# Barrett-Esophagus

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# Who is Who in Esophagology and Pathology ?

**Rupert Barrett**

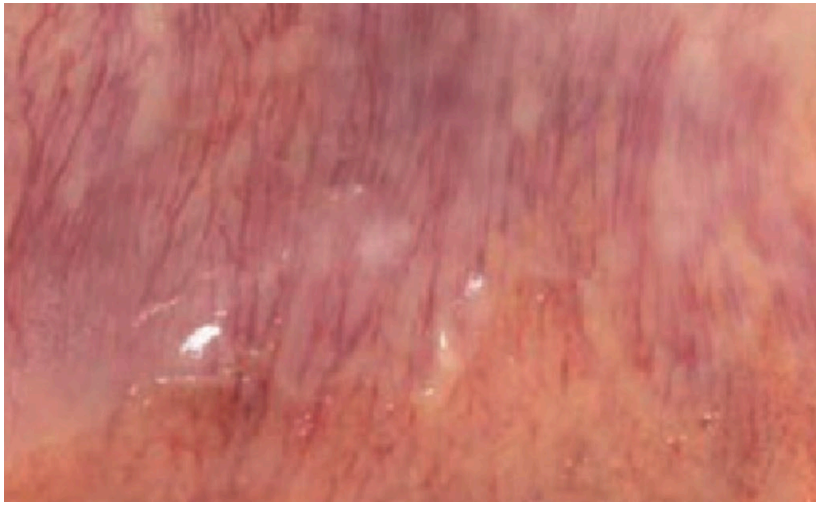
**Rupert Langer**

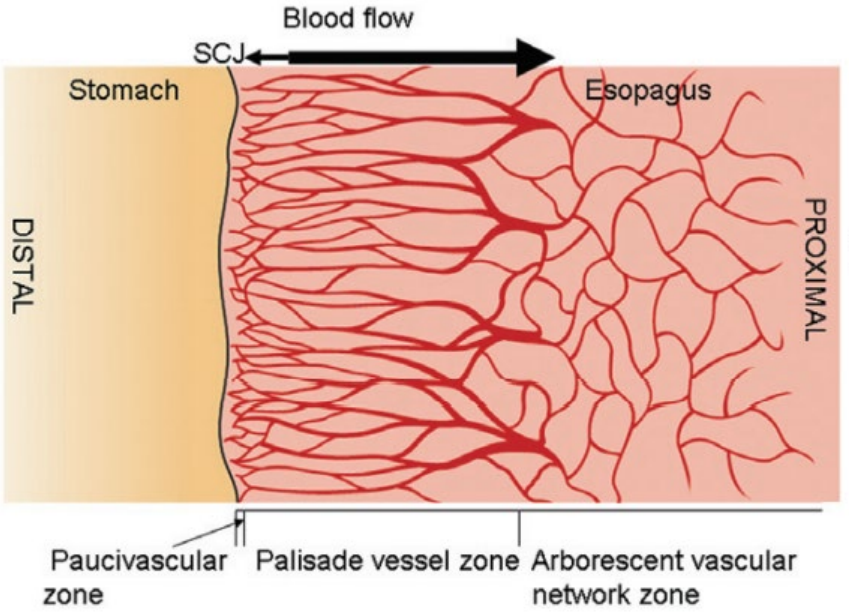
# Definition- Diagnosis

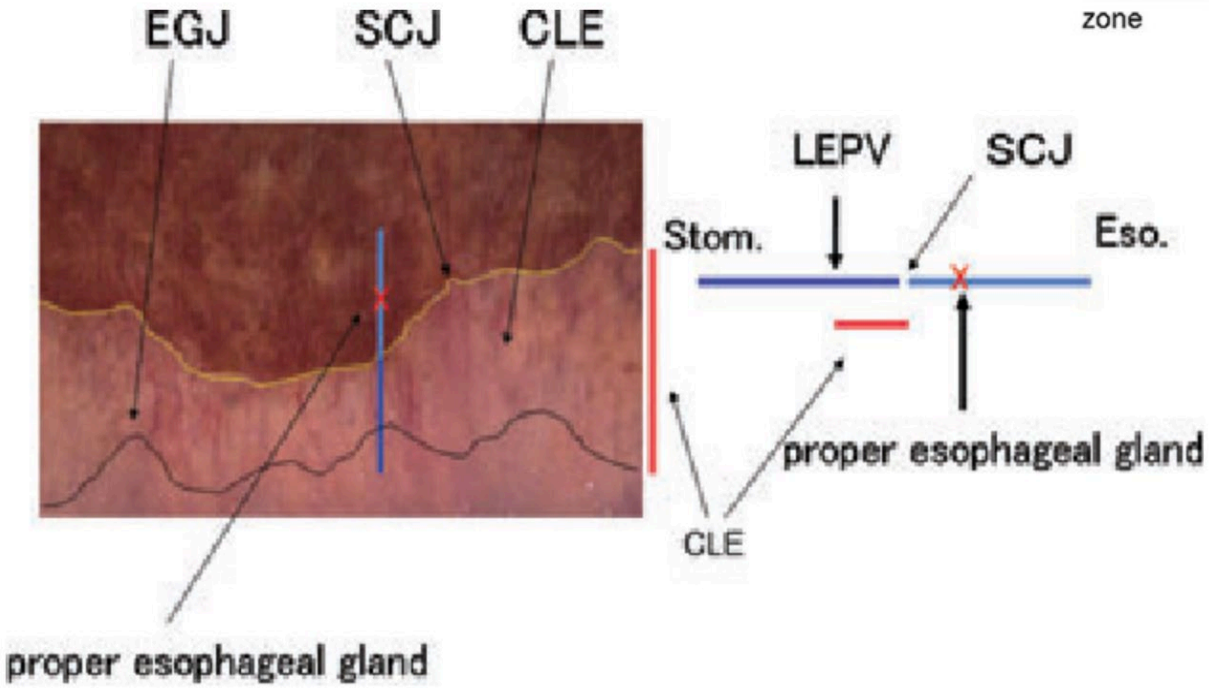
# How is the end of the distal esophagus defined ?

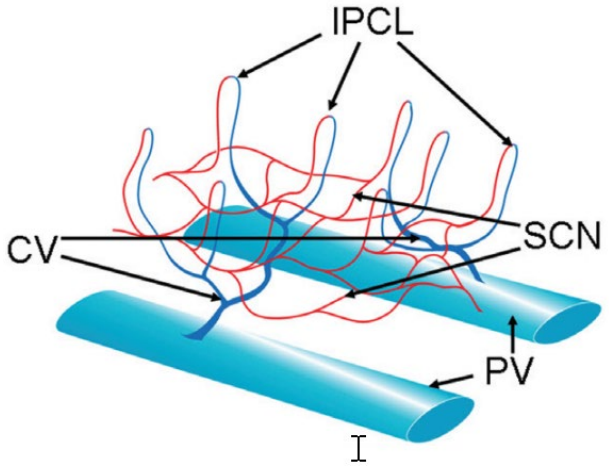
**easiest landmark to delineate the GEJ are proximal limit of longitudinal gastric folds at minimal air insufflation and is the suggested as minimal requirement**

**optional: but not more accurate palisade vessels at the distal end of the esophagus**






Kumagai et al. Dis Eso 2012

# How is Barrett-esophagus defined ?

## BSG:

*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oesophagus is defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) above the GOJ and confirmed histopathologically from oesophageal biopsies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).*

## ACG:

BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of IM (strong recommendation, low level of evidence).

# What is the relevance of presence of IM ?

**Of the types of metaplastic columnar epithelium in the oesophagus, intestinal is the most biologically unstable with the greatest risk of neoplastic progression through dysplasia to adenocarcinoma**

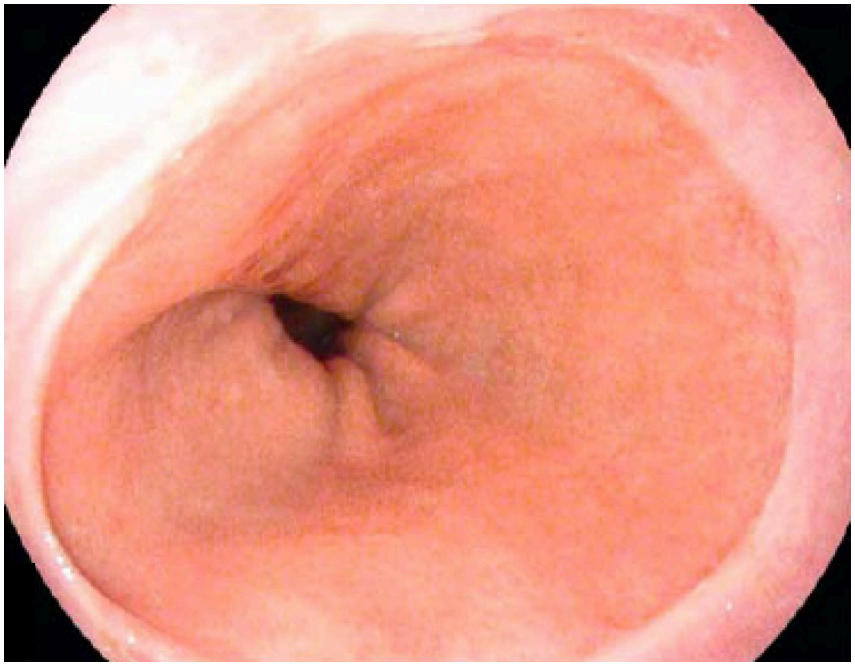
**Smith Am J Surg Pathol 1984**
**Bhat J Nat Cancer Inst 2011**

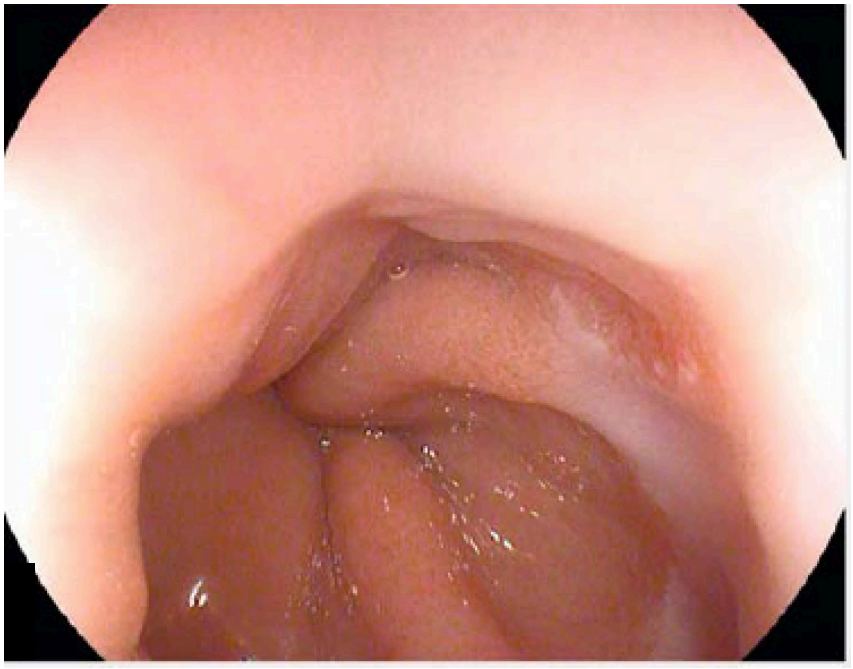
**Higher incidence of HGD and cancer in IM (0.38 vs 0.07 %)**

**Bhat J Nat Cancer Inst 2011**

**IM should be taken into account for surveillance !**

# Is this a barrett-esophagus ?





# Irregular Z-Line

- Squamocolumnar junction appears with tongues of columnar epithelium shorter than 1 cm and with no confluent columnar-lined segment
- Often harboures IM but with unclear significance
- No Bx recommended
- if Bx are taken labelling as GOJ important
- No surveillance in IM at the cardia or irregular Z-Line
- Whether there is IM or not

# How to scope a barrett-esophagus ?

- **Equipment: HD-monitor, -scope, cap**
- **Mucus clearance (aqua-jet) plus**
- **Acidic acid (Chromoendoscopy CE)**
- **Narrow-band-imaging (Virtual CE)**
- **Near-Focus-function**

- **Retroflexion in cardia**
- **Long enough inspection time**
- **Particularly “danger” zone**
- **First biopsy most important**

**CE/VE**
**Absolute increase**
**9 %**
(1-14% 95 CI)
**Relative increase**
**30%**
(14-44% 95CI)
**Dysplasia Detection**

# Barrett-Esophagus-Carcinom: NBI + Near Focus


**Well- differentiated Adeno-Carcinom**
**T1a N0L0V0 G1 R0**

# NBI= BING-Classification in Barrett-Endoscopy

**Endoscopy campus**


| Morphologische Charakteristika | Klassifikation |
|---|---|
| **Mukosale Oberfläche** | |
| Zirkuläres, villöses/gyriertes oder tubuläres Oberflächenmuster | regulär |
| Fehlen o.g. Charakt | irregulär |
| **Mukosale Gefäßar** | |
| Gefäße regelrecht e<br>normaler, längliche | regulär |
| Fokal oder diffus ve cht<br>der Mukosa, kurz und irregulär verzweigt | irregulär |

