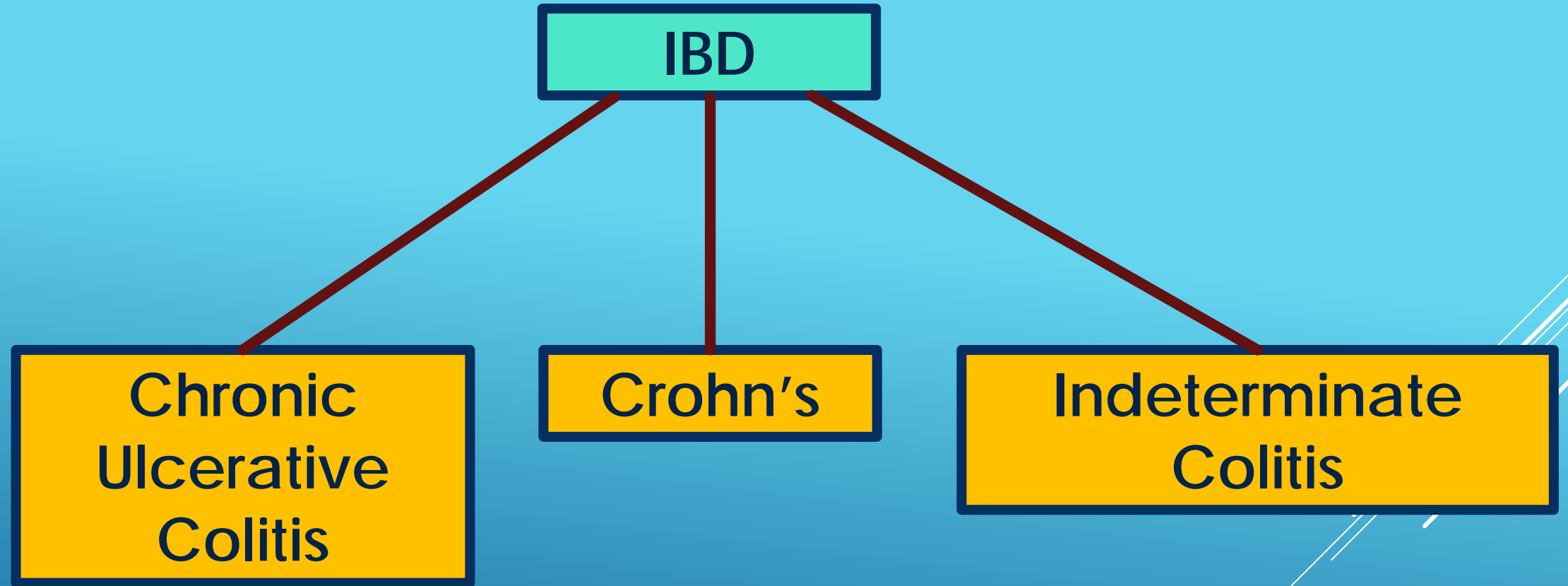


IBD AND CLINICAL ONCOLOGY UPDATE 2018

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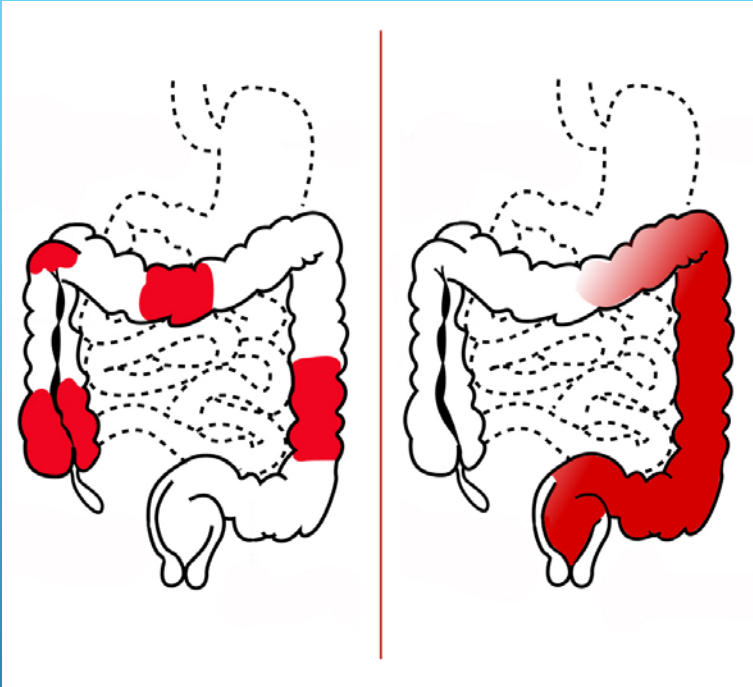
Center for Digestive Health, Orlando FL

Inflammatory Bowel Disease



Crohn's Disease vs. Ulcerative Colitis

Crohn's Disease



- Small bowel and colon
- Patchy involvement
- Transmural inflammation
- Non-caseating granulomas
- Poor response to surgery
- Increased risk for cancer

Ulcerative Colitis

- Colon only
- Continuous involvement
- Superficial inflammation
- No granulomas
- Good response to surgery
- Increased risk for cancer

Indeterminate Colitis

