MANAGEMENT OF BARRETT'S ESOPHAGUS IN 2019

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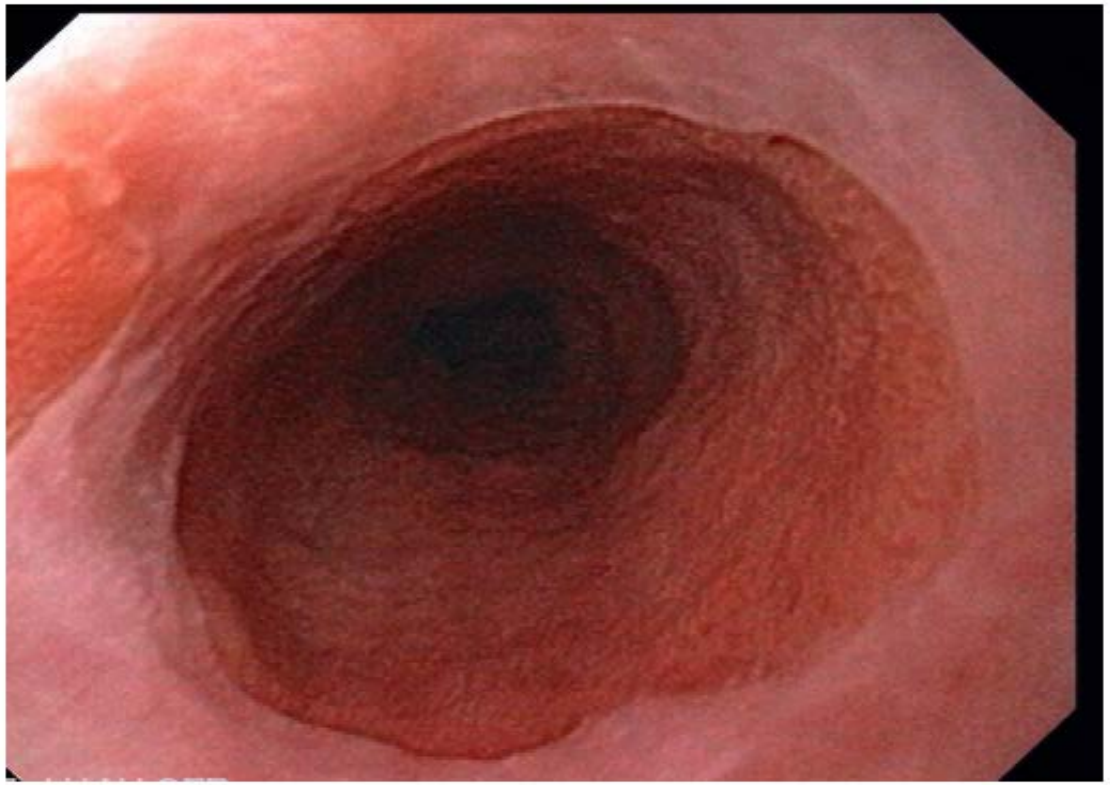
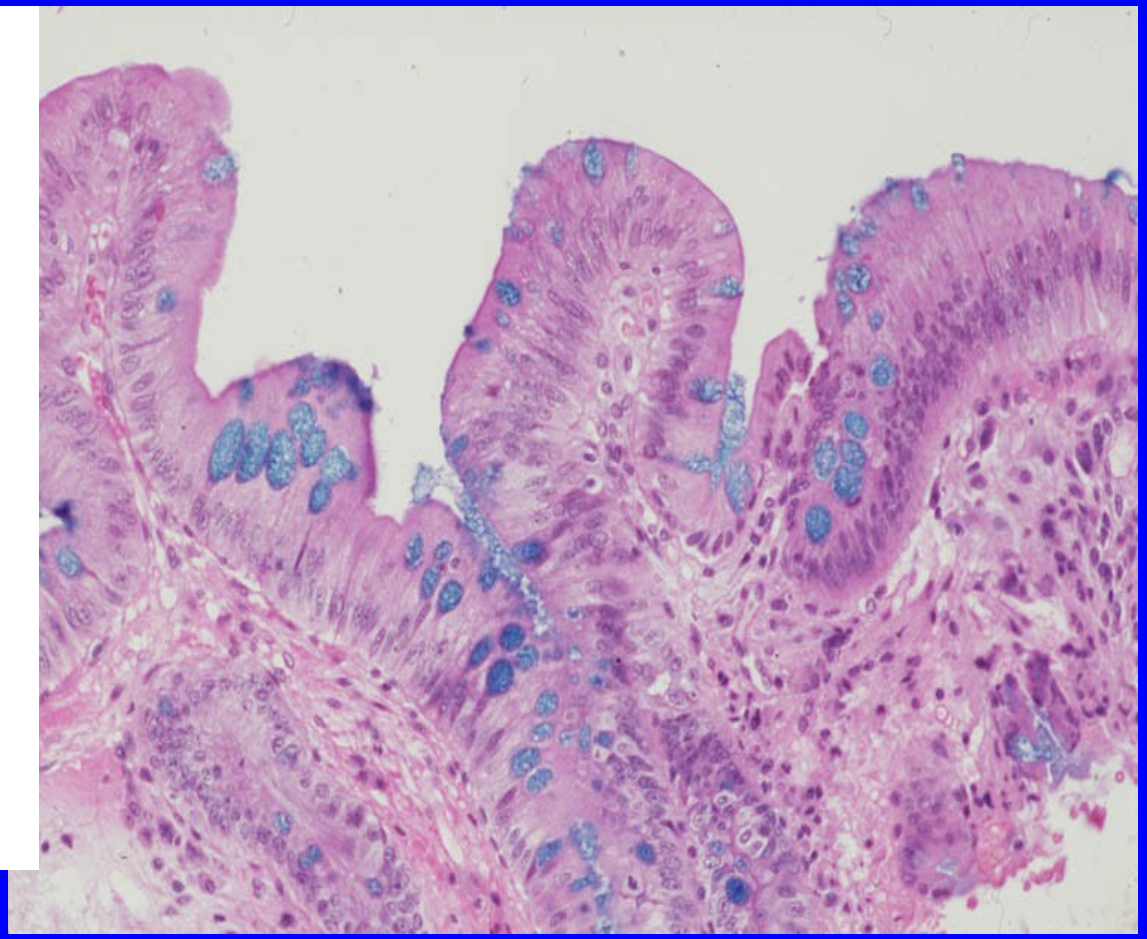
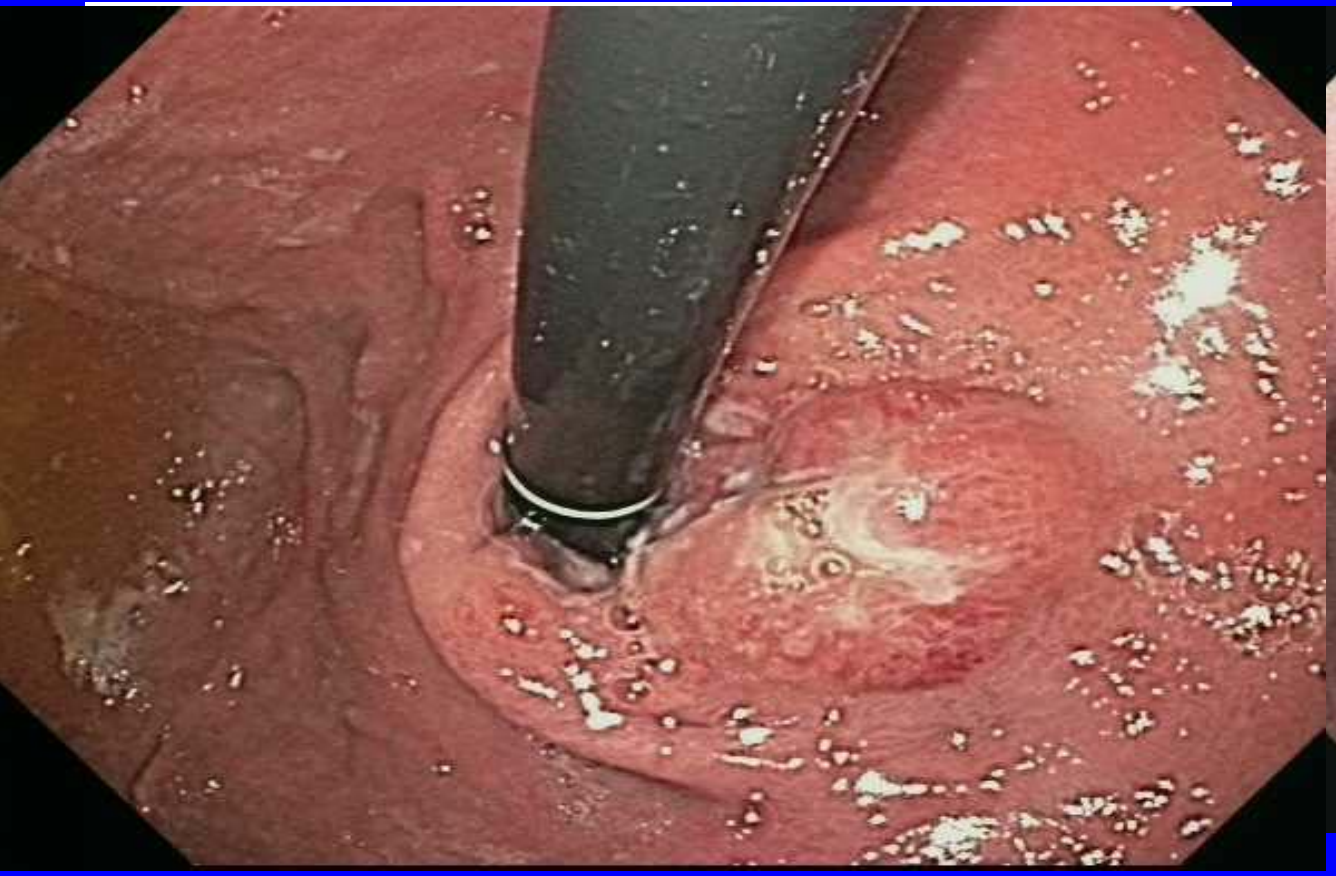
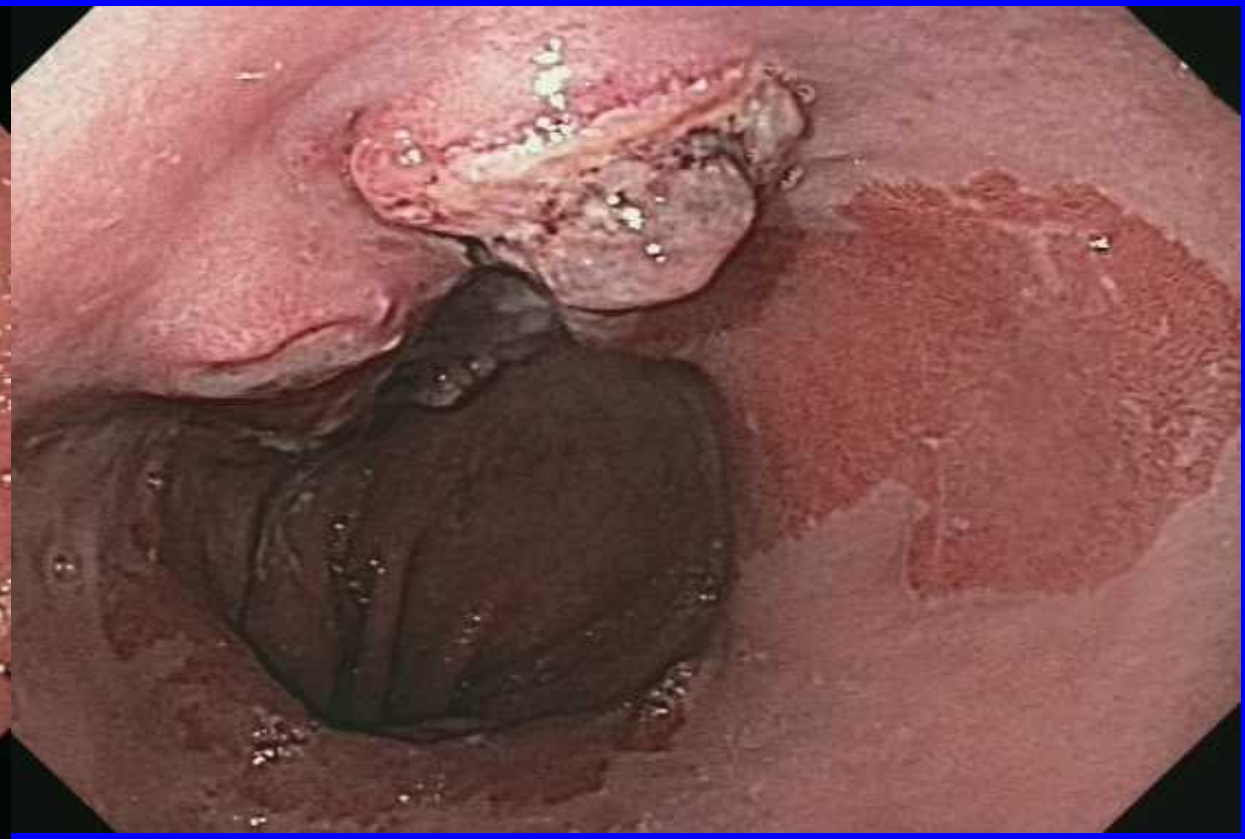
BARRETT'S ESOPHAGUS



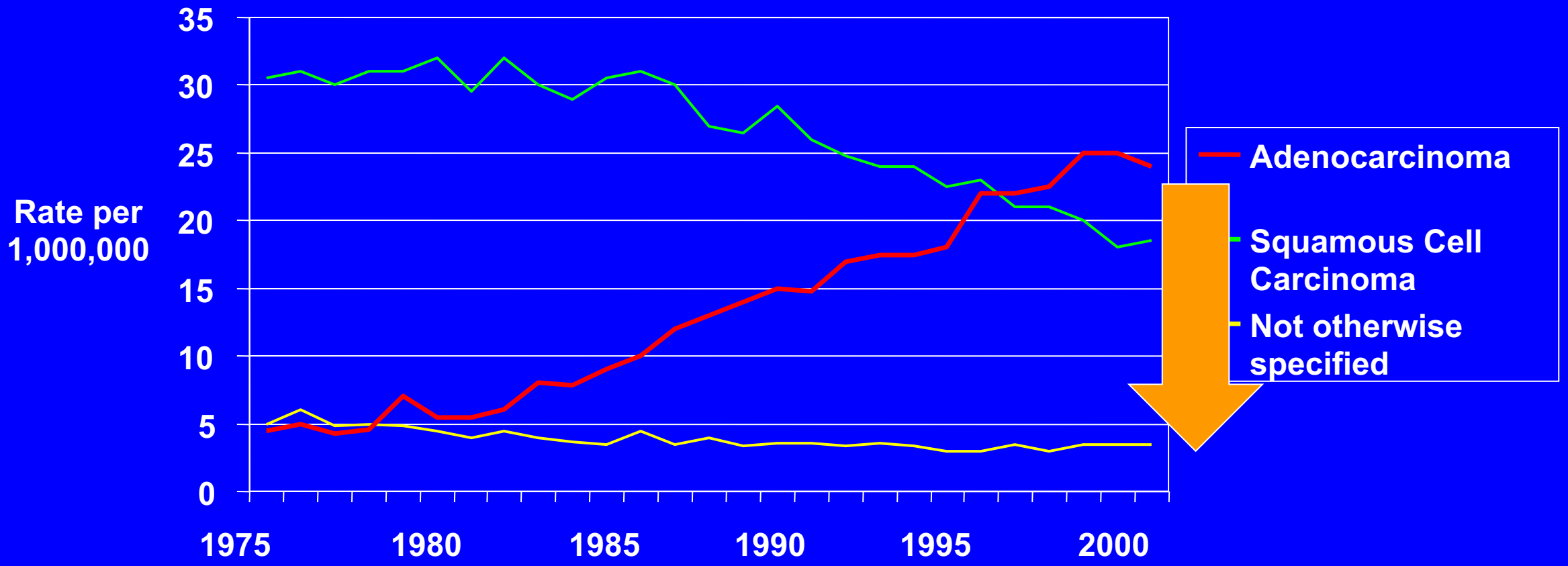


ESOPHAGEAL ADENOCARCINOMA





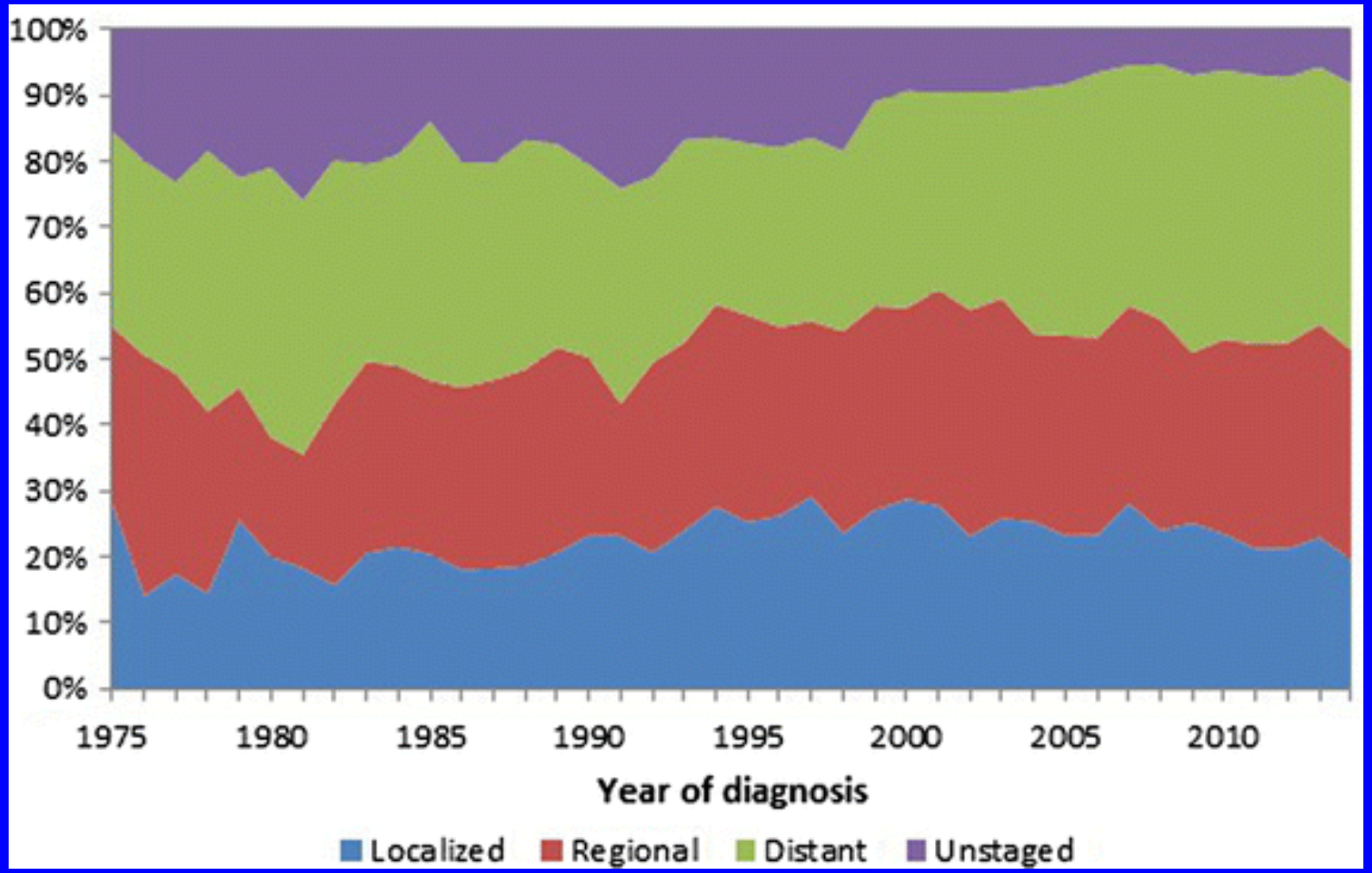
RISING INCIDENCE OF ESOPHAGEAL ADENOCARCINOMA