**when high level of confidence**

**> 90%**
**diagnostic accuracy**

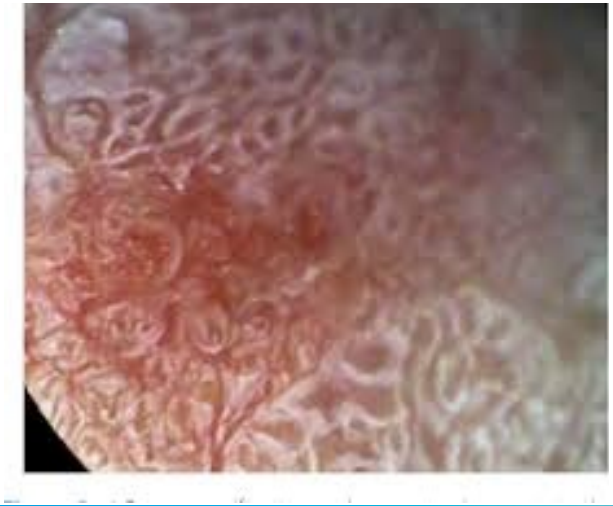
**95% NPV and 89% PPV**

# Barrett esophagus: 3 steps to do (see, capture ……)

**6.5-fold gain**
**in detection of neoplasia**
**Number biopsies required to detect one neoplasia**
**15-times lower**

Tholoor et al. GIE 2014

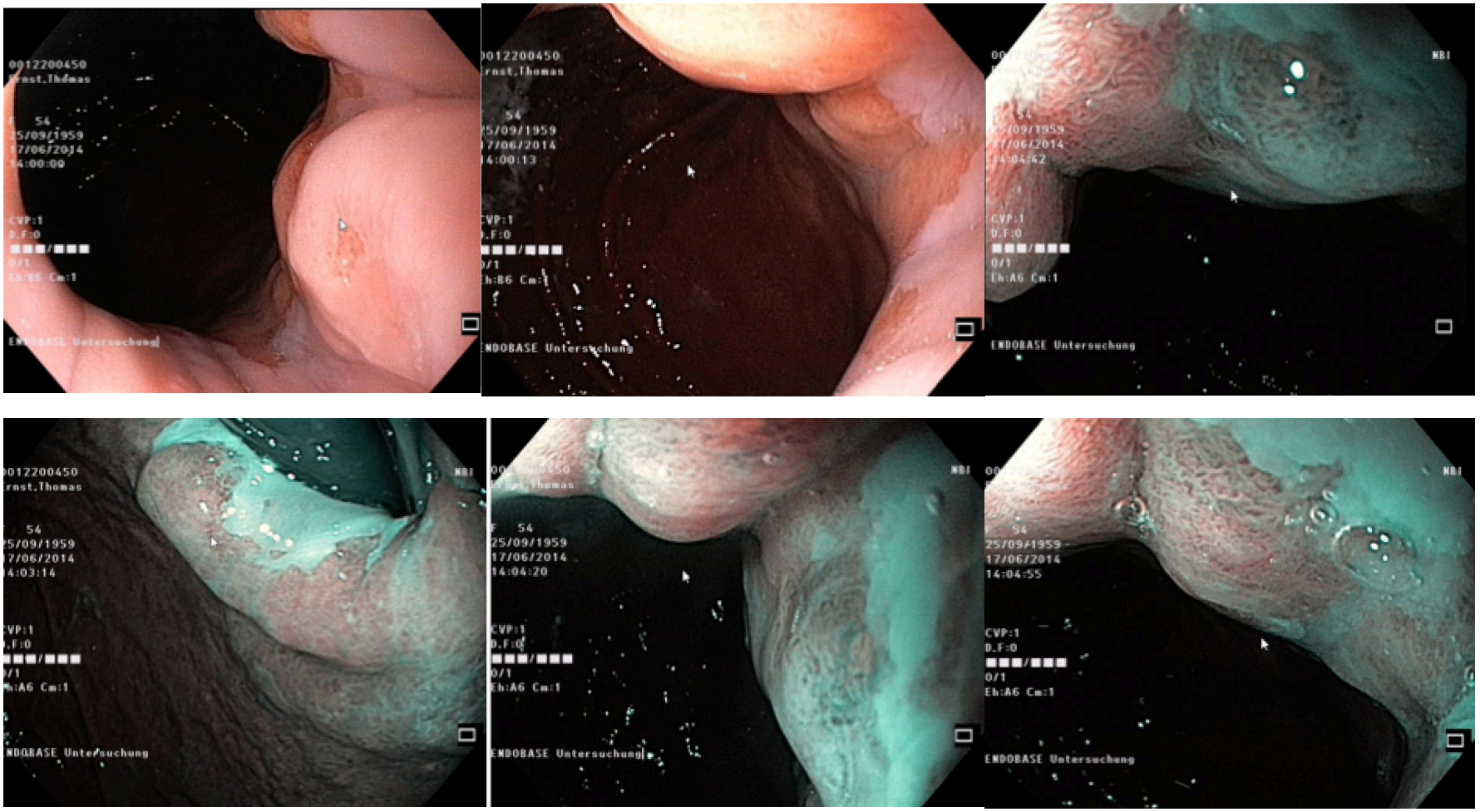
Near Focus



**How long does it take for "loss-of-whitening" ?**

**Up to 2 min**
**(for Dysplasia)**

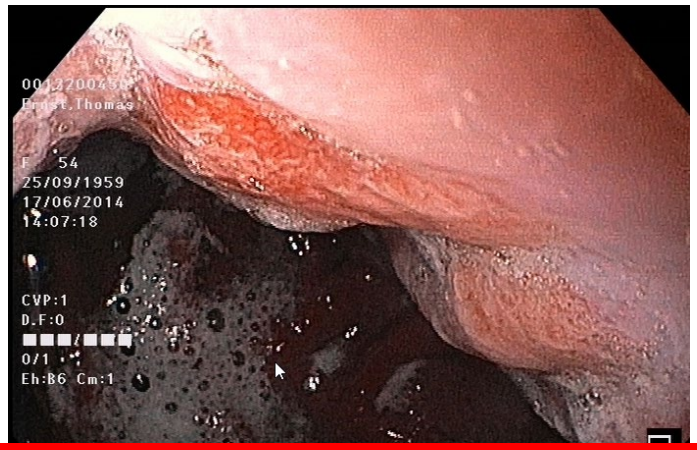
# GE-junction – normal or not ?

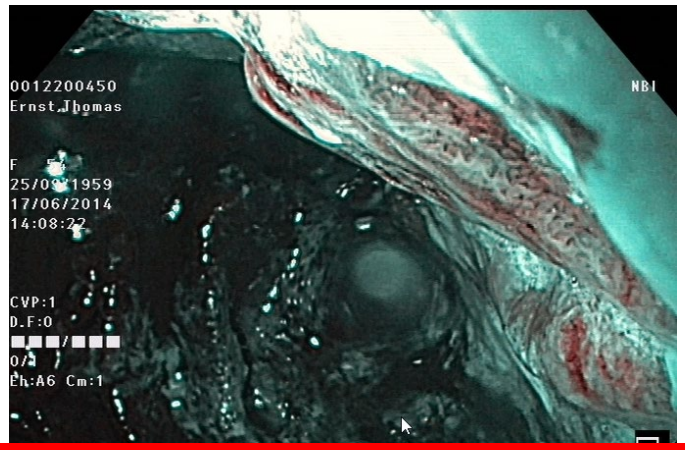




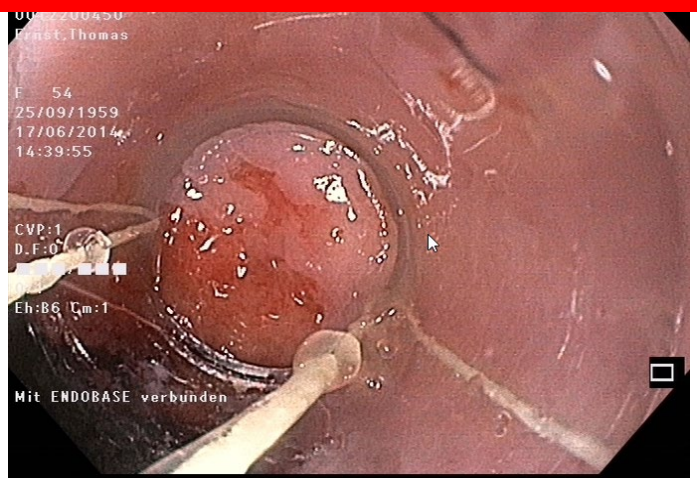

Ernst Thomas 25.9.1959

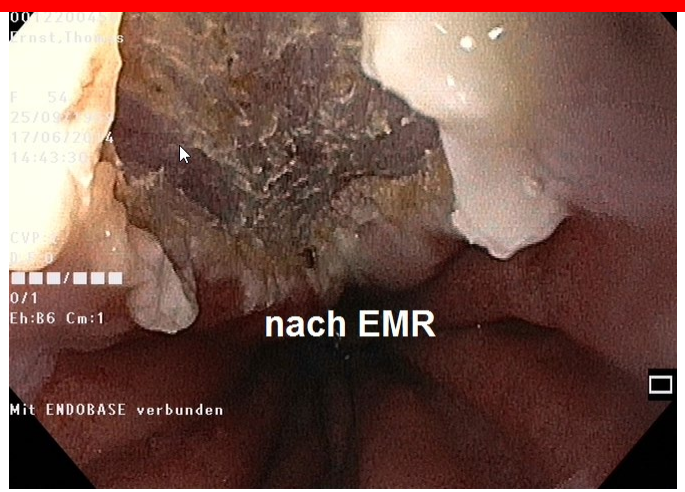
# Barrett-Esophagus-Carcinom




**Moderate differentiated Adeno-Carcinom**
**T1a N0L0V0 G2 R0**



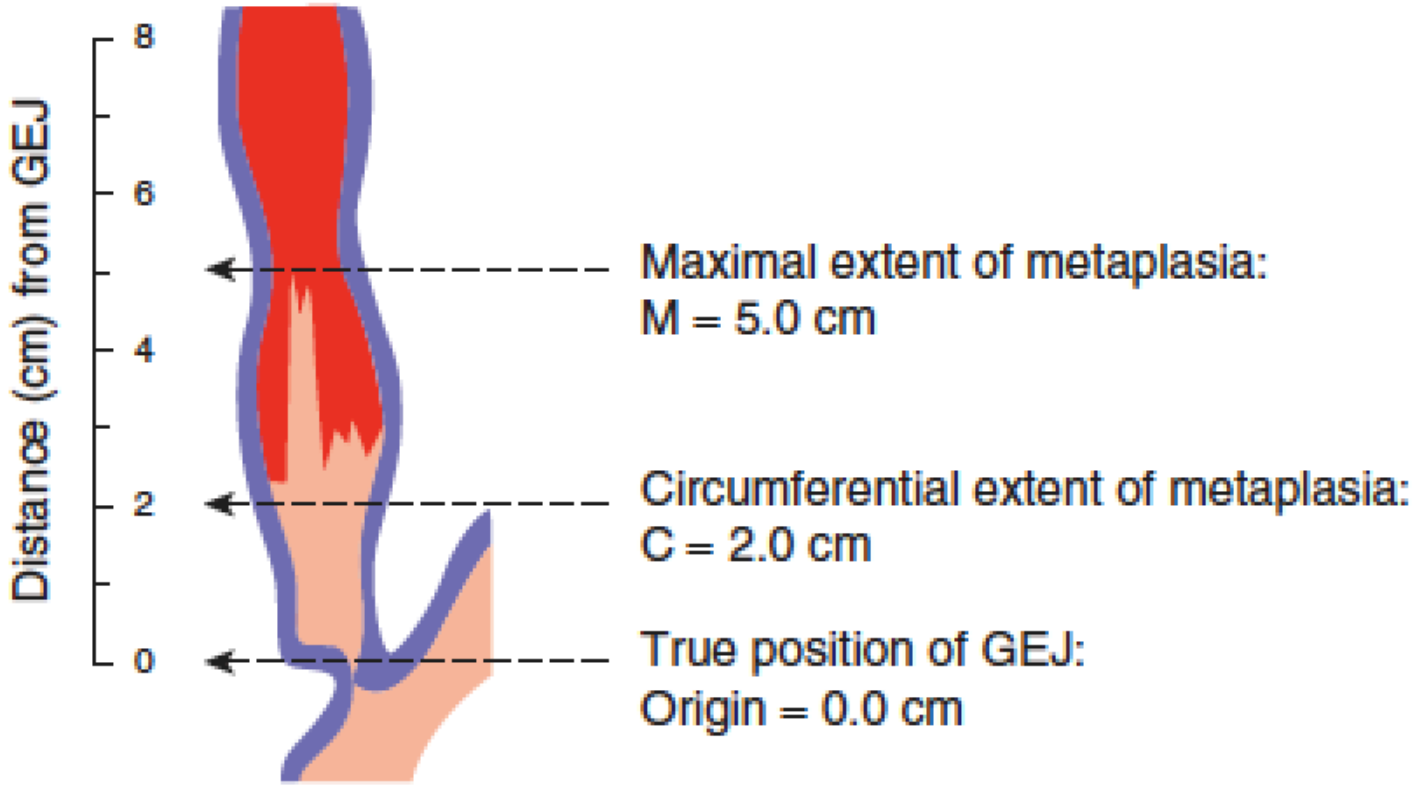



Ernst Thomas 25.9.1959

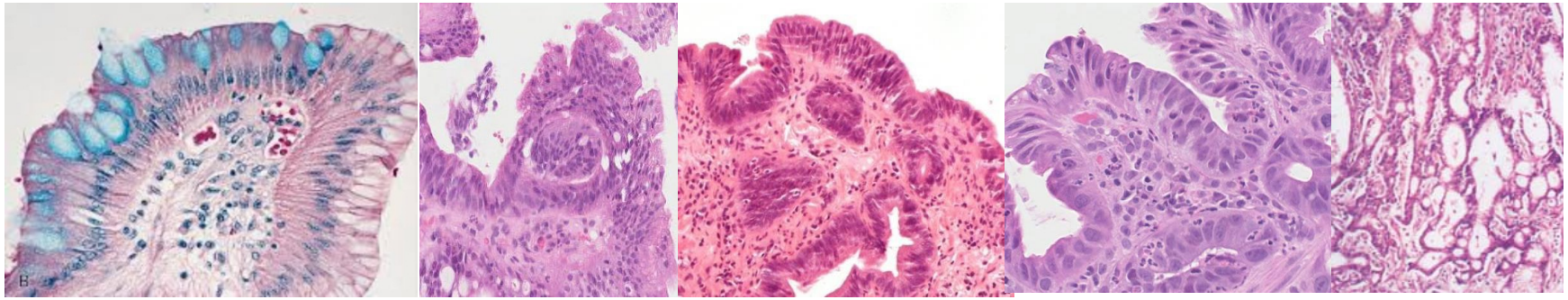
# The big 5: What do you need to document in Barrett-report ?