Features of both CUC and Chron's in the same patient or at different stages in the course of one's illness:

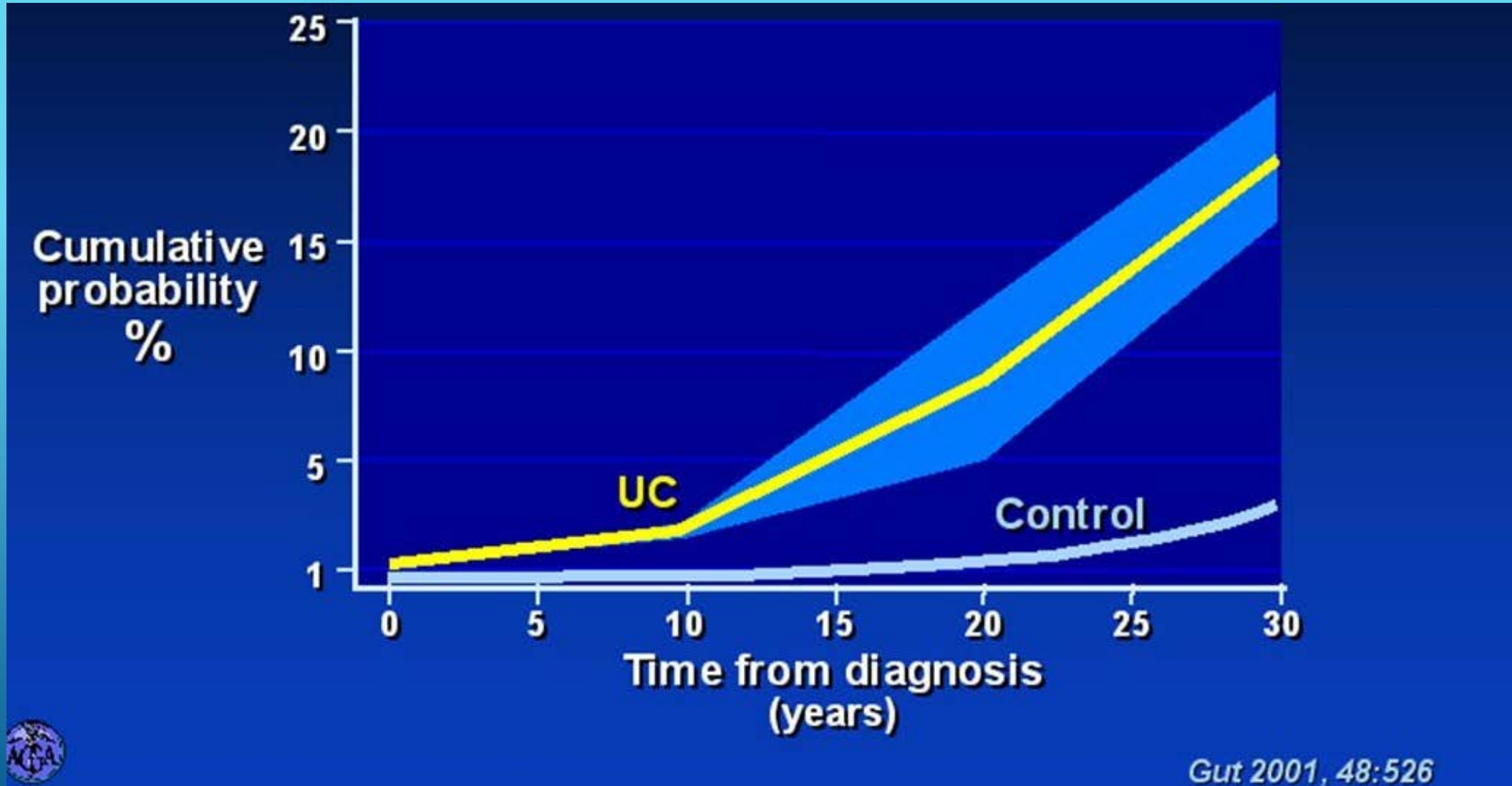
- A changing clinical pattern, identified predominantly by colonoscopy and video capsule
- Role for genetics – More than 225 genes shared by both disease states
- The J-Pouch (IPPA) experience – A surgical procedure credited to Sir Alan Marks in London, first published in 1978, now accepted as the surgical cure for CUC. Over time there are an increasing number of patients who post this surgical procedure develop Crohn's in the residual bowel
- Total lack of data re: Cancer risk in this population of patients, but still carry the drug exposure risks of biologics and immunosuppressants