Pohl H et al, J Natl Cancer Inst 2005, Brown LM et al, J Natl Cancer Inst 2008

ESOPHAGEAL ADENOCARCINOMA

STAGE DISTRIBUTION OF INCIDENT CANCERS



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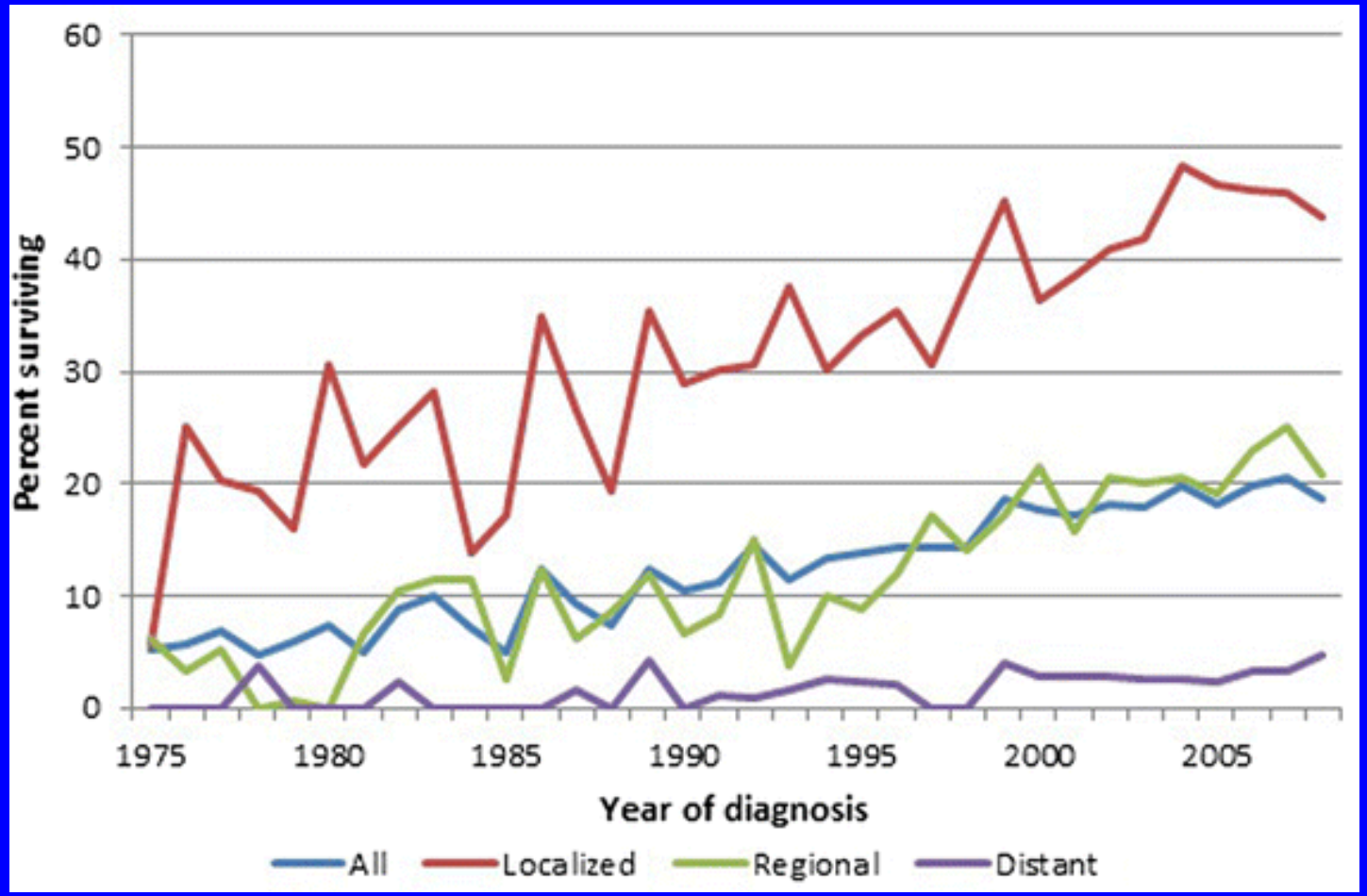
Thrift A. Dig Dis Sci 2018

ESOPHAGEAL ADENOCARCINOMA

5-YEAR AGE-ADJUSTED SURVIVAL RATES



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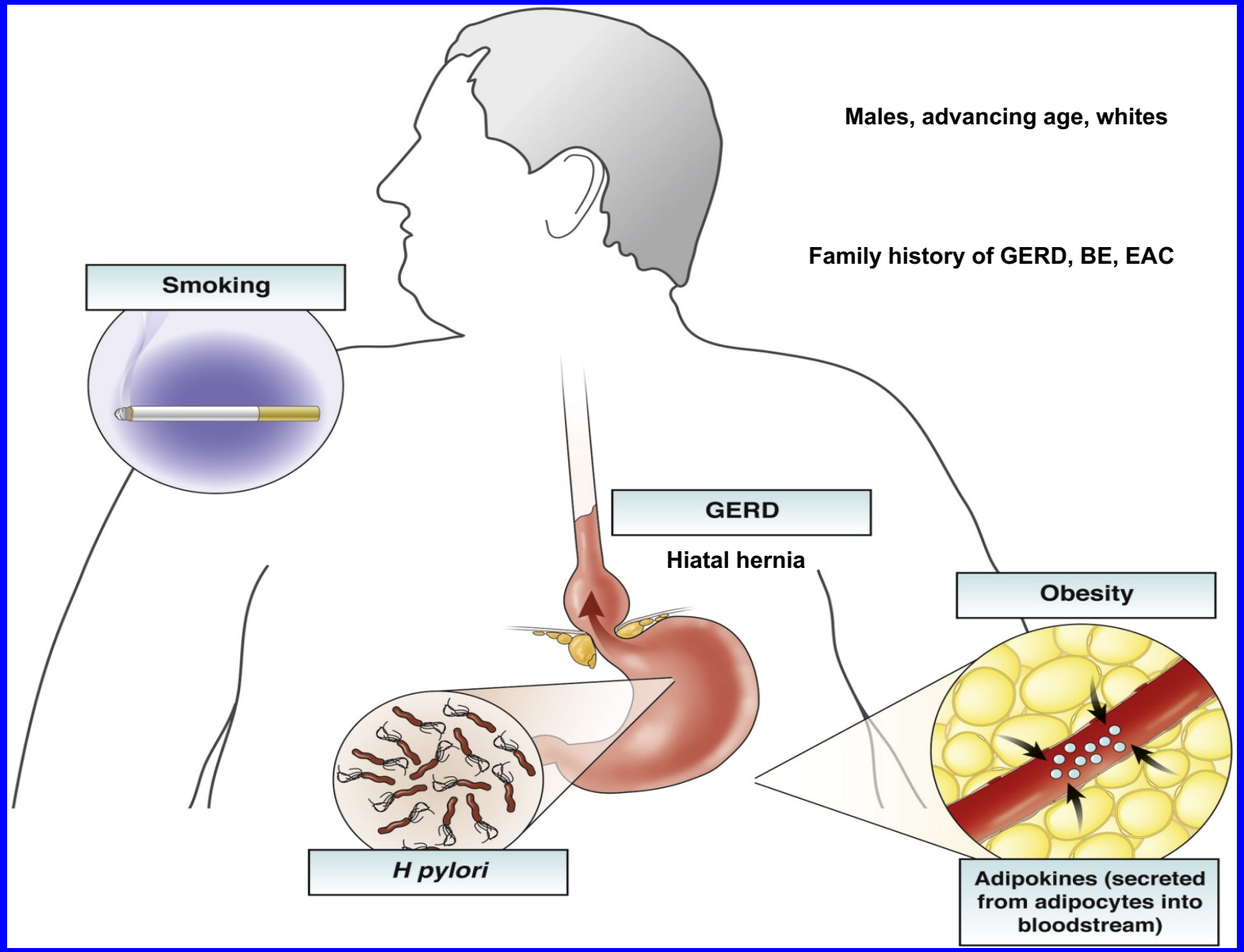
OBJECTIVES

- Screening – is it effective and how will recent advances impact the way we screen for Barrett's esophagus
- Discuss issues with current surveillance and highlight the best practices in surveillance for Barrett's esophagus
- Candidates for endoscopic eradication therapy and pragmatic approach to Barrett's related neoplasia
- Quality indicators for Barrett's esophagus and endoscopic eradication therapy
- Recent guidelines and DDW 2019 updates

EPIDEMIOLOGY – RISK AND PROTECTIVE FACTORS



RISK FACTORS FOR EAC

Factor	Direction of Association	Strength of Association	Type of studies conducted
Physical activity	Inverse	30-40% reduced risk	Cohort and case-control studies
H pylori infection	Inverse	40-60% reduced risk	Meta-analyses of observational studies
NSAIDs	Inverse	32-64% reduced risk	Meta-analyses of population-based studies and RCTs
Statins	Inverse	41% reduced risk	Meta-analyses of population-based studies and RCTs

Coleman et al, Gastroenterology 2018

RATIONALE FOR SCREENING AND SURVEILLANCE

- Esophageal adenocarcinoma is an important health problem
- Screening with endoscopy or other techniques AND surveillance with endoscopy once Barrett's esophagus is diagnosed will allow for detection of cancer at an early stage
- Minimally invasive treatment options exists for early stage disease
- Early detection will ultimately lead to more favorable patient outcomes (improved survival)

SCREENING FOR BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

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SCREENING FOR BARRETT'S ESOPHAGUS

AGA	ACG	BSG
Multiple risk factors (>50 years, male, white race, chronic GERD, hiatal hernia, increased BMI) **Suggest**	Men with chronic +/- frequent GERD symptoms and ≥2 risk factors: age>50, Caucasians, central obesity (WC>102/WHR>0.9), smoking and FH of BE/EAC **Consider**	Chronic GERD and multiple risk factors (≥3): age≥50, white, male, obesity. Threshold lowered in FH of BE or EAC (at least 1, 1st degree) **Consider**

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Fitzgerald R et al, Gut 2014
Shaheen N et al, Am J Gastroenterol 2015
Spechler S et al Gastroenterology 2011

ASGE GUIDELINES FOR SCREENING AND SURVEILLANCE IN BARRETT'S ESOPHAGUS

If screening for Barrett's esophagus is performed, we suggest a screening strategy that identifies an at-risk population – family history (high risk) or patients with GERD plus at least one other risk factor (moderate risk)

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Qumseya B, Wani S. Gastrointest Endosc 2019 (in press)

SCREENING FOR BARRETT'S ESOPHAGUS - LIMITATIONS

- Enormous burden to medical resources – high prevalence of GERD
- Barrett's esophagus in asymptomatic individuals (6-25%)
- 20-50% of EAC patients have no symptoms
- <10% of EAC – prior diagnosis of BE (suggesting that current clinical referral practices fail to identify majority of high-risk patients)

Rex DK et al, Gastro 2003; Gerson LB et al, Gastro 2002
Farrow DC et al, Cancer Causes Control 2000; Lagergren J et al, NEJM 1999
Inadomi J et al, Ann Intern Med 2003

STRATEGIES TO ENHANCE SCREENING

- Cytosponge:
  - Minimally invasive cell collection device
  - 30 mm sponge in a capsule attached to a string
  - Primary care setting
  - Pseudo-biopsy (H&E and TFF-3)

CYTOSPONGE – "BEST" DATA

- **BEST1:**
- GERD individua… …nd GERD care on PPI (>3… …ontrols) – (n=504)
- BE length ≥1 cm… …re
  - Sensitivity 73.3… ….9% (76.4-83),
  - Specificity 93.8… ….6) - ≥3 cm …9.7% (82.3-
- BE length ≥2 cm… …owed twice
  - Sensitivity 90%… ….4% (89.5-94.7)
  - Specificity 93.5…

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…s-Innes CS et al, PLoS Med 2015

CYTOSPONGE – U.S. DATA

- Cross-sectional study – 6 U.S sites
- Eligible patients: ≥18 years, confirmed BE or heartburn or regurgitation for at least monthly for ≥6 months
- All patients underwent upper endoscopy
- Follow-up phone call was performed 7 days post-procedure
- Acceptability using visual analog scale for pain, Impact of Event Scale and patient's willingness to undergo repeat Cytosponge

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Shaheen N, Wani S. DDW 2019

CYTOSPONGE – U.S. DATA

Acceptability Question (n=191, 129 BE, 62 GERD)	Average Rating
On a scale of 0-10 (10=highest acceptability), please rate your experience of the:	
Cytosponge Procedure	7.2 (2.5)
Endoscopy Procedure	8.5 (2.5)
Would you be willing to repeat the Cytosponge procedure?	
Yes	93.1%
What procedure would you prefer to undergo again?	
Traditional upper endoscopy	35.1%
Cytosponge	64.9%

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Shaheen N, Wani S. DDW 2019

CYTOSPONGE – U.S. DATA

Diagnostic Performance	Average Rating
Diagnostic performance all comers	
Sensitivity	75.5% (65.6-83.8)
Specificity	76.7% (64-86.6)
Positive Predictive Value	83.5% (73.9-90.7)
Negative Predictive Value	66.7% (54.3-77.6)
Diagnostic performance (BE ≥3 cm)	
Sensitivity	85.9% (75.6-93)
Specificity	76.6% (62-87.7)
Positive Predictive Value	84.7% (74.3-92.1)
Negative Predictive Value	78.3% (63.6-89.1)

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Shaheen N, Wani S. DDW 2019

STRATEGIES TO ENHANCE SCREENING

- Trans-nasal endoscopy
  - Sensitivity 98%, specificity 100%
  - Feasible in community
  - Non-physician/non-GI providers (35 cases)
  - Well tolerated
  - Limitations: inability to intubate nasopharynx, discomfort, inferior endoscopic quality
  - Participation higher compared to sedated endoscopy for screening (45.7% vs. 40.7%)
  - Similar complete evaluation with EGD, shorter recovery times
  - Lower successful biopsy acquisition (83% vs. 100%)

Peery AF et al, GIE 2012,
Sami S et al, Am J Gastroenterol 2015

ELECTRONIC NOSE BREATH TESTING

- Device detects and profiles volatile organic compounds of human and gut bacterial metabolism
- Profiling study of 66 BE patients and 56 controls – sensitivity 82%, specificity 80%, AUROC 0.79
- Enrollment rate 95%

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Chang DK et al, Gastroenterology 2017

STRATEGIES TO ENHANCE SCREENING

- Tethered capsule endomicroscopy
- Liquid biopsies/circulating tumor cells
- Oral microbiome testing

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Gora et al. Nature Medicine 2013,
Elliott et al, Lancet Gastroenterol Hepatol 2017

STRATEGIES TO ENHANCE SCREENING – GREAT IDEAS OR GREAT PRACTICE?

- Understanding failure of screening strategies – failure to refer patients with GERD symptoms OR failure of patients to follow recommendations
- Barrett's risk score
  - Using models
  - Incorporates risk factors such as age, race, GERD symptoms, smoking, waist circumference
  - Blood biomarker

SURVEILLANCE IN BARRETT'S ESOPHAGUS

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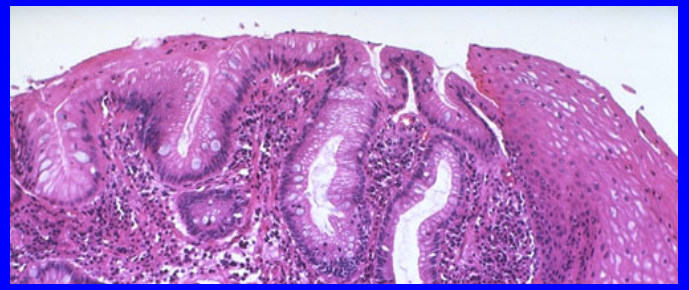
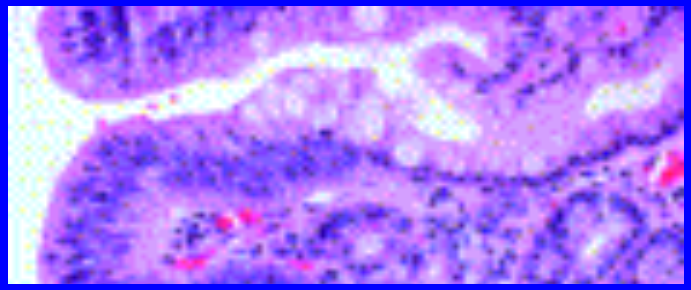
STEPWISE PROGRESSION OF BARRETT'S ESOPHAGUS TO ESOPHAGEAL ADENOCARCINOMA

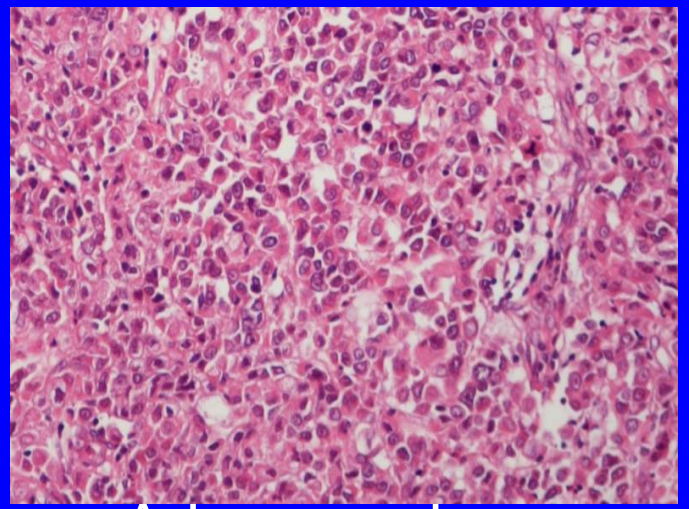
Non-Dysplastic BE



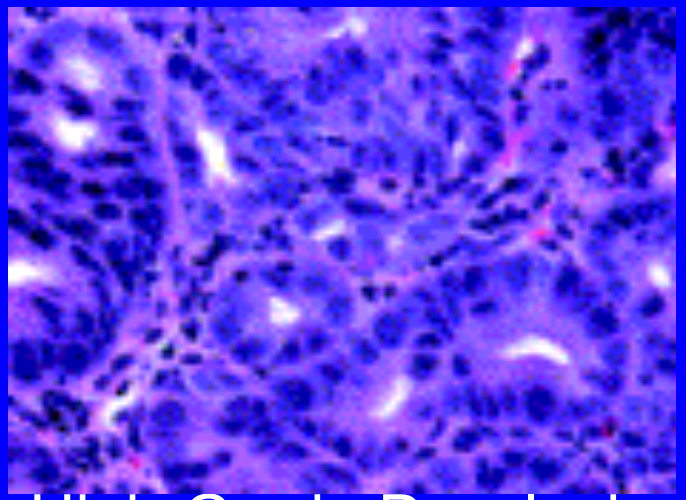
Low-Grade Dysplasia



Degree of dysplasia within BE - best current biomarker to predict progression to EAC and determine management (surveillance vs. endoscopic eradication therapy)



Adenocarcinoma



High-Grade Dysplasia

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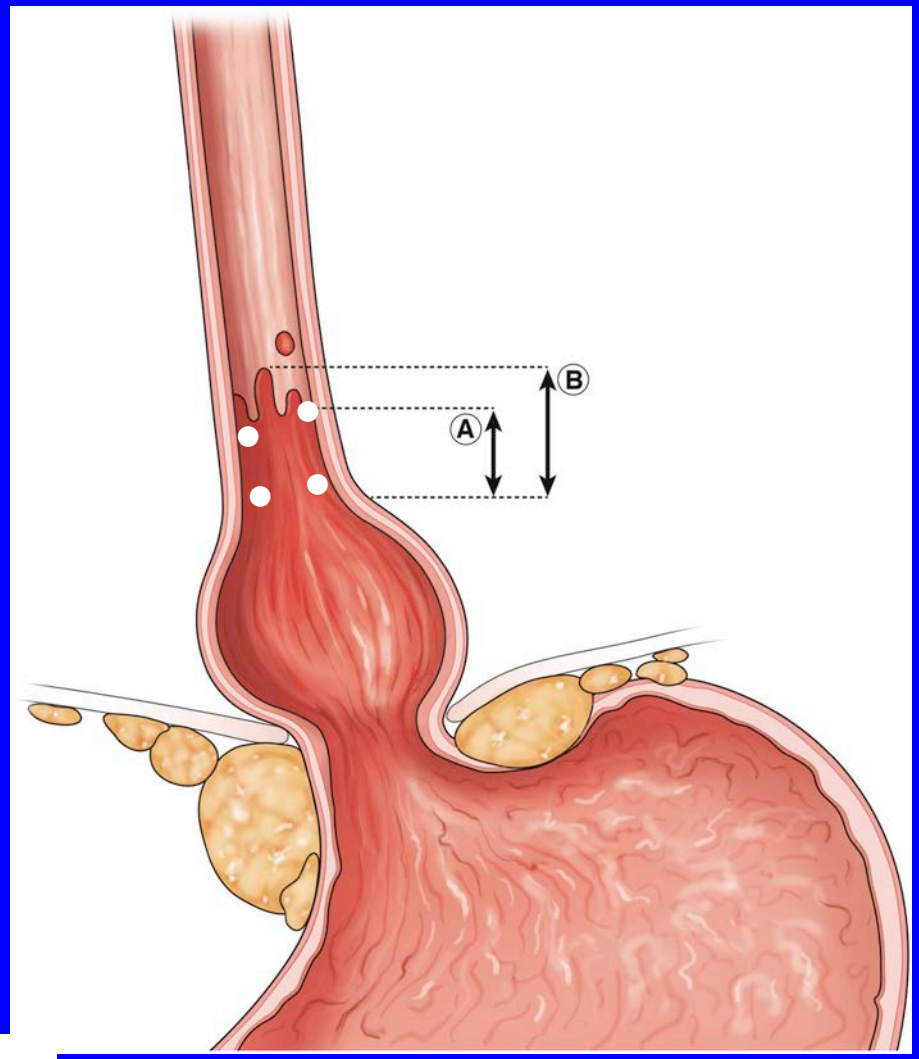
DOES SURVEILLANCE IMPACT MORTALITY?