1. Extent of BE: Prag-Classification + any separate island
2. Visible lesion: size, Paris-classification and location
   -in cm from incisors and clockwise orientation
3. Presence or absence of
   -Esophagitis/GERD: Los Angeles classification
   -Hiatal hernia ? (Hill-Classification)
4. Biopsies: locations (in cm from incisors), numbers
5. Photo-documentation of landmarks, lesions

# Prague-criteria and classification



# Epidemiology- Cancer Risk



| BE | indefinete | LGD | HGD | adenocarcinoma |
|---|---|---|---|---|

**Incidence ratio of AC 11.3**

# What are pre-/incidence of BE ?

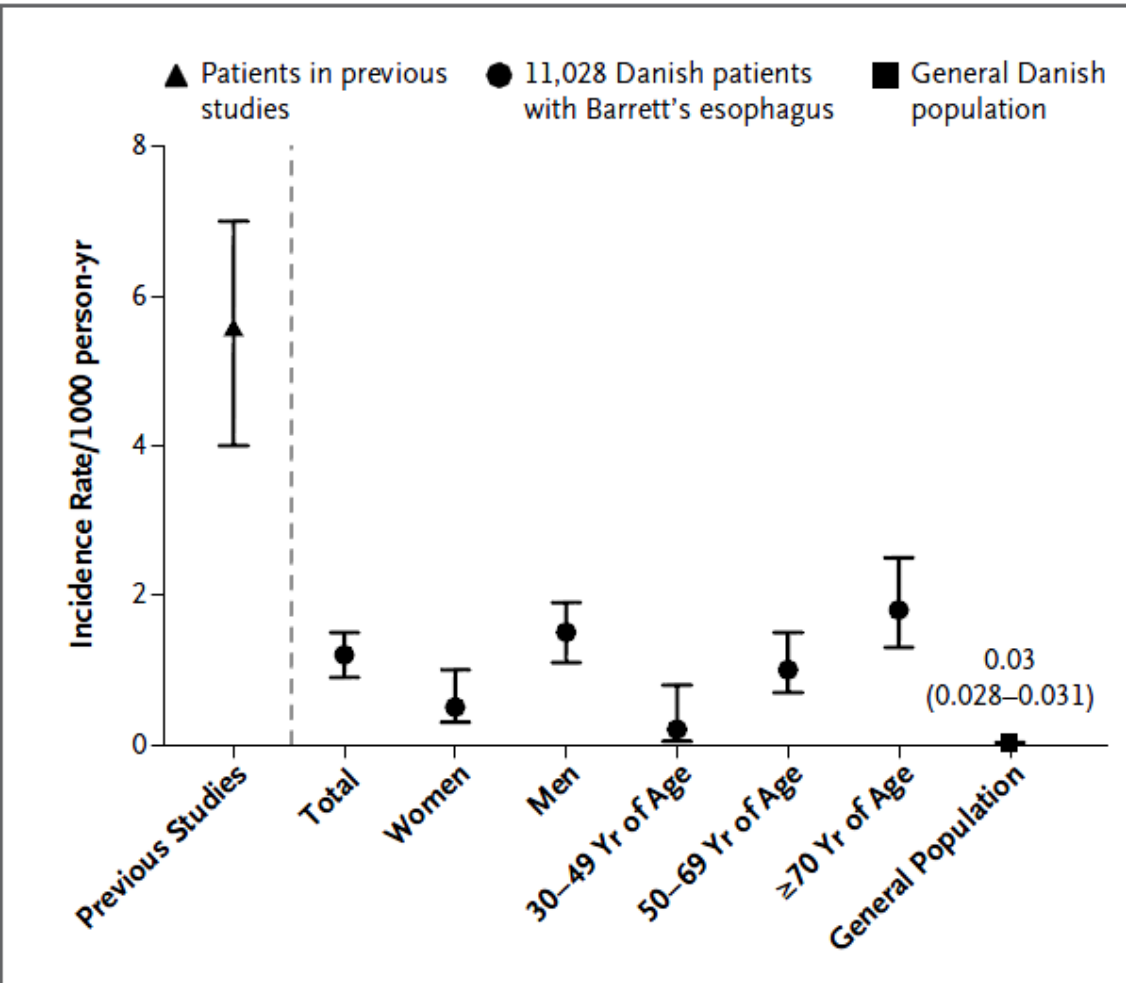
- Prevalence of Barrett: 1.3-1.6 % overall (Zagari Gut 2008)
  - –Asymptomatic: 1,4 % Symptomatic GERD: 2,3 %
    *but < 40 % of CA do not have GERD*
  - –High risk : 13,2 %

*Westhoff, Gastrointest Endosc 2005; Ronkainen, Gastroenterology 2005*

- BE incidence in Eastern Switzerland
  15.5/100,000 inhabitants 1998

Hurschler D swiss med wkl 2003

- new diagnosed esophageal cancers in CH
  381 (2013) and 497 (2019: Krebsregister Schweiz)




**follow up: 5,2 years**

## Incidence of Adenocarcinoma among patients with Barrett's Esophagus

lower than in historical data

**0.12 % vs 0.5 %**

*Frederik Hvid-Jensen et al. N Engl J Med 2011*

# What risk factors for BE development do you know – when to screen ?

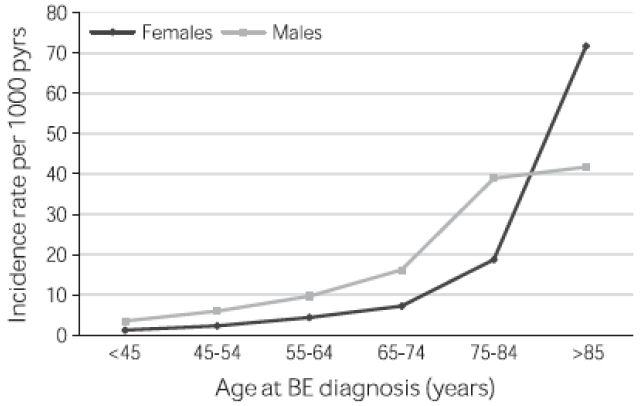
- male gender,
- caucasian ethnicity
- older age (> 50 ly; OR ≈1.5-2.0
- GERD (chronic > 5y OR≈ 3, > 1
- cigarette smoking (OR ≈ 2)
- abdominal/Central obesity (OR ≈2)
- axial hernia (OR for long-segment BE ≈12)

**Screen when multiple (at least 2 or more) risk factors)**

**positive family history – up to OR 12**
**(at least one first-degree relative with BE or AC)**
in case of pos FA lower threshold

# What are risk factors for Adenocarcinoma-development in barretts esophagus ?

- Length of Barrett-mucosa
- Advancing age
- Male sex
- Smoking
- Ulcers, strictures and nodules!
- Lack of PPI, NSAID/ASS, Statins




**Cave: Less than 10% of all esophageal AC have a prior diagnosis of BE**

Plus ….. Krishnamoorti et al. CGH 2018

# Biopsy-regimen / recommendations

**Endoscopic report should include number of biopsy samples**

**<u>Seattle protocol:</u>**
**four-quadrant random biopsies (=4) every 2 cm in addition to targeted biopsies on macroscopically visible lesions**
**If < 2 cm also try to get 8 biopsies**

**Levine DS, Blount PL Am J Gastroenterol 2000**

**Adherance low! -> centres**

# What is the risk for progression to HGD/cancer in BE without dysplasia ?

**Annual progression rate:**

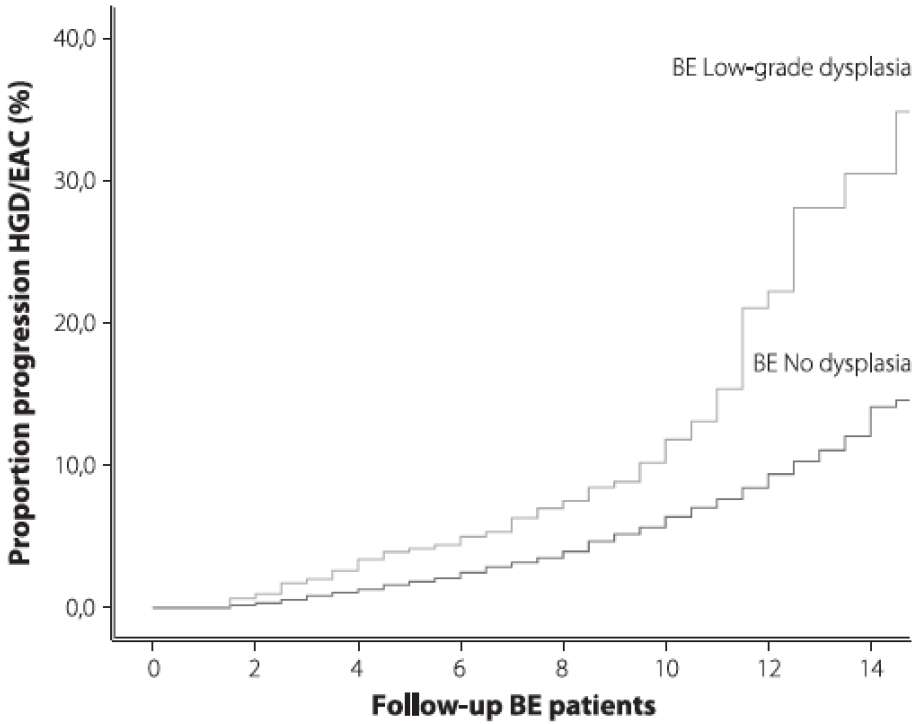
**0.3% for cancer**

**0.5% for HGD**

**Cumulative over time**

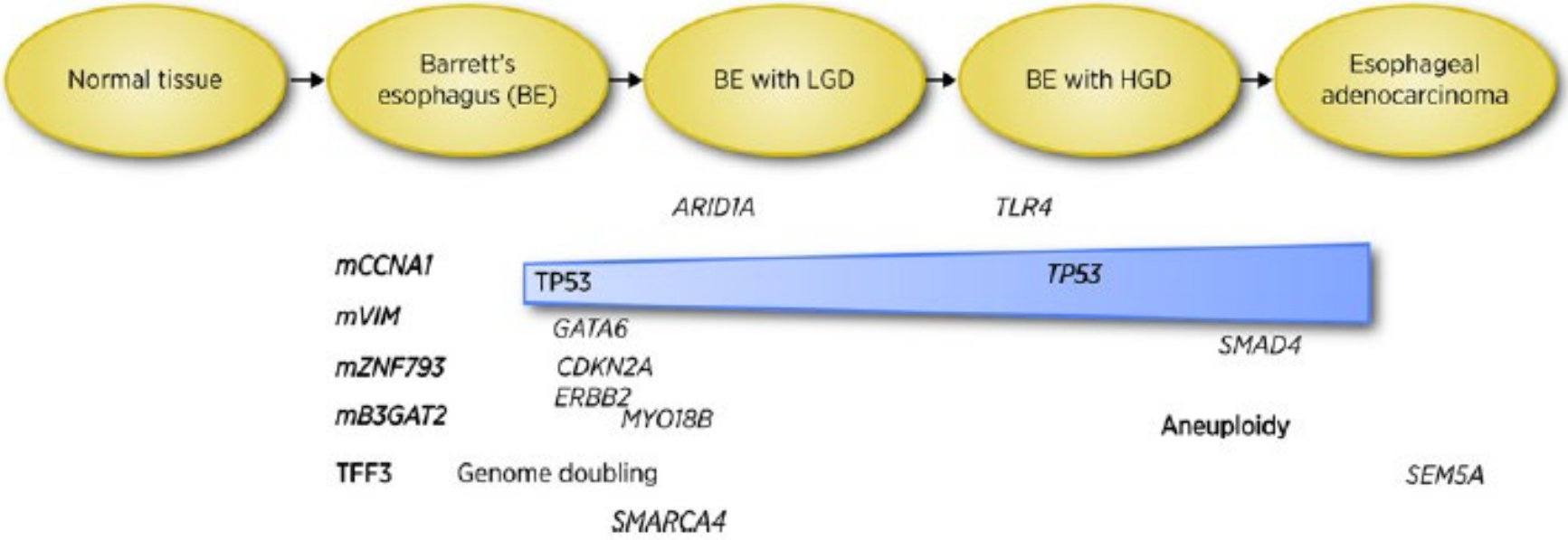
**extreme high NNT**

**to prevent one cancer**




De Jonge et al. Gut 2010

# What potential biomarkers for increased risk in BE do you know ?




Grady W CEBP Focus 2020

# What potential biomarkers for increased risk in BE do you know ?

**helps diagnose dysplasia**

**aberrant P53 mutation**
**= tumorsuppressor gene**
**when mutated = non-functional**
**improves reproducability in diagnosis**
**reduces inter-observer variability**

