INSELGRUPPE

Barrett’s Esophagus

Bible Class Gastroenterologie Inselspital

01/24

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Definition

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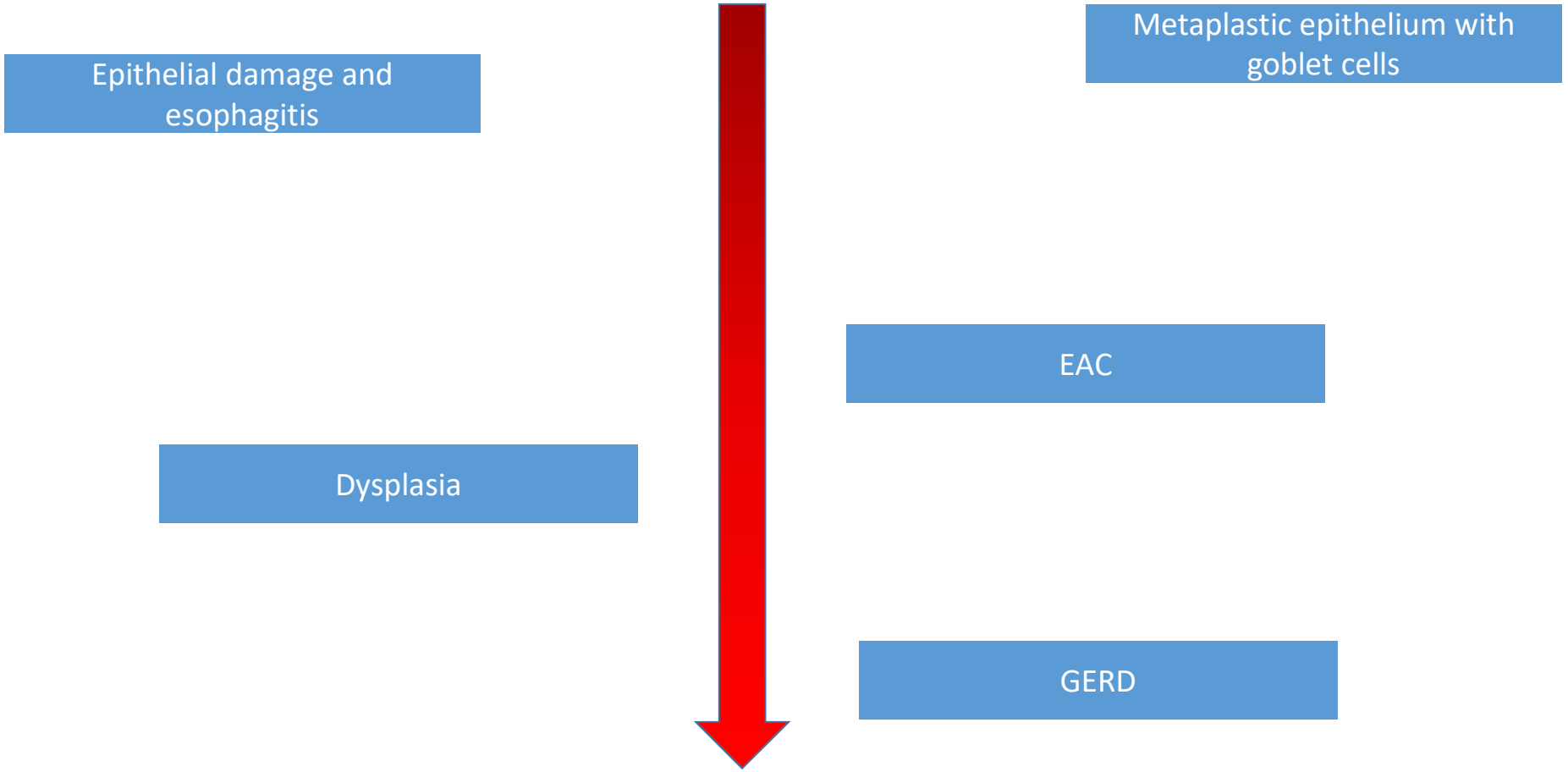
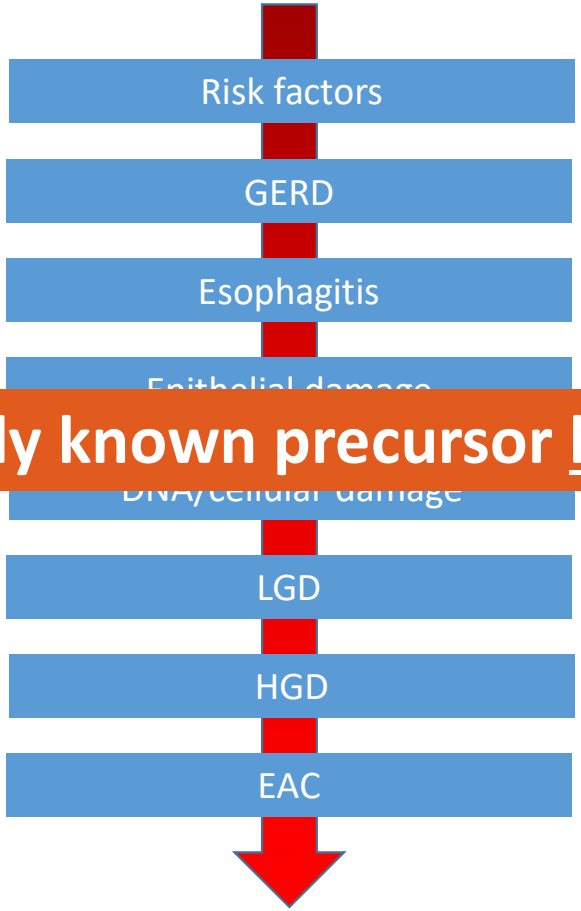
What is Barret's Esophagus?

«A metaplastic change of the distal esophagus, whereby the normal squamous epithelium is replaced by specialized columnar epithelium with goblet cells (...). BE is the only known precursor lesion to EAC. »


Epithelial damage and esophagitis
Metaplastic epithelium with goblet cells
EAC
Dysplasia
GERD



BE is the only known precursor lesion to EAC

Which of the following is true?

- Most EACs stem from SIM (true)
- The survival rate of EAC is 20% at 5y (true)
- There is no RCT evidence on EAC mortality reduction by BE screening (true)
- Helicobacter pylori has been associated with a decreased risk of EAC (true)

Coleman et al., Gastroenterology 2018;154:390–405

Epidemiology

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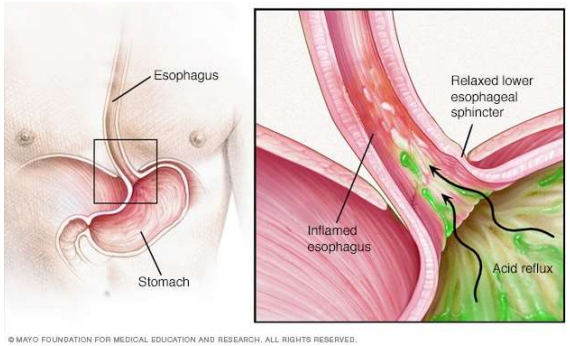
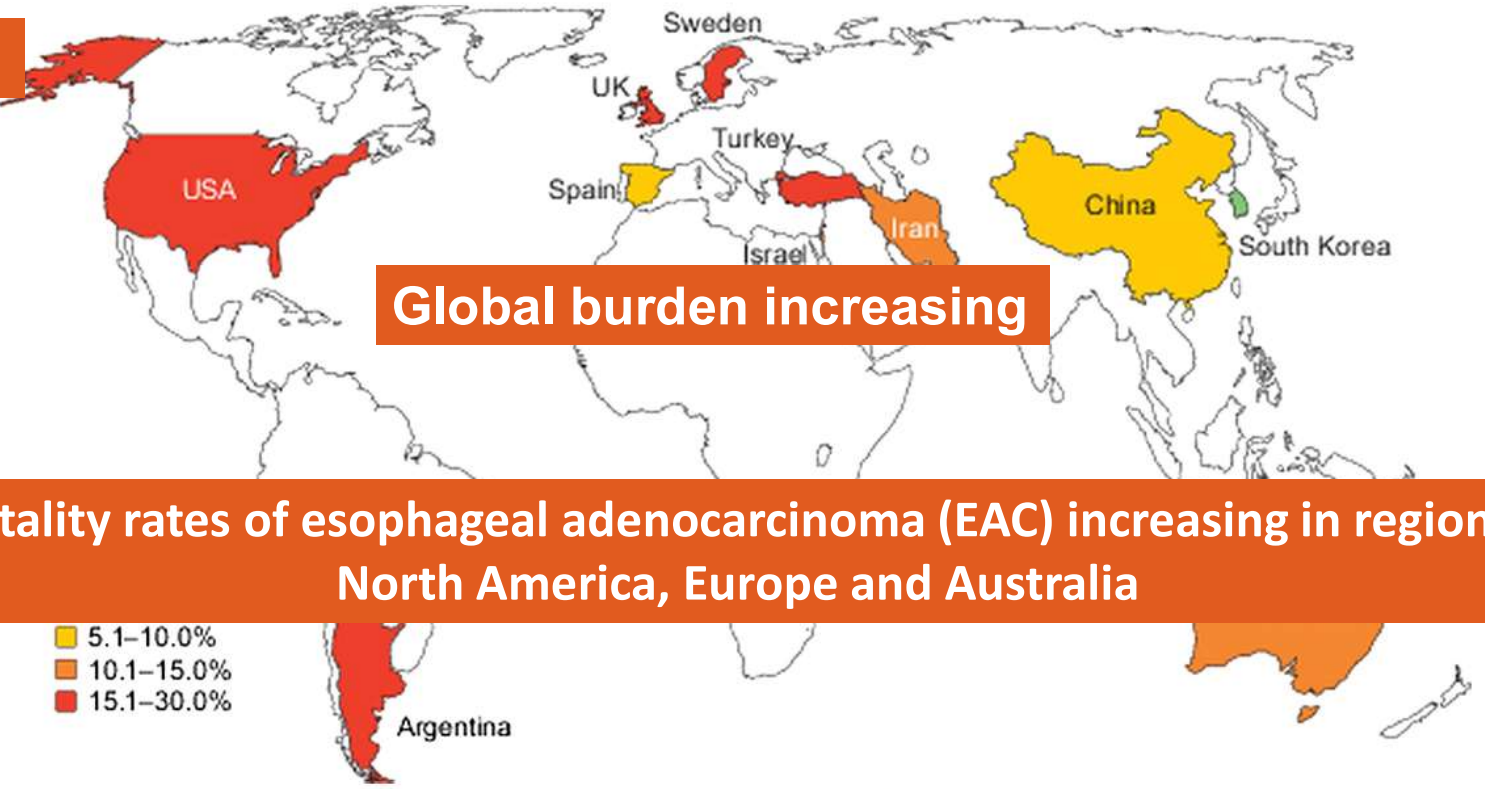
Risk factors



Family history of BE/EAC: 23%

Trends



Global burden increasing

Mortality rates of esophageal adenocarcinoma (EAC) increasing in regions of North America, Europe and Australia

Figure 2 Global distribution of the burden of gastro-oesophageal reflux disease. Sample-size weighted mean estimates of the prevalence of at least weekly heartburn and/or regurgitation in each country.

