

Endoscopic Resections of the GI Tract: Pathological Evaluation

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**Rodger C. Haggitt Gastrointestinal Pathology Society
USCAP- 2018**

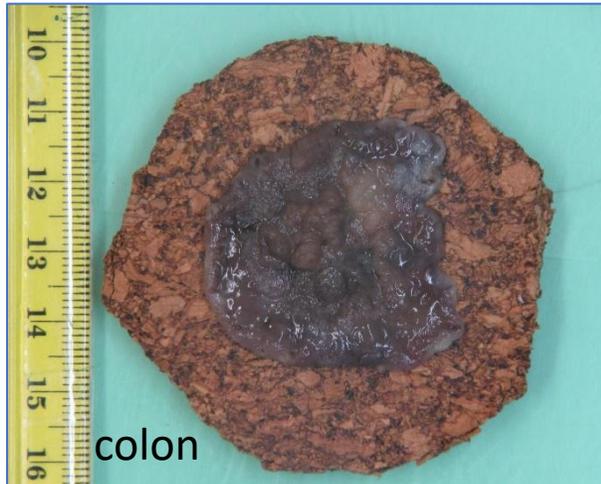
Plan

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

Endoscopic Resections: evolution

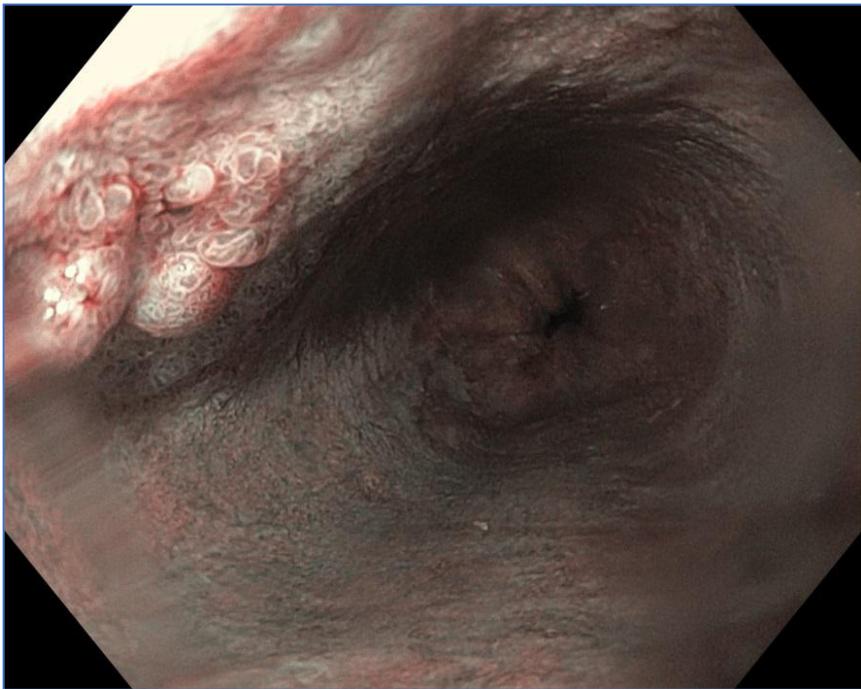
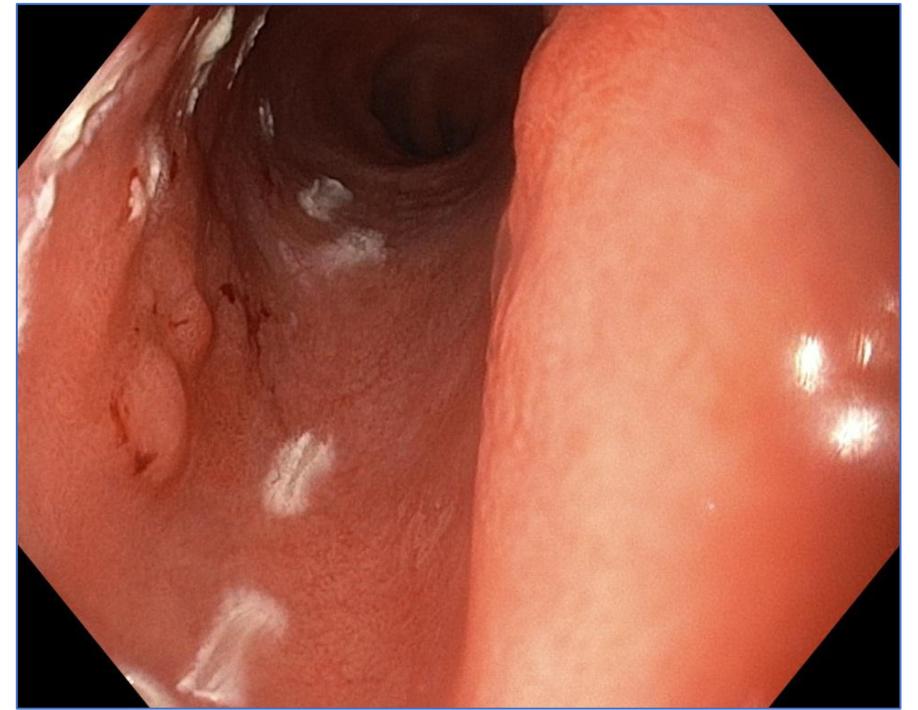
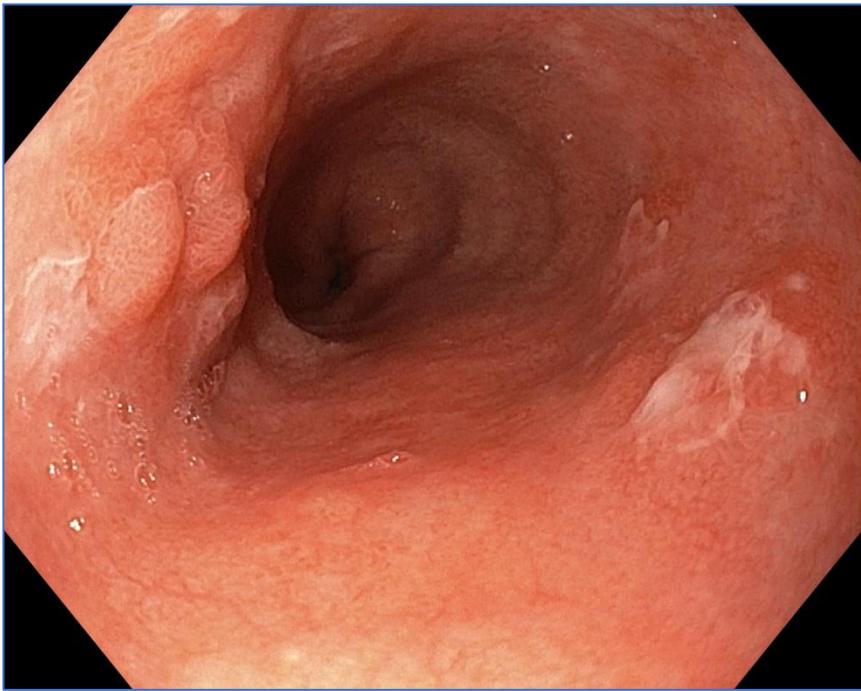
- **Last century** : Resection techniques were largely limited to ‘polypectomy’
- **1990s**: Endoscopic mucosal resection (EMR)
- **Early 2000s**: Endoscopic submucosal dissection (ESD)
- **Current**:
 - Considered curative in a large proportion of
 - Early gastric carcinoma
 - Early Barrett related 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)

