  - o Complications: Conversion to DLBCL
  - o Tx
    - ▪ Lugano Stage I w/ mucosa/submucosa involvement (75%) = HP eradication
      - Assess for HP Eradication at 8wks via HPSA/UBT or CLO during EGD
        - o NB 20% will need reTx
        - o NB HP negative pts generally do not respond to antibiotic Tx but some cases have been documented in the literature nevertheless these pts should be Tx w/ radiation
      - Assess for Histologic Response at 8wks then Q3mo via EGD until Complete Histologic Remission and then follow Q6mo x2yrs then only if Sx return
        - o NB biopsy technique and definition of "Complete Histologic Remission" is unclear, the Witherspoon histological index is often used, Grade 0-2 = complete remission, 3 = partial remission, 4 = no remission, GET INDEX FROM UTD
      - ~75% achieve complete remission at a median time of 15mo (range: 5-36mo)
        - o NB ~90% remaining in remission at ~3yrs vs 10% relapse (Tx w/ radiation)
        - o NB even w/ complete histologic remission 50% of pts will still have monoclonal lymphocytes (the clinical significance of this clonality is unclear)

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- ~25% do not reach remission
    - NB most have t(11;18) or t(1:14)
    - NB always rule out conversion to DLBCL
    - sometimes remission takes a long time (up to 36mo in some pts) hence do not call "partial/no remission" until ~12mo
    - NB recent studies suggest that Tx w/ unimodality therapy (radiation) or single chemotherapy (rituximab, cyclophosphamide, cladribine, bortezomib) is highly effective w/ ~90%? Achieving complete remission but at the cost of more complications (hence not the primary Tx)
- Lugano Stage I w/ muscularis propria or serosa involvement, II, III (15%) = HP eradication then unimodality therapy (radiation or R-CHOP chemotherapy)
- Lugano Stage IV (10%) = HP eradication then trimodality therapy (radiation + chemotherapy + surgery)
    - NB aside for advanced stage surgery is generally reserved for complications (perforation, hemorrhage, obstruction)

- **DLBCL (55%)**
    - Type: high-grade w/ larger atypical lymphocytes
    - Mech: poorly understood but about 1/3 seem to arise from low-grade MALToma as some have HP infection and respond w/ HP eradication and have focal areas that look just like MALToma
    - Gross: usually seen as a unifocal large mass and not multifocal infiltration commonly seen in MALToma, can occur anywhere in the GI tract
    - S/S: unlike MALToma local Sx (obstruction and bleeding) and systemic Sx (?) are more common
    - Prognosis: unlike MALToma DLBCL have more advanced stage and worse prognosis
    - Tx: for all stages HP eradication (if present) followed by bimodality therapy (RCHOP chemotherapy and radiation, NB given dramatic regression w/ bimodality therapy bleeding and perforation is a distinct complication occurring during Tx in 5% of pts) w/ surgery reserved for complicated advanced staged cases
- **Other: Mantle Cell, Follicular, Peripheral T-cell (rare)**

- Small Intestine (25% of primary GI lymphomas, 15% SI malignancies)
    - NB radiation/surgery is generally avoided b/c intestinal lymphoma is usually multifocal
- **Enteropathy-Associated T Cell Lymphoma (EATL) (refer to CD)**
- **Immunoproliferative Small Intestinal Disease (IPSID) aka Alpha Heavy Chain Disease aka Mediterranean Lymphoma**
    - Epidemiology: ~20yo, occurs in Mediterranean and Middle East, lower socioeconomic status w/ poor sanitation
    - Mech: microbial antigens from underlying GI infection (esp *Campylobacter jejuni*) → stimulate plasma cell differentiation → conversion to neoplastic plasma cells which produce unusual amounts of heavy chain IgA
    - Gross: generalized nodular thickening to discrete mass in the proximal SI w/ surrounding mesenteric LAD (intestine appears immobile and indestinsible)
    - Histology: plasma cell infiltration in mucosa w/ broaden villi and shorten crypts
    - S/S: malabsorption diarrhea, ab pain, anorexia, significant weight loss, fever, clubbing, peripheral edema
    - Labs: anemia, vitamin deficiencies, high ESR
    - Dx: histology (sometimes Bx is not deep enough and thus some recommend staging laparotomy for full thickness Bx) and presence of alpha heavy chain in all body fluids (serum/urine/saliva) via SPEP and tissue via IHC
    - Tx: intensive nutritional support, Tetracycline or Flagyl/Amp x6-12mo and if poor response or advanced dz then CHOP-chemotherapy
- **Marginal Zone B Cell Lymphoma of MALT Type aka MALTomas**
    - Mech: similar to gastric MALToma but HP infection is usually not the cause however some studies have demonstrated responses w/ HP eradication
    - Gross: single annular exophytic mass
    - Tx: surgery
- **Mantle Cell Lymphoma aka Multiple Lymphomatous Polyposis**
    - Gross: multiple lymphoid polyps at ICV
- **Other: DLBCL**, **Follicular**, **Burkitt's** (refer)

- Oropharynx along Waldeyer's Ring (5%, EBV associated, Types: DLBCL, MALToma, Peripheral T-cell lymphoma, et al, S/S: airway obstruction, hearing pain, enlarging painless mass, dysphagia, foreign body sensation in the

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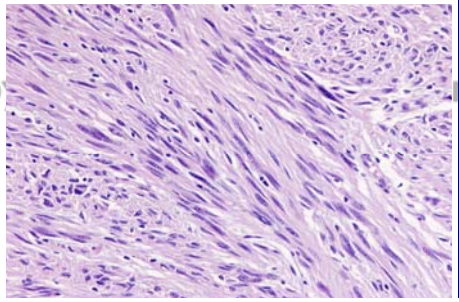
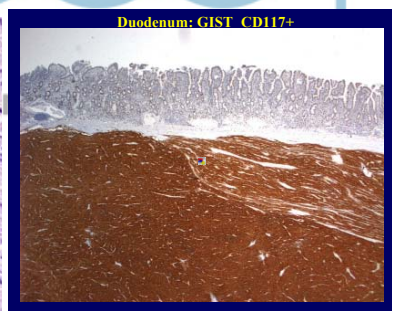
throat, cervical LAD, Gross: tonsil, nasopharynx, tongue base, sometimes hard to distinguish from SCC, Tx: chemoradiation)
        - Colorectum (5%)
        - Esophagus (rare, usually mets from cervical or mediastinal secondary lymphoma or primary gastric lymphoma, only 30 cases of primary esophageal lymphoma reported in the literature, seen mainly in HIV pts, most are DLBCL, Sx similar to other esophageal malignancies)
- **GastroIntestinal Stromal Tumors (GISTs)**
    - Pathophysiology
        - b/f 1999 a collection of GI tumors were clumped together as variants of sarcomas but after 1999, based on advanced IHC, they are now separated into sarcomas (smooth muscle lineage, **+SMA** IHC), plexosarcomas (neurogenic lineage, **+S100** IHC) and GIST (stromal lineage deriving from Interstitial Cells of Cajal (ICC), **+CD117** IHC)
        - c-KIT binds Receptor Tyrosine Kinase (RTK) aka CD117 Ag which activates the kinase causing signal transduction and subsequent cellular proliferation (NB this system not only exists in ICC but also melanocytes, RBCs, germ cells, mast cells, hence tumors of these cells can be misinterpreted as GISTs), in GISTs there is an activating mutation of RTK
    - Epidemiology
        - 5000k/yr in the US, ~60yo, M>F
        - 2% of all GI tumors
        - Most are idiopathic but some familial and if so there are other S/S including skin lesions (hyperpigmentation, urticaria pigmentosa, etc), some GISTs are associated w/ NF-1 and Carney Triad (GIST + pulmonary chondromas + extra-adrenal paragangliomas)
    - S/S
        - Often asymptomatic found incidentally otherwise non-specific S/S depending on size and location: 1° stomach (65%), 2° SI (25%, NB worse prognosis), 3° esophagus / colon / mesentery / omentum / retroperitoneum (10%)
        - metastasis to liver (50%) and lung (50%) NB not LNs
    - Dx
        - Since these tumors are typically deep in GI wall hence mucosal biopsies are often normal therefore you need EUS (hypoechoic b/t muscularis propria and musclaris mucosa) guided FNA of deeper tissue w/ subsequent *c-kit* staining
        - Overlying mucosa appears as a smooth protrusion
        - Lesions are often vascular therefore Bx can be dangerous in addition tumor seeding of peritoneum/mesentery if tumor ruptures
        - Always get a CT-A/P to ensure no other lesions are present
        - PET scan is important to assess response of Gleevec
        - Histology: monomorphic spindle cell (70%), epithelioid large round cell (20%), mixed (10%)
        - IHC: KIT 95% (negative KIT are due to PDGFRA mutation), CD34 65%, SMA 35%
        - Malignant potential is high if >5cm and >5 /HPF mitotic count
        - Check for mets and LN involvement