El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63: 871–80

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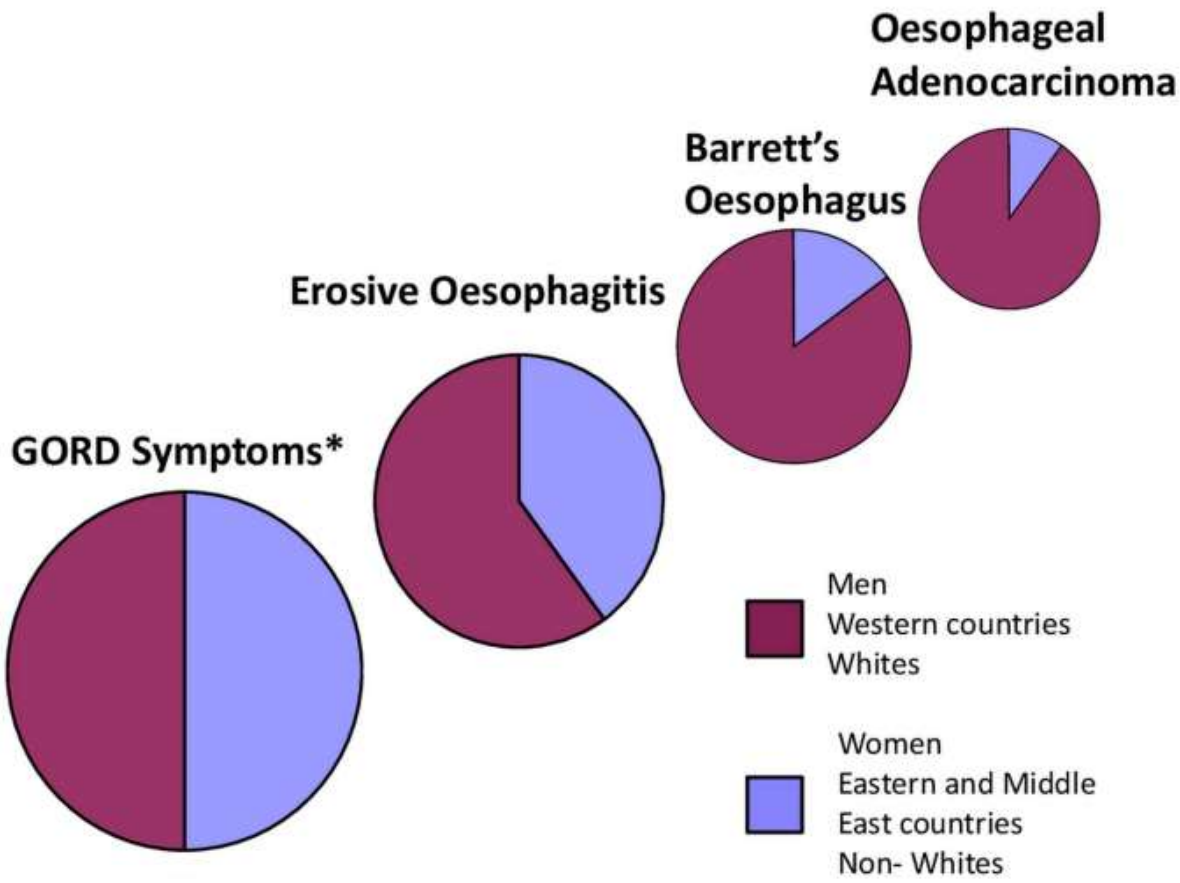
Trends



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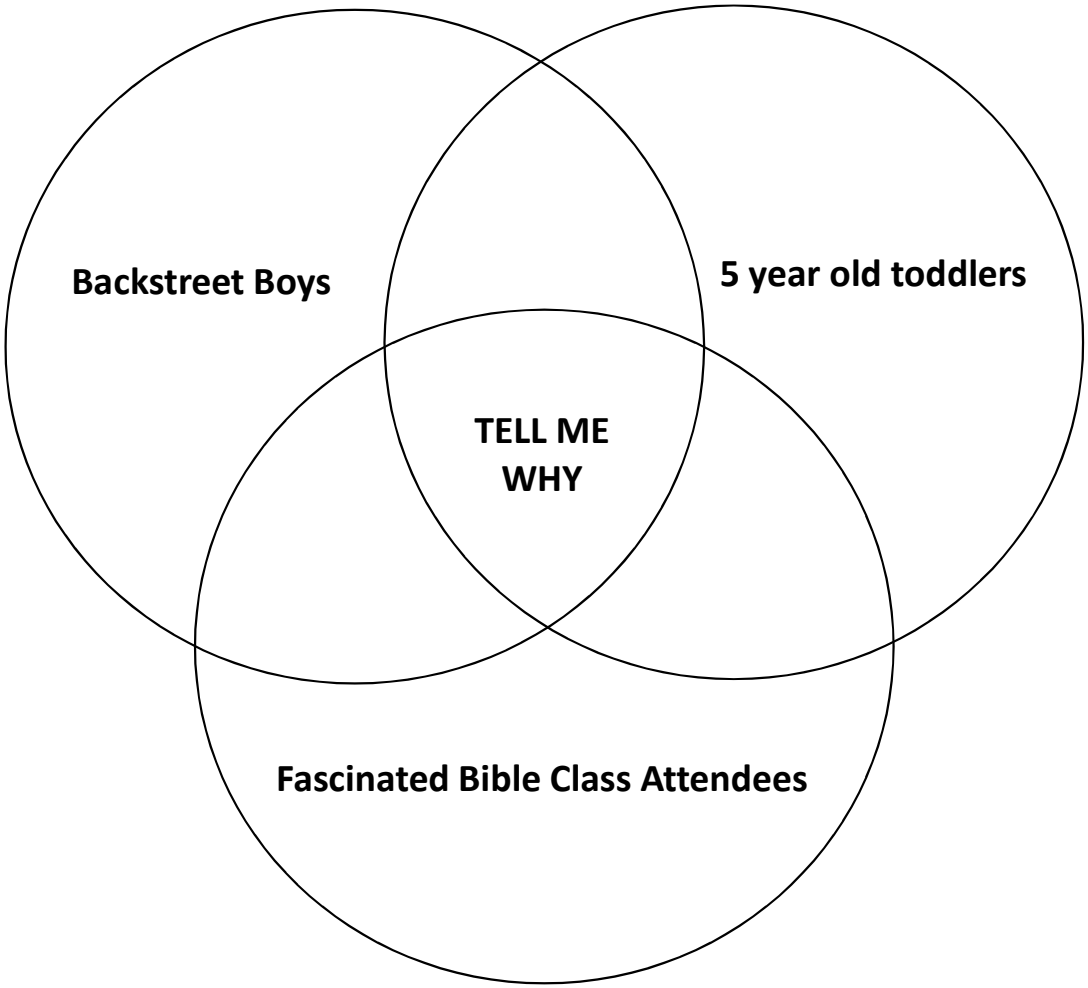
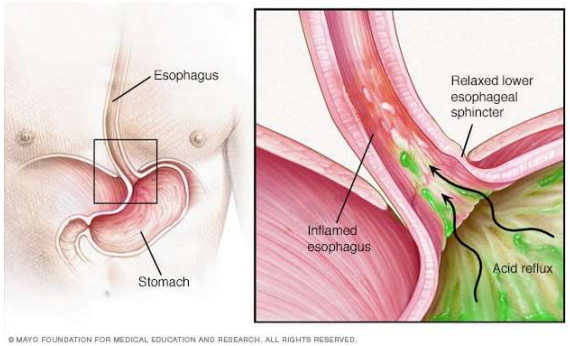
Trends



The (short) story behind the trends

Screening

Screening?



+ ≥ 3 of

Risk prediction scores: as of 2024 unconvincing evidence

Alternative to screening by endoscopy? For whom?

Table 4. Summary of performance characteristics of minimally invasive nonendoscopic swallowable cell collection devices combined with biomarkers for the nonendoscopic detection of BE

Device Biomarker used Country of origin	Design Sample size	Sensitivity (%)	Specificity (%)
30-mm capsule sponge (Cytosponge) (226) TFF3 United Kingdom	Case-control Cases: 647 Controls: 463	80[a]	92
30-mm capsule sponge (Medtronic) (227) TFF3 United States	Case-control Cases: 129 Controls: 62	76	77
25-mm capsule sponge (EsophaCap) (228) MDMs United States	Case-control Cases: 112 Controls: 89	92	94
25-mm capsule sponge (EsophaCap) (229) MDMs United States	Case-control Training set: cases 110, controls 89 Test set: cases 60, controls 29	93	93
18-mm swallowable and inflatable balloon (EsoChek) (230) MDMs United States	Case-control Cases: 50 Controls: 36	92	88
20-mm capsule sponge (EsophaCap) (231) MDMs United States	Case-control Training set: cases 18, controls 34 Test set: cases 14, controls 14	94	62

Figure 3. N ted and expanded Cytosponge device. (**b** and **c**) Encapsulated and expanded Es

Diagnosis

A diagnosis of Barrett requires (y/n)

- An endoscopy demonstrating Barrett's Esophagus >1cm, regardless of biopsies
- Biopsies from the Esophagus demonstrating specialized IM
- GERD symptoms and/or a positive pH Metry
- An endoscopy demonstrating Barretts' Esophagus (any length)

