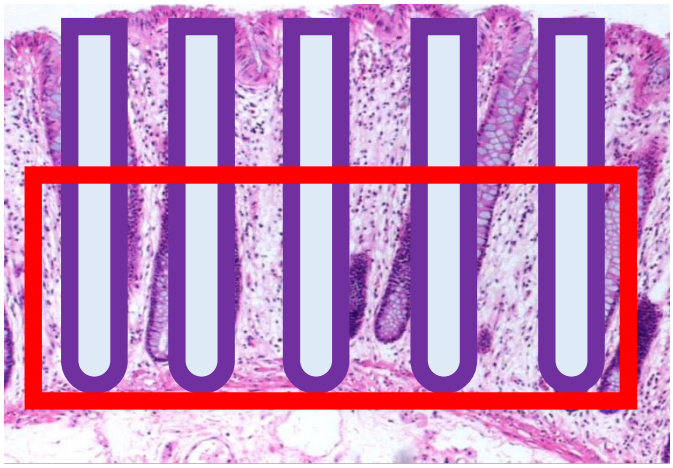
Inflammatory Bowel Disease

Normal Colon

Crypts should be oriented parallel to one another, perpendicular to the surface (like test tubes in a rack), resting on the muscularis mucosae.

Regional Variation	
Right Colon	**Left Colon**
More lymphocytes	Less lymphocytes
Paneth cells normal	Paneth Cells abnormal
Fewer goblet cells	More goblet cells



Some architectural distortion and muciphages in the rectum is considered *normal*.
Intraepithelial lymphocytes (and even rare neutrophils) over lymphoid follicles is also *normal.*

Patterns of Damage in IBD

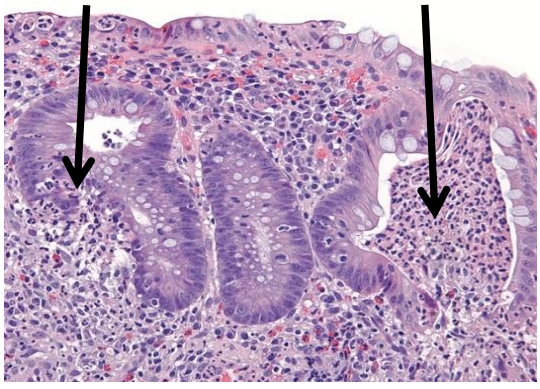
The inflammation in IBD is characterized by the presence/absence of "Activity," defined as neutrophilic inflammation of the epithelium and lamina propria, and "Chronicity," including architectural distortion, a basal lymphoplasmacytosis, and Paneth cell metaplasia.

These words are combined such that you can have an "Active colitis," a "Chronic active colitis," or a "Chronic inactive colitis," which is also sometimes called "Quiescent colitis."

Activity = Neutrophils

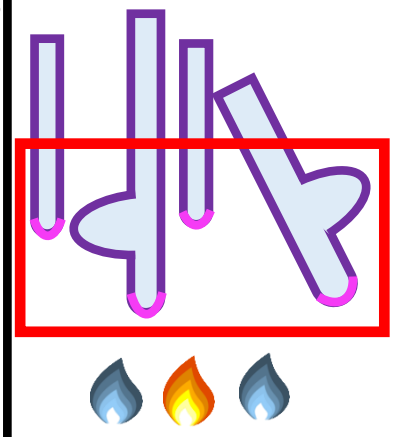
Cryptitis
PMNs in crypt epithelium

Crypt Abscess
PMNs in crypt lumen



Chronicity

Think of those test tubes being melted (like a by a torch)



Crypt architectural distortion
- Crypt shortening
- Crypt branching
- Crypt dropout
- Loss of crypt parallelism
- Villiform surface

Basal lymphoplasmacytosis

Paneth cell metaplasia and hyperplasia

Pyloric gland metaplasia

Lamina propria and submucosal fibrosis

New onset, untreated IBD (hasn't had time for chronicity to develop)
Active Colitis

