Image enhanced endoscopy for neoplasia surveillance in IBD

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Disclosures

None

Learning Objectives

- Review historical concepts guiding IBD neoplasia surveillance recommendations and rationale for advanced surveillance methods

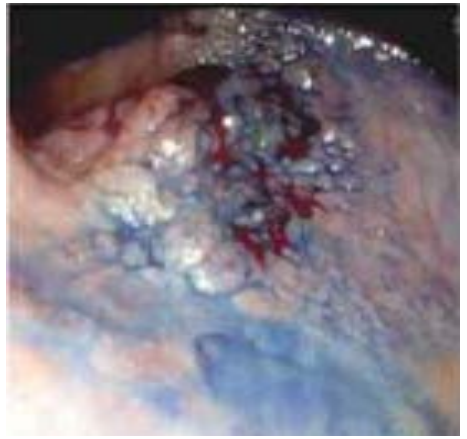
- Review the role of image enhanced endoscopy (IEE) in neoplasia surveillance in IBD, with a focus on chromoendoscopy

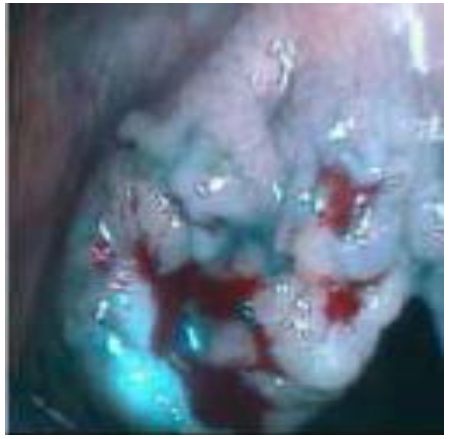
Tumorigenesis in IBD

- "**Field carcinogenesis**" – multifocal genetic aberrations in colitic mucosa
  - ? multifocal tumour development
  - ? accelerated progression

- Irregular lesions that are difficult to delineate with high cancer risk
  - Stricturing lesions
  - Laterally-spreading tumours
  - Irregular plaques and nodules

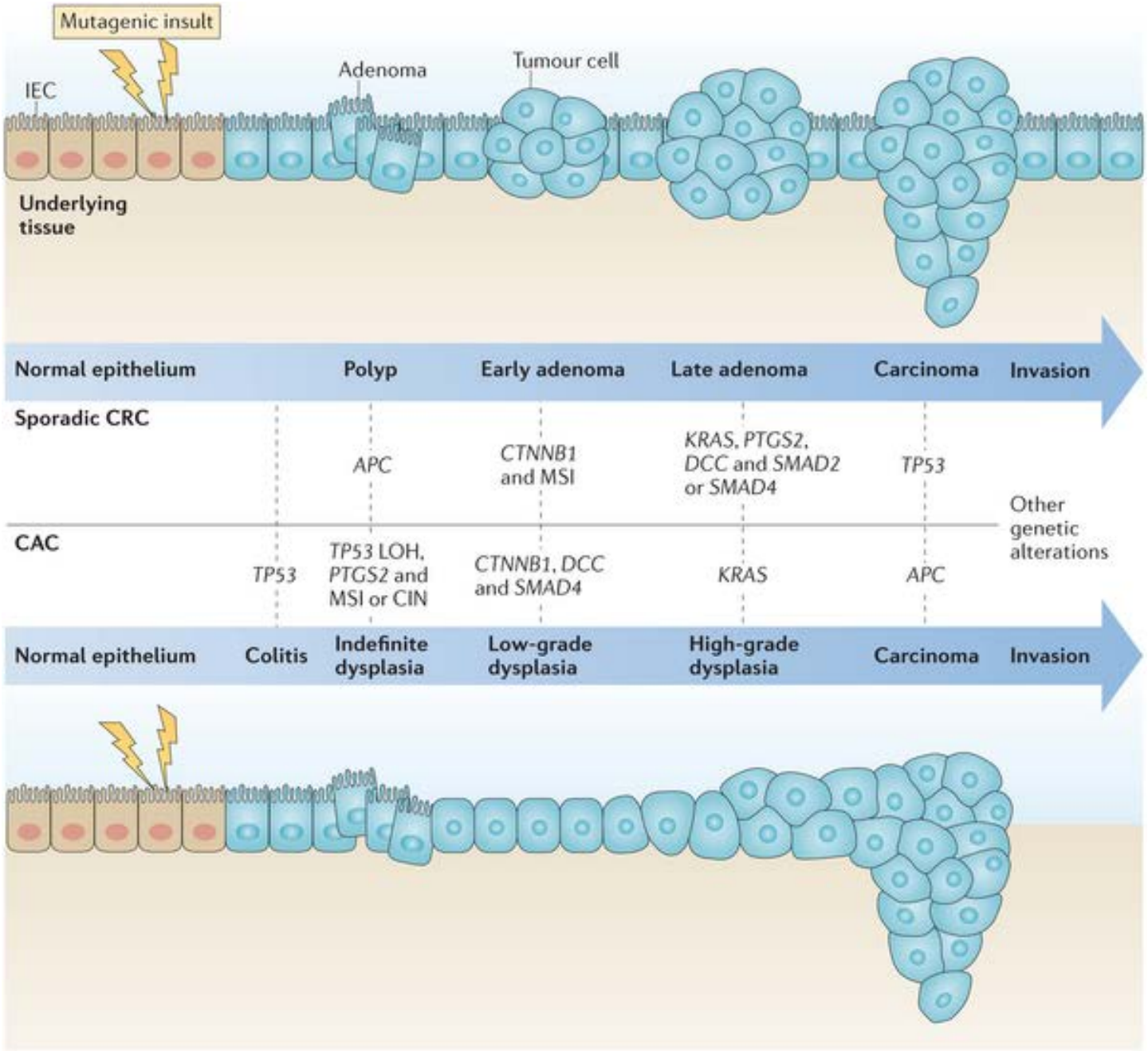
- "Invisible" flat neoplastic lesions





Rubin, Gastro 1992; Lofberg, Gastro 1992; Soderlund, IBDJ 2011

Flat Neoplastic Growth in IBD



Nature Reviews | Immunology

Historical CRC Risk in IBD Dysplasia

High-grade dysplasia

- 40 - 70% rate of synchronous CRC
- 25 - 30% rate of metachronous CRC

DALM

- 42 to 45% rate of synchronous CRC

Low-grade dysplasia

- 20 to 25% rate of synchronous CRC

Rutter et al., Gastro 2006;
Bernsteinet al., Lancet 1994;
Connell et al., Gut 1994;
Taylor et al., Dis Col Rectum 1992;
Ullman et al., Gastro 2003

Perception – IBD colitis is associated with insidious and accelerated neoplasia development that evades endoscopic detection

Traditional Guidance for Neoplasia Surveillance in IBD

- Interval q 1-3 (U.S.) or q 1-5 (Europe) years, guided by other risk factors
  - Disease duration/extent/severity, family history of CRC, past neoplasia, PSC
  - Annually – PSC, FDR < age 50, previous neoplasia, stricture

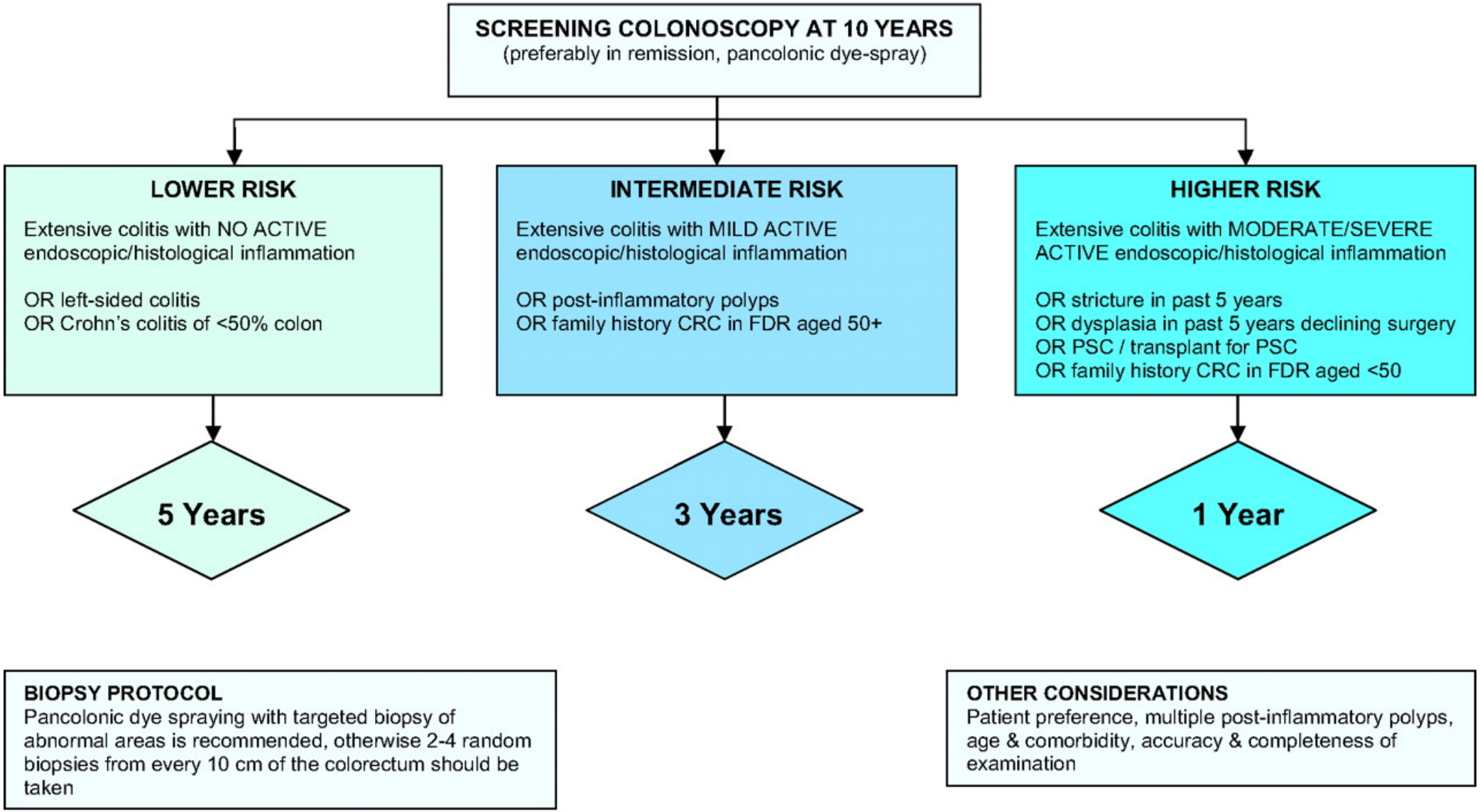
- ≥ 33 random biopsies throughout colon to detect “invisible lesions”; targeted biopsies of visible lesions