**P53 Immuno-staining**

**presence in LGD= independent predictor for progression**
**increases relative risk for progression by factor 12**
**PPV 54% and NPV 95%!**

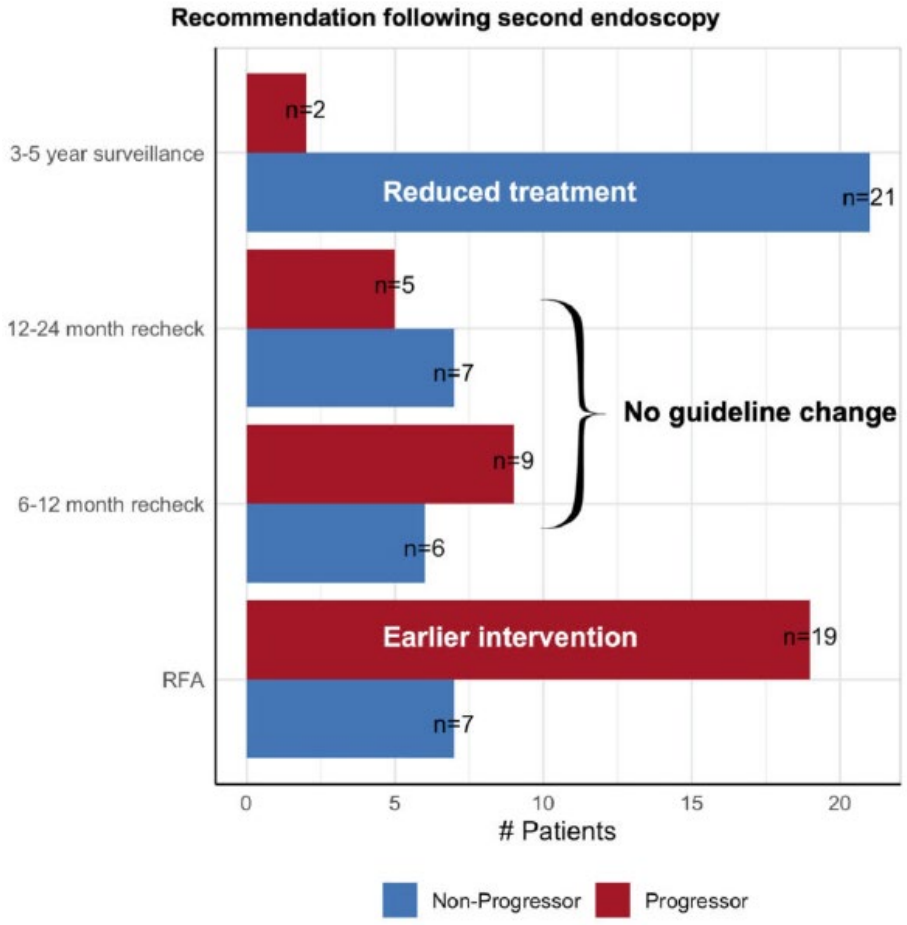
45% of patients have aberrant p53expression
up to 5 years prior to progression

Davelaar AL Genes Chromosomes Cancer 2015

Kastelein F Gut 2013

# What potential biomarkers for increased risk in BE do you know ?

- Genomic copy numbers
- DNA content abnormalities
- Chromosomal abnormalities
- Gene mutations
- Methylation changes




**But:**

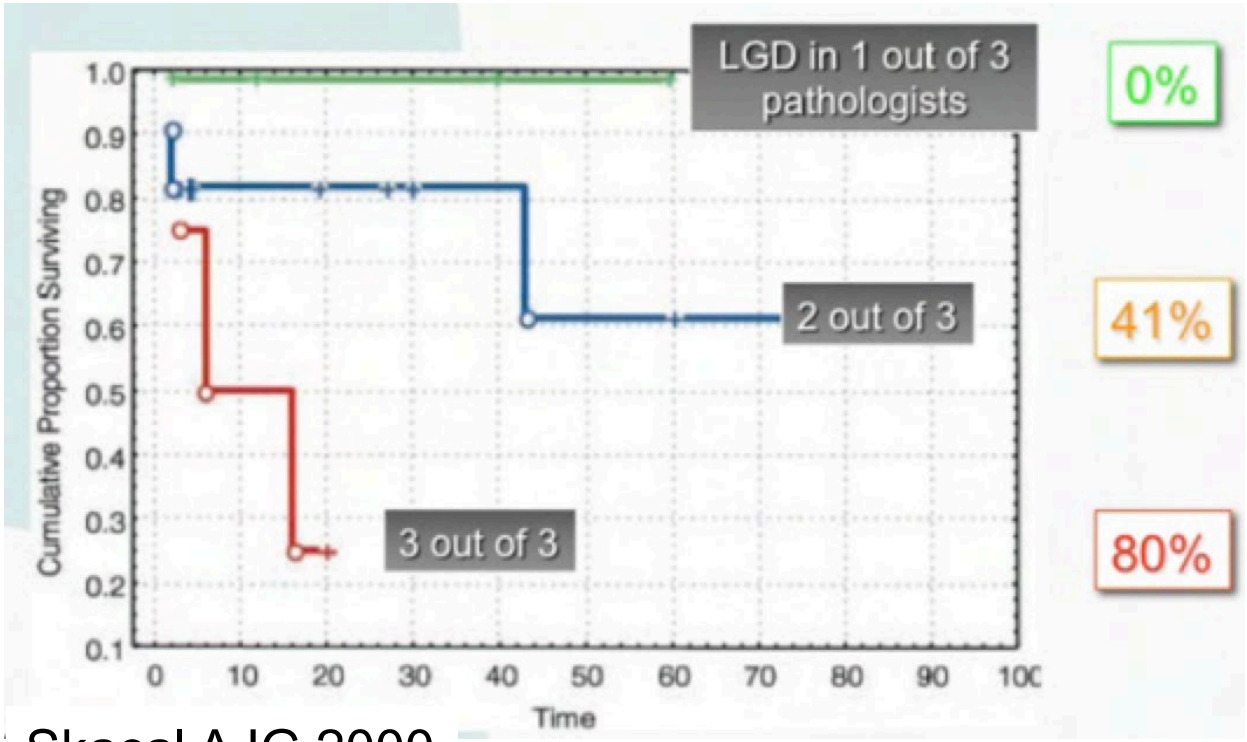
**no single biomarker is adequate for risk stratification…..**

# What you know about agreement of pathologists on dysplasia – e.g. LGD ?

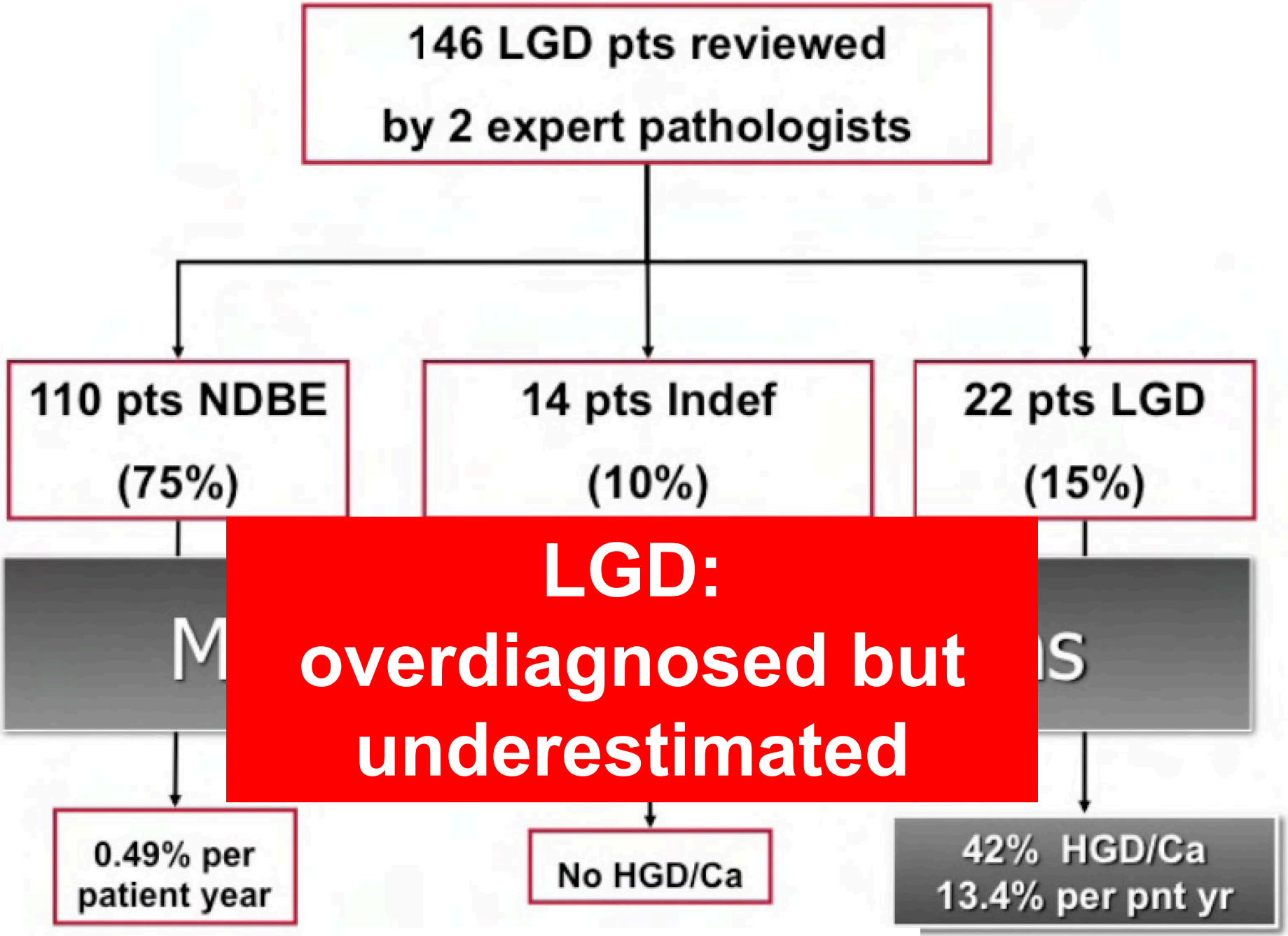
**Correctly diagnosing LGD is tough**

*Consensus diagnosis (3 pathologists):*
*high risk of progression*

**agreement between any two pathologists Kappa -0-4 to 0.28 = poor**

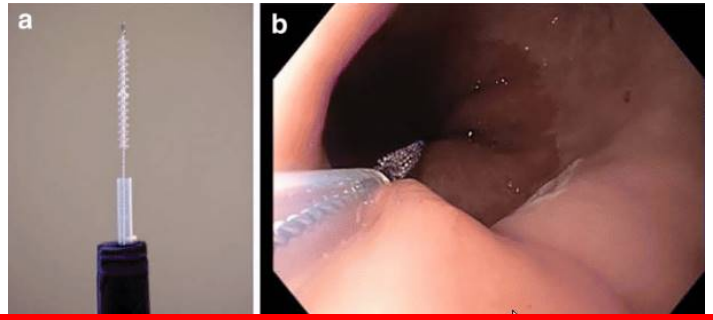



Skacal AJG 2000



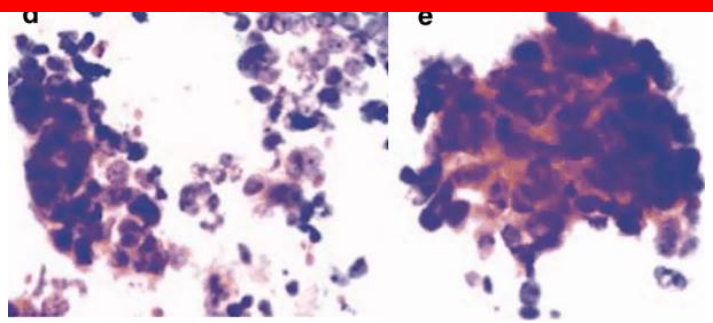

Curvers et al. AJG 2010

# What is the role of WATS-3D for detection of dysplasia ?




**Special abrasiv brush**
**getting deep layers**
**uncut preserved 3 D structure**
**=larger surface area > biopsy**

**All studies sponsored by manufacturer**
**Benefit mainly in LGD-detection**
**But no standard definition in computer-based system as compared to histopathology**