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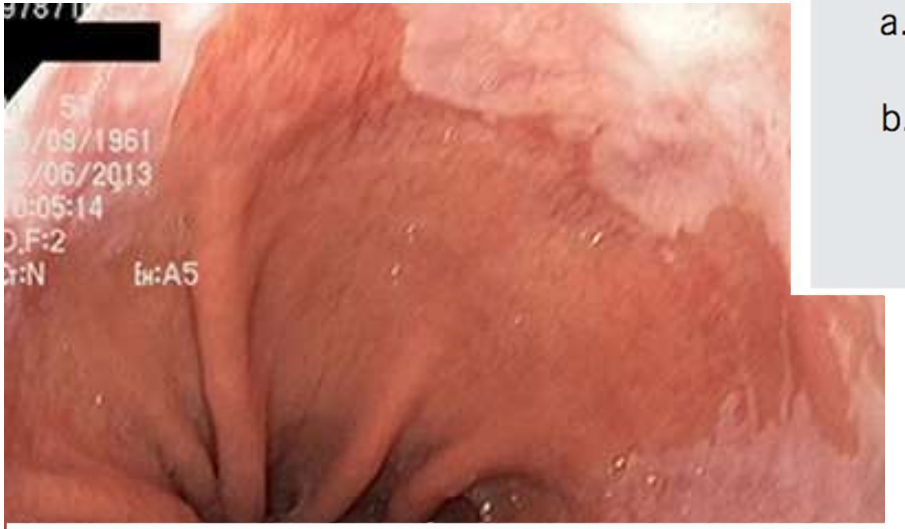
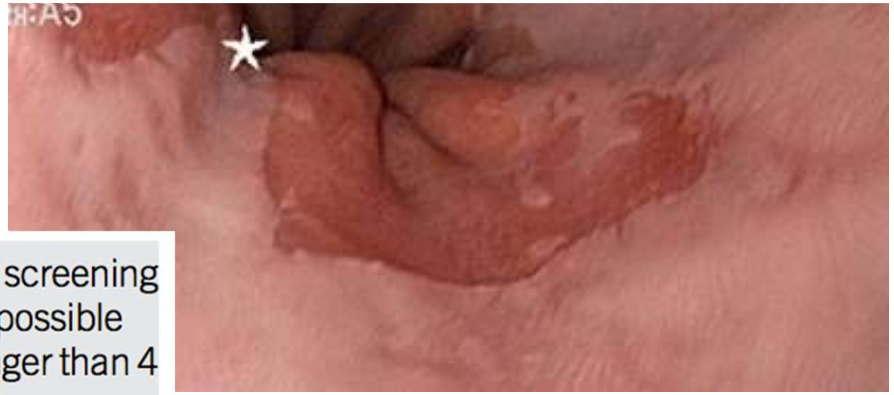
Prague classification?
Bx (how many? Spec

2. We suggest that columnar mucosa of at least 1 cm in length be necessary for a diagnosis of BE, and that:

   a. Patients with a normal-appearing Z line should not undergo routine endoscopic biopsies.

   b. In the absence of any visible lesions, patients with a Z line demonstrating <1 cm of proximal displacement from the top of the gastric folds should not undergo routine endoscopic biopsies (quality of evidence: low; strength of recommendation: conditional).

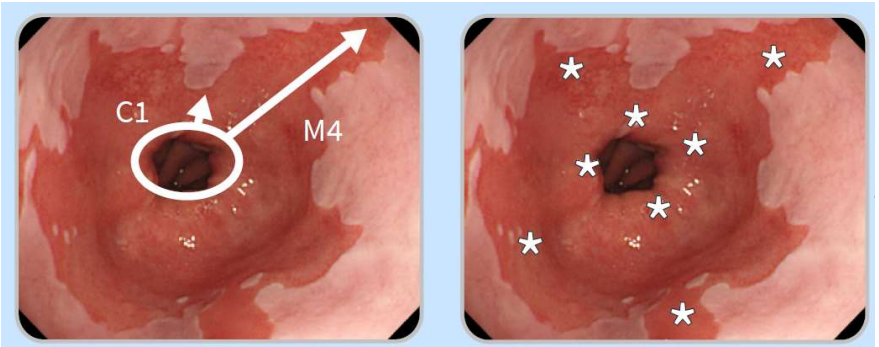




3. We suggest at least 8 endoscopic biopsies be obtained in screening examinations with endoscopic findings consistent with possible BE, with the Seattle protocol followed for segments of longer than 4 cm (quality of evidence: low; strength of recommendation: conditional).

Endoscopy

- Use the best scope you have
- Chromoendoscopy (AA, NBI)
- Seattle protocol (4 Bx at =< 2cm intervals, if prior dysplasia q1cm)
- https://best-academia.eu/



Prague-classification

Seattle protocol 4Q/2 cm

Table 1 Different definitions of Barrett's oesophagus

Society	Length of CE	Intestinal metaplasia	GOJ
AGA	Any length	Required	PEGF
BSG	≥1 cm	Not required	PEGF
JES	Any length	Not required	DEPV
APAGE	≥1 cm	Not required	PEGF
ACG	≥1 cm	Required	PEGF
ESGE	≥1 cm	Required	PEGF

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; APAGE, Asian Pacific Association of Gastroenterology; BSG, British Society of Gastroenterology; CE, Columnar epithelium; DEPV, distal end of palisade vessels; ESGE, European Society of Gastrointestinal Endoscopy.; GOJ, Gastrooesophageal Junction; JES, Japan Esophageal Society; PEGF, proximal end of gastric folds.

Diagnosis

- Barrett's oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies (Recommendation grade C).
- The proximal limit of the longitudinal gastric folds with minimal air insufflation is the easiest landmark to delineate the GOJ and is the suggested minimum requirement (Recommendation grade B).

BSG 2013

Sugano K, *et al*. *Gut* 2022;**71**:1488–1514. doi:10.1136/gutjnl-2022-327281

Why all the fuss about the irregular Z Line, BO and IM?

- >8 Bx required to demonstrate IM
- Poor reproducibility in the finding of IM between two endoscopic examinations performed only 6W apart
- Many with IM => no IM in a follow-up procedure
- Many with no IM => IM in a follow-up procedure
- Columnar epithelium without IM can have genetic alterations that might predispose to cancer development.
- Several reports suggest EAC can develop in columnar epithelium without IM

Kim SL, Waring JP, Spechler SJ, *et al*. Diagnostic inconsistencies in Barrett's esophagus. *Gastroenterology* 1994;107:945–9.

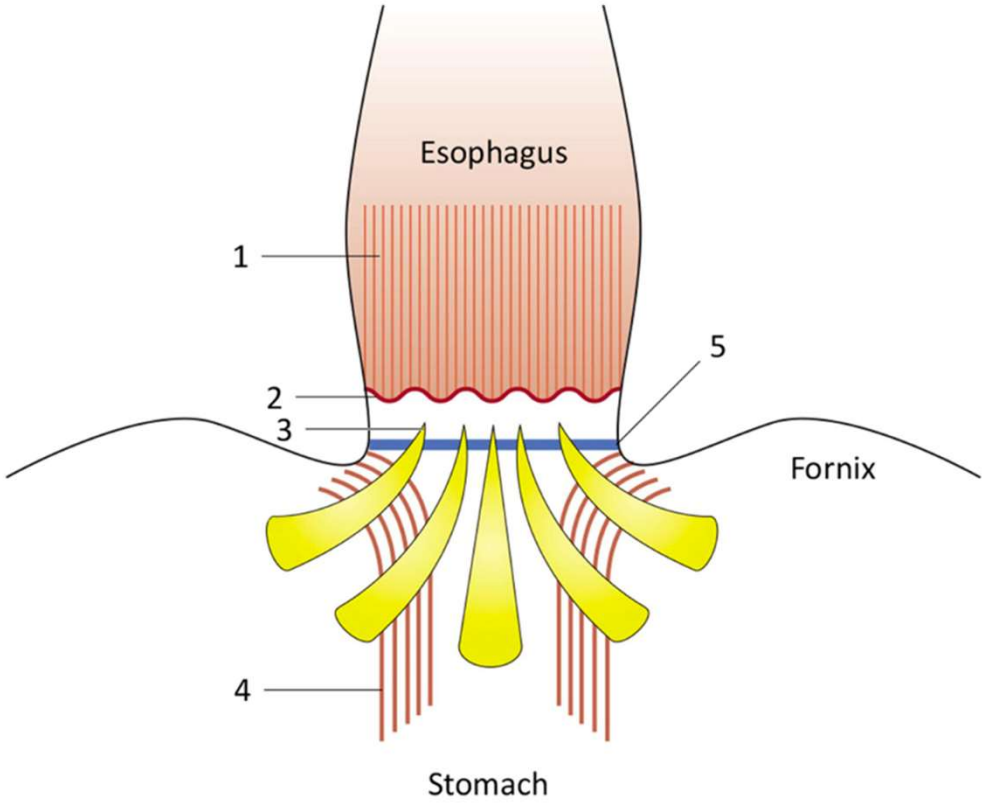
Kyoto international consensus report on anatomy, pathophysiology and clinical significance of the gastro-oesophageal junction

Kentaro Sugano [1], Stuart Jon Spechler [2], Emad M El-Omar [3], Kenneth E L McColl,[4] Kaiyo Takubo,[5] Takuji Gotoda [6], Mitsuhiro Fujishiro,[7] Katsunori Iijima,[8] Haruhiro Inoue,[9] Takashi Kawai,[10] Yoshikazu Kinoshita,[11] Hiroto Miwa,[12] Ken-ichi Mukaisho,[13] Kazunari Murakami,[14] Yasuyuki Seto,[15] Hisao Tajiri,[16] Shobna Bhatia,[17] Myung-Gyu Choi,[18] Rebecca C Fitzgerald,[19] Kwong Ming Fock,[20] Khean-Lee Goh,[21] Khek Yu Ho [22], Varocha Mahachai,[23] Maria O'Donovan,[24] Robert Odze,[25] Richard Peek,[26] Massimo Rugge [27], Prateek Sharma,[28] Jose D Sollano,[29] Michael Vieth,[30] Justin Wu,[31] Ming-Shiang Wu [32], Duowu Zou,[33] Michio Kaminishi,[34] Peter Malfertheiner [35,36]

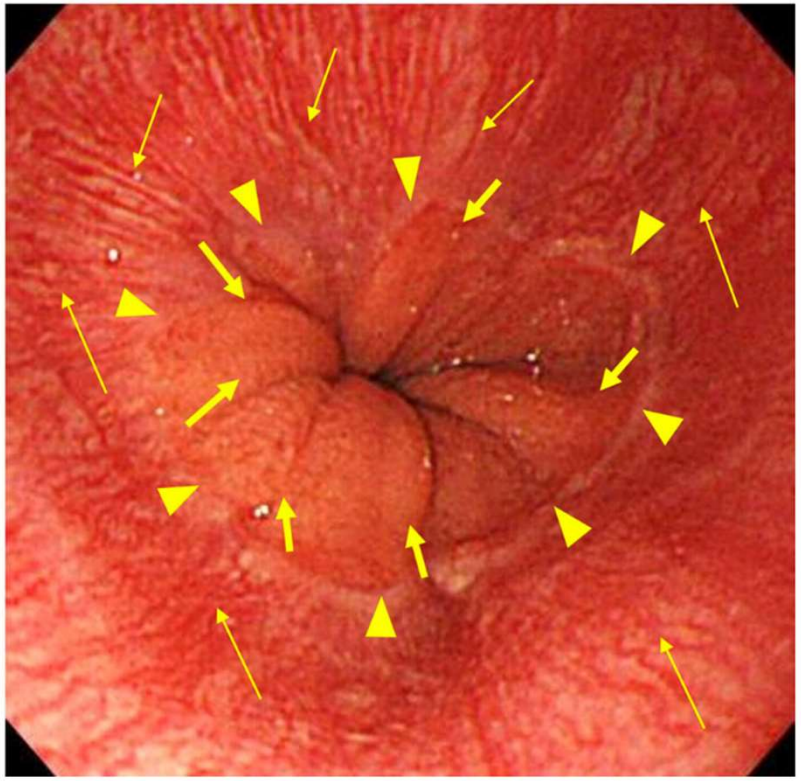
- In this consensus conference, the new definition of BO was created in which both length limitation and the presence of IM were lifted from the definition of BO.