- Meta-analysis of 4 cohort studies reported lower EAC-related and all-cause mortality associated with regular surveillance (RR 0.6; 95% CI 0.5-0.71 and HR 0.75, 95% CI 0.59-0.94)
- Meta-analysis of 12 cohort studies reported lower EAC-related and all-cause mortality among surveillance-detected EAC vs. symptom detected EAC (RR 0.73; 95% CI 0.57-0.94 and HR 0.59; 95% CI 0.45-0.76)

Codipilly D et al, Gastroenterology 2018

ENDOSCOPIC SURVEILLANCE IN BARRETT'S ESOPHAGUS



Seattle Protocol

- Systematic biopsies should be taken from every 1-2 cm in 4 quadrants throughout the extent of the endoscopically involved segment
- Biopsies from any visible lesion (no matter how subtle) should be obtained and processed separately from the systematic biopsies

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NATURAL HISTORY OF NON-DYSPLASTIC BARRETT'S ESOPHAGUS

1204 patients with non-dysplastic BE

Mean follow-up: 5.52 years

Diagnosis	Number of incidence cases	Incidence rate %/year (95% CI)
LGD	217	3.6 (3.19-4.16)
HGD	32	0.48 (0.34-0.68)
EAC	18	0.27 (0.17-0.43)
HGD/EAC	42	0.63 (0.47-0.86)

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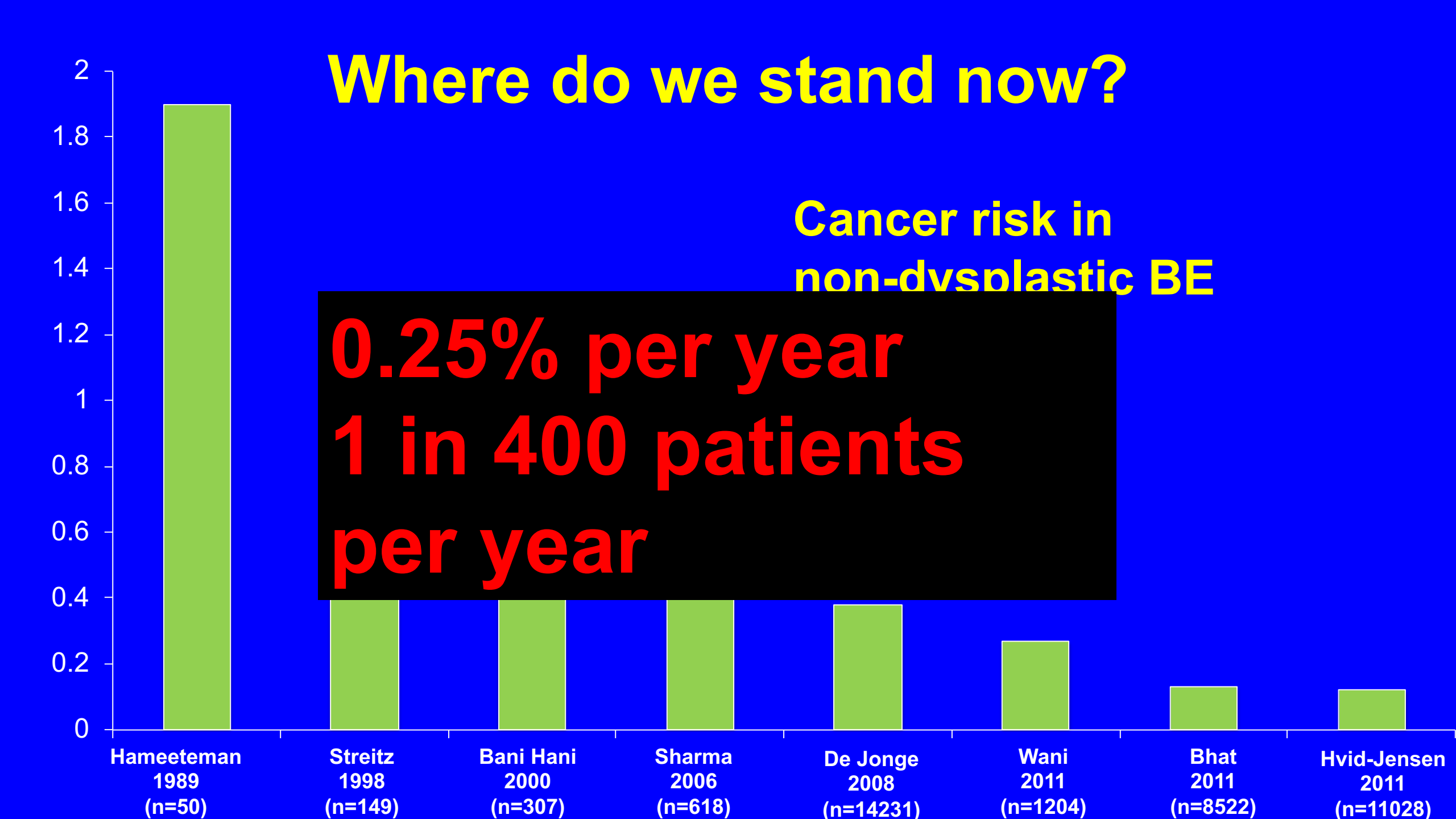
Wani S et al, CGH 2011

Where do we stand now?



SURVEILLANCE ISSUES
WHERE WE ARE

- Dysplasia and early EAC indistinguishable from NDBE
- Patchy distribution
- Biopsy small fraction of Barrett's segment
- Sampling errors
- Time consuming and expensive
- Variability in techniques and surveillance intervals not followed

Wani et al, Gastroenterology 2007

SURVEILLANCE ISSUES WHERE WE ARE

- **Magnitude of missed EAC after BE diagnosis:**
  - Systematic review and meta-analysis of cohort studies of patients with NDBE and BE with LGD
  - Primary aim: assess pooled proportion of missed (diagnosed within 1 year) and incident (diagnosed more than 1 year after initial endoscopy) EAC
  - 24 studies included 820 EAC cases
  - Missed EAC – 25.3% (95% CI16.4-36.8)
  - Similar rates when only NDBE patients included

Visrodia et al, Gastroenterology 2016

QUALITY INDICATORS FOR BARRETT'S ESOPHAGUS – AGA

- If a patient with known BE undergoes surveillance endoscopy, surveillance biopsies should be taken from every 1 to 2 cm in 4 quadrants throughout the extent of the endoscopically involved segment (Grade of recommendation: strong, quality of evidence: moderate)
- If systematic surveillance biopsies performed in a patient known to have BE show no evidence of dysplasia, follow up surveillance endoscopy should be recommended no sooner than 3-5 years (Grade of recommendation: weak, quality of evidence: low)

ENDOSCOPISTS OVERUTILIZE ENDOSCOPY AND BIOPSY THE LEAST WHO NEED IT THE MOST

- Data from a National Benchmarking Registry (GIQuIC)
- EGD records: 1/2012 – 9/2017
- 58,709 EGDs in 53,541 patients
- Mean BE length: 2.3 (SD 2.31)
- Adherence to Seattle protocol defined by dividing BE length by no. of jars - ratio of ≥ 2.0
  - Rounding down (lenient definition)
  - Rounding up (stringent definition)
- Adherence to 3-5 year surveillance interval assessed

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Wani S et al, Am J Gastroenterol 2019 (in press)
Wani S et al, Gastrointest Endosc 2019 (in press)

ENDOSCOPISTS OVERUTILIZE ENDOSCOPY AND BIOPSY THE LEAST WHO NEED IT THE MOST

- **Adherence to Seattle biopsy protocol:**
  - Lenient definition: 77.5%, stringent definition: 73%
  - BE length strongest predictor for non-adherence (OR 0.69)

- **Adherence to 3-5 year surveillance intervals:**
  - 30% procedures non-adherent and brought back too soon
  - 10-year time frame: excess of 42,786 EGDs or additional 40% EGDs

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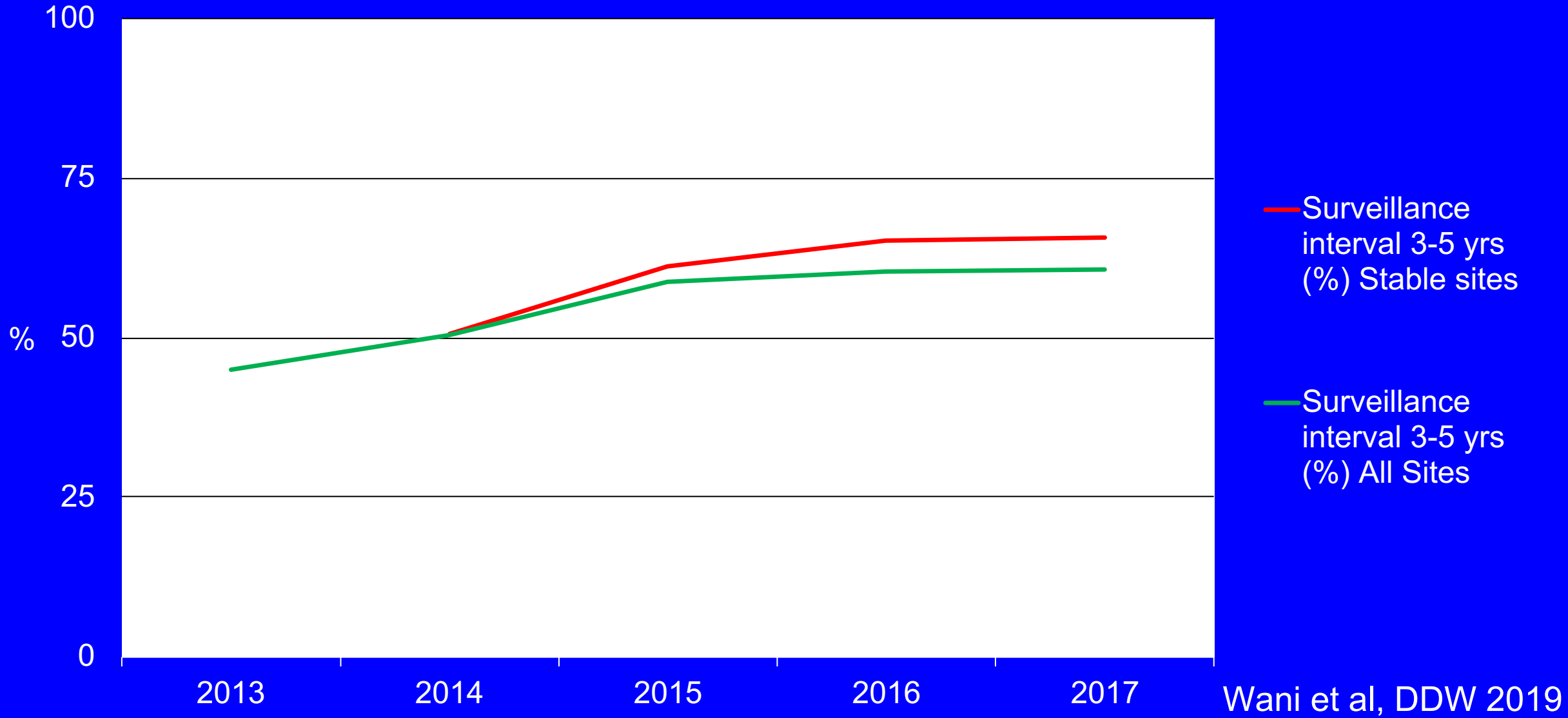
Wani S et al, Am J Gastroenterol 2019 (in press)
Wani S et al, Gastrointest Endosc 2019 (in press)

ADHERENCE TO QUALITY INDICATORS

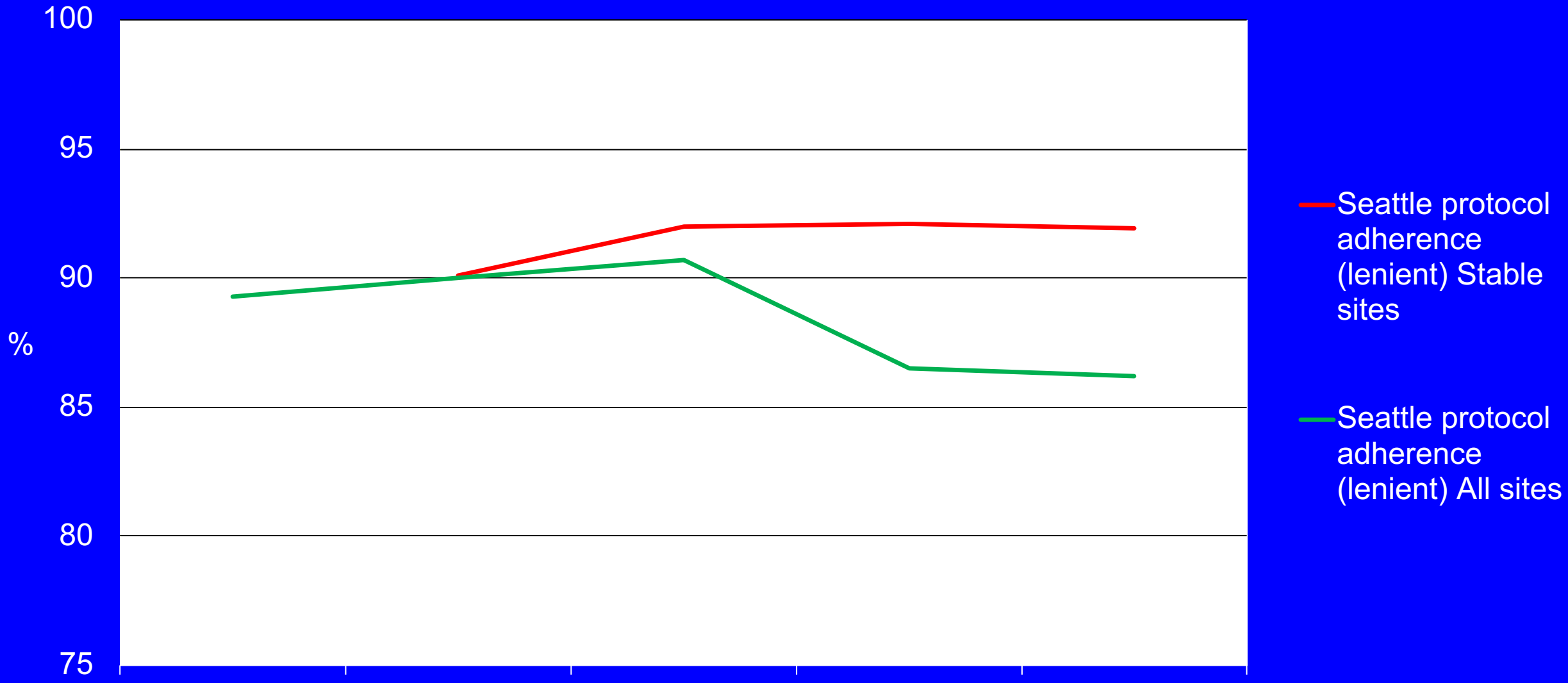
Time Trends in NDBE Surveillance Adherence, 2013-17



Wani et al, DDW 2019

ADHERENCE TO QUALITY INDICATORS

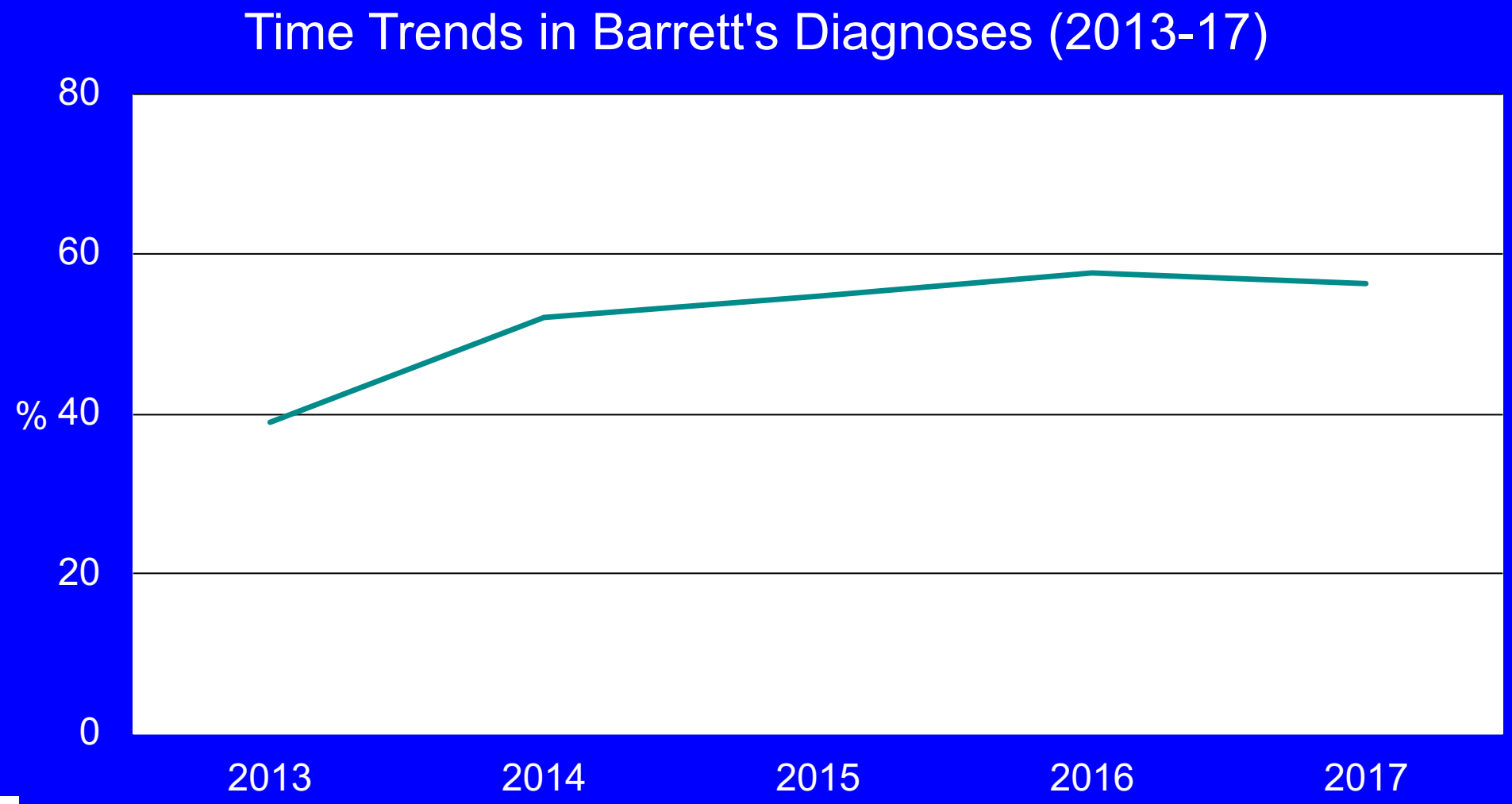
Time Trends in Seattle Protocol Adherence (Lenient) - 2013-17



Wani et al, DDW 2019

DETECTION OF BARRETT'S ESOPHAGUS

Time-trend analyses



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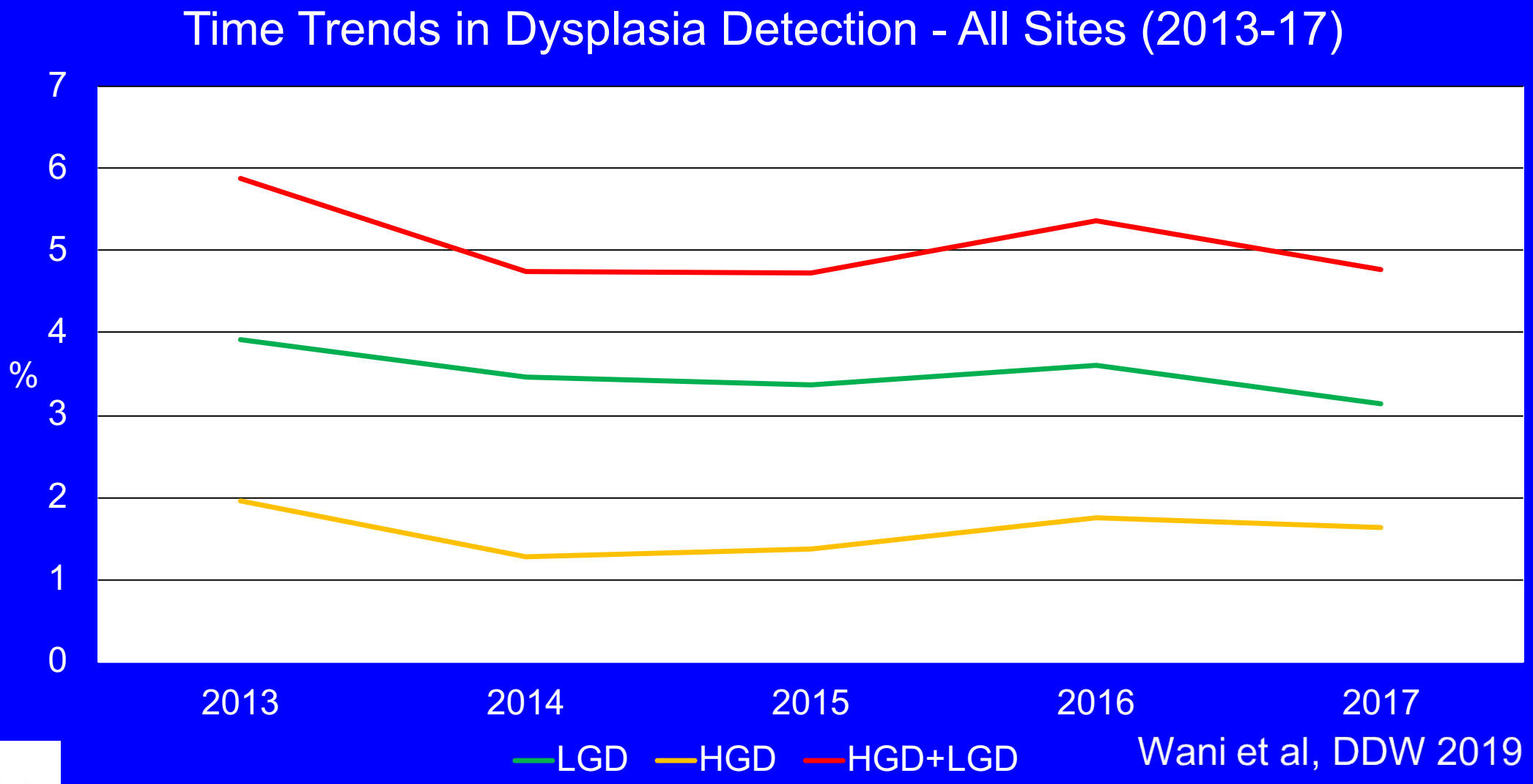
Wani et al, DDW 2019

