

Endoscopic Resections of the GI Tract: Pathological Evaluation

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USCAP- 2018**

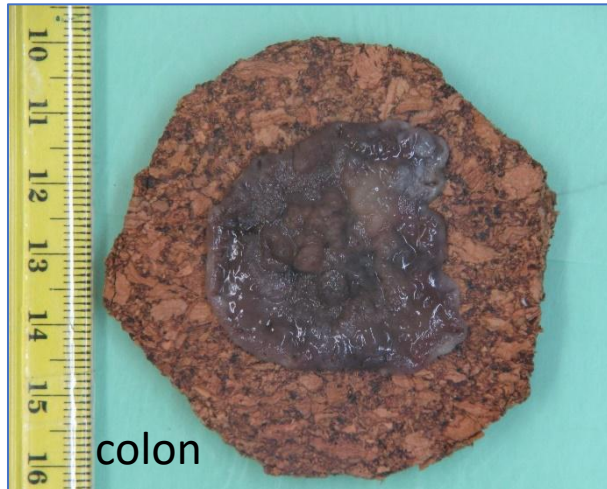
Plan

- Introduction
- Common facts and issues throughout GIT
- Site specific issues

Endoscopic Resections: evolution

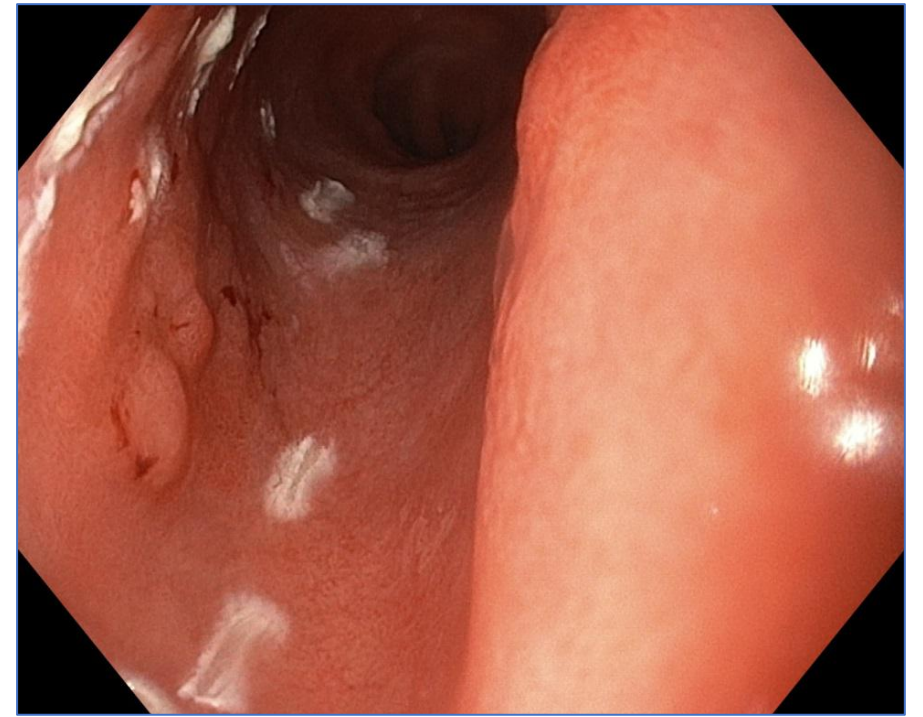
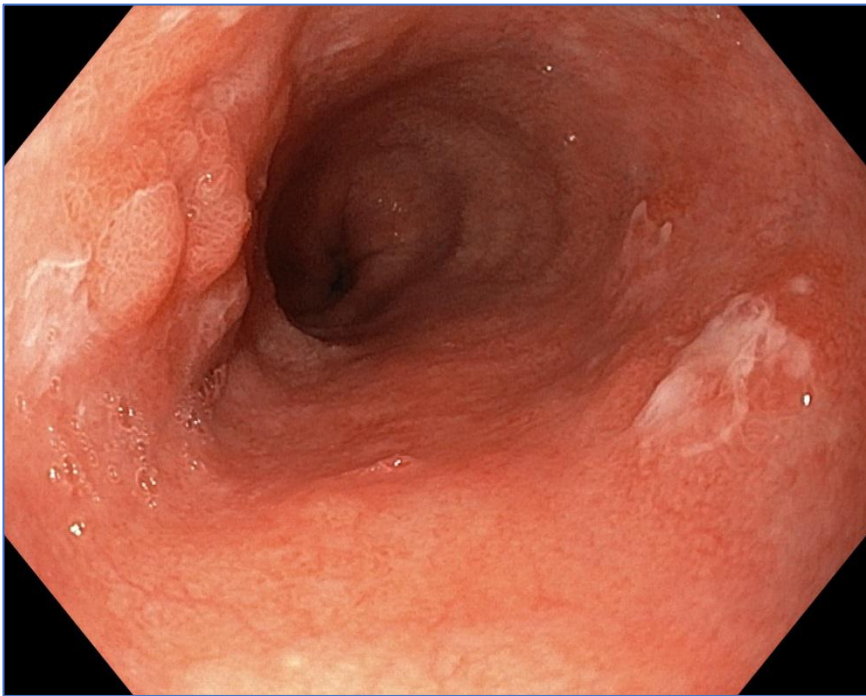
- **Last century** : Resection techniques were largely limited to ‘polypectomy’
- **1990s**: Endoscopic mucosal resection (EMR)
- **Early 2000s**: Endoscopic submucosal dissection (ESD)
- **Current**:
 - Considered curative in a large proportion of
 - Early gastric carcinoma
 - Early Barrett related and squamous cell neoplasia of the esophagus
 - Low risk submucosal invasive cancer (LR-SMIC) and large advanced/laterally spreading adenomas of the colon.
 - Complement surgery and not competing
 - Allows optimal T-staging, with organ preservation and prognostication and stratification for additional treatment, including surgery if needed

Endoscopic mucosal resections (EMR) VS. Endoscopic submucosal dissection(ESD)

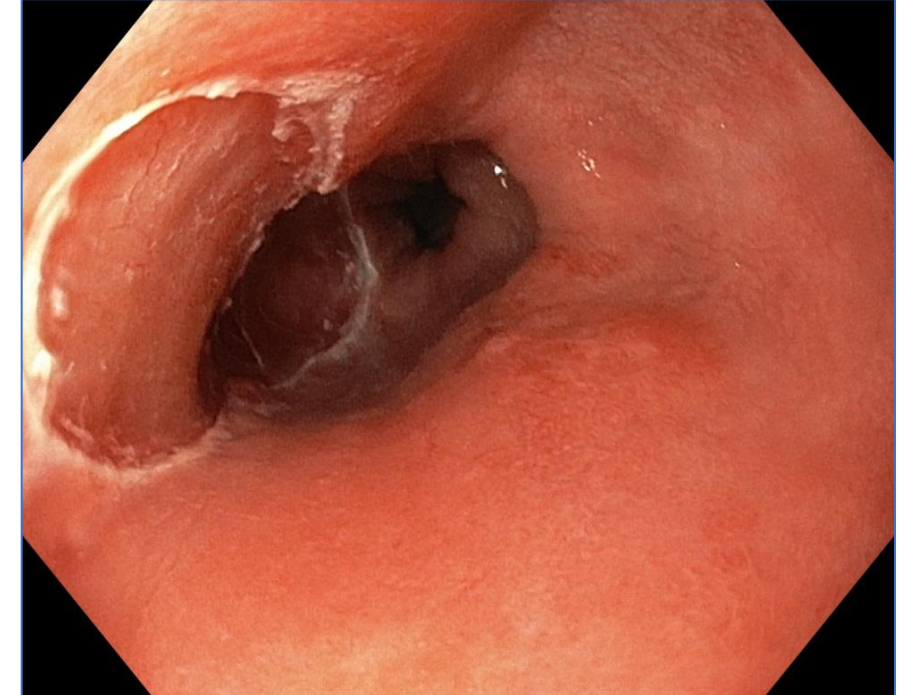
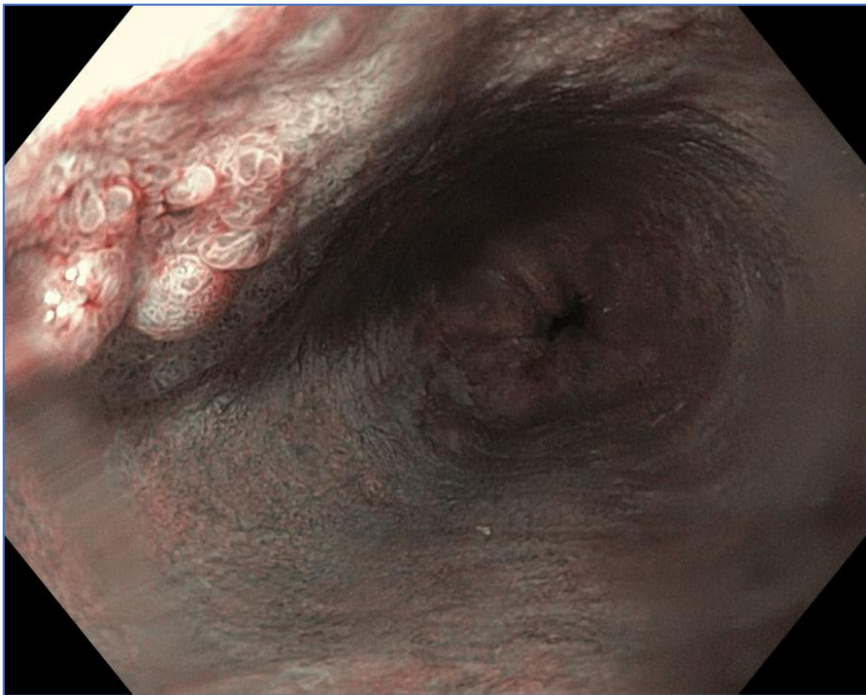


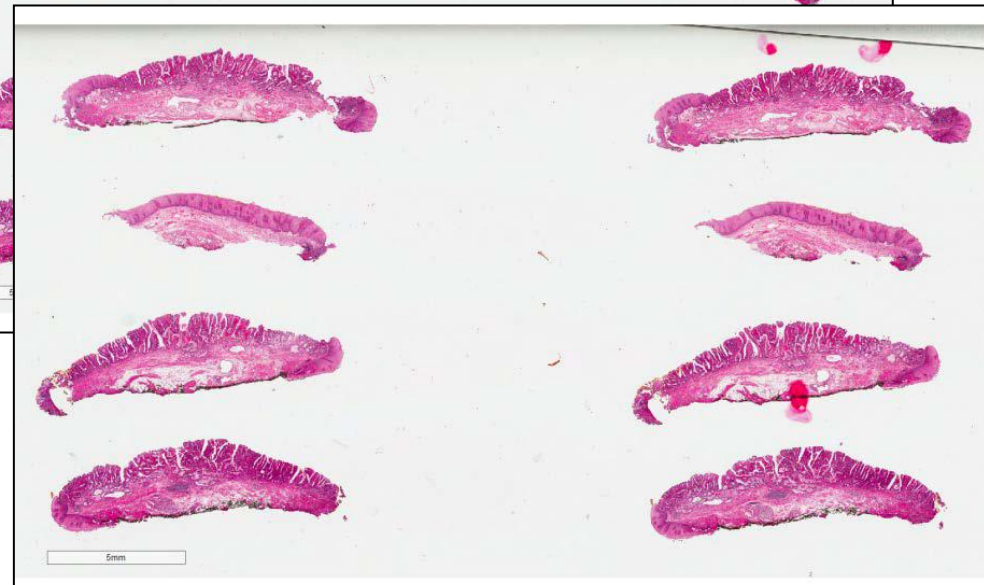
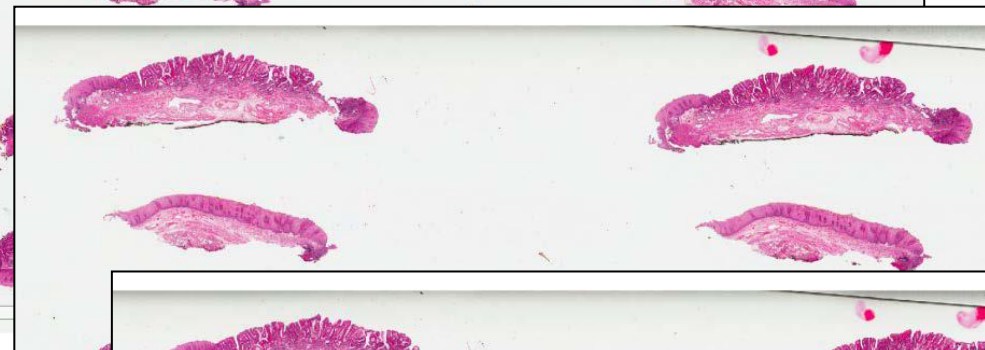
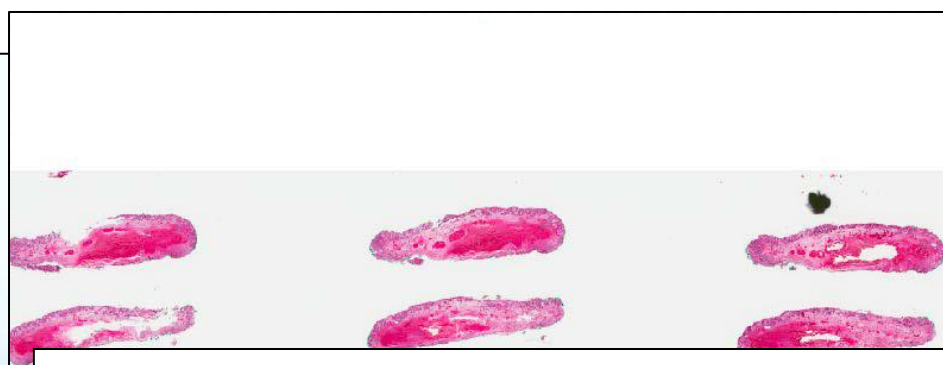
| | EMR | ESD |
|--------------------------------------|----------|----------|
| Type of specimen received | Limited | En bloc |
| Determination of curative resection | Limited | Accurate |
| Determination of resection margins | Limited | Accurate |
| Accuracy of a pathological diagnosis | +++ / ++ | +++ |
| Technical precision | + / ++ | +++ |
| Technical challenge | + / ++ | +++ |
| Resource utilization | + / ++ | +++ |
| Procedure related complications | + / ++ | +++ |