~ 1 month untreated →

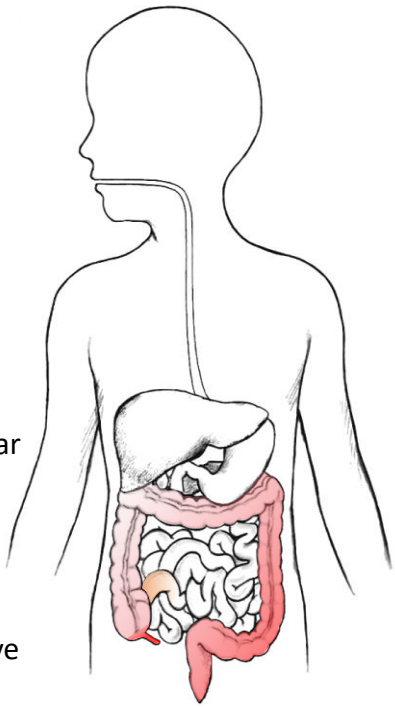
Typical appearance of active disease
Chronic Active Colitis

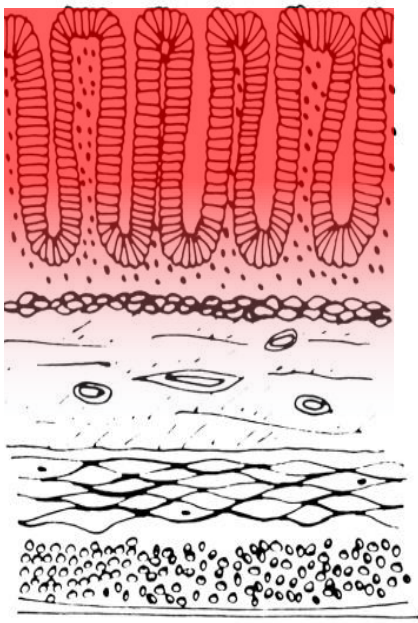
Treatment →

IBD in recent remission (eventually it can normalize)
Chronic inactive (Quiescent) Colitis

IBD General Info:
Chronic, idiopathic, relapsing and remitting inflammatory disease of the gastrointestinal tract resulting from inappropriate mucosal immune activation. Thought to involve aberrant immune response with altered intestinal microbiome in genetically susceptible individuals.
More common in industrialized nations, where there are fewer parasites/infections to train/distract the immune system ("Hygiene hypothesis").

Ulcerative Colitis





Chronic active inflammation in the **rectum** proceeding proximally in **continuous, diffuse** pattern

Typical findings:
Chronic Active Colitis limited to mucosa and superficial submucosa with ulceration

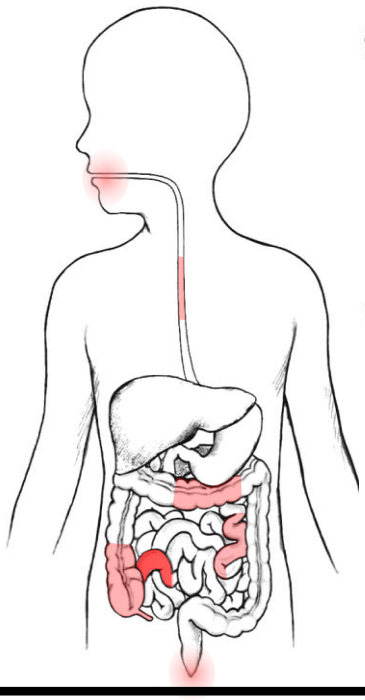
Can see deeper inflammation with severe "fulminant" colitis

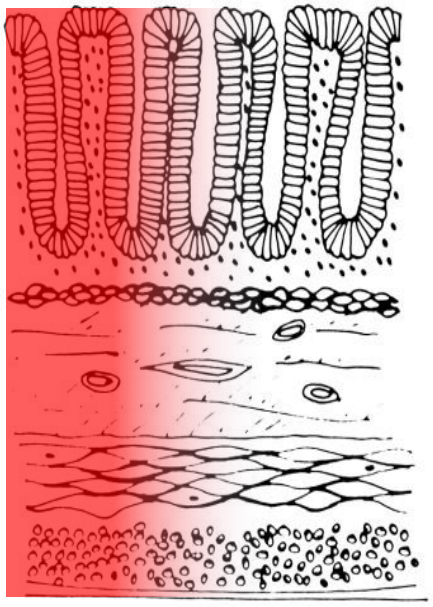
Can have increased inflammation in cecum near appendiceal orifice ("cecal patch")

Can have inflammation in terminal ileum ("backwash ileitis").

In Kids, can have upper tract findings, relative rectal sparing, and less *initial* chronicity.