Sugano K, *et al*. *Gut* 2022;**71**:1488–1514. doi:10.1136/gutjnl-2022-327281

A



B



Sugano K, *et al*. *Gut* 2022;**71**:1488–1514. doi:10.1136/gutjnl-2022-327281

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Diagnosis: C0M1 NDBE. What now? Fill the blanks

Table 5. Recommended endoscopic surveillance intervals based on degree of dysplasia and segment length

Baseline endoscopic finding	Suggested endoscopic surveillance
Nondysplastic BE of <3 cm length	EGD every 5 yr
Nondysplastic BE of ≥3 cm length	EGD every 3 yr
BE indefinite for dysplasia, any length (confirmed by a second pathologist)	Repeat EGD within 6 mo after increasing PPI to twice-daily dosing, if not already on high-dose PPI If repeat EGD yields diagnosis of NDBE or LGD, treat using that algorithm If repeat EGD demonstrates BE indefinite for dysplasia, EGD annually
BE with LGD (confirmed by a second pathologist and opting for endoscopic surveillance)	EGD at 6 mo from diagnosis EGD 12 mo from diagnosis EGD annually thereafter

BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy; LGD, low-grade dysplasia; NDBE, nondysplastic BE; PPI, proton pump inhibitor.

HGD

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Surveillance

- What is the goal of surveillance?

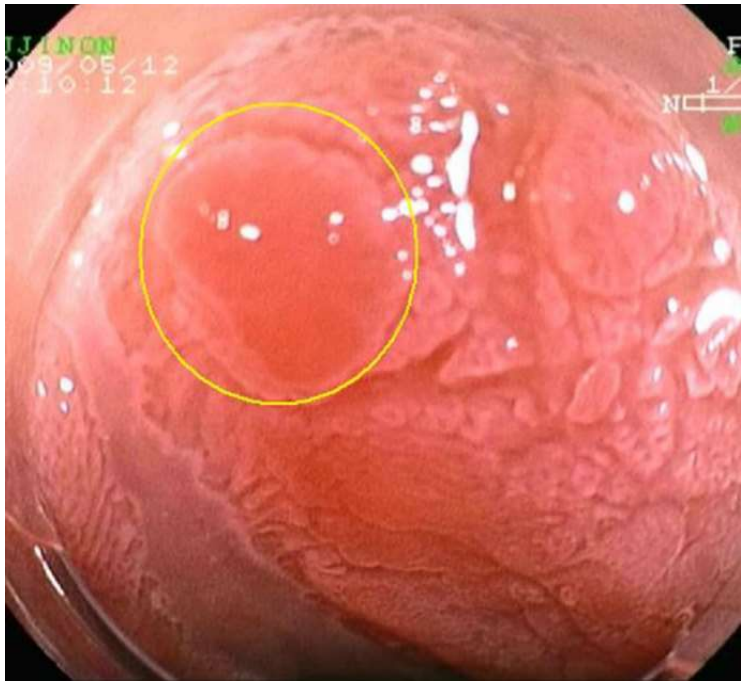
The detection of dysplasia or carcinoma at an early, treatable stage

Endoscopy

- Best Endoscope you have
- Clean the esophagus before assessment
- Document according to Prague Classification
- Document Lesions according to the Paris classification
- Retroflex!

Acetic acid

- Absorbable
- Reversible acetylation of nucleus proteins leading to vascular congestion => better differenciation of vascular structures
- Dysplastic tissue loses whitening earlier



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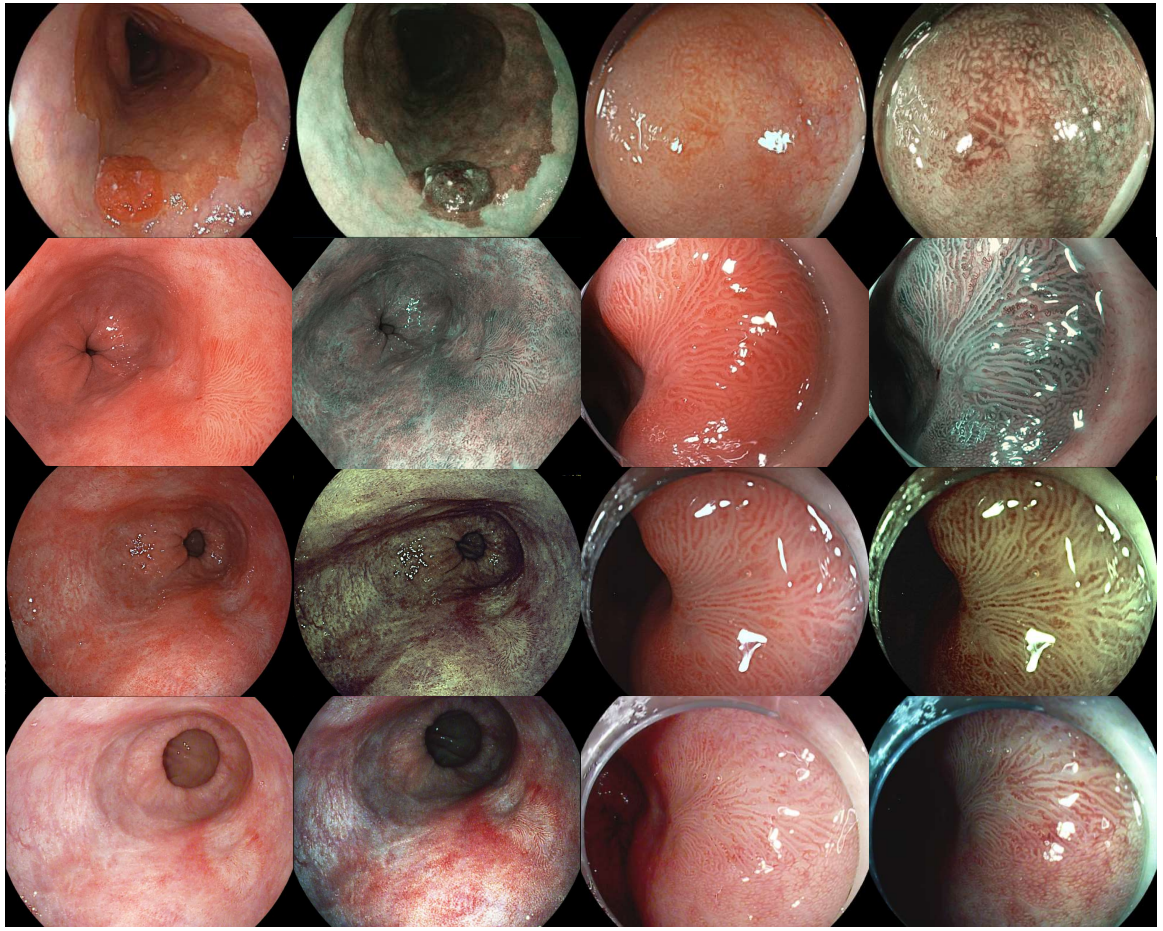
Endoscopy: appearance

