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# REFLUX OESOPHAGITIS, INCLUDING BARRETT AND DYSPLASIA

Cord Langner, MD
Diagnostic & Research Institute of Pathology
Medical University of Graz / Austria

# Agenda

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- Role of pathology in the diagnosis of gastro-oesophageal reflux disease
- Histology of gastro-esophageal reflux disease
  - Active oesophagitis
  - Chronic oesophagitis
- Morphogenesis of columnar lined oesophagus and the definition of Barrett oesophagus
- Diagnosis of dysplasia
- Take home messages

CME

# Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD[1], Lauren B. Gerson, MD, MSc[2] and Marcelo F. Vela, MD, MSCR[3]

*Am J Gastroenterol* 2013; 108:308–328; doi:10.1038/ajg.2012.444; published online 19 February 2013

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**Table 2. Diagnostic testing for GERD and utility of tests**

| Diagnostic test | Indication | Highest level of evidence | Recommendation |
|---|---|---|---|
| PPI trial | Classic symptoms, no warning signs, | Meta-analysis | Negative trial does not rule out GERD |
| Barium swallow | Not for GERD diagnosis. Use for evaluation of dysphagia | Case–control | Do not use unless evaluating for complication (stricture, ring) |
| Endoscopy | Alarm symptoms, screening of high-risk patients, chest pain | Randomized Controlled Trial | Consider early for elderly, those at risk for Barrett's, non-cardiac chest pain, patients unresponsive to PPI |
| Esophageal biopsy | Exclude non-GERD causes for symptoms | Case–Control | Not indicated for diagnosis of GERD |
| Esophageal manometry | Preoperative evaluation for surgery | Observational | Not recommended for GERD diagnosis. Rule out achalasia/ scleroderma-like esophagus preop |
| Ambulatory reflux monitoring | Preoperatively for non-erosive disease. refractory GERD symptoms, GERD diagnosis in question | Observational | Correlate symptoms with reflux, document abnormal acid exposure or reflux frequency |

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

- General opinion: The sensitivity and specificity of histologic findings is of limited clinical usefulness.
- **The use of routine biopsy of the esophagus to diagnose GERD cannot be recommended** in a patient with heartburn and a normal endoscopy based on current literature.
- In addition, the practice of obtaining mucosal biopsies from a normal appearing gastro-esophageal junction **has not been demonstrated to be useful** in GERD patients.

American College of Gastroenterology. Am J Gastroenterol 2013

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# Traditional parameters of histological GERD diagnosis

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- Proliferative changes of the squamous epithelium
  - Basal cell layer hyperplasia
  - Papillary elongation
  - Dilation of intercellular spaces

# Traditional parameters of histological GERD diagnosis

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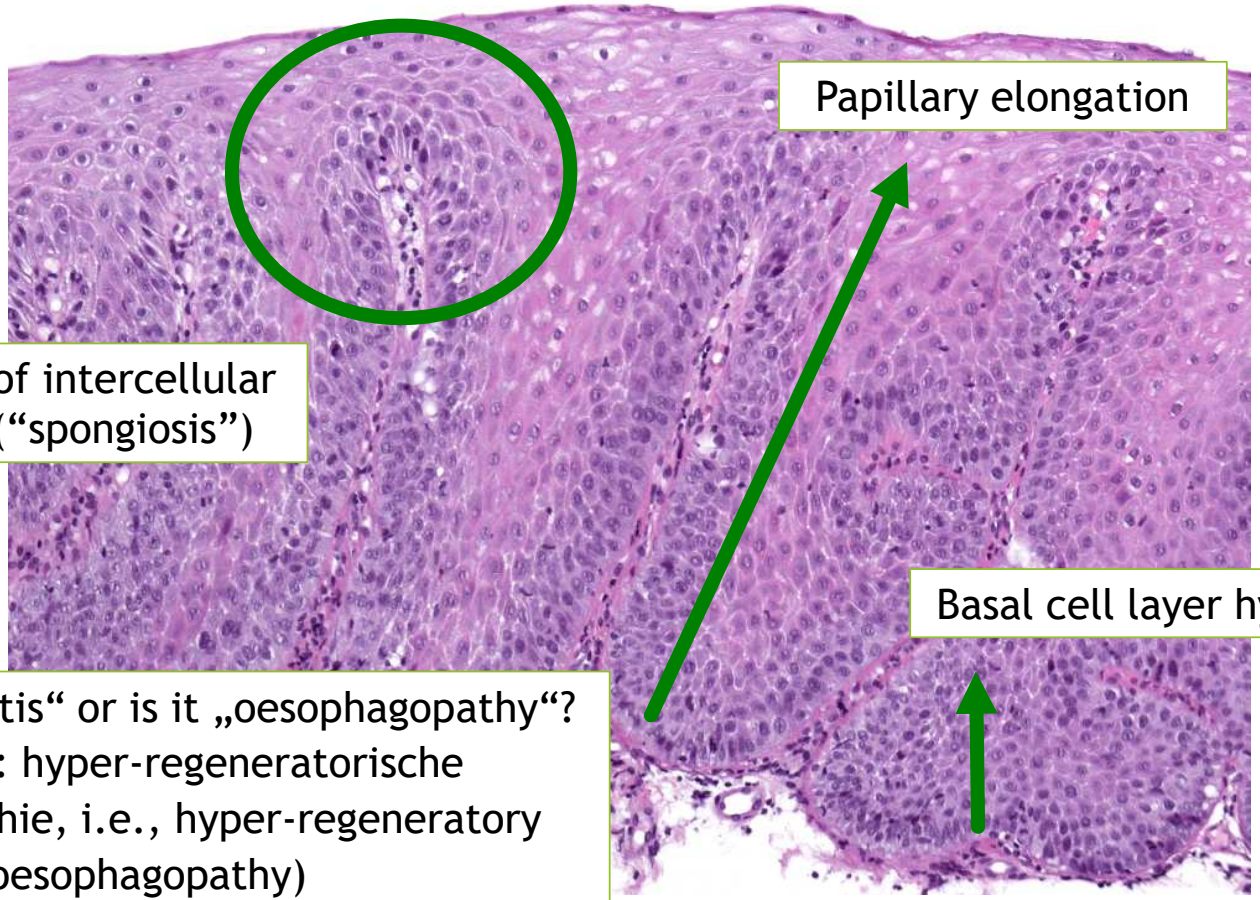

Papillary elongation

Dilation of intercellular spaces ("spongiosis")

Basal cell layer hyperplasia

Is it„oesophagitis" or is it „oesophagopathy"? (German: hyper-regeneratorische Ösophagopathie, i.e., hyper-regeneratory oesophagopathy)

# Traditional parameters of histological GERD diagnosis

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- Proliferative changes of the squamous epithelium
  - Basal cell layer hyperplasia
  - Papillary elongation
  - Dilation of intercellular spaces
- Inflammatory infiltrate
  - Intraepithelial eosinophils
  - Intraepithelial neutrophils
  - Lymphocytes (and plasma cells)

# Traditional parameters of histological GERD diagnosis

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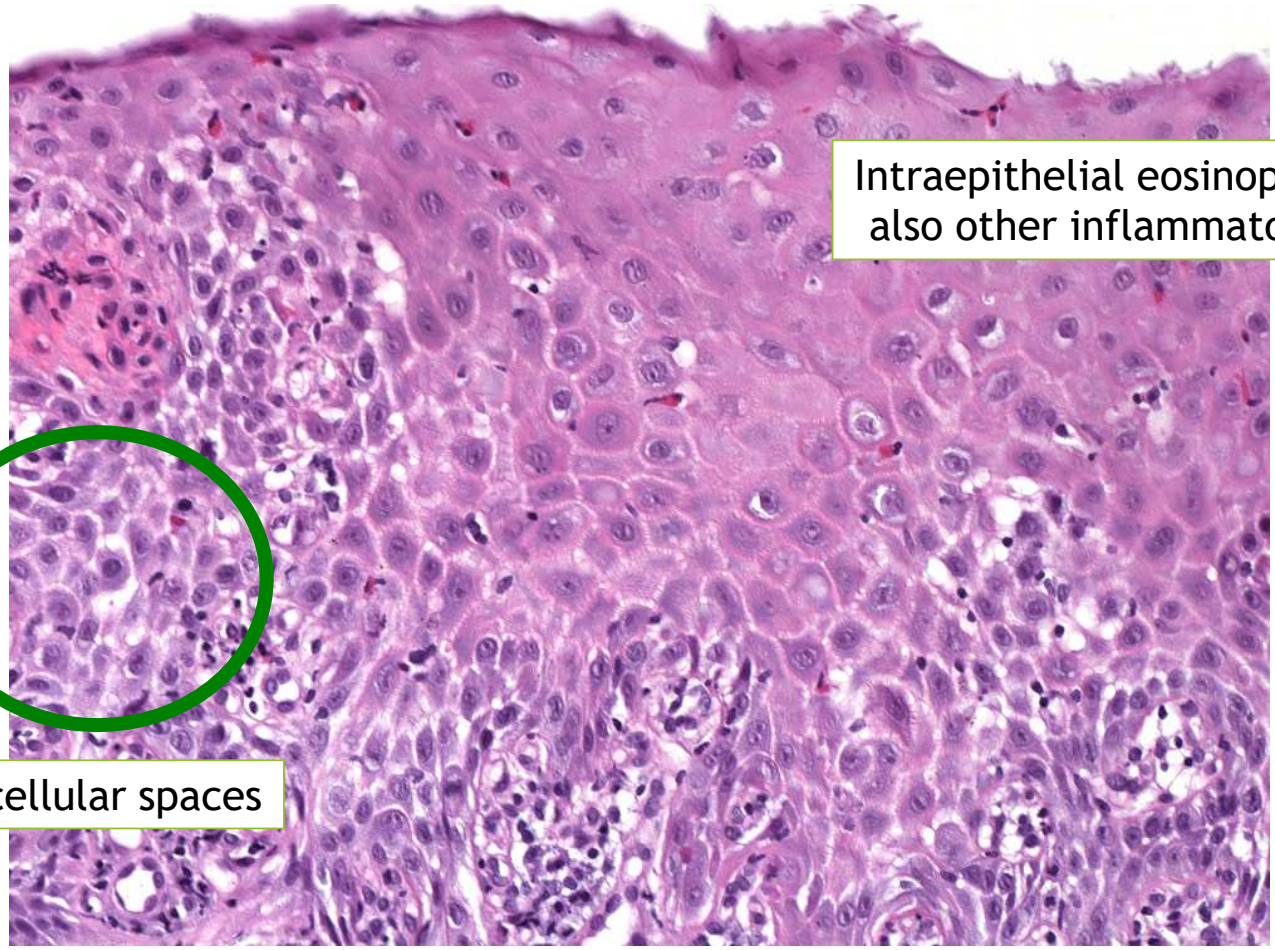