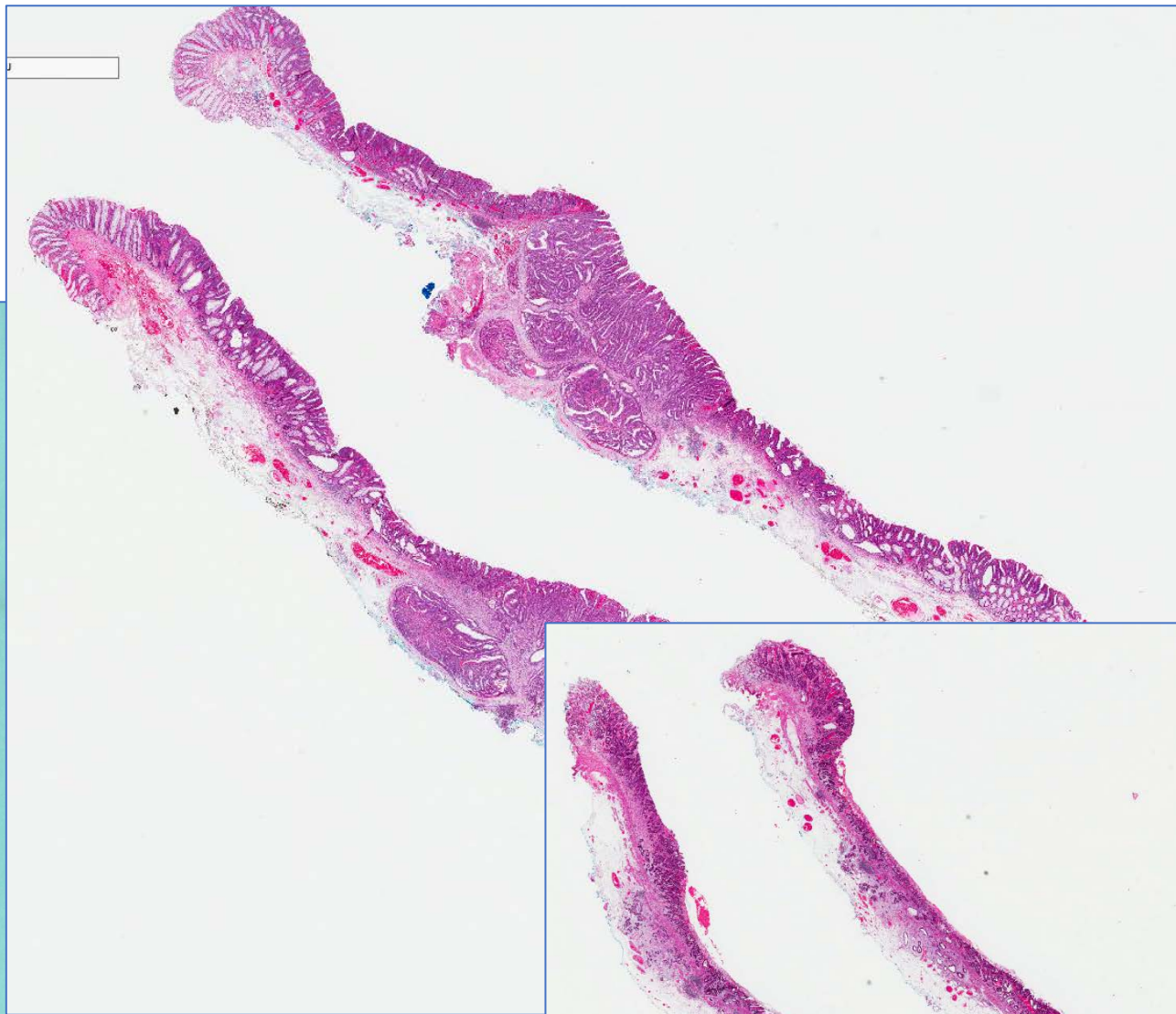
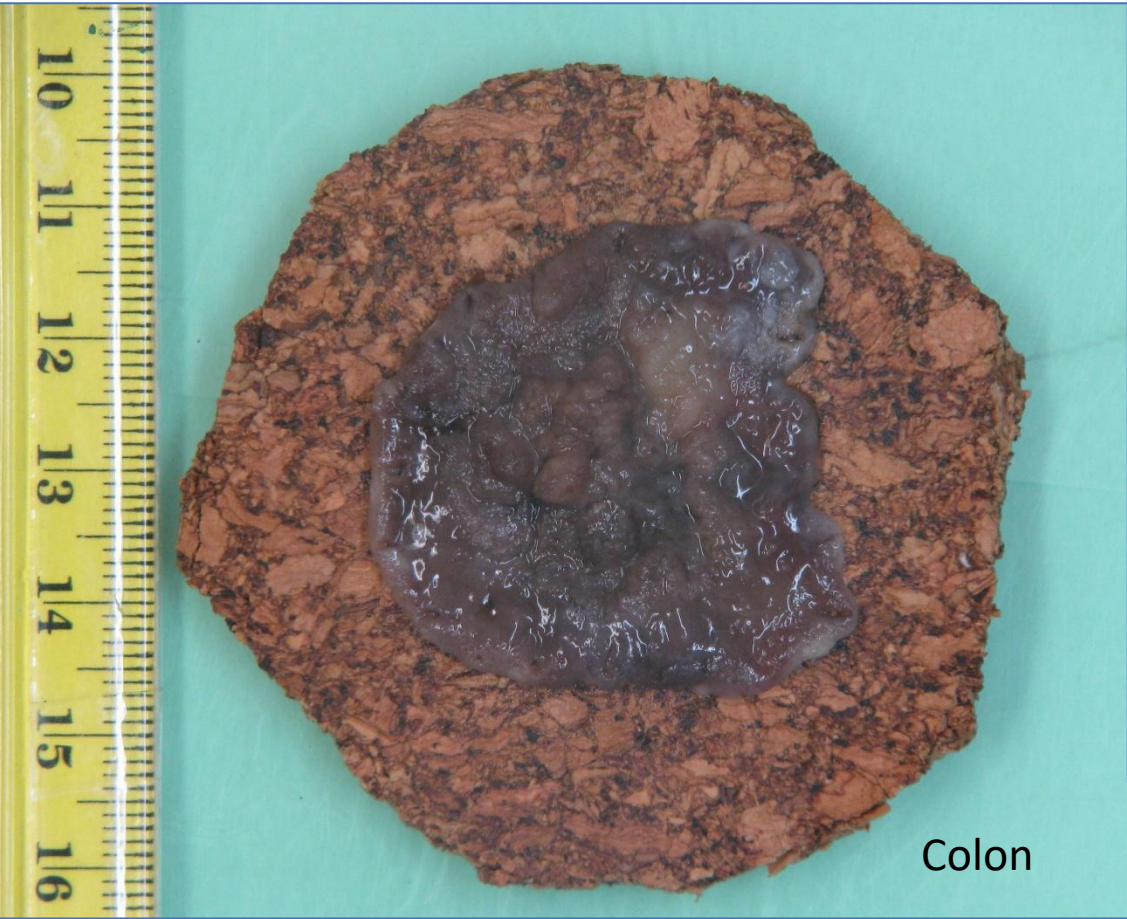
Resources vs Outcome



- Inject and lift EMR.
- Cap EMR.
- Band EMR
- Underwater EMR
- Precut EMR and Hybrid ESD.
- Endoscopic Submucosal Dissection (ESD)







Endoscopic resections

- Diagnostic
 - **ER diagnosis is superior to endoscopic biopsy**
- Curative
 - Intraepithelial neoplasia (IEN) including advanced adenomas
 - **Early invasive/low risk** invasive carcinomas
- Prognostication by assessing **pathological risk factors** and **Staging**

Endoscopy 2017; 49: 270–297

Gastrointest Endosc 2008 ; 67 : 604 – 9.

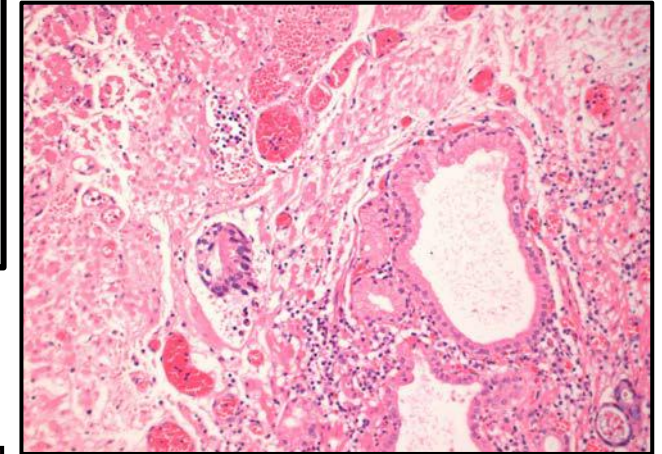
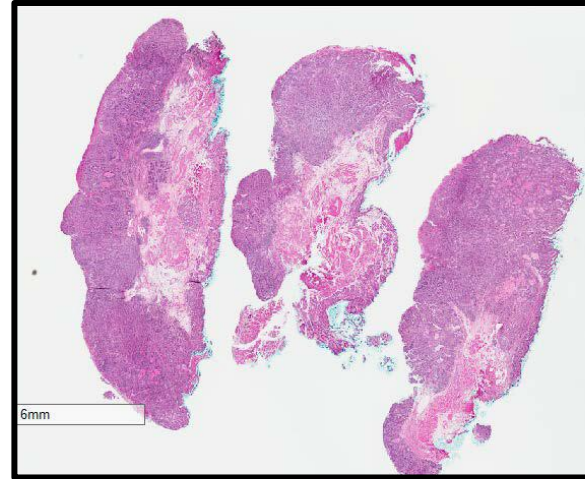
Gastrointest Endosc 2007 ; 66 : 660 – 6 .