Crohn's Disease





Patchy Transmural chronic active inflammation in **any** part of the GI tract

Typical findings:
Transmural inflammation

Skip areas and **patchy** inflammation, both microscopically and grossly

Granulomas

Ulcers: superficial apthous to fissuring

Muscle and nerve hypertrophy

Pyloric gland metaplasia (esp. in TI)

Fibrosis and strictures

Fistulas

Indeterminate Colitis

aka: IBD, type unclassified

Approximately 10% of patients unclassifiable, due to the pathologic and clinical overlap between UC and CD. Placeholder term--this is *NOT* a specific entity. Often due to insufficient data or fulminant colitis.

Differential Diagnosis: *IBD is a diagnosis of **exclusion**!*

Active Colitis
(aka Acute Self-limited Colitis)

Causes: E. Coli, Salmonella, Shigella, Campylobacter, Viruses

E. coli O157:H7→ ischemic changes

Neutrophilic Cryptitis
But, Chronicity ABSENT

Relatively more neutrophils in superficial lamina propria (away from crypts)
Crypt abscesses
Hemorrhage, edema
Possible erosions

Looks similar: Some medications (e.g., NSAIDS, Checkpoint inhibitors), New onset IBD

Focal Active Colitis

FOCAL Neutrophilic Cryptitis
Chronicity ABSENT

Causes:
NSAIDS → + Increased apoptoses, ischemic-like changes
Bowel preparation artifact → + Increased apoptoses, edema, mucin depletion
Early infection → Days 0-4 after onset
Ischemic changes → often with lamina propria hyalinization, crypt withering

Microscopic Colitis

Increased Intraepithelial Lymphocytes (IELs)
Neutrophils rare to absent

Lymphocytic Colitis
IEL ≥20/100 surface epithelial cells
Normal architecture
Chronic inflammation in lamina propria (usu. superficial)

Collagenous Colitis
IEL >10-20/100 surface epithelial cells
Increased Subepithelial Collagen
Entraps capillaries and lymphocytes
Highlighted by Trichrome stain

Additional Diagnoses to Consider:

Top infectious causes of colitis in patients with IBD: CMV and C. difficile→ always get CMV IHC in a patient with refractory IBD now with severe disease on treatment (esp. steroids)

If Older→ Especially rule out Medication-effect and Diverticular disease

Common Drug pattern: Intraepithelial lymphocytes, relatively preserved crypt architecture, apoptoses, with some neutrophils

Ischemic colitis → Hyalinized lamina propria, withered crypts, minimal inflammation

Radiation colitis → Ischemic changes, Atypical stromal cells, Telangiectatic blood vessels

Diverticular disease–associated colitis → In colonic segment with diverticulosis

Diversion colitis → Colon isolated from fecal stream, Follicular lymphoid hyperplasia

Prolapse → Fibromuscular hyperplasia, Angulated diamond-shaped crypts

Vasculitis → Inflammatory destruction of vessels, Fibrinoid necrosis

Eosinophilic/Allergic Colitis → >60 Eos/10 HPF, Few PMNs, Absent chronicity

STD Proctitis → Often chlamydia or syphilis due to anal receptive intercourse. Lots of ulceration, plasma cells, and histiocytes. Confined to rectum.

Medical Management

Usually 2 phases: 1) ***Induction*** (to induce remission) and 2) ***Maintenance*** (to maintain remission)
These may use same or different medications/dosages.

Old management model: "**Step-up** therapy," start with a mild drug (e.g., mesalamine) and only move up to a more powerful drug if they "fail" that drug.

Modern Management model: "**Top down,**" start with a more powerful medication (e.g., monoclonal antibody). This shows better complication-free long-term survival.

Three pillars of modern IBD care: 1)Early intervention, 2)Treat to target, 3)Tight control
Treat to specific measurable endpoints, like normal Fecal Calprotectin (a good surrogate marker for inflammation), mucosal healing (an endoscopic impression), or histologic normalization. Engage in frequent monitoring to ensure ideally "deep remission."

Medications:

Generally, reduce autoimmune inflammation by immunosuppression via a variety of mechanisms.
Often increased risk of infection (somewhat drug dependent).

"Classic" medications
Mesalamine (5-ASA) – mechanisms of action unknown. Low activity. Usually used orally or rectally for mild UC.
Sulfasalazine – like 5-ASA (mechanism of action unknown). Usually used for mild ileocolic CD.
Budesonide – steroid taken orally with little system effect (mainly works on GI tract).
Prednisone – oral steroid often used to induce remission in active IBD. Long-term use limited due to side effects. Use in both CD and UC.
Azathioprine/6-Mercaptopurine – Thiopurines, inhibit DNA synthesis, thereby reducing WBC production and inflammation. Risk of lymphoma. Used in both CD and UC.