DYSPLASIA DETECTION RATES

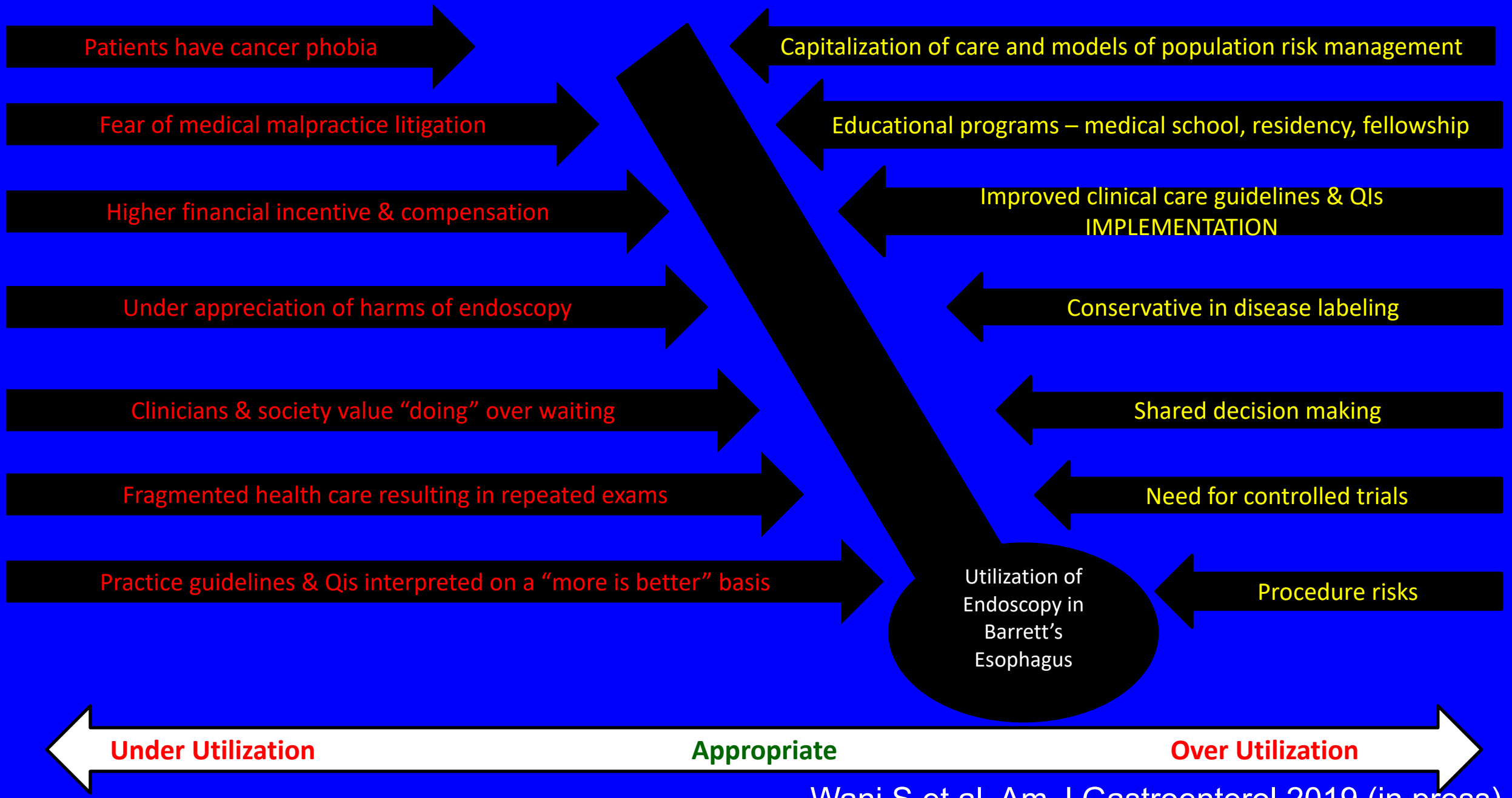
Time-trend analyses



Wani et al, DDW 2019

IMPLICATIONS AND FUTURE DIRECTIONS

- Future intervention studies need to focus on improving **Dysplasia Detection Rate** at a population level:
  - educational tools to detect dysplasia during endoscopy
  - improved adherence to Seattle biopsy protocol
  - improved sampling techniques that reduce the risk of sampling errors



Wani S et al, Am J Gastroenterol 2019 (in press)

WHAT IS THE APPROPRIATE AGE TO STOP ENDOSCOPIC SURVEILLANCE – A COST-EFFECTIVENESS ANALYSIS

Comorbidity level	EACMo Model	Erasmus/UW Model	Average
None	81	83	**83**
Mild	81	83	**82**
Moderate	78	80	**79**
Severe	74	76	**75**

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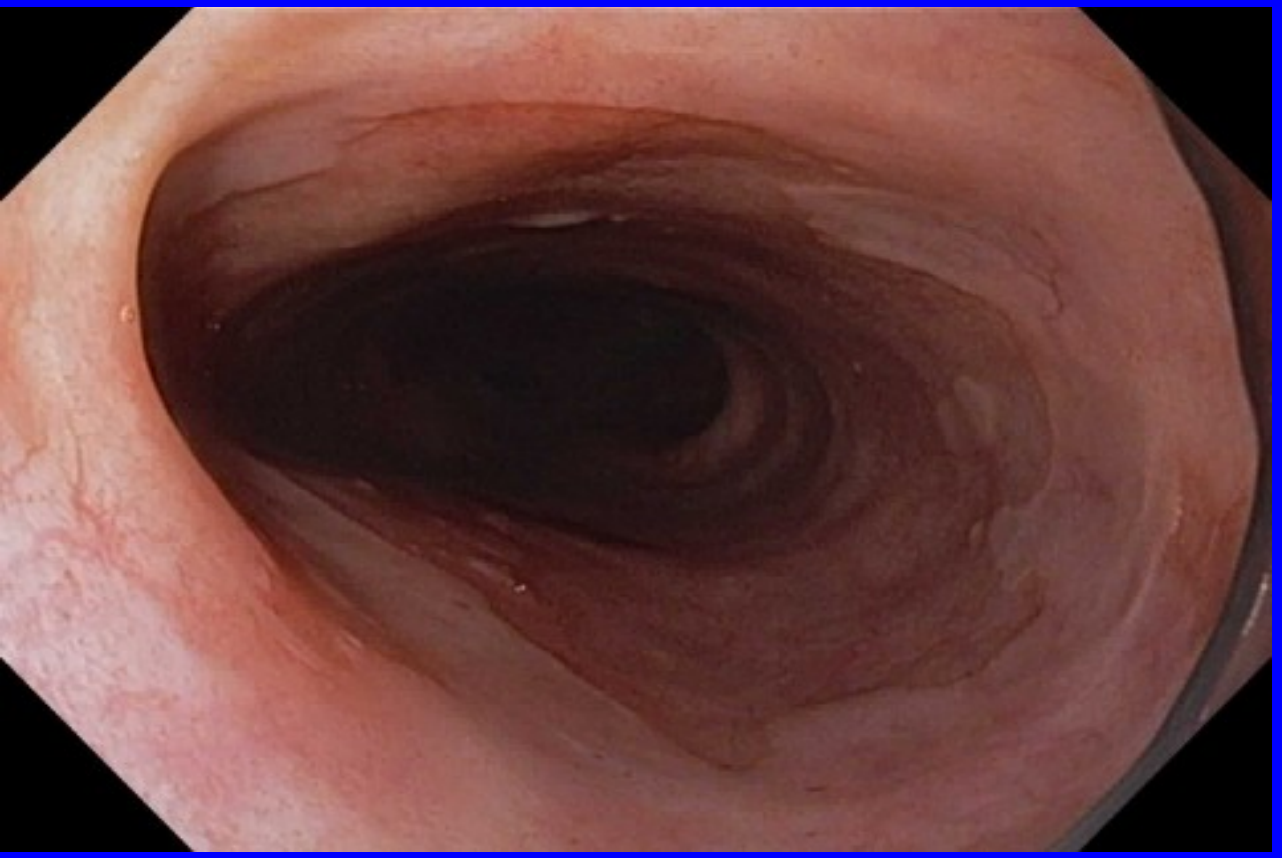
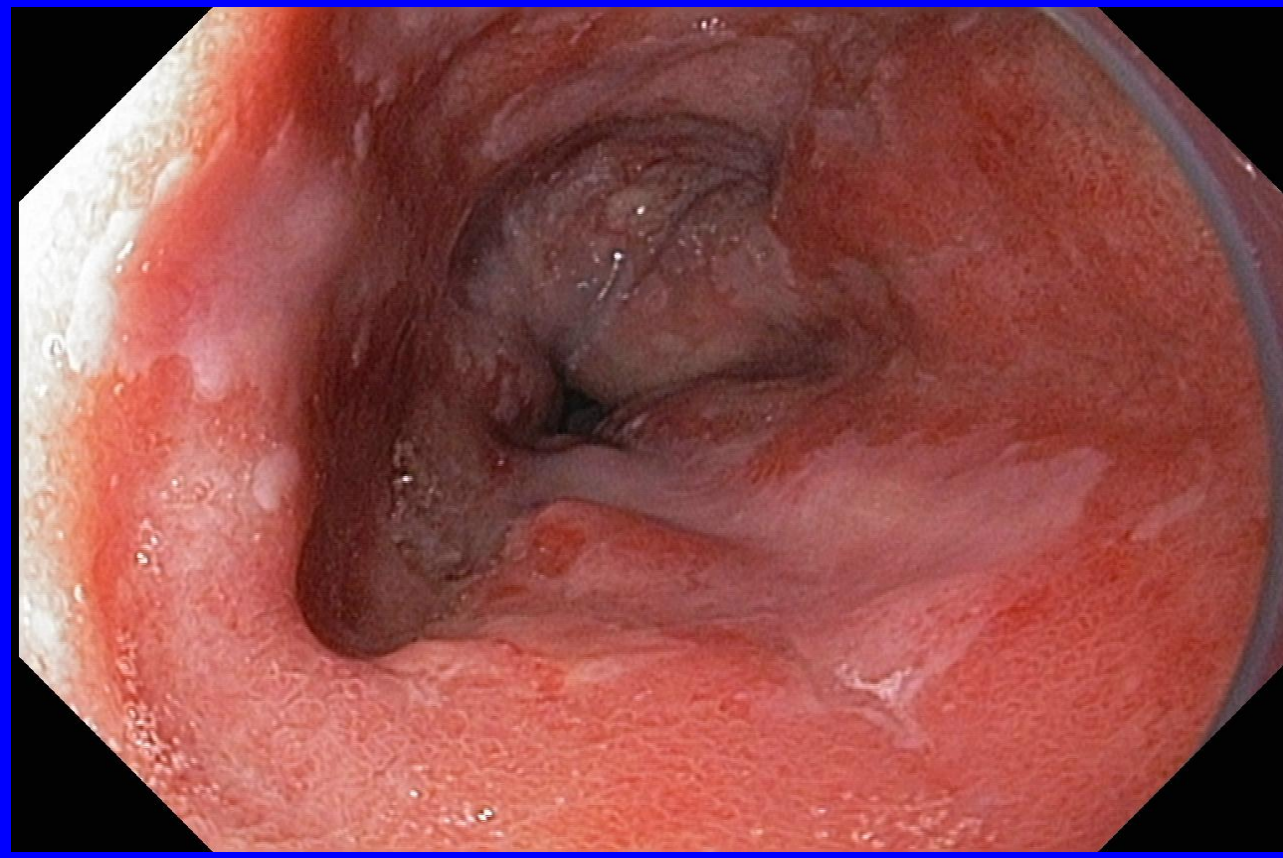
Omidvari A et al, DDW 2019

HOW CAN SURVEILLANCE BE OPTIMIZED?
HIGH RESOLUTION ENDOSCOPY





STANDARD OF CARE

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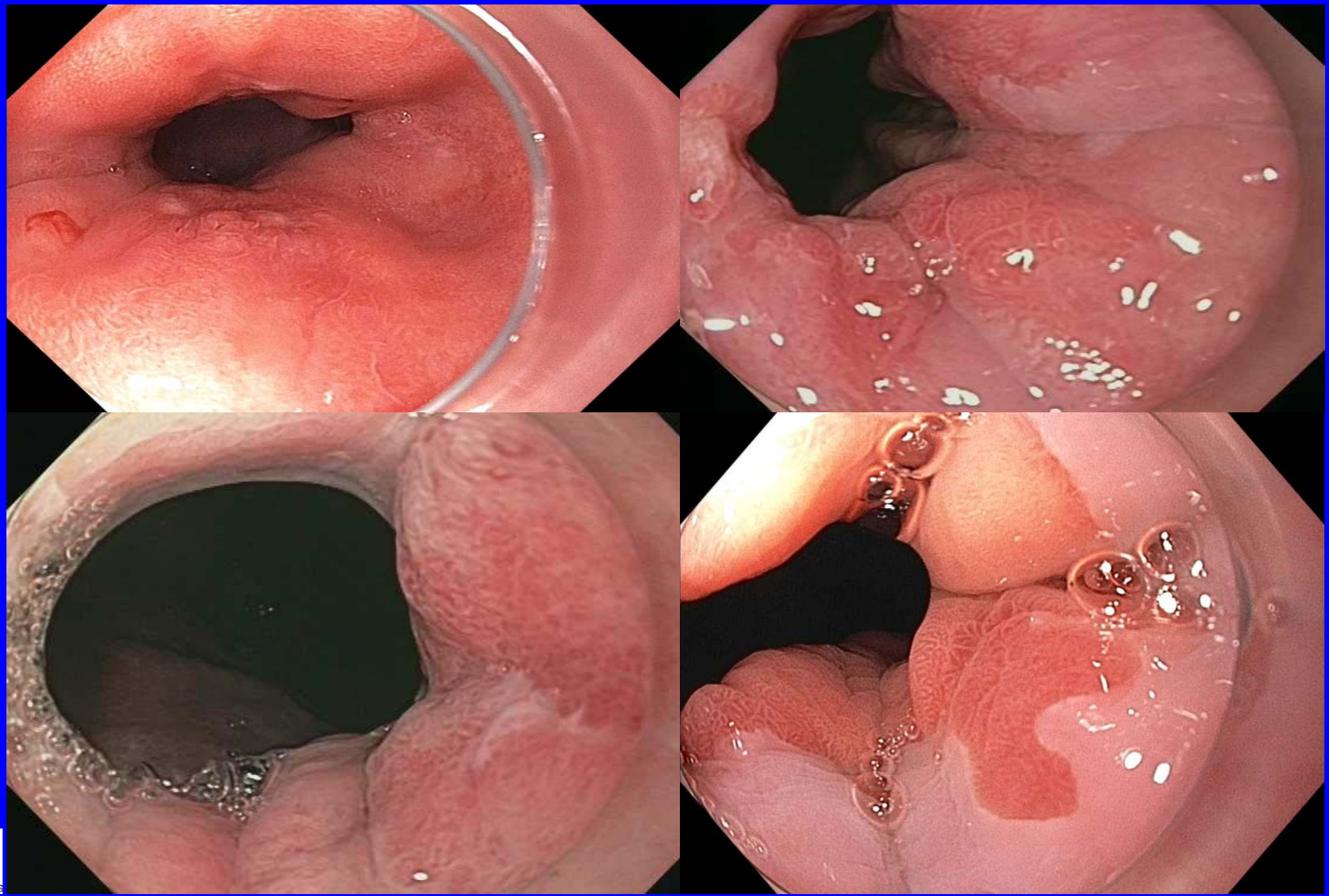

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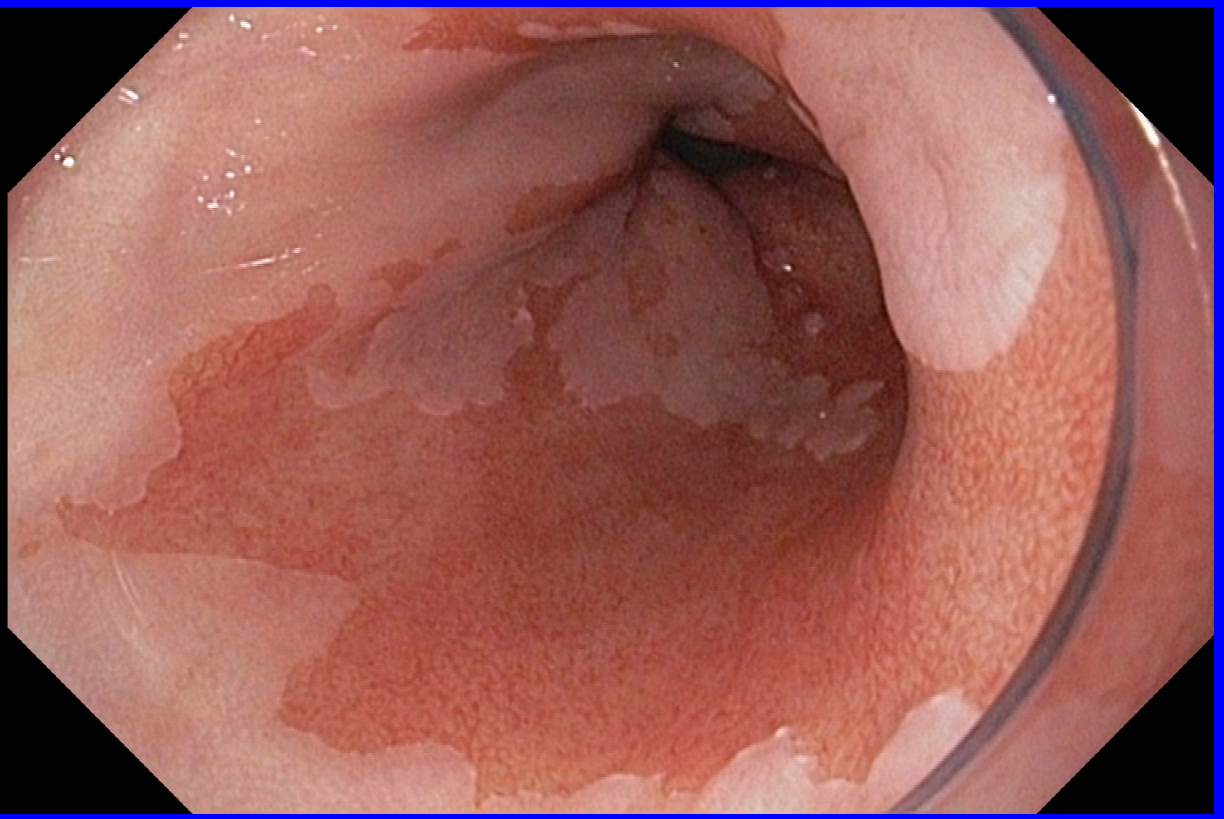
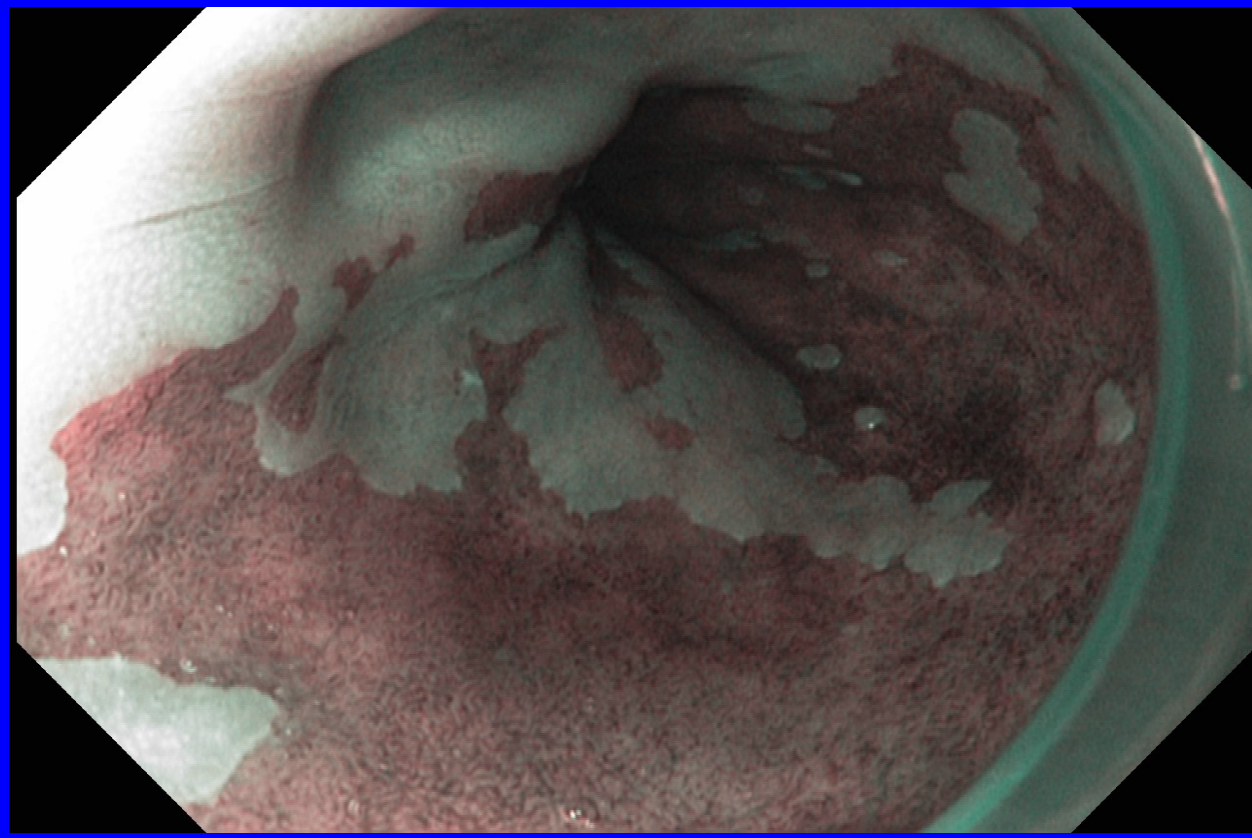
ADVANCED IMAGING TECHNIQUES

- Chromoendoscopy
- Magnification endoscopy
- Optical electronic chromoendoscopy (NBI)
- Autofluorescence endoscopy
- Confocal endomicroscopy
- Optical coherence tomography
- High-resolution microendoscopy
- Multispectral scanning
- Molecular imaging
- ARTIFICIAL INTELLIGENCE

NARROW BAND IMAGING





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STANDARDIZED CONSENSUS DRIVEN CLASSIFICATION SYSTEM

Regular Pattern	Irregular Pattern
Mucosal Circular, ridge/villous, or tubular pattern	**Mucosal** Absent or irregular patterns
Vascular Blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long branching patterns	**Vascular** Focally or diffusely distributed vessels not following normal architecture of the mucosa

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Sharma et al, Gastroenterology 2016