- Colectomy for any invisible, indistinct, irregular, or high-grade neoplasia, due to fears of being unresectable and harbouring cancer

Laine et al., GIE 2015
Farraye et al., Gastro 2010
Kornbluth et al., AJG 2010
Cairns et al., Gut 2010
Itzkowitz et al. IBDJ 2005

COLITIS SURVEILLANCE

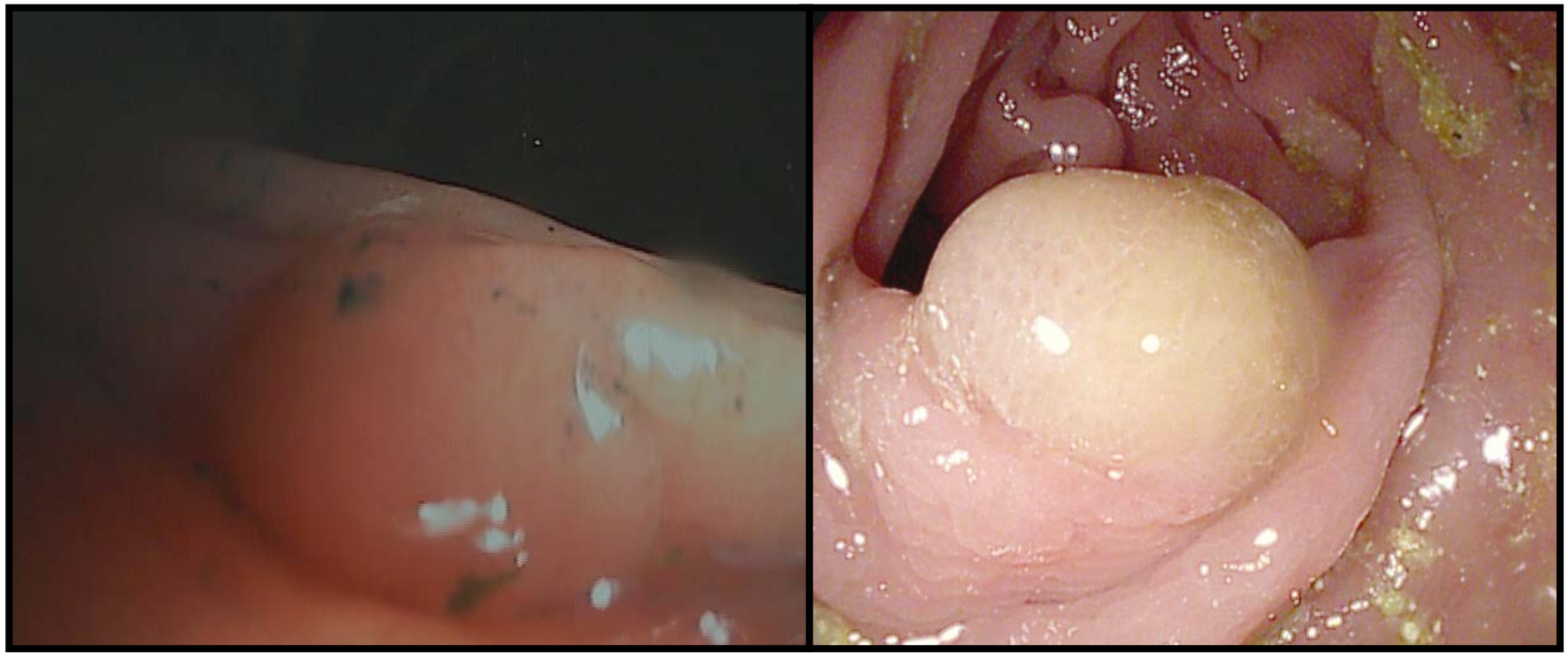
BSG 2010



Limitations of Older Studies of CRC Risk

- **Effective treatments for IBD → T2T (mucosal healing)**
- **Improved resolution of endoscopes**
- Better bowel preparation regimens
- Recognition of quality metrics for colonoscopy (+ ADR, training, etc.)
- Adoption of systematic surveillance protocols before mid-90’s

High-Definition Endoscopy

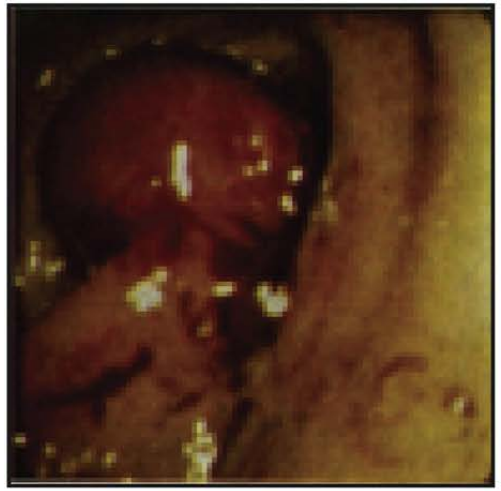


Standard Definition Image

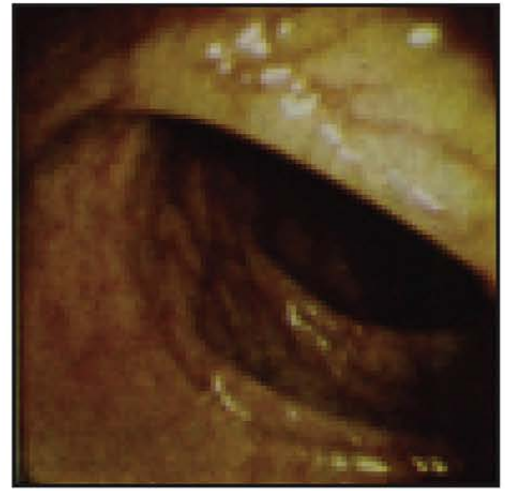
High Definition Image

HDE associated with 2 fold higher neoplasia detection rate in UC

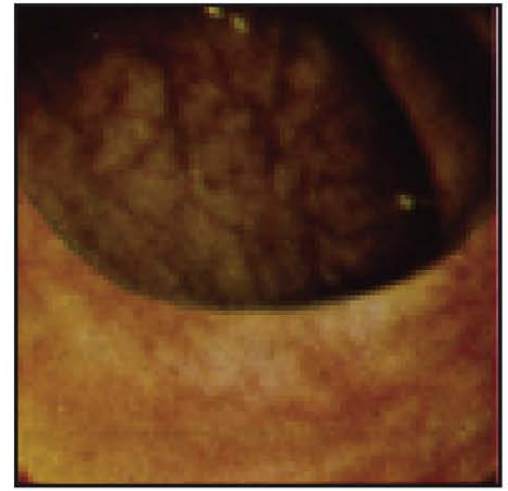
Subramanian et al., IBDJ 2013



Pedunculated sigmoid polyp.



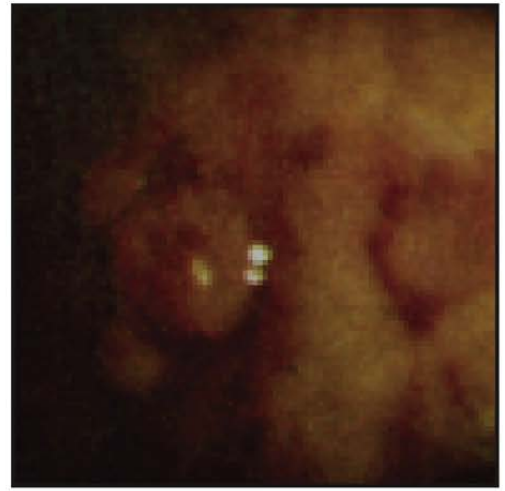
Normal sigmoid colon as seen with colonoscope, showing depth of focus.



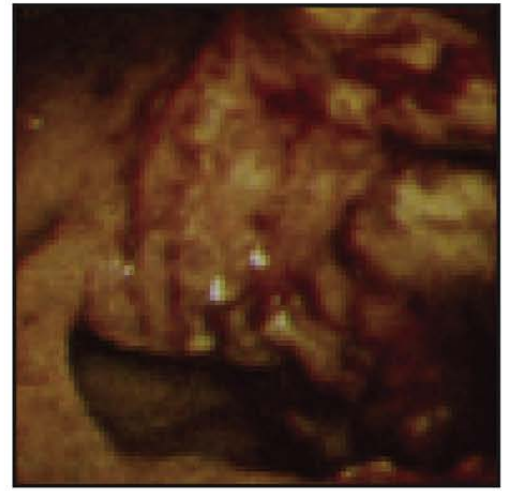
Normal sigmoid colon as seen with colonoscope showing details of vascular pattern.

1971 Images obtained from fiberoptic sigmoidscope

Salmon PR, Branch RA, Collins C, Espiner H, Read AE. Clinical evaluation of fibreoptic sigmoidoscopy employing the Olympus CF-SB colonoscope. Gut 1971;12:729-35.



Inflammatory pseudopolyps (rectum).



Carcinoma of rectum.

Colonic IBD is a Risk Factor for Colorectal Cancer (CRC)

	Relative Risk (versus non-IBD)	
Population-Based Studies	**Ulcerative Colitis**	**Crohn's Disease**
Ekbom (NEJM 1990)	5.7 (4.6 – 7.0)	--
Bernstein (Cancer 2001)	2.75 (1.91 – 3.97)	2.64 (1.69 – 4.12)
Gillen (Gut 1994)	19.2 (12.9 – 27.5)	18.2 (7.8 – 35.8)
Herrington (Gastro 2012)	1.6 (1.3 – 2.0)	1.6 (1.2 – 2.0)
Jess (Gastro 2012)	2.4 (0.6 – 6.0)	1.9 (0.7 – 4.1)

Meta-analyses of recent population-based studies: **CRC risk 1.5 to 2-fold** higher for both Crohn's disease (CD) and ulcerative colitis (UC)

Castano-Milla C, et al. Aliment Pharmacol Ther 2014;39:645-59; Jess T, et al . Am J Gastroenterol 2005;100:2724-9; Jess T, et al. Clin Gastroenterol Hepatol 2012;10:639-45; Laukoetter MG, et al. J Gastrointest Surg 2011;15:576-83; Lutgens MW, et al. Inflamm Bowel Dis 2013;19:789-99.