Anti-TNFα antibodies: Suppresses TNF-mediated inflammatory response.
Used in UC and CD. Good for penetrating disease. May develop drug antibodies, limiting use.
Examples: Adalimumab (Humira), Infliximab (Remicade), and others, including generic biosimilars.

Janus kinase (JAK) inhibitor: interfering with the JAK-STAT signaling pathway in lymphocytes.
Oral pill. Powerful & fast. Used for UC more than CD.
Examples: Tofacitinib (Xeljanz), Upadacitinib (Rinvoq)

Anti-α4β7 antibody: anti gut-specific integrin→ inhibiting WBC diapedesis to gut
Used in both CD and UC, but likely better for UC. Very few side-effects as gut-specific.
Examples: Vedolizumab (Entyvio)

Anti-IL23/12 and anti-IL23 antibody: blocks cytokines that activate certain T-cells.
Used more in CD, but can use in UC. Good for penetrating disease. Good safety profile.
Examples: Ustekinumab (Stelara), Risankizumab (Skyrizi)

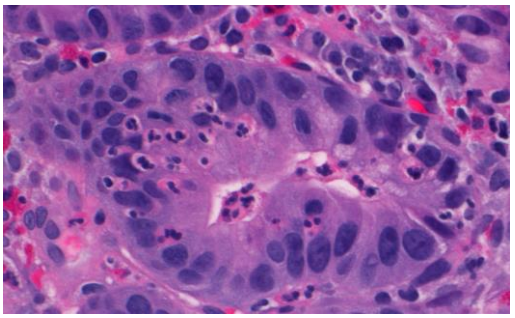
Sphingosine-1-Phosphate Receptor (S1PR) agonist: Sequester lymphocytes to peripheral lymphoid organs, away from their sites of chronic inflammation. Oral therapy for UC.
Examples: Ozanimod (Zeposia)

Pre-malignant and Malignant lesions in IBD:

Generally, follows stepwise progression of: Non-neoplastic → Low-grade dysplasia → High-grade dysplasia → Adenocarcinoma. However, there are cases where it appears to go from low-grade (or even normal appearing) to adenocarcinoma very quickly or directly.

Conventional **Dysplasia** (look like usual colon adenomas):

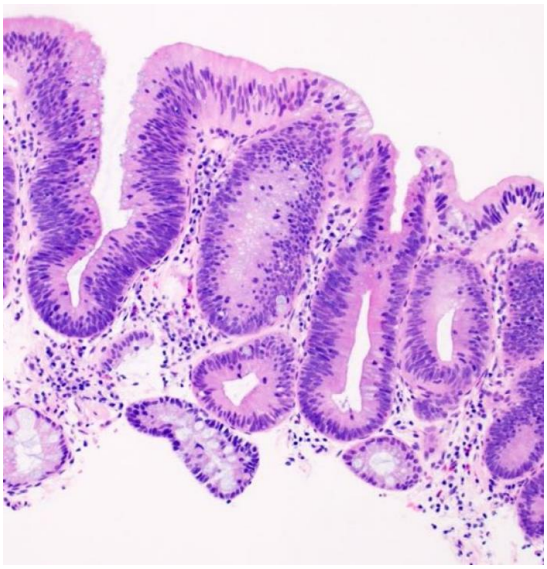
Indefinite for Dysplasia



Unable to classify as definitely reactive or dysplastic.
Often atypia in setting of severe inflammation or ulceration.
Sometimes surface not present for evaluation.

Management: Treat active disease and repeat biopsy in 3-12 months.

Low-Grade Dysplasia

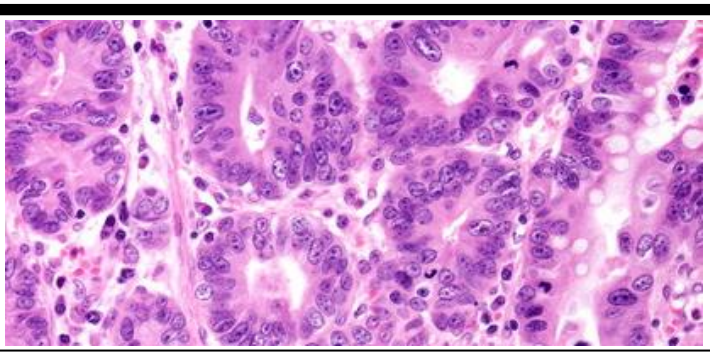


Looks like a sporadic **Adenoma**.
Enlarged, hyperchromatic, smooth, "pencillate" nuclei.
Pseudostratified nuclei with maintained basal orientation.
Higher N:C ratios; **Little to no surface maturation.**
Often abrupt transition (corresponding with clone)
Prominent apoptoses.