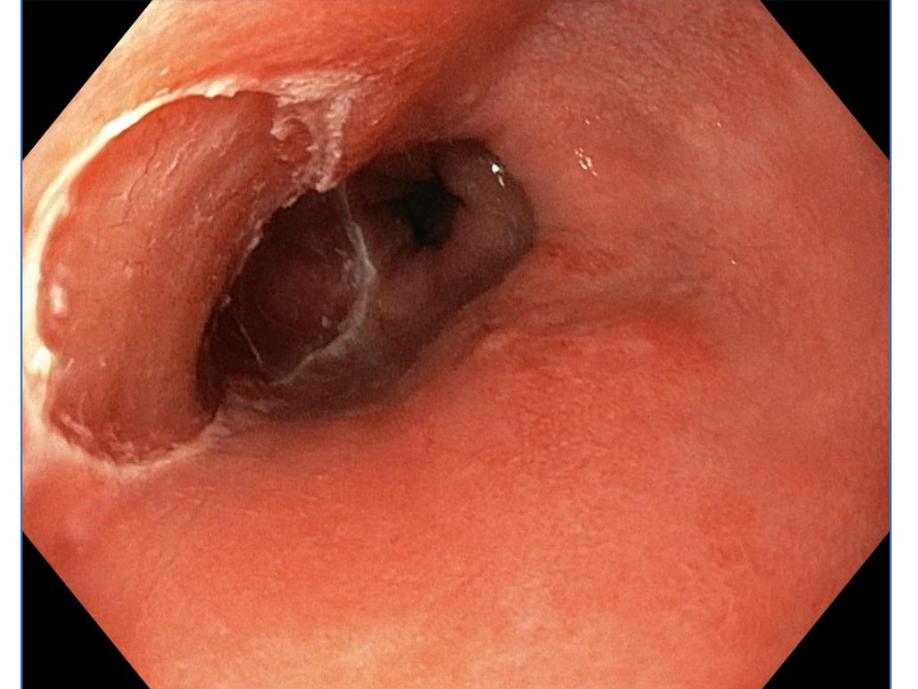


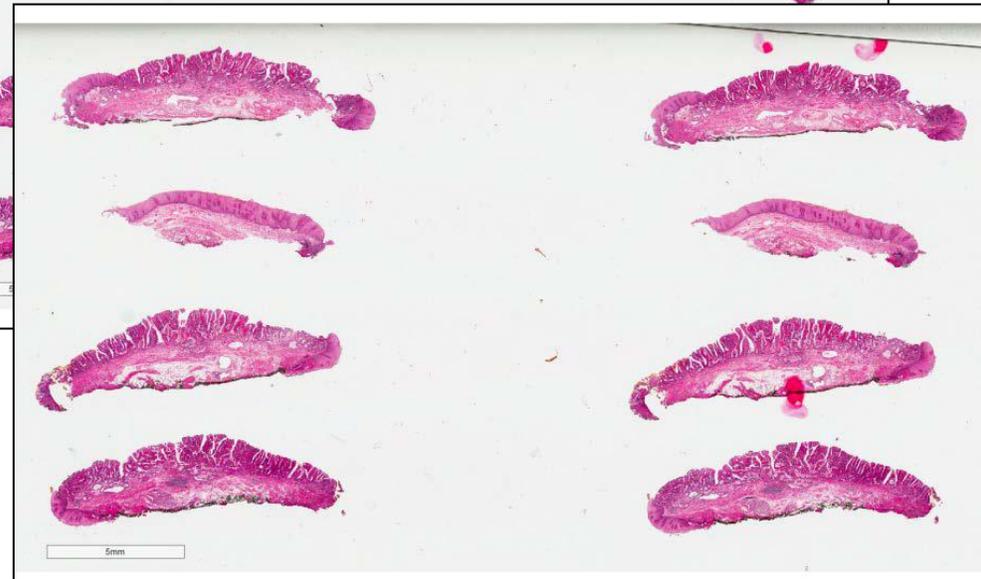
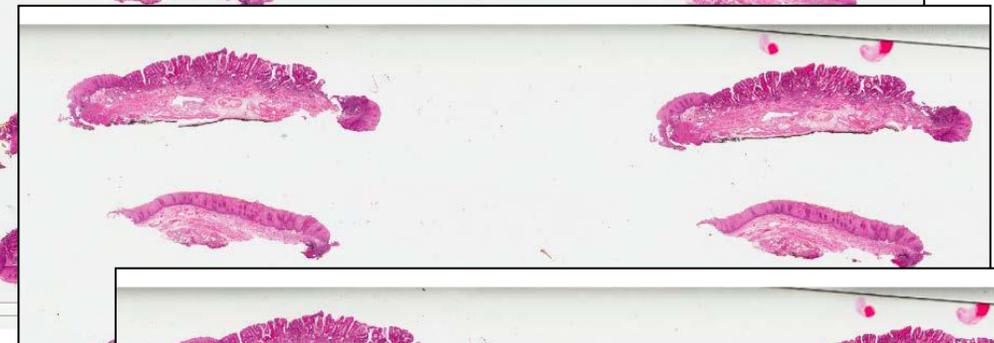
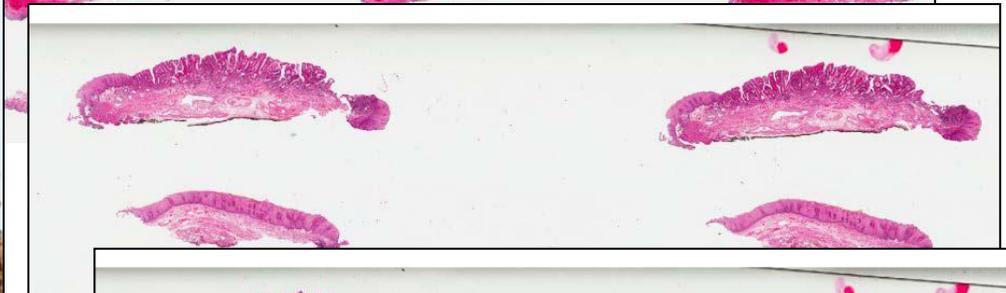
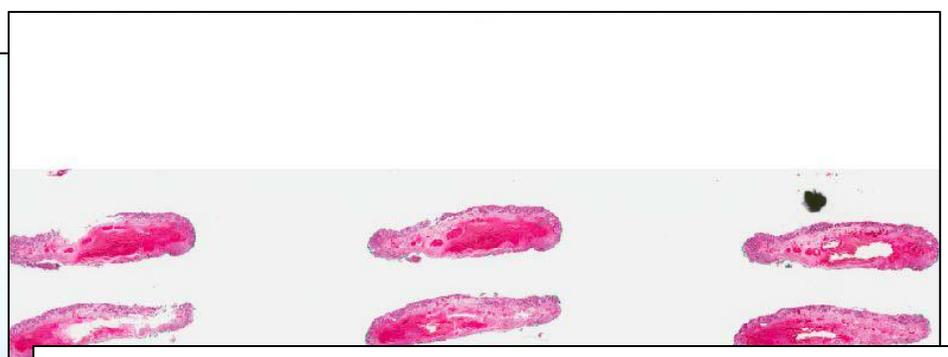
	EMR	ESD
Type of specimen received	Limited	En bloc
Determination of curative resections	Limited	Accurate
Determination of resection margins	Limited	Accurate
Accuracy of a pathological diagnosis	+++ / ++	+++
Technical precision	+ / ++	+++
Technical challenge	+ / ++	+++
Resource utilization	+ / ++	+++
Procedure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

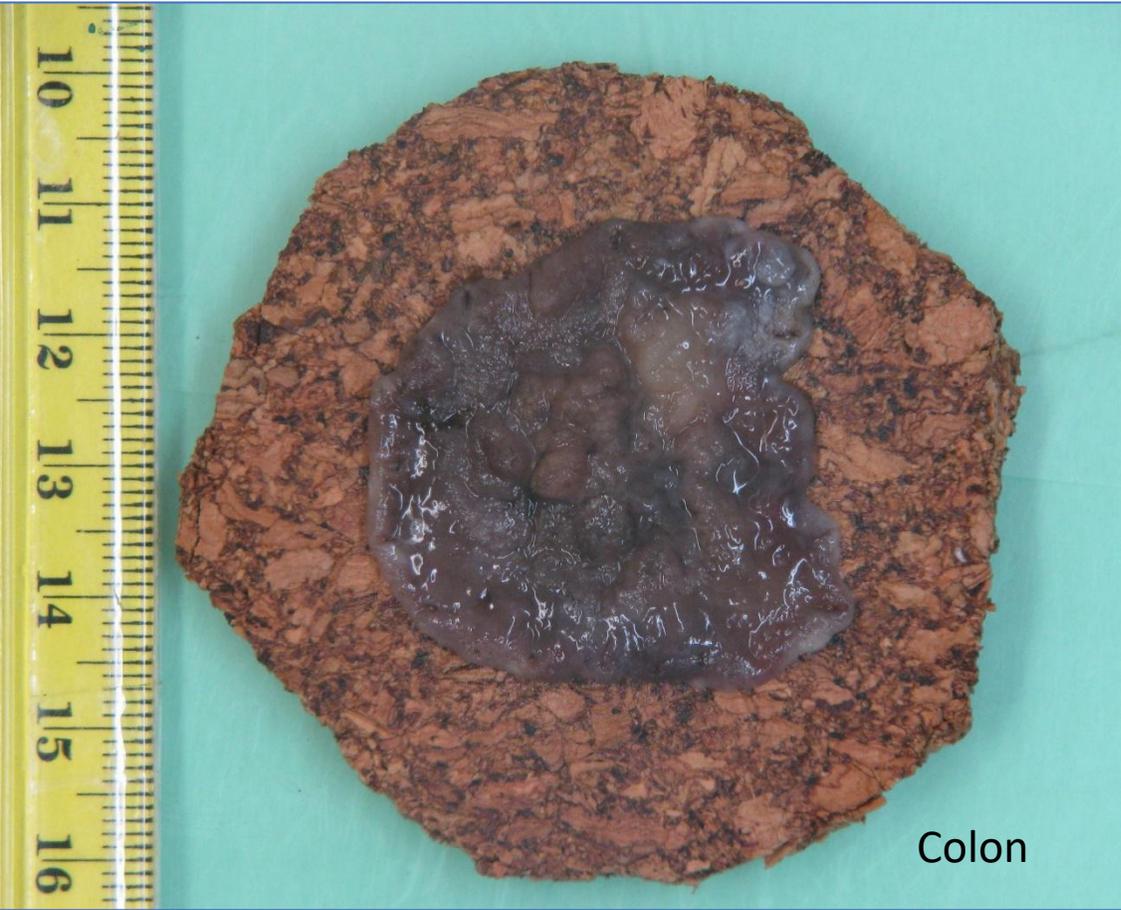
Resources vs Outcome



- 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.

