

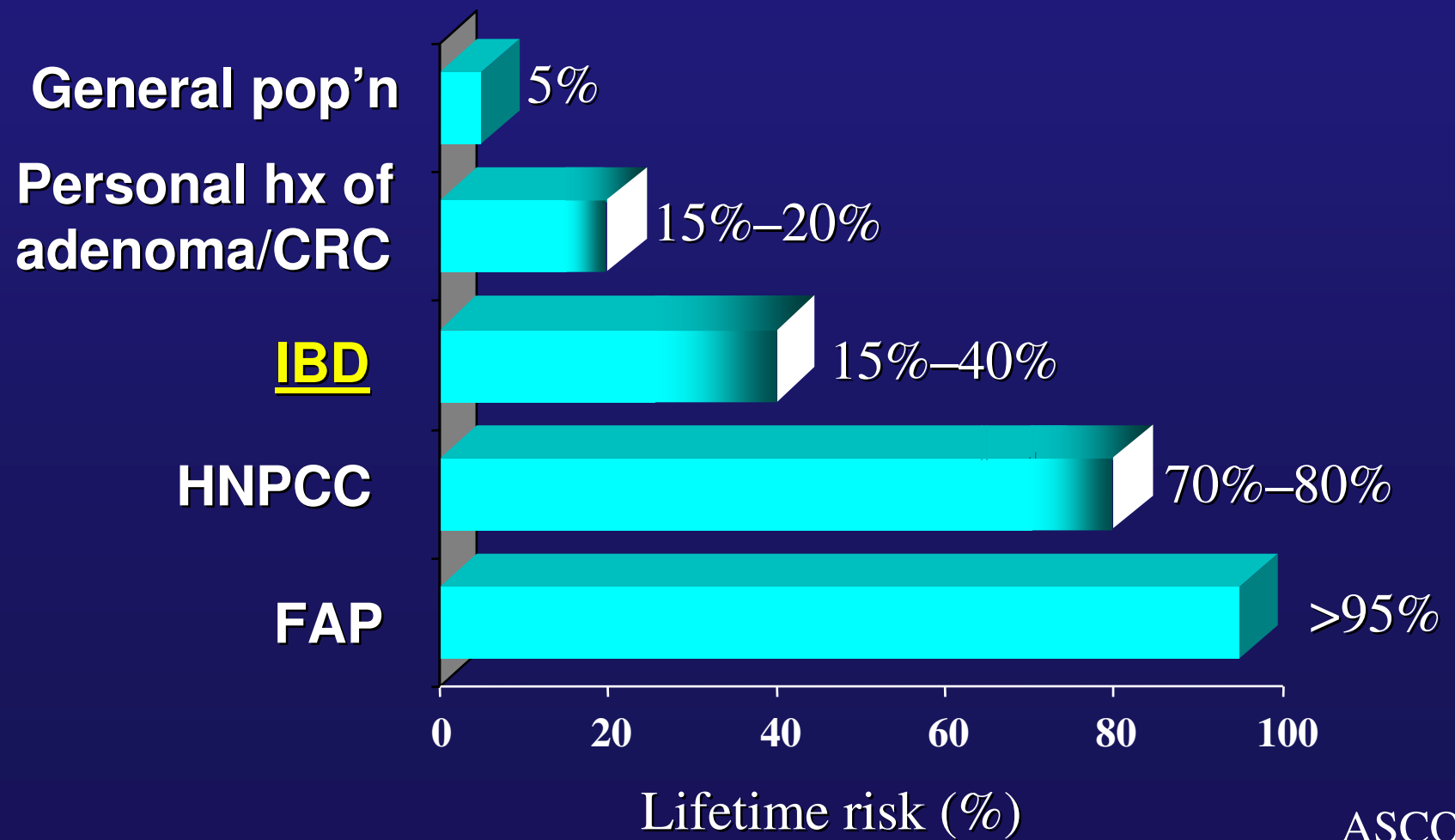
Management of Dysplasia in Inflammatory Bowel Disease

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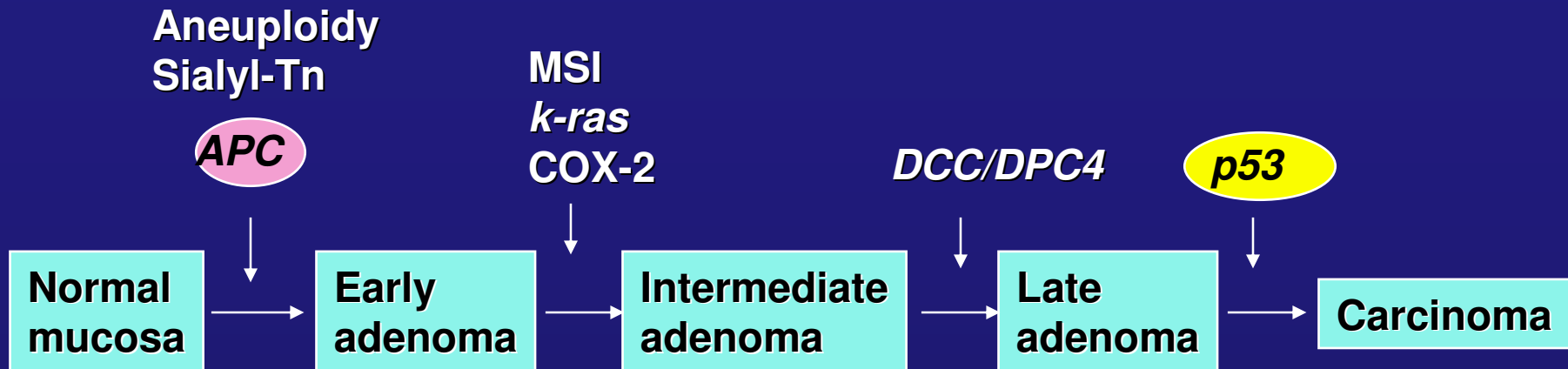
Risk of Developing Colorectal Cancer