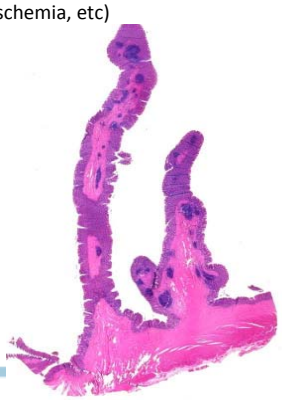


    - Prognosis
        - Some are benign and some are malignant but you cannot tell based on histology as you do with other cancers rather benign is seen in small tumors w/ low number of mitoses and EUS showing regular margins and homogenous appearance
        - 5yr-survival of 50% if appropriately Tx
    - Tx
        - Localized/Resectable/Initial: surgery then adjuvant imatinibe (Gleevec)
        - Metastatic/Unresectable/Recurrent: tyrosine kinase inhibitors like imatinibe (Gleevec), chemoembolization of liver lesion, NB if initially unresectable you can try neo-adjuvant imatinibe (Gleevec) to reduce to a resectable size w/ max effect after 3-6mo of Gleevec
            - SEs of Gleevec: facial edema, D, myalgia, rash, HA, hemorrhage (most important one) but SEs are only temporary
            - Use PET scan 1d after start of Gleevec to asses immediate response to Gleevec
            - Duration of Gleevec is lifetime
            - Sunitinib (Sutent) general TK inhibitor and used in Gleevec resistant cases

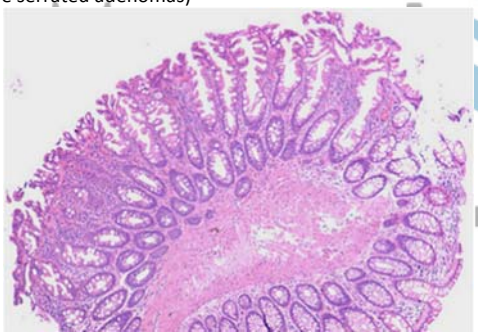
- NB traditional cytotoxic chemo does NOT work at all
  - why? there is high expression of MDR-1 which pumps out chemo from inside tumor cell
- NB radiation does NOT work at all

Non-Neoplastic Growths (NO cellular dysplasia)

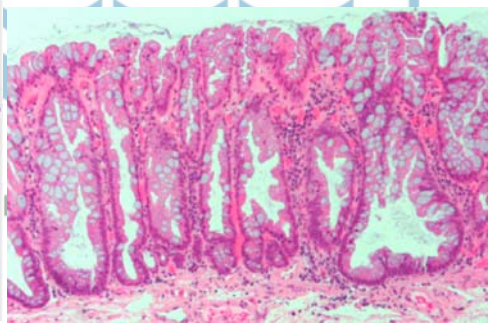
- Mucosal
  - Other
    - **Benign Lymphoid Polyp** (polyps that develop in response to rectal irritation)
    - **Psuedopolyp** (isolated regeneration of inflammatory to normal mucosa, seen in any chronic colitis (IBD, amebic colitis, ischemia, etc)



    - **Neurofibromas/Ganglioneuromas** (overgrowth of nerve tissue, seen in NF, MEN, etc)
    - **Nodular Lymphoid Hyperplasia** (very common but if large consider FAP, CVID, lymphoma)
    - **Mucosal Polyp** (normal tissue that appears as a polyp)
    - **Rectal Carcinoids**
    - **Cecal Lipomas**
    - **Endometriosis**
    - **Colitis Cystica Profunda** (refer)
    - **Pneumatosis Cystoides Coli** (refer)
- Serrated Polyp (NB can develop adenomatous changes if dysplasia is present turning them into hyperplastic adenomas or sessile serrated adenomas)



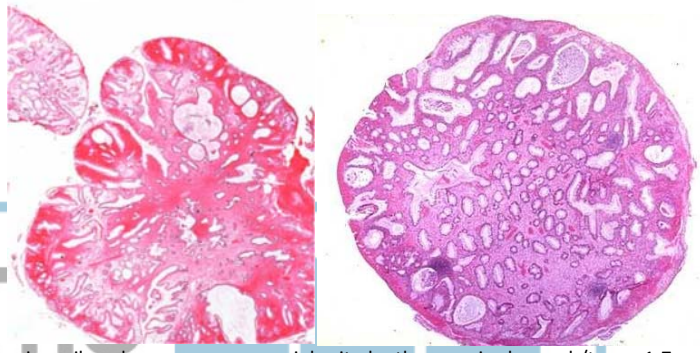
Hyperplastic



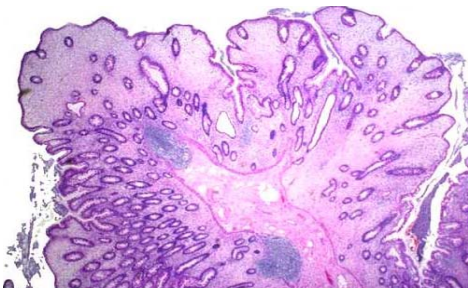
Serrated Adenoma

  - **Hyperplastic Polyps/Adenomas (HP/HA)**
    - Histology: epithelial cells and goblet cells grow in number at the surface outgrowing space creating a "frilly" surface and star shaped lumen on cross-section of crypt
    - Mechanism: migration of epithelial cells up to colonic crypt is slow and mature cells fail to detach
    - Endoscopy: small (<5mm), found in 10% of adults >50yo, represent 20% of diminutive polyps, more common in rectosigmoid region
    - Risk of Cancer: Low
  - **Sessile Serrated Polyps/Adenomas (SSP/SSA)**
    - Histology: looks like a hyperplastic polyp but the hyperplasia extends down into the crypt bases creating more dilated/branching/"boot-shaped"/"L-shaped" bases
    - Incidence: 8% of CRC screening colonoscopies
    - Endoscopy: mucus cap (very important sign), same color as surrounding mucosa, smoother surface than adenomas, edges less distinct that adenomas, decreased vasculature on surface, R sided, larger, sessile, multiple in number w/ high r/o synchronous/metachronous polyps (generally very subtle b/c all the changes occur at the base of crypts)
    - SSPs can develop adenomatous features and thus should be called SSAs