Shortcomings of Traditional Guidance

- No RCTs evaluating the optimal surveillance technique, timing or frequency or whether surveillance colonoscopy is even effective in IBD

- Low yield of random biopsies with latest technologies

  → ~ 0.1 % of biopsies; ~ 1% of patients Laine et al., GIE 2015

- > 90% of neoplastic lesions are visible using HD-WLE

  Laine et al., GIE 2015

- **More sophisticated technologies now exist to allow better detection and management of neoplastic lesions in IBD**

Updated Guidance (SCENIC-AGA, ASGE, ECCO, BSG)

- Chromoendoscopy (dye spray colonoscopy, DSC) with targeted biopsies alone is the preferred strategy for neoplasia surveillance
- Random biopsies may be performed if using WLE
- Virtual chromoendoscopy (NBI, iScan, FICE) is not recommended over DSC or WLE for neoplasia detection
- Endoscopic resection with continued surveillance is recommended over colectomy for lesions with (i) clear borders; (ii) no invasive features; and (iii) clear endoscopic and histologic resection margins (complete removal)
- Surveillance with DSC is recommended in the setting of invisible dysplasia

Dye Spray Colonoscopy (DSC)

Contrast or absorptive dyes sprayed throughout colonic mucosal surface during colonoscopy (catheter or water jet)

→ Methylene blue 0.04% (absorptive), indigo carmine 0.03% (contrast)

Enhances borders and surface architecture ("unmasks lesions")

- **Seconds** – dye fills lesion borders and colonic pits → demarcates lesion and highlights surface pattern
- **≥ 1 min** (methylene blue) – dye is taken up preferentially by non-neoplastic epithelial cells → contrasts lesion from surroundings

Technique of DSC

- Cleaning and suctioning during entry – identify if DSC feasible
- Prepare dye if adequate bowel preparation and minimal inflammation → 20 mL of 10mg/mL (1% w/v) stock MB in 500 cc sterile water (0.04%)
- Switch water bottle to dye in cecum
- Apply generously t/o, esp to anti-gravity side in segments (AC, TC, DC, RS)
- Re-intubate each segment, suction excess dye and inspect carefully

SURFACE Criteria for DSC

Strict patient selection → Colonic IBD ≥ 8 years' duration, in clinical remission

Unmask the mucosal surface → Excellent bowel preparation

Reduce peristaltic waves → Consider spasmolytic agent

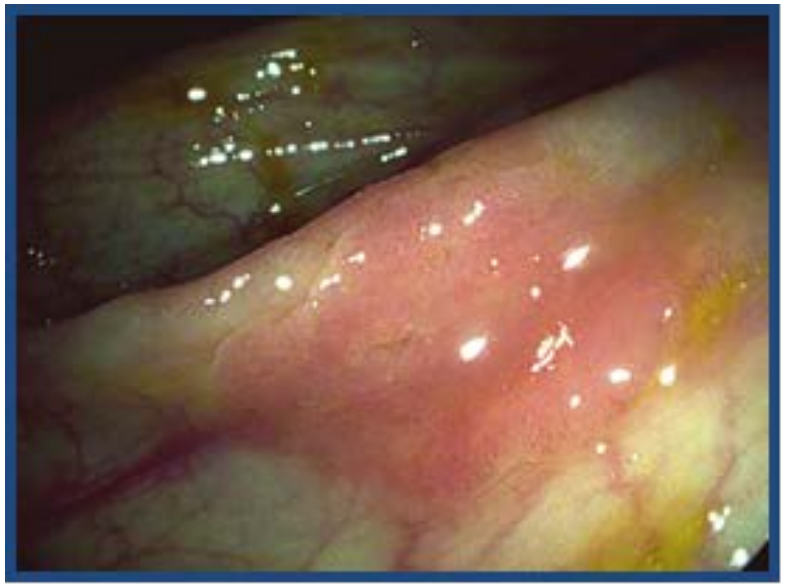
Full length staining of the colon → Panchromoendoscopy

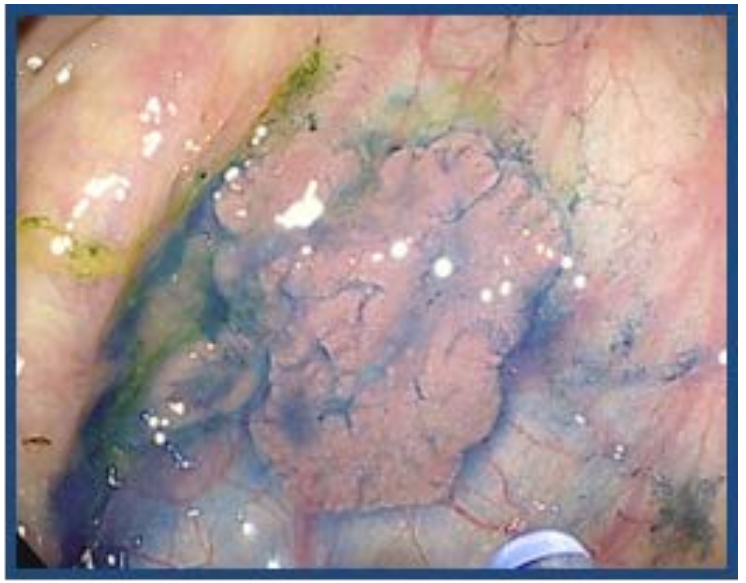
Augment detection with dyes → indigo carmine or methylene blue

Crypt architecture analysis → Pit pattern classification

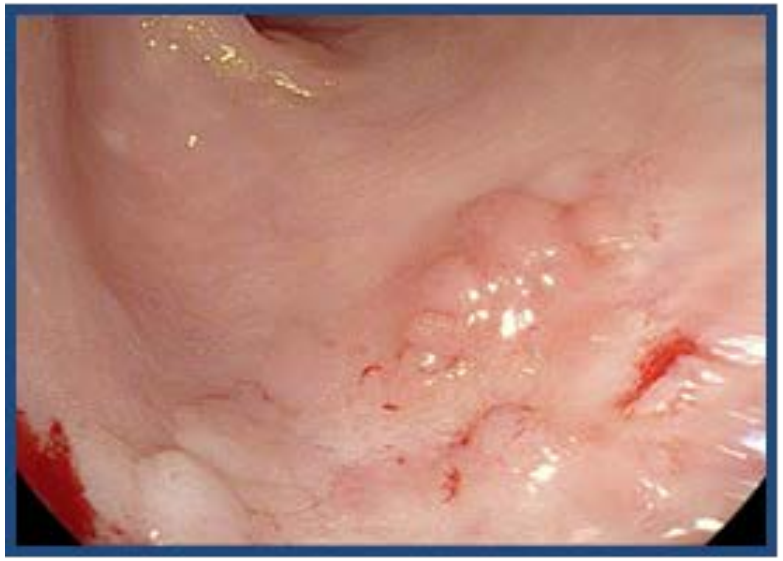
Endoscopic targeted biopsies of suspicious lesions

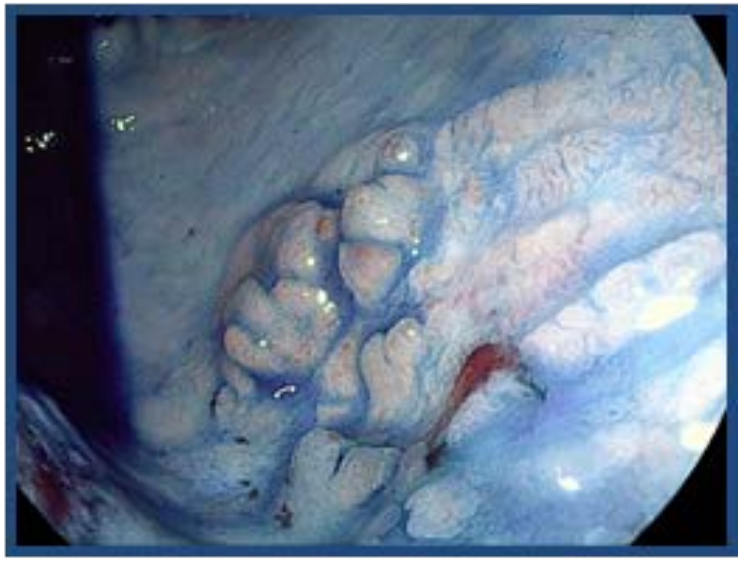
Kiesslich R. and Neurath M.,
Gastroenterol. Clin. North Am, 2012





Flat lesion
(Paris IIa)