BLI

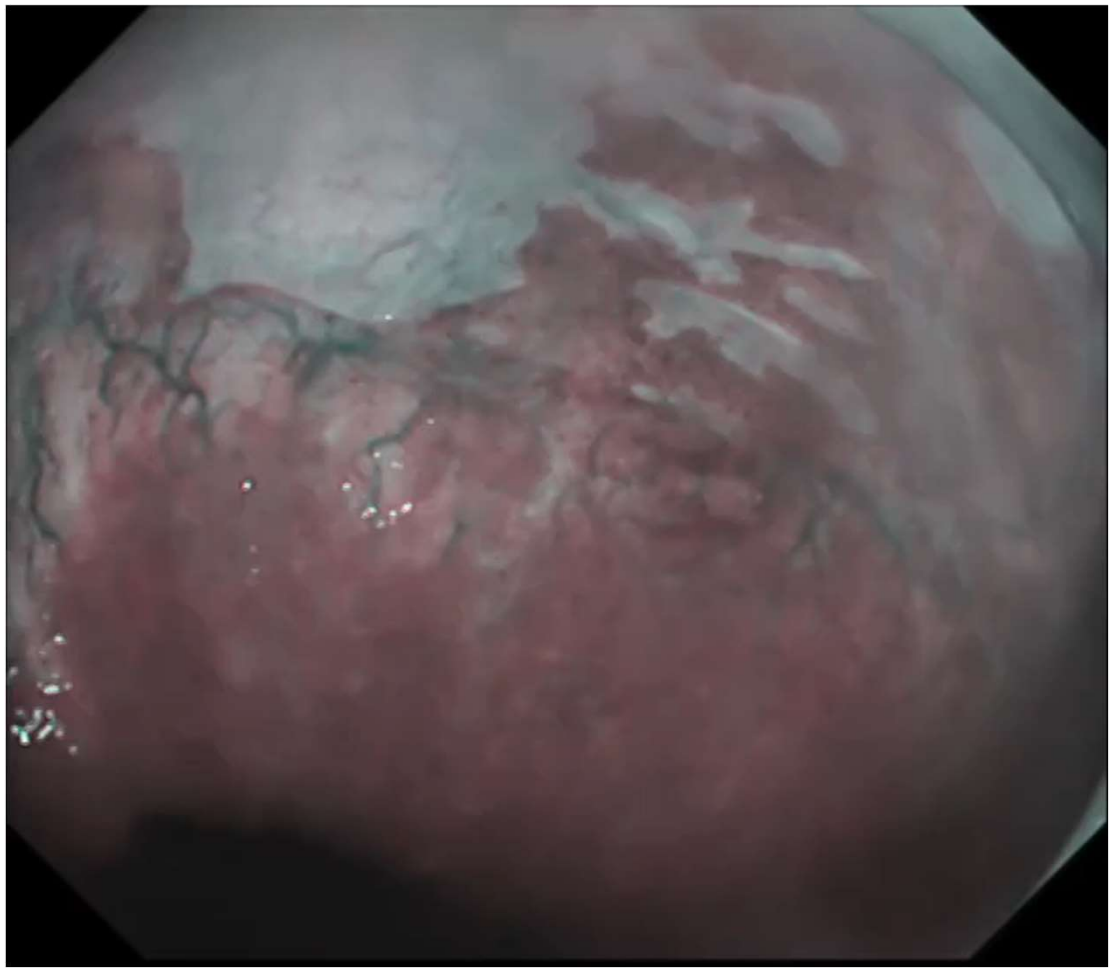
NBI

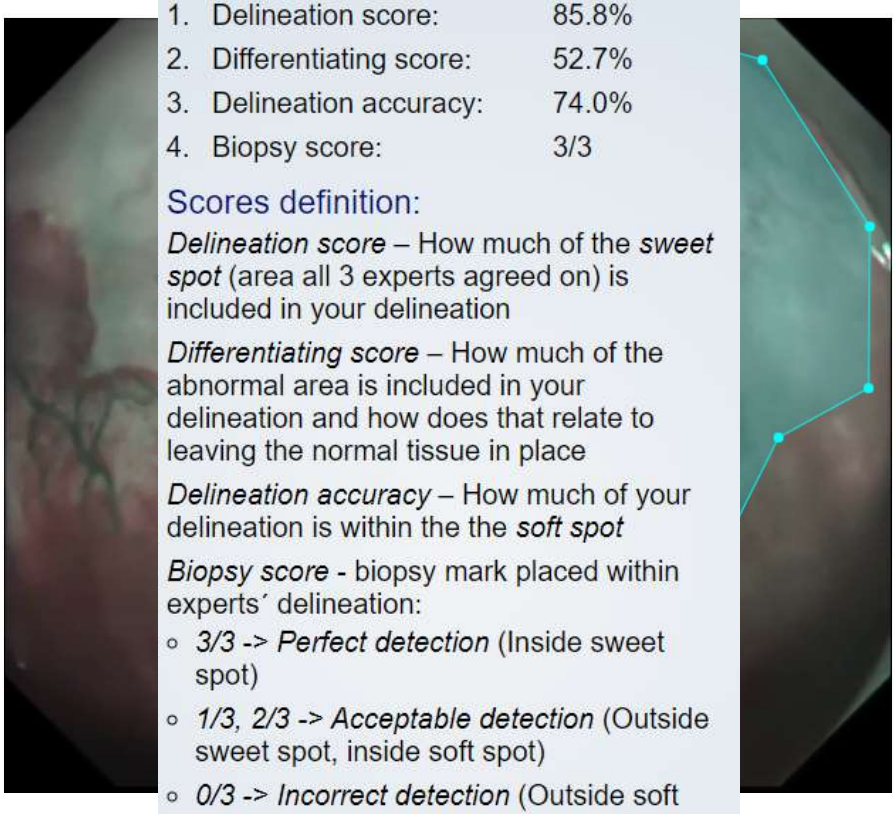
FICE

I-scan



BEST ACADEMIA





Your results:

1. Delineation score: 85.8%
2. Differentiating score: 52.7%
3. Delineation accuracy: 74.0%
4. Biopsy score: 3/3

Scores definition:

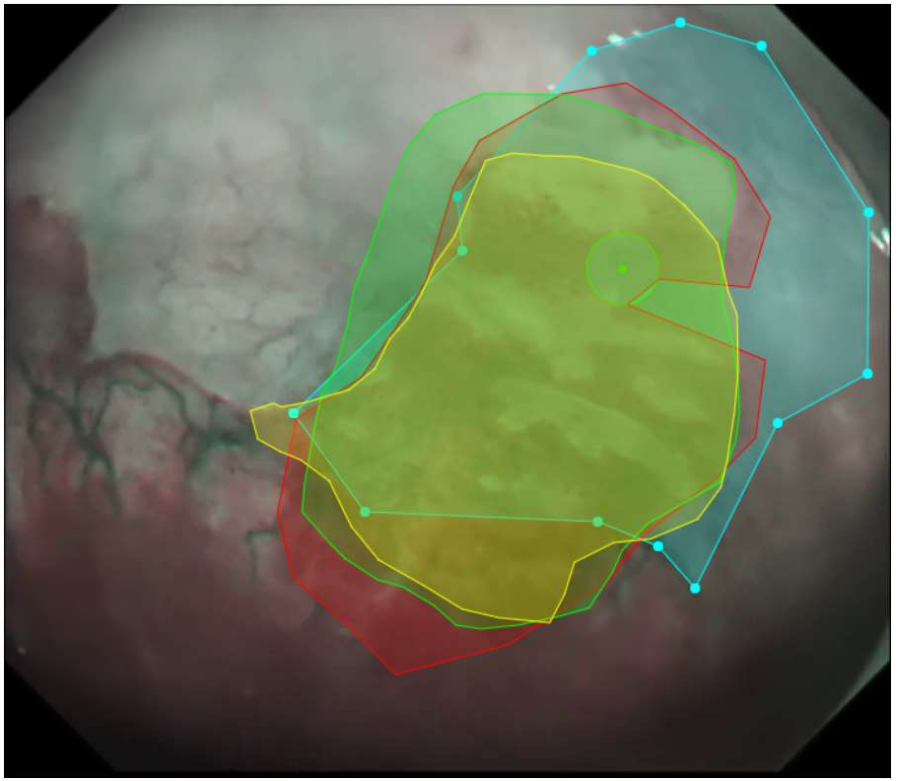
Delineation score – How much of the *sweet spot* (area all 3 experts agreed on) is included in your delineation

Differentiating score – How much of the abnormal area is included in your delineation and how does that relate to leaving the normal tissue in place

Delineation accuracy – How much of your delineation is within the the *soft spot*

Biopsy score - biopsy mark placed within experts´ delineation:

- *3/3 -> Perfect detection* (Inside sweet spot)
- *1/3, 2/3 -> Acceptable detection* (Outside sweet spot, inside soft spot)
- *0/3 -> Incorrect detection* (Outside soft spot)

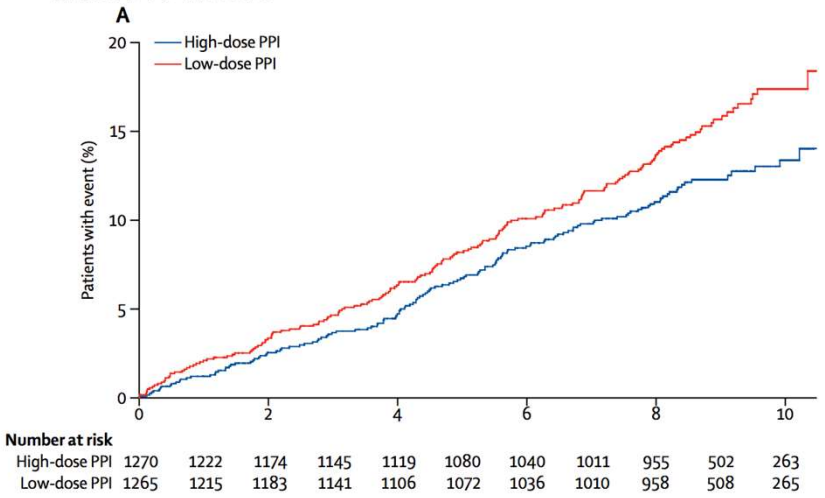


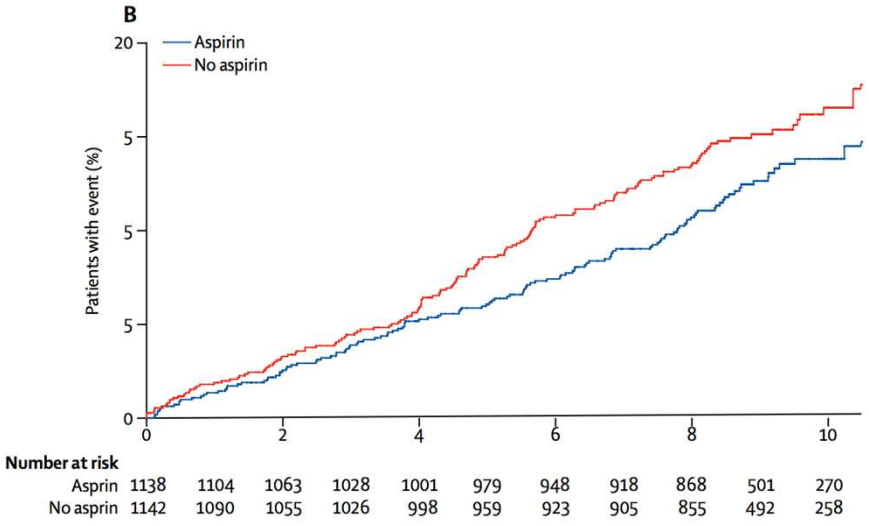
Non-endoscopic treamtent

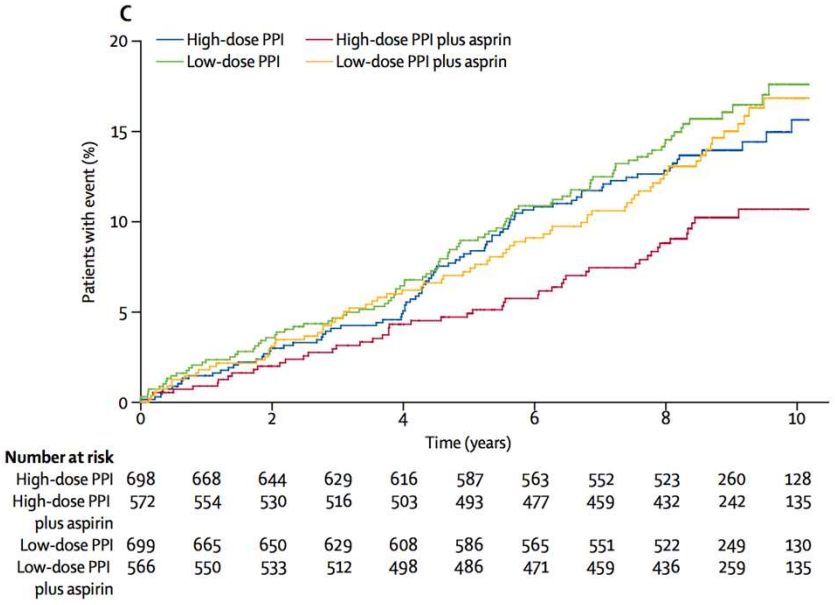
- PPI
- ASA + PPI in patients with BE to reduce the risk of progression to HGD/EAC?
- Surgery: not as an antineoplastic measure