        - Risk of Cancer: High
        - Genetic Pathway: CIMP Pathway & BRAF Mutation
        - There is some suggestion that there is progression of right sided HPs to SSPs to SSAs
    - **Traditional Serrated Adenoma** (very rare, unclear)
    - **NB Serrated Polyposis** (formerly called Hyperplastic Polyposis Syndrome)
        - Criteria (any type of serrated polyp)
            - ≥20 serrated polyps of any size distributed throughout the colon
            - ≥5 serrated polyps proximal to sigmoid and ≥2 of which are ≥1cm
            - Any serrated polyp proximal to sigmoid in a first degree relative of a pt w/ serrated polyposis
        - 25% lifetime risk of CRC
        - Surveillance: Qyr colonoscopy
- Hamartomatous Polyps (tissue components are normal w/o overgrowth of epithelial cells BUT tissue is disorganized in some way)
    - **Tuberous Sclerosis** (?)
    - **Juvenile Polyposis Syndrome** (dilated/distorted cystic glands otherwise normal tissue)



        - NB non-syndrome juvenile polyps can occur, non-inherited rather acquired, seen b/t ages 1-7yo, usually solitary polyp, 3mm-2cm, polypoid w/ long stalk, often rectosigmoid region, painless hematochezia or prolapse, do not recur after polypectomy, no malignancy potential
        - Mechanism: 2/3 sporadic vs 1/3 genetic alteration in the **TGF-β Signaling Pathway** 2/2 AD mutation of **MADH4/SMAD4** gene OR the **BMPR1A** gene
        - S/S
            - **JPS and HHT b/c similar genetic mutations!!!**
            - GI (not only polyps but also Meckel's diverticulum and malrotation)
                - 5-100 polyps in the colon >>> stomach > small intestine
                - Some of these polyps are hamartomatous and adenomatous polyps
                - FTT, anemia, intussusception, diarrhea, protein loss, rectal bleeding, obstruction
                - Cancer (50% develop colon/gastric cancer and 20% develop upper GI cancer by 35yo b/c of the coexistence of adenomatous polyps not b/c of the juvenile polyps)
            - CNS (macrocephaly, hydrocephalus)
            - Heart (coarctation of the aorta, atrial septal defect, tetralogy of fallot)
            - Urogenital (undescended testicles, bifid uterus/vagina, unilateral renal agenesis)
        - Screen: first degree relatives
        - Surveillance: pan endoscopy Q1-3yrs starting at 15yo and also look for HHT
        - Tx: polypectomy but some consider subtotal colectomy w/ ileorectal anastomosis
    - **Cronkhite-Canada Syndrome - CCS** (similar to JPS polyps but there is additional mucosa injury w/ edema and eosinophil/lymphocyte inflammation in the lamina propria w/ foci of adenomatous/hyperplastic/harmartomous tissue)



        - General
            - Historical
                - C and S in 1955 reported two cases (42yo & 75yo female) of sub-acute presentation of N/V/D w/ generalized polyposis and dermatologic changes, both

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pts were Tx w/ “symptomatic therapy and dietary supplements” along w/ quinidine/TOO/cortisone in one pt, despite Tx both pts died at 8-10mo after presentation
        - In their discussion they highlight two other polyposis disorders, one likely FAP and the other PJS and recognize that these two pts did not fall into either of these syndromes
        - Since first description ~500 cases have been reported in the literature w/ most reports from Asia and a most being case reports w/ only a few series w/ the largest from Mayo (14pts b/w 1955 and 2009)
    - Epidemiology
        - ~60yo 3M>2F
        - can develop in every ethnic group but some Asian predominance
        - uncommon w/ an incidence of ~1/1,000,000
- Mechanism
    - poorly understood but bot believed to be inherited rather the prevailing theory is that it is acquired or be autoimmune condition
        - often precipitated by a disturbance in immune fxn (eg infection, concomitant neoplasm), mental stress, physical fatigue, et al
        - some reports of improvement w/ HP Tx suggesting a link but universally seen in all pts
        - some reports of increased concurrent autoimmune conditions (eg. SLE, RA, scleroderma, et al)
        - recent evidence suggests that it falls under the IgG4 autoimmune spectrum w/ + IgG4 staining
- S/S (p/w acutely ill w/ GI and dermatologic Sx, early Sx are very non-specific)
    - GI
        - General
            - Sudden onset (many times pts have recent prior endoscopies which were entirely normal)
            - Diffuse involving the entire GI tract (except esophagus w/ colon/stomach > small bowel)
            - Characterized by mucosal injury followed by polyp formation
            - Early on often confused for IBD, TB, etc
        - Mucosal Injury
            - Endoscopy: ?
            - Histology: ?
            - Complications: cancer, protein loosing enteropathy, abdominal pain, malabsorptive diarrhea, weight loss, anorexia, hypo/dysgeusia, electrolyte abnormalities, GIB
        - Polyposis
            - Endoscopy: multiple erythematous polyps, superficial erosions/ulcers
            - Histology: refer above
            - Complications: cancer, intussusception, prolapse
            - NB looks quite similar to JPS but intervening mucosa is abnormal AND histologic changes are more significant
    - Derm (can manifest before/during/after (most common) GI dz, therefore the original belief that these changes are sequela of malnutrition may not be true)
        - Nail Dystrophy (thinning, splitting, onycholysis)
        - Cutaneous Hyperpigmentation (patchy pattern, extremities uniquely involving palms/soles along w/ face and trunk, histologic examination is consistent w/ increased melanin deposition not increased melanocytes)
        - Alopecia
        - Pitting Edema
- Dx: clinical dx based on combination of GI and dermatologic findings (rule out other polyposis syndromes) no evidence that screening family is helpful
- Cancer Surveillance
    - Risk not well defined but believed to occur in 25% of pts at 5yrs based on case series w/ the longest f/u
    - r/o colon/gastric (primarily right colon) > small bowel cancer
    - 8M>1F
    - no agreed upon surveillance protocol but some recommend gastroscopy/colonoscopy Q1-3yrs
    - unclear if cancer arises from polyp or just background chronic mucosal inflammation (akin to IBD) b/c of this unclear if polyps should be removed or should one just Bx polyps and mucosa

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- if any Bx or polypectomy shows any dysplasia then total colectomy/gastrectomy has been recommended
  - Tx
    - 25% obtain long term remission w/ supportive Tx (electrolyte replacement, parenteral nutrition)
      - definition varies b/t studies but likely resolution of dermatologic changes and GI Sx, ?polyps
      - occasionally extensive polyp burden requires surgical resection
    - 75% need more aggressive Tx (no evidence based therapies just case reports) w/ another 25% achieving remission
      - 1° corticosteroids w/ prednisone 40mg QD x1wk then taper over 1mo (most experience, if relapse then consider re-Tx w/ steroids and start immunomodulating therapy)
      - 2° other therapies w/ documented success: acid suppression, cromolyn, 5-ASAs, anabolic steroids, antibiotics
  - Prognosis: 50% mortality at 5yr despite Tx above w/ pts dying from malnutrition, GIB, infection rarely cancer
- **Peutz-Jeghers Syndrome** (arborized muscular bundles fanning out into the head of polyp)