**48%**
(34- 60%; 95CI)
**in**
**dysplasia detection**

# What is the risk for progression to HGD/cancer in dependency on degree of dysplasia ?

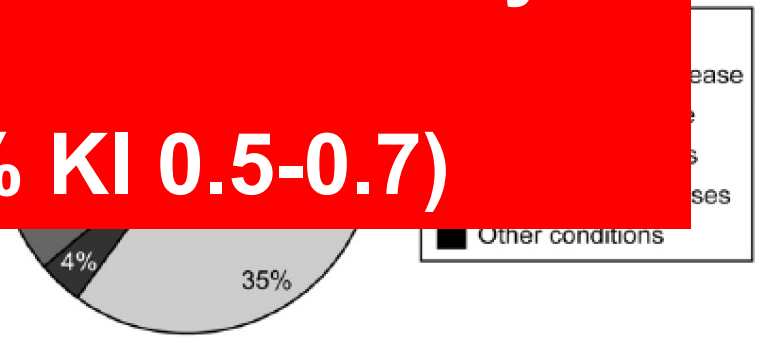
| | | EAC | HGD |
|---|---|---|---|
| LGD: incidental/all | → | 0.5% | 1.7% |
| uni- vs. multifocal (for EAC or HGD) | → | 1.4% vs. 3.5% | |
| HGD: any type | → | 7-19% | |

# What is the likelihood to die of a BE-unrelated cause in non-dysplastic BE ?

**But:**
**Surveillance in non-dysplastic BE reduces AC-related mortality**

**RR 0.60 (95% KI 0.5-0.7)**

**fro**
**Incide**
**3/1000 person-years**



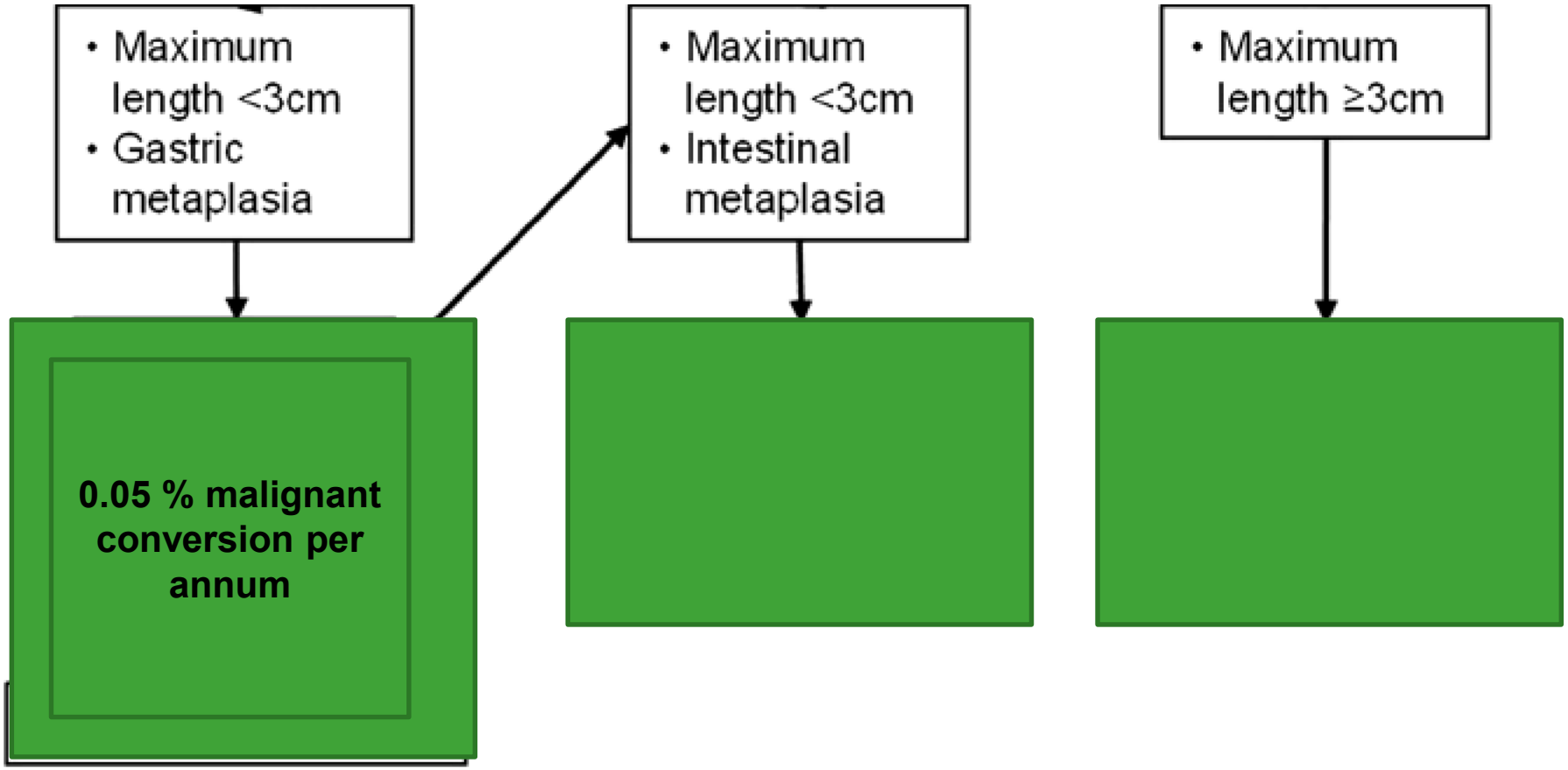

**only 7% of deaths from AC**

Sikkema et al. CGH 2010

# Treatment and Surveillance

# How is surveillance recommended in non-dysplastic BE ?

**ECOG score 0-2 (self care possible) – fit for endoscopy**



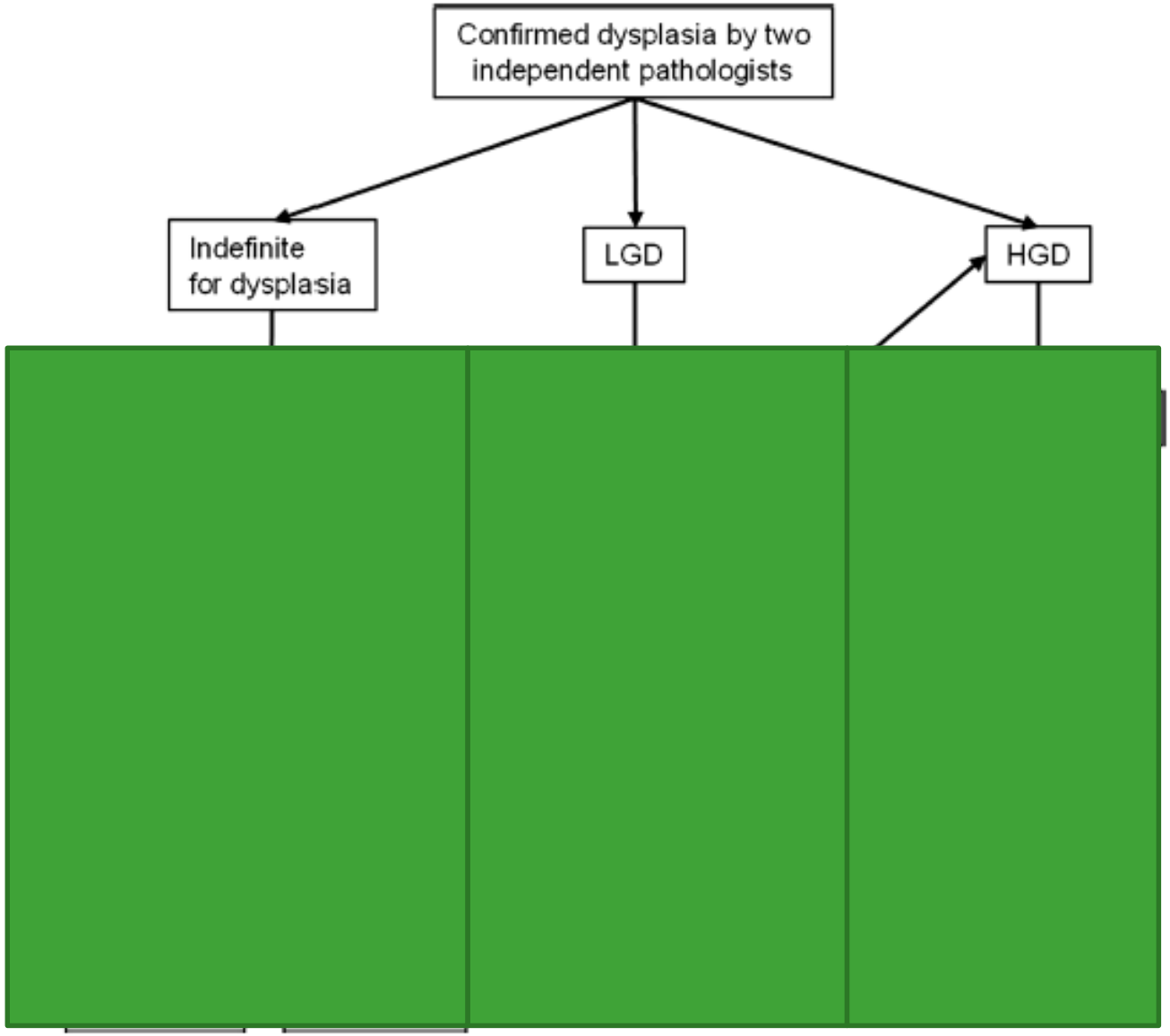
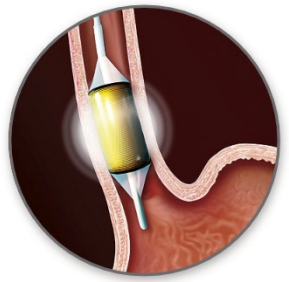


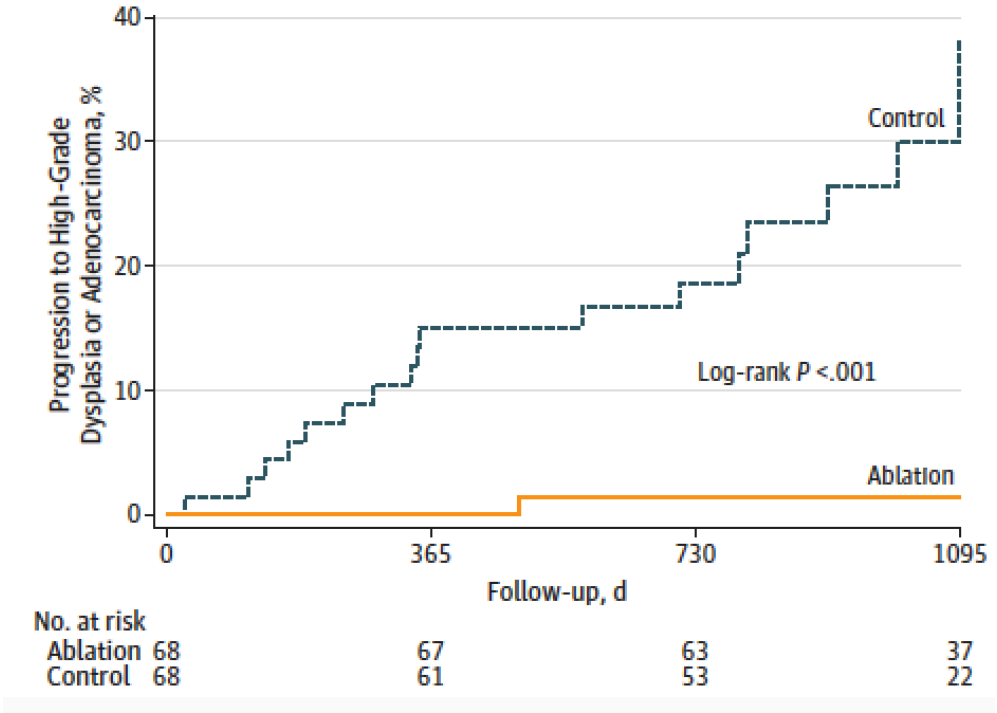

**Figure 4** Surveillance flow chart for dysplastic Barrett's oesophagus (BO). A pathological finding of indefinite for dysplasia does not exclude the presence of dysplasia, therefore a 6-month follow-up is warranted. Six-monthly surveillance and endoscopic treatment are generally recommended for low-grade and high-grade dysplasia, respectively. MDT, multidisciplinary team; OGD, oesophagogastroduodenoscopy.