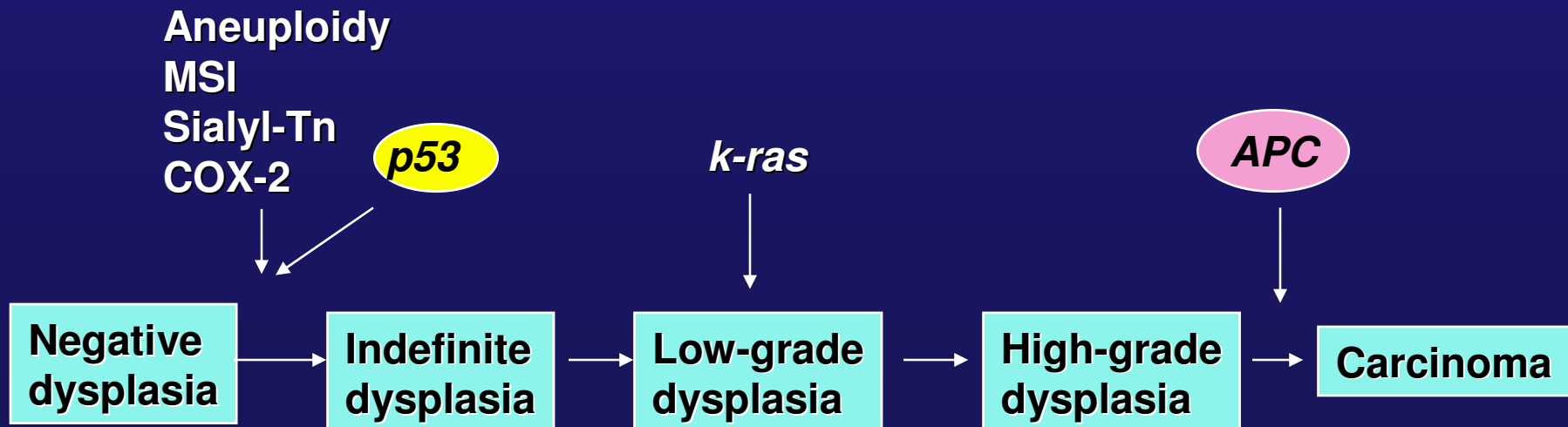
Clinicopathological Features of CRC

	<u>Sporadic</u>	<u>IBD</u>	<u>HNPCC</u>
Dysplasia:	polyp	flat/polyp	polyp
Age @ cancer:	60's	30's	30's
Multiple cancers:	2-3%	10-15%	10-15%
CRC location:	distal	prox>distal	prox>distal
Histologic type			
mucinous:	rare	common	common
poorly diff'd:	rare	common	common
low-grade TGA	very rare	11%	?
Surveillance interval	5-10 yr	1-2 yr	1-3 yr
Genetic v. Environ:	Env>Gen.	Env>Gen	Gen>Env.