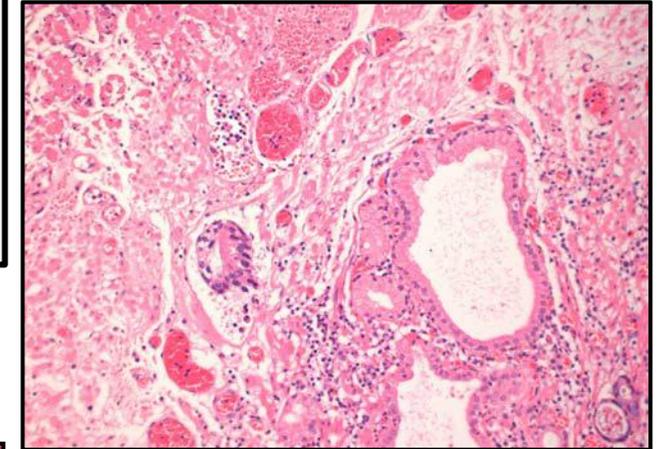
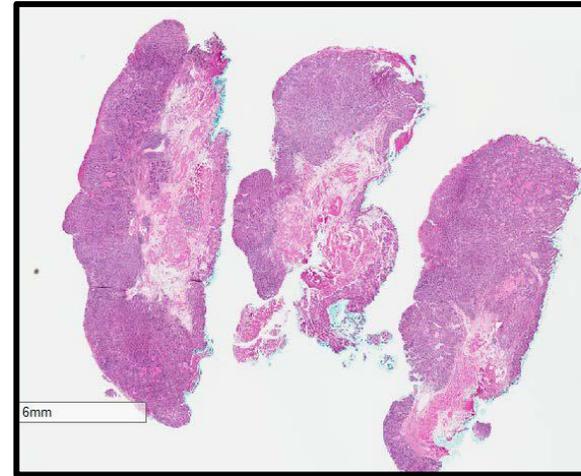
Gastrointest Endosc 2007 ; 66 : 660 – 6 .

Am J Surg Pathol 2006;30:114–118)

Pathological risk factors

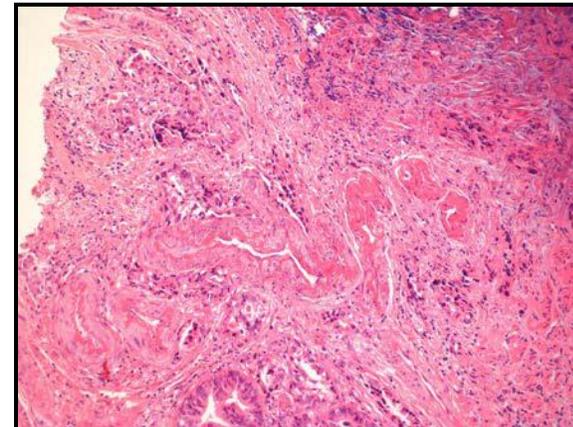
Adverse pathological (histological) features throughout the GIT

- 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

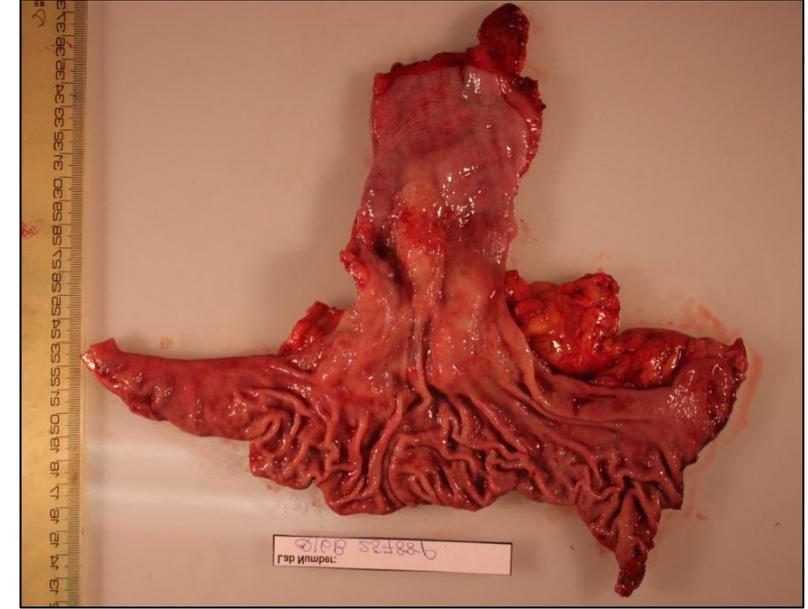
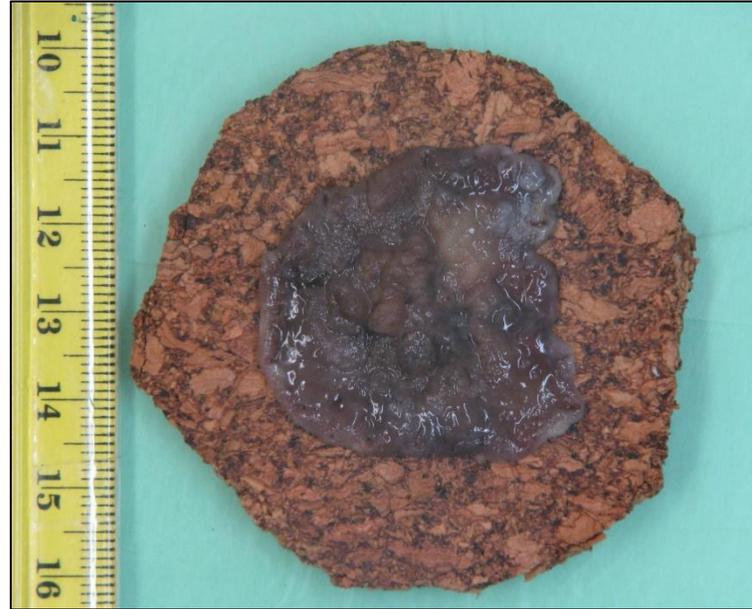
Modern Pathology (2009) 22, 489–498

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

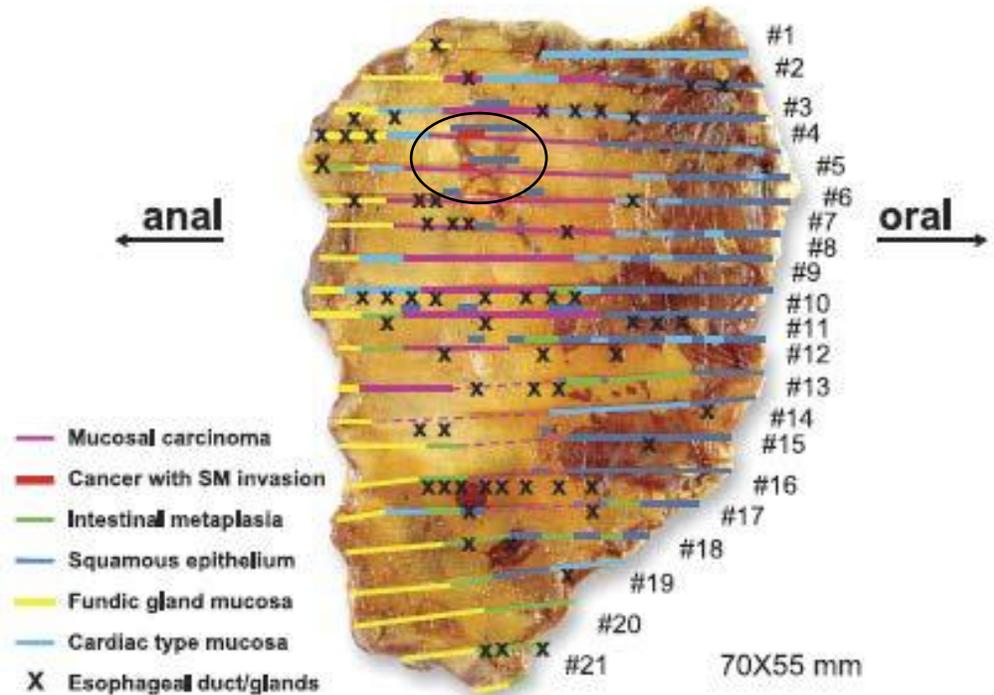
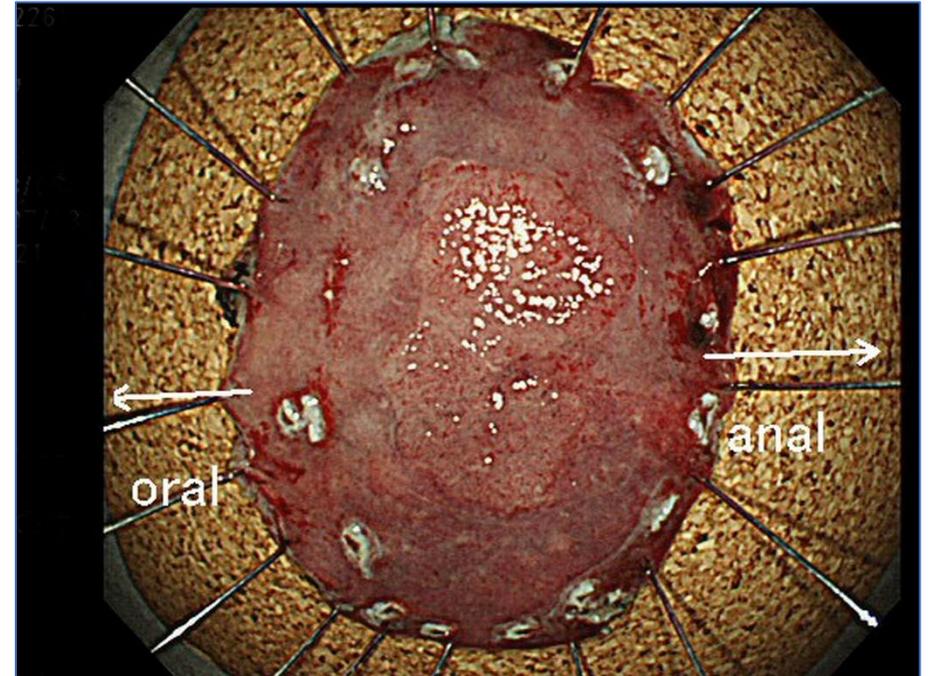


Figure 3 Pathologic assessment and mapping of gastroesophageal junction ESD with Barrett's esophagus and adenocarcinoma invading the submucosa. (Color figure is available online at www.techgastroscopy.com.)