Intraepithelial eosinophils, but also other inflammatory cells

Dilation of intercellular spaces

# Traditional parameters of histological GERD diagnosis

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- Esohisto Consensus Guidelines
  - Exact definitions / grading of severity (0-2)
  - Score for the histological diagnosis of GERD
  - Evaluation of interobserver variability (interobserver agreement)

Fiocca et al. Hum Pathol 2010

# Development of consensus guidelines for the histologic recognition of microscopic esophagitis in patients with gastroesophageal reflux disease: the Esohisto project☆,☆☆

Roberto Fiocca MD[a,*], Luca Mastracci MD[a], Robert Riddell MD[b], Kaiyo Takubo MD[c], Michael Vieth MD[d], Lisa Yerian MD[e], Prateek Sharma MD[f], Paula Fernström MSc[g], Magnus Ruth MD[g]

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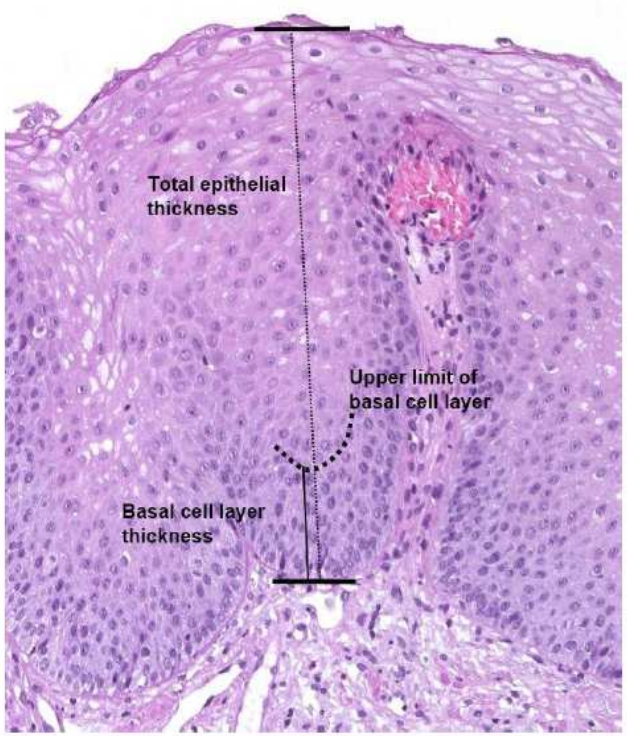
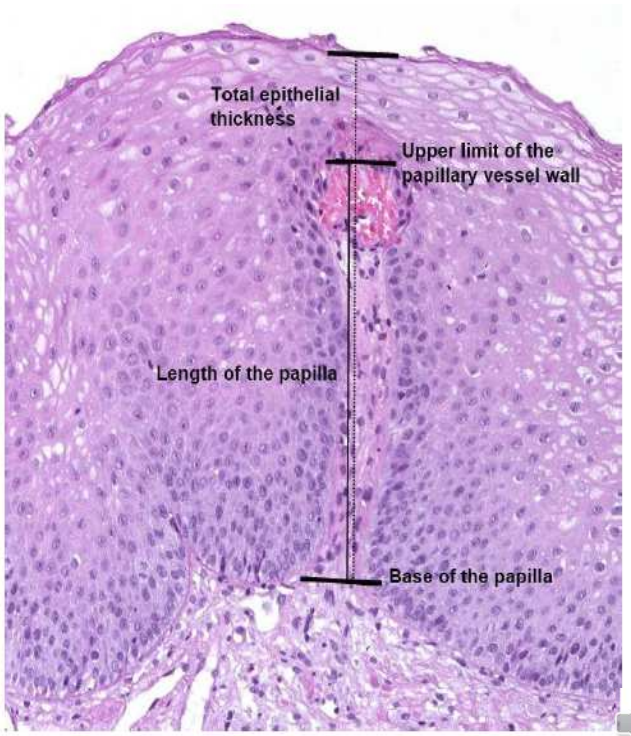
**Table 1** Phase I histologic criteria used for the assessment of biopsy specimens

| Criterion | Assessment method | Scoring |
|---|---|---|
| Basal cell layer thickness | Measured in μm (using a micrometer) and assessed by sight as a percentage of the total epithelial thickness | 0 (<15%)<br>1 (15%-30%)<br>2 (>30%) |
| Papillary length | Measured in μm and assessed as a percentage of the total epithelial thickness | 0 (<50%)<br>1 (50%-75%)<br>2 (>75%) |
| Intraepithelial eosinophils and neutrophils | Counted in the most affected high-power field (×40) | 0 (absent)<br>1 (1-2 cells)<br>2 (>2 cells) |
| Intraepithelial mononuclear cells | Counted in the most affected high-power field (×40) | 0 (<10 cells)<br>1 (10-30 cells)<br>2 (>30 cells) |
| DIS "bubbles" | Identified as irregular round dilations | 0 (absent)<br>1 (small)<br>2 (large/very large) |
| DIS "ladders" | Identified as diffuse widening of intercellular spaces | 0 (absent)<br>1 (small)<br>2 (large/very large) |

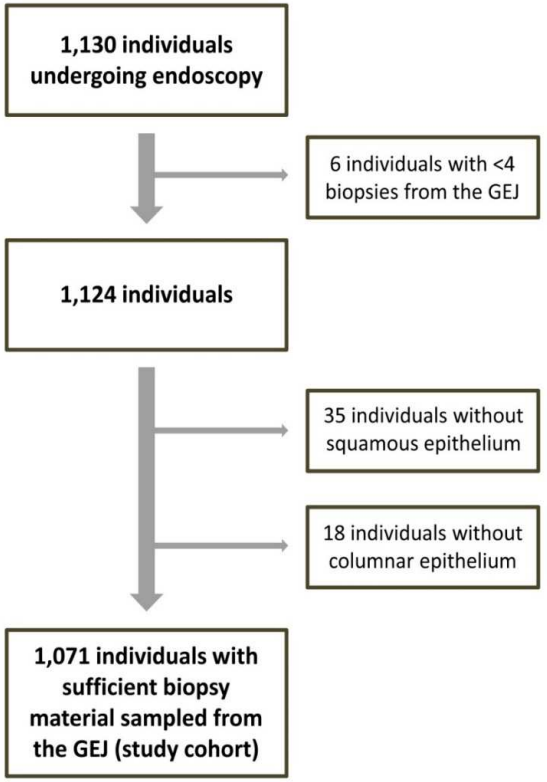



Fiocca et al. Hum Pathol 2010

# Traditional parameters of histological GERD diagnosis

- Esohisto Consensus Guidelines
  - Exact definitions / grading of severity (0-2)
  - Score for the histological diagnosis of GERD
  - Evaluation of interobserver variability (interobserver agreement)
- Clinical Validation (histoGERD Trial)
  - Correlation between histology and clinical data
  - Correlation between histology and endoscopy



# Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (*histo*GERD Trial)☆

Nora I. Schneider[a], Wolfgang Plieschnegger MD[b], Michael Geppert MD[c], Bernd Wigginghaus MD[d], Gabriele M. Hoess MD[e], Andreas Eherer MD[f], Eva-Maria Wolf MD[a], Peter Rehak PhD[g], Michael Vieth MD[h], Cord Langner MD[a,*]

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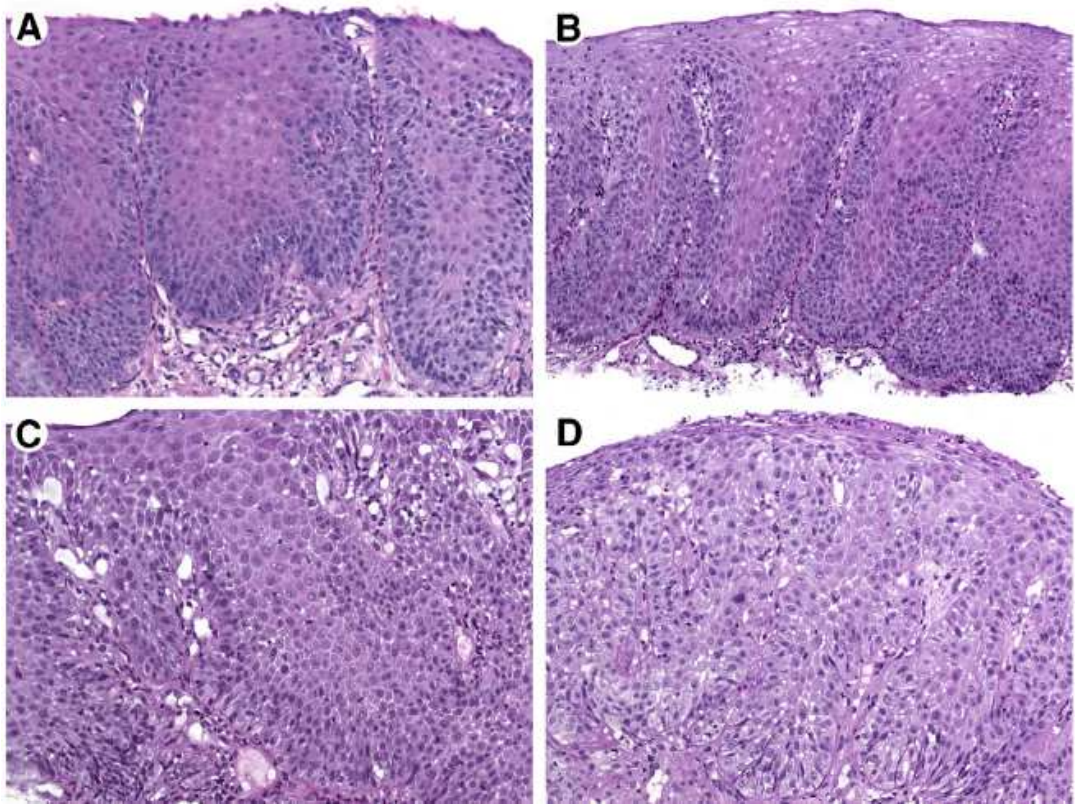
**Table 2** Histologic criteria for the recognition and assessment of microscopic lesions (and combined severity score for the diagnosis of esophagitis according to Esohisto guidelines) related to the presence of symptoms indicating esophageal disease, such as heartburn, acid regurgitation, or both at least once a week while not consuming antireflux medication and/or dysphagia

| Criterion | Severity score | Symptoms of esophageal disease | | *P* |
|---|---|---|---|---|
| | | Absent (n = 619) | Present (n = 452) | |
| Basal cell layer hyperplasia | 0 | 208 (33.6%) | 119 (26.3%) | .012 |
| | 1 | 281 (45.4%) | 210 (46.5%) | |
| | 2 | 130 (21%) | 123 (27.2%) | |
| Papillary elongation | 0 | 228 (36.8%) | 128 (28.3%) | .0019 |
| | 1 | 271 (43.8%) | 202 (44.7%) | |
| | 2 | 120 (19.4%) | 122 (27%) | |
| Dilation of intercellular spaces | 0 | 292 (47.2%) | 191 (42.3%) | .28 |
| | 1 | 265 (42.8%) | 211 (46.7%) | |
| | 2 | 62 (10%) | 50 (11.1%) | |
| Intraepithelial eosinophils | 0 | 568 (91.8%) | 411 (90.9%) | .77 |
| | 1 | 27 (4.4%) | 24 (5.3%) | |
| | 2 | 24 (3.9%) | 17 (3.8%) | |
| Intraepithelial neutrophils | 0 | 601 (97.1%) | 428 (94.7%) | .047 |
| | 1 | 5 (0.8%) | 12 (2.7%) | |
| | 2 | 13 (2.1%) | 12 (2.7%) | |
| Intraepithelial mononuclear cells | 0 | 341 (55.1%) | 220 (48.7%) | .11 |
| | 1 | 253 (40.9%) | 210 (46.5%) | |
| | 2 | 25 (4%) | 22 (4.9%) | |
| Combined severity score | Normal | 228 (36.8%) | 124 (27.4%) | .003 |
| | Mild | 237 (38.3%) | 186 (41.2%) | |
| | Severe | 154 (24.9%) | 142 (31.4%) | |




The histological diagnosis of GERD is related to reflux symptoms!