SPORADIC COLON CANCER



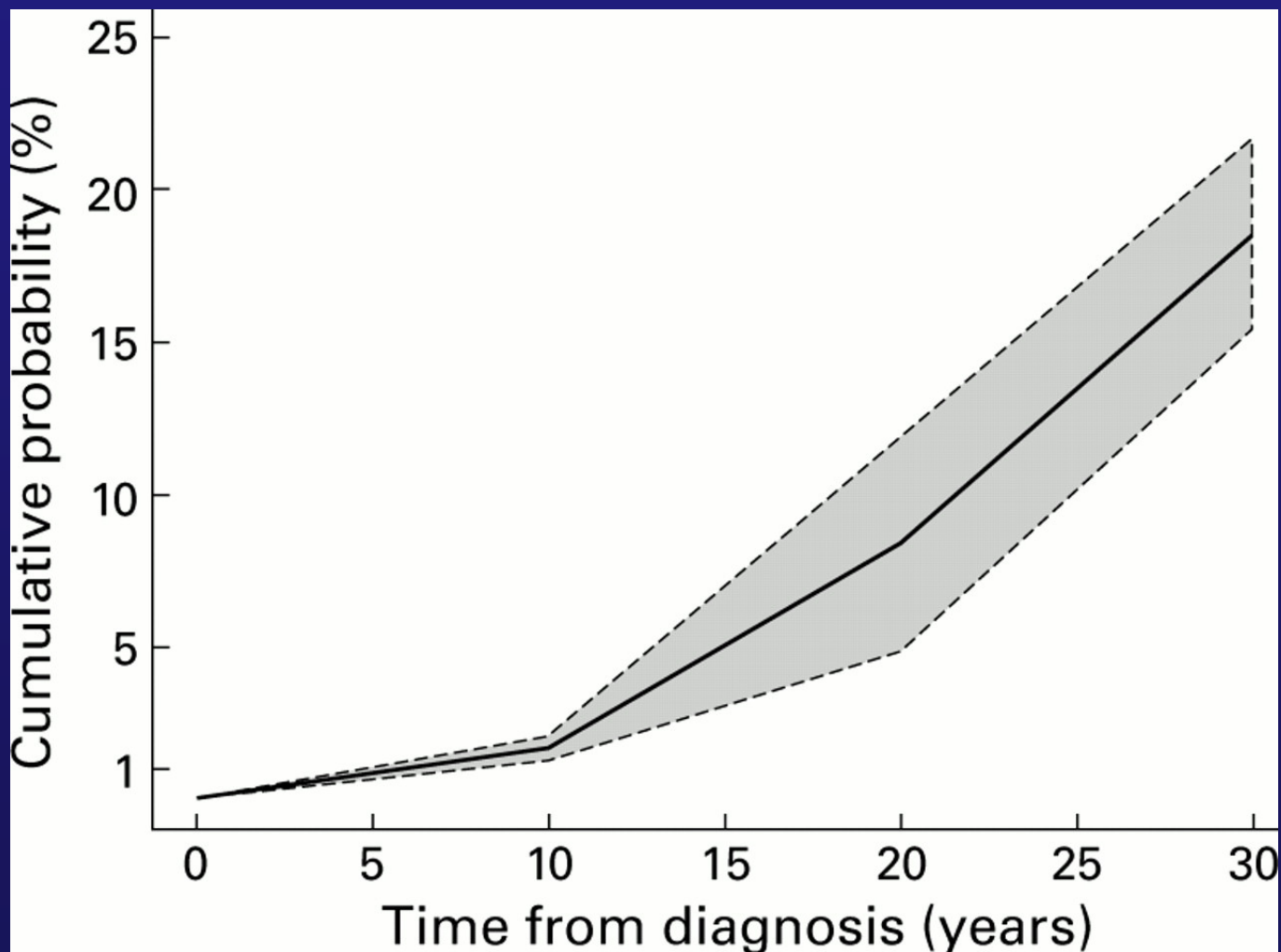
COLITIS-ASSOCIATED COLON CANCER



Itzkowitz and Harpaz. Gastroenterology 126:1634, 2004.

Cumulative Risk of CRC in UC

0.5-1.0% per year after 10 years of disease



Eaden et al. *Gut* 48:526, 2001

Options for the Patient

Prophylactic proctocolectomy = Totalitarianism

Ignore cancer risk = Anarchy

Surveillance program = Democracy

Winston Churchill



**“Democracy is the worst form of government
... (except for all the others).”**

Is the Incidence of CRC Declining?

<u>Cumulative Incidence of CRC</u>				
<u>Study</u>	<u>Location</u>	<u>10 yrs</u>	<u>20 yrs</u>	<u>30 yrs</u>
Eaden '01	Meta-anal.	1.6%	8.3%	18.4%
Winther '04	Denmark	0.4%	1.1%	2.1%
Rutter '06	St. Mark's	0%	2.5%	7.6%
Lakatos '06	Hungary	0.6%	5.4%	7.5%

Population Based Studies of CRC in IBD

	<u>Country</u>	<u>Dates</u>	<u>Annual Inc. Rate</u>	<u>Relative Risk</u>
Palli	Italy	1978-92	0.12%	1.79 (0.9-3.3)
Bernstein	Canada	1984-97	0.20%	2.75 (1.9-4.0)
Lakatos	Hungary	1974-2004	0.15%	--
Jess	Minn.	1940-2001	0.10%	1.1 (0.4-2.4)