# What to do when LGD is confirmed ?

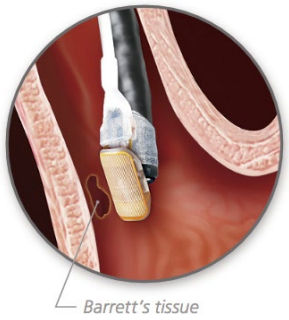
HALO$^{360}$ Ablation Catheter



## RCT: RFA vs. surveillance (3 year follow –up)

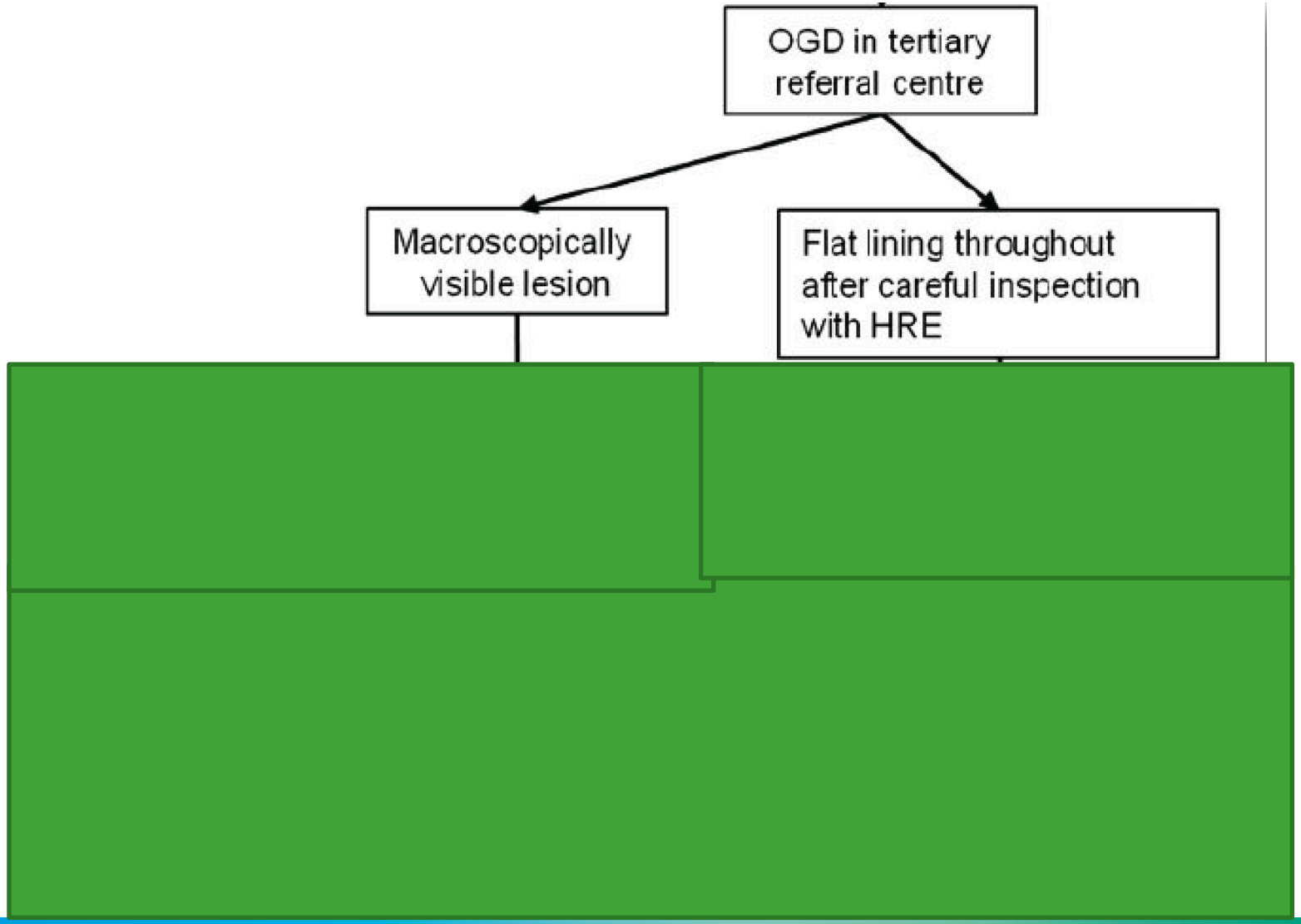



HALO$^{90}$ Ablation Catheter




Phoa et al. JAMA 2014

# What are the therapeutic options for HGD ?



# Refractory Barrett-/IM after RFA – frequency, risk factors ?

**Average number RFA to completely eradicate all BE > 2**

**No current accepted definition for refractory BE**

**But > 3 RFA sessions ……**

If after 1st RFA < 50% BE eradicated indicates poor response:
less likely to achieve complete eradication,
more RFA sessions (median treatment >12 months and >3 RFA)

**Risk factors for failure to achieve complete eradication:**

**ongoing reflux exposure (acidic and biliary)*, hiatal hernia**

**BE-length > 5cm**

*: optimize before RFA/treatment

# Refractory Barrett-/IM after RFA – proceedings ?

**Up to 15 % fail to eradicate BE within 3 RFA-sessions**
**Do all you can to optimize anti-reflux-measures:**

-Patient education on appropriate use of PPI, 30 mins before meal
-Medication reconciliation and documentation of PPI compliance
-On-treatment reflux testing (24 h pH impedence) and HRM
-Consider Antireflux surgery

**Salvage-endoscopic treatment:**
**Wide-field EMR**
**Evtl. Plus APC (Cryoablation)**

95%
achieve BE-eradication
by RFA after fundopliatio

# What are adverse events of endoscopic treatment ?

| | |
|---|---|
| **Overall complication rate** | **8.8 %** (95% CI 6-12%) |
| **Stricture rate** | **5.6 %** (95% CI 4-8%) |
| **Bleeding rate** | **1 %** (95% CI 1-3%) |
| **Perforation rate** | **0.7 %** (95% CI 0.3-2%) |

**EMR higher AE-rate vs RFA**
**v.a. only EMR-based eradication**
**v.a. > semicircular procedures**

# When is EMR/ESD curative ?
# when further treatment needed ?

all features

**T1a or T1b**
**sm1**
**G1 or 2**
**L0**
**V0**
**R0**

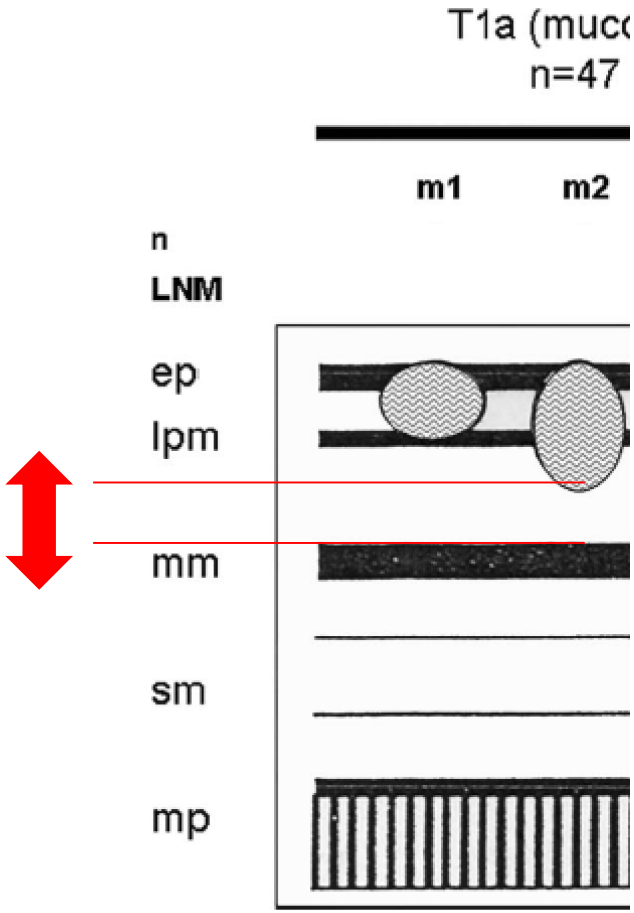
**Lymph node positivity < 2%**

**T1b with**
**> sm1**
**undifferentiated**
**L+**
**V+**
**R1 deep margin**

Any of features

**?**

# Rate of LN-positivity in early BE-cancer




Manner et al. CGH 2013

**Diagnostic accuracy**

**T1b vs. 1a EUS best modality**

**LN+ EUS-FNA + CT/MR (DWI)**

**NPV suboptimal**

**(55 - 90 %)**

## Is (PET)-CT indicated if early esophageal cancer is supposed?

Not strictly

## What about EUS?

Can be done, but frequent over- (15–25%) and understaging (4–12%) of T1 vrs T2

But in CA > T1 predictive for 1-, 3- and 5-year survival

Anandasab et al. DigDis 2011

# How to follow-up after curative EMR (HGD/EAC)

**Eradication of BE by RFA**

**> 80% have remaining dysplasia, 20% metachronous lesions**

**Surveillance every 3 month for 1 year,**
**then 6-months in second year, afterwards annually**

**Biopsies of the prior extend of BE**
**(burried dysplasia!)**
**4-quadrant plus GE-junction (=high-risk zone)**

# How to follow-up after BE-ablation with achieved complete-eradication (=no IM) ?

**Baseline LGD:**

**at 1 and 3 years and thereafter every 2-3 years**

**Baseline HGD/early cancer:**

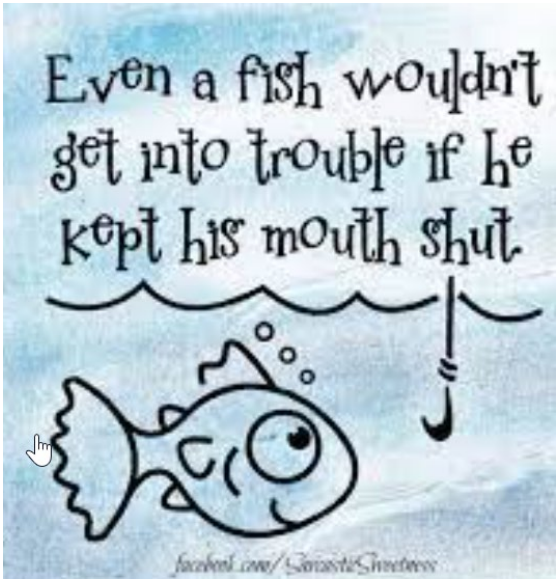
**3, 6 and 12 months and thereafter annually**

# What is the recurrence rate (and risk factors) after BE-ablation ?

**> 20% at 2-3 years or at least 8-10% per patient-year**
**Up to 25% with HGD/EAC**

**Risk factors (HR):**

**long-segment, low-volume-center, baseline-dysplasia**
**effective acid suppression !**




It's much easier to stay
out of trouble now than
to get out of trouble later

Warren Buffett

PICTURE QUOTES.com

**High-dose PPI**
**(plus Aspirin)**
**a day**

**keeps Barrett/Cancer away**


# How should post-therapy recurrence be treated ?

**Per se same tool/strategies as intial**
**= RFA (e.g. add-on express-balloon if not used initially)**
**= EMR (e.g. islands if no EMR before)**

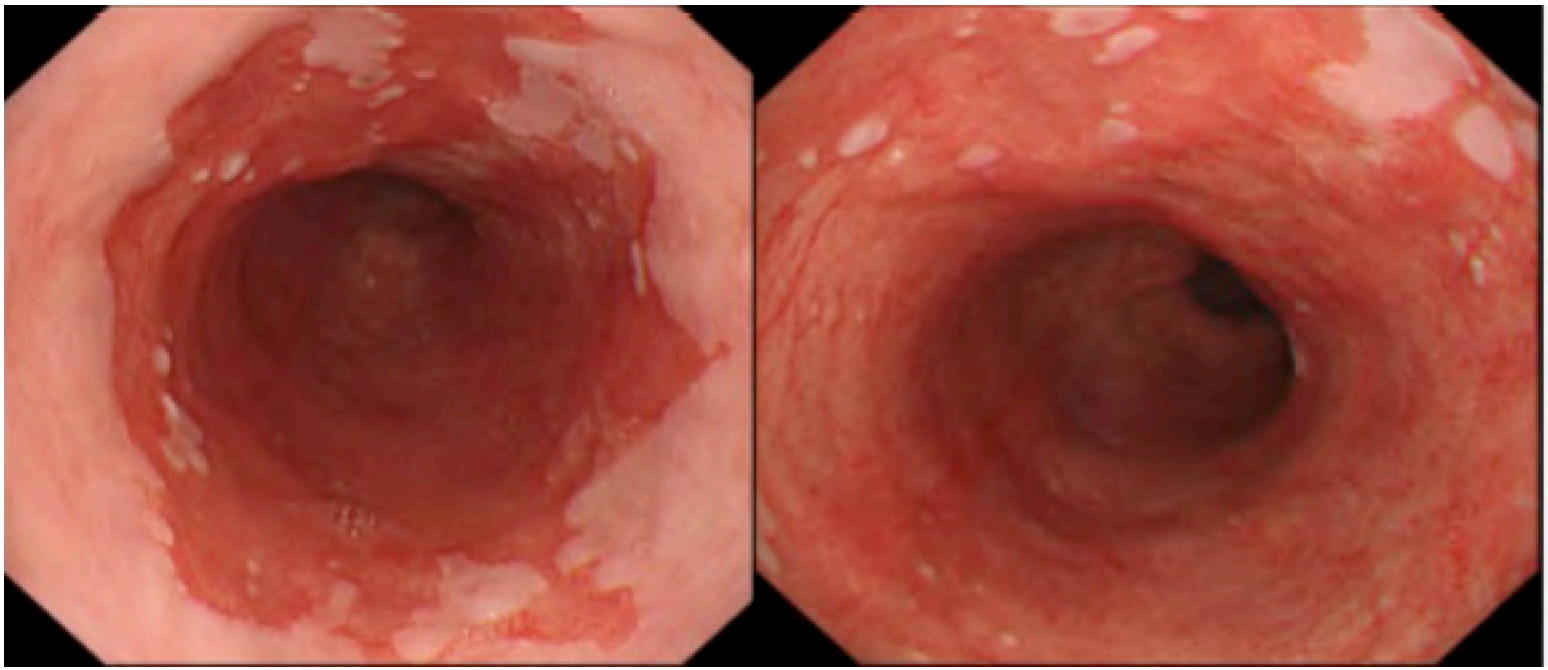
**Recurrence in initial HGD-cases:**
**High-risk situation: surgical consultation**