Schneider et al. Hum Pathol 2014

# Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (*histo*GERD Trial)☆

Nora I. Schneider[a], Wolfgang Plieschnegger MD[b], Michael Geppert MD[c], Bernd Wigginghaus MD[d], Gabriele M. Hoess MD[e], Andreas Eherer MD[f], Eva-Maria Wolf MD[a], Peter Rehak PhD[g], Michael Vieth MD[h], Cord Langner MD[a,*]

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**Table 4** Histologic criteria for the recognition and assessment of microscopic lesions (and combined severity score for the diagnosis of esophagitis according to Esohisto guidelines) related to the endoscopic diagnosis of esophagitis, graded according to the modified Los Angeles classification [2,3]

| Criterion | Severity score | Endoscopic diagnosis of esophagitis | | | | | | *P* |
|---|---|---|---|---|---|---|---|---|
| | | N (n = 450) | M (n = 303) | A (n = 190) | B (n = 110) | C (n = 10) | D (n = 8) | |
| Basal cell layer hyperplasia | 0 | 170 (37.8%) | 93 (30.7%) | 40 (21%) | 17 (15.5%) | 4 (40%) | 3 (37.5%) | <.001 |
| | 1 | 221 (49.1%) | 141 (46.5%) | 86 (45.3%) | 38 (34.5%) | 2 (20%) | 3 (37.5%) | |
| | 2 | 59 (13.1%) | 69 (22.8%) | 64 (33.7%) | 55 (50%) | 4 (40%) | 2 (25%) | |
| Papillary elongation | 0 | 186 (41.3%) | 100 (33%) | 46 (24.2%) | 17 (15.5%) | 4 (40%) | 3 (37.5%) | .027 |
| | 1 | 203 (45.1%) | 141 (246.5%) | 83 (43.7%) | 41 (37.3%) | 2 (20%) | 3 (37.5%) | |
| | 2 | 61 (13.6%) | 62 (20.5%) | 61 (32.1%) | 52 (47.3%) | 4 (40%) | 2 (25%) | |
| Dilation of intercellular spaces | 0 | 229 (50.9%) | 148 (48.8%) | 68 (35.8%) | 29 (26.4%) | 5 (50%) | 4 (50%) | <.001 |
| | 1 | 195 (43.3%) | 135 (44.6%) | 88 (46.3%) | 52 (47.3%) | 4 (40%) | 2 (25%) | |
| | 2 | 26 (5.8%) | 20 (6.6%) | 34 (17.9%) | 29 (26.4%) | 1 (10%) | 2 (25%) | |
| Intraepithelial eosinophils | 0 | 423 (94%) | 283 (93.4%) | 172 (90.5%) | 86 (78.2%) | 9 (90%) | 6 (75%) | <.001 |
| | 1 | 9 (2%) | 9 (3%) | 16 (8.4%) | 15 (13.6%) | 1 (10%) | 1 (12.5%) | |
| | 2 | 18 (4%) | 11 (3.6%) | 2 (1.1%) | 9 (8.2%) | 0 (0%) | 1 (12.5%) | |
| Intraepithelial neutrophils | 0 | 444 (98.7%) | 294 (97%) | 182 (95.8%) | 94 (85.5%) | 10 (100%) | 5 (50%) | <.001 |
| | 1 | 0 (0%) | 2 (0.7%) | 6 (3.1%) | 7 (6.4%) | 0 (0%) | 2 (25%) | |
| | 2 | 6 (1.3%) | 7 (2.3%) | 2 (1.1%) | 9 (8.2%) | 0 (0%) | 1 (12.5%) | |
| Intraepithelial mononuclear cells | 0 | 251 (55.8%) | 162 (53.5%) | 98 (51.6%) | 42 (38.2%) | 4 (40%) | 4 (50%) | .003 |
| | 1 | 186 (41.3%) | 128 (42.2%) | 86 (45.3%) | 55 (50%) | 5 (50%) | 3 (37.5%) | |
| | 2 | 13 (2.9%) | 13 (4.3%) | 6 (3.1%) | 13 (11.8%) | 1 (10%) | 1 (12.5%) | |
| Combined severity score | Normal | 185 (41.1%) | 99 (32.7%) | 45 (23.7%) | 16 (14.5%) | 4 (40%) | 3 (37.5%) | <.001 |
| | Mild | 188 (41.8%) | 125 (41.3%) | 73 (38.4%) | 33 (30%) | 2 (20%) | 2 (25%) | |
| | Severe | 77 (17.1%) | 79 (26.1%) | 72 (37.9%) | 61 (55.5%) | 4 (40%) | 3 (37.5%) | |

The histological diagnosis of GERD is related to the endoscopic diagnosis of GERD, but changes are already observed in individuals with normal endoscopy!

Schneider et al. Hum Pathol 2014

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- Take home messages

## Cardiac mucosa at the gastro-oesophageal junction: indicator of gastro-oesophageal reflux disease? Data from a prospective central European multicentre study on histological and endoscopic diagnosis of oesophagitis (*histo*GERD trial)

Cord Langner, Nora I Schneider, Wolfgang Plieschnegger,[1] Bertram Schmack,[2] Hartmut Bordel,[3] Bernd Höfler,[4] Andreas J Eherer,[5] Eva-Maria Wolf, Peter Rehak[6] & Michael Vieth[7]

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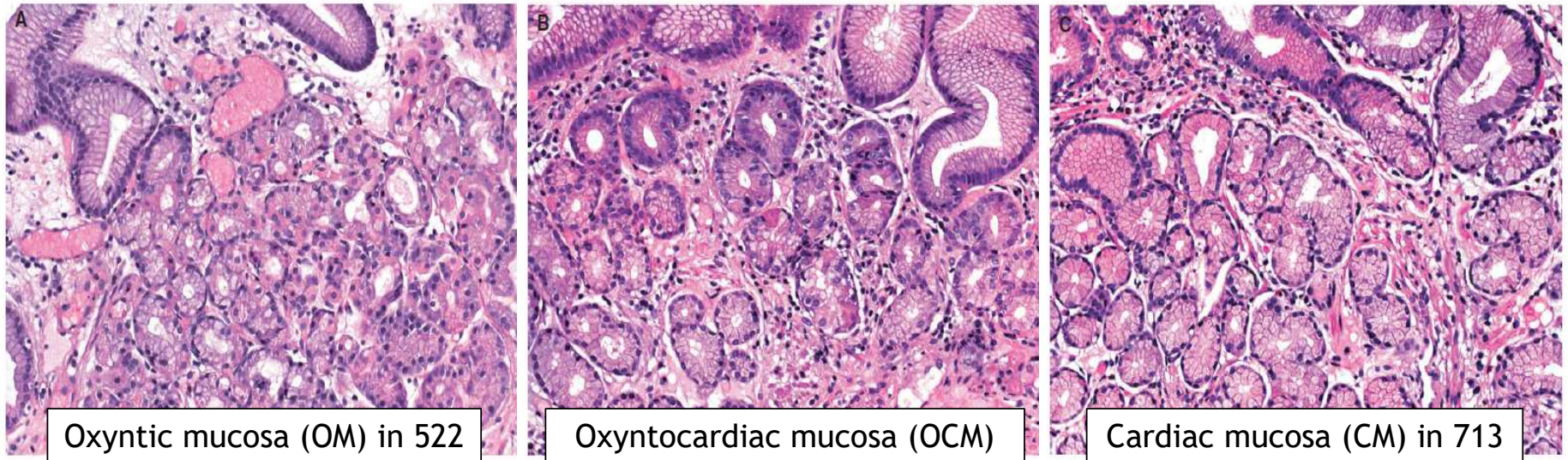


Oxyntic mucosa (OM) in 522 (48.7% individuals)

Oxyntocardiac mucosa (OCM) in 504 (47.1% individuals)

Cardiac mucosa (CM) in 713 (66.6% individuals)

The presence of CM was significantly related to the body mass index ($p<0.001$)

Langner et al. Histopathology 2014

## Cardiac mucosa at the gastro-oesophageal junction: indicator of gastro-oesophageal reflux disease? Data from a prospective central European multicentre study on histological and endoscopic diagnosis of oesophagitis (*histo*GERD trial)

Cord Langner, Nora I Schneider, Wolfgang Plieschnegger,[1] Bertram Schmack,[2] Hartmut Bordel,[3] Bernd Höfler,[4] Andreas J Eherer,[5] Eva-Maria Wolf, Peter Rehak[6] & Michael Vieth[7]

**Table 1.** Cardiac mucosa related to histological findings indicative of gastro-oesophageal reflux disease (GORD)

| | Individuals without cardiac mucosa ($n$ = 358) | | Individuals with cardiac mucosa ($n$ = 713) | | |
|---|---|---|---|---|---|
| Severity | *N* | % | *N* | % | *P*-value |
| Basal cell hyperplasia | | | | | |
| 0 | 175 | 48.9 | 152 | 21.3 | <0.001 |
| 1 | 128 | 35.8 | 363 | 50.9 | |
| 2 | 55 | 15.4 | 198 | 27.8 | |
| Papillary elongation | | | | | |
| 0 | 192 | 53.6 | 164 | 23.0 | <0.001 |
| 1 | 112 | 31.3 | 361 | 50.6 | |
| 2 | 54 | 15.1 | 188 | 26.4 | |
| Dilation of intercellular spaces | | | | | |
| 0 | 232 | 64.8 | 251 | 35.2 | <0.001 |
| 1 | | | | .8 | |
| 2 | | | | 5 | |

| | Individuals without cardiac mucosa ($n$ = 358) | | Individuals with cardiac mucosa ($n$ = 713) | | |
|---|---|---|---|---|---|
| Severity | *N* | % | *N* | % | *P*-value |
| Mononuclear cells | | | | | |
| 0 | 268 | 74.9 | 293 | 41.1 | <0.001 |
| 1 | 70 | 19.6 | 393 | 55.1 | |
| 2 | 20 | 5.6 | 27 | 3.8 | |
| Eosinophils | | | | | |
| 0 | 321 | 89.7 | 658 | 92.3 | 0.047 |
| 1 | 16 | 4.5 | 35 | 4.9 | |
| 2 | 21 | 5.9 | 20 | 2.8 | |
| Neutrophils | | | | | |
| 0 | 340 | 95 | 689 | 96.6 | 0.038 |

The presence of CM is related to the histological diagnosis of GERD!