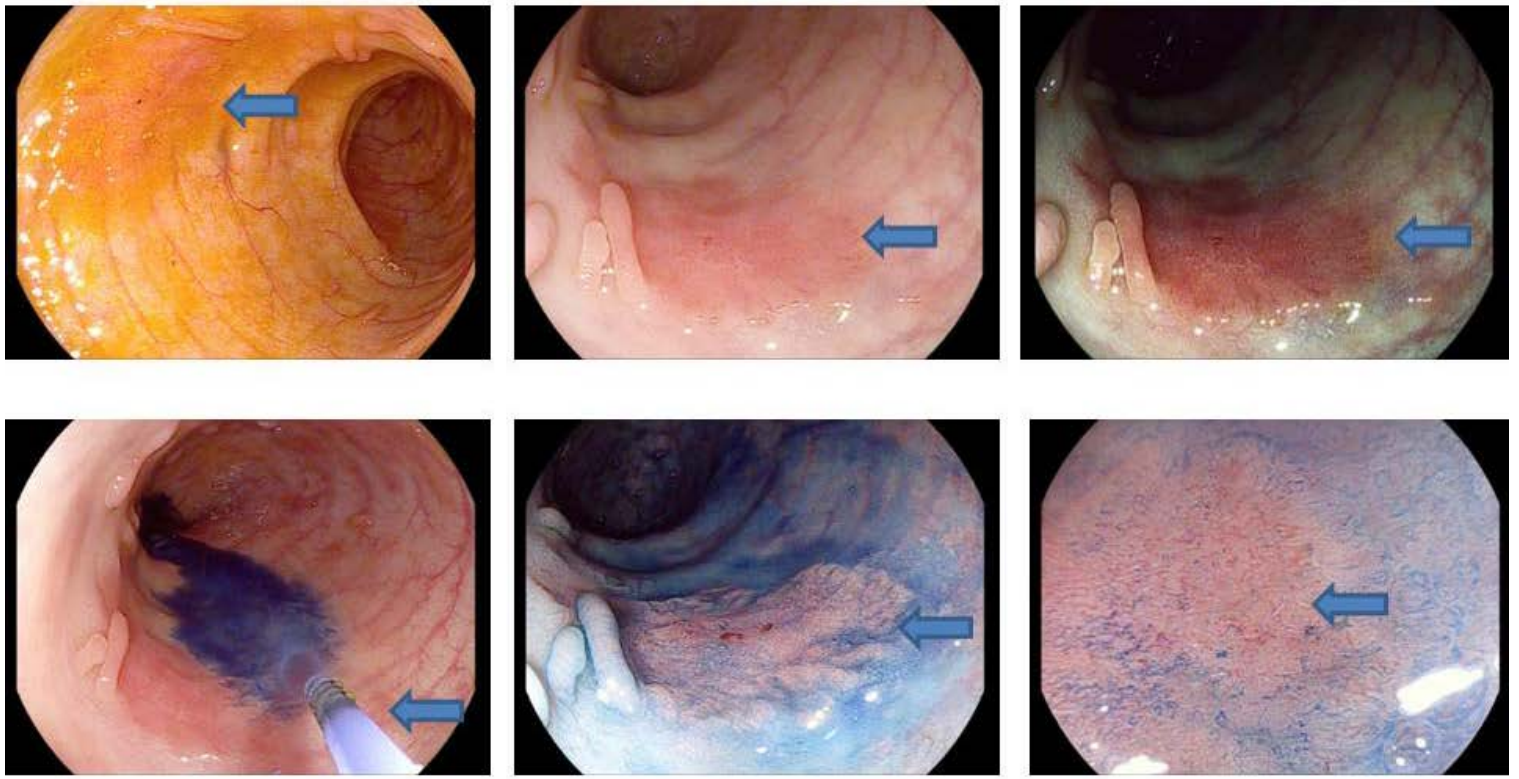


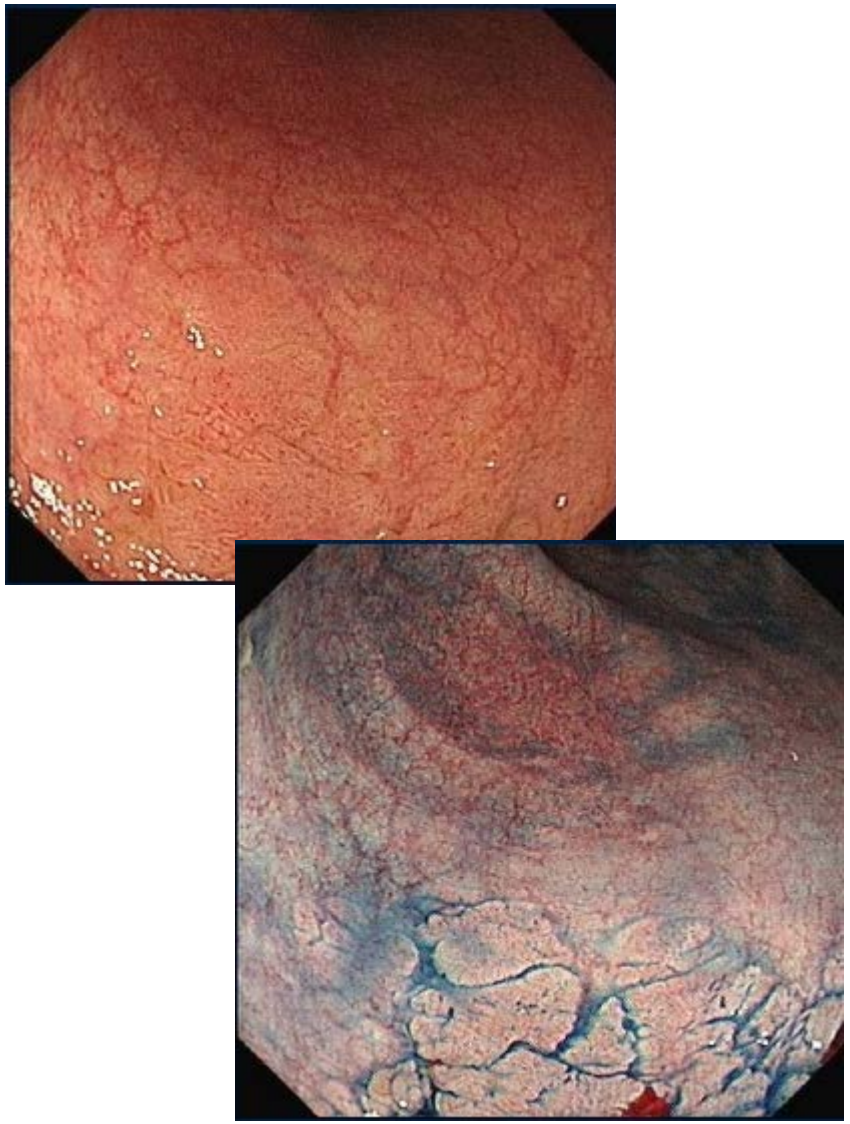


Laterally
Spreading
Tumour

Murthy et al., GIE 2013

Delineation and Characterization of Neoplastic Lesions with CE





Kiesslich R and Neurath M, Gastroenterol Clin North Am 2012

Benefits of DSC

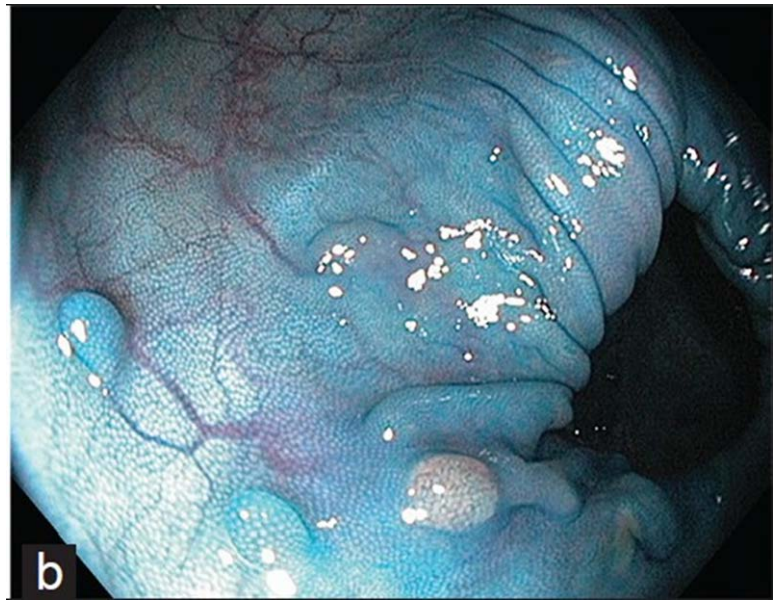
1. Unmasks neoplastic lesions by filling crevices and differential absorption
2. Lesion characterization - differentiate neoplastic and non-neoplastic
3. Facilitates lesion resection by highlighting borders
4. Eliminates need for routine random biopsies
5. Cost-effective relative to WLE + random biopsies Konijeti, GIE 2014

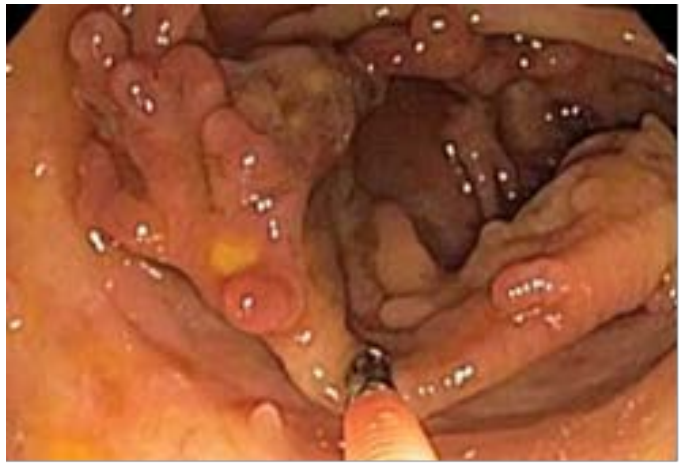
Drawbacks of DSC

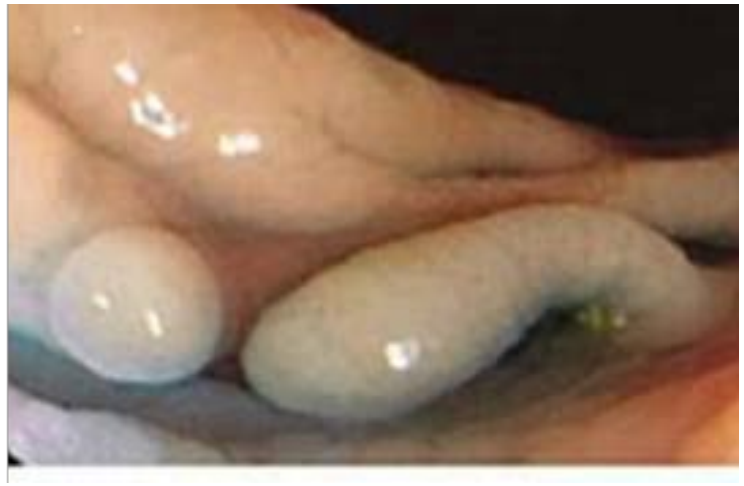
1. Requires meticulous bowel preparation
2. Requires near-complete mucosal healing
3. Inconvenient (labour intensive if using catheter spray; messy)
4. Potential increase in procedure time
5. Unclear clinical and/or cost benefit

How Do I Know if a Lesion is Dysplastic?

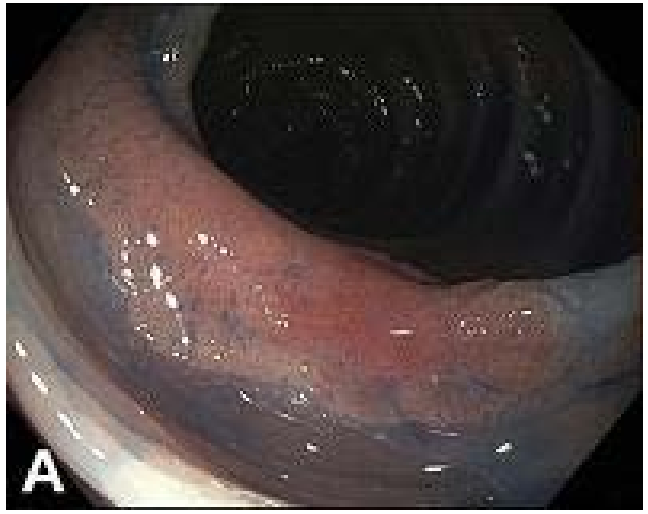
- Look for **circumscribed lesion** or **irregular area** of mucosa → zoom in
- Evaluate **lesion morphology** – finger-like or irregular fleshy projections, or polyps in clusters that are similar in architecture to surrounding mucosa, are typically post-inflammatory polyps
- Evaluate **dye uptake** – dysplastic lesions generally do not take up dye
- Evaluate **surface architecture** and compare to surrounding mucosa → different architecture should be considered suspicious and sampled
- N.B. Kudo classification is not validated in colitis-associated dysplasia