Colorectal Cancer

- 147,000 new cases yearly of colorectal cancer
- 57,000 deaths annually

UC – Complications

Risk of Colorectal Cancer



Risk of Developing Colorectal Cancer in People With IBD

Low Risk:

- Extensive but quiescent Ulcerative Colitis or
- Extensive but quiescent Crohn's Colitis or
- Left-sided Ulcerative Colitis (but not proctitis alone) or Crohn's Colitis of a similar extent.

Intermediate Risk:

- Extensive Ulcerative or Crohn's Colitis with mild inflammation that has been confirmed endoscopically or histologically or
- Post-inflammatory polyps or
- Family History of Colorectal Cancer in a first-degree relative aged 50 years or over.

High Risk:

- Extensive Ulcerative or Crohn's Colitis with moderate or severe active inflammation that has been confirmed endoscopically or histologically or
- Primary Sclerosing Cholangitis (including after liver transplant) or
- Colonic stricture in the past 5 years or
- Family history of colorectal cancer in a first-degree relative under 50
- Crohn's disease with high grade stricture of long duration, any site

J-Pouch Patients at Risk Too!

- 0.5% pooled risk from multiple studies in the pouch itself
- 2.4% at the ileorectal anastomosis
- 2.1% in the rectal stump

International Guidelines:

- Yearly flex sig of pouch patients who are at high risk: previous rectal dysplasia, CRC found at surgery for the creation of the pouch, PSC, Type C Mucosa: Mucosa with permanent atrophy and severe inflammation
- 5 year flex sig if none of the above factors

Recommended Colonoscopy Interval By Professional Society

ECCO (2017)

- 8 years after onset of symptoms if stricture or dysplasia within 5 years **1 year**
- Extensive colitis of first degree relative with CRC older than 50 **2-3 years**

AGA (2010)