Winther	Denmark	1962-87	0.06%	1.05 (0.6-1.8)

Loftus E. Gastro Clin NA 35:517, 2006

Risk of CRC in IBD: Factors that Increase Risk

- **Duration >8-10 years**
- **Extent of colitis:**
 - **universal, left-sided >> proctitis**
 - **backwash ileitis (?)**
- **Family history of colon cancer**
- **Primary sclerosing cholangitis**
- **Histologic & endoscopic activity**
- **Young age at onset of colitis (some studies)**
- **Pseudopolyps (?)**
- **History of dysplasia**

Risk of CRC in IBD: Factors that Decrease Risk

- Surveillance colonoscopy
- Regular doctor visits (?)
- Chemoprevention
 - 5-ASA probably
 - Steroids possibly
 - 6-MP/AZA no
 - Folate not enough data
 - Urso yes (for PSC pts.)



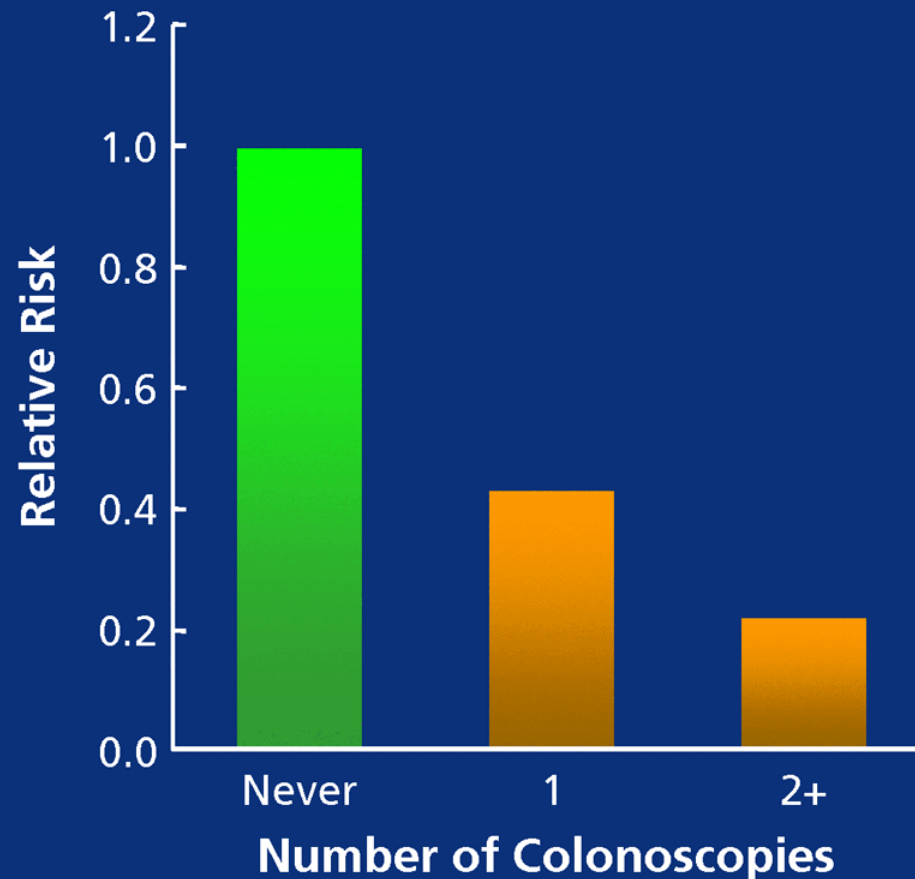
Surveillance Colonoscopy Reduces CRC Mortality in UC

Nested case-control study

- Cases: 40 patients with UC who died of CRC
- Controls: 102 living, matched patients with UC

Relative cancer risk

- No colonoscopy: 1.0
- 1 colonoscopy: 0.43 (95% CI 0.05-3.76)
- ≥ 2 colonoscopies: 0.22 (95% CI 0.03-1.74)



Macroscopic Classification of Dysplasia

A.