Molecular: IBD-associated dysplasia show more copy number aberrations and aneuploidy than sporadic adenomas. TP53 mutations are very frequently present early. Possibly reflecting a faster progression toward cancer.

Hint: Try using a lymphocyte as what is "normochromatic"

High-Grade Dysplasia



Enlarged, hyperchromatic, pleomorphic nuclei.
Often plumper than LGD.
Irregular nuclear contours. Prominent nucleoli.
Loss of nuclear polarity.
Complex architecture: Cribriforming, crypt branching/budding.

Immunohistochemistry in IBD dysplasia: P53 staining often highlights both grades
Dysplasia→ Strong P53 staining (or null). *Some* authors require abnormal p53 *at the surface,* while others just want it to be significantly increased compared to the background colon.

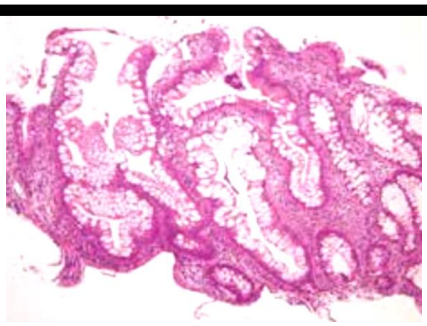
Negative/Indefinite for dysplasia if weak/wild-type staining

SATB2 is frequently lost in IBD dysplasia also, but this is used less often as a marker.

H&E is still the gold standard though, so only do it on cases that are equivocal!

***Non*conventional lesions:** (doesn't look like usual colon adenomas)

Serrated Epithelial Change



Controversial diagnosis, with differing criteria

Original Hopkins Criteria: Serrations at top and bottom of crypts. Distorted crypt architecture where some crypts do **not** reach the muscularis mucosae (unlike SSL). Normal nuclei. Goblet cell-rich epithelium.

UCSF Criteria: Hyperplastic polyp (HP)-like mucosal change without morphologic evidence of dysplasia detected on random biopsy

Controversial risk of CRC. Many studies show increased risk of dysplasia/carcinoma. Essentially, treat as "indefinite."

Note: The colon in IBD patients can show surface serrations/hyperplasia, particularly in the distal colon, making this diagnosis especially hard and controversial.

Non-Conventional Dysplasia

Often present with conventional dysplasia.
More common on left side as polypoid mass.

Hypermucinous—Villous architecture with prominent cytoplasmic mucin.

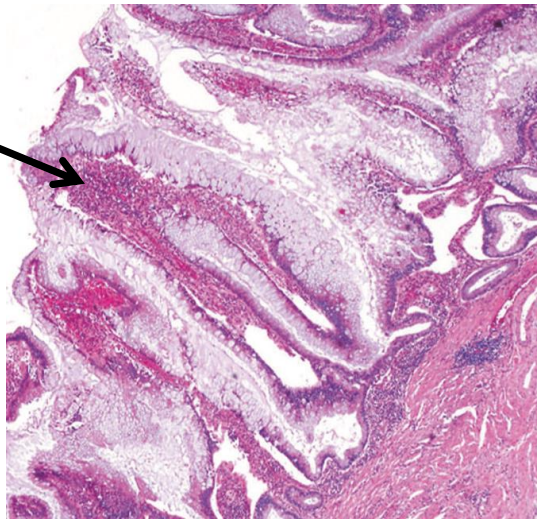
Traditional Serrated Adenoma (TSA)-like

Sessile serrated lesion (SSL)-like

Paneth cell differentiation

Goblet cell deficient—absence of goblet cells

"**Terminal epithelial differentiation,"** TED, or "Crypt cell dysplasia," CCD –flat lesions, round to oval hyperchromatic nuclei. Can be just in crypts.