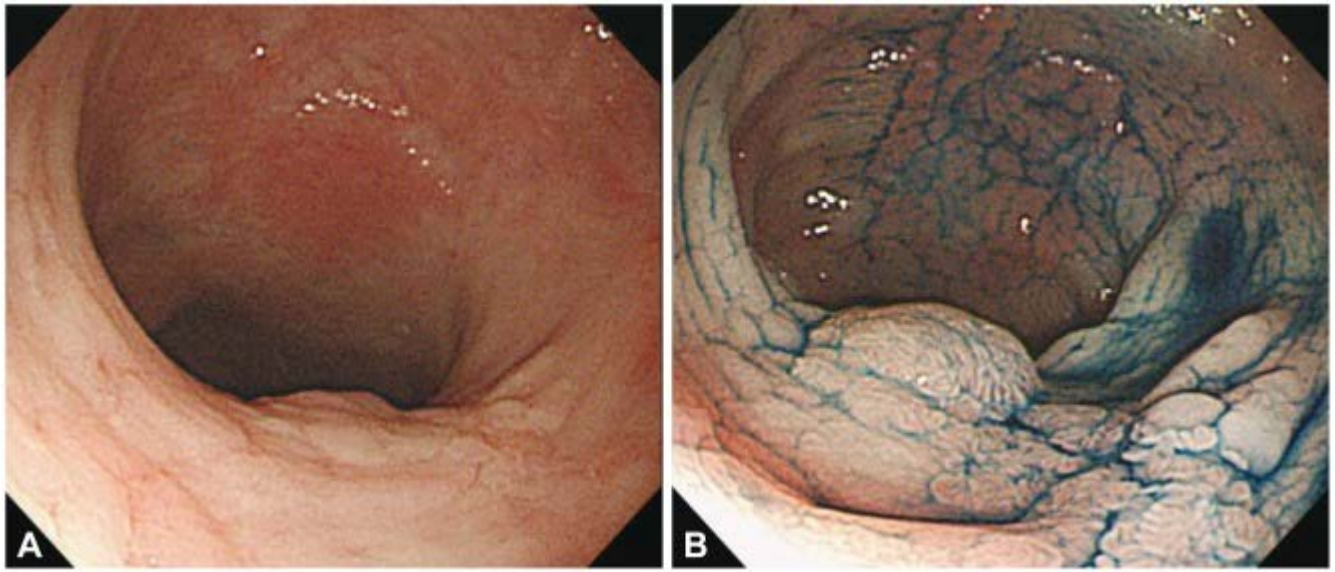




Post-inflammatory polyps



Laterally-spreading tumours



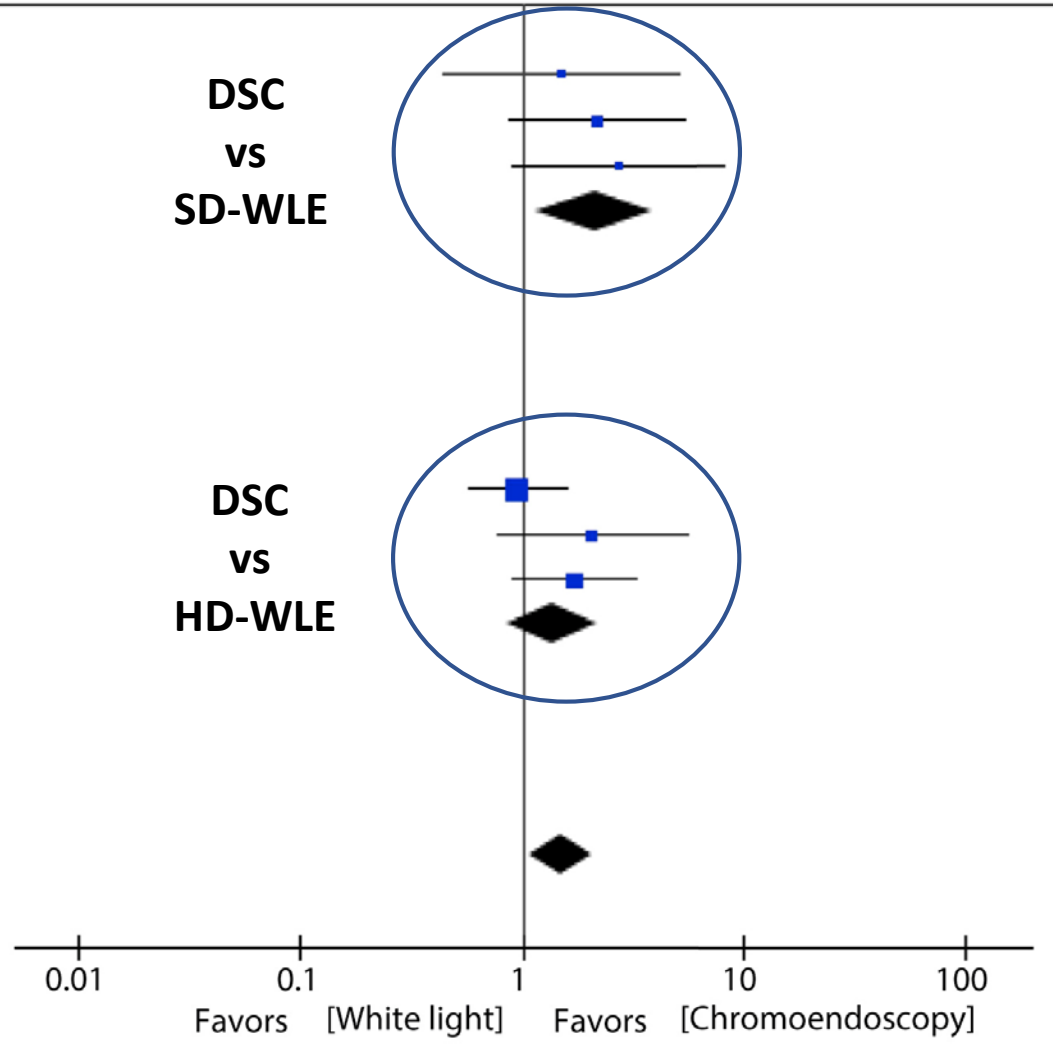
Evidence for DSC vs SD-WLE in IBD

Author	Year	Country	Dye	Staining	Design	No. of pts.	# Pts. with dysplasia	Outcome (chromo vs. standard)
Kiesslich	2003	Germany	MB	Pancolonic	Randomized 1:1	165	19	32 vs. 10 dysplastic lesions
Matsumoto	2003	Japan	IC	Pancolonic	Prospective cohort	57	12	86% versus 38% sensitivity
Rutter	2004	UK	IC	Pancolonic	Prospective cohort	100	7	9 versus 2 dysplastic lesions
Hurlstone	2005	UK	IC	Targeted	Prospective cohort	700	81	69 versus 24 dysplastic lesions
Kiesslich	2007	Germany	MB	Pancolonic	Randomized 1:1	153	15	19 versus 4 dysplastic lesions
Marion	2008	US	MB	Pancolonic	Tandem colonoscopy	102	19	17 versus 3 patients with dysplasia
Günther	2011	Germany	IC	Pancolonic	Randomized 1:1:1	150	6	6 versus 0 patients with dysplasia
Hlavaty	2011	Slovakia	IC	Pancolonic	Tandem colonoscopy	30	7	7 versus 0 patients with dysplasia

SCENIC meta-analysis of 8 studies: Relative benefit 1.8 (1.2-2.6); Absolute benefit 6% (3%-9%)

Randomized Controlled Trials

Study or Subgroup	Chromoendoscopy Events	Chromoendoscopy Total	White light Events	White light Total	Weight	Risk Ratio M-H, Random, 95% CI
Chromoendoscopy vs standard definition white light endoscopy						
Freire 2014	6	81	4	81	7.2%	1.50 [0.44 - 5.12]
Kiesslich 2003	13	87	6	87	12.4%	2.17 [0.86 - 5.44]
Kiesslich 2007	11	81	4	80	8.8%	2.72 [0.90 - 8.17]
Subtotal (95% CI)		**249**		**248**	**28.4%**	**2.12 [1.15 - 3.91]**
Total events	30		14			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 2 (P = .78); $I^2 = 0\%$						
Test for overall effect: Z = 2. 41 (P = .02)						
Chromoendoscopy vs high definition white light endoscopy						
Iacucci 2017	22	90	23	90	36.2%	0.96 [0.58 - 1.59]
Mohammed 2015	11	53	5	50	11.0%	2.08 [0.78 - 5.55]
Park 2016	21	102	13	108	24.4%	1.71 [0.91 - 3.23]
Subtotal (95% CI)		**245**		**248**	**71.6%**	**1.36 [0.84 - 2.18]**
Total events	54		41			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 3.02$, df = 2 (P = .22); $I^2 = 34\%$						
Test for overall effect: Z = 1. 26 (P = .21)						
Total (95% CI)		**494**		**496**	**100.0%**	**1.50 [1.08-2.10]**
Total events	84		55			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.40$, df = 5 (P = .37); $I^2 = 7\%$						
Test for overall effect: Z = 2. 39 (P = .02)						
Test for subgroup differences: $Chi^2 = 1.27$, df = 1 (P = .26), $I^2 = 21.5\%$						



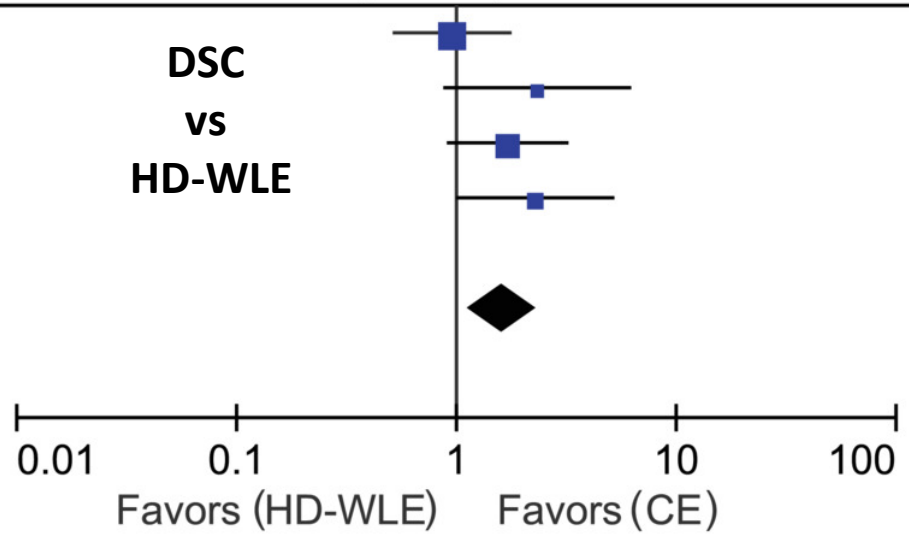
Feuerstein et al., GIE 2019

Randomized Controlled Trials

Study or subgroup	CE Events	CE Total	HD-WLE Events	HD-WLE Total	Weight	Risk ratio M-H, Fixed, 95% CI
Iacucci 2018	11	45	23	90	38.5%	0.96 (0.51, 1.78)
Mohammed 2015	11	50	5	53	12.2%	2.33 (0.87, 6.24)
Park 2016	21	102	13	108	31.7%	1.71 (0.91, 3.23)
Picco 2013	16	75	7	75	17.6%	2.29 (1.00, 5.23)
Total (95% CI)		**272**		**326**	**100.0%**	**1.60 (1.11, 2.29)**
Total events	59		48			