Flat dysplasia

B.



DALM

C.



Adenomatous polyps

D.

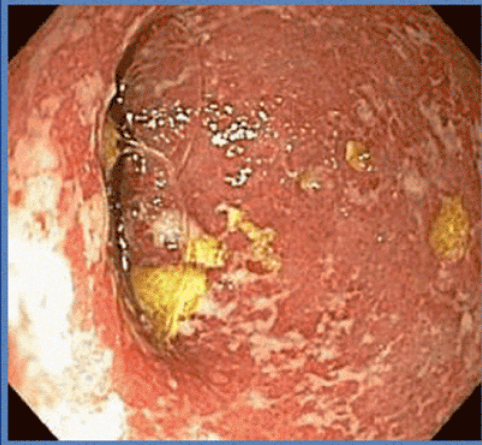


Adenoma-like DALM





Dysplasia in IBD



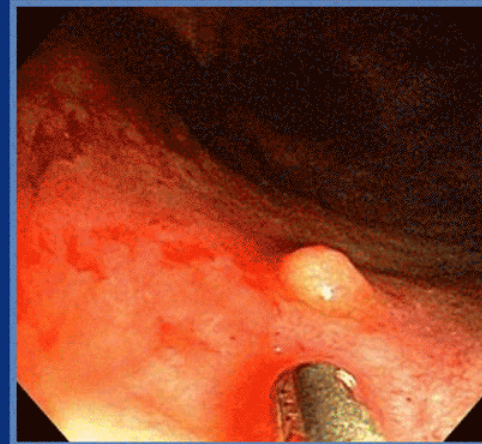
Flat Dysplasia (not macroscopically visible)



DALM (within colitis)



Adenomatous Polyps (proximal to colitis)



Adenomalike DALM (within colitis)

Photos courtesy of David T. Rubin, MD.

Management of Polypoid Dysplasia

Endoscopic polypectomy (without surgical resection) is adequate treatment for adenoma-like polyps in UC patients.

Caveats:

- Polypectomy must be complete.
- The base of the polyp should be separately biopsied and found to have no dysplasia.
- There should be no dysplasia elsewhere in the colon.

Engelsgjerd et al., Gastroenterology 117:1288, 1999

Rubin et al., Gastroenterology 117:1295, 1999

What is the Natural History of High-Grade Dysplasia?

Probability of Finding Cancer

If colectomy done:

	<u>Immediately</u>	<u>After some F/U</u>
DALM ¹	17/40 (43%)	--
High-grade ¹	10/24 (42%)	15/47 (32%)
High-grade ²	8/12 (67%)	--
High-grade ³	5/11 (46%)	2/8 (25%)

¹ Bernstein et al. Lancet 343:71, 1994

² Connell et al. Gastroenterology, 1994

³ Rutter et al. Gastroenterology 130:1030, 2006

What is the Natural History of Low-Grade Dysplasia?

Probability of Finding Cancer

If colectomy done:

	<u>Immediately</u>	<u>After some F/U</u>
DALM	17/40 (43%)	--
High-grade	10/24 (42%)	15/47 (32%)
Low-grade ¹	3/16 (19%)	17/204 (8%)
Low-grade ²	2/11 (19%)	
Low-grade ³	2/10 (20%)	7/36 (19%)

1 *Bernstein et al. Lancet 343:71, 1994*

2 *Ullman et al. Gastroenterology, 2003*

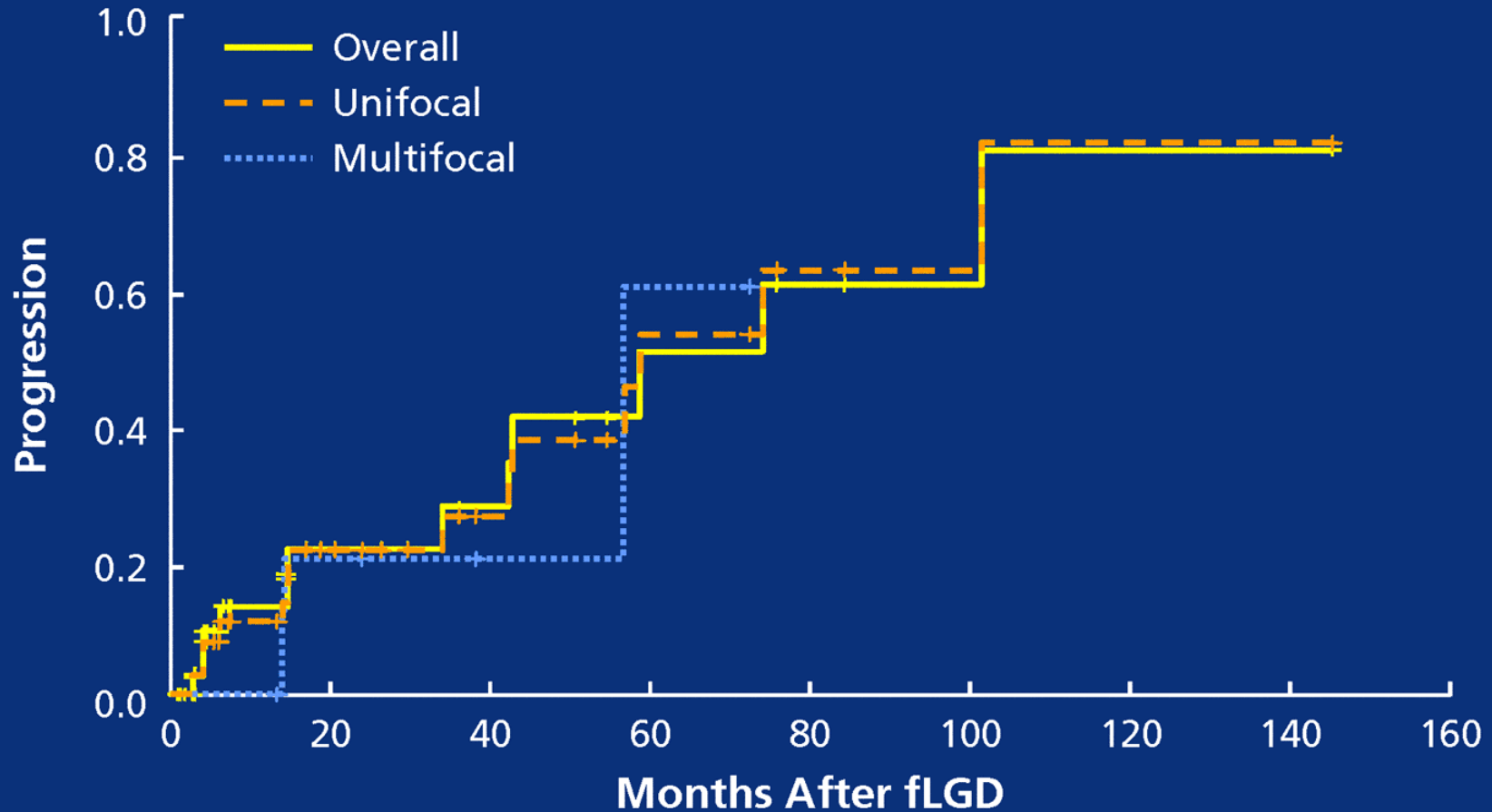
3 *Rutter et al. Gastroenterology 130:1030, 2006*