Am J Surg Pathol 2006;30:114–118)

Pathological risk factors

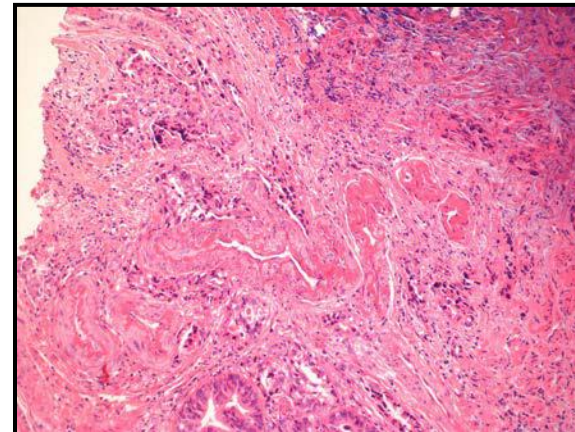
Adverse pathological (histological) features throughout the GIT

- Poor differentiation
- Lymphovascular invasion
- Deeper invasion
- Margin Involvement
- Others- site specific



Predicts the risk of

- Lymph node metastasis
- Residual disease at the ER site



Pathological evaluation

- Should be accurate - critical
- Approach for handling and reporting should be systematic
- Similar to surgical resections

Modern Pathology (2004) 17, 2–8

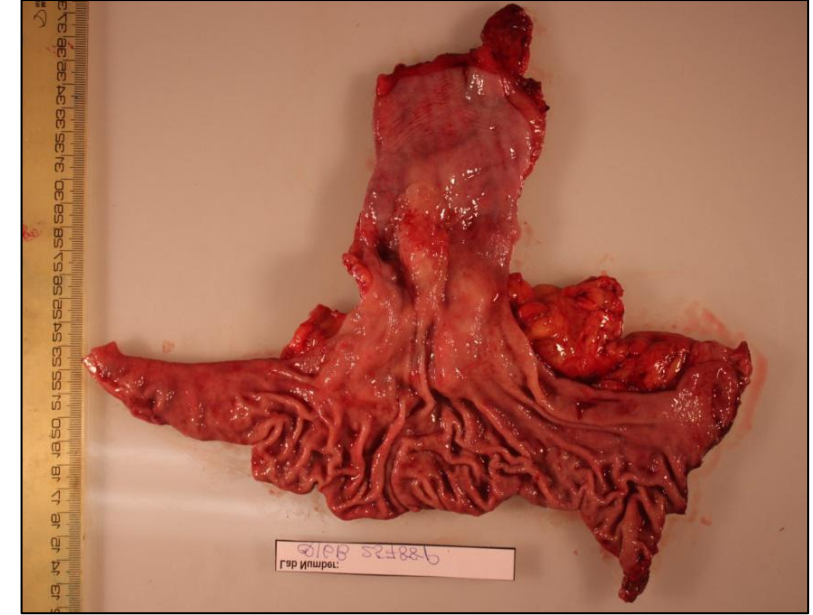
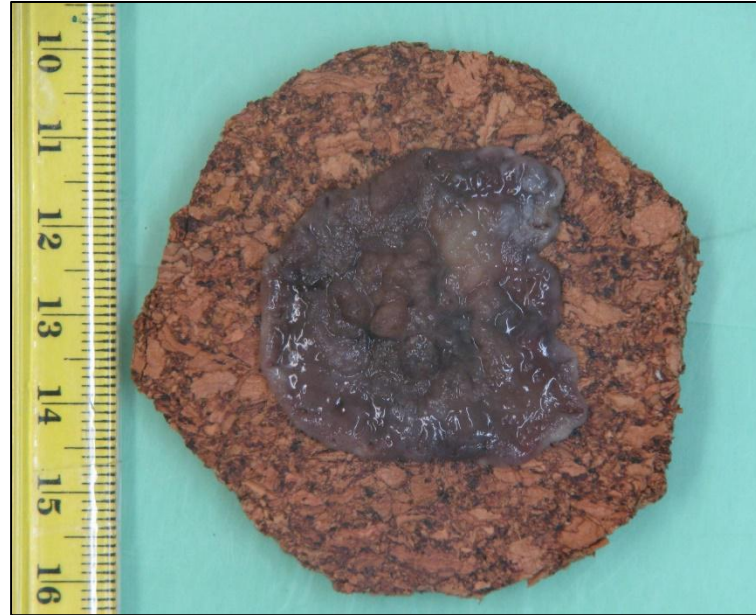
Modern Pathology (2009) 22, 489–498

Techniques in Gastrointestinal Endoscopy (2011) 13, 95–99

RCPA (Royal College of Pathologists of Australasia) (2010- 2014). Structured Pathology Reporting Protocol project for cancers. www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocol.

Pathology (October 2014) 46(6), pp. 473–480

Specimen handling: what's the fuss?



- Small specimens
- Small cancers
- Prognostication and Staging = Surgical specimens

Fuss

Mojtahed and Shimoda Preparation of EMR and ESD Specimens

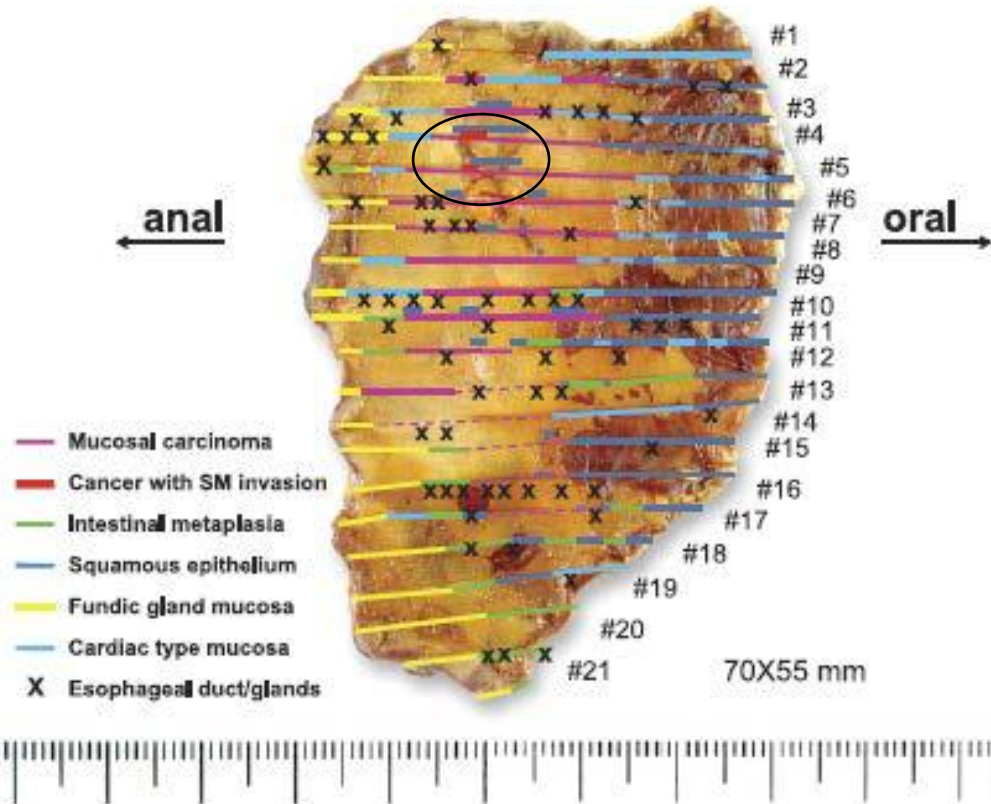
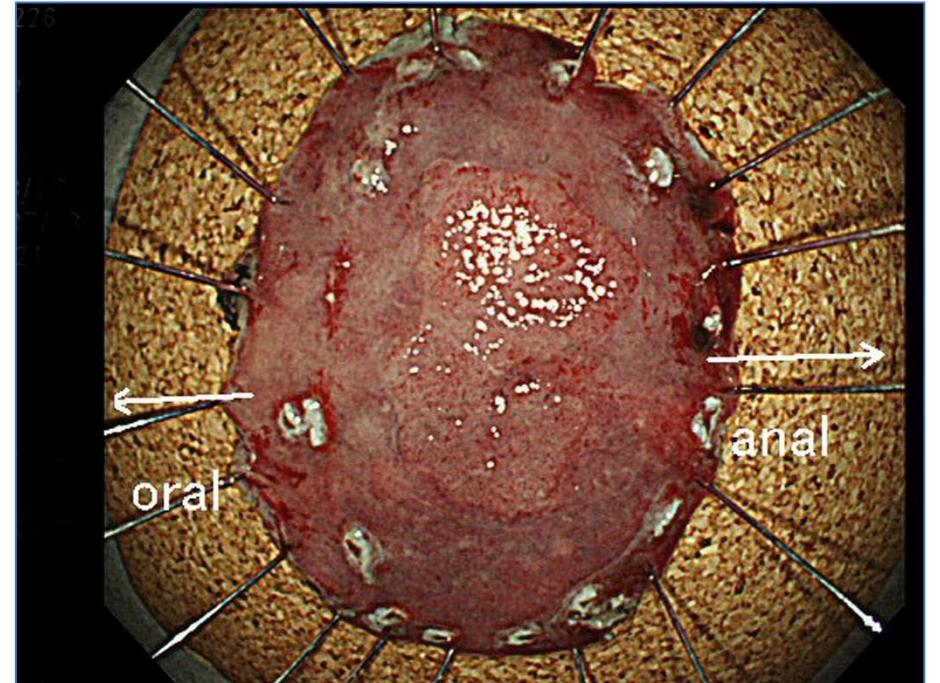


Figure 3 Pathologic assessment and mapping of gastroesophageal junction ESD with Barrett's esophagus and adenocarcinoma invading the submucosa. (Color figure is available online at www.techgastroscopy.com.)

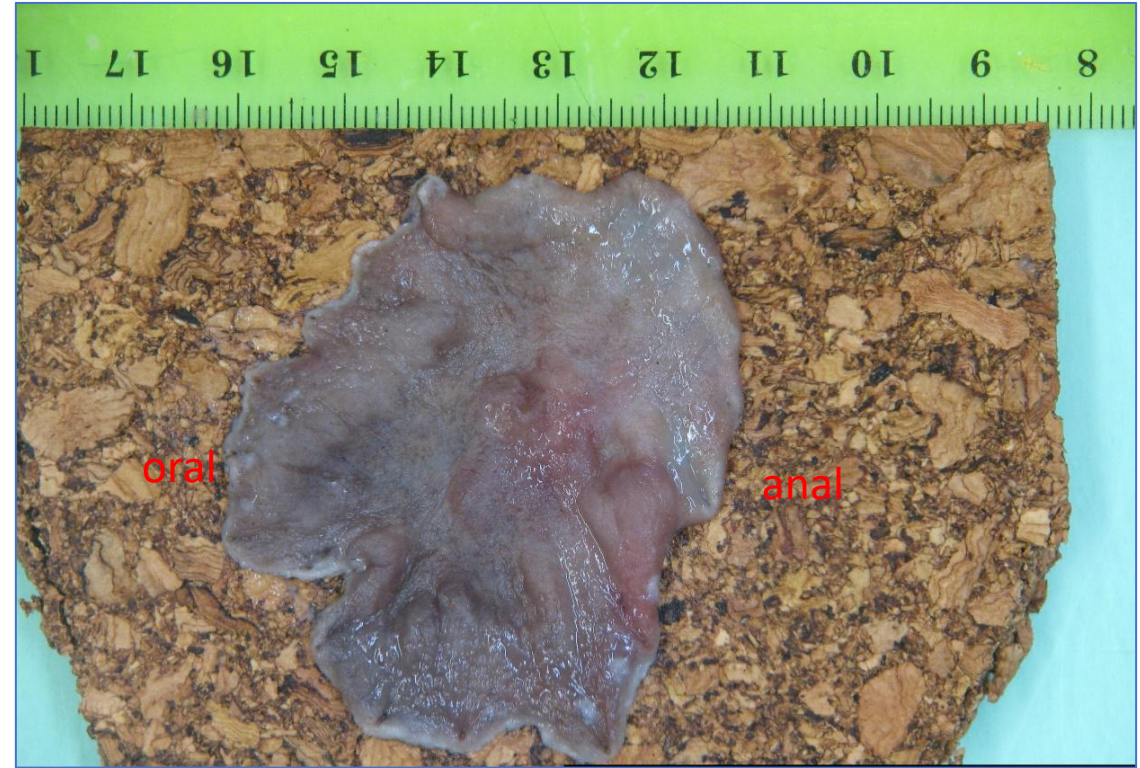
Fuss: Pinning out

- On a hard surface (e.g. corkboard, styrofoam or wax block) with the mucosal side up by the endoscopist : prevents curling and shrinkage
- Overstretching avoided
- Immediate fixation : at least 24 hrs (12-72hrs)
- Photograph: for mapping of the lesion