Heterogeneity: Chi² = 3.93, *df* = 3 (*P* = 0.27); I^2 = 24%

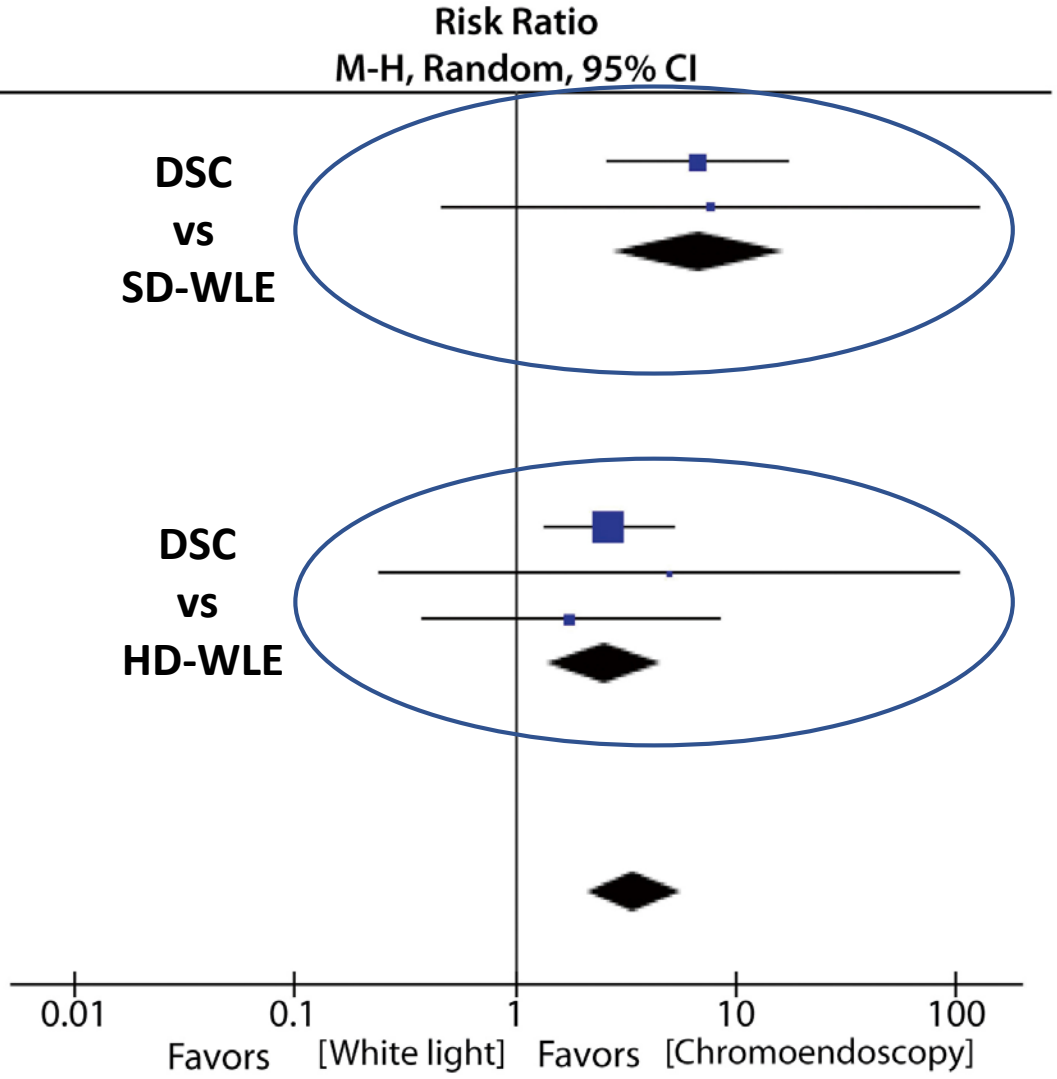
Test for overall effect: Z = 2.55 (*P* = 0.01)



Wan et al., JDD 2019

Non-Randomized Controlled Trials

Study or Subgroup	Chromoendoscopy Events	Total	White light Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chromoendoscopy vs standard-definition white-light endoscopy non-randomzied						
Gasia 2016	9	28	6	126	27.7%	6.75 [2.61-17.42]
Hlavaty2011 (1)	7	30	0	15	3.2%	7.74 [0.47-127.11]
Subtotal (95% CI)		**58**		**141**	**30.8%**	**6.85 [2. 79 -16.81]**
Total events	16		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = .92); $I^2 = 0\%$						
Test for overall effect: Z = 4.20 (P < .0001)						
Chromoendoscopy vs high-definition white-light endoscopy non-randomzied						
Gasia 2016	9	28	22	182	56.2%	2.66 [1 .37- 5.17]
Gunther 2011	2	50	0	50	27%	5.00 [0.25-101.58]
Iacucci 2014	5	35	2	25	10.3%	1.79 [0.38-8.48]
Subtotal (95% CI)		**113**		**257**	**69.2%**	**2.57 [1.41-4.68]**
Total events	16		24			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 2 (P = .82); $I^2 = 0\%$						
Test for overall effect: Z = 3.08 (P = .002)						
Total (95% CI)		**171**		**398**	**100.0%**	**3.48 [2.11-5.73]**
Total events	32		30			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.61$, df = 4 (P = .46); $I^2 = 0\%$						
Test for overall effect: Z = 4.90 (P < .00001)						
Test for subgroup differences: $Chi^2 = 3.16$, df = 1 (P = .08), $I^2 = 68.4\%$						



Footnotes

(1) Chromoendoscopy arm included use of both chromoendoscopy and confocal microscopy

Feuerstein et al., GIE 2019

Reasons for Limited Uptake of DSC

- Uncertain benefit over HD-WLE
- Uncertain impact on CRC or CRC-related mortality
- Uncertainty of surveillance intervals if dysplasia detected
- Uncertain cost implications (with more frequent surveillance)
- Inadequate training and/or experience
- Requirement for healed bowel, meticulous cleansing
- Inconvenient → time-consuming, messy
- Lack of re-imbursement
- Availability of dye, staining of colonoscopes
- Patient reticence → bluish-green discoloration of stool and urine

However, please consider that . . .

- DSC is extremely easy to do
- Time to clean and stain the colon ≈ time to take and document 32+ random biopsies
- DSC with targeted biopsies forces careful inspection of mucosa
- DSC aids in the detection and resection of flat lesions
- Methylene blue is cheap ($60/250 mL at Amazon) = < $5 per procedure
- On a per-procedure basis, DSC with targeted biopsies is <u>much</u> cheaper than WLE with non-targeted and targeted biopsies (~ 50% cheaper)
- Unmasking lesions with DSC may identify patients at increased risk of CRC

Virtual Chromoendoscopy

- Light filters (NBI) or post-image processing (*i*scan, FICE) to focus on narrow wavelengths of light

- Highlights vascular pattern → indirect appreciation of pit pattern

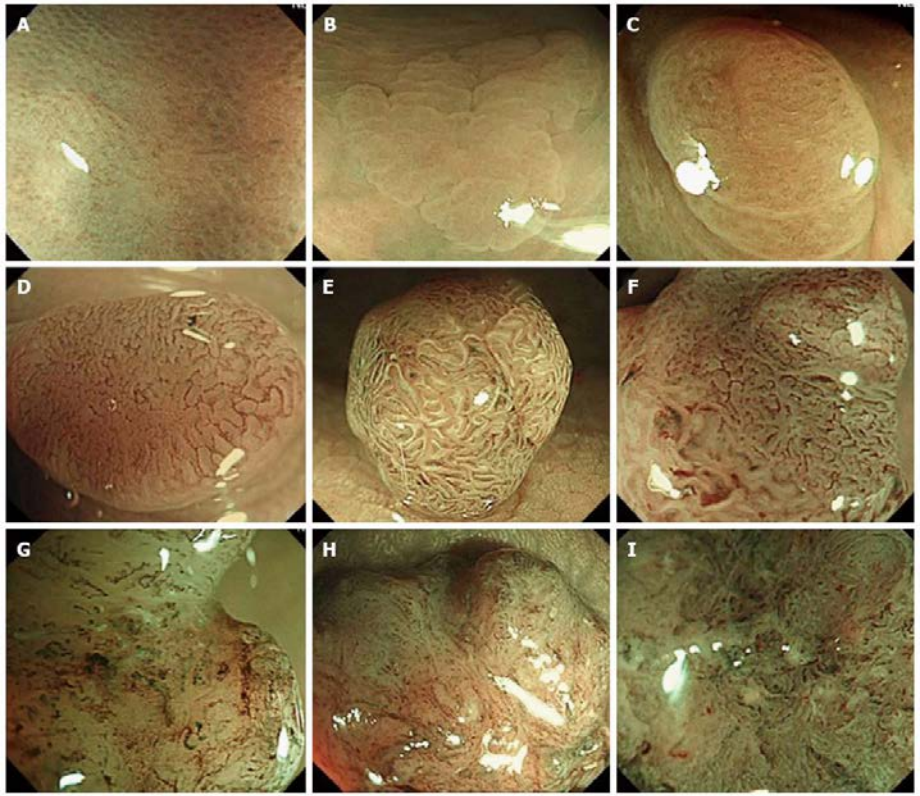
- Earlier studies showed that NBI was not superior to SD-WLE or HD-WLE for lesion detection, but similar to DSC for lesion characterization

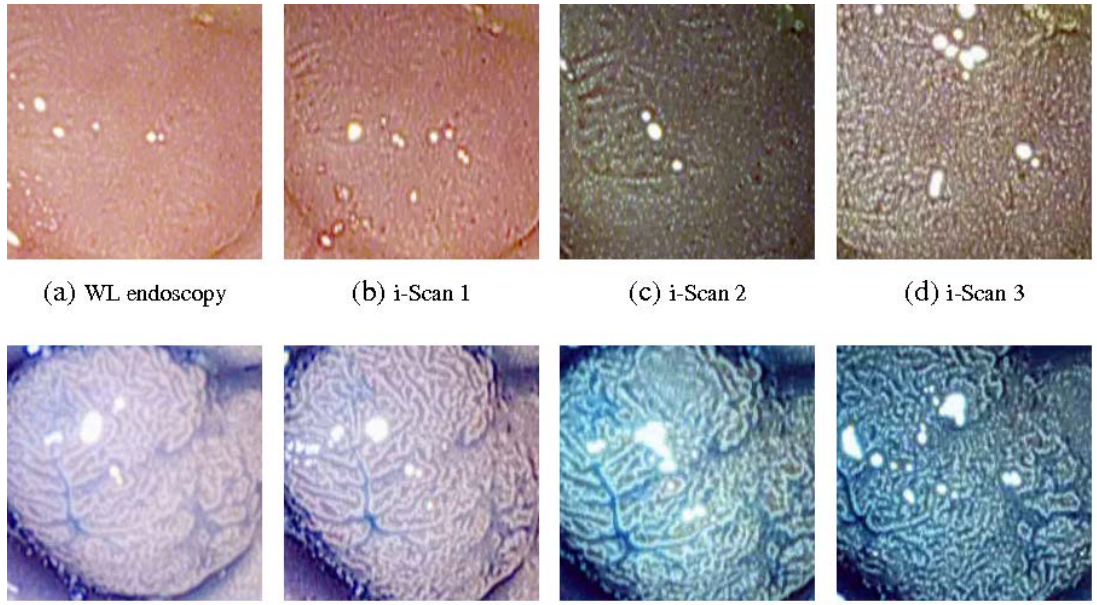
Chiu et al., Gut 2007; Rastogi et al., GIE 2007; Ignjatovic et al., AJG 2012; van de Broek et al., Endoscopy 2011