  - Epidemiology: 1/200k, 20yo
  - Mechanism: incomplete penetrance AD mutation in **STK11/LKB1** gene
  - S/S
    - GI Polyps/Cancer
      - Polyps in small bowel esp duodenum > colon > stomach
      - Intussusception (2/2 large SI polyps, some suggest enteroscopic surveillance for removal polyps given the fact that surgery is needed to Tx intussusception if they occur), Bleeding, Obstruction
    - Non-GI Cancers (93% life time risk of developing any type of cancer!!!)
      - Cancer (breast-55%, colon-40%, pancreas-35%, stomach-30%, ovary/testis-20%, lung-15%, SI-15%)
      - Unusual Ones
        - Testi Sertoli Cell Tumor = premature adolescence
        - Cervical Adenoma Malignum = very aggressive cancer
    - Derm
      - Lentigines
        - small brown/black macules around vermillion border of lips, buccal mucosa, bridge of nose, palms, soles, perianal, around eyes
        - fade over time
        - unlike freckles these are present at birth

  - Screen: first degree relatives at 8yo
  - Surveillance
    - Breast Exam & Mammogram @25yo and then Q6mo
    - Colonoscopy @18yo and then Q3yrs
    - MRCP, EUS and CA 19-9 at 25yo and then Qyr
    - EGD/CE @10yo and then Q2yrs
    - Pelvic Exam, TV-US and CA-125 at 20yo and then Qyr

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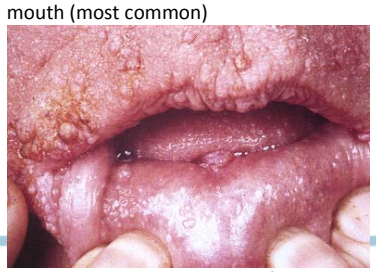
        - Testicular Exam @ Birth and then Qyr
    - Tx: polypectomy if complicated or >0.5-1.5cm
- **Cowden Syndrome** (similar to PJS polyps)
    - Epidemiology: 20y
    - Mechanism: AD mutation in **PTEN** gene (NB 20% do not have this mutation)
    - S/S
        - GI: polyps throughout GI tract but esp at rectosigmoid junction
            - Esophageal glycogenic acanthosis
            - Generally do not cause Sx
            - NB initially believed to have no link w/ colon cancer but in 2010 it was concluded that the risk is higher = screening at 35yo
        - Derm (portend onset of extra-GI cancer)
            - Trichilemmomas
                - skin/pink/brown colored flat papules ~warts on around eyes, nose, mouth (most common)



            - translucent punctuate keratosis of palms/soles
            - hyperkeratotic flat-topped papules on dorsum of hands/forearms
            - buccal mucosa/gingival/labial/palatal papules that coalesce giving a cobblestone appearance
            - furrowed tongue
            - penile freckling
            - microstomia, pointy nose
        - MS
            - macrocephaly (most common)
            - kyphoscoliosis
            - high arched palate
        - CNS
            - Lhermitte-Duclos Disease (hamartomas causing mass effect in the cerebellum causing hydrocephalus/herniation, may need surgery if significant Sx)
            - Autism
            - MR
            - Seizures
            - Ganglioneuroms/Meningiomas
        - GU
            - Breast fibrocysts/cancer (28% lifetime risk)
            - Uterine fibroids/cancer (60% lifetime risk)
        - Endo
            - Thyroid nodules/goiter/cancer (3% lifetime risk)
    - Surveillance: thyroid/breast/uterine/colon cancer, start screening 18/25/35/35yo or 5yrs younger first degree relative
    - Tx:
    - NB **Bannayan-Ruvalcaba-Riley Syndrome**
        - PTEN mutation (40% do not have this mutation) and thus some consider to be a different phenotype of Cowden's occurring in young males w/ primarily intestinal polyps, macrocephaly, developmental delay, pigmented spots on penis, thyroiditis, lipoma, hemangioma, AV malformations

Neoplastic Growths (cellular dysplasia)

- History
    - 1970's Rockefeller discovered oncogenes vs tumor suppressor genes
    - 1980's Volgestein using RFLPs discovered paternal vs maternal genes and concept of LOH in Chromosome 17p which codes for p53 in CRC
    - 1990-2000's (below)
- Symptoms
    - Presentation (ascending 25%, transverse 10%, descending 5%, rectum 60%)

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        - R Colon (big diameter w/ liquid feces = perforation, Abdominal Mass then Sharp Constant Somatic Pain (peritonitis), occult bleeding or melena, no change in bowel habits
        - L Colon (Small Diameter and Solid Feces, Large Bowel Obstruction, Dull Crampy Visceral Pain 2/2 Obstruction with Tenesmus if Rectal, Hematochezia, Alternating C/D as feces is blocked then released with smaller stool caliber)
        - Other
            - usually silent early on
            - microcytic anemia in male or postmenopausal female is colon cancer until proven otherwise
            - stretching of neurovascular bundle as stool passes polyp can cause pain
            - also there is Acanthosis Nigricans (refer to gastric cancer), Sign of Leser-Trelat (refer to gastric cancer), Hypertrichosis Lanuginosa (lanugo hair on face, seen in many other cancers including lung, hematologic, pancreas, gallbladder, breast, genitourinart tract)
            - occult or overt bleeding 2/2 surface erosion (most common)
            - electrolyte loss and watery diarrhea esp w/ >3cm rectosigmoid villous adenomas (in contrast to the absorption of water and sodium and secretion of potassium by normal colonic mucosa, villous adenomas exhibit a net secretion of water and sodium and an exaggerated secretion of potassium, and b/c these polyps are in the rectosigmoid region there is little surface area distal to tumor for reabsorption of water and electrolytes)

- Mechanism
    - Early: Aberrant Crypts (only crypt architecture is different, when methylene-blue stained mucosa is viewed with a magnifying endoscope the lumens of aberrant crypts are elliptical/irregular vs circular, macroscopically the mucosa appears perfectly normal)
    - Late
        - Pedunculated/Sessile (Paris I) (as cells continually divide in adenomas instead of cells sloughing off to allow for new cells, the proliferative cells just accumulate branching outward (tubular) or infolding downward (villous) creating new glands)
            - Tubular: Pedunculated (aka w/ stalk), >80% of glands are complex branching glands, NO surface finger like villi, Hard, Mild Dysplasia, Smaller
            - Tubuvillous
            - Villous: Sessile (aka w/o stalk), >80% of glands are simple long straight glands, MANY surface finger like villi, Soft w/ Mucus Secretions, Severe Dysplasia, Larger
        - Flat/Depressed Adenomas (Paris II)
            - flat lesions are no worse than Paris I lesions BUT depressed lesions are much more dangerous
            - high risk of high grade dysplasia
            - may actually be the precursor to the long-recognized but uncommon so-called de novo colon cancer
            - often missed on endoscopy therefore techniques using endoscopic magnification or chromoendoscopy in which dyes are sprayed to generate contrast relief are being employed
            - seen as an opacification of blood vessels
    - Polyp
        - Adenoma NB darker than nl epithelium
            - Low Grade Dysplasia (epithelial become dysplastic (darker, irregular, elongated) w/ loss of goblet cells) vs High Grade Dysplasia (cribriforming glands aka glands fuse and have clear spots w/in them) vs CIS (dysplastic epithelial cells cross the basement membrane suggested by a jagged surface and a desmoplastic response of the lamina propria) vs AC
                - NB LGD involves the entire length of the gland, if normal superficially then likely reactive change
            - Tubular (normal smooth surface and parallel crytps) vs Villous (finger like surface)