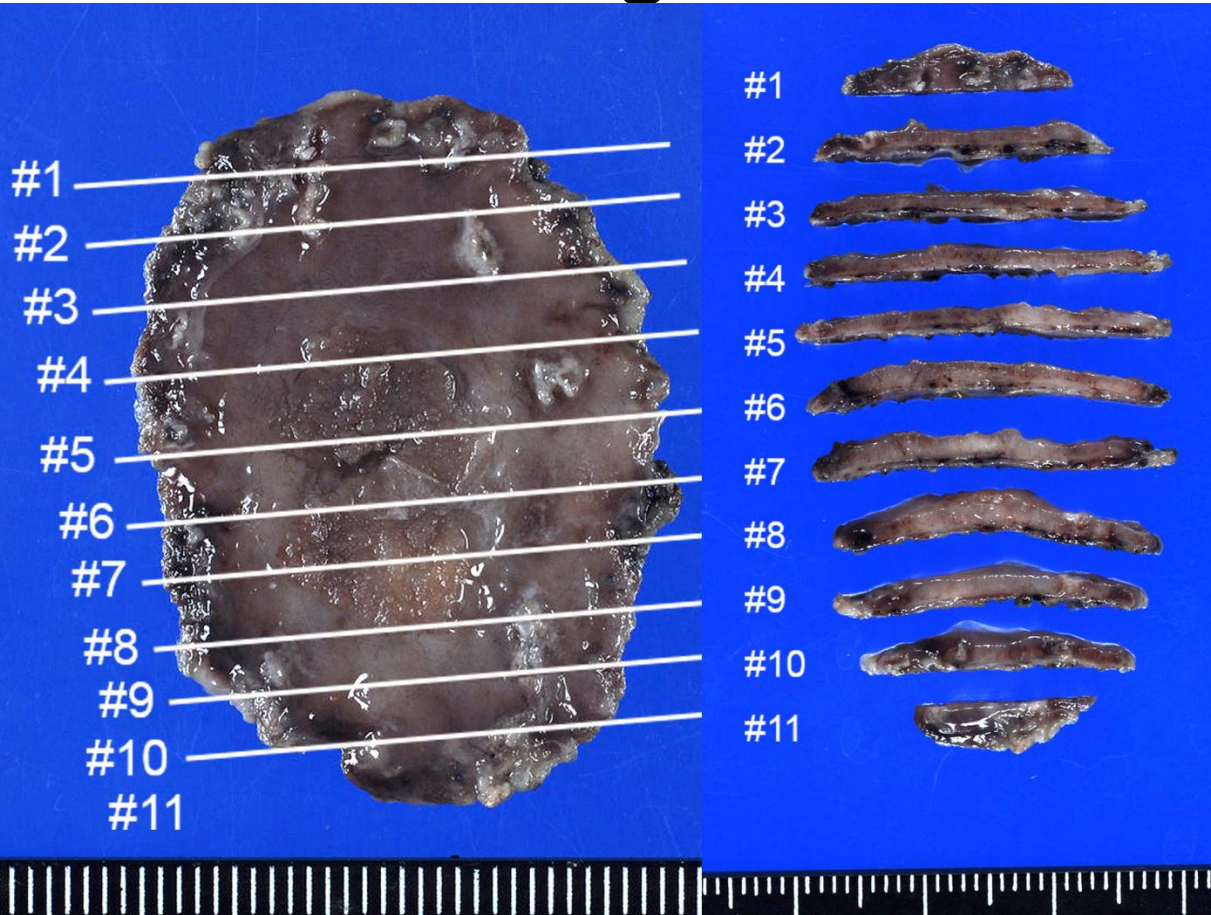


Macroscopic examination: after fixation

- Two dimensions of the lesion(s)
- Inking
 - Deep and circumferential/radial margin
 - Other orientations : ESDs
- Macroscopic type (i.e., polypoid, elevated, depressed, flat)



Sectioning



- First Sections targeting lesion
- Serially sectioning **at 2-3 mm thickness**
(Too thin: Incomplete sections)
- The first and last slice may be flipped: allows the margin to be sectioned first for histological evaluation
- Large specimens (ESDs): the first/ and the last slices – cut perpendicular

Numbering and orientation of slices into cassettes: Tissue embedding

A critical step in producing high quality diagnostically accurate sections

- Embedded 'en face' or on edge
- Slices laid sequentially in the cassette .
- 3-4 slices can go in one block , not more
- Poor orientation of tissue : loss of
 - small /superficial tumor through trimming
 - deep submucosal tissue and deep margin

Microscopic examination- General rules

- Initially 2-3 H&E stained levels per block
- Deeper levels
 - Incomplete sections
 - Small lesions on endoscopy : missed/hidden
 - Incomplete margins (ink not visible)
 - Small amounts of SM



Microscopic evaluation

Similar to surgical specimens

1. Confirmation of the diagnosis

Intraepithelial neoplasia (dysplasia): Grading of IEN, Radial margin status

2. Invasive carcinoma : Pathological risk factors

Depth of Invasion : Risk of Lymph node metastases in early invasive carcinomas of GIT

| Depth of invasion | | Esophagus | | Stomach | Colon |
|-------------------|---------|----------------|------|---------|-------|
| | | Adenocarcinoma | SCC | | |
| Mucosa | | 0-2% | 0-5% | 0-3% | 0% |
| Submucosa: | Overall | 26% | 45% | 19% | 5-10% |
| | Sm1 | 10% | 24% | 7% | <3% |
| | Sm2 | 21% | 37% | 16% | 8% |
| | Sm3 | 49% | 48% | 26% | 23% |

Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol.* 2012;107(6):850-62.

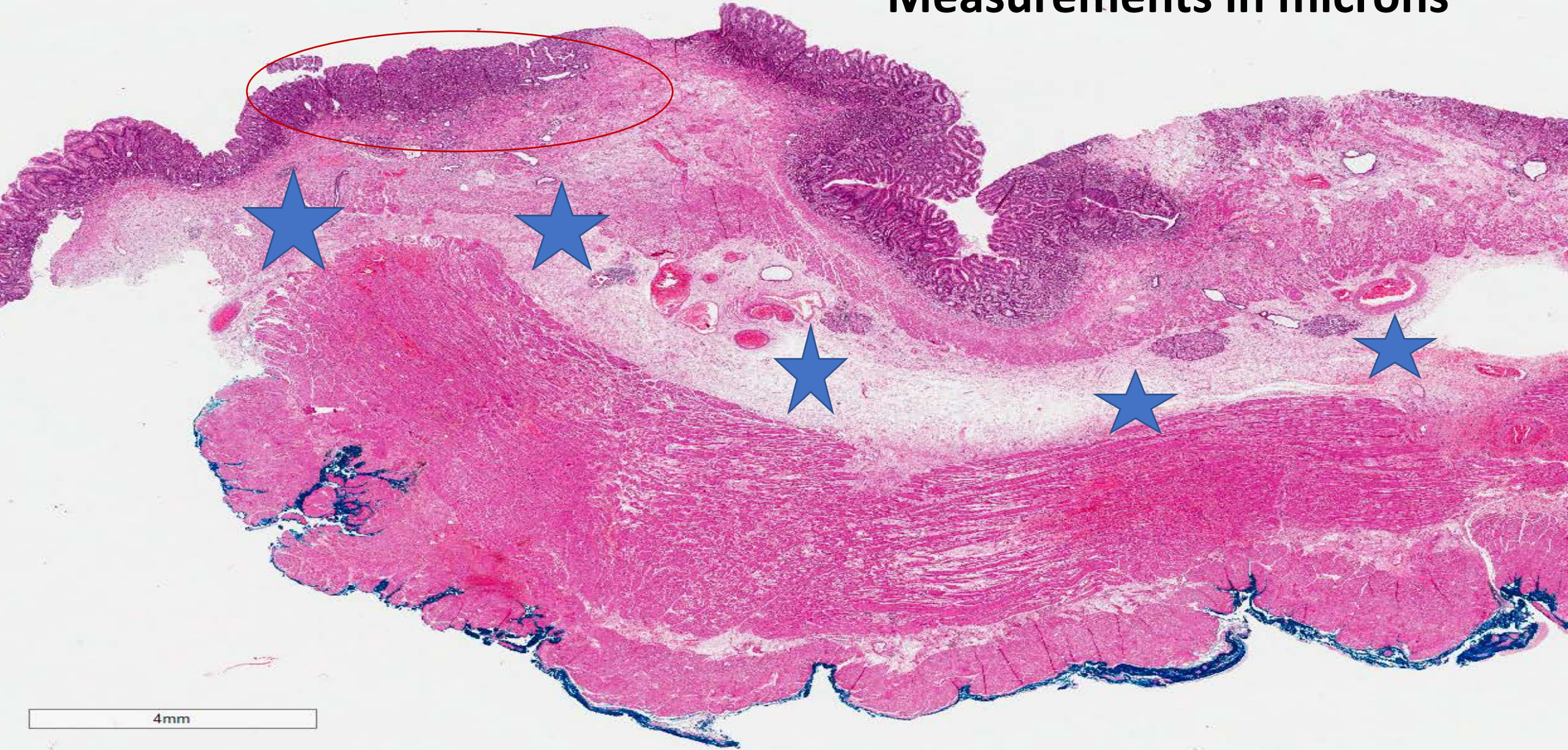
Scourakis G, et al. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. *World J Gastroenterol.* 2013;19(9):1424-37.

Vieth M, Stolte M. Pathology of early upper GI cancers. *Best Pract Res Clin Gastroenterol.* 2005 Dec;19(6):857-69.

kwee RM, Kwee TC. Predicting lymph node status in early gastric cancer. *Gastric Cancer* 2008;11:138-48. (meta-analysis)

Nascimbeni R, et al. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002;45:200-206.

Measurements in microns



4mm

Oesophagus: Barrett associated neoplasia early esophageal adenocarcinoma

EMR : *Safe, quicker, curative and cost effective*

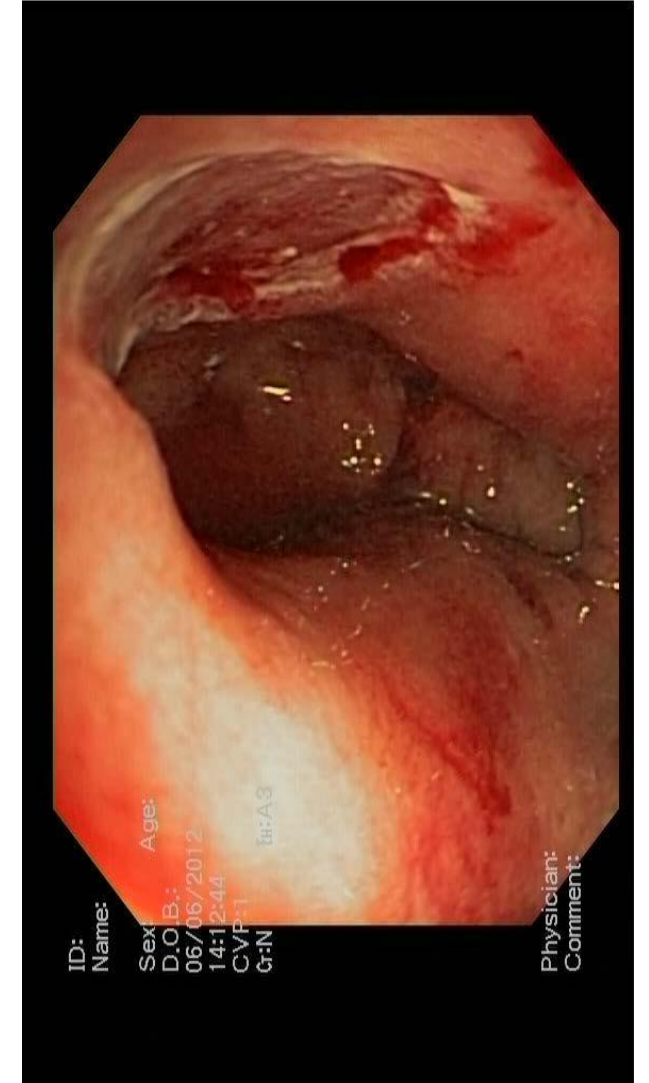
- EMR with further piecemeal EMR of the residual Barrett's segment
- Barrett's cancer
 - against a background of a "field defect"
 - after resection recurrent lesions in 30% within 3 years
 - remainder of the Barrett's segment requires further therapy.