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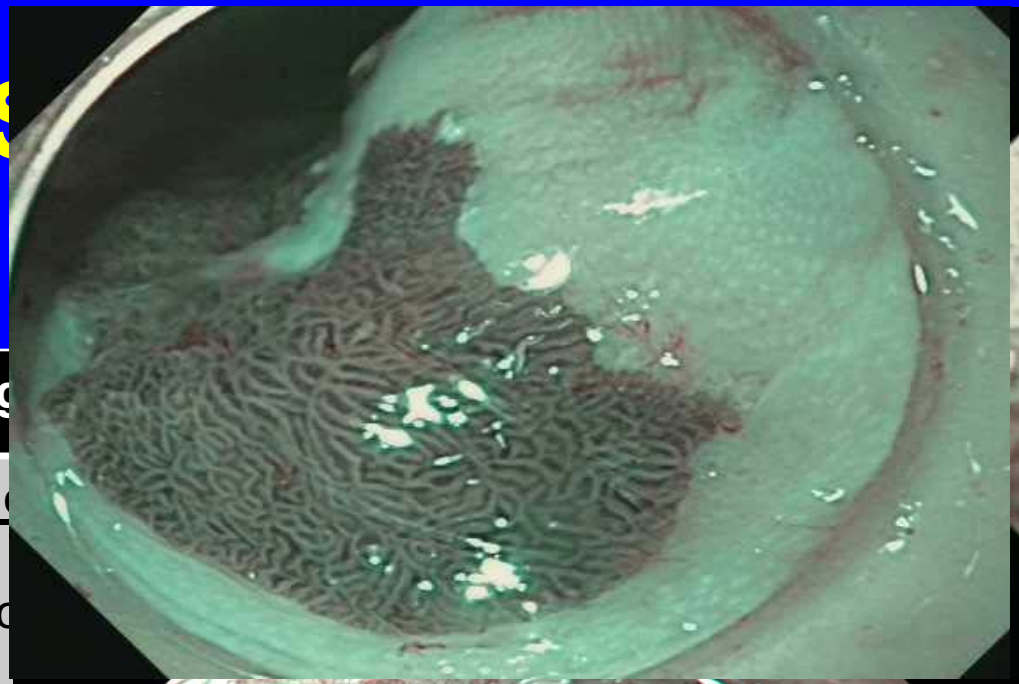

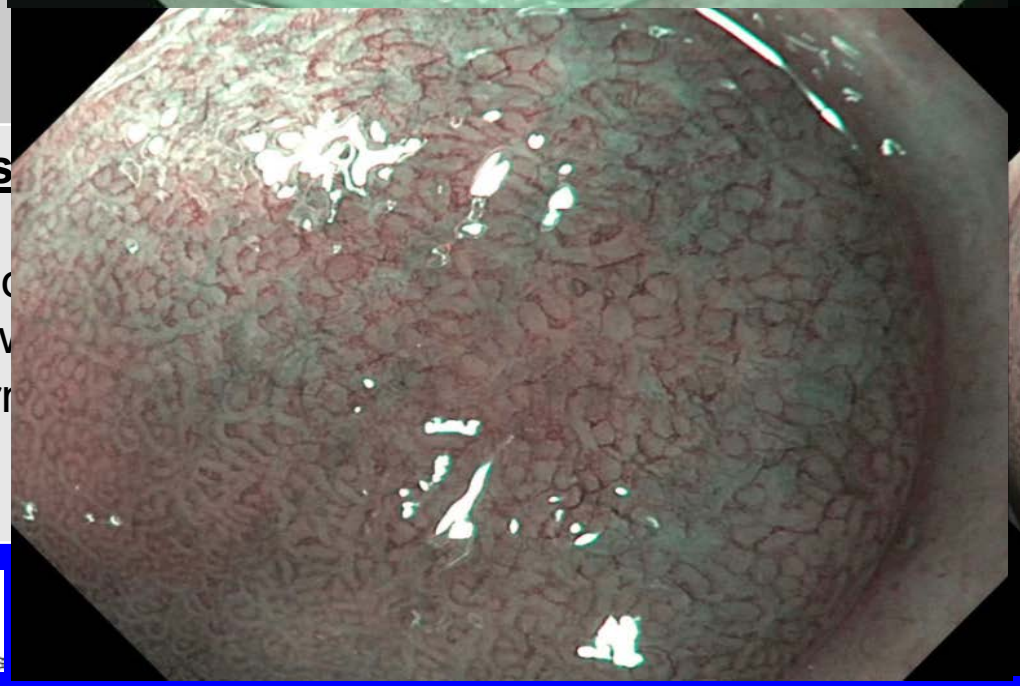

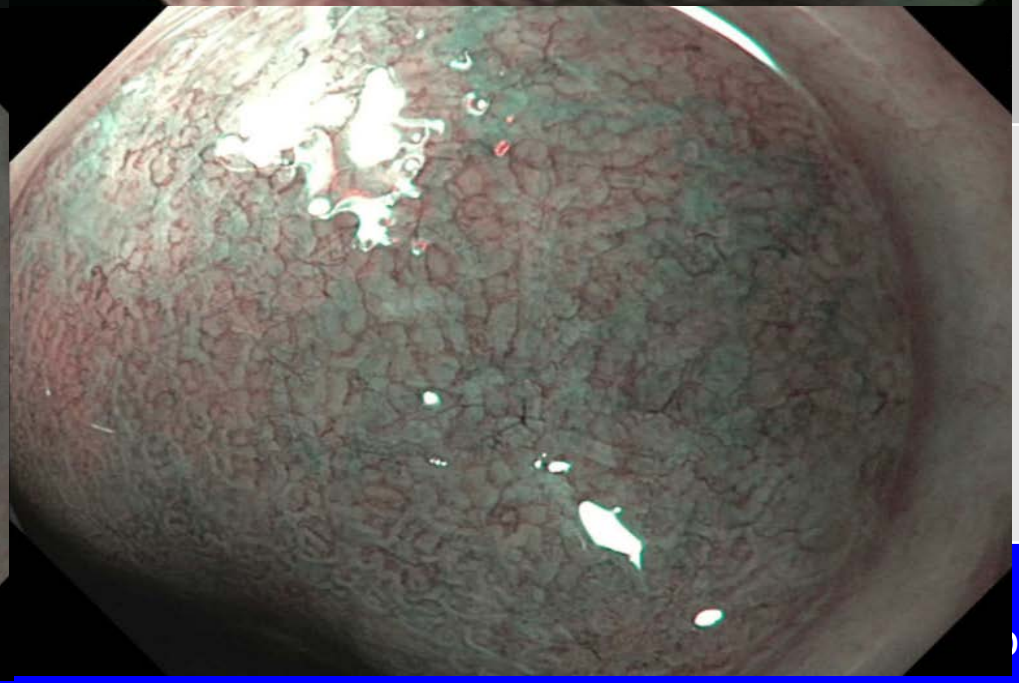

University of Colorado
Anschutz Medical Campus

ogy 2016

STANDARDIZED CONSENSUS DRIVEN CLASSIFICATION SYSTEM

Regular Pattern	Irregular Pattern
Mucosal Circular, ridge/villous, or tubular pattern	**Mucosal** Absent or irregular patterns
Vascular Blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long branching patterns	**Vascular** Focally or diffusely distributed vessels not following normal architecture of the mucosa

University of Colorado
Anschutz Medical Campus

Sharma et al, Gastroenterology 2016

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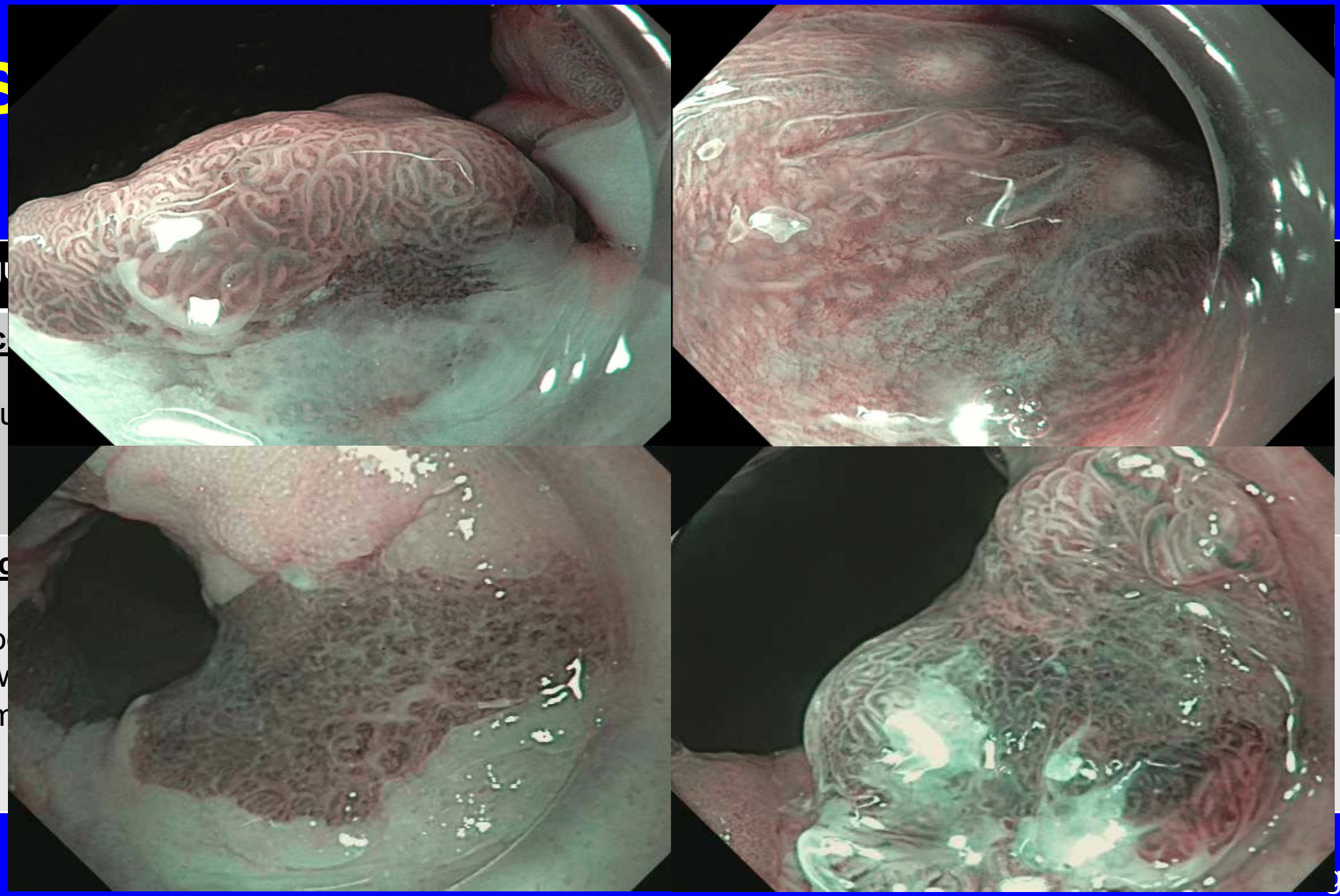

University of Colorado
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gy 2016

STANDARDIZED CONSENSUS DRIVEN CLASSIFICATION SYSTEM

Predictions	Accuracy 95% CI	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI
Overall	85.4 (82.6-87.9)	80.4 (75.6-85.1)	88.4 (85.4-91.4)	80.7 (75.9-85.4)	88.3 (85.2-91.2)
High-confidence	92.2 (89.3-94.5)	91.1 (86.8-95.4)	92.9 (89.8-95.9)	88.5 (83.7-93.2)	94.6 (91.8-97.2)
Low-confidence	74.1 (68.4-79.2)	62.4 (52.9-71.8)	81.1 (75.1-87)	66.3 (56.8-75.8)	78.3 (72.1-84.4)

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Sharma et al, Gastroenterology 2016

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Sharma et al, Gastroenterology 2016

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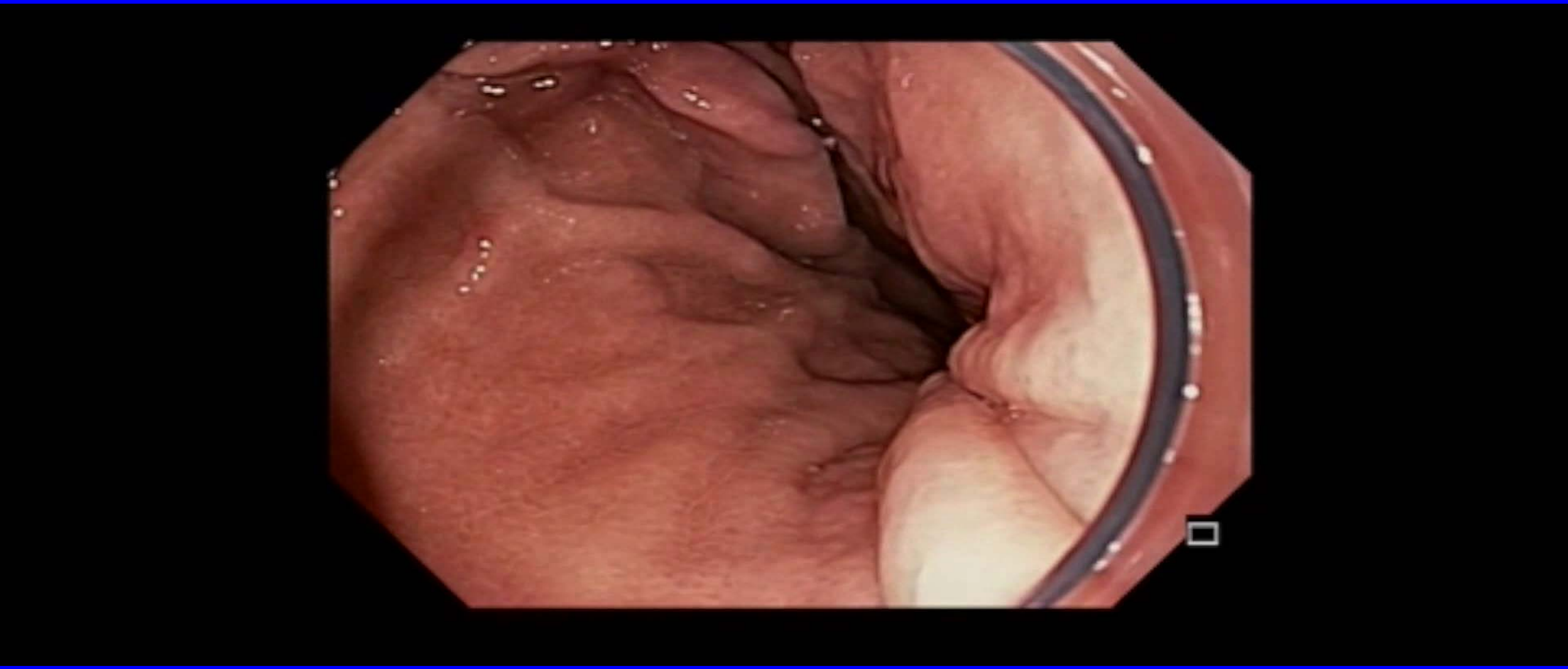
Sharma et al, Gastroenterology 2016

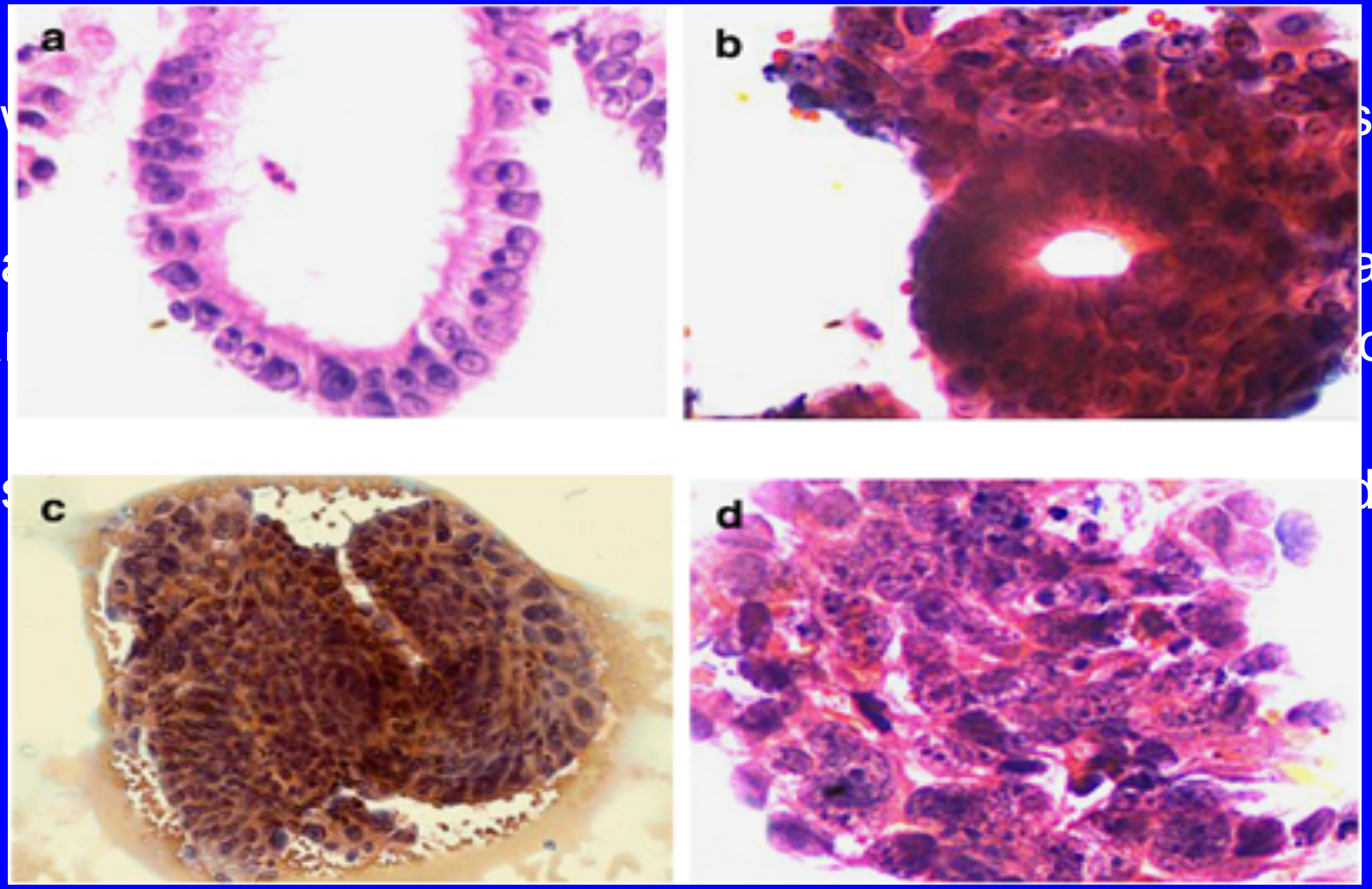


WIDE-AREA TRANSEPITHELIAL SAMPLING (WATS)

- Provides wide-area tissue sampling using minimally invasive brush biopsy
- Abrasive and sample deeper layers (including muscularis mucosa)
- Sample analyzed – high-speed computer scan that identifies abnormal cells, cell clusters and abnormal glandular cells
- Pathologists review these “suspicious” cells on high-resolution video monitor

WIDE-AREA TRANSEPITHELIAL SAMPLING (WATS)

- Provides v sh biopsy
- Abrasive a a)
- Sample a ormal cells, cell
- Pathologis deo monitor



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WIDE-AREA TRANSEPITHELIAL SAMPLING (WATS)

- Randomized controlled trial – BE patients undergoing surveillance at 16 centers
- 160 patients
- Addition of WATS to standard Seattle biopsies yielded additional 23 cases of HGD/EAC (relative increase 428.6% (30/7); 95% CI: 193.9-947.1%, absolute increase 14.4%, 95% CI 7.5-21.2%)
- WATS missed 1 case of HGD/EAC

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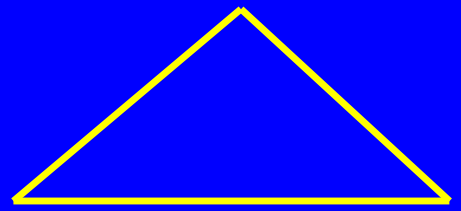
Vennalaganti et al, Gastrointest Endosc 2018

SURVEILLANCE TRIAD FOR OPTIMIZING DETECTION OF BARRETT'S NEOPLASIA

PHYSICIAN FACTORS (TECHNICAL)

- Spend adequate time for inspection
- Systematic and meticulous approach during inspection
- Photo-document landmarks, standardized grading systems
- Seattle protocol for biopsies



PHYSICIAN FACTORS (COGNITIVE)

- Knowledge of grading systems
- Training and familiarity of key signs for detecting early neoplasia
- Training in use of HD-WLE and NBI