- Association with the histological diagnosis of intestinal metaplasia at the GEJ (p<0.001)
- Association with the endoscopic diagnosis of GERD (p<0.001)
- No association with the endoscopic diagnosis of Barrett oesophagus

Langner et al. Histopathology 2014

**Multilayered epithelium at the gastroesophageal junction is a marker of gastroesophageal reflux disease: data from a prospective Central European multicenter study (*histo*GERD trial)**

Cord Langner · Eva-Maria Wolf · Wolfgang Plieschnegger · Michael Geppert · Bernd Wigginghaus · Gabriele M. Höss · Andreas Eherer · Nora I. Schneider · Peter Rehak · Michael Vieth

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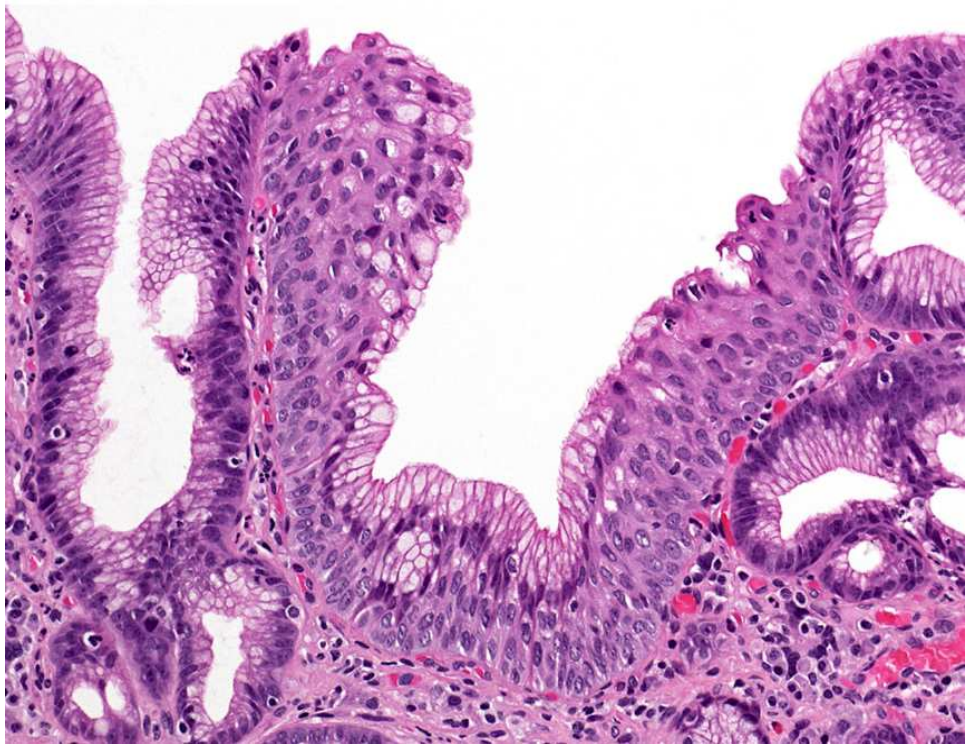
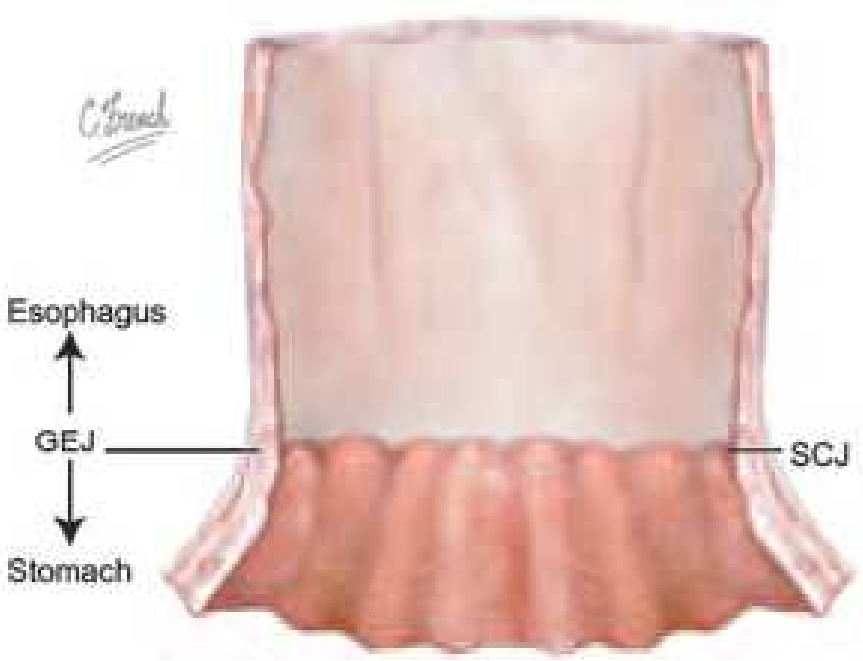


- Prevalence: 9.6% (103/1071)
- Significant associations with age ($p<0.001$) and body mass index ($p=0.03$)
- Association with proliferative changes of the squamous epithelium, such as basal cell layer hyperplasia ($p=0.018$), papillary elongation ($p=0.047$) and dilated intercellular spaces ($p=0.005$)
- **Association with cardiac mucosa ($p<0.001$)**
- Association with the endoscopic diagnosis of Barrett oesophagus ($p<0.001$)

Langner et al. Virchows Arch 2014

# Summary: histological GERD diagnosis




Markers of active disease (active or acute GERD)

Chronic consequences of GERD (chronic GERD)

Problem: The vast majority of endoscopists take their biopsies at the ”gastro-esophageal junction”, the ”squamocolumnar junction” or the ”ora serrata”, but they do not really know, whether they obtain the biopsies from the distal oesophagus or proximal stomach!

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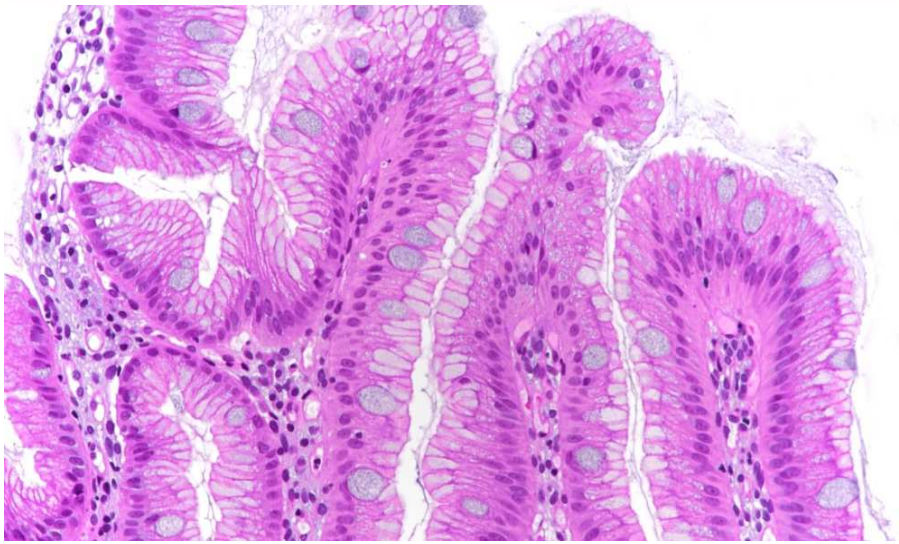
## Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement

ESGE

Medical University of Graz

**STATEMENT 1**

The diagnosis of BE is made if the distal esophagus is lined with columnar epithelium with a minimum length of 1 cm (tongues or circular) containing specialized intestinal metaplasia at histopathological examination.



- The diagnosis of Barrett oesophagus is a combined diagnosis (endoscopy plus histology)
- Formally, the pathologist can no longer make a diagnosis of Barrett oesophagus alone
- We can only state "goblet cells present" and leave the rest to the endocopist (…compatible with Barrett oesophagus, provided the biopsy material was sampled within the distal oesophagus and the respective segment has a minimum length of 10 mm)
- Is this clever? Surely not, but it is easy…
- DD intestinal metaplasia of the cardia (which is extremely rare): always ask for additional biopsy material from the stomach

Weusten et al. Endoscopy 2017

# The morphogenesis of columnar epithelium within the distal oesophagus

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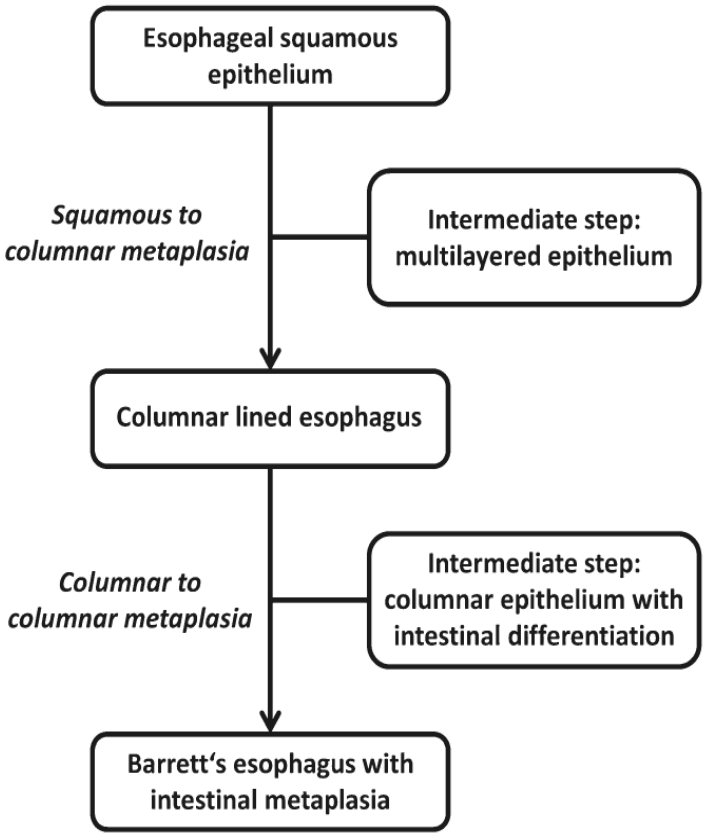