ESD: *Complete en bloc resection*

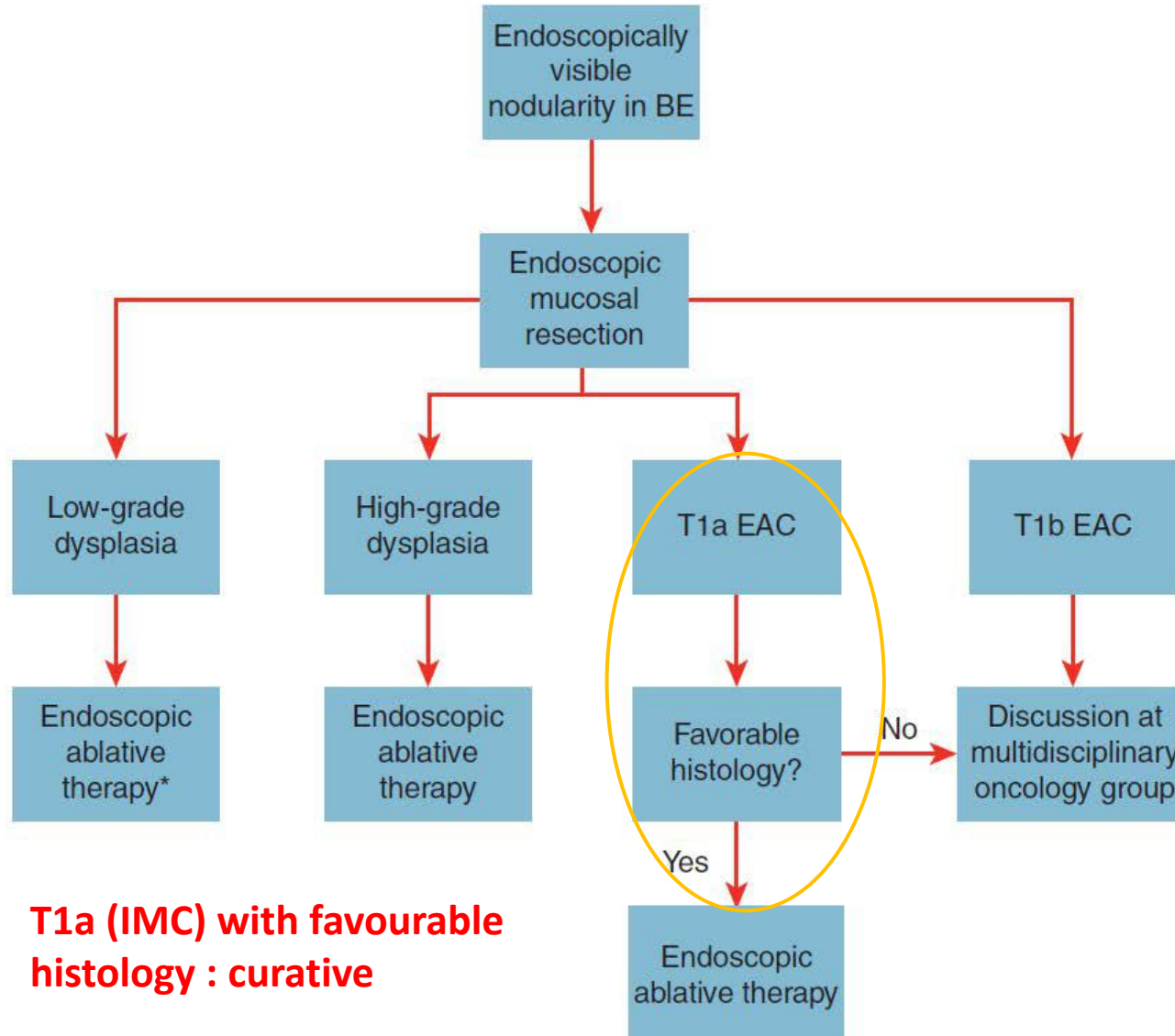
- Particularly for larger SM invasive lesions (T1b).
- **Only <10% of cases of early esophageal neoplasia**
- ESD achieves a higher radical (RO) resection

Gastroenterology 2000; 118: 670–677.

Gut 2008 ; 57 : 1200 – 6.



Barrett associated neoplasia



T1a (IMC) with favourable histology : curative

Oesophagus: adenocarcinoma (T1b)

Risk of LN metastases

High: Up to 50%

- ? Overestimated
- Retrospective, surgical series, No distinction
- between levels of SM invasion

Low: 0-2% ??

- On small endoscopic series
- T1b, $\leq 500 \mu\text{m}$, adequately resected

WITHOUT high risk pathological features:

Endoscopic therapy followed by vigilant endoscopic follow-up

| Depth of invasion | | Esophagus |
|-------------------|---------|-------------------------------------|
| | | Adenocarcinoma |
| Mucosa :T1a | | 0-2% |
| SMI: T1b | Overall | 26% |
| | Sm1 | 10% ($\leq 500 \mu\text{m}$) 2%?? |
| | Sm2 | 21% |
| | Sm3 | 49% |

Endoscopic resection: Staging

- Surgical resection pathology VS. ER pathology
 - Tumour staging is accurate (100% correlation)
- Endoscopic ultrasound examination (EUS) VS. ER pathology

“EUS has no role in staging of early esophageal adenocarcinoma”

- Over staging
- Under staging

Am J Gastroenterol 2007;102:2380–2386 ; Gut 2004;53:634–640; Gastrointest Endosc 2001;54:689–696; Am J Surg Pathol 2009; 33: 620–5.

[J Gastrointest Oncol](#). 2012 Dec; 3(4): 314–321; Gastrointest Endosc. 2011;73(4):662-8

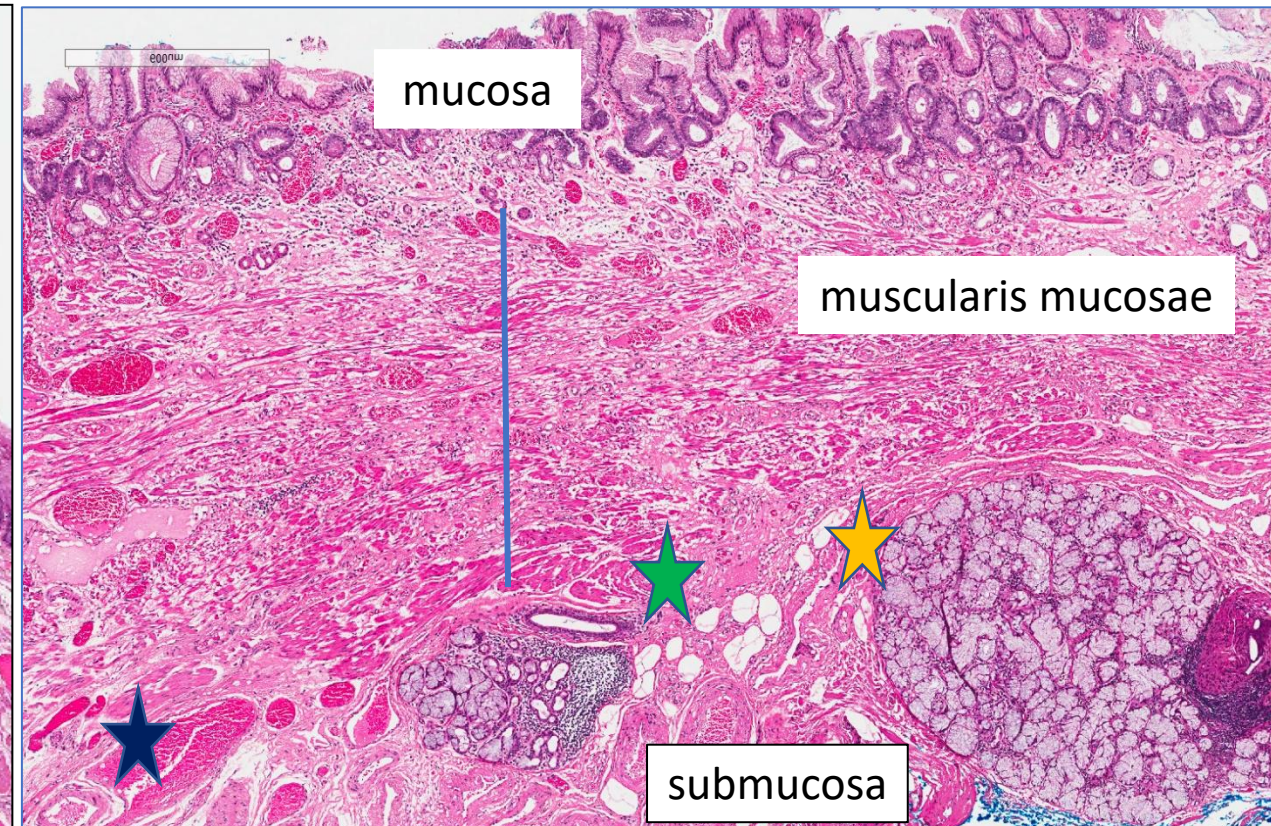
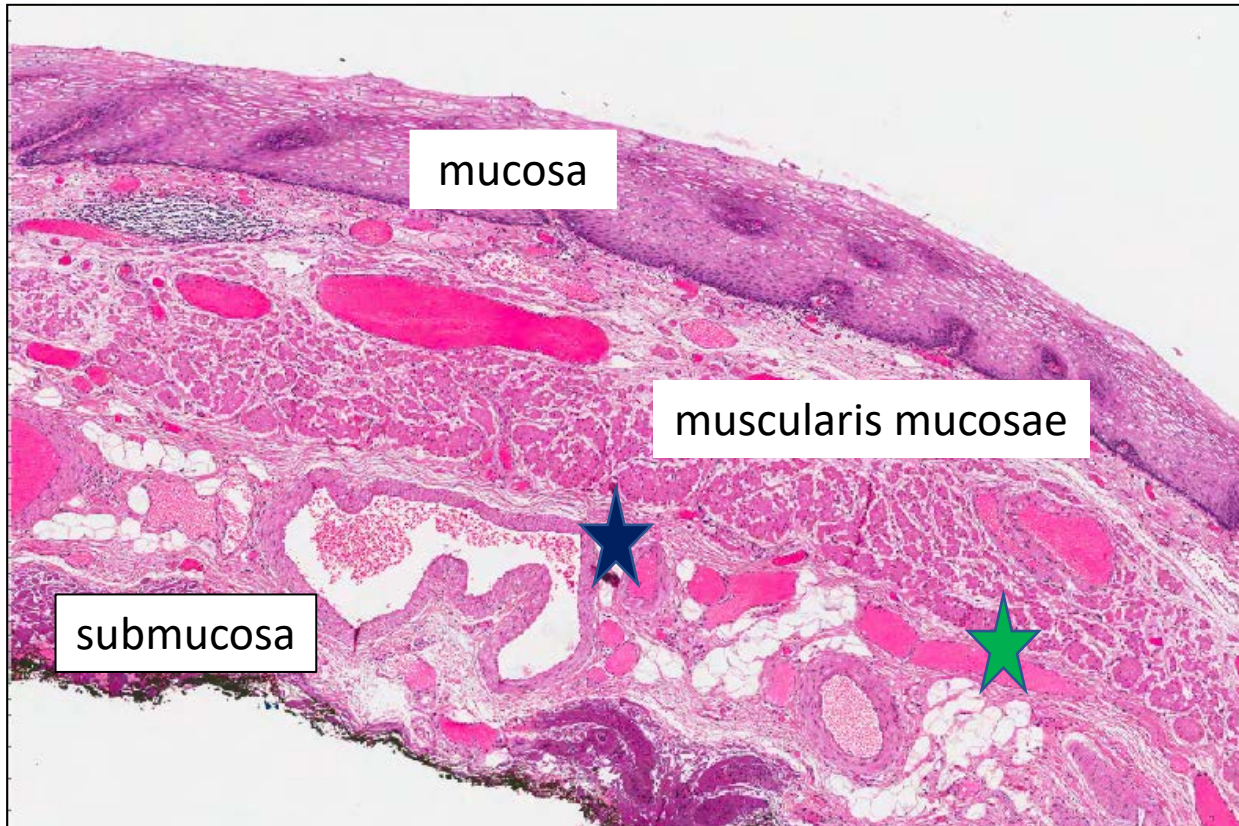
DUPLICATION of MUSCULARIS MUCOSA

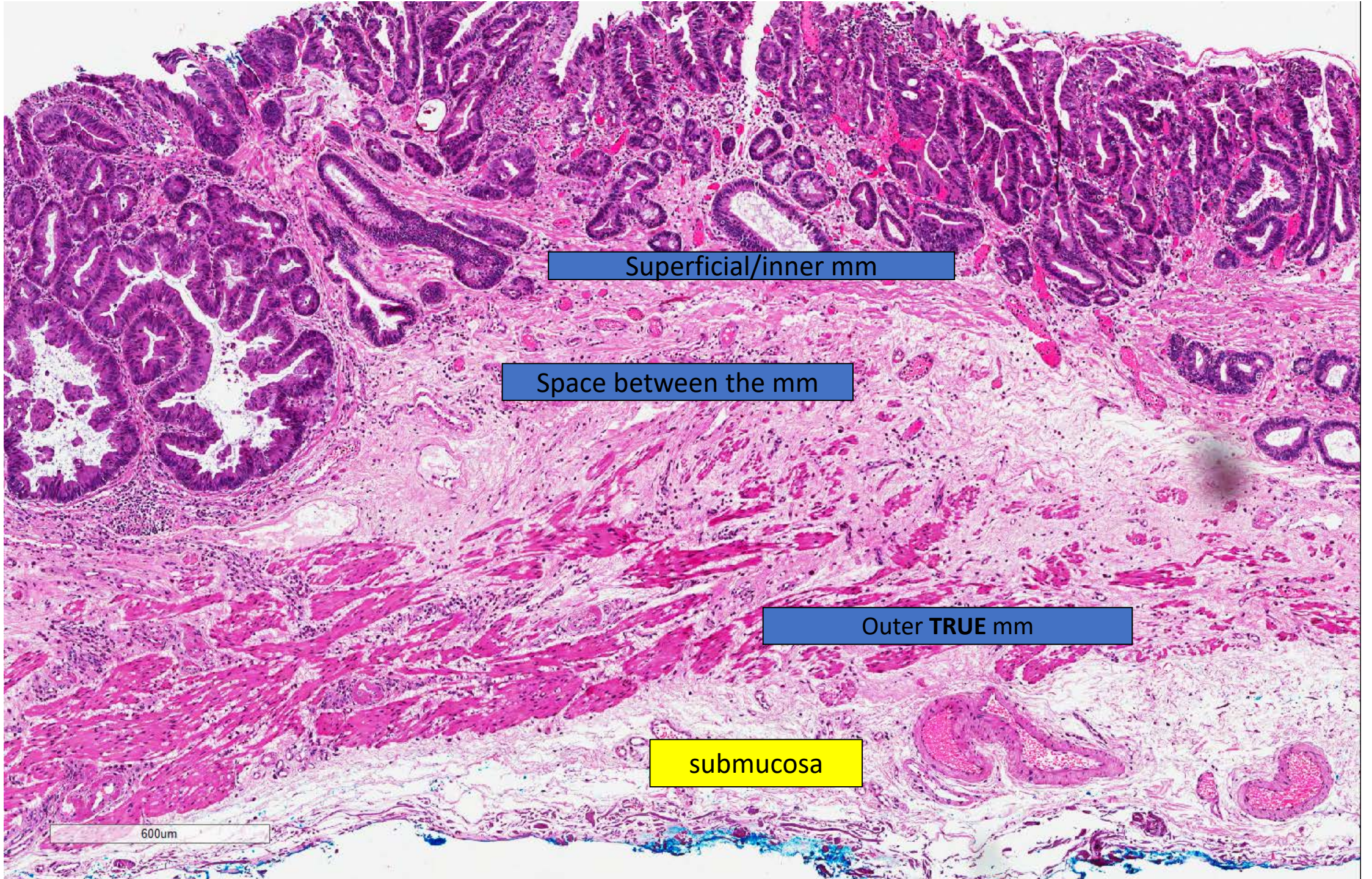
- **A unique feature , seen in 92% of BO (0% of SCC)**
- Frequently unrecognised or misinterpreted
- Impacts on EUS staging