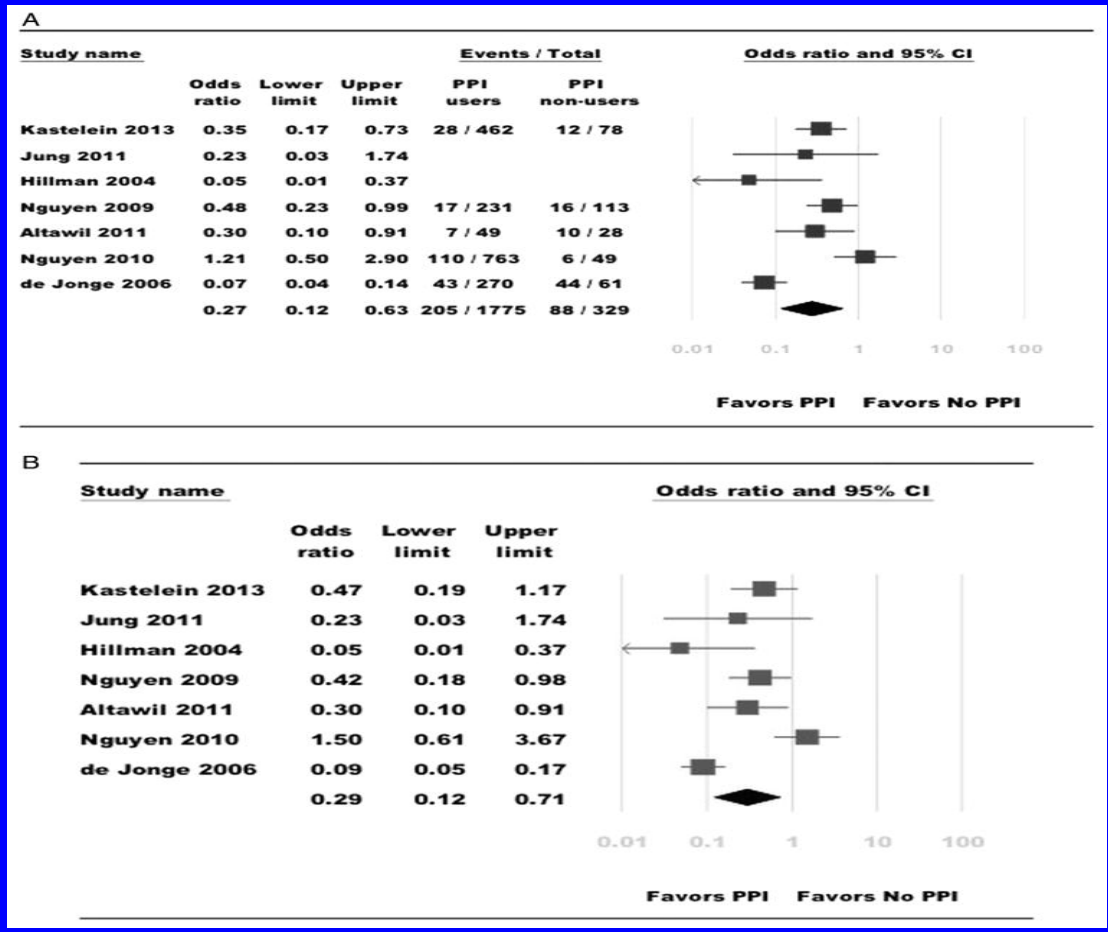
INSTITUTIONAL FACTORS

- Equipment for enhanced imaging techniques (HD-WLE)
- Dedicated endoscopy blocks for surveillance and EET

Wani et al, Am J Gastroenterol 2017

Should PPI be recommended for Barrett's esophagus

- PPI therapy associated with a 71% reduction in risk of EAC and/or BE-HGD (aOR 0.29, 95% CI 0.12-0.79)
- Trend towards a dose-response relationship
- Considerable heterogeneity
- No effect seen with H2RA (only 2 studies)



Singh S et al, Gut 2014

Should PPI be recommended for

Patients with BE should receive once-daily PPI therapy. Routine use of BID dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis

Strength of recommendation: Strong

Quality of evidence: Moderate

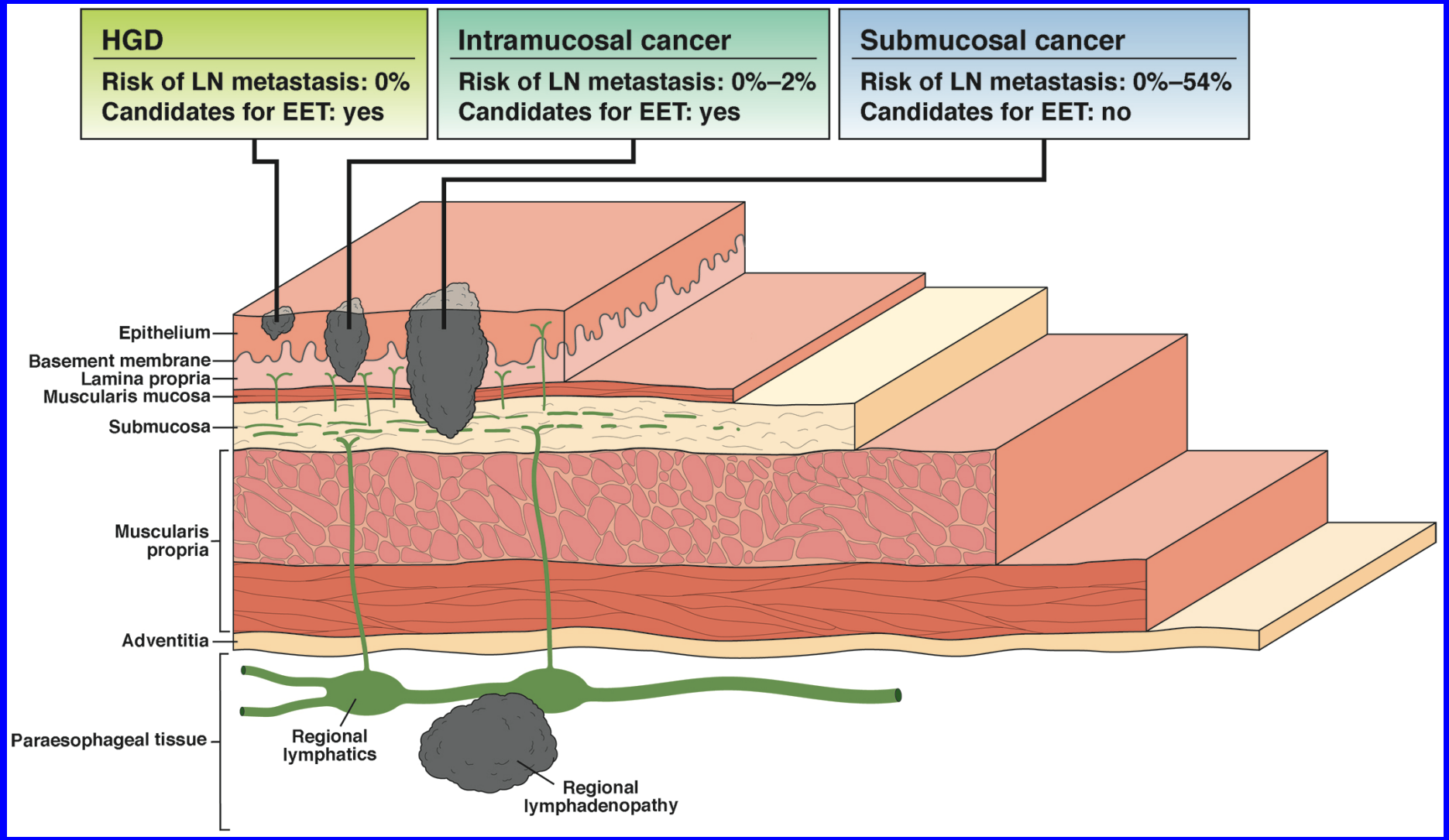
ACG Clinical Guideline 2016

Singh S et al, Gut 2014

OPTIMIZING OUTCOMES – ENDOSCOPIC ERADICATION THERAPY

- Contemporary endoscopic management of Barrett's related dysplasia and intramucosal cancer

BASIS OF ENDOSCOPIC THERAPY



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Komanduri S, Muthusamy V, Wani S, Gastroenterology 2018

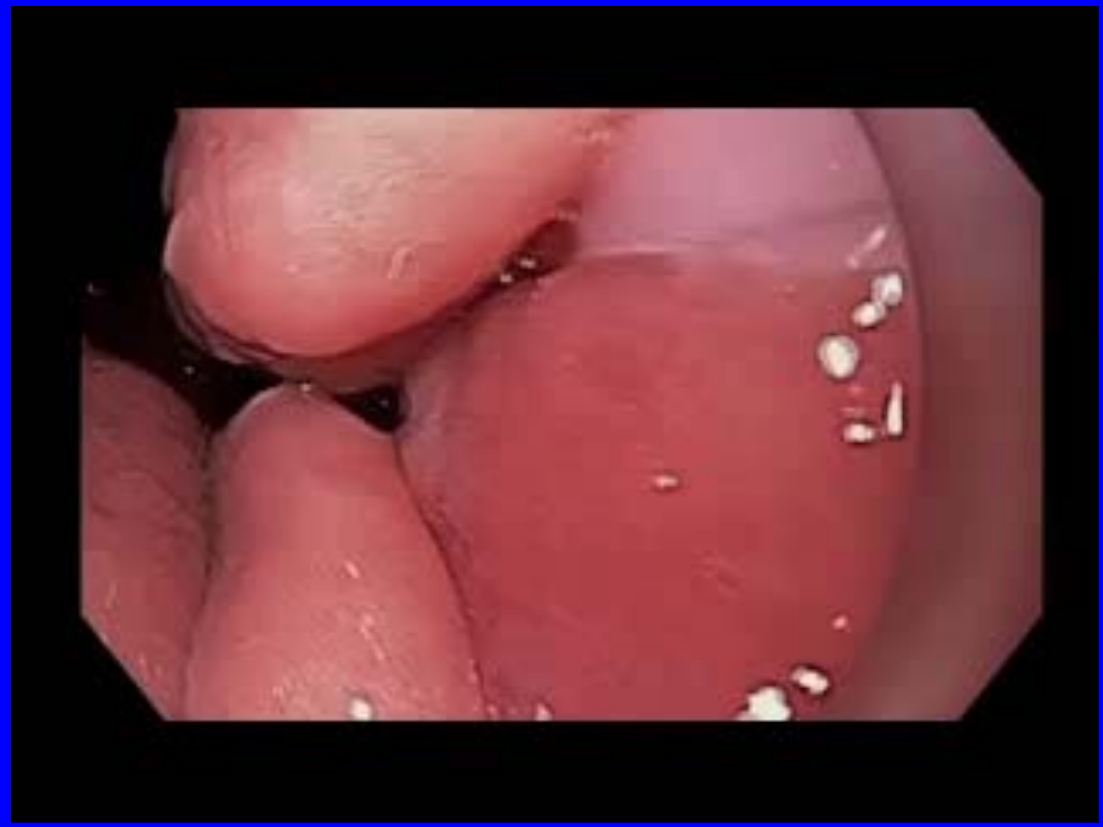
PRINCIPLES OF ENDOSCOPIC ERADICATION THERAPIES

Resection of neoplastic lesion – lesion with highest dysplasia grade

Eradication of remaining Barrett's esophagus (reduce the risk of metachronous neoplasia)

Management of complications

Enrollment in surveillance programs and address recurrences



ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett's esophagus patients with confirmed HGD/IMC, we recommend against surgery compared with EET

Strength of recommendation: Strong

Quality of evidence: Very low

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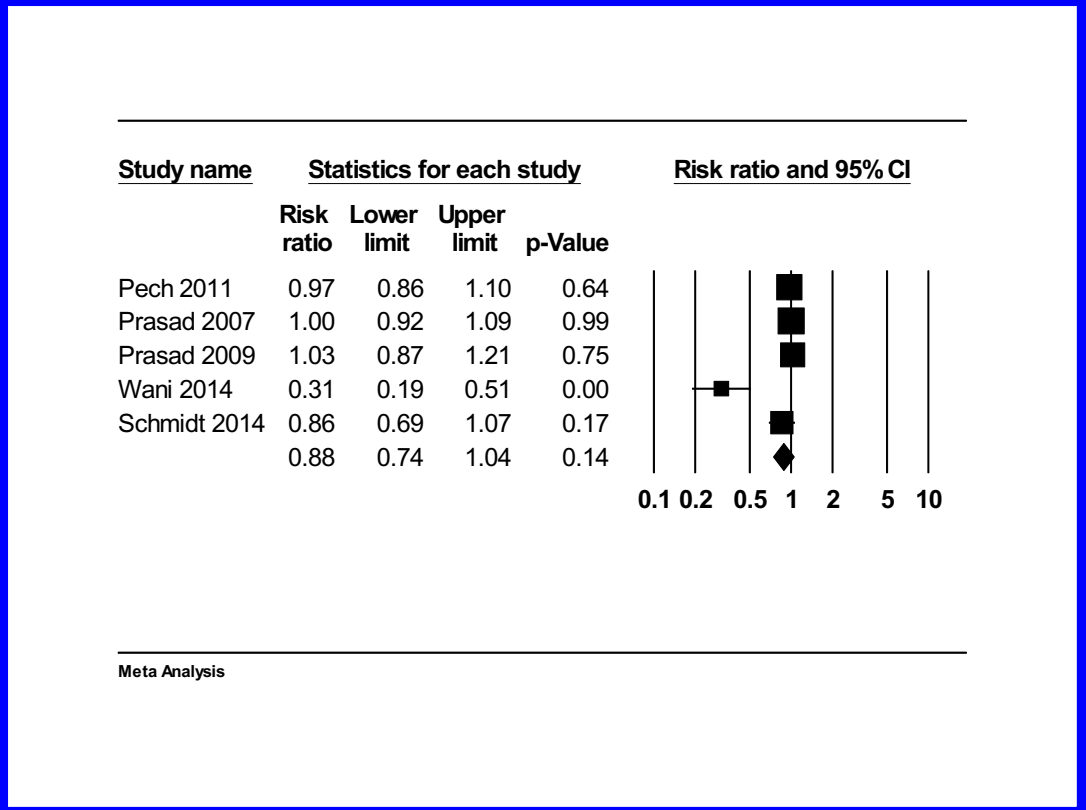
Wani S et al. Gastrointest Endosc 2018

ESOPHAGECTOMY vs. EET



- No difference in complete eradication of HGD/IMC (RR 0.96, 95% CI 0.91-1.01)
- EET group had higher recurrence rates (RR 9.5, 95% CI 3.26-27.75)

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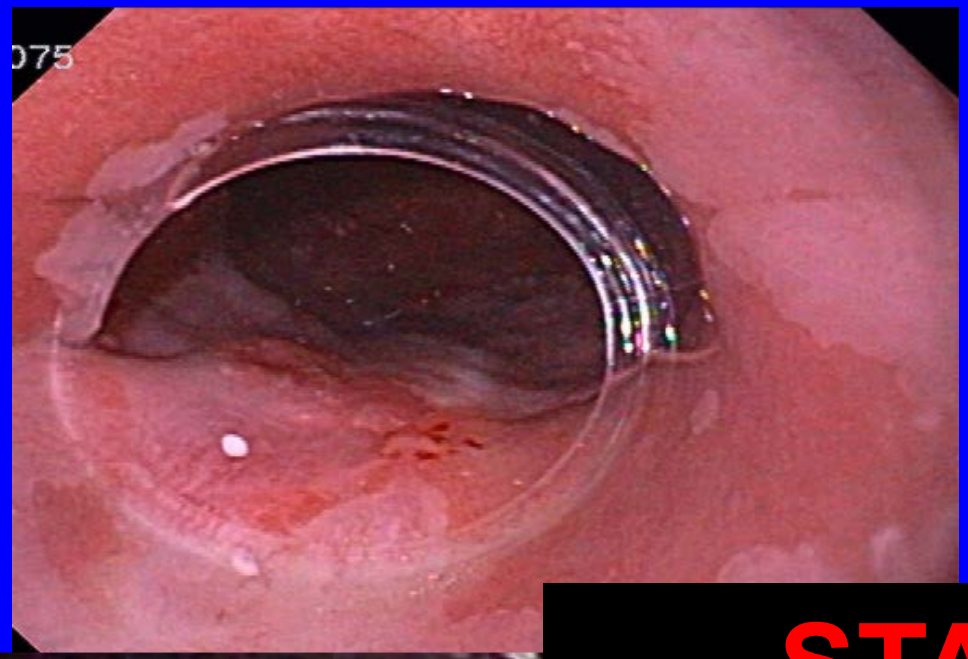
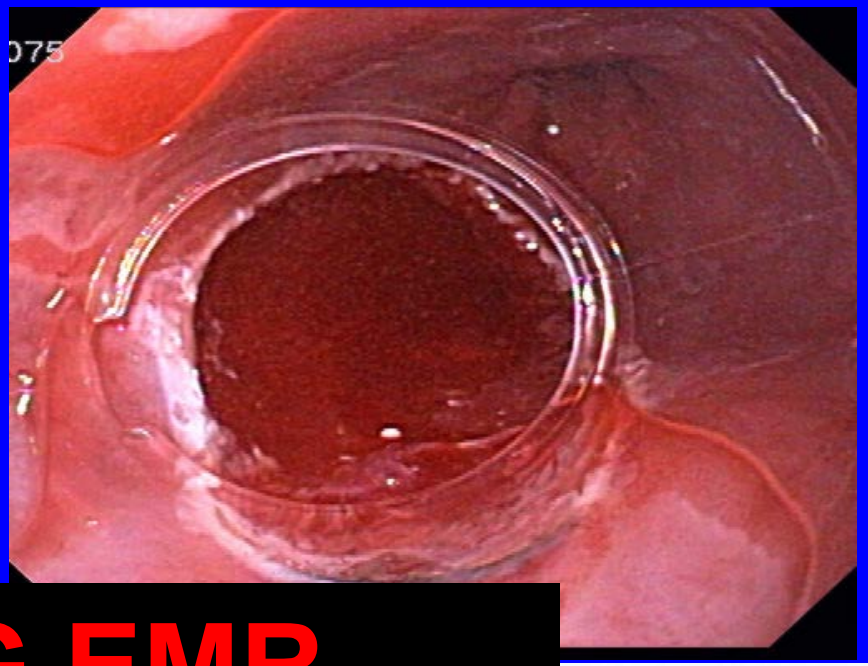
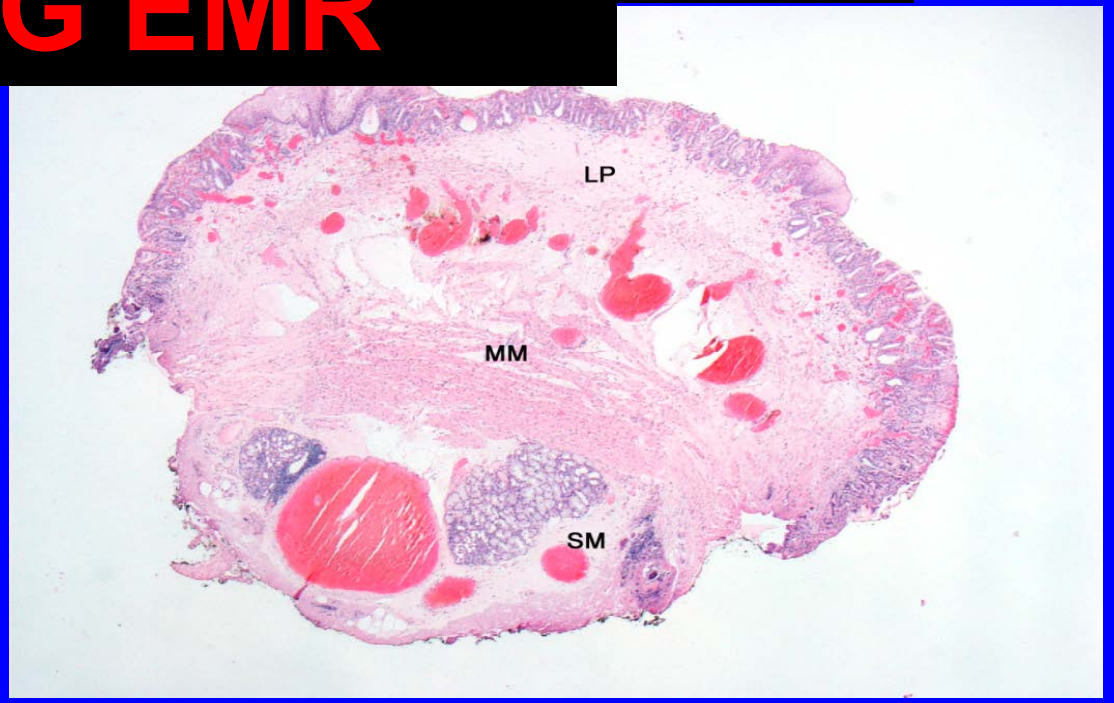
Wani S et al. Gastrointest Endosc 2018





STAGING EMR

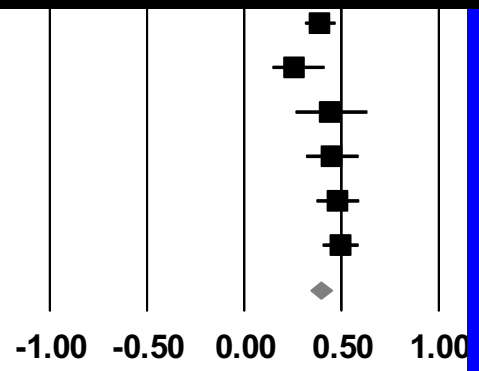


IMPACT OF EMR ON DIAGNOSIS

EMR resulted in change in pathologic diagnosis in 39% (95% CI 34-45) of all patients

Majority of patients were upgraded to a higher pathologic diagnosis

Werbouck	0.39	0.31	0.47	0.01
Conio	0.26	0.14	0.41	0.00
Nijhawan	0.44	0.26	0.63	0.55
Chennat	0.45	0.32	0.59	0.48
Moss	0.48	0.37	0.59	0.73
Konda	0.50	0.40	0.59	0.92
	0.39	0.34	0.45	0.00