- 8 years after disease onset **1 year**
- After 2 negative exams **1-3 years**

ACG (2010)

- 8 years after disease onset **1-2 years**

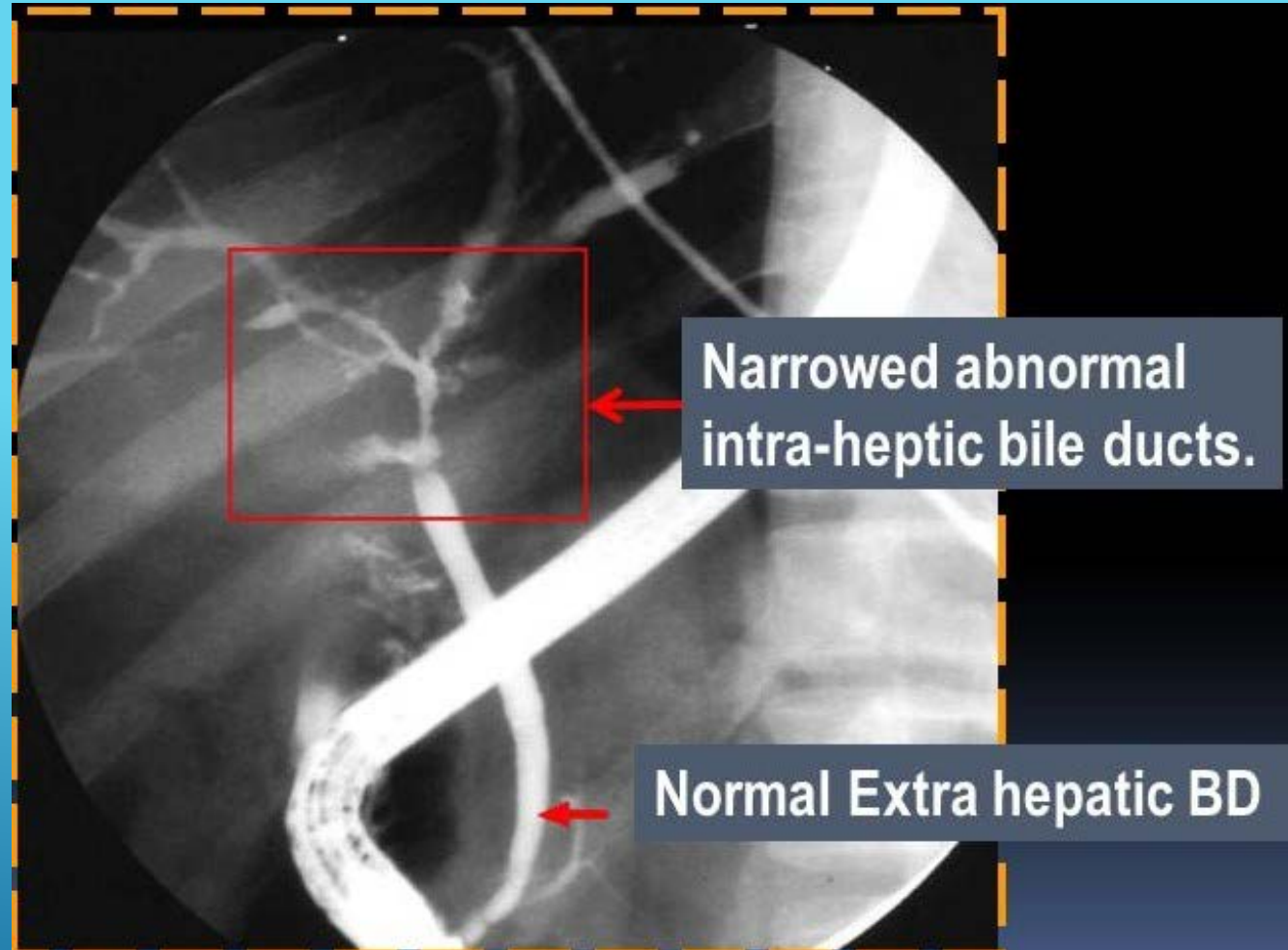
BSG (2010)