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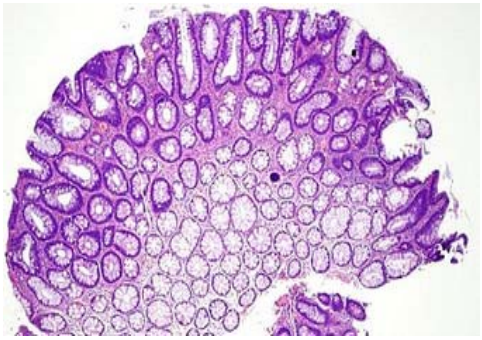
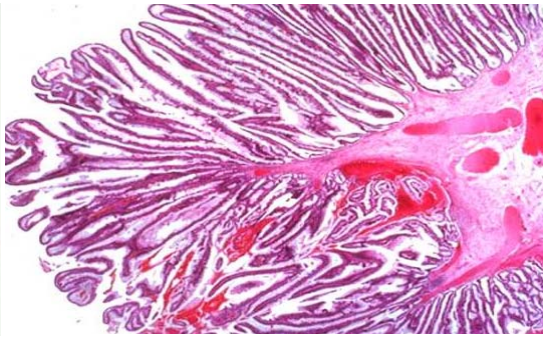
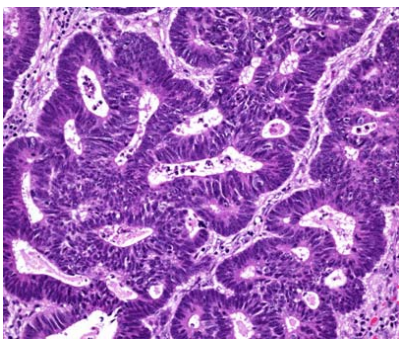
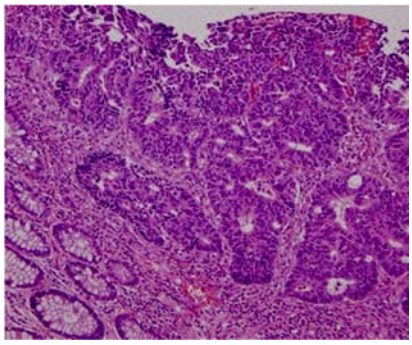

Tubular Adenoma


Villous Adenoma

HGD AC

- Genetics
  - General
    - CRC arises from 1 of 3 patterns (typically one predominates) of instability (below)
    - In some cases these cancers come from adenomas which is the result of activation of the **Wnt Signaling Pathway** but not all cancers come from polyps i.e. flat cancers skip this process and just go on to have mutations in one instability pathway
      - Adenomatous Polyposis Coli (APC) protein (5q) inactivates β-catenin preventing it from stimulating cell proliferation BUT when there is an inactivating mutation of APC or there is an activating mutation of β-catenin then you get cellular proliferation and formation of polyps and these polyps are at increased risk for acquiring mutations in one of the instability pathways b/c they have constantly replicating cells
      - **Adenomas can subsequently undergo CIN creating large villous adenomas w/ dysplasia, CIMP/BRAF creating serrated adenomas, MSI creating ? adenomas**
  - **Chromosome INstability (CIN) Pathway (50%) aka Classic Vogelstein Pathway (Aneuploidy)**
    - Activation of Proto-Oncogenes (K-ras) creates large villous adenomas w/ dysplasia → Loss of Heterozygosity of Tumor Suppressor Genes (p53) creates cancerous polyps
  - **CpG Island Methylation Phenotype (CIMP) Pathway & BRAF (35%) (Euploidy)**
    - Epigenetic silencing hypermethylation of CpG islands (clusters of cytosines followed by guanosines found in the promoter of many genes) in promoters of Tumor Suppressor Genes → Serrated Polyps → CRC (fast progression)
    - NB there is overlap b/t CIMP and MSI in that CIMP can hypermethylate MMR genes
  - **Micro Satellite Instability (MSI) Pathway (15%) (Euploidy)**
    - microsatellites are short (eg. 10-100 bases) simple repeats (eg. all As, ATs, AATTs etc) that are prone to mutations (because of their repetitiveness polymerases slip a lot resulting in frameshift mutations via insertions and deletions) these mutations are repaired by the MMR/BER pathways → CRC (moderate progression)
      - **MisMatch Repair (MMR)** Genes called **MSH2**, **MLH1**, **MSH6**, **PMS2** eg. HNPCC Syndrome = germ line (not sporadic) MMR mutation resulting in accelerated progression phase, few polyps but many turn into cancer b/c they have acquired fast progression rates
      - **Base Excision Repair (BER)** Genes called **MUTMYH** which is a DNA glycosylase that repairs oxidative DNA damage particularly of the APC gene resulting in accumulating transversion mutations (G>T) eg MUTYH Polyposis
    - When there is a mutation in the MMR/BER pathways there is subsequent accumulation of mutations of not only tumor suppressor genes and oncogenes but also microsatellites termed "MicroSatellite Instability (MSI)" thus MSI reflects the degree of mutations specifically in the MMR/BER genes = MSI is easy to detect and thus is used as a surrogate marker for oncogene/TSG mutations (in addition MS are also found w/in oncogene/TSG)
      - degree of MSI is assessed by looking at a panel of five markers defined by the National Cancer Institute
        - 0/5 markers mutated = MS-S (MicroSatellite Stable)
        - 1/5 marker mutated = MSI-L (Low Level of MicroSatellite Instability)
        - ≥2/5 marker mutated = MSI-H (High Level of MicroSatellite Instability)
- Risk Factors
  - **Sporadic (85%)**
    - Epidemiology
      - 3rd most common cancer 150k/yr, 2nd most common cause of cancer death 50k/yr
      - general population has a 6% lifetime risk of developing CRC w/ 25% of pts at 50yo having adenomatous polyps w/ 10% having advanced features
    - Above mutations BUT they are not germline rather they are acquired
    - Lack of Protection
      - ASA → less COX-2 inhibition → less cellular proliferation, more apoptosis, less angiogenesis
        - NB modified NSAIDs eg 17hosphor-sulindac are being developed which have less toxicity
        - NB aspirin ≥81mg for ≥5yrs → decreases incidence/mortality of R/proximal CRC
      - Calcium → less calcium to neutralize the mutagenic effects of bile acids on colonic mucosa
      - Hormone Replacement Therapy
      - Diet high in Selenium, Folate, Carotene, Fiber, Vit C, Vit E, Vit D

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- Fiber → by its mere presence it dilutes any carcinogens (both exogenous and endogenous) because fiber is not absorbed → in addition fiber expedites removal of carcinogens → therefore low fiber diet = colon cancer
- Vegetables/Fruit
- Exercise

- Ethnicity: AA>White
- Age: >50yo
- Gender: M > F BUT F have higher r/o proximal lesions
- Nationality: Japan > Australia > US > Europe > South American > Asia > Africa, Urban > Rural
- Diet: High Fat and Red Meat
- Lifestyle: Obesity, Smoking, Alcohol
- Medical Conditions (periodic surveillance is indicated)
  - **IBD**
  - ***Streptococcus bovis/salivarius & Clostridium septicum* bacteremia and JC Virus???**
    - Increased r/o CRC AND colon polyps
    - Unclear if bacteria causes cancer from the production of carcinogens or cancer allows for translocation nevertheless a clear link exists
    - S. salivarious is also seen in hepatobiliary and C. septicum is also seen in hematologic malignancy
  - **Uretero-sigmoid-ostomy** (ureter diversion procedure in which ureters are connected to sigmoid) → increased urinary amines in colon → fecal flora convert urinary amines into N-nitrosamines which cause polyps (20yrs out) and cancer (25yrs out) in ~30% of pts especially at anastomotic site
  - **Acromegaly** → mechanism unclear (likely increased IGF-1) but especially seen in acromegalics who also are young, have +FHx of colon cancer, have multiple skin tags (acrochordons), and had prior polyps
  - **Pelvic Irradiation**
  - **Dermatomyositis**
  - **Cholecystectomy** (increases bile acid presence in colon which is carcinogenic)