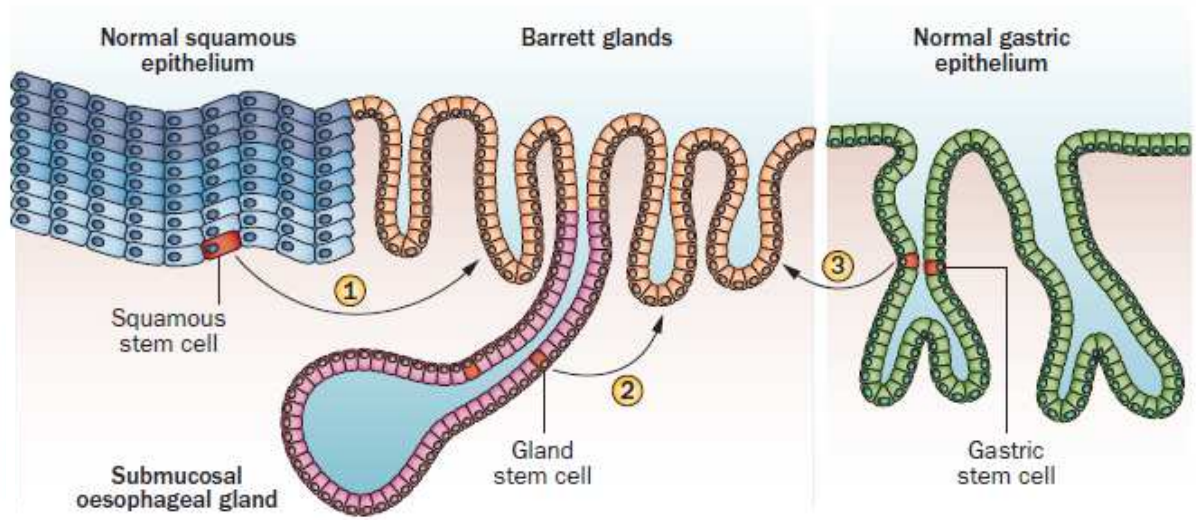


**Figure 4** | The potential sources of Barrett epithelium. (1) From native squamous stem cells, (2) submucosal duct or gland stem cells or (3) gastric glands.

Mc Donald et al. Nat Rev Gastroenterol Hepatol 2014

**REVIEW**

## The Barrett's Gland in Phenotype Space

Stuart A. C. McDonald,[1] Trevor Graham,[1] Danielle Lavery,[1] Nicholas A. Wright,[1] and Marnix Jansen[1,2]

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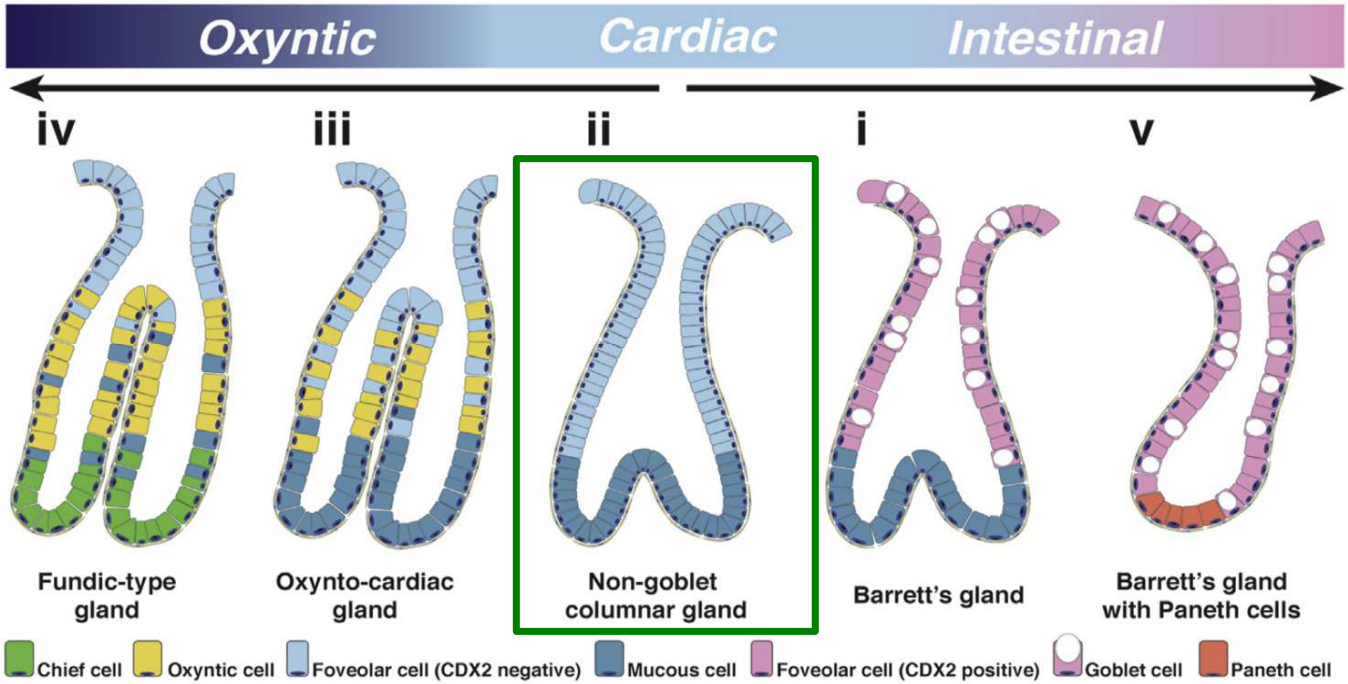


The goblet cell is the risk-indicating cell, but it is not the precursor cell of the neoplastic cascade (the background non-goblet cell epithelium is at risk)

McDonald et al. Cell Mol Gastroenterol Hepatol 2015

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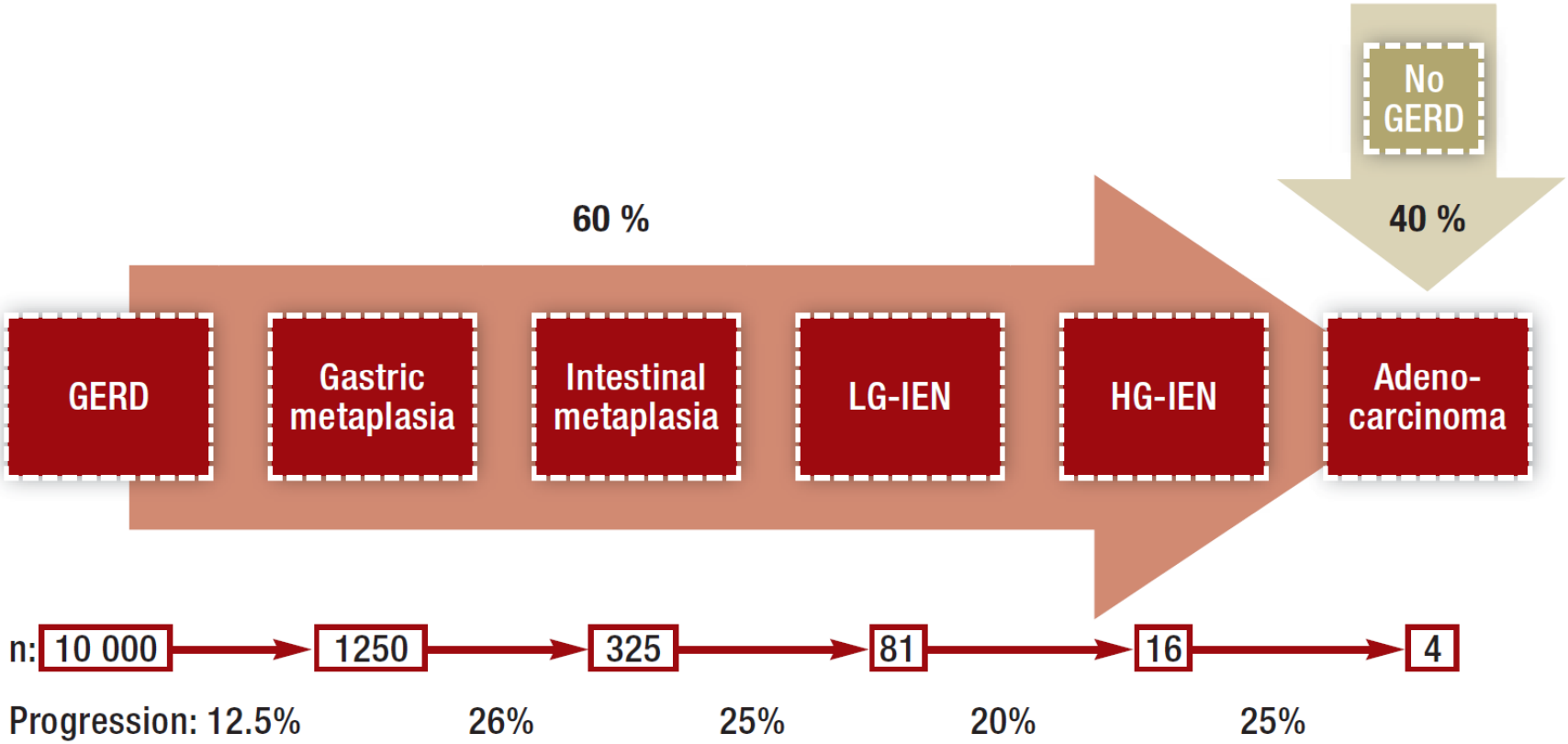
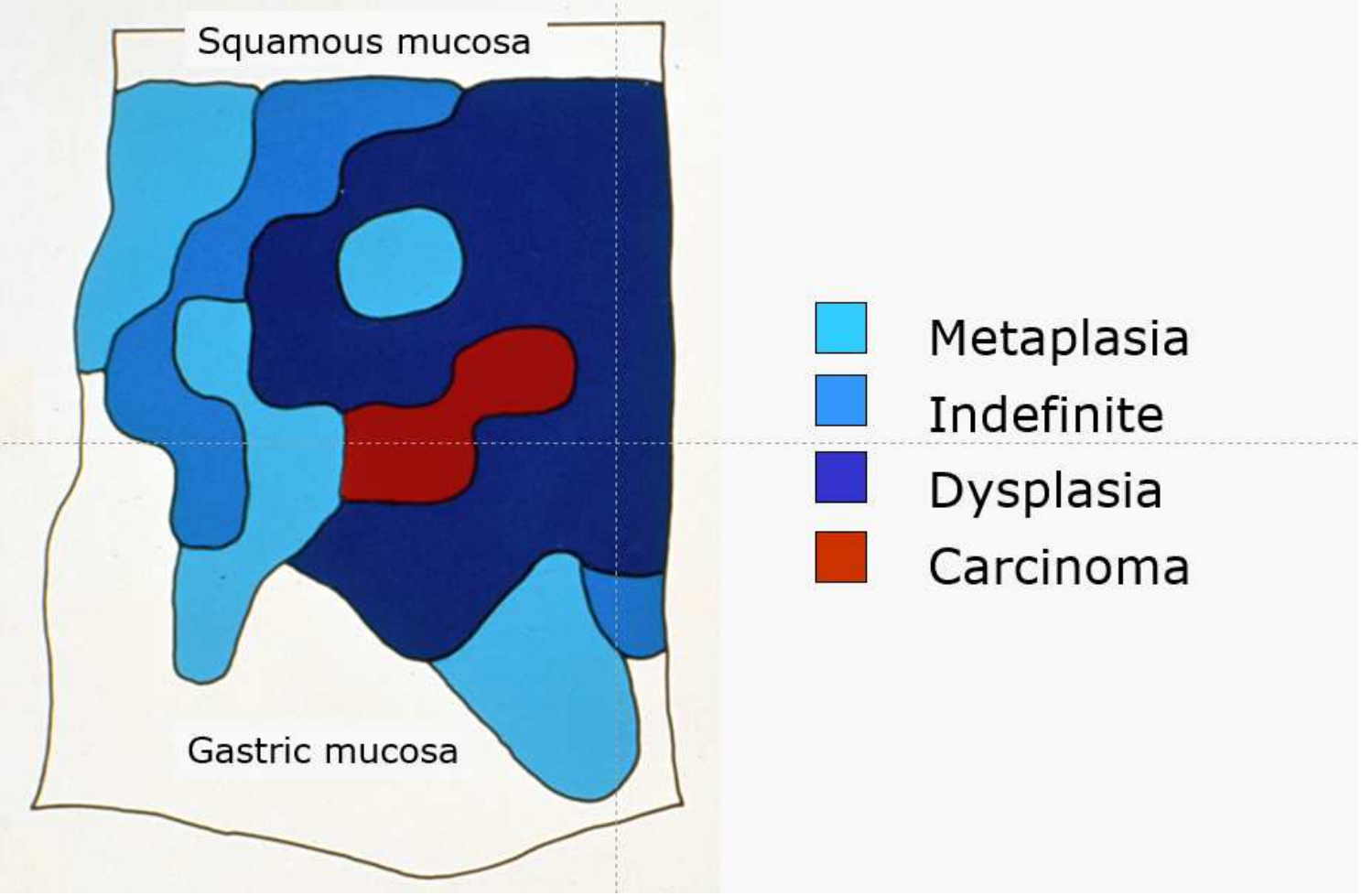
- **Diagnosis of dysplasia**
- Take home messages