Progression of LGD to HGD or Cancer

<u>Study</u>	<u>Hospital</u>	<u>LGD (n)</u>	<u>Rate</u>
Connell ('94)	St. Marks	9	54% @ 5 yrs
Ullman ('03)	Mount Sinai	46	53% @ 5 yrs
Ullman ('02)	Mayo Clinic	18	33% @ 5 yrs
Rutter ('06)	St. Marks	47	23% @ 5 yrs
Lindberg ('96)	Huddinge	37	35% @ 20 yrs
Lim ('03)	Leeds, UK	29	10% @ 10 yrs
Befrits ('02)	Karolinska	60	2% @ ~10 yrs
Jess ('06)	Olmstead Cty	29	0% @ 18 yrs

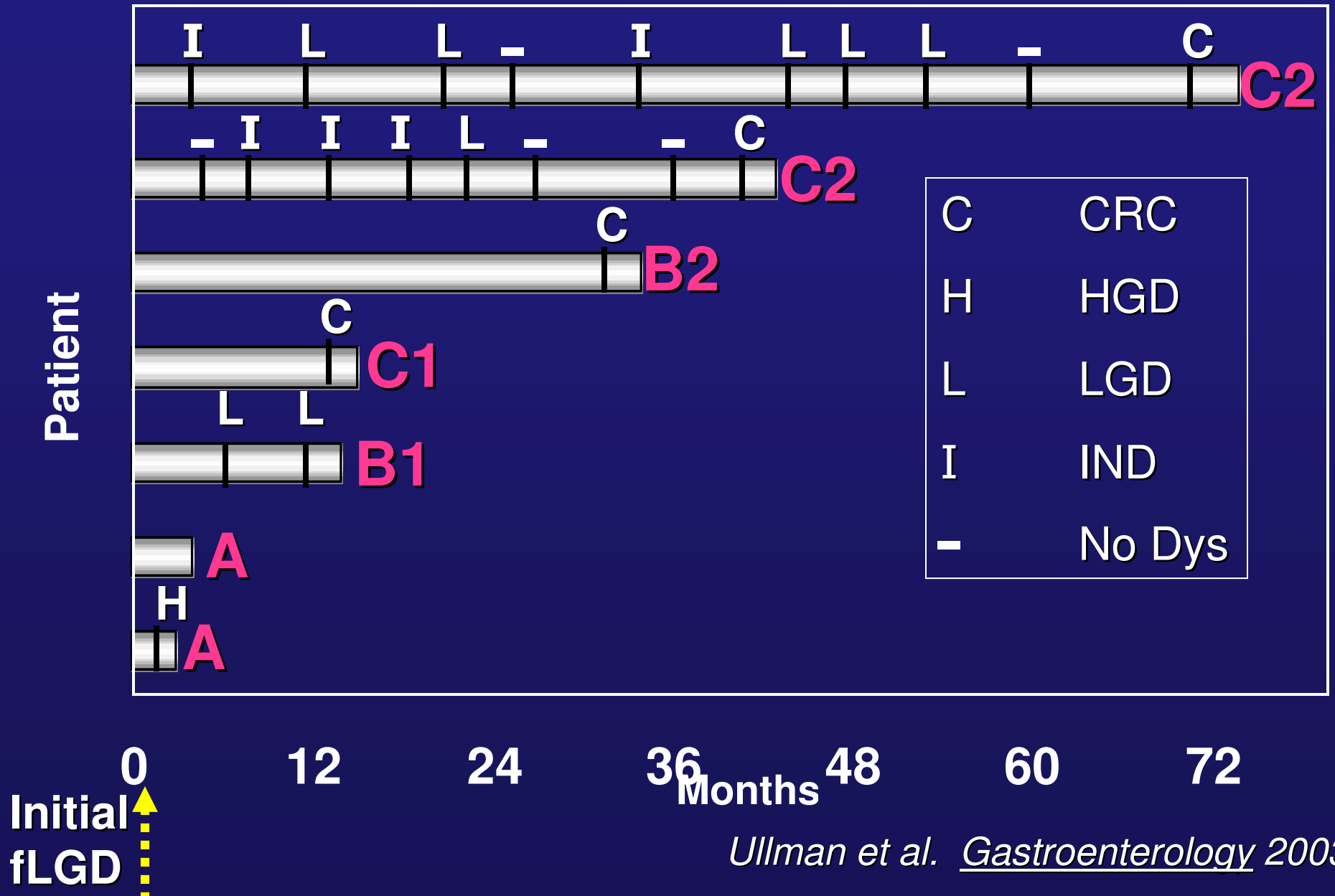


Equal Progression of Unifocal and Multifocal Flat LGD to HGD/Cancer

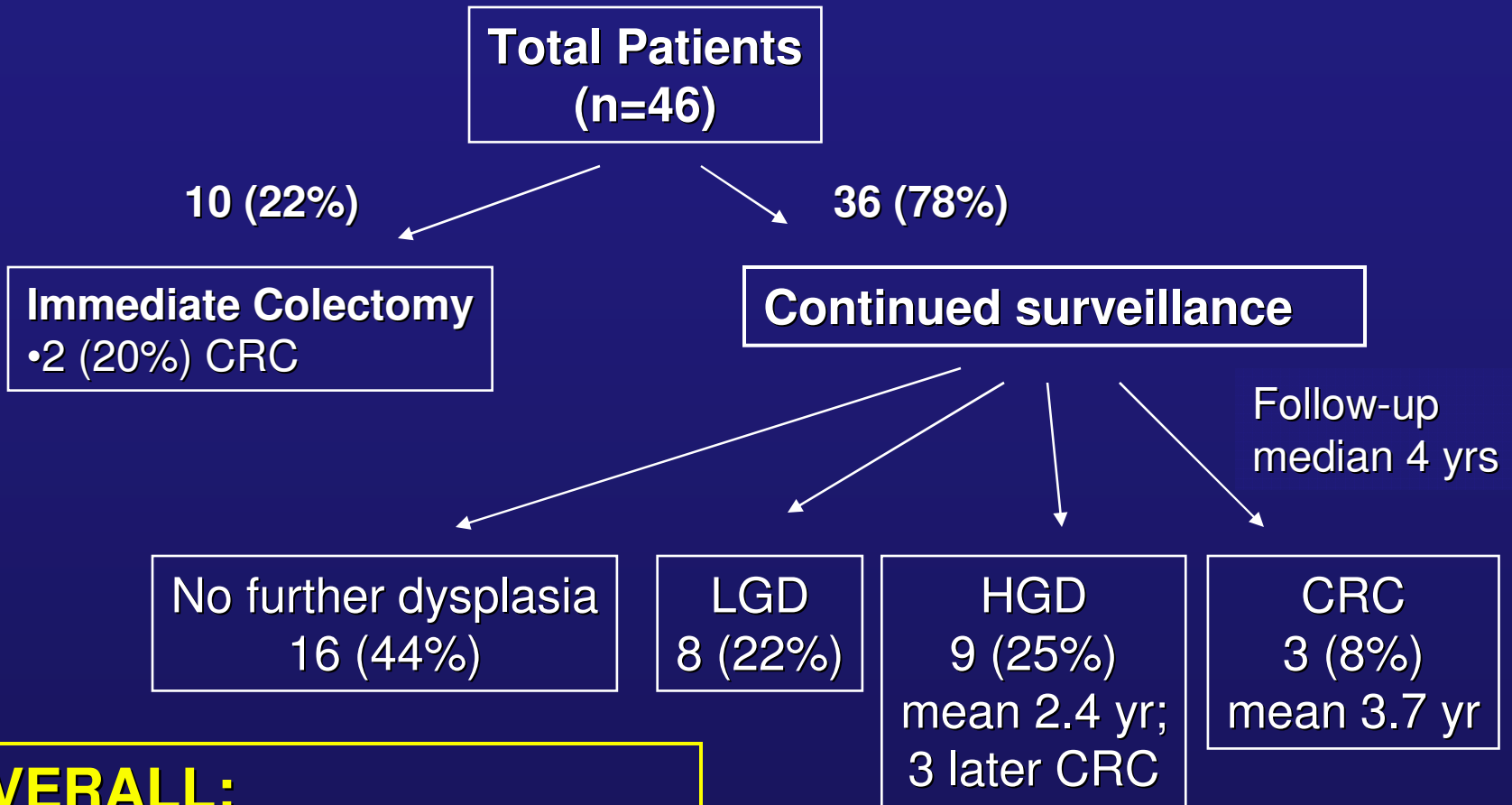


Reprinted from Ullman T, et al. *Gastroenterology*. 2003;125:1311-1319 with permission from the American Gastroenterological Association.