Hum Pathol 1991; 22: 1158–1161, Best Pract Res Clin Gastroenterol 2005; 19: 857–69, Am J Surg Pathol 2007; 31: 1719–25.

Am J Surg Pathol 2008; 32: 566–71, Am J Surg Pathol 2009; 33: 620–5, Am J of Surg Pathol. 2011; 35(7):1045-1053.

DUPLICATION of MUSCULARIS MUCOSA





Superficial/inner mm

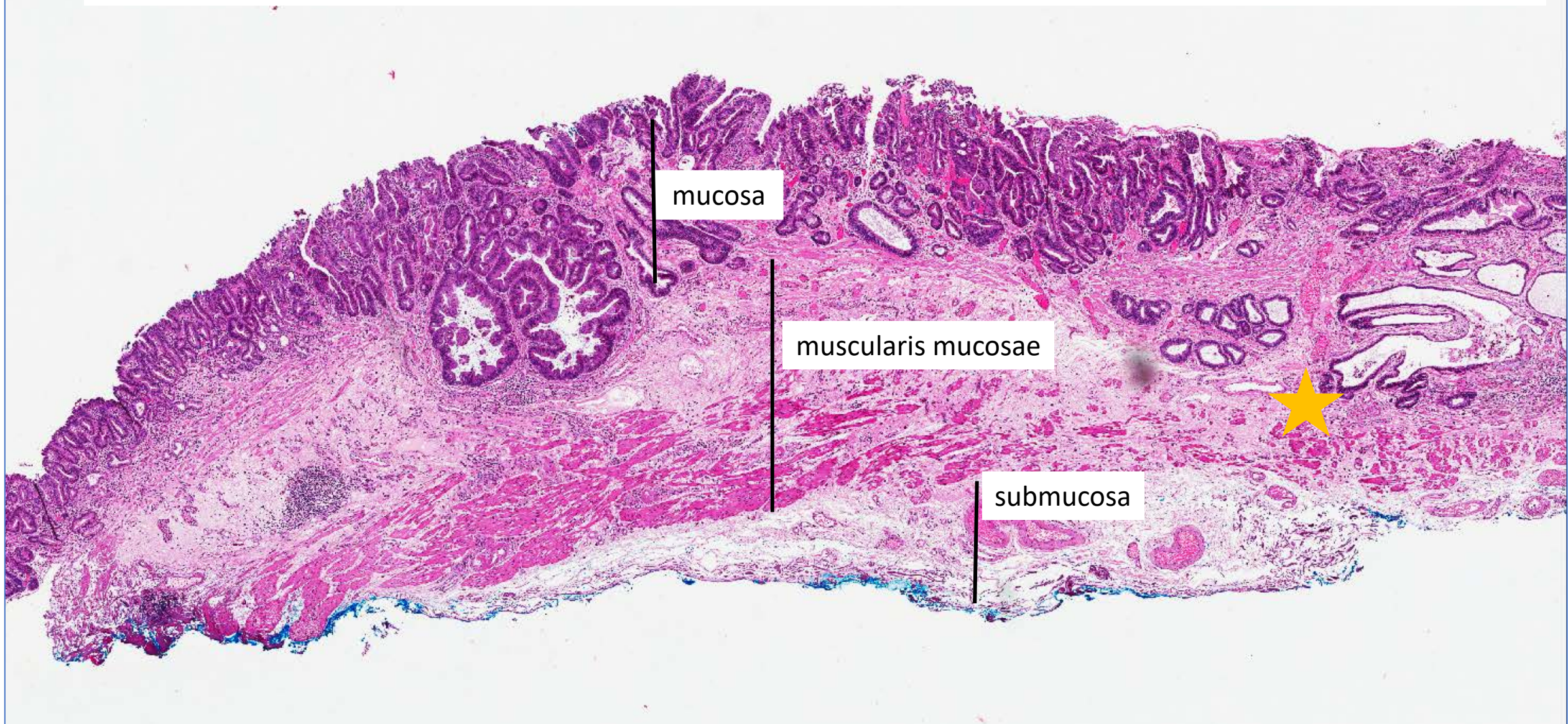
Space between the mm

Outer **TRUE** mm

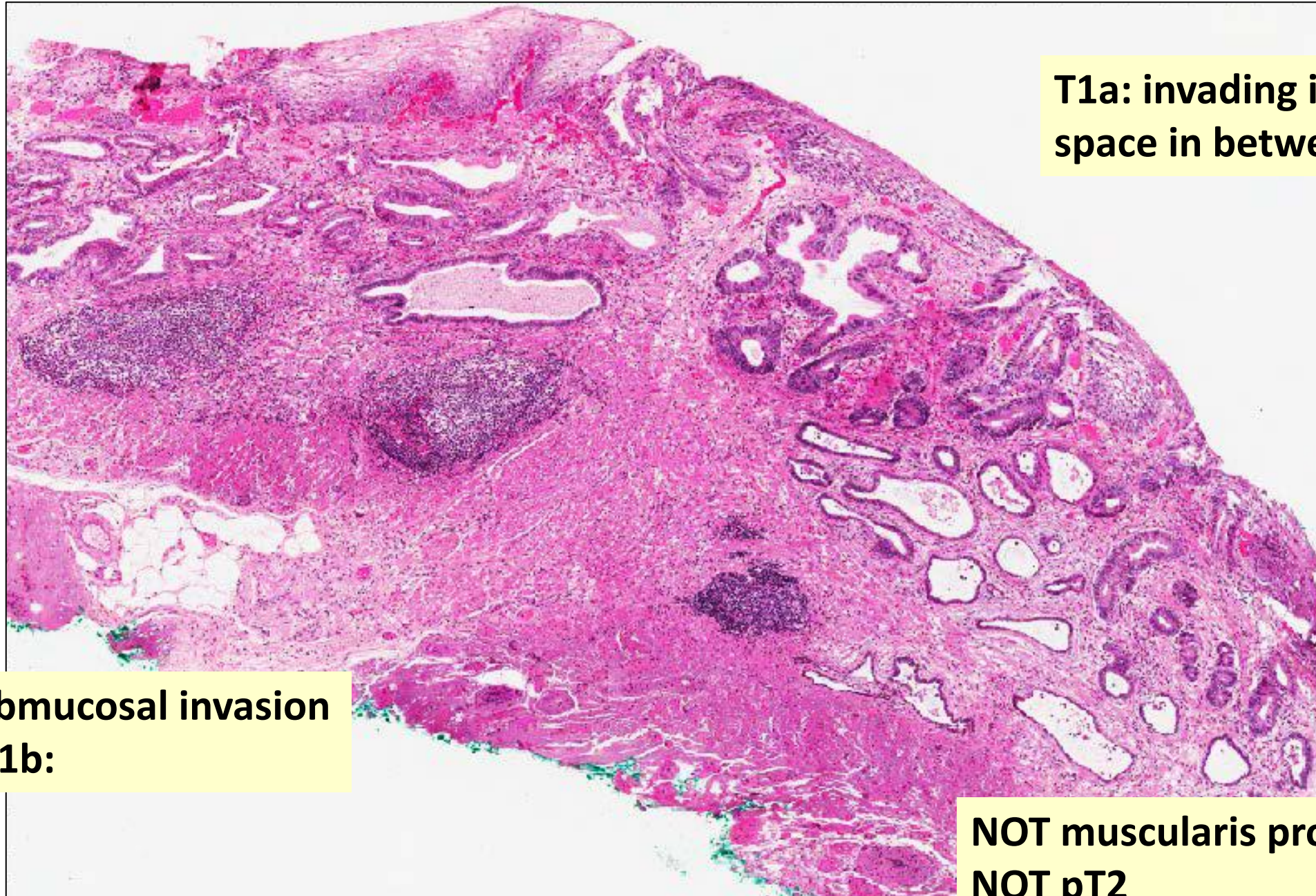
submucosa

600um

pT1a invading into the space in-between the duplicated mm and not pT1b



Misinterpretation of level of invasion



T1a: invading into the space in between MMd

**NOT submucosal invasion
NOT pT1b:**

**NOT muscularis propria invasion
NOT pT2**

Further subdivision of mm invasion: 2 methods

Stolte & Veith:

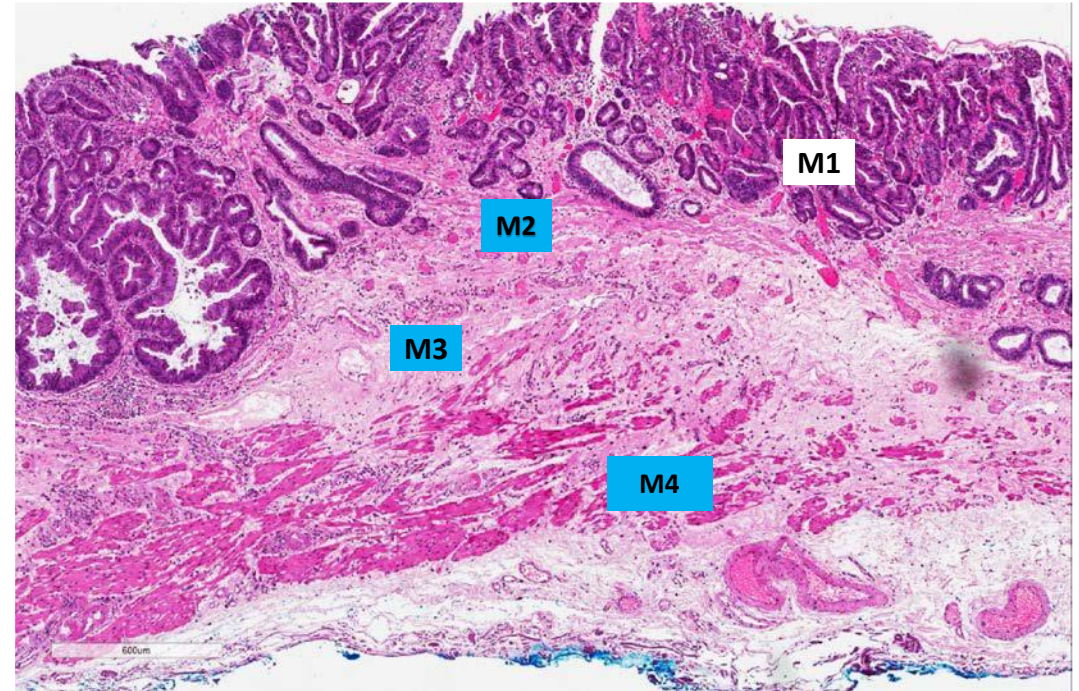
T1a is sub-divided as m1-m4 (**4 tiered**)

- m1 - into the lamina propria
- m2 - into the superficial/inner mm
- m3 - into the space between the layers of the mm
- m4 - into the outer/true mm