# Metaplasia-dysplasia-carcinoma sequence




Labenz et al. Dtsch Arztebl Int 2015

# Metaplasia–dysplasia–carcinoma sequence




Haggitt et al. 1990

# Features to recognise dysplasia and differentiate it from reactive changes ("metaplastic atypia")

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| | Regeneration | Dysplasia |
|---|---|---|
| Inflammation | ++ | variable |
| Ulceration | ++ | variable |
| Surface maturation | + | - |
| Pleomorphism | - | + |
| Loss of polarity | - | + |
| Atypical mitoses | - | + |
| Abrupt transition | - | + |
| Surface proliferation | variable | ++ |
| Mucin depletion | variable | ++ |

# Low grade *versus* high grade dysplasia

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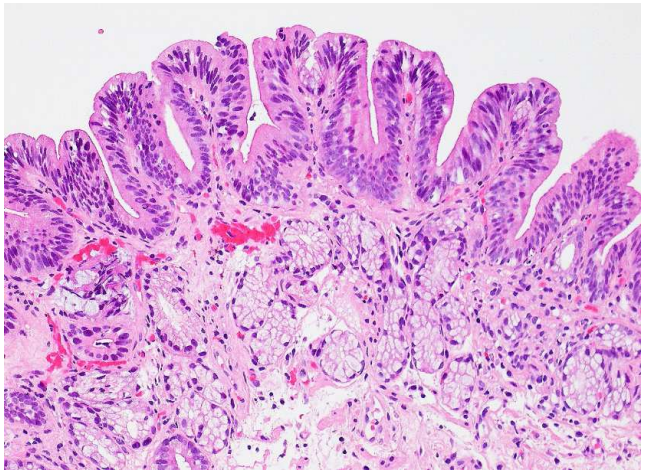
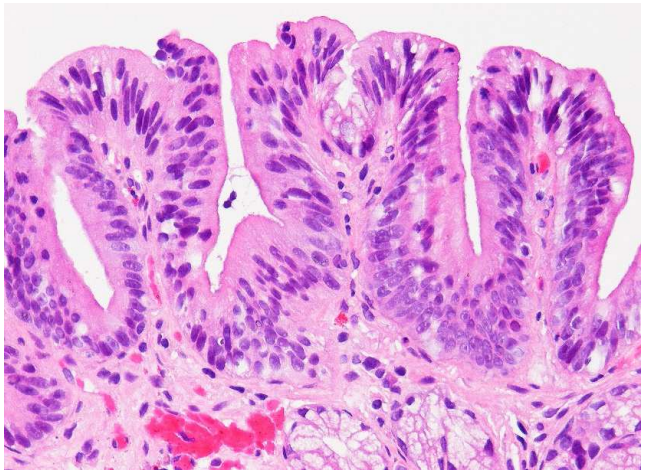
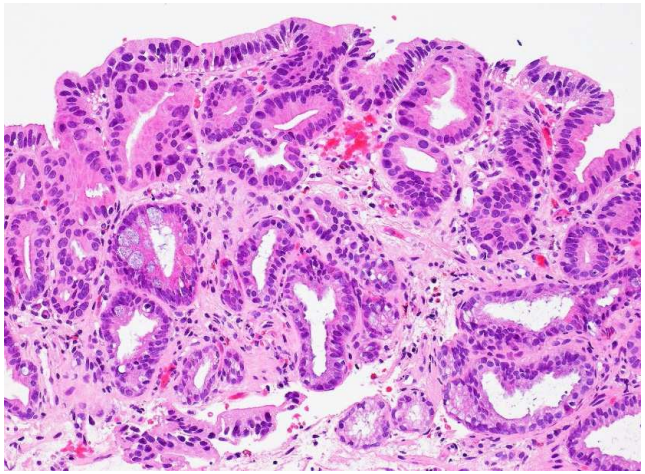
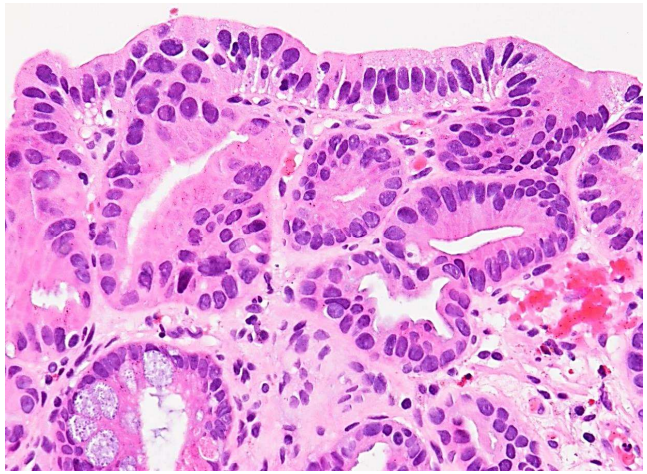




Low Grade Dysplasia (intraepithelial neoplasia)





High Grade Dysplasia (intraepithelial neoplasia)

# Indefinite for dysplasia – what is this?

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- Should be diagnosed when the answer to the following questions is “no”
  - Is this epithelium unequivocally benign or reactive?
  - Is this epithelium unequivocally dysplastic (neoplastic)?
- Two main scenarios in which the diagnosis indefinite for dysplasia is made
  - Biology, that is, mainly inflammation → repeat biopsy after anti-inflammatory treatment
  - Technical issues → short time repeat biopsy
- Should not be diagnosed too often…

# Indefinite for dysplasia – what is this?

Medical University of Graz

- Should be diagnosed when the answer to the following questions is “no”
  - Is
  - Is
- Two
  - Bi
    - Technical issues → short time repeat biopsy
- Should not be diagnosed too often…

Frequency of histological findings suggesting dysplasia in Barrett biopsies

- Indefinite for dysplasia <5% (better 2-3%)
- Low grade dysplasia <5% (better 2-3%)
- High grade dysplasia <5% (better 2-3%)

# Crypt Dysplasia With Surface Maturation

## *A Clinical, Pathologic, and Molecular Study of a Barrett's Esophagus Cohort*

*Leslie C. Lomo, MD,* Patricia L. Blount, MD,†‡ Carissa A. Sanchez, BA,† X. Li,† Patricia C. Galipeau, BS,† David S. Cowan, BS,† Kamran Ayub, MD,§ Peter S. Rabinovitch, MD, PhD,⊥ Brian J. Reid, MD, PhD,†‡¶ and Robert D. Odze, MD**

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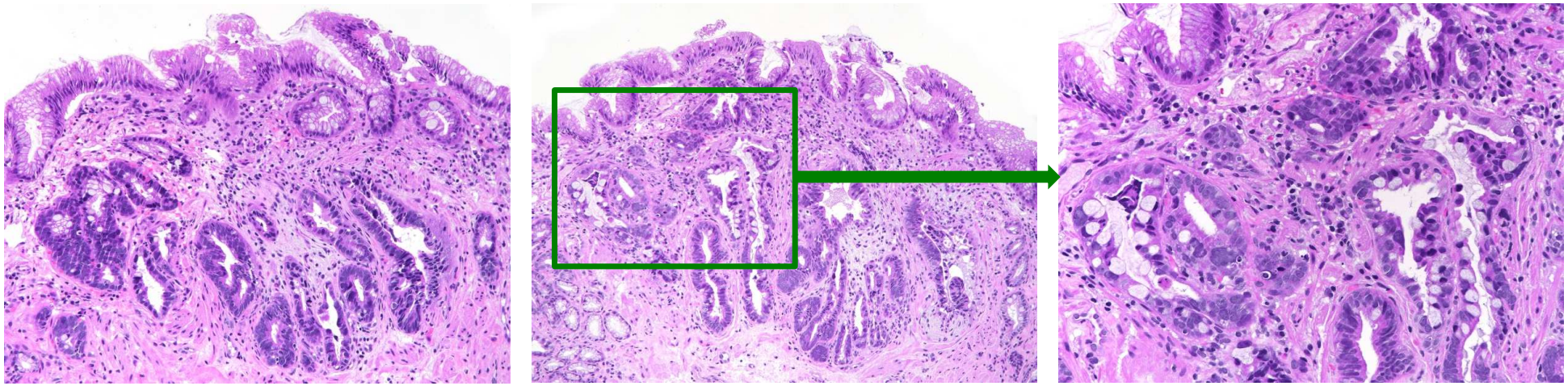