- **Familial (10%)** (>2 CRC in a family but no causative gene is known)
  - CRC Lifetime risk of 15/20% if FDR w/ adenoma/CRC and higher if younger or more than one FDR
  - all types of mutations (major to minor (aka polymorphisms)) of ancillary genes and of genes central to the adenoma-carcinoma pathways below
- **Inherited Syndromes (5%)** (unlike sporadic these cancers have germline mutations of known causative genes w/ 3% Lynch, 1% FAP, 1% other – if a pt has <100 polyps then check both Lynch and FAP but if >100 then just check FAP, other things that suggest inheritance: <50yo, synchronous/metachronous tumors, extracolonic tumors, FHx)
  - **BRCA**
  - **Inherited Syndromes of Hamartomatous Polyp**
  - **Familial Adenomatous Polyposis (FAP) (1%)** (2/3 FHx vs 1/3 Spontaneous Mutation)
    - DDx of Polyposis
      - Adenomas (FAP)
      - Hamartomas (PJS, CCS, JPS, CD, BRRS)
      - Serrated (HPS)
    - Mechanism: germline mutation resulting in many polyps but only some turn into cancer b/c cells still have normal progression/promotion rates but because there are so many cancer risk is increased
    - Two Types
      - **AD** Mutation in **APC** Gene (70%)
        - Onset / Polyp number is determined in part by mutation location but even two pts with the same mutation can have different phenotypes
        - Generally mutations at the ends of the exon cause attenuated FAP while mutations in the middle cause more severe dz
        - I1307K mutation has a much higher r/o CRC than other mutations and is uniquely seen in 6% of all Ashkenazi Jews
      - **AR** Mutation in **BER aka MUTMYH** Gene (30%) = "MUTYH Associated Polyposis" (MAP)
        - unlike in APC parents are normal b/c AR
    - Polyps/Cancer (lifetime risk)
      - **Colon Polyps/Cancer (100%/100%, pt will get colon cancer at some point!!!)**: 100-1000s ("carpet") polyps w/ avg age 15yo, symptomatic w/ avg age 33yo w/ dx 36yo, cancer w/ avg age 39yo w/ death at 42yo
      - **Duodenal/Periampullay/Ampullary Polyps/Cancer (90%/10%)**: 124x increased risk compared to general population, not just duodenum but esp ampullary/periampullary, often multifocal, 2nd most common cause of death after colon cancer
        - Tx based on stage is unclear
        - Spigelman Classification
          - Stage 0 = 0 points = Q3yr EGD/Duodenoscope (when screening always take Bx of ampulla even if it appears normal)
          - Stage 1 = 1-4 points = Q2yr EGD/Duodenoscope

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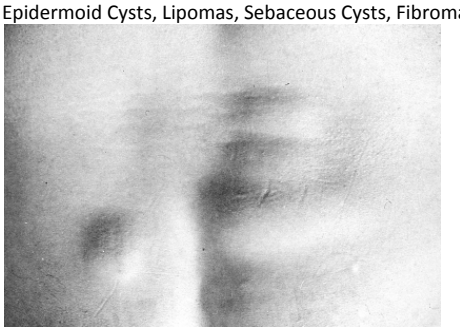
- Stage 2 = 5-6 points = Q1.5yr EGD/Duodenoscope
- Stage 3 = 7-8 points = Q1yr EGD/Duodenoscope
- Stage 4 = 9-12 points = Q6mo EGD/Duodenoscope

	1 Point	2 Points	3 Points
Polyp #	1-4	5-20	>20
Polyp Size (mm)	1-4	5-20	>20
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

- **Gastric Polyps/Cancer (50%/1%)**: fundic gland type (all other polyps in the GI tract are adenomas)
- **Jejunal Polyps/Colon (40%/1%)**
- **Ileal Polyps/Cancer (20%/1%)**
  - NB these pts also have many large lymphoid polyps in the TI
- **Thyroid (rare)**
- **Pancreatic (rare)**
- **Hepatoblastoma (rare)**

- Variants
  - **Attenuated FAP &**
    - Mutations away from center of gene and more towards 5' and 3' ends
    - Later onset (35yo)
    - Fewer polyps (<100)
    - More right sided
    - Lower lifetime risk of CRC (70%)
    - Delayed onset by 10yrs
  - **MUTYH Associated Polyposis (MAP)**
    - Additionally they may have increased risk of breast/ovarian/urinary/skin cancer
    - Never develop Gardner/Crail's Syndrome
  - **Gardner Syndrome (AD) = FAP + Extracolonic Growths**
    - Desmoid Tumors of Abdominal Wall (mainly females, 825x increased risk, usually develop after laparotomy, benign neoplasm of fibroblasts, though no malignant they can grow so big that they causes significant GI morbidity (obstruct viscera, vessels, ureters) such that they are 3rd most common cause of death, Tx is w/ radiation, sulindac, tamoxifen, NB surgery is not very effective unless SI transplant)
    - Bone: Osteomas of Skull, Jaw, Long Bones

    - Skin: Epidermoid Cysts, Lipomas, Sebaceous Cysts, Fibromas



    - Eye: Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE) = melanocytes in the retina

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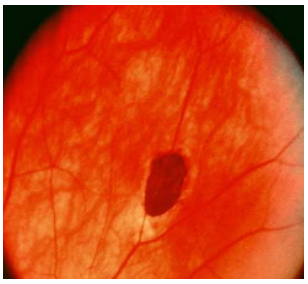

- Mouth: Supernumerary Teeth, Mandibular Cysts, Impacted Teeth
  - **Crail's Syndrome (AR) = FAP + Cerebellar Medulloblastoma**
- B/c AD there will always be a FHx except in three cases
  - (1) de novo case (25% of cases)
  - (2) misattributed paternity (10% of the cases)
  - (3) AR MUTYH Associated Polyposis (30% of cases)
- Screen at risk 1st degree relatives: if genetic testing is not available then flex sig Q1yr at 12-25yo, Q2yrs from 25-35yo, Q3yrs from 35-50yo, average risk from >50yo BUT if available then Genetic Testing w/ Protein Truncation Test (PTT) & In Vitro Synthesized Protein Assay (IVSP) at 10yo and if + then Direct Mutation Analysis
- Tx: once dx is made then total proctocolectomy w/ ileostomy or ileoanal pull through
  - NB polyps can be partially reversed w/ sulindac, ascorbic acid, alpha-tocopherol, fiber
- Surveillance: EGD for gastric polyps and ERCP for duodenal polyps Q6mo-3yrs (based on Spigelman Classification) starting at 25yo, unclear for SI polyps, thyroid US for thyroid cancer Qyr starting at 10yo, Ab US for pancreatic cancer Qyr starting at ?, PEx/Ab-US/AFP Qyr for hepatoblastoma from 0-10yo Qyr, PEx for CNS tumor Qyr