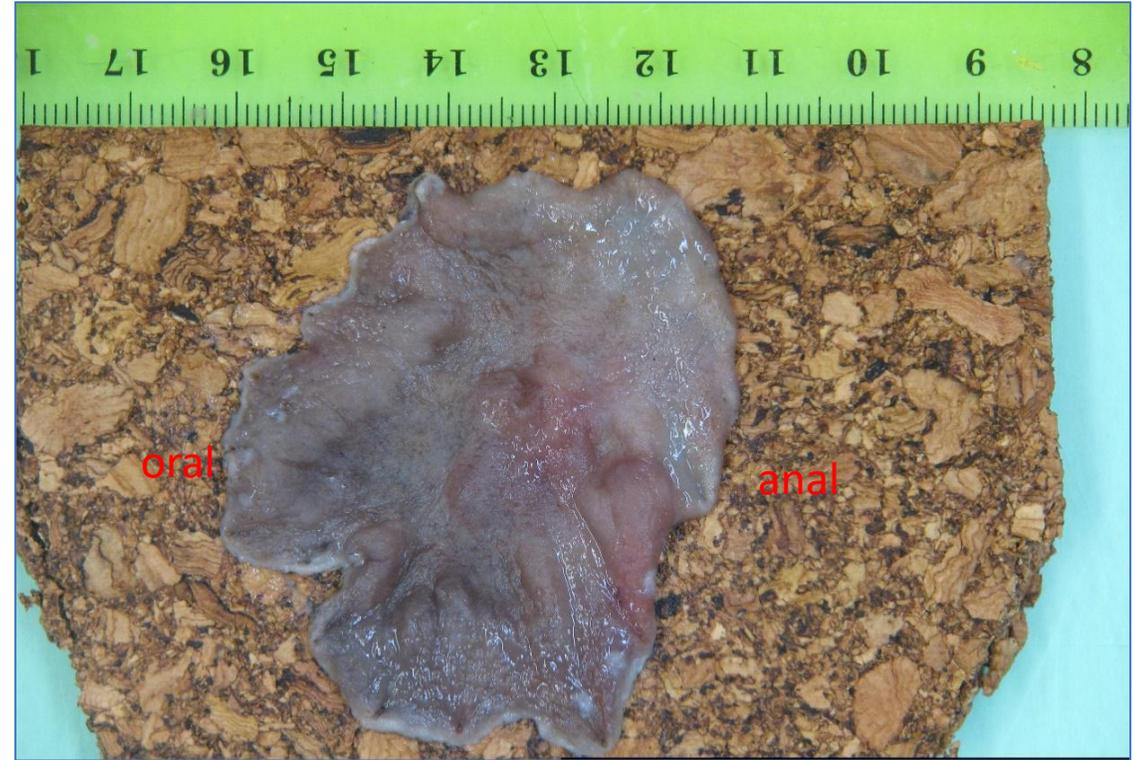
Fuss: Pinning out

- 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

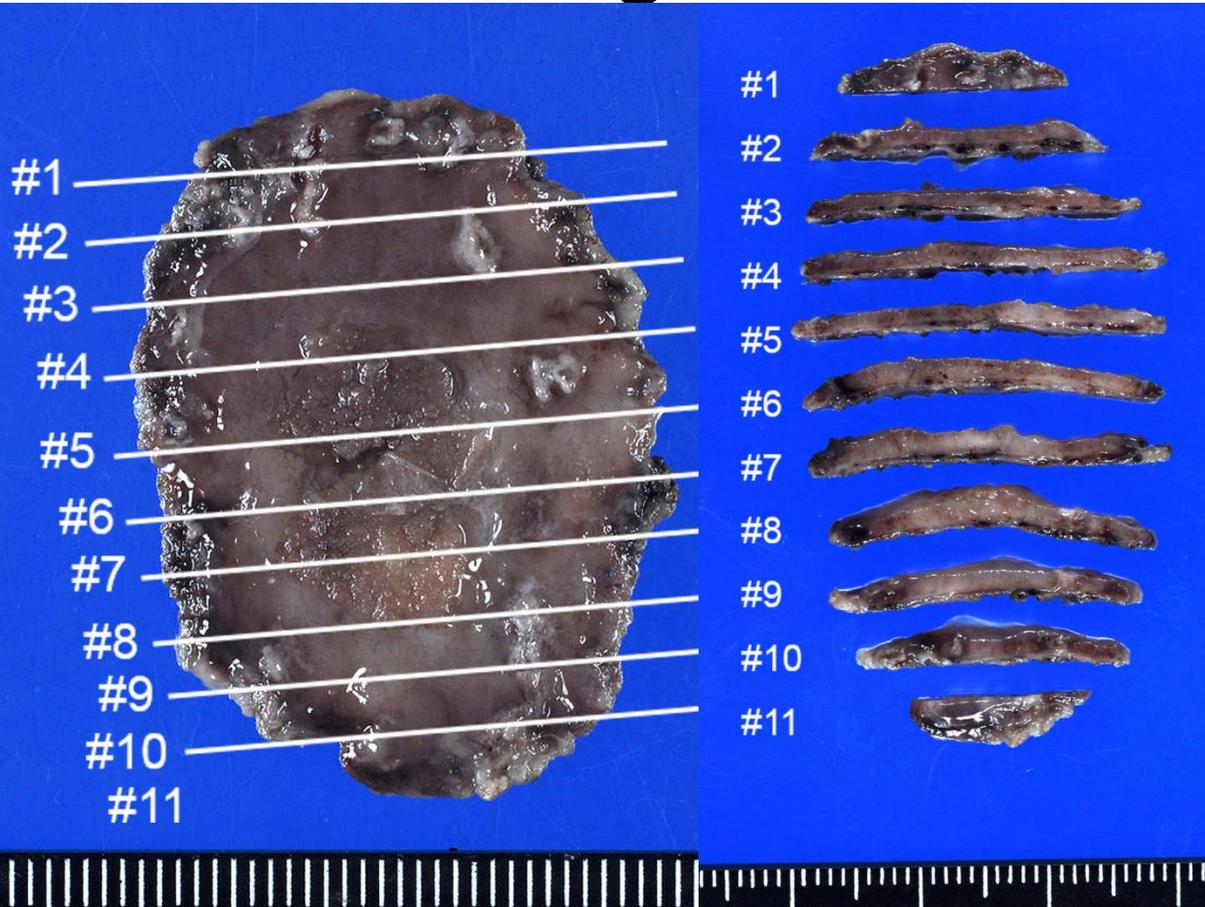


Macroscopic examination: after fixation

- 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

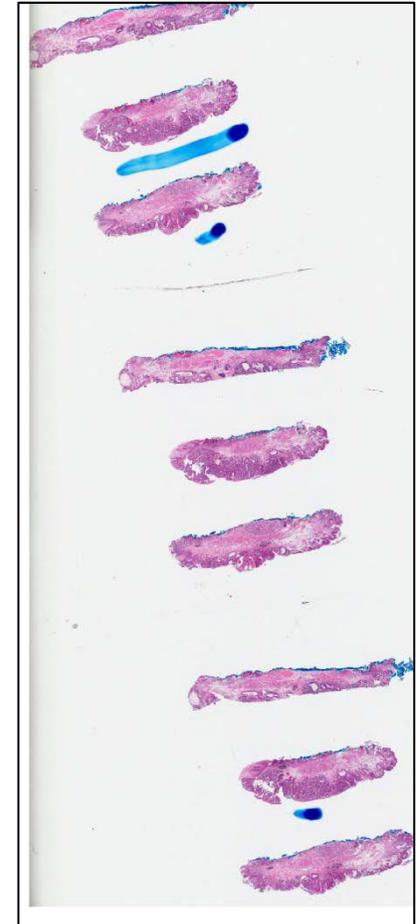
Numbering and orientation of slices into cassettes: Tissue embedding

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.