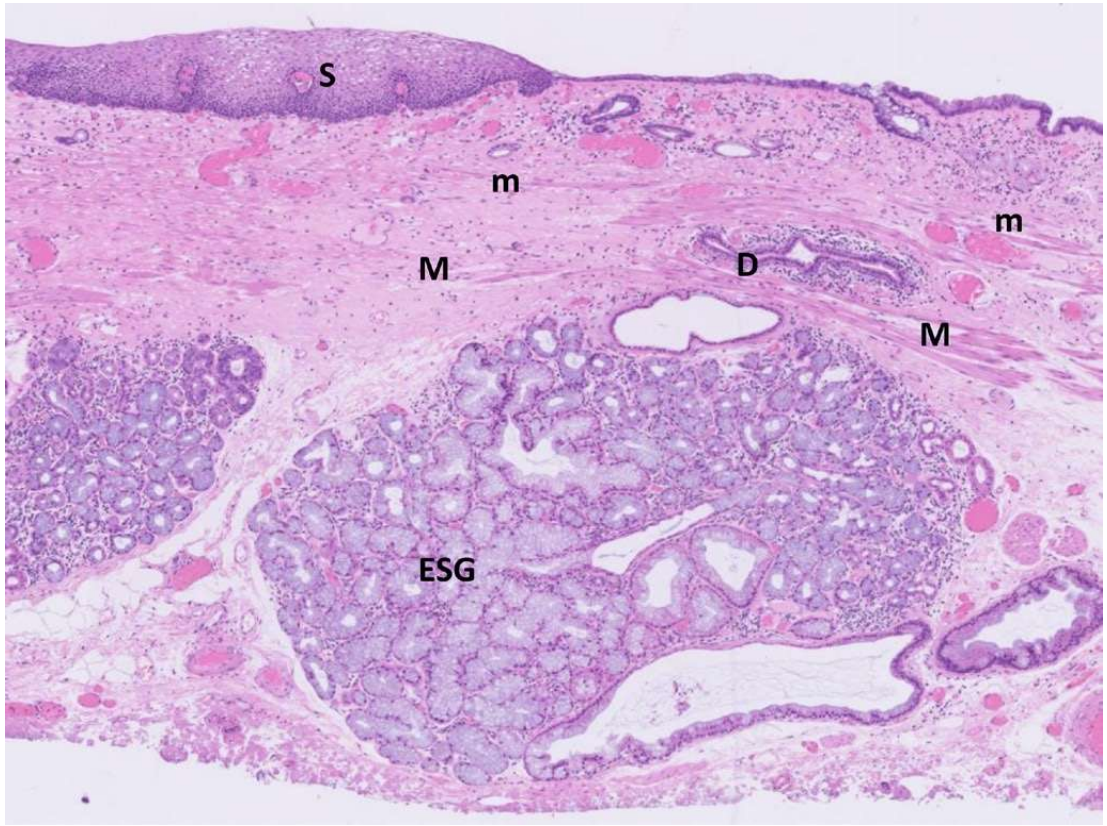
Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Stephen Attwood, Krish Ragunath, Bashir Rameh, Grant Fullarton, Art Tucker, Ian Penman, Colin Rodgers, James Neale, Claire Brooks, Adelyn Wise, Stephen Jones, Nicholas Church, Michael Gibbons, David Johnston, Kishor Vaidya, Mark Anderson, Sherzad Balata, Gareth Davies, William Dickey, Andrew Goddard, Cathryn Edwards, Stephen Gore, Chris Haigh, Timothy Harding, Peter Isaacs, Lucina Jackson, Thomas Lee, Peik Loon Lim, Christopher Macdonald, Philip Mairs, James McLoughlin, David Monk, Andrew Murdock, Iain Murray, Sean Preston, Stirling Pugh, Howard Smart, Ashraf Soliman, John Todd, Graham Turner, Joy Worthingon, Rebecca Harrison, Hugh Barr, Paul Moayyedi



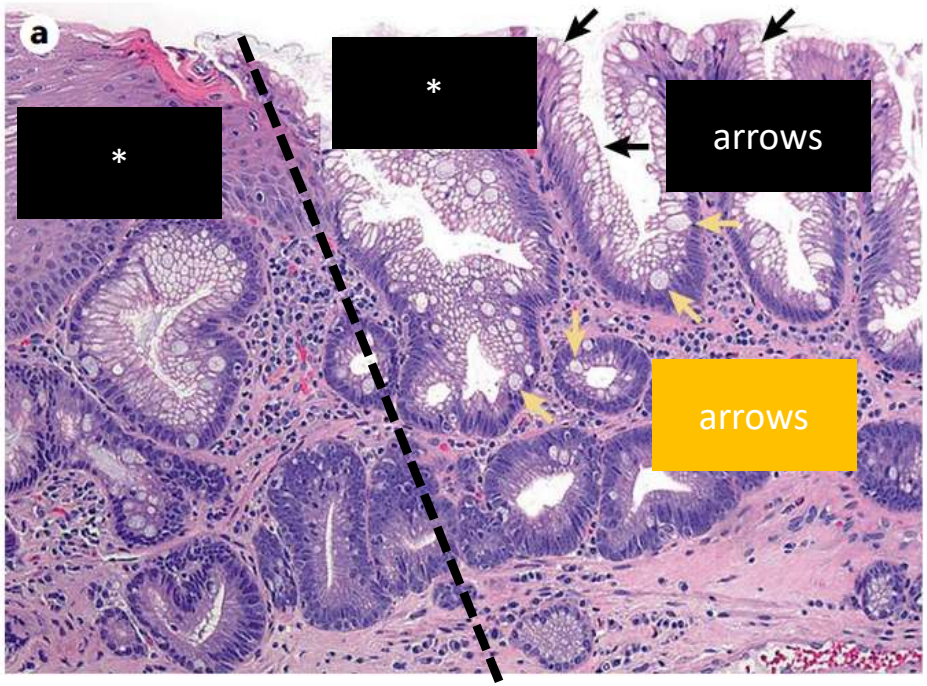






Sugano K, *et al*. *Gut* 2022;**71**:1488–1514. doi:10.1136/gutjnl-2022-32728

Definition - SIM



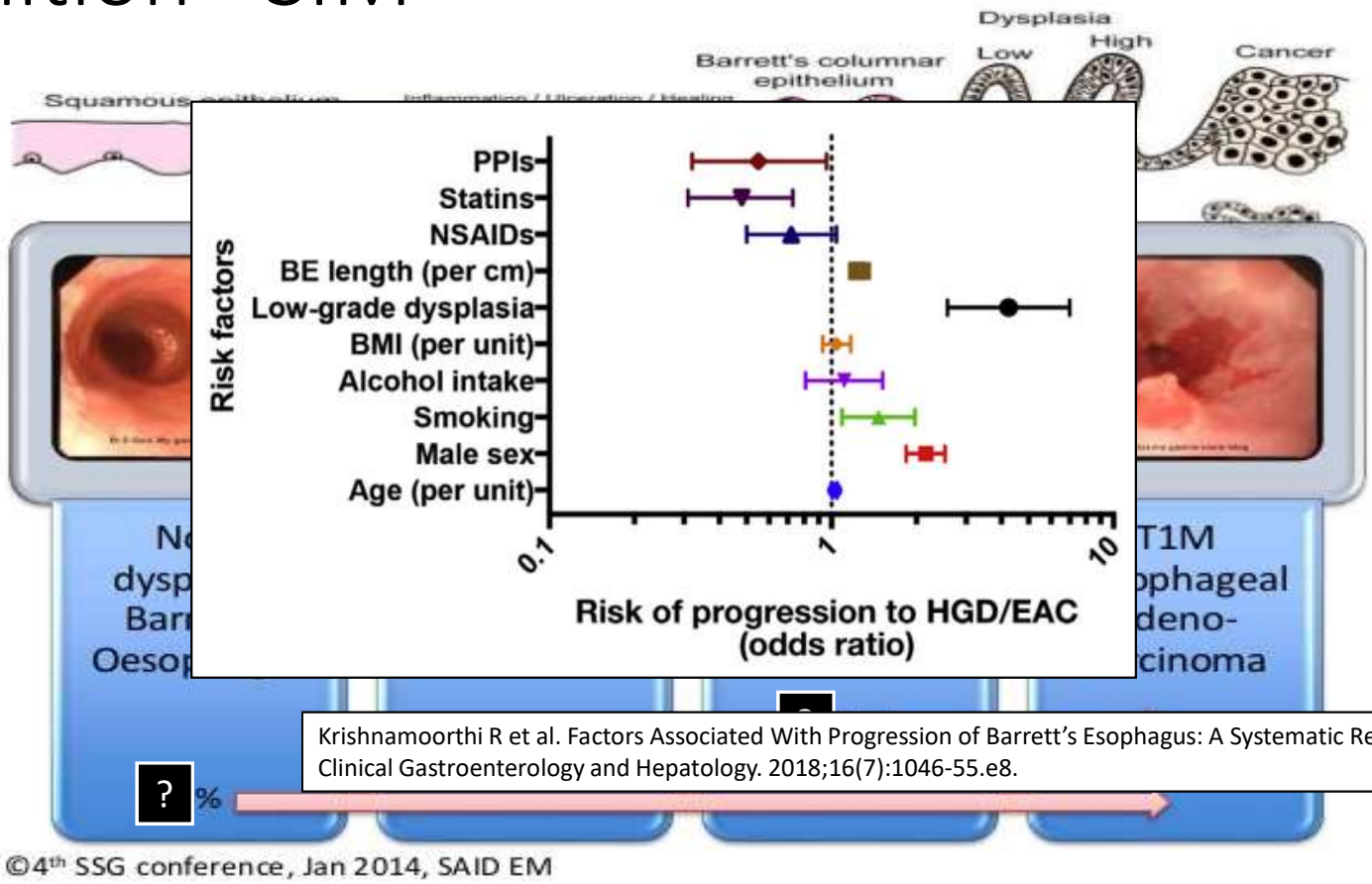
Intestinal-type goblet cells

Mucus-secreting columnar cells

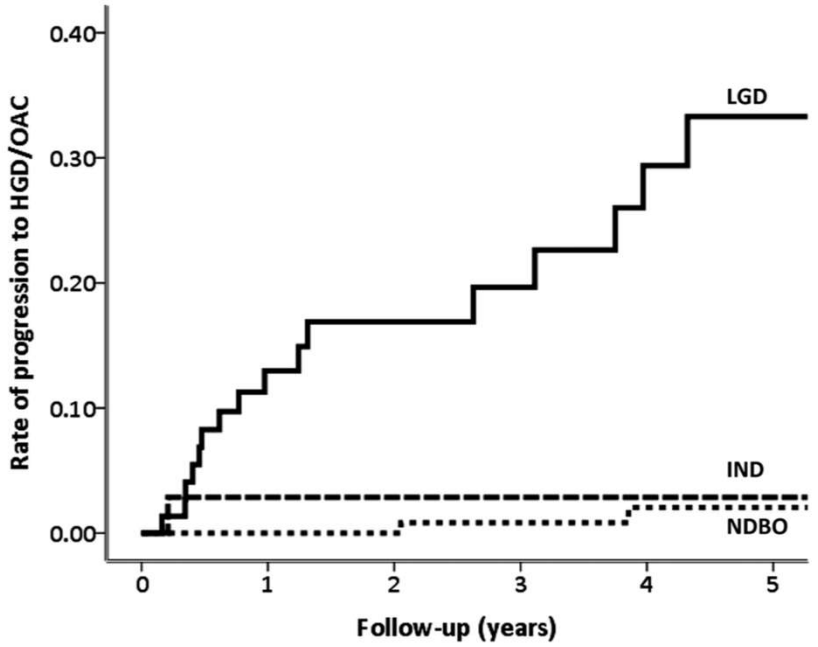
Squamous epithelium

Specialized intestinal metaplasia

Definition - SIM



Krishnamoorthi R et al. Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology. 2018;16(7):1046-55.e8.