- **Lynch Syndrome (3% therefore the most common hereditary cancer syndrome)**
  - NB **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)** is the old name
  - AD mutation (two hit process, one inherited the other acquired) in **Mutation Mismatch Repair (MMR)** Genes (90% have mutations of the MSH2 (60%) and MLH1 (30%) genes aka Classic Lynch vs 10% have mutations of the PMS2 and MSH6 (attenuated form of Lynch w/ latter onset but increased r/o endometrial cancer) aka Attenuated Lynch)
  - Sx: multiple synchronous/metachronous polyps (more than general population but not "polyposis" in number) that are at increased r/o cancer b/c of mutated tumor progression pathway, cancer by avg age 45yo, lifetime risk 70%, right sided tumors
  - Bx: unique pathology ("Tumor Infiltrating Lymphocytes" TILs, mucinous/colloid/signet-cell (also seen in CRC in pts w/ UC), poor differentiated)
  - Types
    - MSH2 (classic)
    - MLH1 (classic)
    - MSH6 (attenuated)
    - PMS2 (attenuated)
    - NB **Muir-Torre Variant** (similar to Garnder's Syndrome) = Lynch + Skin Problems (sebaceous adenomas/carcinomas, keratocanthomas, SCC, BCC, melanoma)
    - NB **Turcot's Syndrome** (similar to Crail's Syndrome) = Lynch + Cerebral Glioblastoma Multiforme
  - Cancer (lifetime risk)
    - Colon (75%M/35%F)
    - GU (endometrium 55%, urinary tract 8%, ovary 7%, breast 5%)
    - GI (stomach 10%, duodenal 5%, biliary 1%, pancreas 1%)
  - Tx: subtotal colectomy when dx of CRC is made and consider TAHBSO
    - NB pts are not candidates of adjuvant chemo b/c there is defective MMR system thus not effective and actually giving chemo decreases survival!!!
    - NB aspirin may reduce risk of CRC and endometrial cancer
  - Surveillance: (unclear about other cancers)
    - Colonoscopy Q2yrs from 20-40yo and then Q1yr >40yo or 10yrs before the youngest relative whichever is younger
    - TV-US w/ Endometrial Bx Qyr when >25yo or 5yrs before youngest relative (once pt is done having children then TAH-BSO)
    - UA Qyr when >25yo if there is a FHx
    - EGD x1 at 40yo if there is a FHx
  - Screen (if genetic testing for MMR mutations is not available then colonoscopy Q2yrs from 20-40yo and then Q1yr >40yo or 10yrs before the youngest relative whichever is younger)
    - 1991 Amsterdam-II Criteria (used to determine if a pt w/ a +FHx should undergo further testing for Lynch) = **if + Amsterdam criteria then genetic testing**

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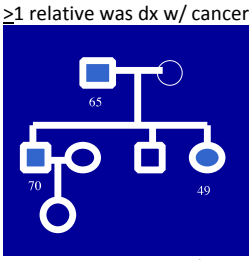
- Criteria "3-2-1" (you need all three)
  - Any Lynch associated cancer in
    - ≥3 relatives one of which is a first degree relative of the other two
    - ≥2 successive generations
    - ≥1 relative was dx w/ cancer <50yo



- 2004 Bethesda Criteria (used to determine which pts w/ CRC should undergo further testing for Lynch) = **if + Bethesda criteria then perform MSI/MMR staining of tumor tissue and if positive then do genetic testing**
  - Criteria (any criteria)
    - CRC in a pt ≤50yo
    - Synchronous or Metachronous Lynch associated cancers
    - CRC w/ MSI-histology in a pt ≤60yo
    - CRC in ≥1 first degree relative ≤50yo w/ Lynch associated cancer
    - CRC in ≥2 first or second degree relatives w/ Lynch associated cancer
  - False Negative: pts who clinically have Lynch BUT are MS-S and have no MMR mutations are termed **"Familial Colorectal Cancer Type X"** and have some other undiscovered mutation but phenotypically look like Lynch except that (1) they do not have increased r/o extra-intestinal cancer and (2) they have reduced penetrance and later onset for CRC
  - False Positive: pts who has MSI-H but nl MMR have an epigenetic mutation in which there is **acquired hypermethylation and subsequent transcription silencing of MLH1 2/2 CIMP/BRAF** therefore check for CIMP/BRAF (this occurs in sporadic CRC representing 15% of cases such that only 1/5 pts w/ MSI-H/+IHC tumors actually have Lynch)

- Diagnosis
  - **Fecal Occult Blood Test** (FOBT)
  - **Flexible Sigmoidoscopy**
  - **Double Contrast Barium Enema (83% sensitive)**
  - **Colonoscopy (97% sensitive)**
    - Some have argued to resect and discard diminutive polyps (based on NBI to determine if hyperplastic vs adenomatous) so as to save more $
    - decreases mortality in distal CRC BUT no decrease in mortality for proximal CRC likely b/c more flat, poorer examination, different genetics
    - overall 30% RRR of CRC
  - **CT Colonography aka Virtual Colonoscopy**
    - Misses flat lesions and polyps <6mm, radiation exposure, still involves oral prep and anal air insufflation, catches other incidental findings, cannot take out something if a lesion is present, a prep-less form is being developed in which feces can be subtracted out
    - Recent NEJM article showed that it is 90% sensitive in picking up adenomas >10cm in average risk pts (aka misses 10% of adenomas)
    - maybe use in incomplete endoscopy to evaluate rest of colon or pt cannot tolerate sedation
    - Big study was by Pickhardt in 2003, did same day CTC and Colonoscopy on 1200 asymp pts, military hospital system
      - CTC/Colonoscopy Sens: 10mm (94/90%), 8mm (94/92%), 6mm (89/92%)
    - In May 2009 CMS decided to NOT cover it
  - **Stool DNA (sDNA) Test**
    - Pioneered by Exact Sciences
    - Currently 85/55% sensitive for picking up CRC/>1cm adenomas w/ 90% specificity
    - not FDA approved but you can still order it over the internet
    - collect 1 full BM
    - detect DNA (kras mutation) shed from tumors and look for specific mutations
    - the problem is that these tests are neither sensitive nor specific but has the potential of being more sensitive than FOBT
- Screening (**if S/S and thus not screening then go straight to colonoscopy**) (based on two large trials in the 1990s: US National Polyp Study & VA Cooperative Study, NPS was a prospective, multicenter study of 1408 pts who underwent a clearing colonoscopy and then were followed over 6yrs, the rate of cancer dropped by 75% compared to pts who did not have a colonoscopy w/ adenoma removal) a 50yo pt

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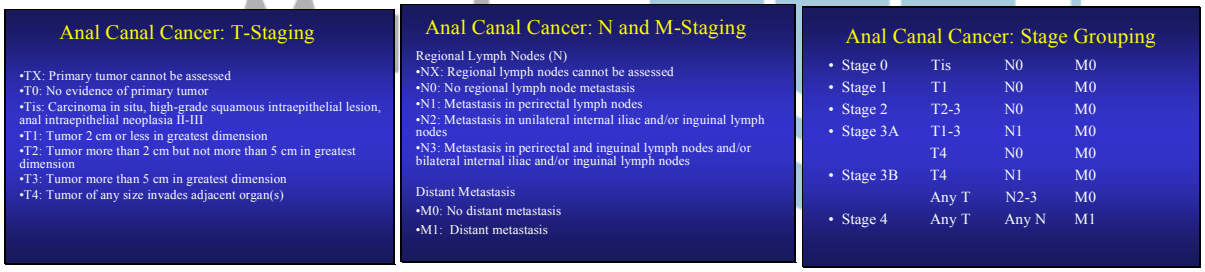
has a 5% chance of developing CRC by 80yo, as polyps grow to >1cm they dedifferentiate and become dysplastic w/ the risk of cancer increasing to 3/17/37% for each change