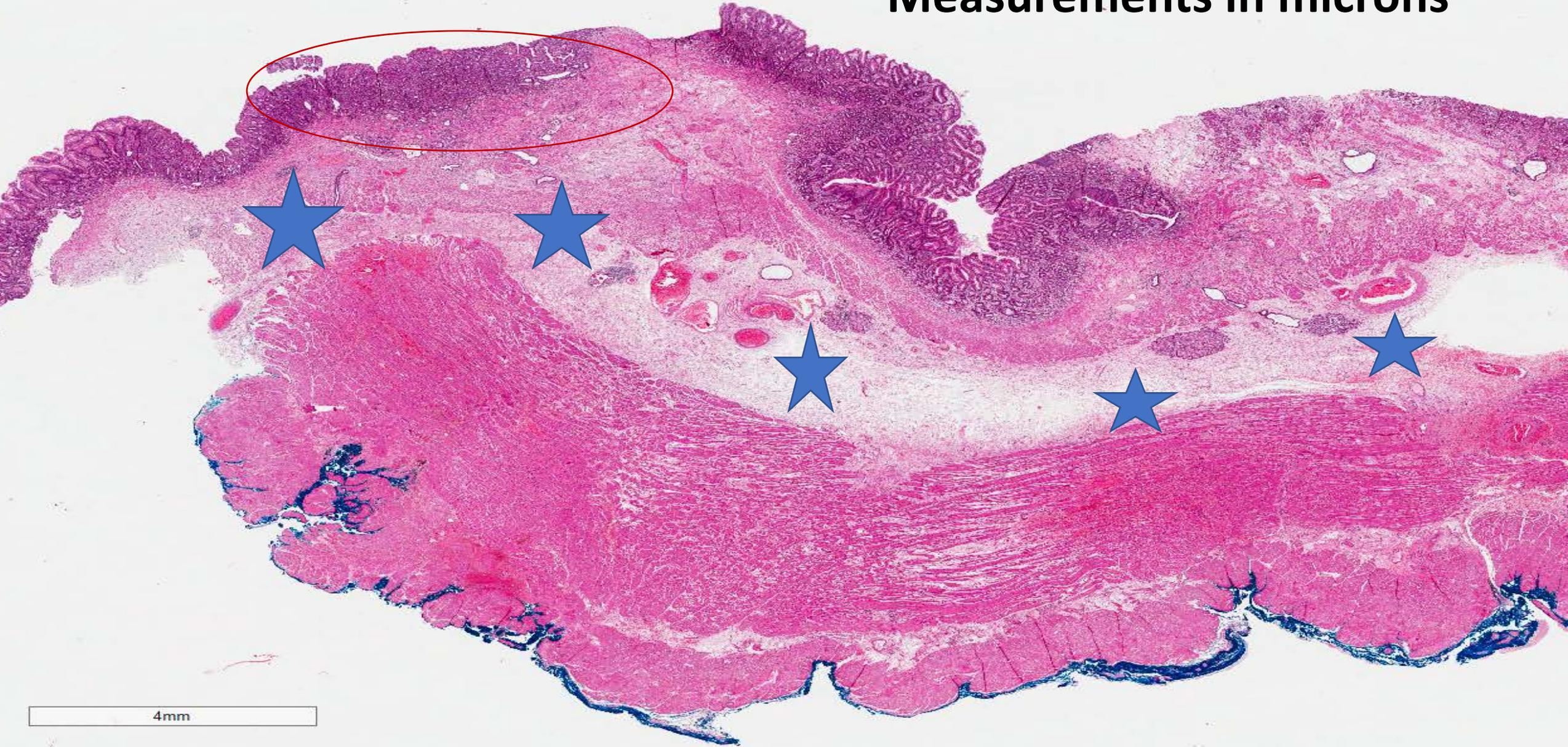
Scourakis G, et al. Endoscopic and surgical resection of T1a/T1b esophageal neoplasms: a systematic review. *World J Gastroenterol.* 2013;19(9):1424-37.

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*

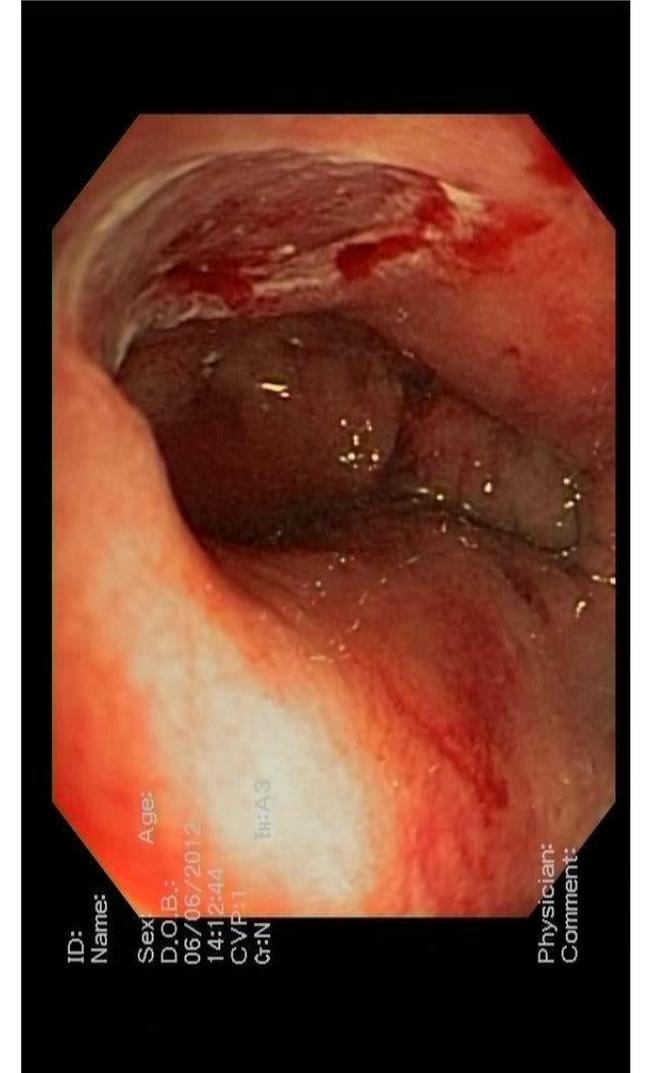
- EMR with further piecemeal EMR of the residual Barrett's segment
- Barrett's cancer
 - against a background of a "field defect"
 - after resection recurrent lesions in 30% within 3 years
 - remainder of the Barrett's segment requires further therapy.

ESD: *Complete en bloc resection*

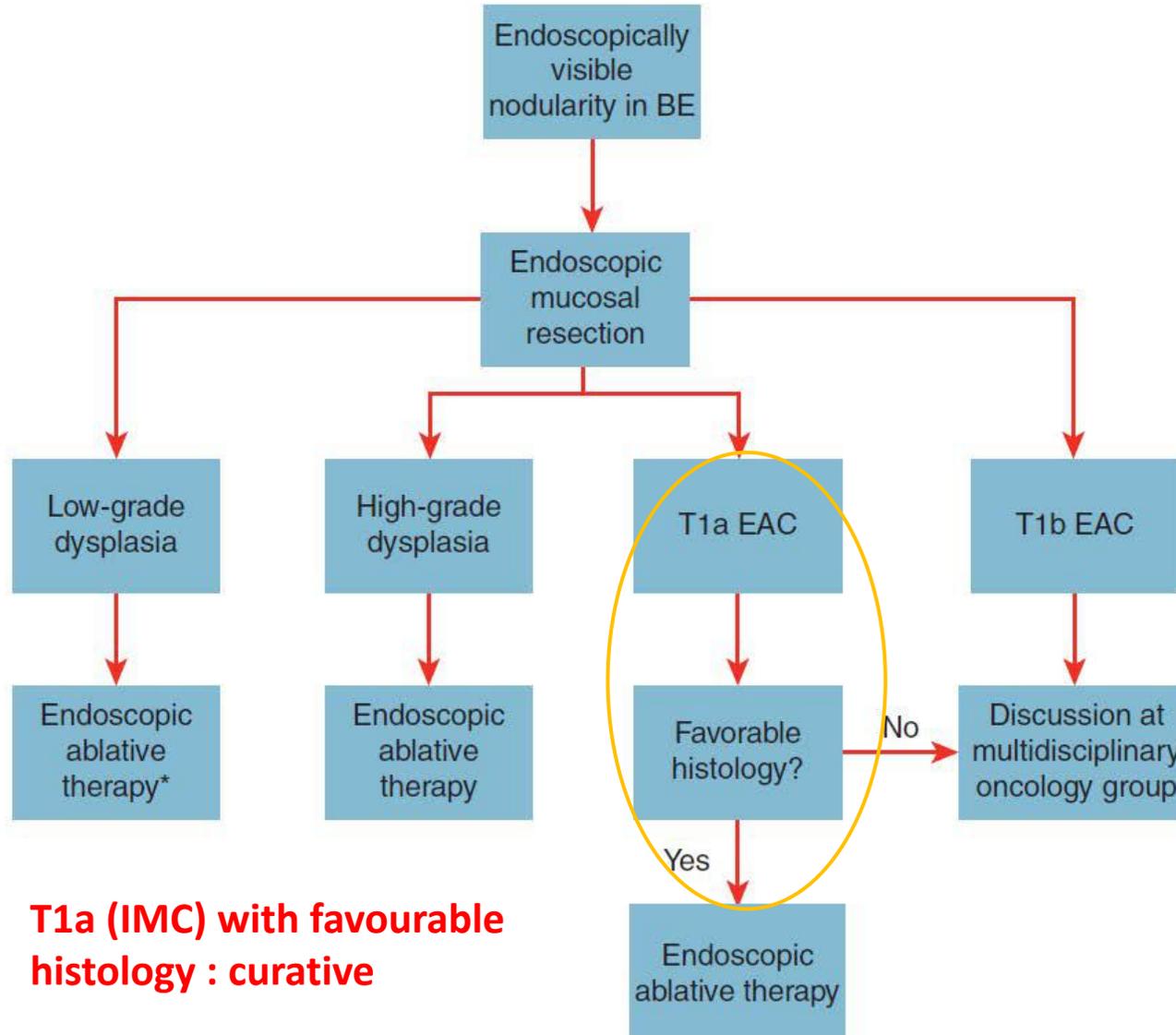
- Particularly for larger SM invasive lesions (T1b).
- **Only <10% of cases of early esophageal neoplasia**
- ESD achieves a higher radical (RO) resection