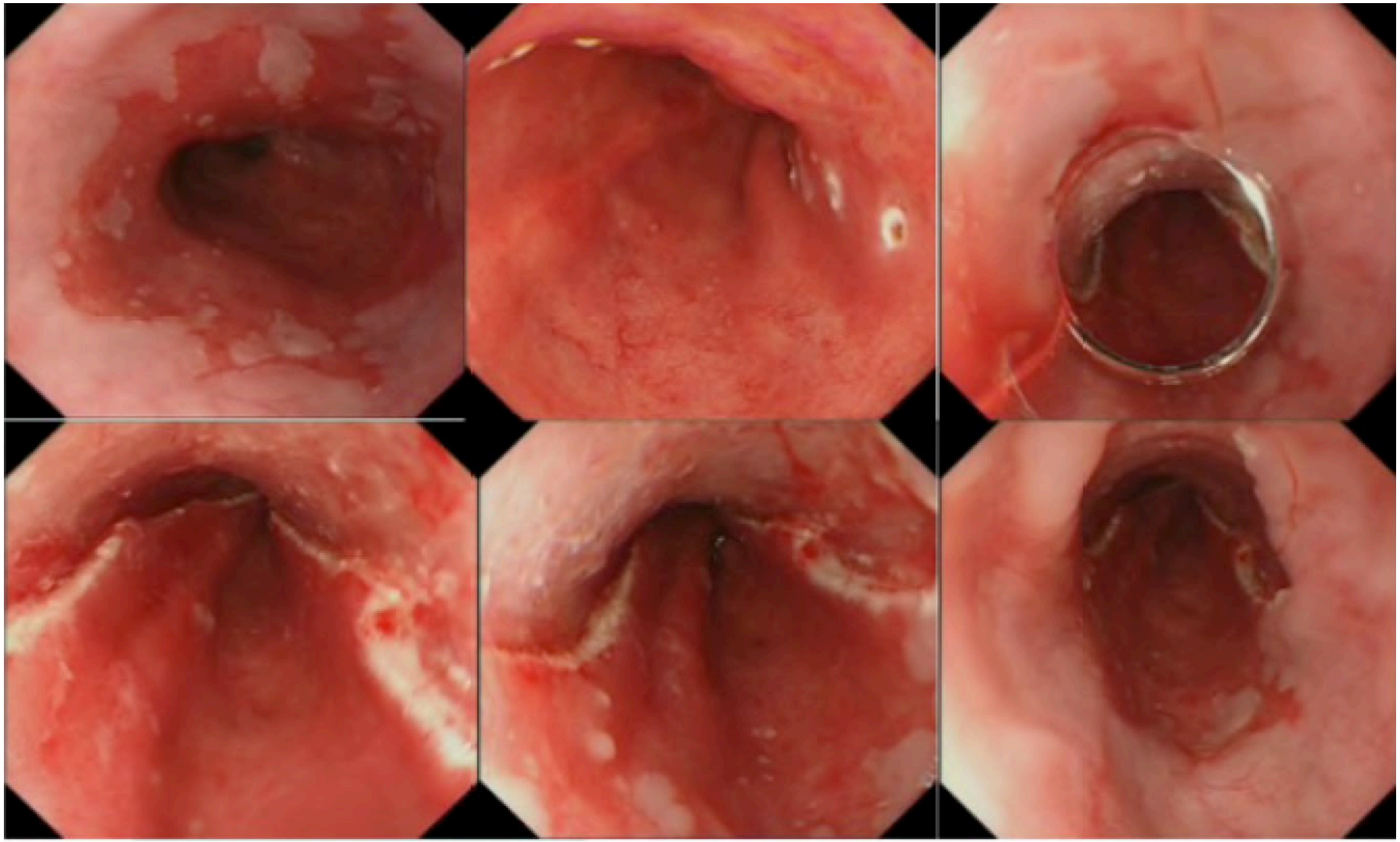
**If you doubt cut it out !**

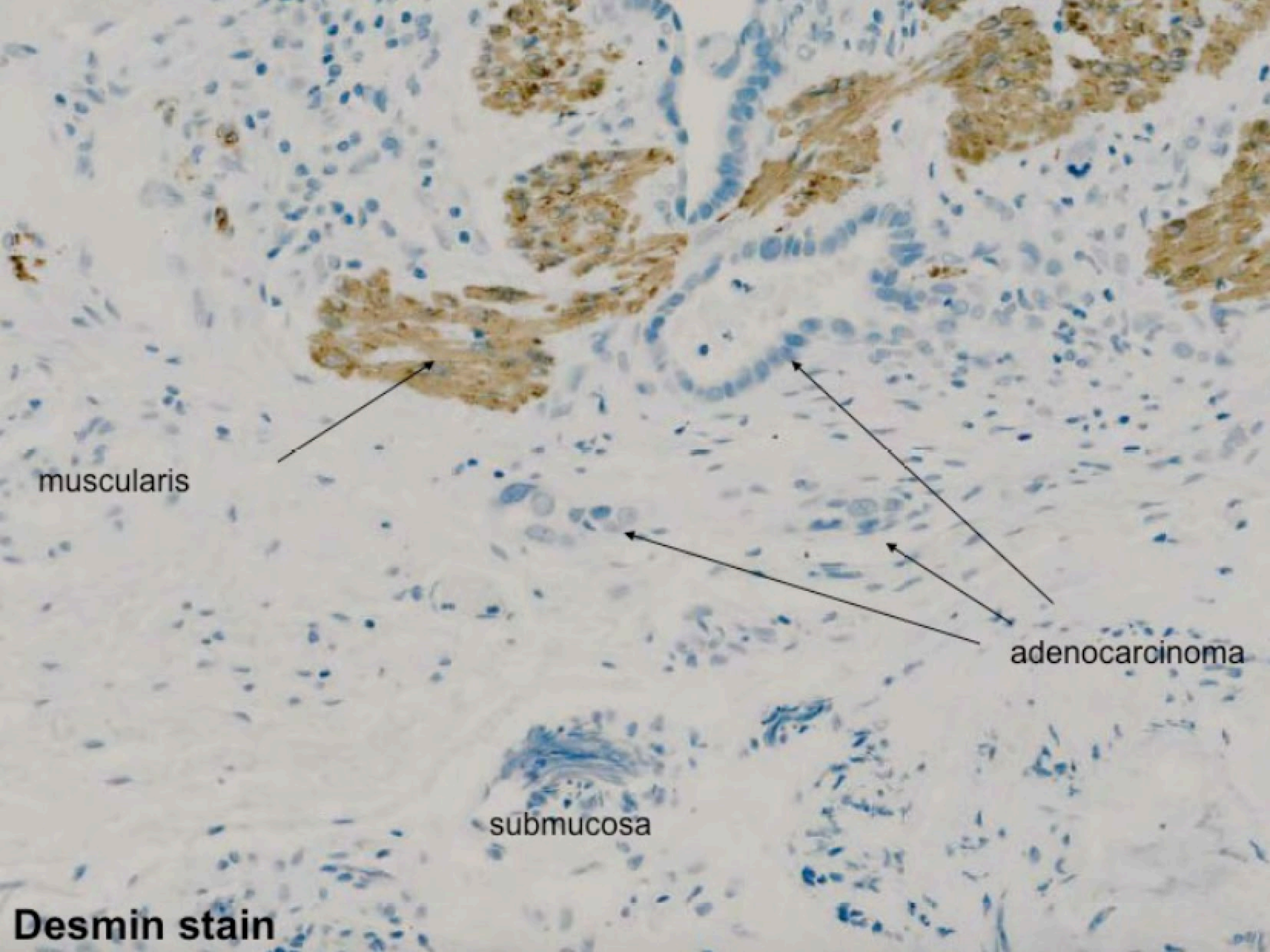
**Every hint on visible lesion**

**when ever you think of that there is something different go for EMR**

- 68 year old male patient.
- C9M10 BE with a subtle visible abnormality upon WLE.
- Treatment: piecemeal endoscopic resection.

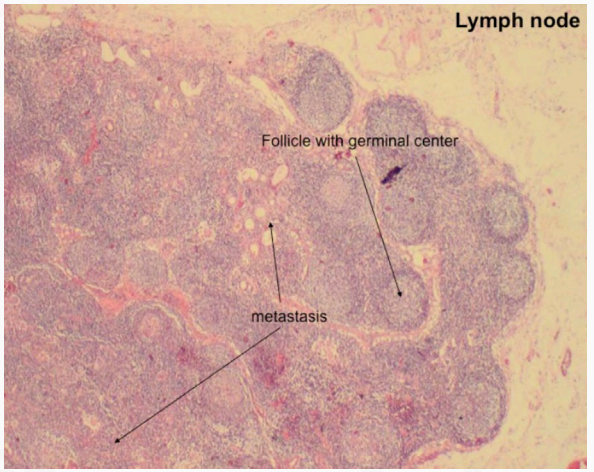






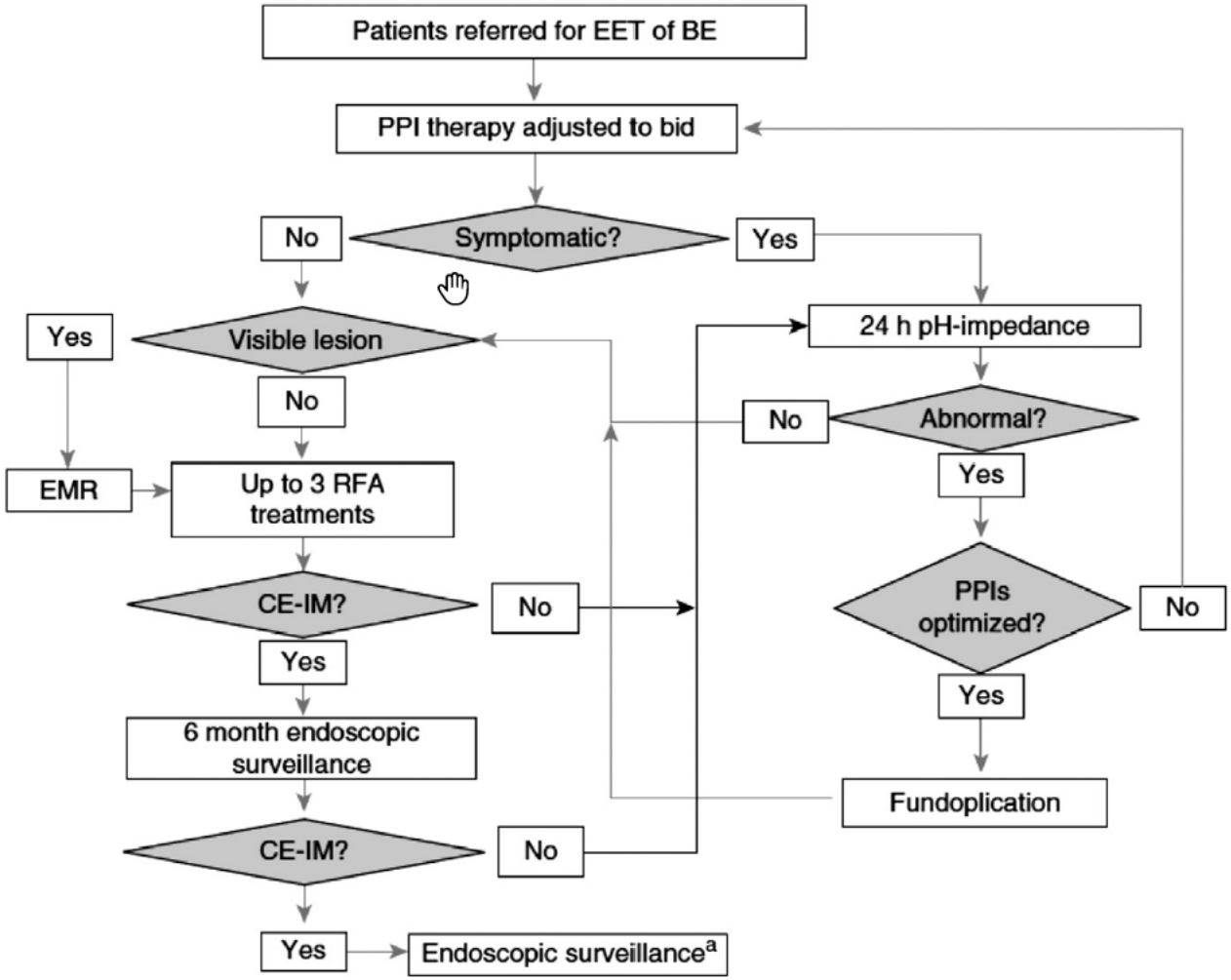

**Desmin stain**

- Poorly differentiated adenocarcinoma.
- Signet-ring cells.
- Submucosal infiltration.
- Vaso-invasion.