- Recent RCTs in IBD and non-IBD have shown more promising results

Bisschops et al., Gut 2018; Iaccuci et al., AJG 2018; Atkinson et al., Gastroenterology 2019

Narrow Band Imaging

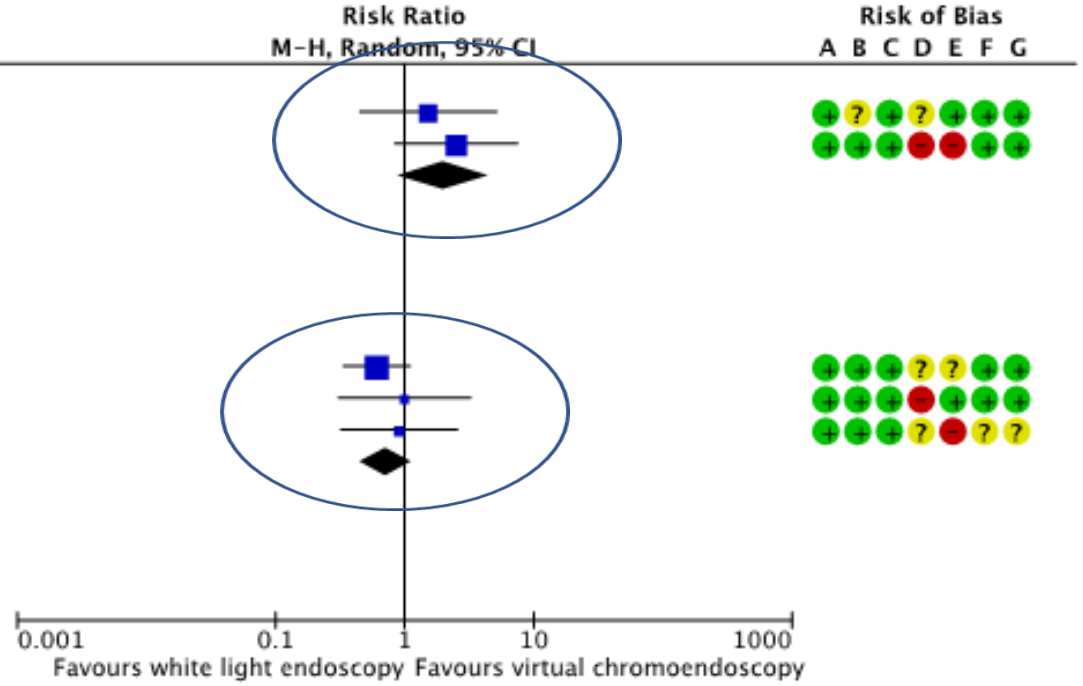




iScan

RCTs of VCE vs WLE

Study or Subgroup	Virtual chromoendoscopy Events	Total	White light colonoscopy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Virtual chromoendoscopy vs. SD white light endoscopy						
Freire 2014	6	72	4	73	44.7%	1.52 [0.45, 5.16]
Kiesslich 2007	11	80	4	73	55.3%	2.51 [0.84, 7.53]
Subtotal (95% CI)		**152**		**146**	**100.0%**	**2.01 [0.89, 4.54]**
Total events	17		8			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 1.67 (P = 0.10)						
6.1.2 Virtual chromoendoscopy vs. HD white light endoscopy						
Iacucci 2017	14	90	23	90	63.2%	0.61 [0.34, 1.11]
Ignjatovic 2012	5	56	5	56	16.1%	1.00 [0.31, 3.26]
Van den 2010	5	23	6	25	20.7%	0.91 [0.32, 2.57]
Subtotal (95% CI)		**169**		**171**	**100.0%**	**0.72 [0.45, 1.15]**
Total events	24		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 1.38 (P = 0.17)						



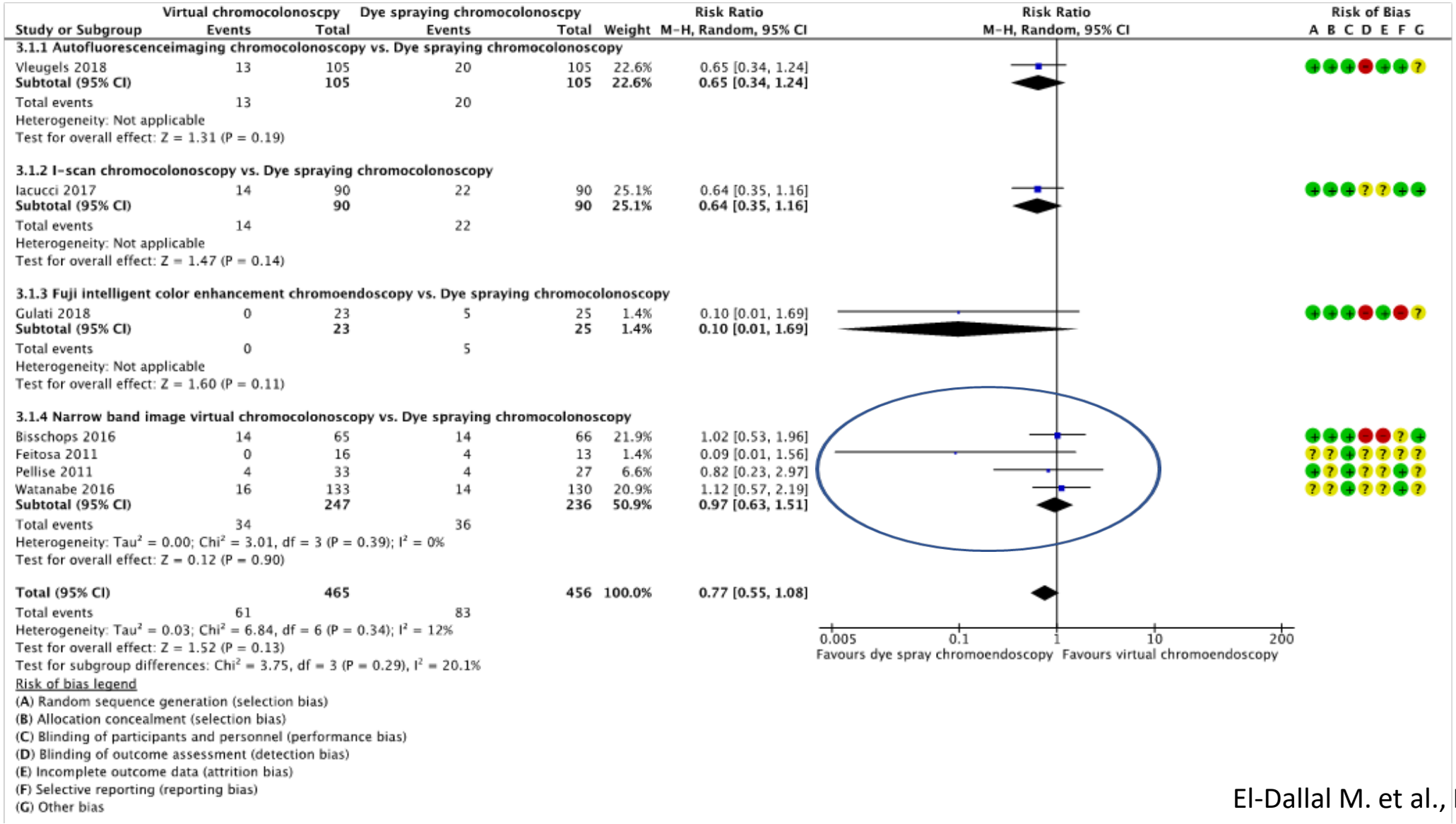
Test for subgroup differences: $Chi^2 = 4.57$, df = 1 (P = 0.03), $I^2 = 78.1\%$

Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

El-Dallal M. et al., IBDJ 2020

RCTs of VCE vs DSC



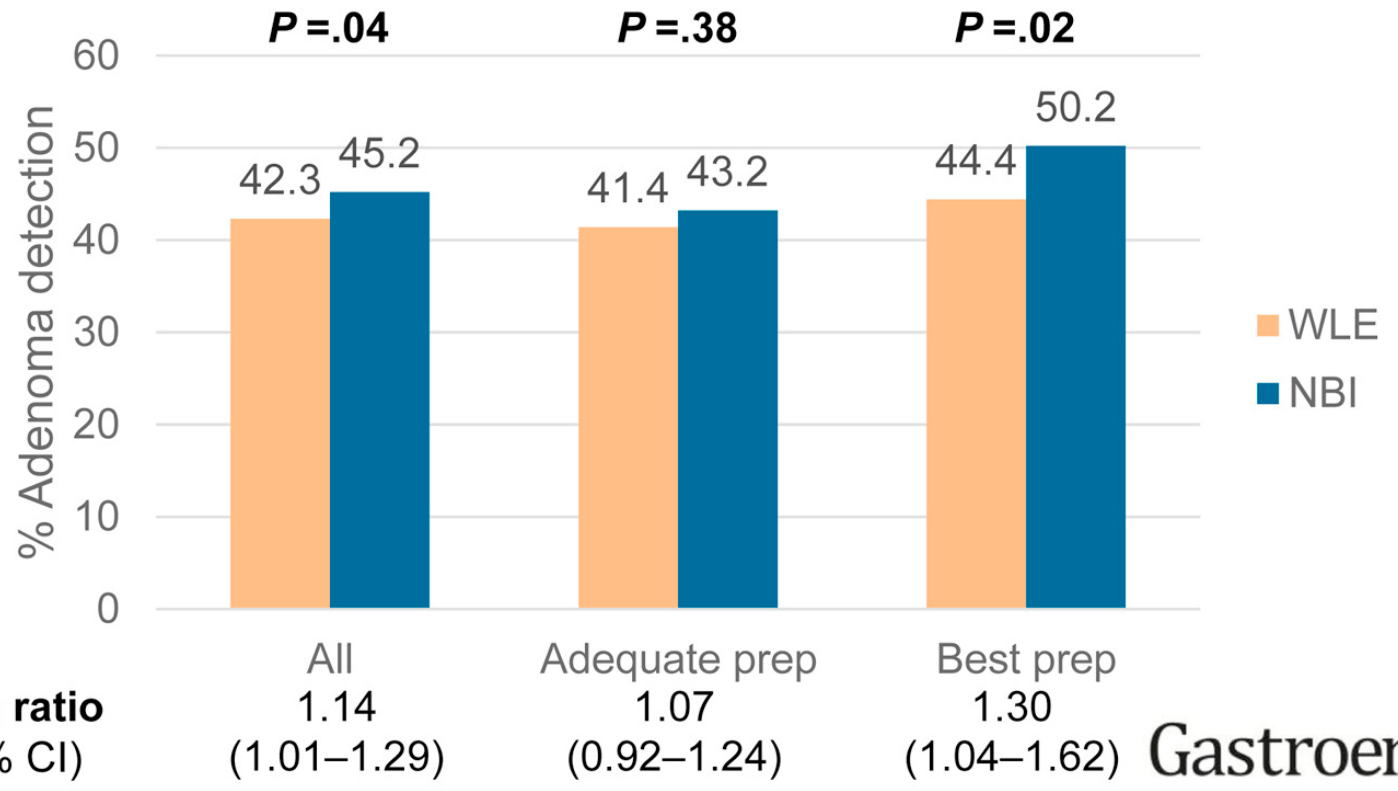
El-Dallal M. et al., IBDJ 2020

RCTs of VCE vs CE and HD-WLE in non-IBD

Individual patient level data meta-analysis for high definition White Light Endoscopy (WLE) vs Narrow Band Imaging (NBI) stratified by bowel preparation