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

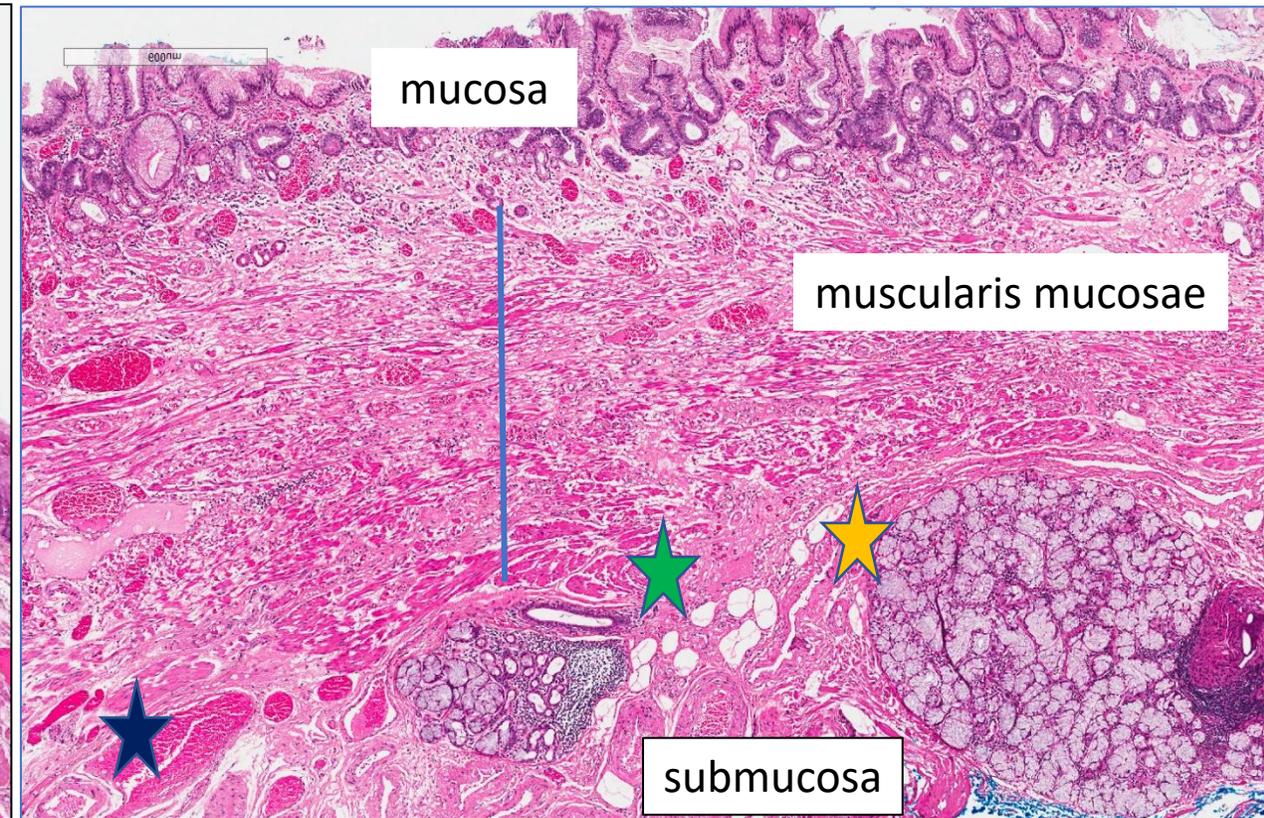
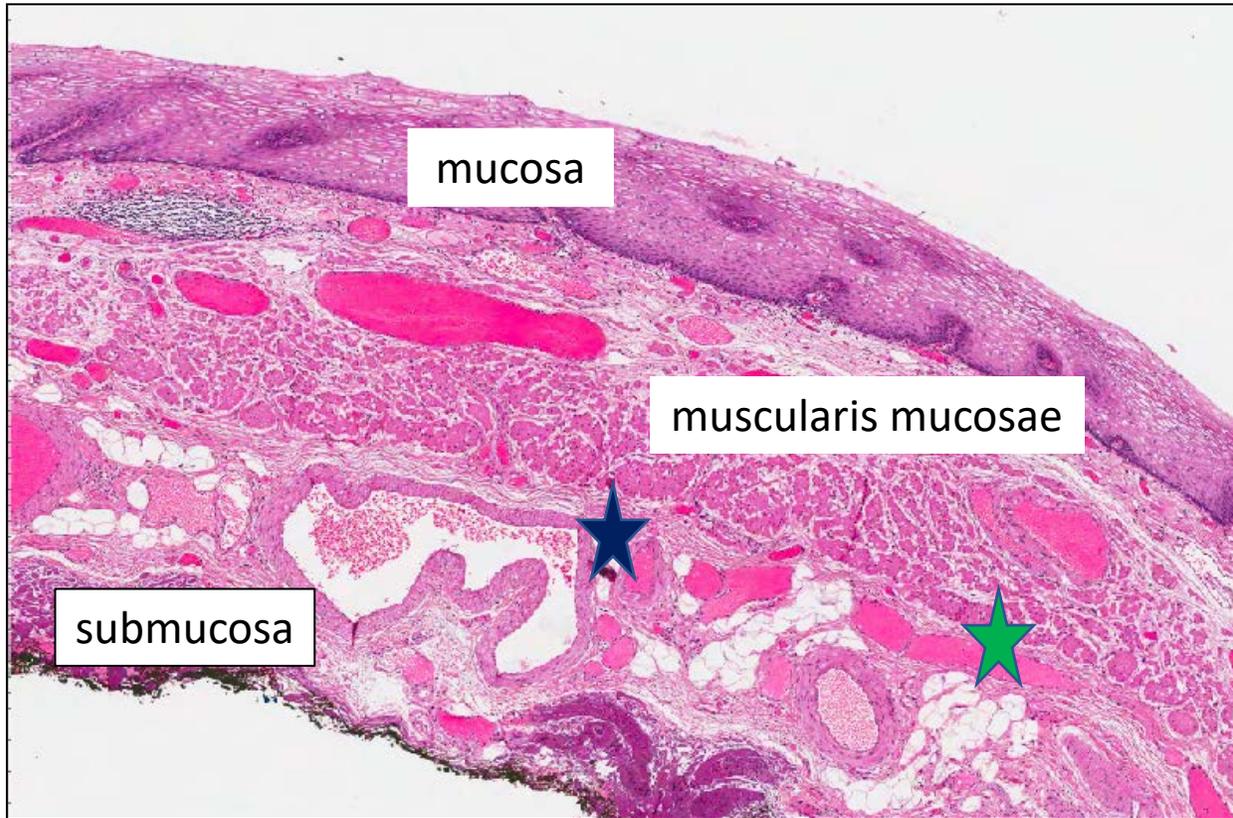
DUPLICATION of MUSCULARIS MUCOSA

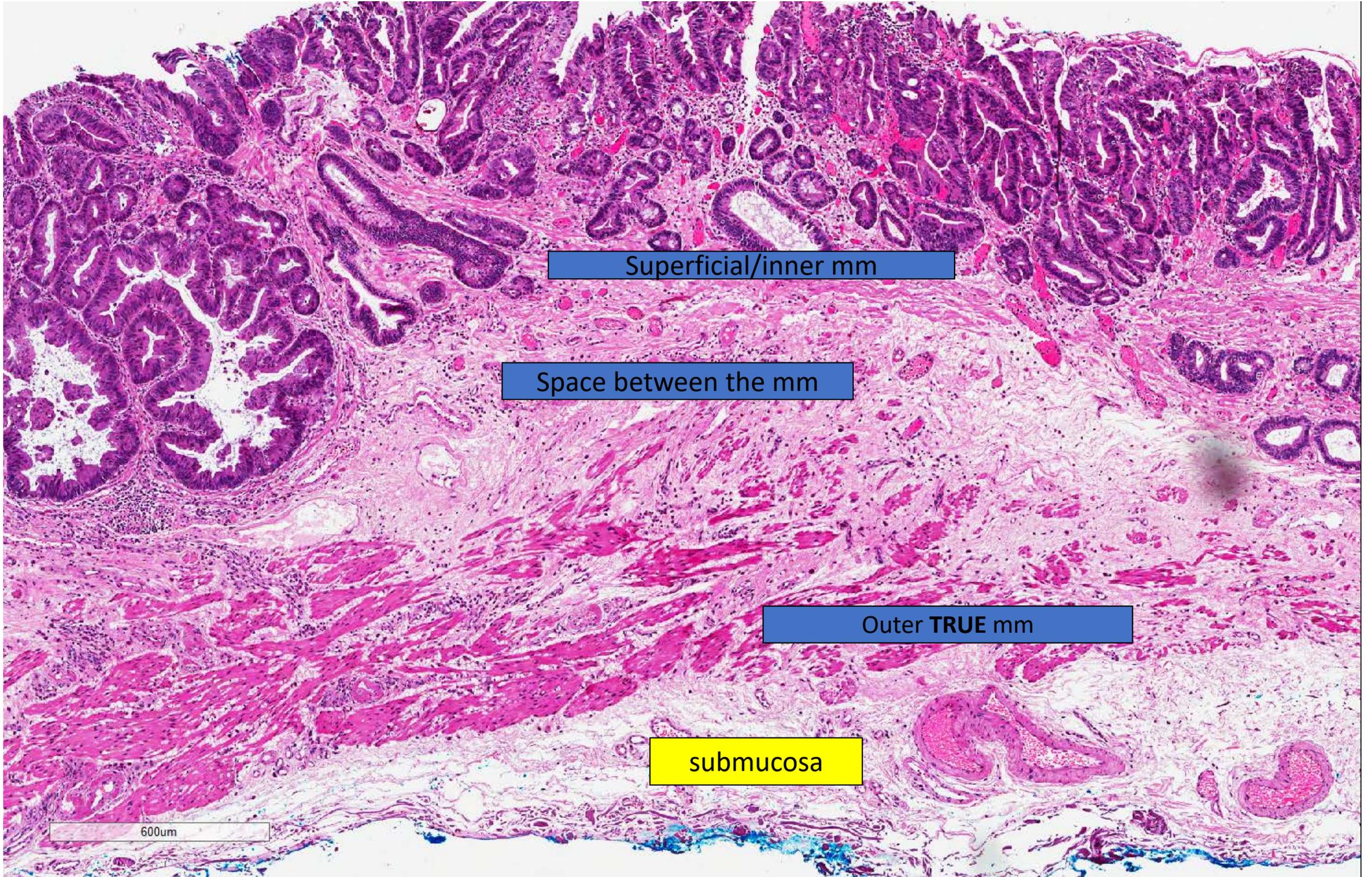
- **A unique feature , seen in 92% of BO (0% of SCC)**
- Frequently unrecognised or misinterpreted
- Impacts on EUS staging