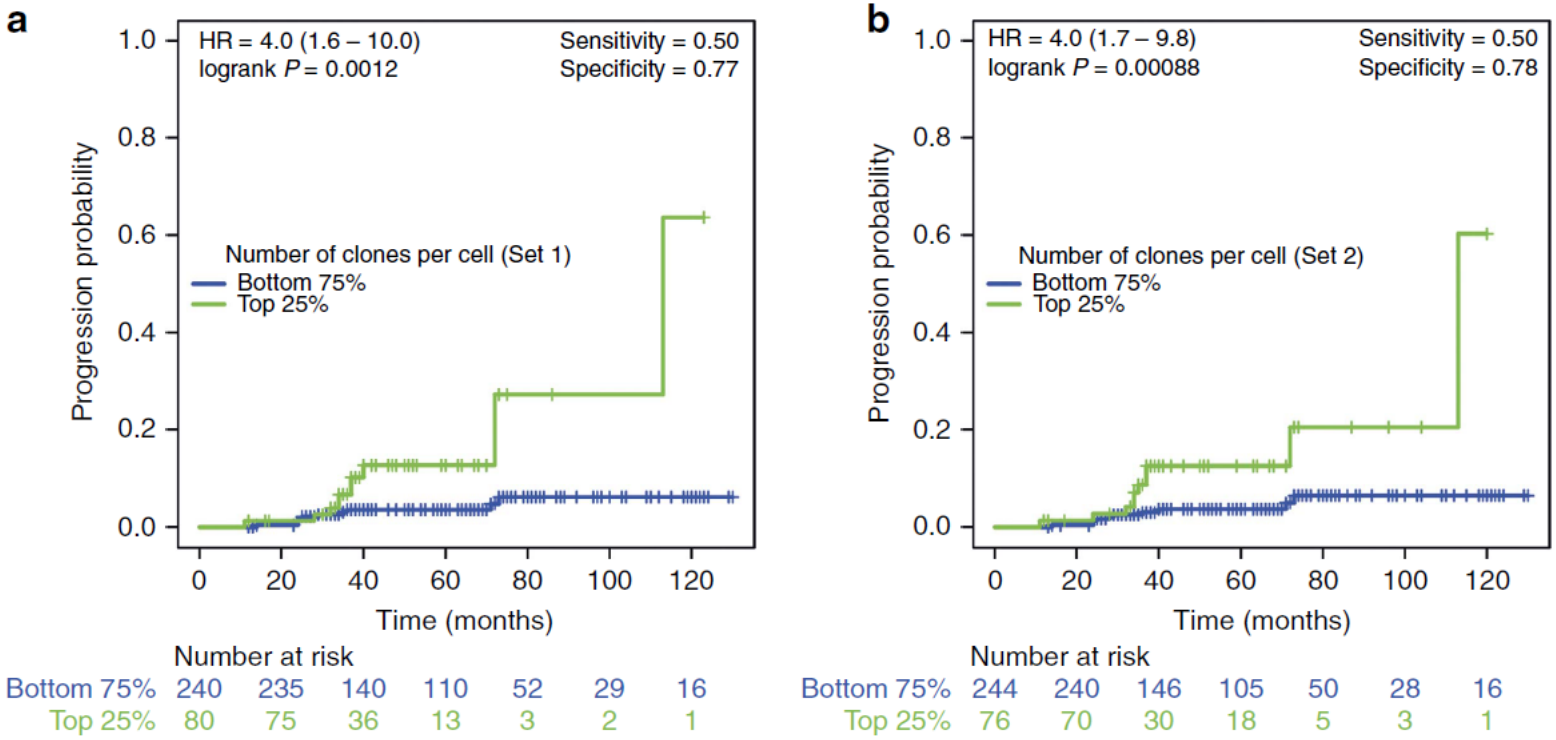



## Esophagectomy

**T1sm3 G3 V1 L1 N1**


Patients referred for EET of BE
PPI therapy adjusted to bid
Symptomatic?
No
Yes
Visible lesion
Yes
No
EMR
Up to 3 RFA treatments
CE-IM?
No
Yes
6 month endoscopic surveillance
CE-IM?
No
Yes
Endoscopic surveillance[a]
24 h pH-impedance
No
Abnormal?
Yes
PPIs optimized?
No
Yes
Fundoplication

# Clonal evolution at single cell resolution:

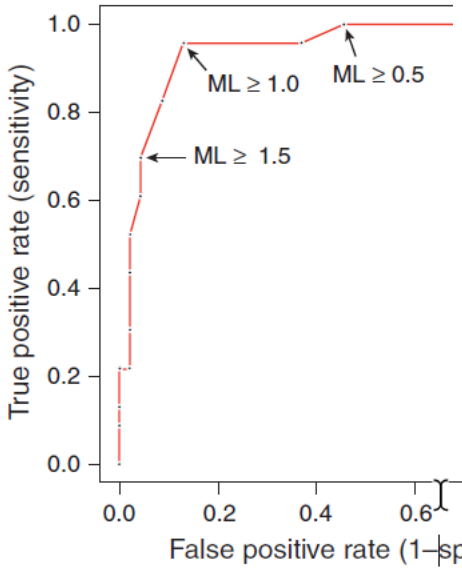


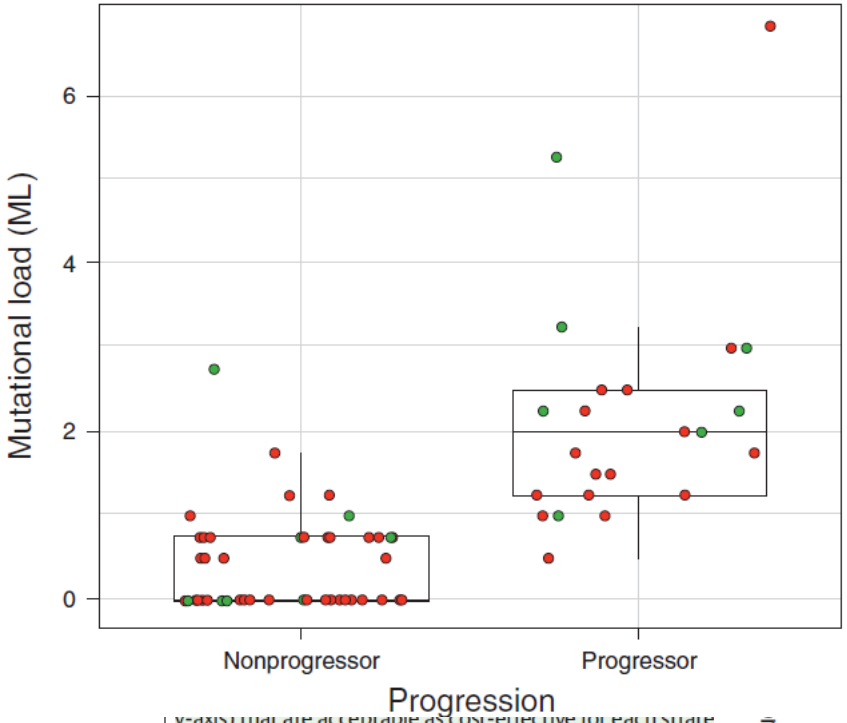

# Baseline genetic diversity predicts progression

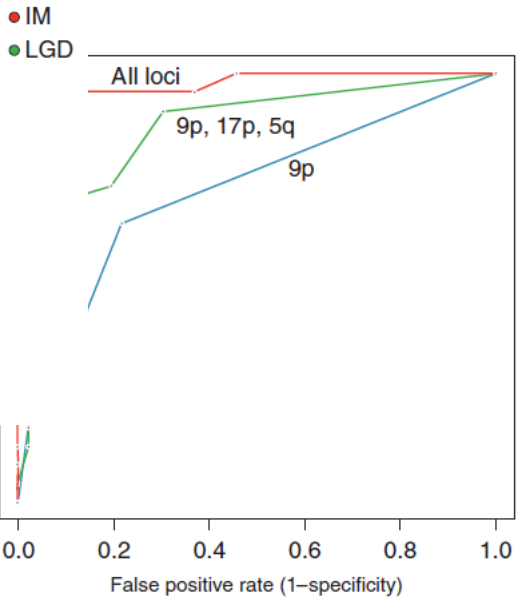
Martinez P et al. Nature Com 2016

ML assessments were made with a previously reported panel of 10 genomic loci using 24 DNA markers (26–31). The following genomic loci (with associated tumor suppressor genes) were included in the panel: 1p (CM (MCC, APC), 9p (CDKN2A 17q (NME1), 18q (DCC), 2 The presence of loss of het consistent with microsatellit using PCR and quantitative

Strategy I. "Natural history" of NDBE: No surveillance or interventions were used for NDBE with this strategy.
Strategy II. "Guideline-recommended surveillance" of NDBE: This strategy followed the ACG treatment guidelines for NDBE.
ients with NDBE: Preventative endo- NDBE was modeled primarily after a re with the HALO Ablation System California, USA).
stratification" according to levels of s assessed with BarreGen and *Path-* stics, Pittsburgh, Pennsylvania, USA;



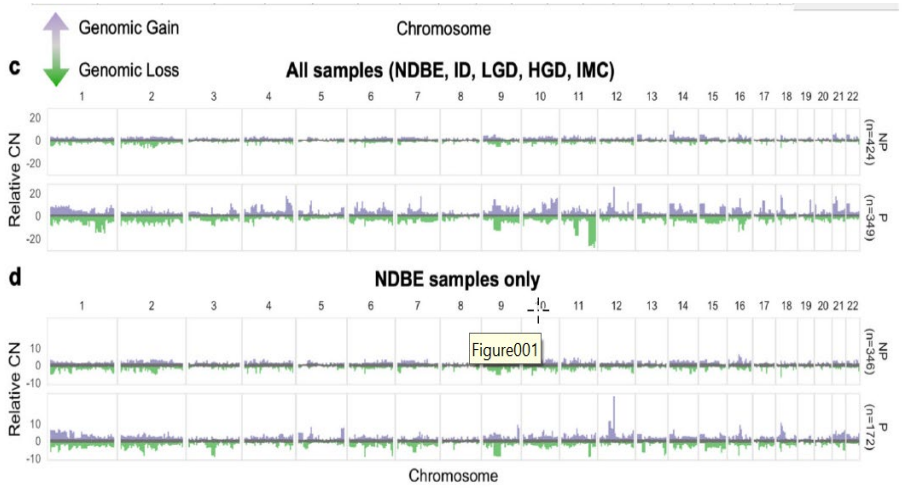

y-axis) that are acceptable as cost-effective for each strate
g willingness to pay (x-axis). A strategy of risk stratificatio
al load (strategy IV, blue) was the most cost-effective str
incremental net health benefit, particularly when compar
ntly practiced strategy of endoscopic surveillance (strate

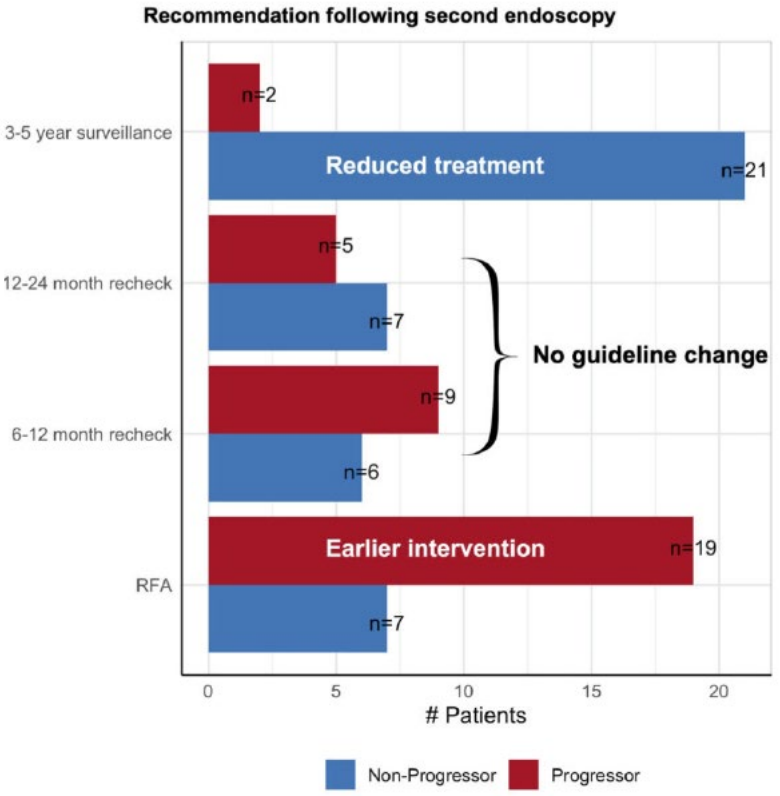
*Nat Med*. Author manuscript; available in PMC 2020 November 21.

Published in final edited form as:

*Nat Med*. 2020 November 01; 26(11): 1726–1732. doi:10.1038/s41591-020-1033-y.

# Genomic copy number predicts esophageal cancer years before transformation




Killcoyne S et al. Nature 2020

# Chemoprevention in barrett-esophagus – what to do?

**PPI-therapy: at least once daily**

**Most likely twice daily better in delaying AC/HGD**

**Aspirin 300mg in combination with high-dose PPI**

**strongest protective effect**

## 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 Worthington, Rebecca Harrison, Hugh Barr, Paul Moayyedi*

Lancet 2018: 392: 400ff

Plus Editorial Hvid et al. Lancet 2018