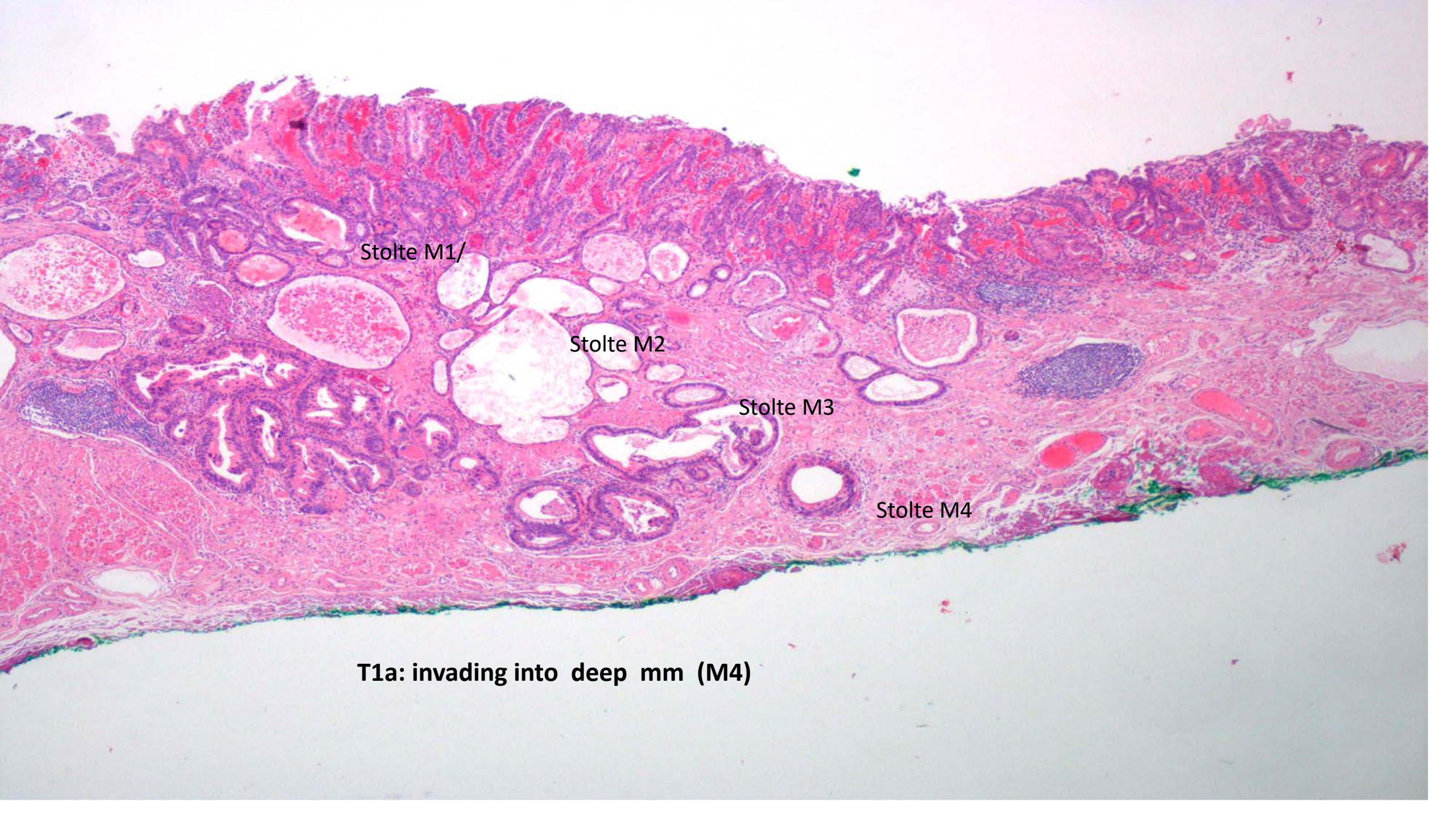
AJCC 7th edition:

T1a is sub-divided to m1-m3 (**3 tiered**)

- m1- in situ
- m2 - into the lamina propria
- m3 – into the muscularis mucosae



Possible prognostic implications of M4 vs M1 ?
Difficulties in M4 vs. SM1 interpretation



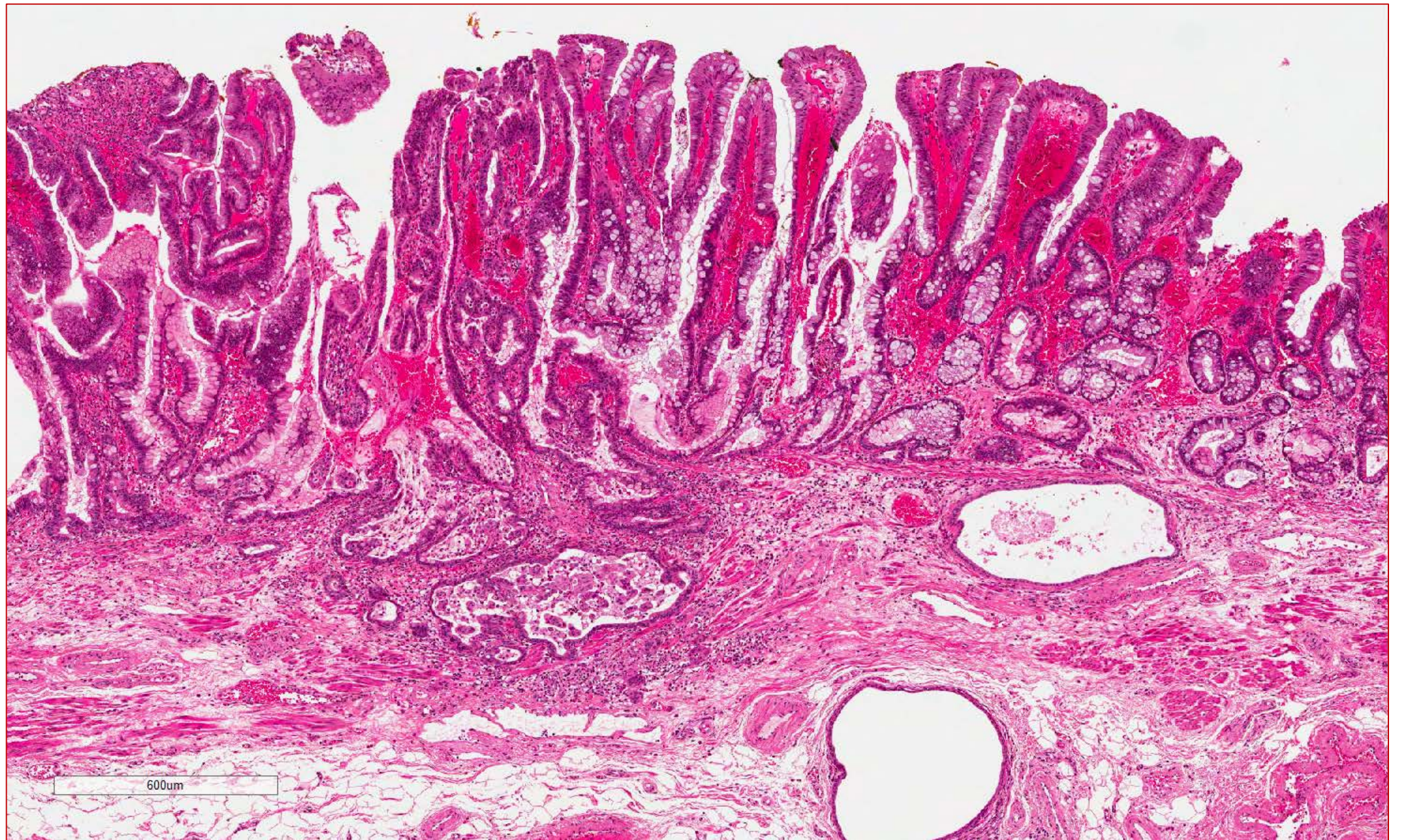
Stolte M1/

Stolte M2

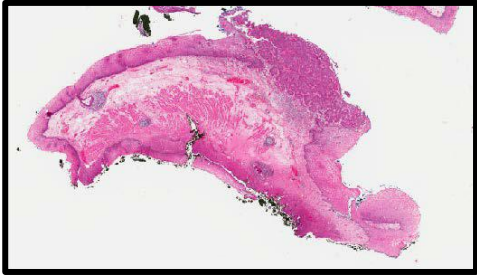
Stolte M3

Stolte M4

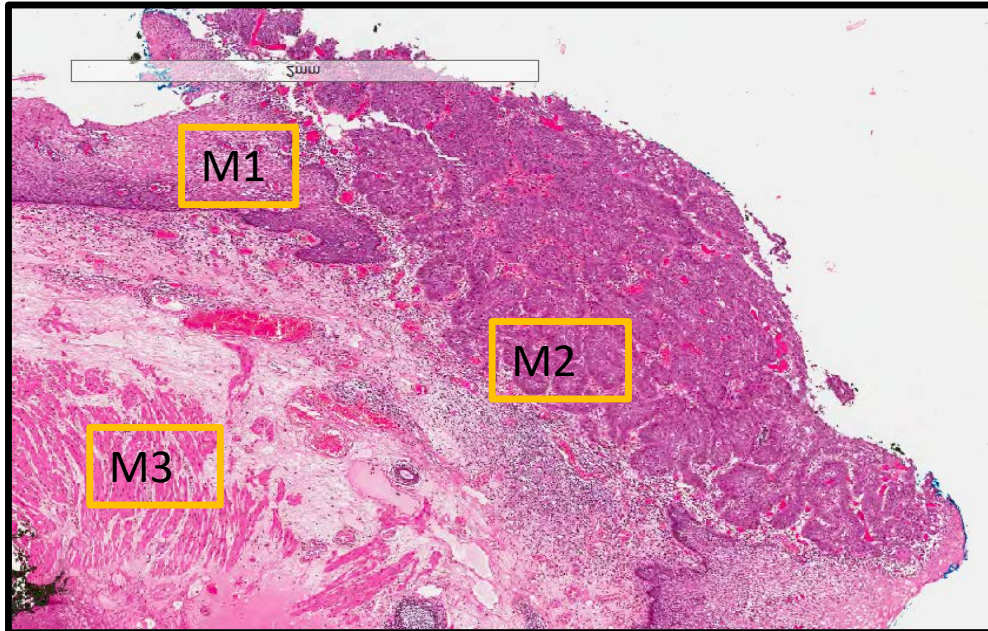
T1a: invading into deep mm (M4)



Esophagus – Early squamous neoplasia



ER curative: Lesions limited to the epithelium (m1) or lamina propria (m2) and completely resected: very low risk of lymph node metastasis

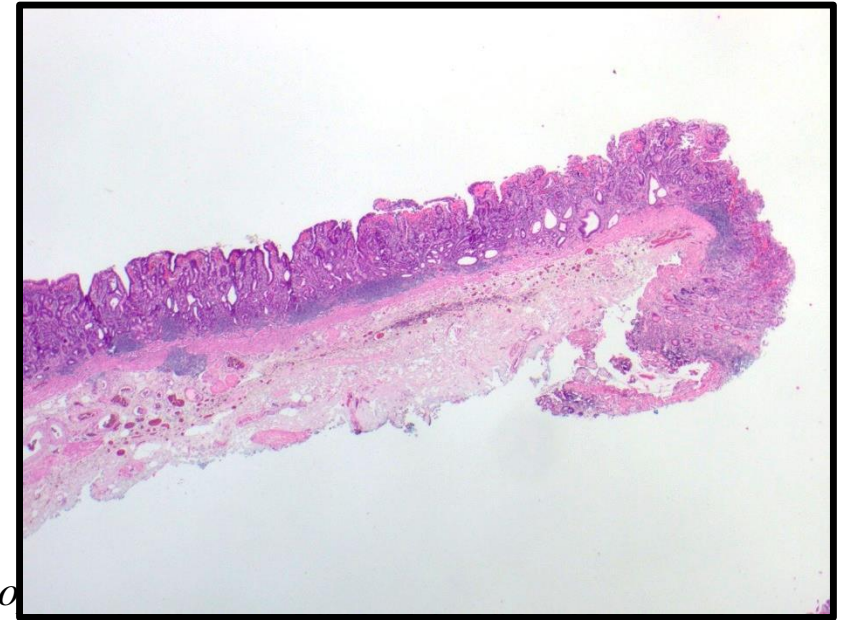


| Depth of invasion | | Esophagus | |
|-------------------|---------|----------------|--------------|
| | | Adenocarcinoma | SCC |
| Mucosa :T1a | | 0-2% | 0-5% |
| Submucosa: T1b | Overall | 26% | 45% |
| | Sm1 | 10-2% (500 μm) | 24%(≤200 μm) |
| | Sm2 | 21% | 37% |
| | Sm3 | 49% | 48% |

Stomach

Evaluation of curability is based on pathological risk factors

- **Size:** $\leq 2\text{cm}$
- **No Ulceration**
- Differentiated
- No vascular invasion
- Depth of invasion : pT1a



Digestive Endoscopy 2016; 28:3 –15 ,Gut 2001;48:225–229,Digestive Endoscopy Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101 –12. Gastric Cancer (2017) 20:1–19

Risk of Lymph node metastases in early gastric carcinoma

| | | |
|-------------------|---------|-------------------------------|
| Depth of invasion | | Stomach |
| Mucosa :T1a | | 0-3% |
| Submucosa: T1b | Overall | 19% |
| | Sm1 | 7% ($\leq 500 \mu\text{m}$) |
| | Sm2 | 16% |
| | Sm3 | 26% |

Dunbar KB, Spechler SJ. The risk of lymph-node metastases in patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus: a systematic review. *Am J Gastroenterol.* 2012;107(6):850-62.