11 international centers

4491 individual patient datasets



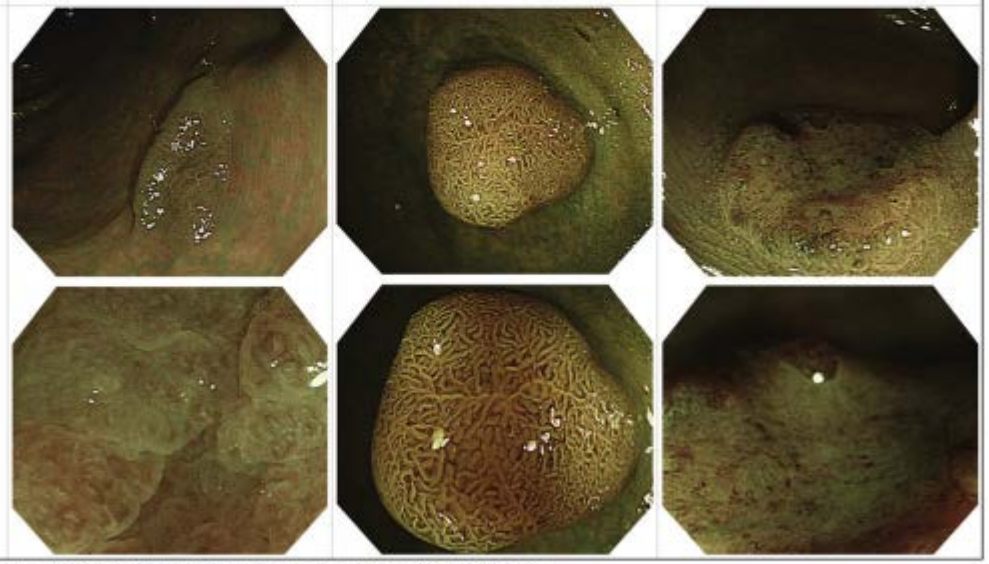
Gastroenterology

Also improved adenoma detection only with second-generation bright NBI

Atkinson et al., Gastroenterology 2019

Lesion Characterization (CE/VCE)

NBI International Colorectal Endoscopic (NICE) Classification*

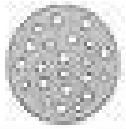
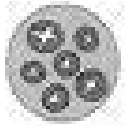
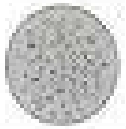
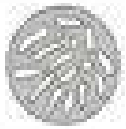
	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Kudo

I		Round pit (normal pit)
II		Asteroid pit
IIIS		Tubular or round pit that is smaller than the normal pit (Type I)
IIIL		Tubular or round pit that is larger than the normal pit (Type I)
IV		Dendritic or gyrus-like pit
VA		Irregular arrangement and sizes of IIIL, IIIS, IV type pit pattern
VN		Amorphous or non-structural pit pattern

Other Methods (not currently in routine use)

- **Autofluorescence** → shown to be inferior to DSC in recent pilot RCT (Vleugels et al., Lancet Gastroenterol Hepatol 2018)

- **Confocal Endomicroscopy** – allows real-time in vivo histology

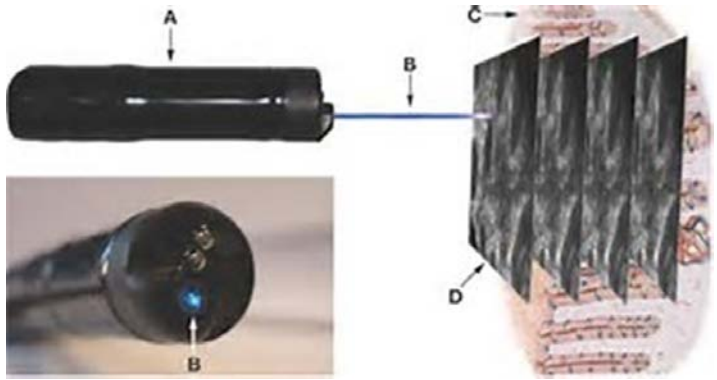
→ Not useful for improving detection over large surface areas

→ Improves lesion characterization slightly over current IEE methods

→ Time-consuming, costly, large training curve

→ Unclear cost advantage over current methods

→ Not practical for commercial use



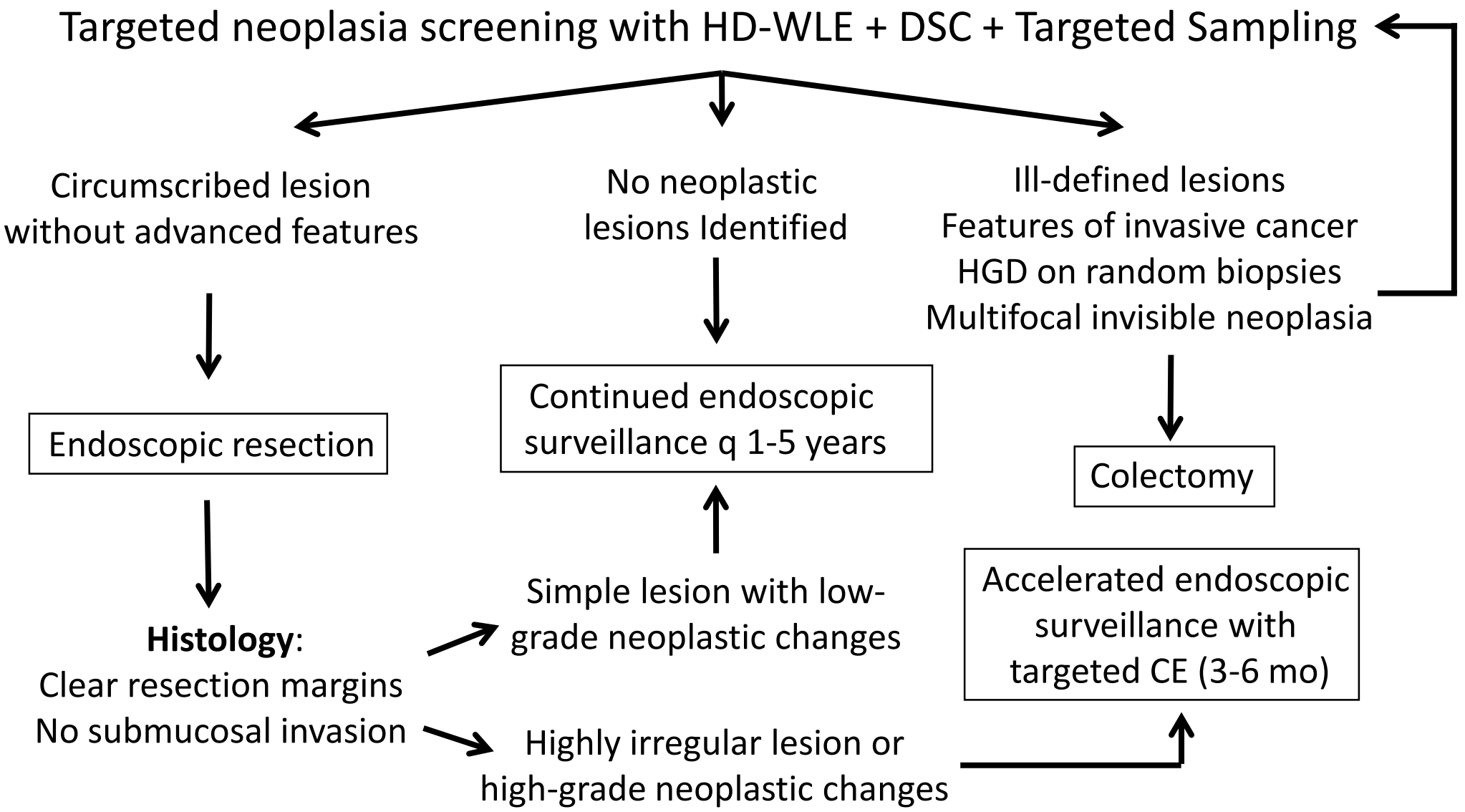
Real-Time Lesion Characterization

Differentiation of Neoplastic and Non-Neoplastic Lesions					
Technique	**Setting**	**SENS**	**SPEC**	**Accuracy**	**Reference**
Chromoendoscopy	UC	93%	88-93%	~90%	Kiesslich, Gastro 2003 Hurlstone, Endoscopy 2005
Chromoendoscopy	Non-IBD	83-96%	83-93%	85-94%	Van den Broek, GIE 2009
NBI	UC	75-80%	65-81%	~70%	Van den Broek, Gut 2008 Van den Broek; Endoscopy 2011
NBI	Non-IBD	89-94%	80-91%	87-91%	Van den Broek, GIE 2009
Endomicroscopy	UC			97%	Hurlstone, CGH 2007
Endomicroscopy	Non-IBD	97	99	99%	Kiesslich, Gastro 2004

Summary

- Neoplasia surveillance techniques in IBD are evolving
- DSC with targeted biopsies offers a safe, simple and economical alternative to WLE with non-targeted and targeted biopsies
- Further data is required to define the utility of DSC in the context of HD-WLE and the impact of DSC on CRC rates
- Further data is required to define the utility of random biopsies with either strategy and to better define optimal surveillance intervals

Modified Algorithm for Neoplasia Surveillance in IBD



THE END ☺