- Moderate inflammation, stricture or dysplasia, PSC, first degree relative with CRS less than 50 YOA, at least 10 years of Disease **1 year**
- Mild inflammation, stricture or dysplasia, PSC, first degree relative with CRS less than 50 YOA **3 years**
- No active inflammation, left-sided UC or CD Colitis affecting more than 50% of the surface area of the colon **5 years**

Chromoendoscopy

In patients at particularly high risk for colorectal neoplasia (e.g., personal history of dysplasia, primary sclerosing cholangitis), chromoendoscopy should be used during colonoscopy, as it may increase the diagnostic yield for detection of colorectal dysplasia, especially compared with the standard definition white light endoscopy (conditional recommendation low level of confidence)

Primary Sclerosing Cholangitis

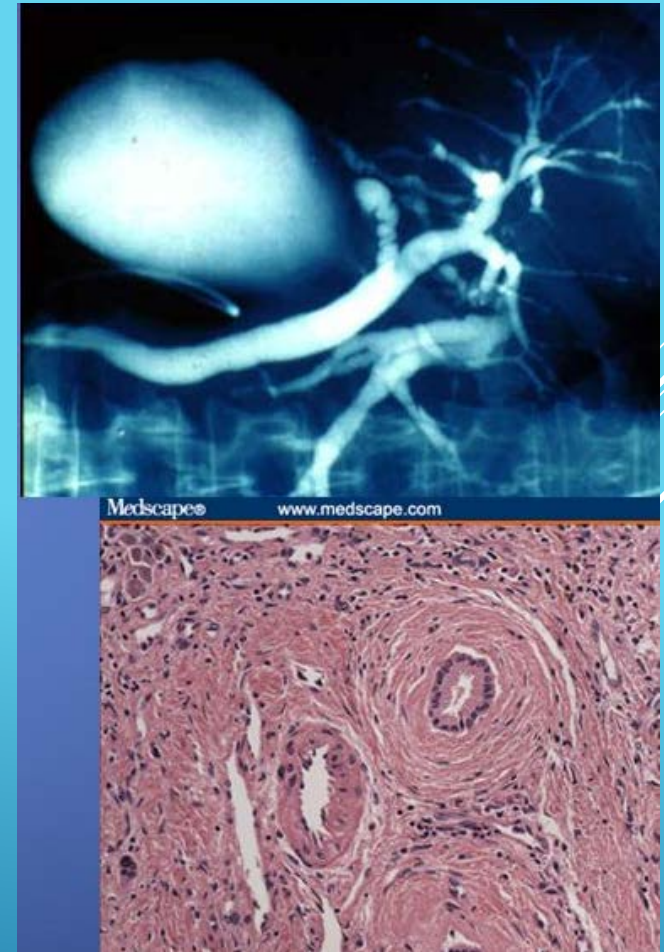


Primary Sclerosing Cholangitis

- Strongly associated with inflammatory bowel disease
- There is a 75% association with Ulcerative Colitis
- The prevalence of PSC among Ulcerative Colitis patients is approximately 5% with an overall 10-15% prevalence of hepatic abnormalities
- PSC may complicate large bowel Crohn's disease

Primary Sclerosing Cholangitis

- An autoimmune fibrosis of large bile ducts
- Clinical: RUQ pain, fatigue, weight loss
- 70% of cases associated with ulcerative colitis
- Increased risk of cholangiocarcinoma
- Diagnose with ERCP
 - Beading of the bile ducts on ERCP/MRCP
 - 10-15% get bile duct carcinoma