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Vieth M, Stolte M. Pathology of early upper GI cancers. *Best Pract Res Clin Gastroenterol.* 2005 Dec;19(6):857-69.

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Duodenum

- **Adenomas: ER- more conservative local excision vs radical surgery**
- **In good hands: Complete removal: 59 – 100%**
- **Ampullary involvement: ER vs. surgical management (e.g. Whipple resection)**
- **Distal CBD/Ampullary duct resection margin**
- **Limited data on the risk of lymph node metastases in early duodenal cancer after ER (vs stomach and colon) ?**
- Adverse pathological features : poor differentiation, lymphovascular invasion, involved margins.
- Submucosal invasion – surgical resection



Colon

- **Current:** ERs curative for
 - Advanced adenomas > 20 mm
 - Low risk submucosal invasive cancer (LR –SMIC)

- **Last century:** surgery for above

Gastroenterology 2011;140: 1909–18, *Gastroenterology*. 2017 Sep;153(3):732-742, *Digestive Endoscopy* 2015; **27**: 417–434

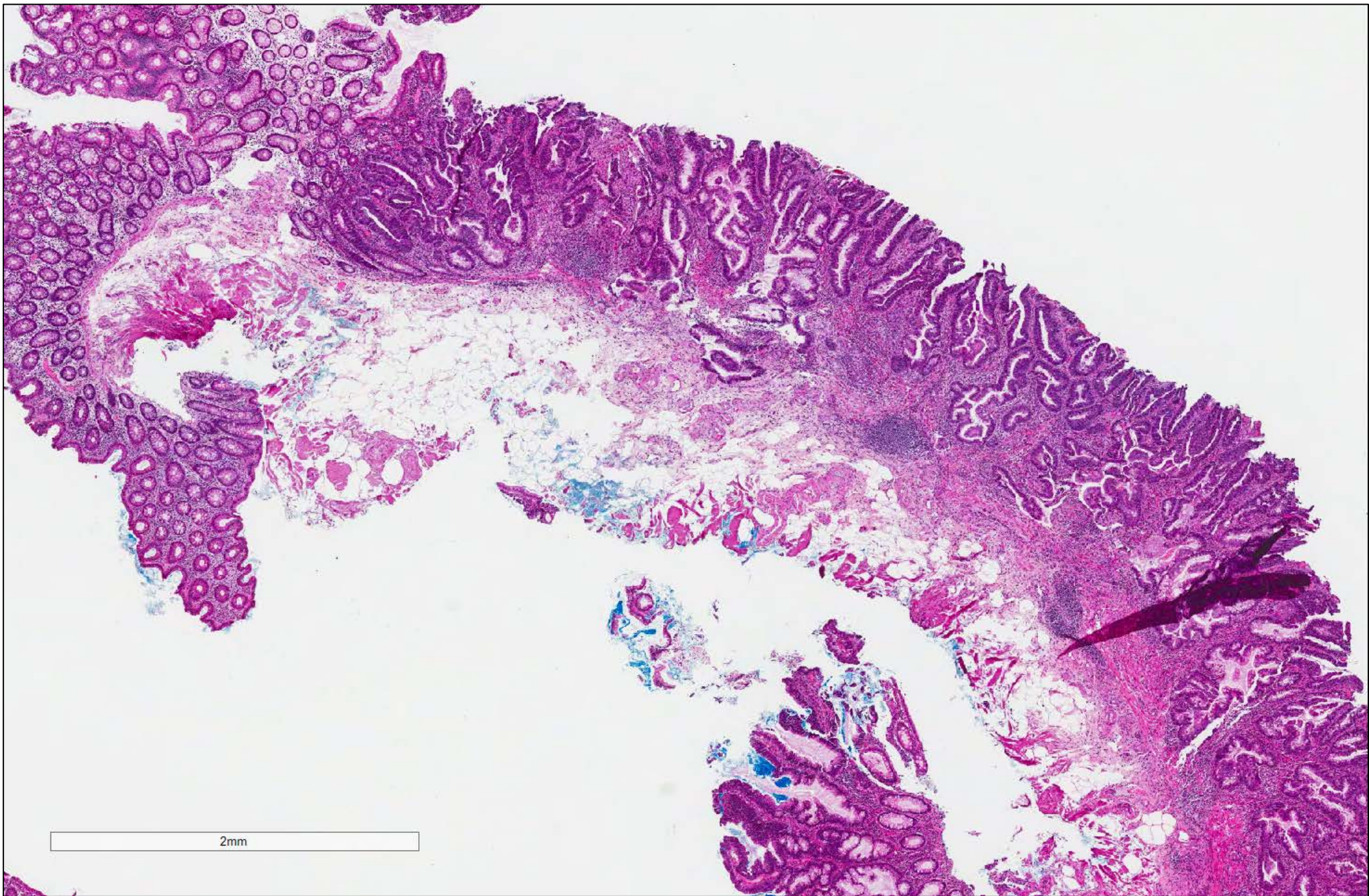
Low risk submucosal invasive cancer (LR –SMIC)

Adenocarcinomas

- Low grade
- No lymphovascular invasion
- Submucosal invasion $\leq 1000 \mu\text{m}$
- Completely resected
- **No tumor budding**
- Clear margins (2 or 1 mm)

Low risk submucosal invasive cancer (LR –SMIC) with low absolute risk of nodal metastasis

Colorectal Dis. 2013 Jul;15(7):788-97, Dis Colon Rectum 2002;45:200–206, Mod Pathol; 2005;28:872–87,Gastroenterology.2004.127:385-394.,J Clin Pathol. 2016;69(4):292-9, Digestive Endoscopy 2015; 27: 417–434



2mm

Risk of Lymph node metastases in early invasive carcinomas of GIT

| Depth of invasion | | Esophagus | | Stomach | Colon |
|-------------------|---------|----------------------------------|--------------------------------|--------------------------|--|
| | | Adenocarcinoma | SCC | | |
| Mucosa :T1a | | 0-2% | 0-5% | 0-3% | pTis: 0% |
| Submucosa: T1b | Overall | 26% | 45% | 19% | pT1: 5-10% |
| | Sm1 | 10-2% ($\leq 500 \mu\text{m}$) | 24% ($\leq 200 \mu\text{m}$) | 7% ($500 \mu\text{m}$) | pT1: $< 3\%$ ($\leq 1000 \mu\text{m}$) |
| | Sm2 | 21% | 37% | 16% | pT1: 8% |
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Ancillary studies

- **Diagnosis** classic neoplasia: limited
 - p53
 - Poorly differentiated carcinoma (squamous vs glandular)
- **Confirmation** of pathological risk factors

Histochemistry

- VVG for large vessel invasion; muscle stains in BE

Immunohistochemistry

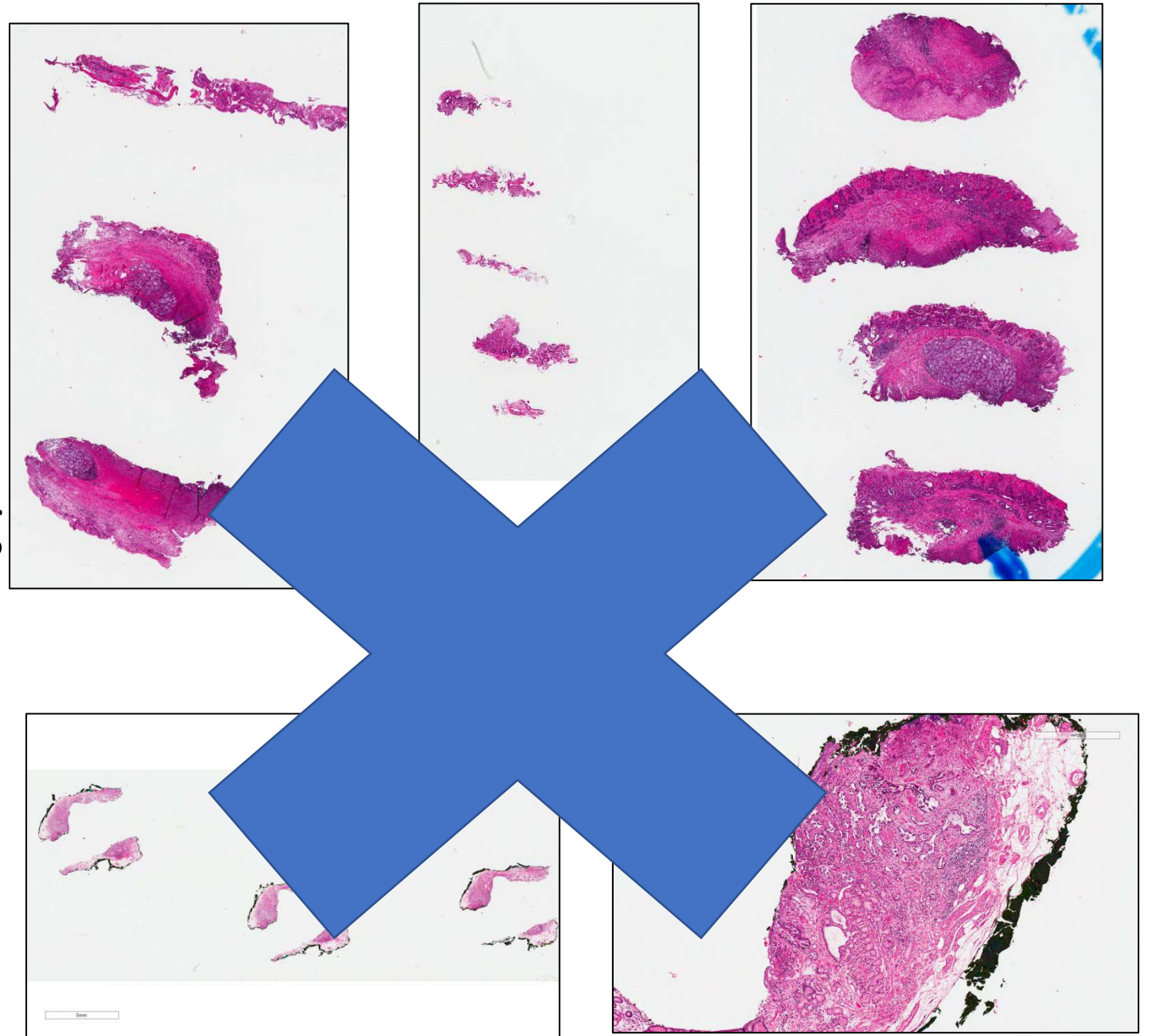
- Cytokeratin (AE1/AE3)- detection of single infiltrating cells
- Vascular markers: D2 40, CD31, ERG
- Desmin for mm
- **MMRP: Colon**, other GIT tumors....
- HER2 ?
- PDL1 ?

Technical artefacts

- Hemorrhage
- Electro diathermic burns
- Tears due to stretching
- Too thin sections

Limit the histologic interpretation

Communication....



Criteria for cure in early GI carcinomas

| | Absolute criteria | Extended criteria |
|--------------------|---|---|
| Esophagus-squamous | T1a, M2 without any other histological risk factors for lymph node metastasis and radical vertical resection margin. | T1a M3-and sm1 (i.e. submucosal invasion $\leq 200 \mu\text{m}$) without any other histological risk factors for lymph node metastasis and radical vertical resection margin. |
| Esophagus- | T1a without any other histological risk factors for lymph | T1bSm1 (i.e. submucosal invasion ≤ 500 |

Pathological evaluation is pivotal

| | | <ul style="list-style-type: none"> 3. Undifferentiated only 4. <3 cm, pT1b (SM1, $\leq 500 \mu\text{m}$) |
|------------------|---|--|
| Colon and rectum | T1 , without any other histological risk factors , submucosal invasion $\leq 1000 \mu\text{m}$ and without tumor budding, completely resected and clear deep margin by 2mm | T1 , without any other histological risk factors , submucosal invasion $\leq 1000 \mu\text{m}$ and without tumor budding, completely resected and clear deep margin by 1mm |

Acknowledgments

- *Duncan McLeod*
- *Ian Brown*
- *Spiro Raftopoulos*
- *Michael Bourke*
- Greg Lauwers
- Peter Draganov
- Tetsuo Ushiku
- Cathy Streutker