CRC can develop without prior HGD



Outcome of LGD: St. Mark's Hospital

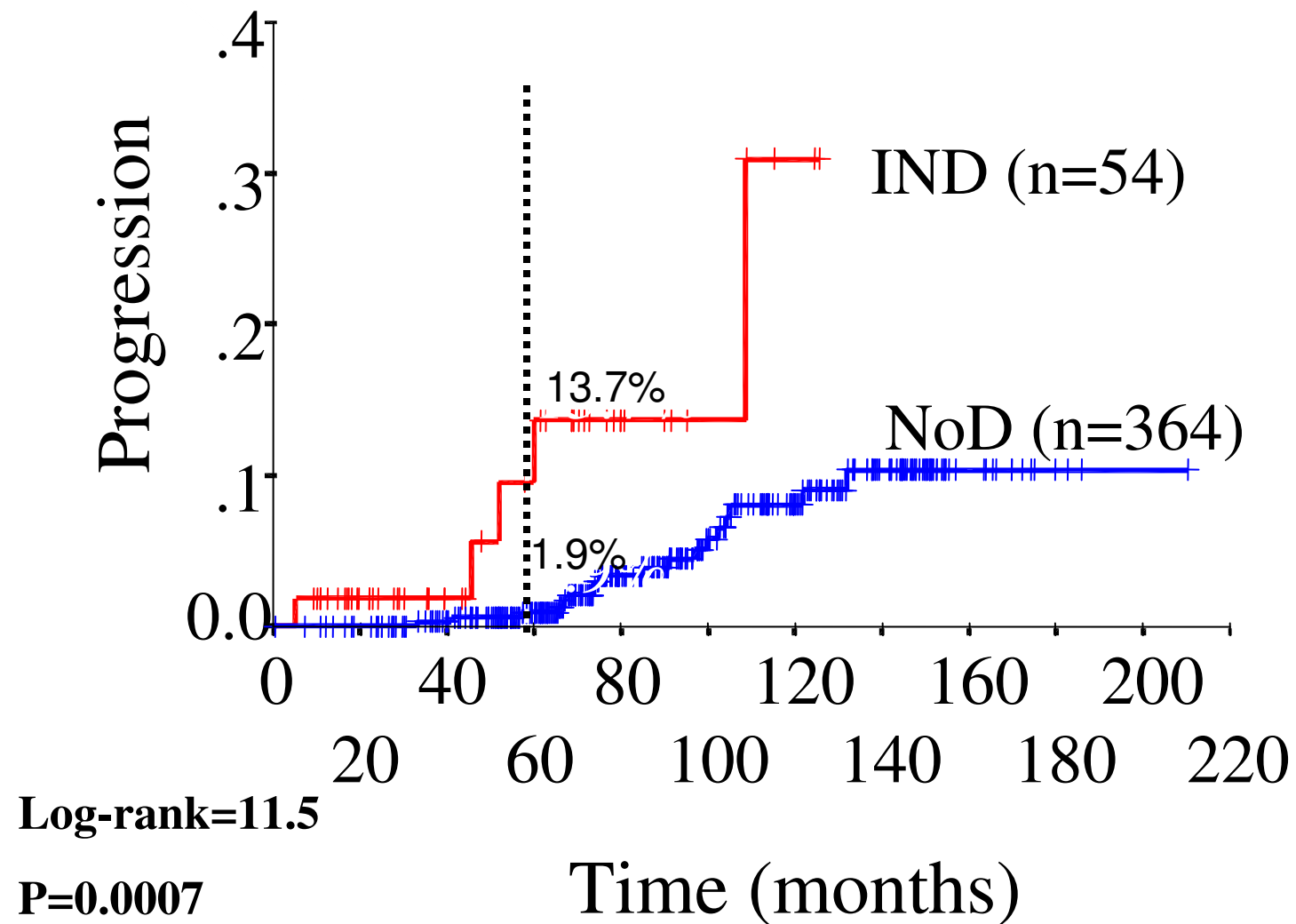


OVERALL:

- 9 (19.6%) CRC
- 18 (39%) HGD or CRC

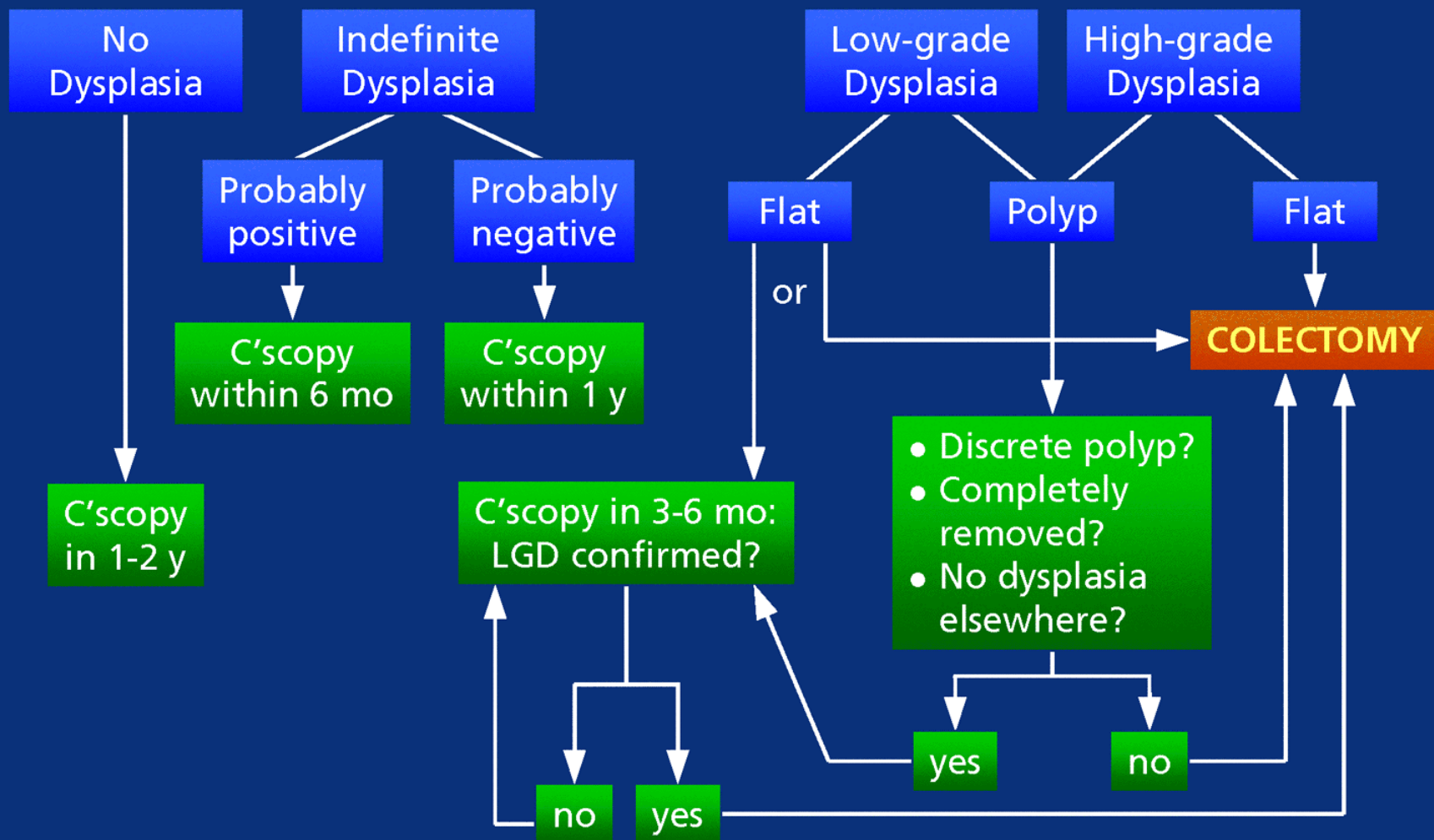
What is the Natural History of Indefinite Dysplasia?