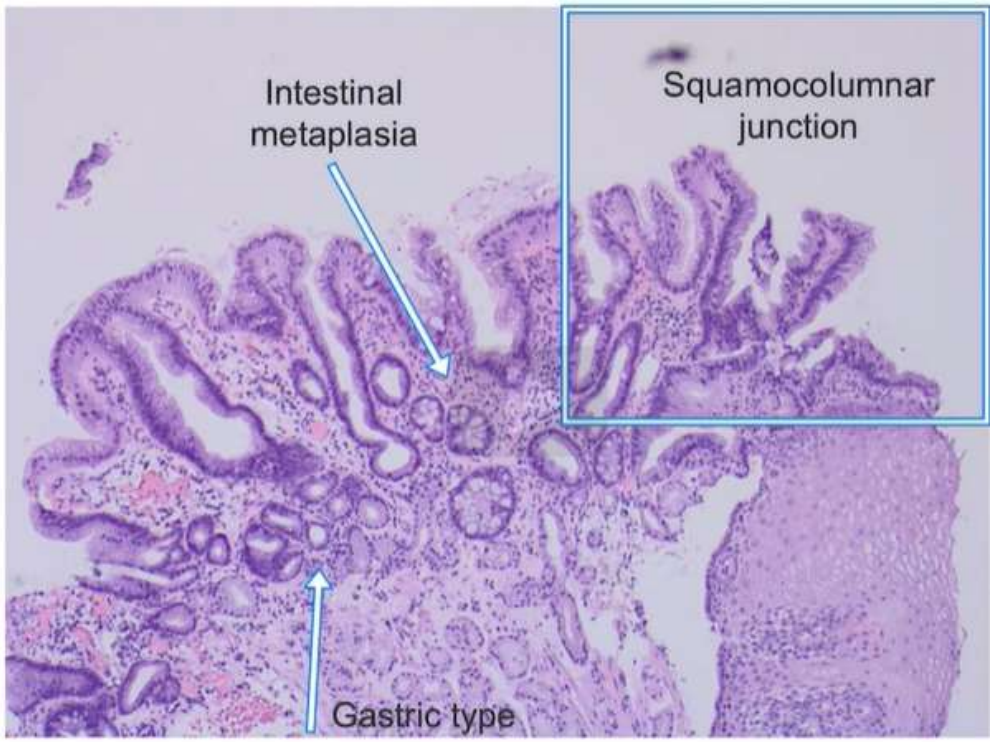


Number at risk at time (years)	1	2	3	4	5
LGD	49	33	27	21	16
IND	30	19	16	12	9
NDBO	137	125	104	75	59

Duits LC, et al. Gut 2014;0:1–7. doi:10.1136/gutjnl-2014-307278

NDBE

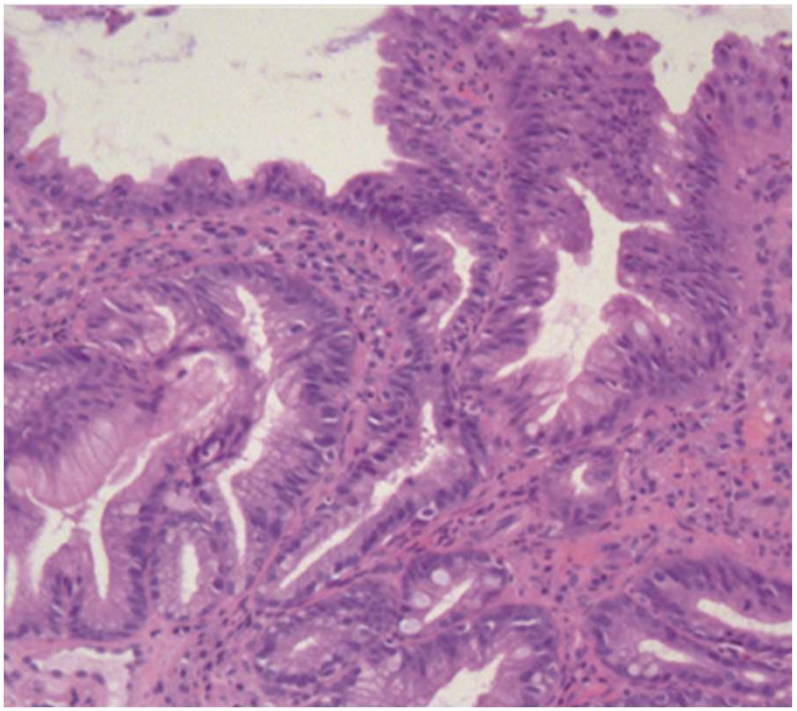
- Goblet cells
- Surface maturation
- Regular architecture
- Normal sized nuclei
- No mitotic figures



Source: ueg.eu

LGD

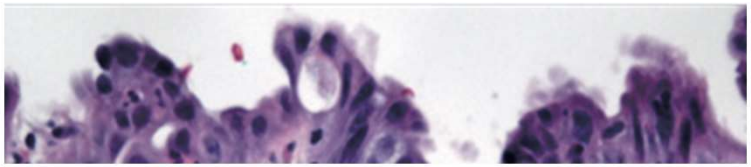
- Maintained architecture
- Elongated nuclei
- Nuclear stratification
- Abrupt morphologc changes
- p53: improves inerobserver variability



Source: ueg.eu

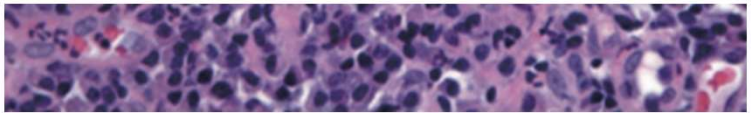
HGD

- Loss of epithelial maturation

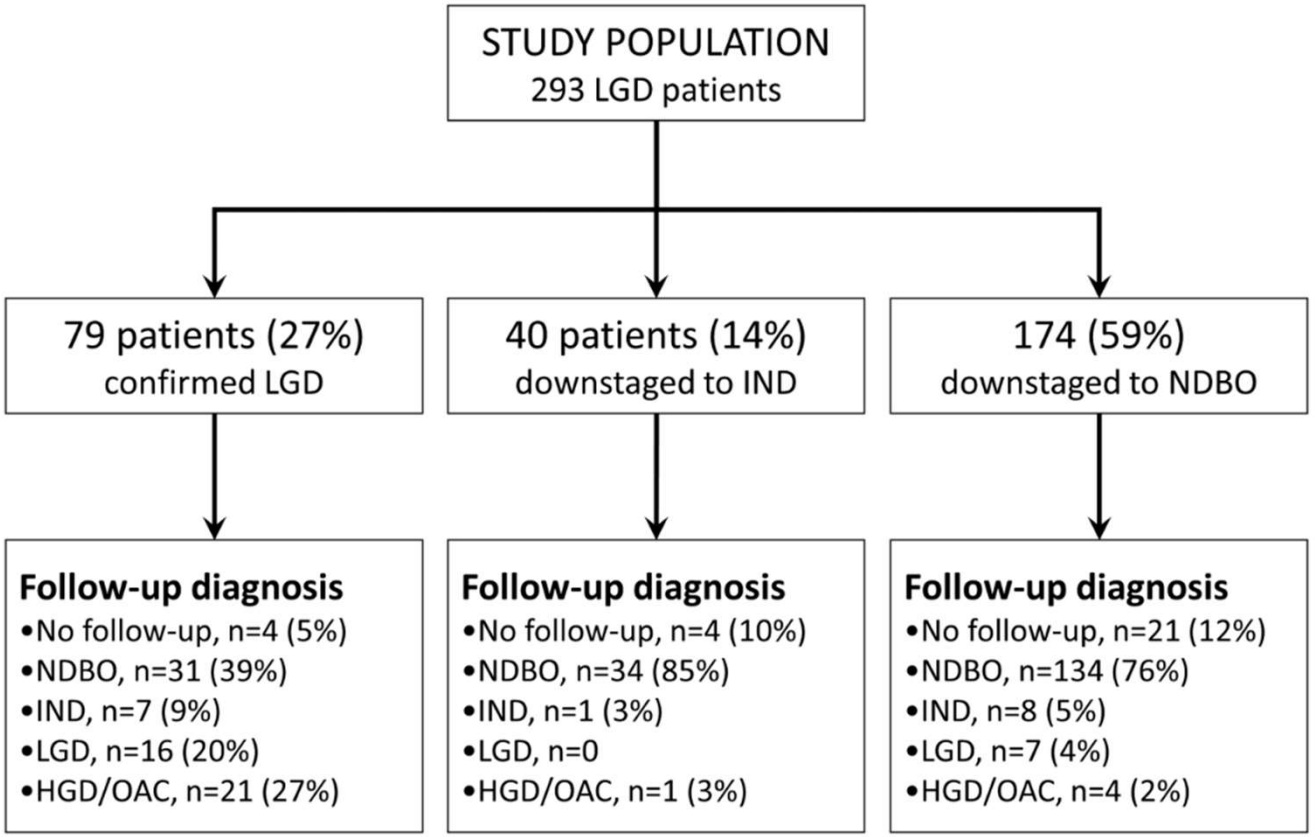


4. We recommend that dysplasia of any grade detected on biopsies of BE be confirmed by a second pathologist with expertise in gastrointestinal (GI) pathology (quality of evidence: low; strength of recommendation: strong).