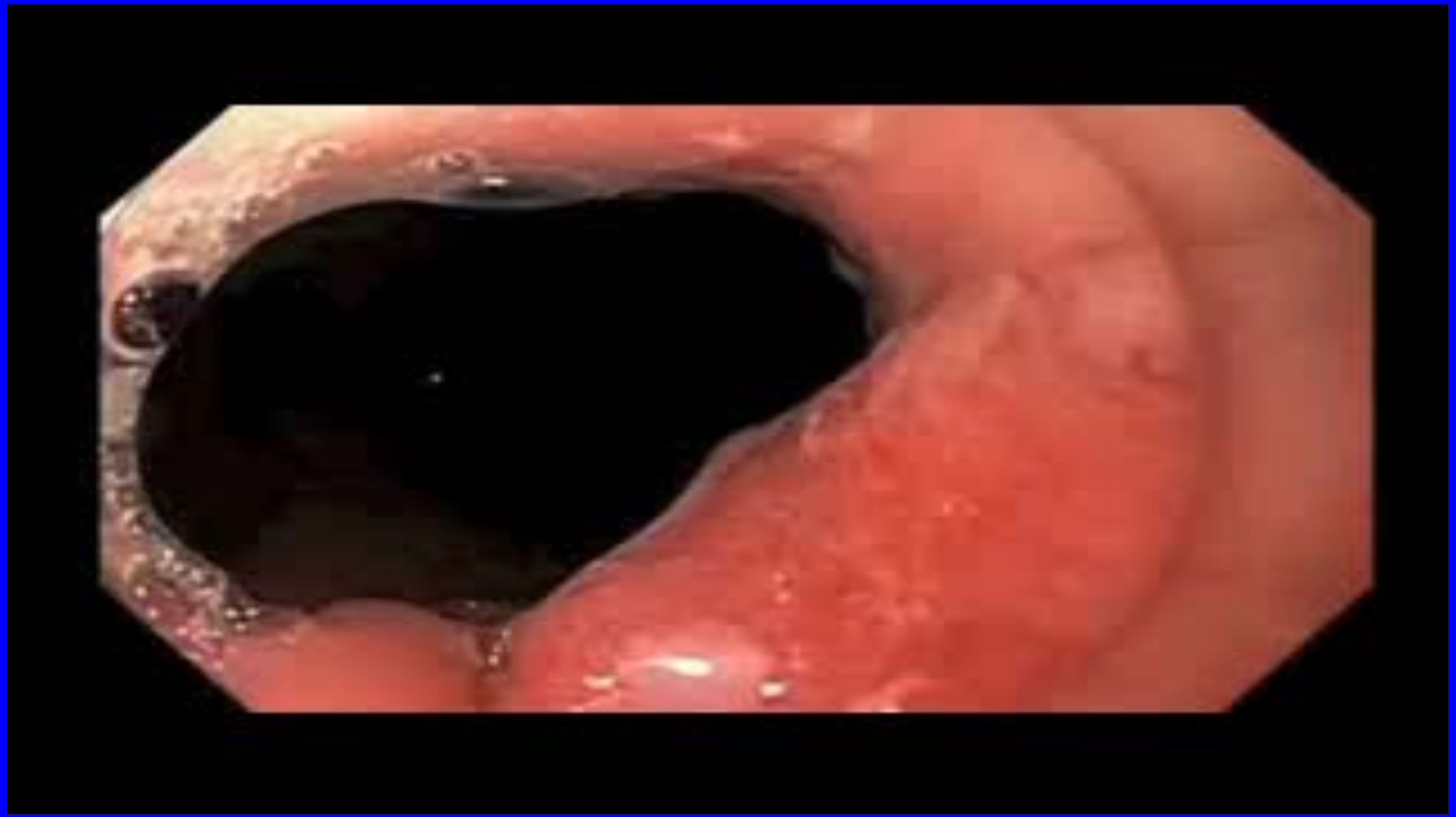
ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett's esophagus patients referred for EET, we recommend endoscopic resection of all visible lesions compared to no endoscopic resection of visible lesions

Strength of recommendation: Strong

Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc 2018



INTEROBSERVER VARIABILITY AMONG PATHOLOGISTS

Diagnosis	Biopsy Kappa (95% CI) Strength of agreement	EMR Kappa (95% CI) Strength of agreement
NDBE	0.57 (0.52-0.62) Moderate	0.51 (0.46-0.56) Moderate
LGD/IND	0.22 (0.17-0.27) Fair	0.33 (0.28-0.39) Fair
HGD	0.35 (0.3-0.4) Fair	0.43 (0.38-0.48) Moderate
EAC	0.71 (0.66-0.76) Substantial	0.68 (0.63-0.73) Substantial

Wani S et al, CGH 2010

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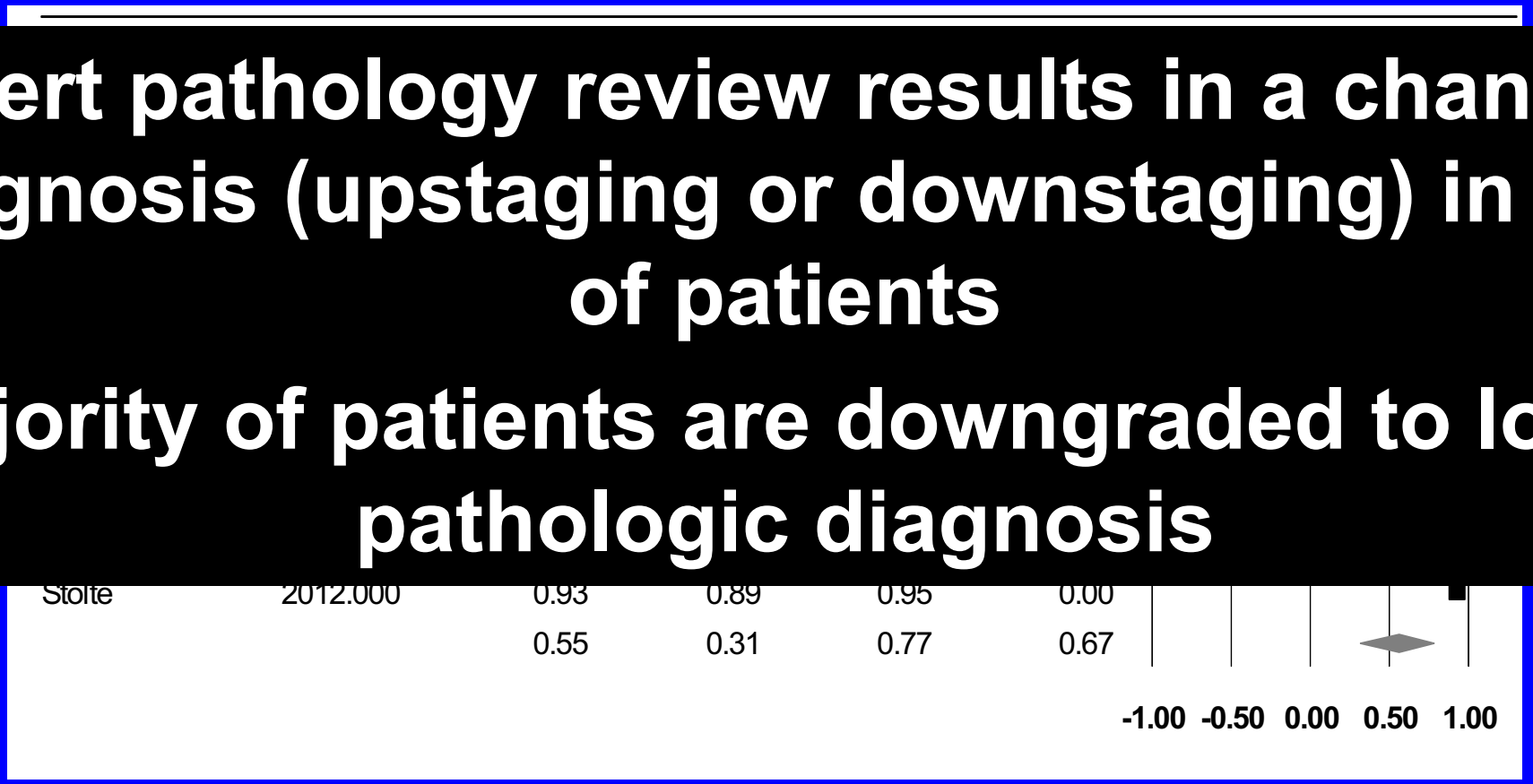
EAC	0.71 (0.66-0.76) Substantial	0.68 (0.63-0.73) Substantial

Wani S et al, CGH 2010

CHANGE IN DIAGNOSIS BASED ON EXPERT PATHOLOGY REVIEW

Expert pathology review results in a change in diagnosis (upstaging or downstaging) in 55% of patients

Majority of patients are downgraded to lower pathologic diagnosis



Wani S et al. Gastrointest Endosc 2018

ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett's esophagus patients with LGD AND HGD being considered for EET, we suggest confirmation of diagnosis by at least one expert GI pathologist or panel of pathologists compared to review by a single pathologist

Strength of recommendation: Conditional

Quality of evidence: Low

Wani S et al. Gastrointest Endosc 2018

Grade of dysplasia & Cancer Risk

Grade	Cancer Incidence	(95% CI)	Cancer Risk
IM	0.598%/yr	0.516-0.7	Low
LGD	1.70%/yr	1.31-2.09	Intermediate
HGD	6.58%/yr	4.97-8.18	High

Rastogi et al. Gastrointest Endosc 2008
Wani S et al. Am J Gastroenterol 2009

Natural History of LGD

Diagnosis	Incident cases	Incidence rate %/year (95% CI)	Mean time to development (years, SD) range
HGD	21	1.6 (1.05-2.46)	2.86 (4.22)
EAC	6	0.44 (0.2-0.98)	4.41 (1.49)
HGD/EAC	24	1.83 (1.23-2.74)	3.08 (2.57)

Wani S et al, Gastroenterology 2011

HOW EFFECTIVE IS EET FOR BE WITH HGD?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 28, 2009 VOL. 360 NO. 22

Radiofrequency Ablation in Barrett's Esophagus with Dysplasia

Nicholas J. Shaheen, M.D., M.P.H., Prateek Sharma, M.D., Bergein F. Overholt, M.D., Herbert C. Wolfsen, M.D., Richard E. Sampliner, M.D., Kenneth K. Wang, M.D., Joseph A. Galanko, Ph.D., Mary P. Bronner, M.D., John R. Goldblum, M.D., Ana E. Bennett, M.D., Blair A. Jobe, M.D., Glenn M. Eisen, M.D., M.P.H., M. Brian Fennerty, M.D., John G. Hunter, M.D., David E. Fleischer, M.D., Virender K. Sharma, M.D., Robert H. Hawes, M.D., Brenda J. Hoffman, M.D., Richard I. Rothstein, M.D., Stuart R. Gordon, M.D., Hiroshi Mashimo, M.D., Ph.D., Kenneth J. Chang, M.D., V. Raman Muthusamy, M.D., Steven A. Edmundowicz, M.D., Stuart J. Spechler, M.D., Ali A. Siddiqui, M.D., Rhonda F. Souza, M.D., Anthony Infantolino, M.D., Gary W. Falk, M.D., Michael B. Kimmey, M.D., Ryan D. Madanick, M.D., Amitabh Chak, M.D., and Charles J. Lightdale, M.D.

SURVEILLANCE vs. ABLATION IN LGD

- Ablation reduced risk of progression to HGD/EAC by 25%
  - 1.5% ablation vs. 26.5% controls (95% CI 14.1-35.9%, p<0.001)
- Ablation reduced risk of progression to EAC by 7.4%
  - 1.5% ablation vs. 8.8% controls (95% CI 0-14.7%, p=0.03)

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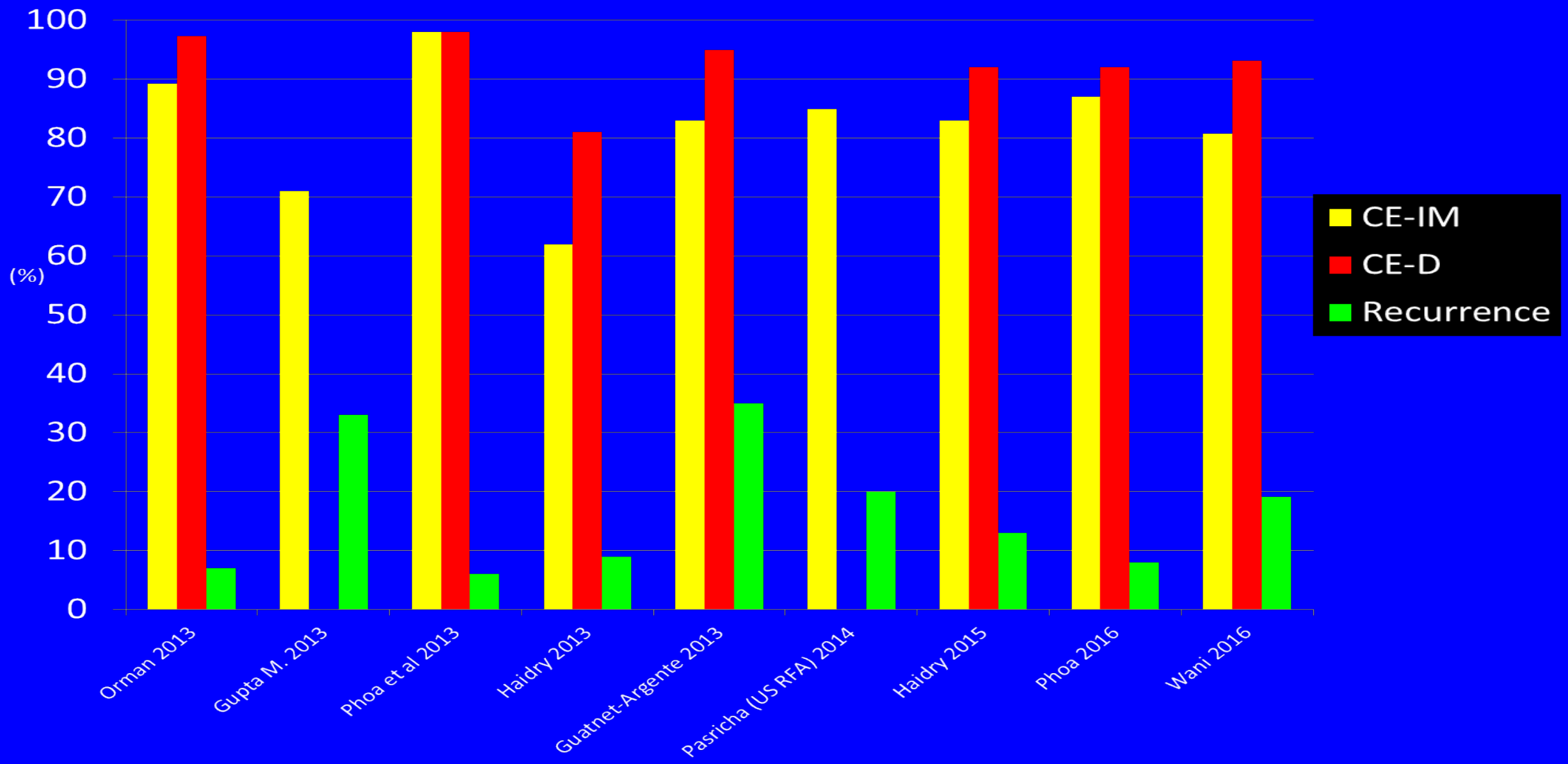
Phoa et al, JAMA 2014

EFFECTIVENESS DATA



ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett's esophagus patients with confirmed HGD, we recommend EET compared to surveillance

Strength of recommendation: Strong

Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc 2018

Gastroenterology 2016;151:822–835

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Diagnosis and Management of Low-Grade Dysplasia in Barrett's Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association

Sachin Wani,[1] Joel H. Rubenstein,[2,3] Michael Vieth,[4] and Jacques Bergman[5]

[1]University of Colorado, Anschutz Medical Campus, Aurora, Colorado; [2]Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; [3]University of Michigan Medical School, Ann Arbor, Michigan; [4]Klinikum Bayreuth, Bayreuth, Germany; and [5]Academic Medical Center, Amsterdam, The Netherlands

ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In Barrett's esophagus patients with LGD, we suggest EET compared to surveillance; however, patients who place a high value on avoiding adverse events related to EET may choose surveillance as the preferred option

Strength of recommendation: Conditional

Quality of evidence: Moderate

Wani S et al. Gastrointest Endosc 2018

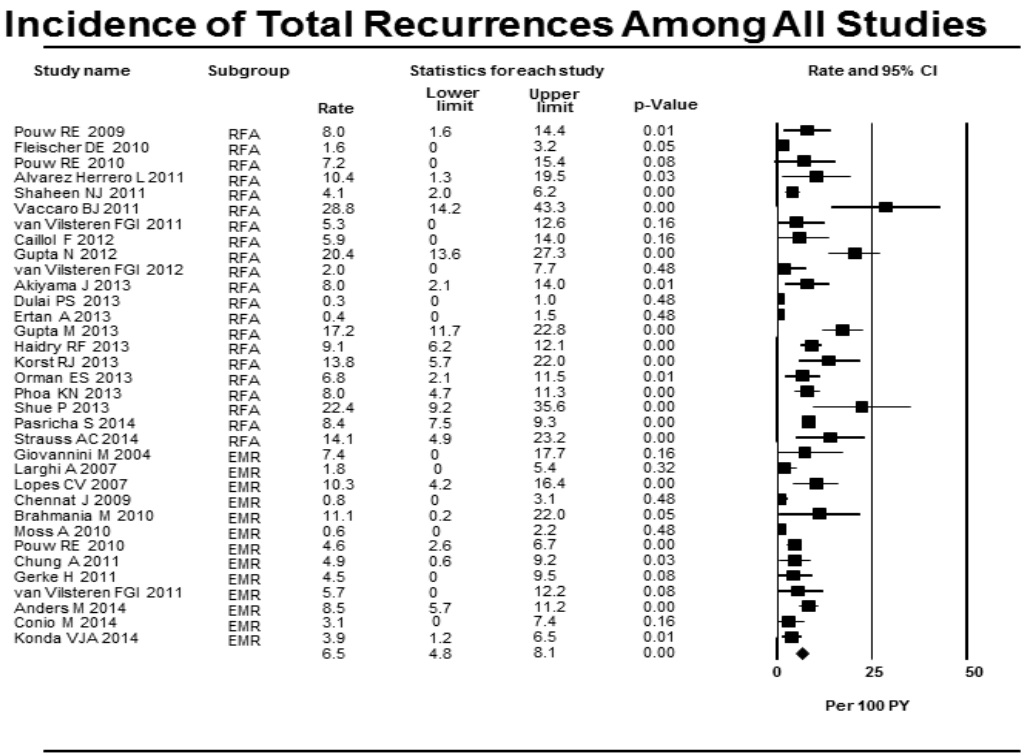
Adverse Events

- Meta-analysis – 37 studies
- Pooled rate (RFA +/- EMR): 8.8% (95% CI 6.5-11.9)
- **Strictures: 5.6% (95% CI 4.2-7.4)**
- **Bleeding: 1% (95% CI 0.8-1.3%)**
- **Perforation: 0.6% (95% CI 0.4-0.9)**
- Adverse events higher with EMR (RR 4.4)
- BE length and baseline histology predictors of adverse events

Qumseya et al CGH 2016

RECURRENCE OF INTESTINAL METAPLASIA AND NEOPLASIA

- Meta analysis – 33 studies
- Pooled incidence any recurrence: 6.5 (95% CI 4.8-8.1)/100 patient-years
- Incidence of IM: 4.2 (95% CI 2.9-5.4)/100 patient-years
- Incidence of early neoplasia: 1.4 (95% CI 0.9-1.8)/100 patient-years



Fuji et al, Endosc Int Open 2017

ASGE GUIDELINES FOR ENDOSCOPIC ERADICATION THERAPY

In BE patients with dysplasia and IMC who have achieved CE-IM after EET, we suggest surveillance versus no surveillance

Strength of recommendation: Conditional

Quality of evidence: Very low

Wani S et al. Gastrointest Endosc 2018

WHEN SHOULD WE LOOK FOR RECURRENCE?

- The TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Study – multi-center outcomes project
  - University of Colorado Anschutz Medical Campus, Aurora, Colorado
  - Northwestern University, Chicago, Illinois
  - Washington University in St. Louis, St. Louis, Missouri
  - University of California in Los Angeles, Los Angeles, California
- Developed to assess clinical outcomes after EET and establish quality indicators in EET

Wani S et al. DDW 2019

WHEN SHOULD WE LOOK FOR RECURRENCE?