AJCC TNM Staging System	**TNM Staging (pathologist Dr. Dukes described the relationship b/t depth of invasion and survival in 1932, since then almost 8 modifications have been made over the years w/ the most common one being be Atler and Coller modification in 1974 but it has now been replaced by the AJCC TNM Staging System)** ▪ Poor Prognostic Factors once a dx of CRC is made: left sided, higher TNM but not overall size, poorly differentiated, mucinous/colloid/signet-cell histology, scirrhous histology, vessel/nerve invasion, less inflammation, less polypoid, ulcerated, symptomatic, younger age, high CEA				
Stage 0			Non-Invasive Carcinoma: Carcinoma-In-Situ CIS (not yet breached the BM) → Intra-Mucosal-Carcinoma IMC (breached the BM to lamina propria but since lymphatics are not present above muscularis mucosae it is still considered non invasive) → muscularis breaching carcinoma (invasive) BELOW (the progression takes ~7-10yrs)		
Stage I 50%	T1-2N0M0		T1 = into submucosa (Dukes A) T2 = into muscularis propria	5-year survival 90%	Surgery
Stage II 20%	T3-4N0M0	A B C	T3 = below serosa (Dukes B) T4a = beyond serosa T4b = invades surrounding tissue	5-year survival 70%	Surgery (some give chemo in certain cases)
Stage III 15%	T#N1-3M0	A B C	T1-2N1, T1N2 T3-4aN1, T2-3N2, T1-2N2 T4aN2a, T3-4aN2, T4bN1-2 N1 = 1-3 pericolic LNs vs N2 = ≥4 pericolic LNs (Dukes C) MRI is best for staging rectal cancer and if MRI is equivocal than EUS	5-year survival 35%	Surgery + Chemo
Stage IV 15%	T#N#M1-2		M = Metastasis (Dukes D) = liver, lung, peritoneum and non-peri-colic LNs: common iliac, external iliac, paraaortic, supraclavicular M1a (one organ site) vs M1b (multiple organ sites)	5-year survival 5% w/ median survival 22mo!!!	Chemo + Biologics

NB rectal mets can spread to contiguous tissue b/c there is no adventitia/serosa as there is over the colon hence most rectal cancers spread via para-vertebral venous/lymphatic systemic to lung bypassing liver unlike colon which goes to liver first



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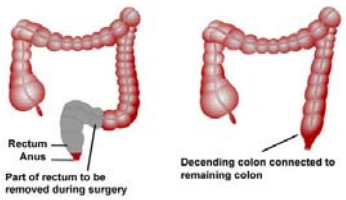
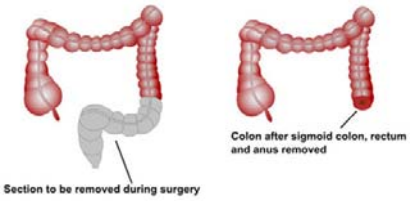
- Treatment (National Polyp Study demonstrated that removal of adenomatous polyps reduced once risk of CRC)
  - Cancer
    - If COLON then **surgery** (**partial colectomy with 5cm margins and with lymphovascular mesenteric pedicle removal w/ direct anastomosis**) ± **postop chemo** x6mos
    - If RECTUM and **T#N1-2 or ≥T3N0** then **neoadjuvant chemoradiation** x6wks then **surgery** then **postop chemo** x6mos
      - If T1-2 then consider local resection but if T3-4 then surgery
      - Why Radiation? rectum is defined as that of the bowel that extends from the dentate line to where the bowel no longer is covered by peritoneum but surrounded by lymphatic connective tissue called meso-colon therefore direct extension of rectal cancers to surrounding tissue is very easy hence the use of XRT which decreases recurrence from 25% to 15% and with chemo to 10%
      - If proximal rectal cancer then Lower Anterior Resection (LAR) followed by anastomosis



    - If distal rectal cancer then Abdomino Perineal Resection (APR) followed by colostomy



- Chemo & Biologics
  - History
    - Anti-Helmenthic (lavamisole) (1985) NB found to have some modest anti-CRC effects which was a small step forward b/c prior only surgery was the treatment
    - 5-FU (1991) NB oral form is called Xeloda
    - 5-FU + Leucovorin (1998) NB leucovorin is reduced to folic acid which enhances effect of 5-FU
  - Current Chemo Regimens
    - **FOL-FOX** = FOLic acid + 5-Fu + OXaliplatin
    - **FOL-FIRI** = FOLic acid + 5-Fu + IRInotecan
    - **Cape-OX** = Capecitabine + OXaliplatin
    - **FOL-FOXIRI** = FOLic acid + 5-Fu + OXaliplatin + IRInotecan
  - Biologics
    - VEGF inhibitors: bevacizumab (Avastin) = for mutated KRAS
    - EGFR inhibitors: cetuximab (Erbitux), panitumumab (Vectibix) = for wild type KRAS
  - Mutation Chemo Associations
    - + CIMP/MSI-H = 5-FU less effective
    - + BRAF/KRAS = EGFR less effective
  - Mets
    - if good performance status then chemo
    - if liver mets then locoregional Tx
  - Consider starting aspirin

- Follow-Up
  - **Polyps (1/3 of pts who have an adenoma will develop another a recurrent adenoma at 1yr)**
    - **If Incomplete polypectomy then f/u at 3mo AND 1yr**
    - **If cancer in polyp then no surgery if well/moderately (not poorly) differentiated carcinoma and MARGINS ARE NEGATIVE BY >2mm, DOES NOT INVOLVE VESSELS, DOES NOT INVOLVE SUBMUCOSA otherwise surgery is needed**
    - **If Advanced Adenoma (High Grade Dysplasia OR VA OR ≥3-10/≥1cm TA/SSP) then surveillance at 3yrs and if negative then at 5yr**
      - **If ≥10 polyps then surveillance at <3yrs and consider syndrome w/u**
    - **If NON-Advanced Adenoma (Low Grade Dysplasia AND 1-2/<1cm TA/SSP) then surveillance at 5-10yrs and if negative then 7yr**
    - **If hyperplastic polyps then surveillance at 10yrs unless >5mm or ≥4 and prox to sigmoid then at 5yrs**
    - **If poor prep quality would do sooner 6mo-5yrs depending on how bad the prep was**
  - **Cancer** (90% recurrence after 3yrs???, most recurrence occurs at anastomosis (best) or in the resection bed or in the contiguous periaortic/paracaval LNs (worst))
    - PEx & Labs (LFTs, CEA): Q2mo x2yrs then Q4mo x3yrs then Qyr
      - **CarcinoEmbryonic Antigen (CEA)** not specific for colon cancer but sensitive (increases with cirrhosis, pancreatitis, RF, ulcerative colitis) therefore not good for making diagnosis but good for following treatment: measure before surgery (b/c if high then acts also as a poor prognostic indicator)
      - NB 1/3 of recurrences have nl CEA esp in poorly differentiated tumors
    - Imaging w/ CT-C/A/P: Qyr x5yrs
    - Colonoscopy at post-op to look for synchronous lesions then at 1yr then Q3-5yrs to look for metachronous lesions

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