nuclei



Source: ueg.eu



Duits LC, et al. Gut 2014;0:1–7. doi:10.1136/gutjnl-2014-307278

Endoscopic treatment

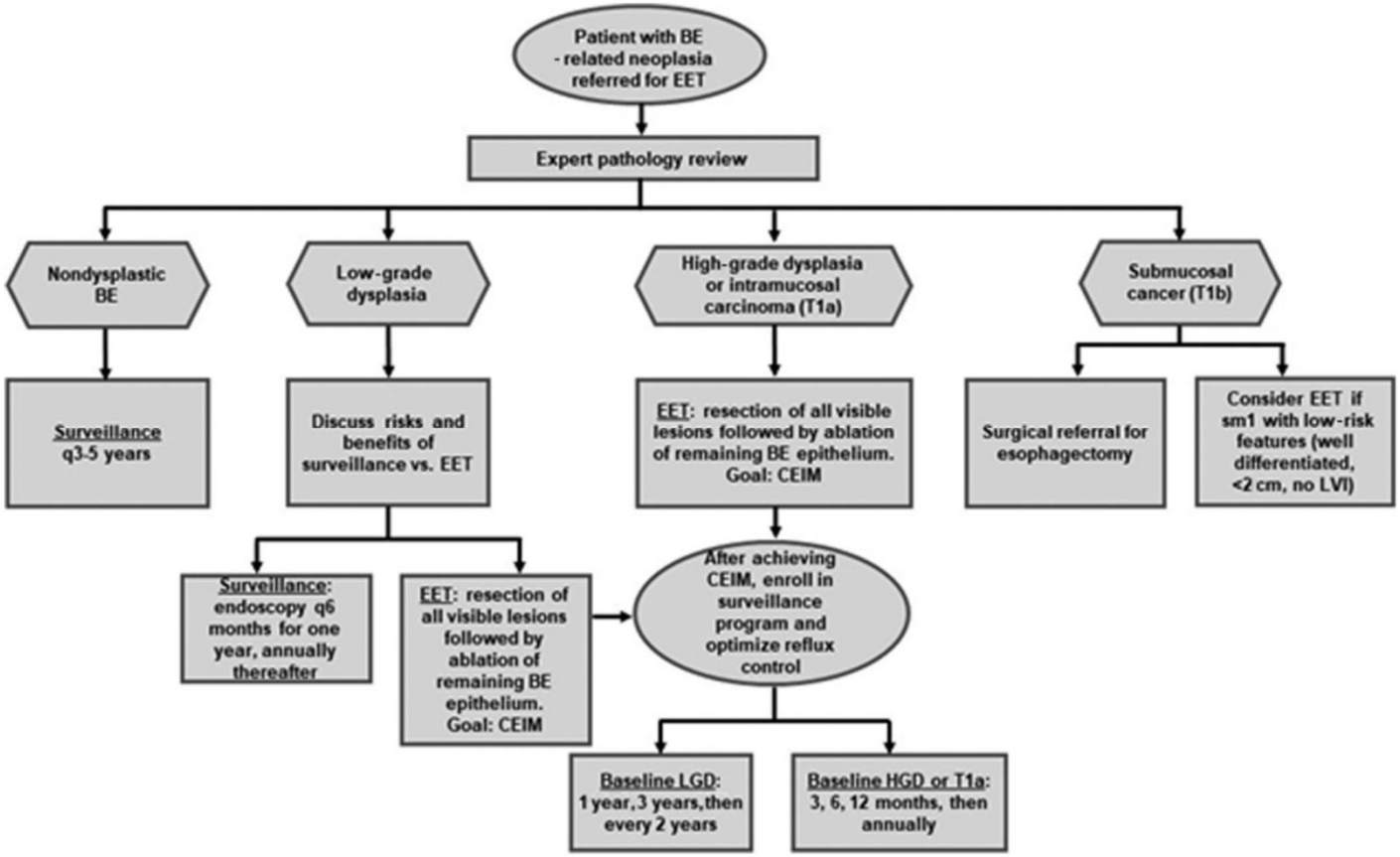
18. We suggest endoscopic therapy in patients with BE with confirmed LGD to reduce the risk of progression to HGD/EAC, with endoscopic surveillance of confirmed LGD as an acceptable alternative (strength of recommendation: conditional; quality of evidence: moderate).

Patients with LGD should have a repeat endoscopy in 6 months time. If LGD is found in any of the follow up OGDs and is confirmed by an expert GI pathologist, the patient should be offered endoscopic ablation therapy after review by the specialist MDT. If ablation is not undertaken, 6-montly surveillance is recommended *(Recommendation grade A for endoscopic therapy and C for surveillance)*. (A+ 56%, A 33%, D 11%)

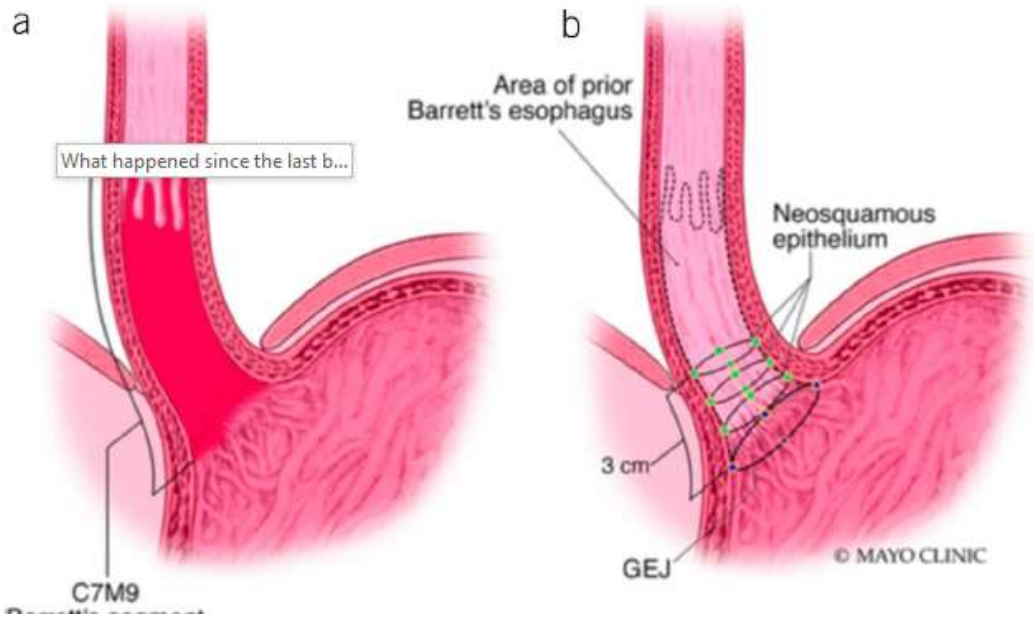
BSG 2015 Addendum to 2013 Guidelines

Key concepts

- In HGD, remove all visible lesions
- Consider cessation of surveillance


Patient with BE - related neoplasia referred for EET
Expert pathology review
Nondysplastic BE
Low-grade dysplasia
High-grade dysplasia or intramucosal carcinoma (T1a)
Submucosal cancer (T1b)
Surveillance q3-5 years
Discuss risks and benefits of surveillance vs. EET
EET: resection of all visible lesions followed by ablation of remaining BE epithelium. Goal: CEIM
Surgical referral for esophagectomy
Consider EET if sm1 with low-risk features (well differentiated, <2 cm, no LVI)
Surveillance: endoscopy q6 months for one year, annually thereafter
EET: resection of all visible lesions followed by ablation of remaining BE epithelium. Goal: CEIM
After achieving CEIM, enroll in surveillance program and optimize reflux control
Baseline LGD: 1 year, 3 years, then every 2 years
Baseline HGD or T1a: 3, 6, 12 months, then annually

After EET


a
What happened since the last b...
C7M9
b
Area of prior
Barrett's esophagus
Neosquamous
epithelium
3 cm
GEJ
© MAYO CLINIC

Useful practical resources

- Narrow Band Imaging (NBI) - Olympus Professional Education On-Demand Library (olympusprofed.com)
  - https://www.olympusprofed.com/gi/nbi/
  - Lots of other modules! (EUS, Colo, …)

- NBI Online Training for Barrett´s Esophagus (mediamotor.academy)
  - https://mediamotor.academy/otm/index.php?p=3201

INSELGRUPPE

What happened since the last bible class on barretts (2021)

- **Updated Guidelines for Diagnosis and Management**: The American College of Gastroenterology (ACG) has revised guidelines for diagnosing and managing Barrett's Esophagus. These include the use of Prague criteria for grading BE, care algorithms for patients with columnar mucosa in the tubular esophagus, nonendoscopic detection devices for BE, and an algorithm for patients referred for endoscopic eradication therapy. The guidelines also detail surveillance strategies post-treatment of dysplastic BE

- => look for it:

•. 2022 Apr 1;117(4):559-587.
doi: 10.14309/ajg.0000000000001680.

Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline

Nicholas J Shaheen[1], Gary W Falk[2], Prasad G Iyer[3], Rhonda F Souza[4], Rena H Yadlapati[5], Bryan G Sauer[6], Sachin Wani[7]
Affiliations

•PMID: 35354777
•PMCID: PMC10259184
•DOI: 10.14309/ajg.0000000000001680
Free PMC article

- **Advances in Endoscopic Techniques**: Recent reviews have highlighted the use of narrow-band imaging in diagnosing Barrett's Esophagus, endoscopic mucosal resection for dysplastic segments, and radiofrequency ablation for dysplastic mucosal areas.
- Kahn, A., McKinley, M.J., Stewart, M. *et al.* Artificial intelligence-enhanced volumetric laser endomicroscopy improves dysplasia detection in Barrett's esophagus in a randomized cross-over study. *Sci Rep* **12**, 16314 (2022). https://doi.org/10.1038/s41598-022-20610-z

07/22

- **Genetic Insights into BE and Esophageal Adenocarcinoma (EAC)**: A genome-wide association study (GWAS) meta-analysis involving over 16,000 patients identified 27 BE and/or EAC risk loci, including 11 novel loci. The study also investigated the genetic correlations and differences in the etiology of BE and EAC, suggesting that gastroesophageal reflux disease contributes more to the metaplastic transformation in BE than to the development of EAC
- Schröder J, GWAS meta-analysis of 16 790 patients with Barrett's oesophagus and oesophageal adenocarcinoma identifies 16 novel genetic risk loci and provides insights into disease aetiology beyond the single marker level. Gut. 2023 Apr;72(4):612-623. doi: 10.1136/gutjnl-2021-326698. Epub 2022 Jul 26. PMID: 35882562. => **DO NOT USE IT AS PAPER, TOO STATISTICAL**

04/2023

- **Extrachromosomal DNA and Cancerous Transformation**: Research has identified the presence of extrachromosomal DNA (ecDNA) in tumors from patients with early-stage and late-stage EAC but not in non-dysplastic BE or low-grade dysplasia (LGD) cases. This suggests a potential role of ecDNA in the progression of BE to EAC.

- Luebeck, J., Ng, A.W.T., Galipeau, P.C. *et al.* Extrachromosomal DNA in the cancerous transformation of Barrett's oesophagus. *Nature* **616**, 798–805 (2023). https://doi.org/10.1038/s41586-023-05937-5

- **Risk Stratification and Management**: Studies have explored the evolutionary dynamics in Barrett's Esophagus, its progression to dysplasia and EAC, and the implications for patient management, including surveillance and therapy.

- **Risk Factors for Progression to High-Grade Dysplasia (HGD) and EAC**: A study identified various risk factors for the progression of BE to HGD and EAC. These include age, Hispanic race, abdominal obesity, history of diabetes mellitus, oral non-metformin anti-diabetic medications, and certain lifestyle factors like caffeine intake and smoking. Protective factors identified include the usage of selective serotonin reuptake inhibitors (SSRIs)

- Issue of PEEC (post endoscopy EAC): incidince in Barrett (make it a question): 3-13% (AGA clinical practice update)
  - Dev ofv hgd/dyspl in <1cm risk?