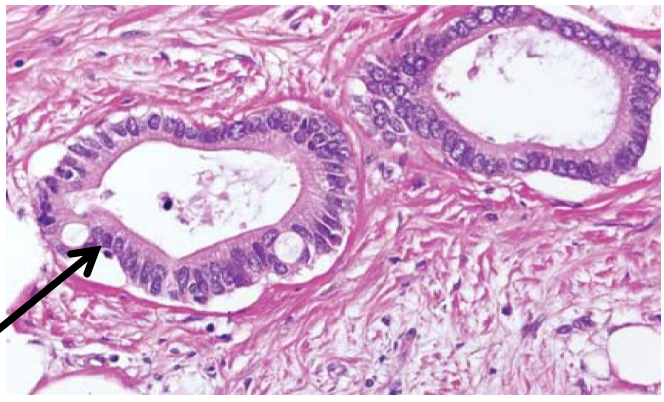


Helpful tip: **Must see cytologic atypia (hyperchromatic, crowded nuclei).**
In uncertain cases, get p53 IHC. If not altered→ better to hedge as "indeterminate for dysplasia" and state change type (e.g., "Hypermucinous epithelium, Indefinite for dysplasia)

Adenocarcinoma

Invasive through basement membrane:
- Infiltrating glands/cells
- Broad, expansive confluent growth of glands

Compared to Sporadic, IBD-associated CRC is:
- More often multifocal (field defect)
- More often higher grade
- More often advances stage
- More often signet-ring or mucinous



Unique variant:
Low-grade tubuloglandular adenocarcinoma—very bland small to medium-sized round glands that invade with little desmoplastic stroma. Often CK7 (+). Loss of SATB2. Frequent IDH1 mutations.

Cancer Risk and Screening

Cancer Risk:
Ulcerative colitis = ~2.4 fold risk
Crohn's Disease = ~1.9 fold risk **(~ 2x risk)**

Inflammation → DNA oxidation/damage → Cancer
Risk proportional to severity/duration of inflammation.

Screening recommendations:
First **8-10 yrs** after diagnosis→ No increased screening (not enough time for carcinogenesis).
Exception: Individuals with PSC, who are at dramatically increased risk of sever inflammation and cancer → start annual screening colonoscopies *at* diagnosis.

After first screening, space out as below.

C **Timing of next colonoscopy when no dysplasia detected at present colonoscopy**

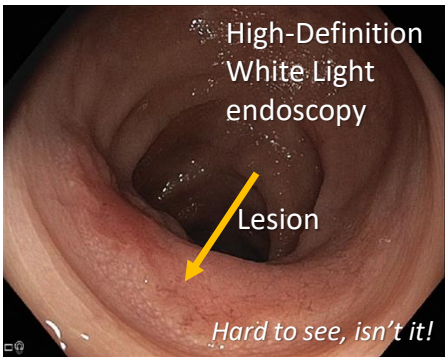
Physicians should err towards the more frequent surveillance category if at least one higher risk factor exists. Timing based on past and ongoing CRC risk factors and mucosal features that may obscure dysplasia.

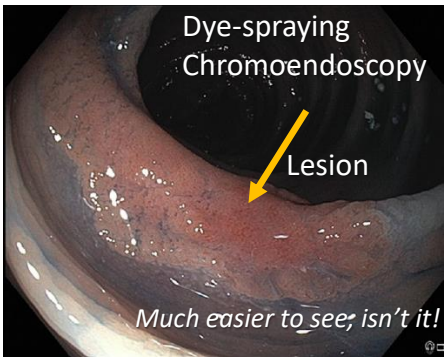
1 year	2 or 3 years	5 years
• Moderate or severe inflammation (any extent) • PSC • Family history of CRC in first degree relative (FDR) age < 50 • Dense pseudopolyposis • History of invisible dysplasia or higher-risk visible dysplasia < 5 years ago	• Mild inflammation (any extent) • Strong family history of CRC (but no FDR < age 50) • Features of prior severe colitis (moderate pseudopolyps, extensive mucosal scarring) • History of invisible dysplasia or higher-risk visible dysplasia > 5 years ago • History of lower risk visible dysplasia < 5 years ago	Continuous disease remission since last colonoscopy with mucosal healing on current exam, plus either of: • ≥ 2 consecutive exams without dysplasia • Minimal historical colitis extent (ulcerative proctitis or < 1/3 of colon in CD)

Note: Isolated ileal Crohn's disease without colonic inflammation should undergo CRC screening with colonoscopy same as average-risk population. Guidance for endoscopic severity, Simple Endoscopic Score for Crohn's (SES-CD) and Mayo endoscopic score for UC. Moderate-severe: SES-CD ≥ 7/ Mayo 2/3; Mild: SES-CD 3–6/ Mayo 1; No active disease: SES-CD 0–2/ Mayo 0.