- Synonym: basal gland dysplasia
- Often associated with classical dysplasia (low or high grade) or carcinoma
- DD metaplastic atypia (be cautious in tangential embedding)
- DD lateral extension from a carcinoma that is not seen in the biopsy piece / level of evaluation → cutting of deeper levels strongly recommended

Lomo et al. Am J Surg Pathol 2009

# Early Barrett‘s adenocarcinoma

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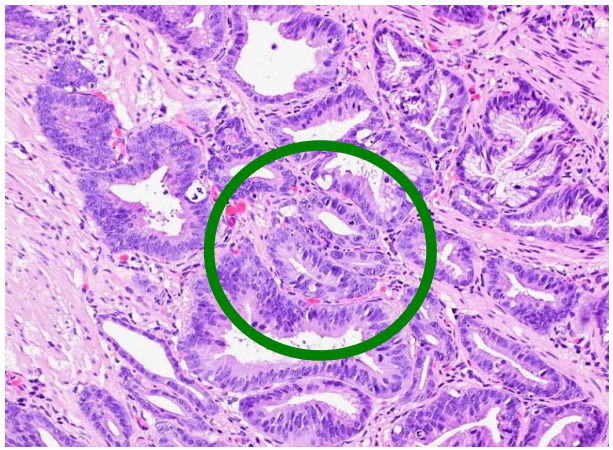

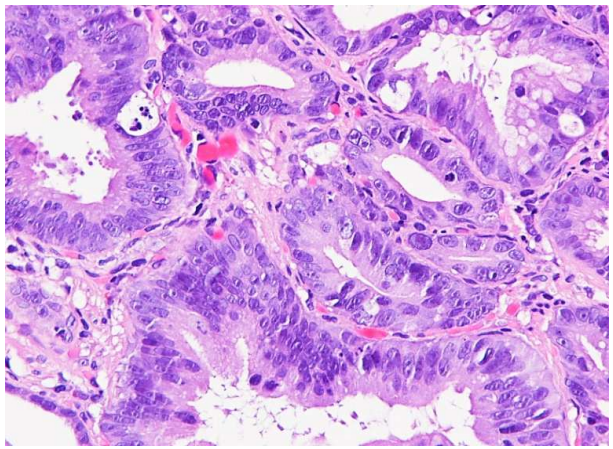

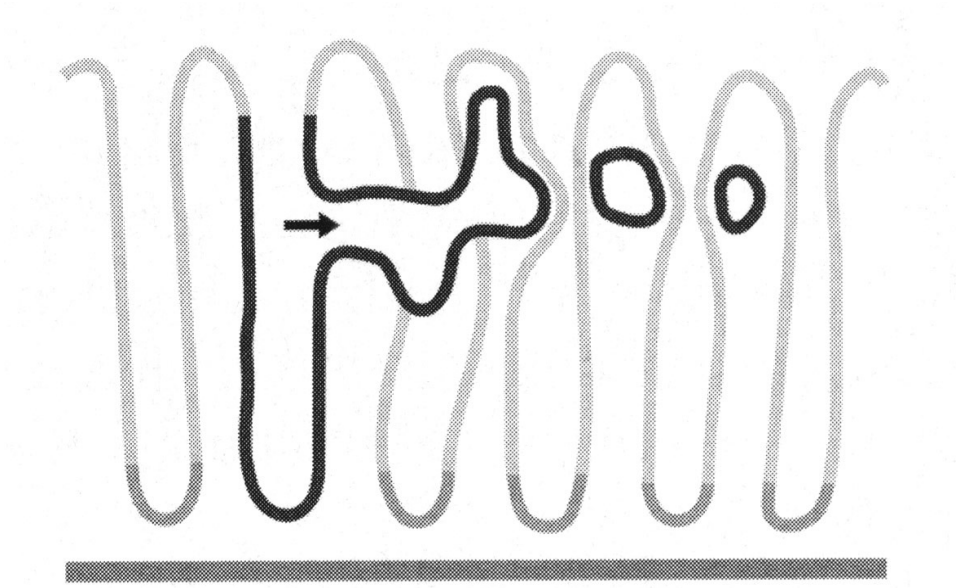

- Latero-lateral expansion and bridging (“hand-in-hand” sign), back-to-back microglands, “dirty necrosis” in glands is suggestive, single cell invasion is not required
- Please note: no desmoplasia in mucosal adenocarcinoma
- Do not overlook angioinvasion

# Summary of histological features

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| | Metaplasia | LG Dysplasia | HG Dysplasia | Carcinoma |
|---|---|---|---|---|
| Glands | no branching | no branching | slightly irregular, branching uncommon | irregular, branching, bridging, cribriform |
| Surface maturation | + | - | - | - |
| Goblet cells | ++ | + / (+) | (+) / - | - |
| Nuclei | small, basal | elongated ("pencillate") | markedly enlarged, round | markedly enlarged, may be vesicular |
| Chromatin | unaltered | + | ++ | ++ / +++ |
| Nuclear pleomorphism | - | (+) | + / ++ | ++ / +++ |
| Nuclear stratification | - | + | ++ | variable |
| Nuclear polarity | retained | retained | lost | lost |
| Nucleoli | none | none | mainly small | often prominent |

# p53 immunostaining as additional tool

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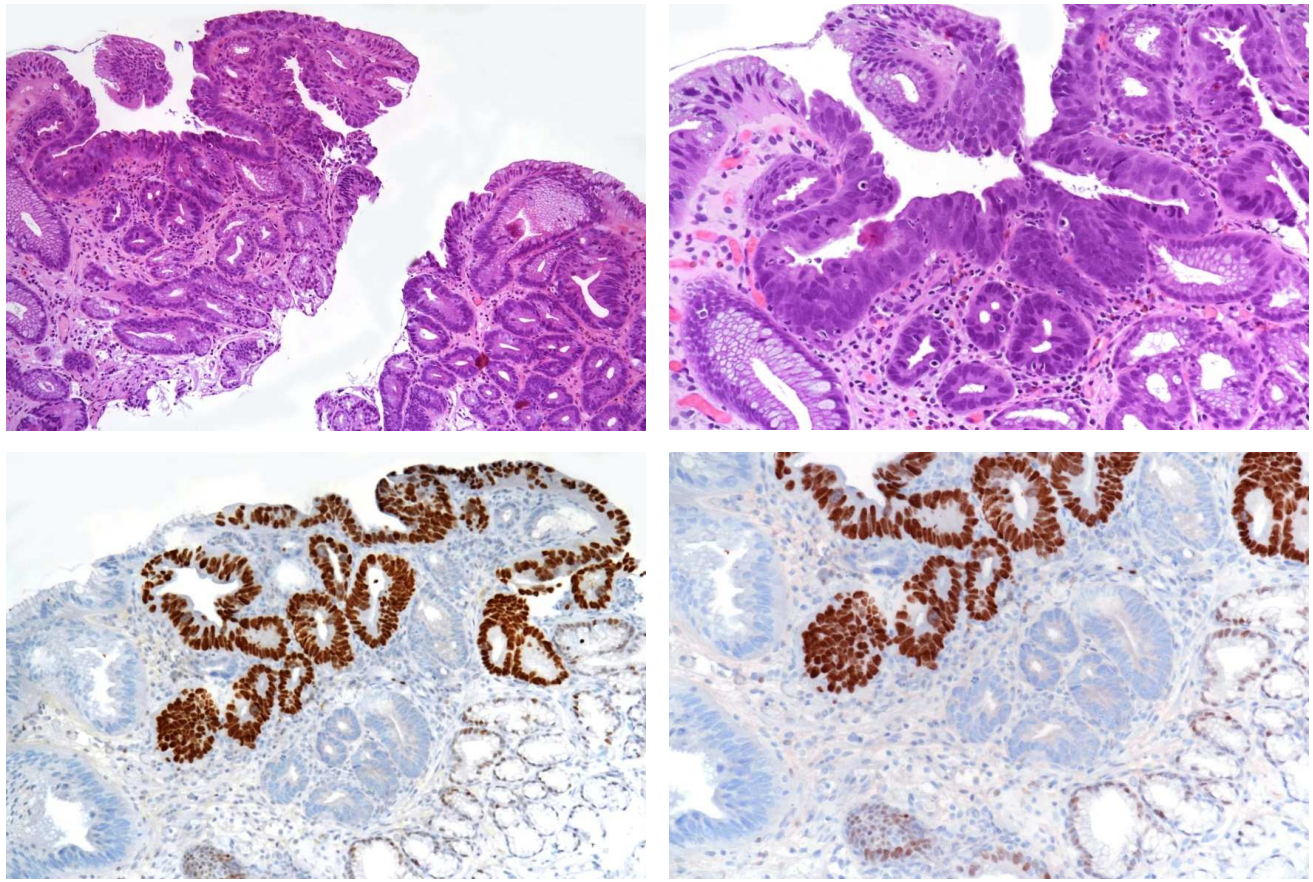

**Two principal patterns of abnormal p53 staining („all or nothing“):**

Strongly positive (due to impaired protein degradation)

Completely negative (due to protein truncation, not recognized by the antibody)

Kaye et al. Histopathology 2010

# Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement

ESGE

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**STATEMENT 6**
Biopsy samples should be taken from all visible mucosal abnormalities. In addition, random 4-quadrant biopsies should be collected every 2 cm within the Barrett's segment, starting from the upper end of the gastric folds. Biopsies from each level should be collected in and presented to the pathologist in a separate container.

**STATEMENT 9**
The diagnosis of any degree of dysplasia (including "indefinite for dysplasia") in BE requires confirmation by an expert GI pathologist.

**STATEMENT 11**
Patients with visible lesions in BE diagnosed as dysplasia or early cancer should be referred to a BE expert center. All visible abnormalities, regardless of the degree of dysplasia, should be removed by means of endoscopic resection techniques in order to obtain optimal histopathological staging.

**STATEMENT 12**
Patients with LGD on random biopsies confirmed by a second expert GI pathologist should be referred to a BE expert center. A surveillance interval of 6 months after confirmed LGD diagnosis is recommended.
i. If no dysplasia is found at the 6-month endoscopy, the interval can be broadened to 1 year. After two subsequent endoscopies negative for dysplasia, standard surveillance for patients with nondysplastic BE can be initiated.
ii. If a confirmed diagnosis of LGD is found in the subsequent endoscopies, endoscopic ablation should be offered.