PROGRESSION TO HGD or CRC





Suggested Surveillance Strategy



Adapted from Itzkowitz S, et al. *Gastroenterology*. 2004;126:1634-1648 with permission from the American Gastroenterological Association.

Recommended Surveillance Practice

- **4-quadrant biopsies every 10 cm**
- **Separate pathology jars; tattoo lesions**
- **Attention to polyps/raised lesions**
- **Biopsy flat mucosa adjacent to any polypectomy sites**
- **Stricture in UC = CANCER (until proven otherwise)**
- **Do for Crohn's colitis what you would do for UC**

Number of Biopsies Needed To Detect Dysplasia

- With 95% confidence:
56 biopsies needed
- With 90% confidence:
33 biopsies needed

Rubin et al, Gastroenterology 1992

Are Gastroenterologists Taking Enough Biopsies?

Survey of 298 British gastroenterologists:

<i># of Biopsies</i>	<i>% of GI's</i>
0-5	7
6-10	50
11-15	31
16-20	10
>20	2

Eaden, GI Endoscopy, 2000

Reasons to Favor Colectomy for LGD

1. CRC may already be present (20%)
2. The actuarial 5-year progression to HGD or CRC may be as high as 23-50%
3. Unifocal LGD may be just as likely to progress as multifocal LGD
4. LGD may not progress through HGD before CRC develops
5. Once LGD is diagnosed, a subsequent negative exam does not diminish risk of progression
6. Some CRC's may arise directly from LGD (Low-grade tubulo-glandular adenoca.)

Improving Upon Surveillance

- **Chromoendoscopy**
 - Better detection of dysplasia by colonoscopy
- **Chemoprevention**
- **Stool DNA testing (colonic PAP smear)**
 - More extensive sampling of the mucosa



Chromoendoscopy Can Elucidate Areas of Abnormality

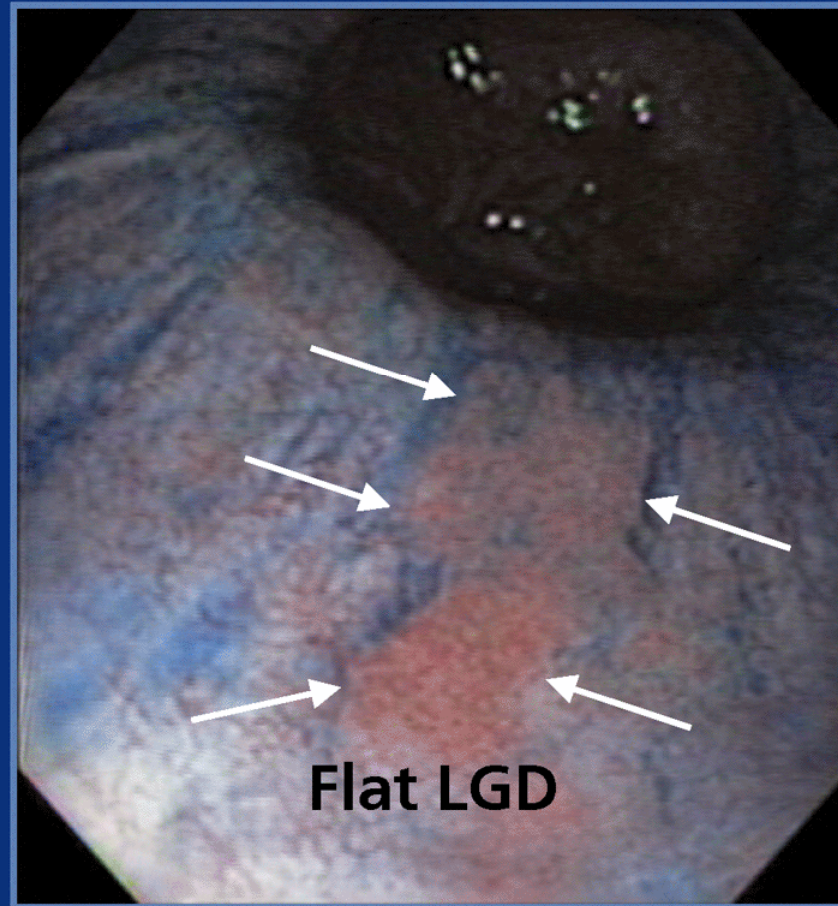


Photo courtesy of Jerome Waye, MD.

Chromoendoscopy

	Group A	Group B	
	<u>Chromo.</u>	<u>C'scopy</u>	<u>P value</u>
N=	84	81	
Patients with IN	13	6	NS
Total No. of IN's	32	10	<i>0.003</i>
LGD	24	8	--
HGD	8	2	--
Cancer	3	1	NS
Polypoid INs	8	6	NS
Flat INs	24	4	<i>0.0007</i>

Kiesslich et al. Gastroenterology 124:880, 2003



Unresolved Questions:

1. Will chromoendoscopy alter the natural history of LGD?
2. Does chemoprevention alter the natural history of dysplasia?
3. Is the incidence of dysplasia/cancer decreasing?
If so, why?