From: Murthy SK, et al. Gastroenterology. 2021 Sep;161(3):1043-1051 PMID: 34416977.

Chromoendoscopy:
Allows for better visualization of the bowel surface and crypt pattern (which is often altered in dysplasia). This can be done via spraying of dye that settles in crypts (e.g., methylene blue) or "virtually" via technologies like narrow band imaging.





Screening principles:
Targeted biopsies should be performed where mucosal findings are suspicious for dysplasia or are inexplicably different from the surrounding mucosa.

Endoscopic resection is preferred to biopsies when lesions are clearly demarcated without stigmata of invasive cancer or submucosal fibrosis. Mucosal biopsies surrounding a resected lesion are not required unless there are concerns about resection completeness.

Dye-spraying chromoendoscopy should be considered, but virtual chromoendoscopy (VCE) is a suitable alternative when using high-definition endoscopy.

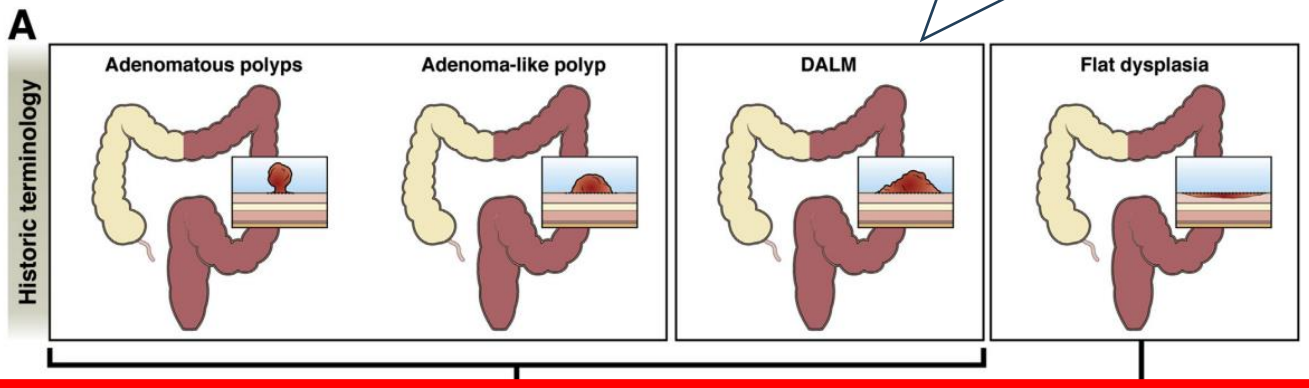
If chromoendoscopy is being used, then non-targeted biopsies are not routinely required, but should be considered if there is a history of dysplasia or primary sclerosing cholangitis.

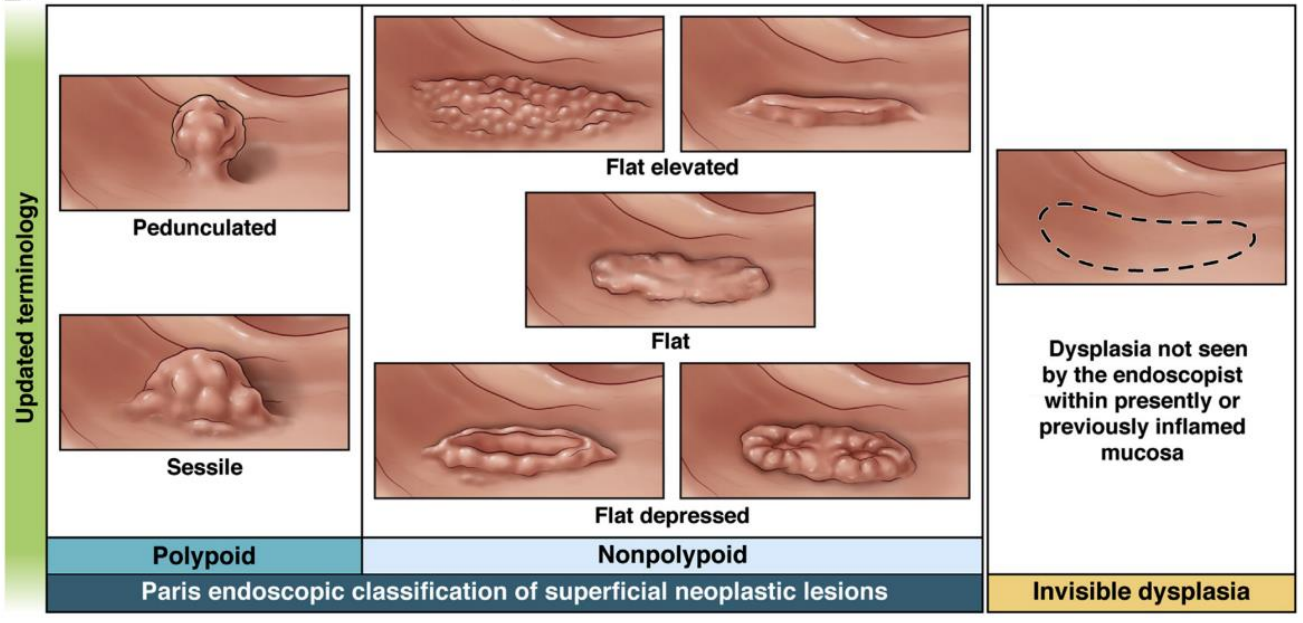
If *NOT* using chromoendoscopy: Extensive nontargeted biopsies (roughly 4 adequately spaced biopsies every 10 cm) should be taken from flat colorectal mucosa in areas previously affected by colitis.