**STATEMENT 13**
Patients with HGD confirmed by a second expert GI pathologist should be referred to a BE expert center. In the expert center, a high-definition endoscopy should be repeated according to the following guidelines.
i. All visible abnormalities should be removed by endoscopic resection techniques for adequate histopathological staging.
ii. If no lesions suspicious for dysplasia are seen, random 4-quadrant biopsies should be taken; if these biopsies are negative for dysplasia, endoscopy should be repeated at 3 months. If these biopsies confirm the presence of HGD, endoscopic ablation is recommended, preferably with RFA.

**STATEMENT 14**
Endoscopic resection is the first-choice therapy for T1a EAC.

**STATEMENT 15**
In patients with T1b EAC, the optimal treatment strategy depends on histopathological characteristics of the endoscopic resection specimen. Endoscopic resection may be a valid alternative to surgery and is recommended in patients who are borderline fit for surgery, if the endoscopic resection specimen meets all of the following criteria:
i. submucosal invasion limited to < 500 µm;
ii. tumor differentiation grade: *well* or *moderate*;
iii. absence of tumor invasion in lymphatic vessels or blood vessels;
iv. absence of tumor infiltration in the deep resection margin.

Weusten et al. Endoscopy 2017

# Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement

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Weusten et al. Endoscopy 2017

# Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

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<table>
<tr><th></th><th colspan="3">VM0</th><th>VM1</th></tr>
<tr><td rowspan="2">En bloc HM0</td><td colspan="3">R0</td><td rowspan="2">R1</td></tr>
<tr><td>No submucosal invasion</td><td>< Cutoff*,<br>L0 & V0,<br>Well moderately differentiated</td><td>> Cutoff*, or<br>L1 or V1, or<br>Poorly differentiated</td></tr>
<tr><td></td><td colspan="2">Low-risk resection<br>(endoscopic follow-up is enough)</td><td>High risk resection<br>(i. e. surgery +/– adjuvant treatment recommended)</td><td>High risk resection<br>(i. e. surgery +/– adjuvant treatment recommended)</td></tr>
<tr><td rowspan="2">En bloc HM1c<br>En bloc HM1d<br>Piecemeal</td><td colspan="3">RX</td><td>R1</td></tr>
<tr><td colspan="2">Local-risk resection<br>(endoscopic follow-up and putative therapy may be possible)</td><td>High risk resection<br>(i. e. surgery +/– adjuvant treatment recommended)</td><td>High risk resection<br>(i. e. surgery +/– adjuvant treatment recommended)</td></tr>
</table>

Notation: VM, vertical margin; HM, horizontal margin; R. resection; L, lymphatic invasion; V, vascular invasion; c, carcinoma; d, dysplasia

**Fig. 2** Pathological criteria for determining whether to consider the resection as low risk, local risk (risk of local recurrence), or high risk (to be adjusted according to organ and size if required). * Cutoff will differ: SCC ≤ 200 µm, Barrett's or gastric adenocarcinoma ≤ 500 µm and colorectal adenocarcinoma ≤ 1000 µm

Pimentel-Nunes et al. Endoscopy 2015

# The pathologist‘s to do list in EMR/ESD specimens

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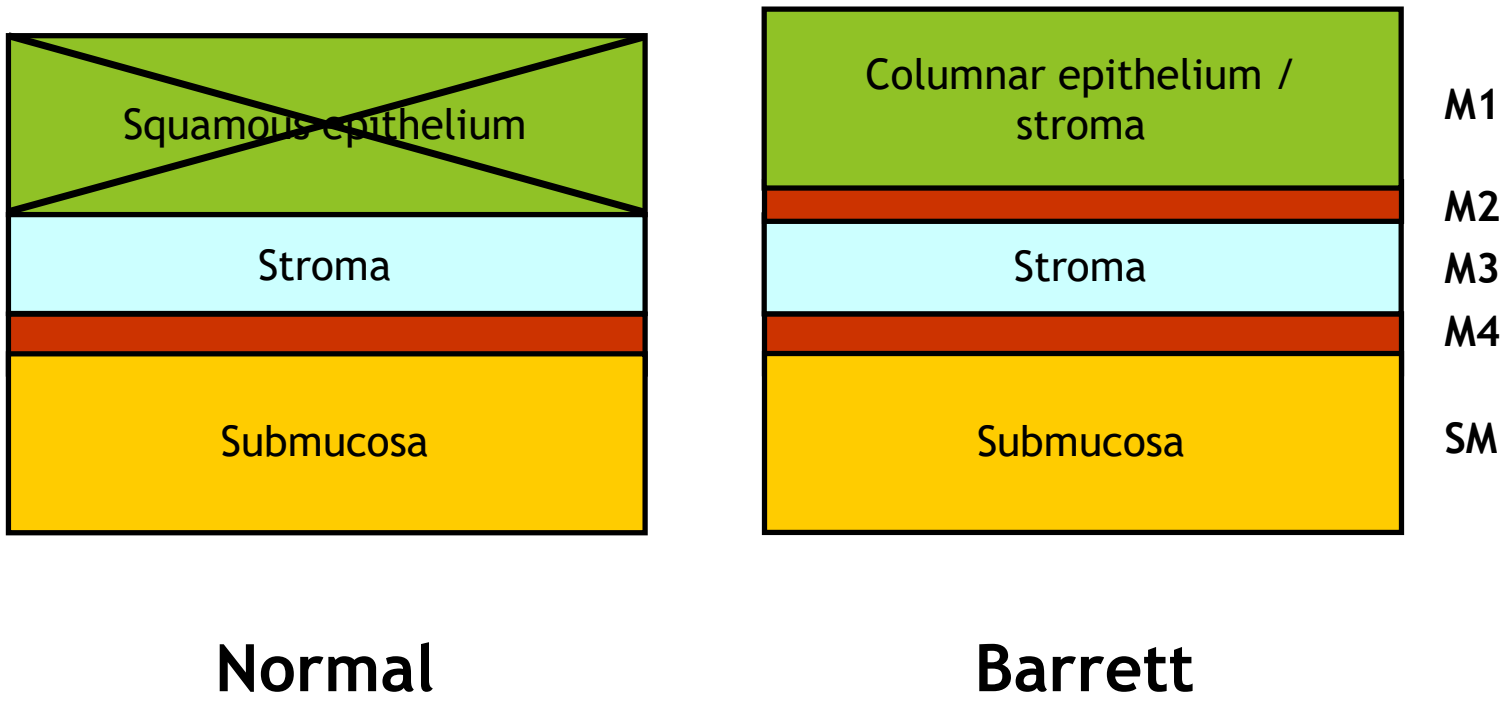
- Accurate diagnosis of the lesion: dysplasia (low-grade versus high-grade) or carcinoma (well/moderately versus poorly differentiated)
- In case of carcinoma, assess the depth of invasion, mucosal (pT1a) versus submucosal (pT1b) cancer, in case of the latter measure the depth of invasion into the submucosa in micrometres
- Assess the margin (resection status) horizontally and vertically (refer to both in the pathology report)
- Carefully check for the presence of angioinvasion (L1, V1), by cutting several levels and/or immunohistochemistry (D2-40, CD31)

# Disorganized (duplicated) muscularis mucosae: do not overdiagnose pT1b cancer



# Pathologists are able to differentiate reliably the lamina propria associated with Barrett's musculofibrous anomaly from submucosa in oesophageal endoscopic resections

Philip V Kaye, Maria O'Donovan,[1] Nicholas Mapstone,[2] Babett Disep,[3] Marco Novelli[4] & Krish Ragunath[5]

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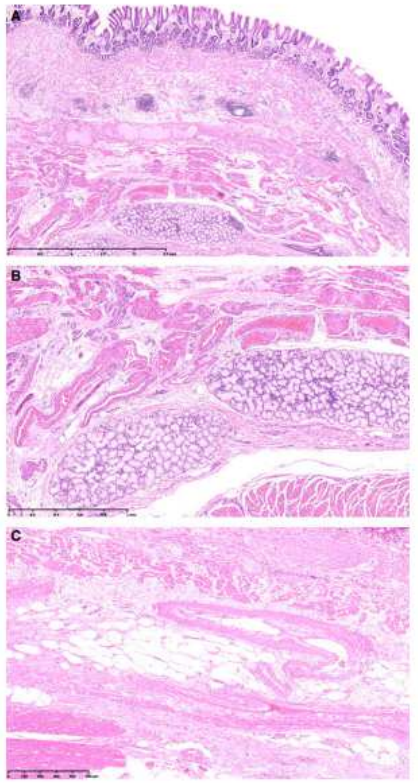
**Table 2.** Differing classifications of layers for oesophageal intramucosal carcinoma

| Classification | *In-situ* disease | Lamina propria | Inner muscularis | Deep lamina propria | Outer muscularis |
|---|---|---|---|---|---|
| Paris classification[11] | M1 | M2 | M2 | M2 | M3 |
| Takubo[4] | | Superficial LP | Superficial MM | Deep LP | Deep MM |
| Buskens[12] | M1 | M2 | M2 | M2 | M3 |
| Lewis[8] | Not included | 1 | 2 | 3 | 4 |
| Estrella[5] | Not included | 1 | 1 | 2 | 2 |
| Vieth[9] | Not included | M1 | M2 | M3 | M4 |
| Kaneshiro[10] | Not included | LP | Inner MM | Between MM | Outer MM |

MM, Muscularis mucosae; LP, lamina propria.




A, Low-power view showing split muscularis mucosa. B, **Submucosal glands** and **large calibre thick-walled vessels** indicate true submucosa. C, Thick-walled vessels and **adipose tissue** denoting true submucosa.

**When you are not sure: use a desmin stain to highlight the two levels!**

Kaye et al. Histopathology 2015

# Take home messages

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- The role of pathology in the diagnosis of gastro-oesophageal reflux disease is limited currently
- Changes within the squamous epithelium reflect current ("active injury") GERD, whereas changes below the squamocolumnar junction reflect the metaplastic consequences of GERD ("chronic injury")
- The ESGE definition of Barrett oesophagus is a combined endoscopic and histological diagnosis

# Take home messages

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- Do not overdiagnose metaplastic atypia as low grade dysplasia, also try to reduce the use of the term “indefinite for dysplasia” (unless for technical reasons)
- p53 immunostaining may be of help in difficult cases and shows two distinct patterns: overexpression versus absent staining (“null type”)
- The work up of endoscopic resections (EMR, ESD) requires a systematic approach, the result of which should be discussed in the multidisciplinary team (e.g. within tumour boards)

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# Thank you very much for your kind attention!

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