Lymphoma Risk

- 6MP/Imuran/Azathioprine as #1 offender, all equally
- Trivial role of biologics which was proven with the “sonic trial”
- Incidence is quite variable in adult series, ranging from 2.8% to 9.2% dependent predominantly on use of MP, Imuran, and Azathioprine
- Greatest risk after one year of continuous drug exposure
- Greatest risk in males under 35 YOA or males greater than 50 YOA
- Not EBV/H.Pylori related like other lymphomas

Lymphoma Risk

- Hepatosplenic T-Cell Lymphoma (HSTCL)
 - Rare
 - More males than females and almost always younger than 30YOA
 - Acute onset with rapid downhill course, usually
 - Always associated with thiopurines
- Total of 2 cases in the literature of Methotrexate associate lymphoma in IBD patients (total gray zone as overlap with thiopurines during treatment)
- Totally unknown: Risk of lymphoma after discontinuation of thiopurines having received them for more than one year...no data!

Skin Cancer Risk

- Any biologic or thiopurines increases risk
- Increased risk of basal cell carcinoma, squamous cell carcinoma, and melanoma
- Melanoma risk increases 37 times compared with patients without these drugs who develop melanoma
- Other increased risk factors:
 - Family history of skin cancer or personal history of prior skin cancers
 - Magnitude of sun exposure
 - Blue or green eye color
 - Blond or red hair
- As a result, recommendation of now every two years minimum for a head-to-toe dermatology exam

Yet to be decided is the duration of follow-up necessary when these drugs are discontinued!

PIBD and Cancer

Total number of PIBD patients reported in literature
who developed cancer or fatal outcome
(N = 271)

Infantile IBD (0-2 years)
(N = 19)

PIBD patients diagnosed in childhood or
adolescence (2-18 years)
(N = 252)

CD
(N = 140)

IBD-U
(N = 2)

UC
(N = 107)

UNK
(N = 3)

Non-Fatal Cancer

Lymphoma	29
Leukemia	12
Liver	21
Intestinal Carcinoma	19
Skin Cancer	8
Cervical Cancer	1
Other	13
Total:	103

Fatal Cancer

Lymphoma	24
Leukemia	6
Liver	10
Intestinal Carcinoma	34
Skin Cancer	0
Cervical Cancer	0
Other	3
Total:	77

Fatal Outcome Unrelated to Cancer

Gastrointestinal	18
Infectious Disease	24
Post Operative	6
Liver Disease	8
Dehydration	1
Suicide	1
Other	16
Total:	72

Entyvio=Vedolizumab

- Monocolonal antibody
- Specifically binds to Alpha487 integrin of T Cells and blocks the interaction between Alpha487 and MADCAM-1, which is expressed on GI tract endothelium, and thereby prevents passage of T Cells from the vascular space to the gut epithelium
- In other words, it selectively inhibits T Cell migration from the vascular space into inflamed tissue of the GI tract non- systematic effects
- Because of its mechanism of action within the GI tract only, there is theoretically (and practically borne out) no risk of lymphoma or melanoma!
- Therefore it is the ideal agent for:
 - Males under 35 YOA
 - Patients with a history or family history of melanoma
 - Patients with psoriasis (which can be induced by any of the biologics)
 - ?Patients with any prior history of non-GI tract solid tumors (especially breast)

Common Clinical Scenarios in Practice

- Biologics in patients with solid tumors: Breast, kidney, prostate, uterine or cervical, melanoma
- Do we stop the medication or treat the IBD, preventing potential advancement of disease and complications/surgery?...no data exists!
- Gardiseal and regular pap smears of limited value but recommended as “best practices”
- Regular dermatology checkups head-to-toe
- Close link between GI and oncology is a must for maximal patient care
- Ultimately, each patient will be likely treated independent of others secondary to the complexity of the issue
- If additional GI tract drugs could be developed and proven efficacious, this certainly would lessen this quagmire
- Further definition of genetics to know those at the greatest risk: The New Frontier!

Thank You!