Endoscopic Lesion Terminology

Lesions are now described using the Paris system (see below) based on size, morphology, clarity of borders, presence of ulceration, location, presence within an area of past or current colitis, perceived completeness of resection, and whether any special techniques were used for visualization.

This is the old terminology you *may* see





In addition to Paris classification, report lesion size, morphology, border clarity, ulceration, location, if within area of colitis, completeness of resection, and any special techniques used to visualize.

From: Murthy SK, et al. Gastroenterology. 2021 Sep;161(3):1043-1051 PMID: 34416977.

This is the current terminology you *should* see

Treatment of Dysplasia

Once a dysplastic lesion has been resected, in the absence of surrounding dysplasia, ongoing meticulous colonoscopic surveillance is appropriate.

Proctocolectomy is usually only recommended for dysplasia if endoscopic resection is not possible, or if nonvisible high-grade dysplasia or adenocarcinoma or invisible multifocal dysplasia are found.

A Management of visible and invisible dysplasia within a colitis field*

Endoscopic assessment	Management	Next colonoscopy and comments
• < 2cm + resectable (clear border, no features of submucosal invasion or fibrosis) + no histologic features of invasive cancer	Endoscopic resection with continued surveillance	• 3–6 months: high-grade dysplasia or incomplete resection • 12 months: > 1cm, low-grade dysplasia (LGD) • 24 months: < 1cm or pedunculated, LGD
• Large (≥ 2cm) • Complex (i.e. lateral spreading, highly irregular or indistinct border) • Incomplete resection after several attempts • Local recurrence	Endoscopic resection with intensive surveillance vs surgery	• Every 3–6 months for first year (if resect) • Decision to resect based on lesion details, local expertise, disease activity
• Unresectable due to size, location, features of invasive cancer or submucosal fibrosis • Invasive cancer on histology	Surgery	
• Invisible dysplasia (non-targeted biopsy) or subtle/ poorly delineated lesion (targeted biopsy)	• Confirm histology with second pathologist • Treat inflammation • Perform dye spray chromoendoscopy (DCE)	• Use DCE to unmask subtle lesions. If no lesion seen, take extensive non-targeted biopsies in area of prior dysplasia. Use box A or B to manage.

B Management when no visible dysplasia is detected on DCE*

Histologic assessment	Management	Next colonoscopy and comments
• Persistent high-grade or multifocal invisible dysplasia	Surgery	
• Persistent unifocal low-grade invisible dysplasia	Intensive surveillance with DCE **	• 3–6 months if prior high-grade or multifocal dysplasia; 6–12 months if prior low-grade dysplasia. Continue intensive surveillance until 2 consecutive negative high quality DCE exams.
• No histologic dysplasia		

*Consider expert opinion if uncertainty; ** Although intensive surveillance proposed, long-term management is uncertain. Discuss risks and benefits of surgery vs surveillance based on current and past inflammatory burden, quality of mucosal visualization, mucosal details from where dysplasia initially detected, and other CRC risk factors.

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