Recurrence of IM and dysplasia

- Follow-up period of 2317 person-years (PY)
- Mean follow-up of 3.3 years (SD 2.7), 2.9 years/patient, range: 0.3-13.2 years
- **Recurrence of IM:** 121 (15%) for an incidence rate of 5.2 per 100 PYs
- **Recurrence of dysplasia**: 36 (4.5%) for an incidence rate of 1.6 per 100 PYs

Wani S et al. DDW 2019

Histologic grade of recurrence by baseline histology

Baseline histology	Recurrence of intestinal metaplasia	Recurrence of LGD	Recurrence of HGD	Recurrence of EAC
NDBE (n=61)	12 (100%)	0 (0%)	0 (0%)	0 (0%)
LGD (n=239)	20 (80%)	5 (20%)	0 (0%)	0 (0%)
HGD (n=332)	21 (56.8%)	2 (5.4%)	14 (37.8%)	0 (0%)
EAC (n=175)	12 (50%)	2 (8.3%)	1 (4.2%)	9 (37.5%)

Wani S et al. DDW 2019

Predictors of recurrence

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	1.02 (0.99-1.04)	0.07	1.01 (0.98-1.03)	0.53
Caucasian Race	7.7 (1.03-56.83)	0.05	4.35 (0.58-32.6)	0.15
BMI	0.98 (0.95-1.02)	0.36	NA	
Baseline histology LGD HGD/EAC	**Reference 3.23 (2.3-6.5)**	**<0.001**	**Reference 4.19 (1.87-9.4)**	**<0.001**
Presence of GERD symptoms	**4.35 (2.4-7.9)**	**<0.001**	**12.13 (4.3-34.1)**	**<0.001**
Hiatal hernia	**1.88 (1.15-3)**	**0.01**	**13.8 (3.4-56.4)**	**<0.001**
Size of hiatal hernia	**0.61 (0.45-0.84)**	**0.002**	**2.33 (1.3-4.2)**	**0.005**

Wani S et al. DDW 2019

Predictors of recurrence

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
BE length	1.23 (1.13-1.35)	<0.001	1 (0.87-1.16)	0.99
Duration of BE	1.02 (0.98-1.06)	0.4	NA	
Prior fundoplication	0.88 (0.38-2.04)	0.77	NA	
Treatment RFA RFA+EMR Cryotherapy EMR alone	 0.51 (0.06-4.3) 0.72 (0.09-6.15) 1.7 (0.16-17.3) 1 (0.1-9.6)	 0.53 0.77 0.59 0.99	NA	
Number of EET sessions to achieve CE-IM	**1.52 (1.3-1.79)**	**<0.001**	**1.78 (1.44-2.21)**	**<0.001**

Wani S et al. DDW 2019

SURVEILLANCE INTERVALS

Pre-treatment histology	Surveillance interval post CE-IM
Non-dysplastic BE or indefinite for dysplasia	Deferred as EET not recommended for NDBE
Low-grade dysplasia	1 and 3 years
High-grade dysplasia	3 months, 6 months, 1 year and then annually

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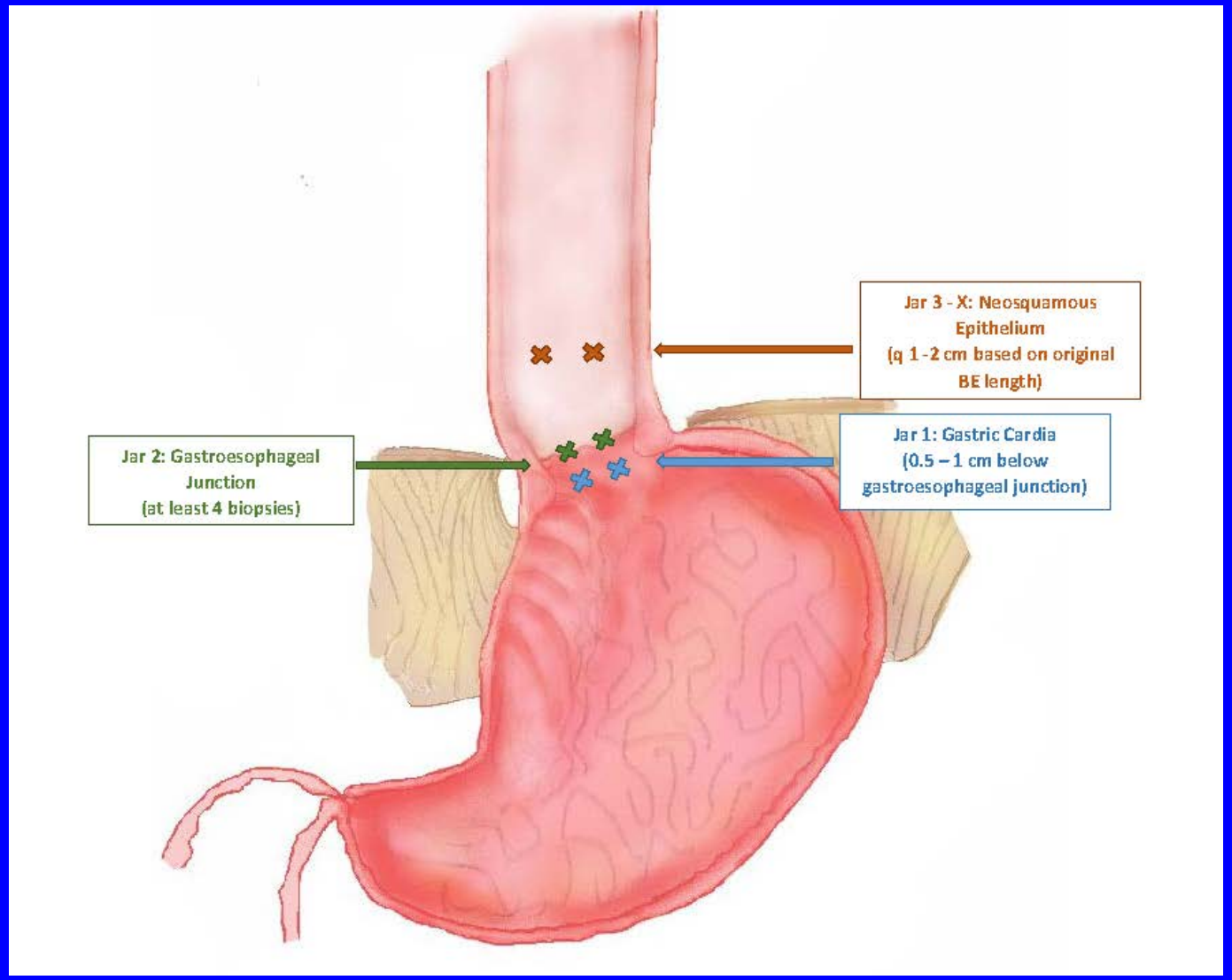
Cotton et al, Gastroenterology 2018

SURVEILLANCE INTERVALS



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Omar M, Thaker AM et al, Gastrointest Endosc 2019 (in press)

Development of Quality Indicators for Endoscopic Eradication Therapies in Barrett's Esophagus: The TREAT-BE (Treatment With Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium

Sachin Wani, MD[1,*], V. Raman Muthusamy, MD[2,*], Nicholas J. Shaheen, MD, MPH[3], Rena Yadlapati, MD[4], Robert Wilson, BA[1], Julian A. Abrams, MD[5], Jacques Bergman, MD, PhD[6], Amitabh Chak, MD[7], Kenneth Chang, MD[8], Ananya Das, MD[9], John Dumot, MD[7], Steven A. Edmundowicz, MD[1], Glenn Eisen, MD[10], Gary W. Falk, MD[11], M. Brian Fennerty, MD[12], Lauren Gerson, MD, MPH[13], Gregory G. Ginsberg, MD[11], David Grande, BA[4], Matt Hall, PhD[1], Ben Har[illegible] MLIS[1], John Inadomi, MD[14], Janusz Jankowski, MD[15], Charles J. Lightdale, MD[5], Jitin Makker, MD[2], Robert D. Odze, MD[16], Olive[illegible], George Triadafilopoulos, MD[20], Michael B. Wallace, MD[21], Kenneth Wang,[illegible]

Am J Gastroenterol advance online publication, 1 June 2017; doi:10.1038/ajg.2017.166

QUALITY INDICATORS FOR GI ENDOSCOPIC PROCEDURES

Development of quality indicators for endoscopic eradication therapies in Barrett's esophagus: the TREAT-BE (Treatment with Resection and Endoscopic Ablation Techniques for Barrett's Esophagus) Consortium

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This document was reviewed and approved by the governing boards of the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology. It appears simultaneously in *Gastrointestinal Endoscopy* and the *American Journal of Gastroenterology*.

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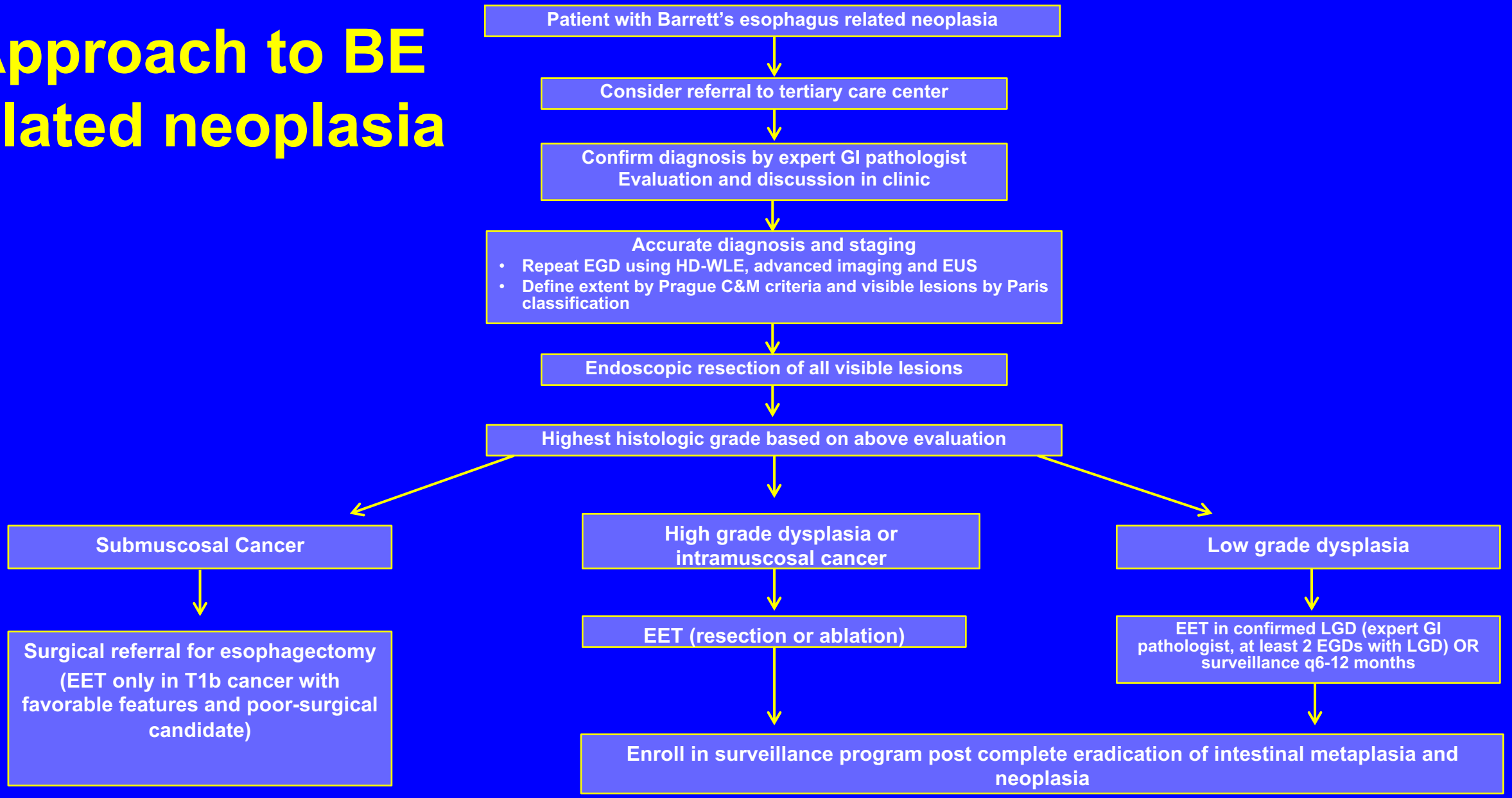
Approach to BE related neoplasia



Wani et al, Gastrointest Endosc 2018

Esophageal & Gastric Multidisciplinary Clinic

Established August 2013

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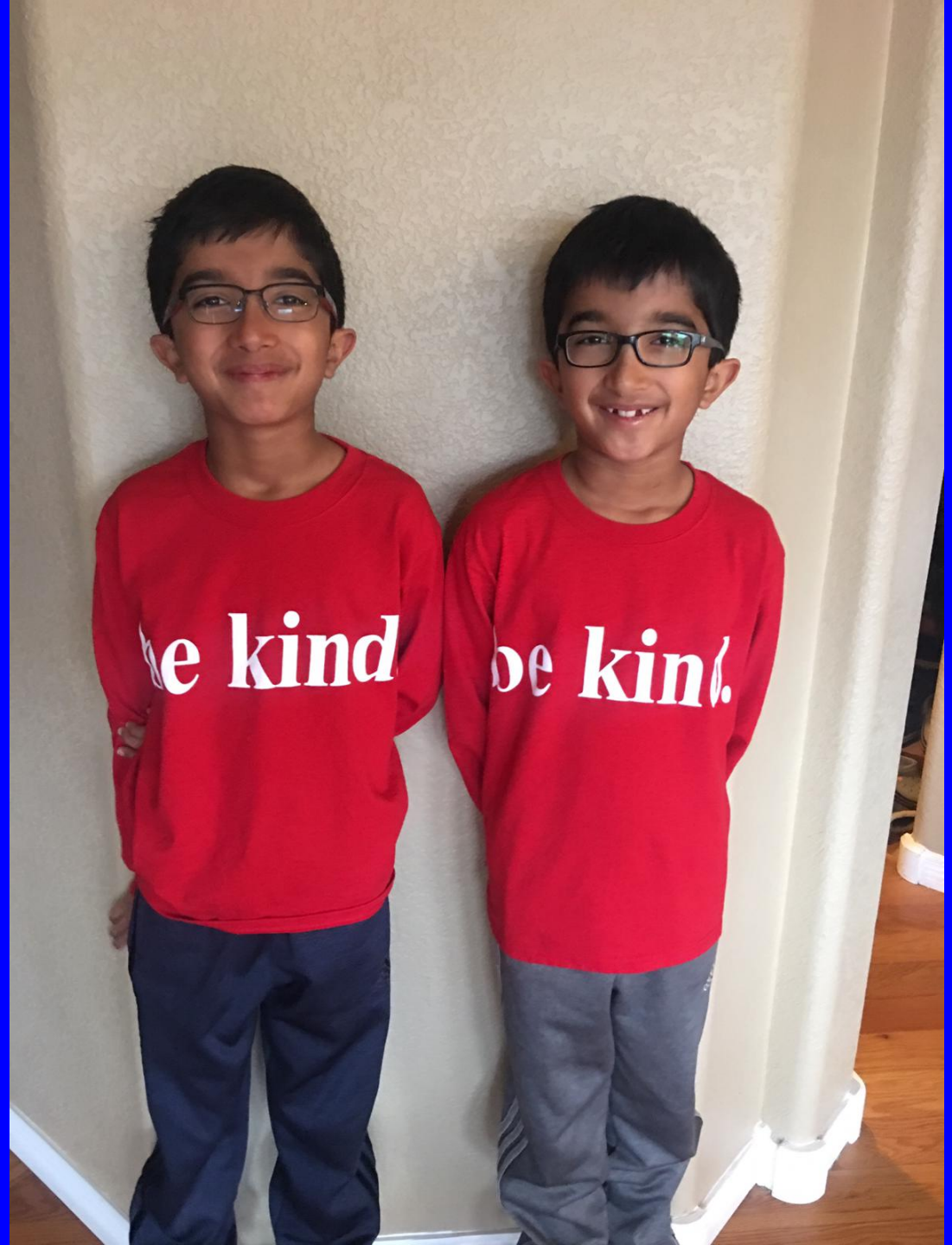
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THANK YOU

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Should PPI and aspirin be recommended for BE

- Indirect evidence until recently that ASA associated with lower risk of EAC
- ASA and NSAIDs inhibit several pathways in oncogenesis (inhibition of cyclooxygenase)
- Associated with side-effects, some that are serious and catastrophic

Gammon M et al, Cancer Epidemiol Biomarkers 2004;
Corley D et al, Gastroenterology 2003; Masclee et al BMJ Open 2015;
Beales IL et al, Eur J Gastroenterol Hepatol 2012; Omer ZB et al CGH 2012;

Should PPI and aspirin be recommended for BE

- AspECT Trial: Esomeprazole and aspirin in BE
- 2x2 factorial design, 84 centers in UK and one in Canada
- Included BE of ≥1 cm
- High dose PPI (40 mg BID) or low-dose (20 mg once daily) with or without aspirin (300 mg in UK, 325 mg in Canada) – 1:1:1:1 fashion, 8 years
- Primary endpoint: time to all-cause mortality, EAC/HGD

Jankowski J et al, Lancet 2018

Should PPI and aspirin be recommended for BE

- 2557 patients
- Median follow up 8.9 years, 20095 follow up years
- High-dose PPI superior to low-dose PPI [time ratio (TR) 1.27, 95% CI 1.01-1.58]
- Addition of aspirin increased effect but aspirin alone was not associated with improved outcomes
- Combining high-dose PPI with aspirin had strongest effect compared with low-dose PPI without aspirin (TR 1.59)
- 1% participants reported serious adverse events

Jankowski J et al, Lancet 2018

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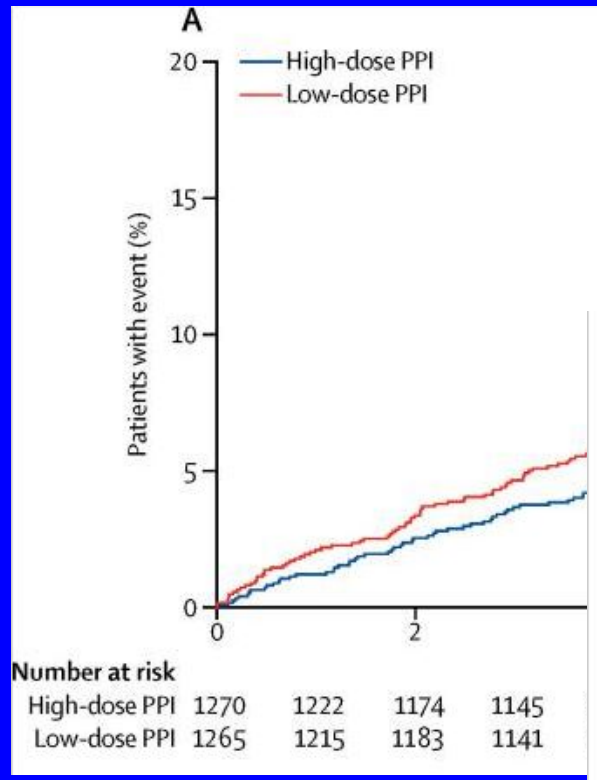
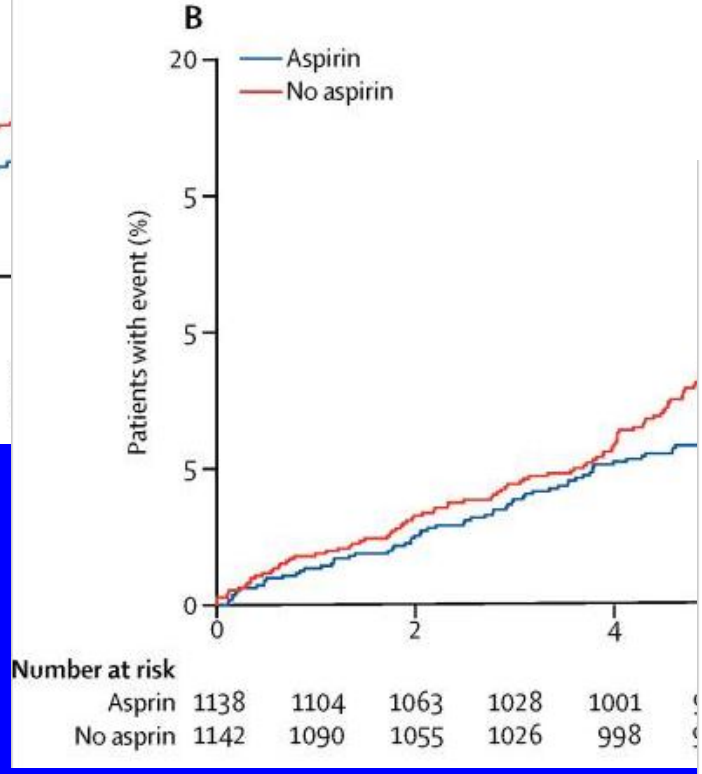
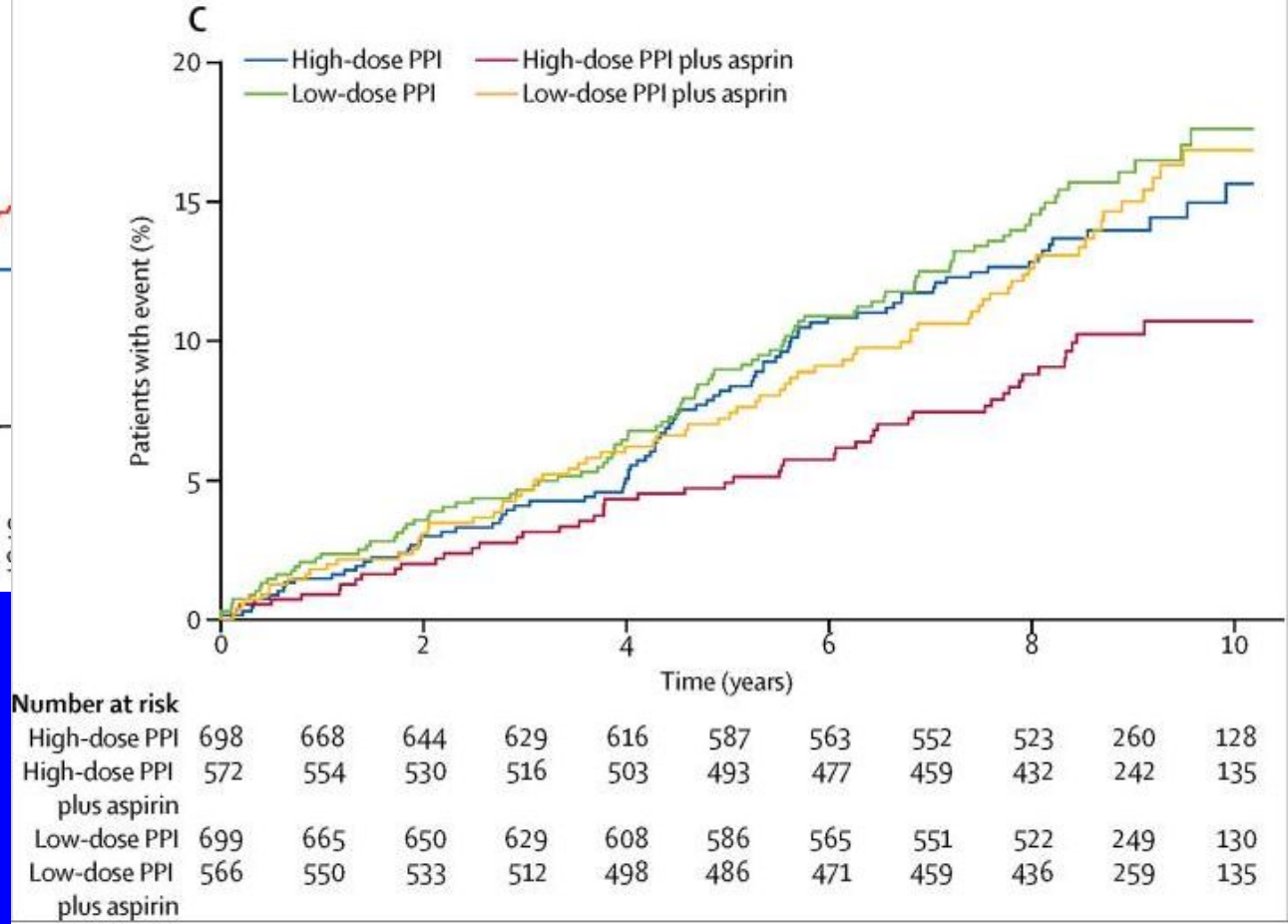
ded for PE







Should PPI and aspirin be recommended for BE

- Did not assess the effect of standard low-dose preventive therapy with aspirin (75 mg)
- No data on adherence
- Further data are required to confirm the reported positive combined effects from aspirin and PPI
- These data suggest a dose-response relationship for PPI and benefits vs. risks should be considered for use of BID PPI therapy

Jankowski J et al, Lancet 2018