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

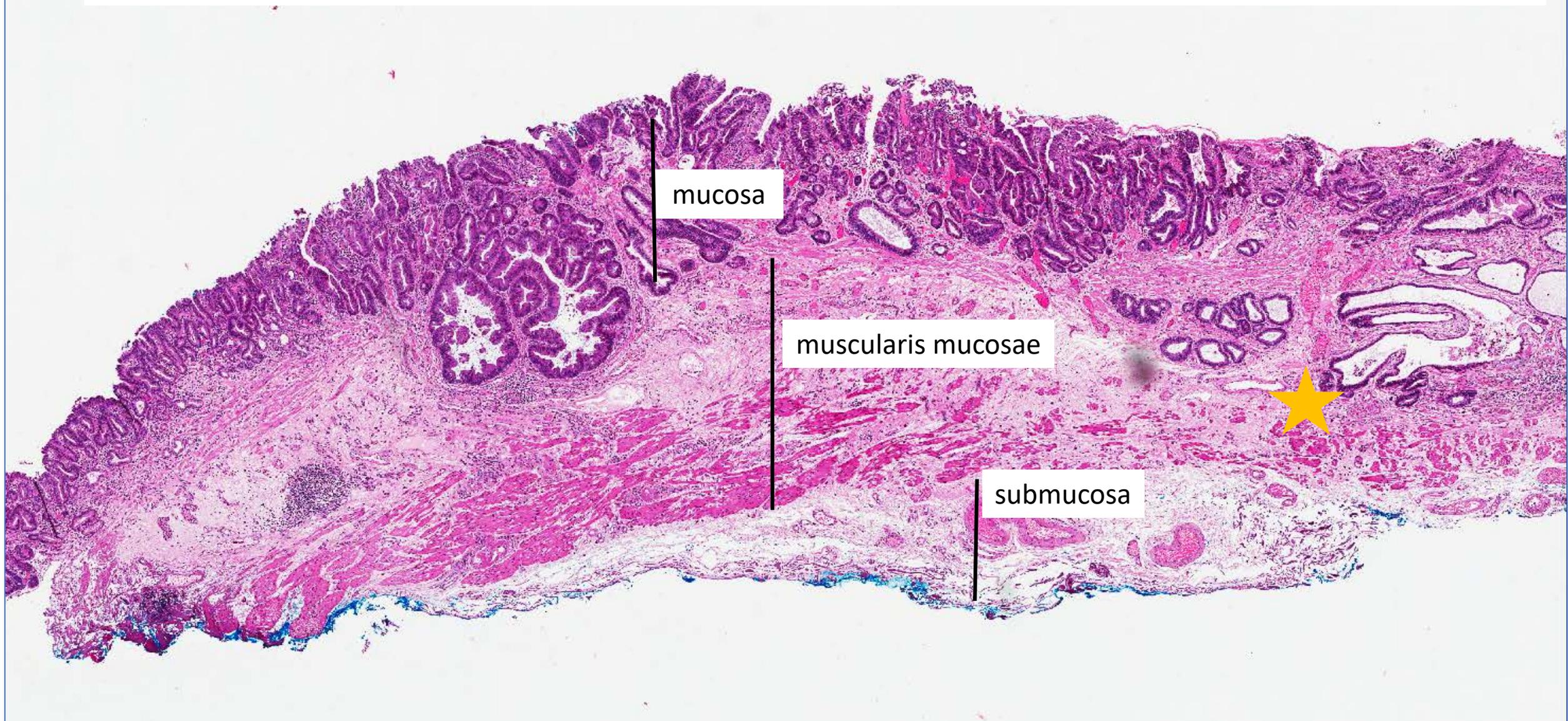
Space between the mm

Outer **TRUE** mm

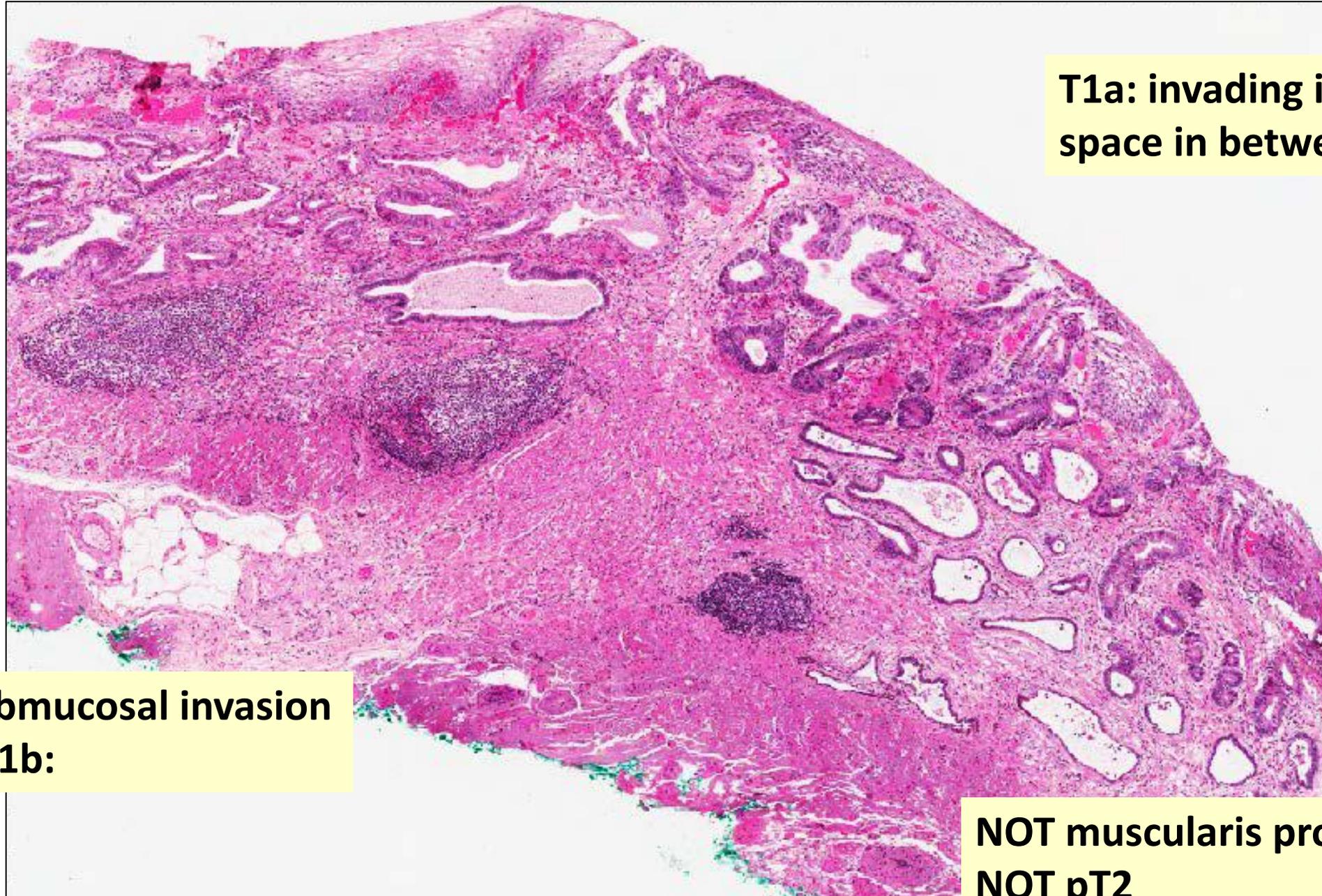
submucosa

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:

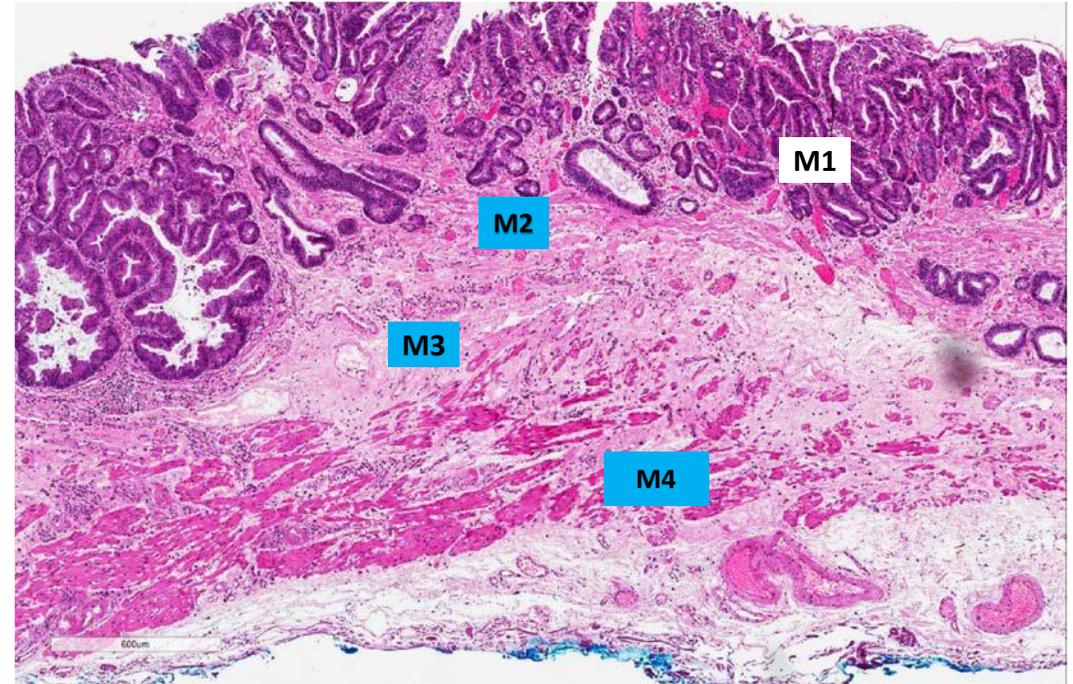
T1a is sub-divided as m1-m4 (**4 tiered**)

- 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

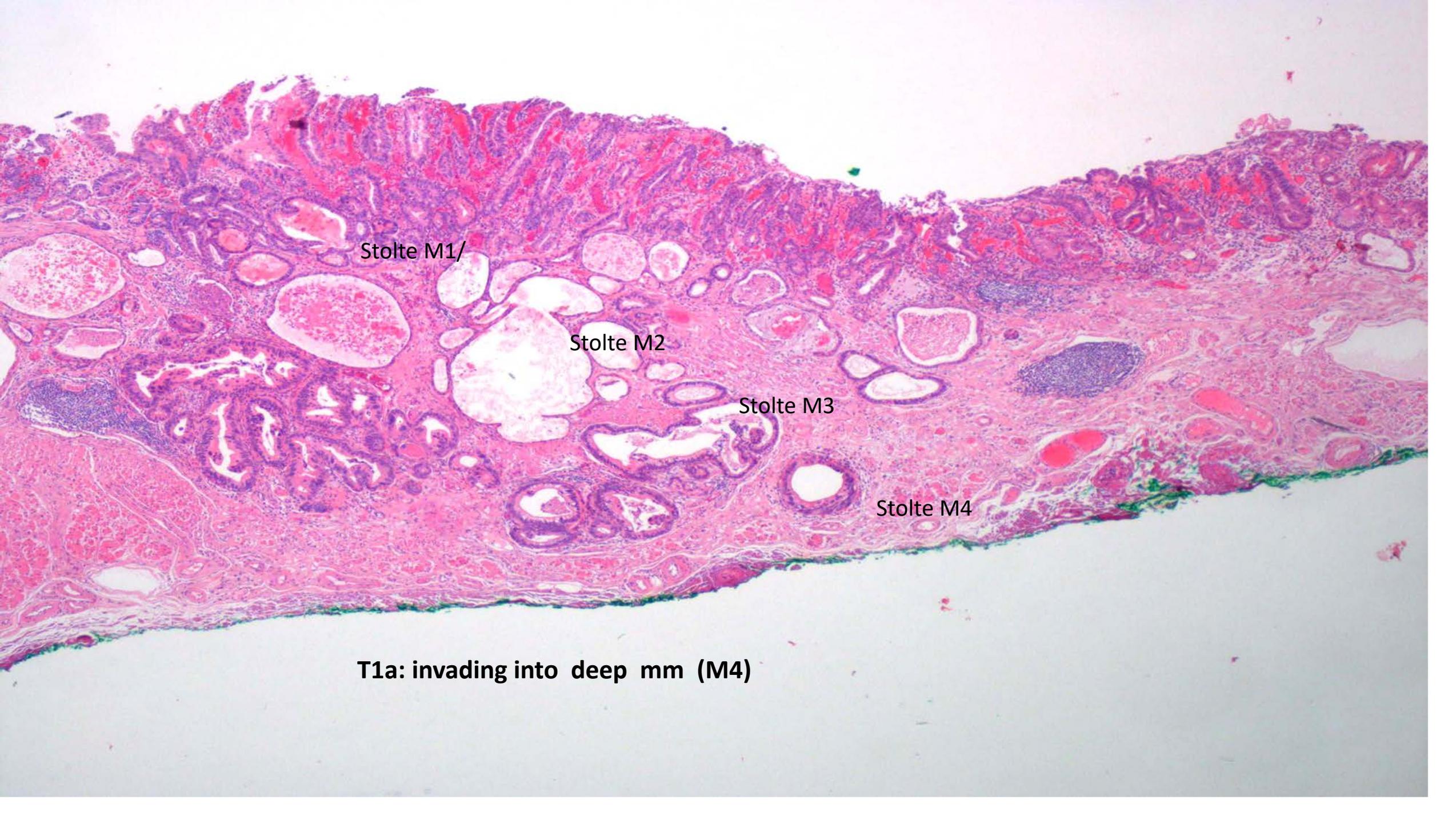
AJCC 7th edition:

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



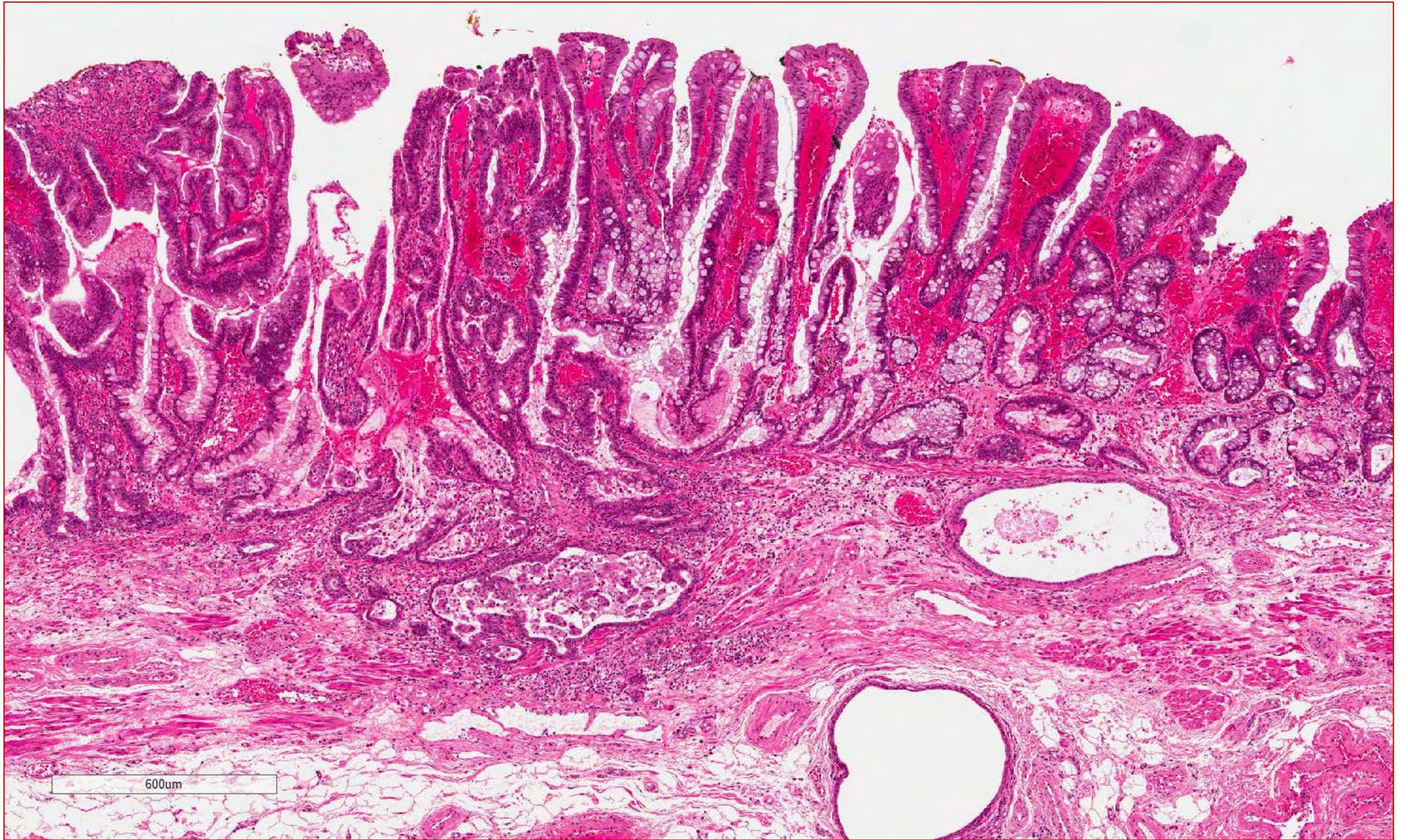
Stolte M1/

Stolte M2

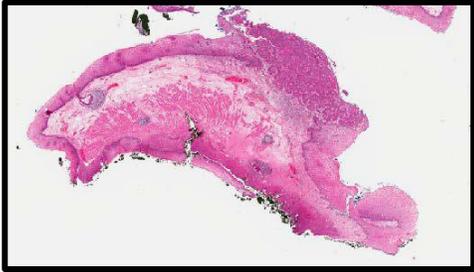
Stolte M3

Stolte M4

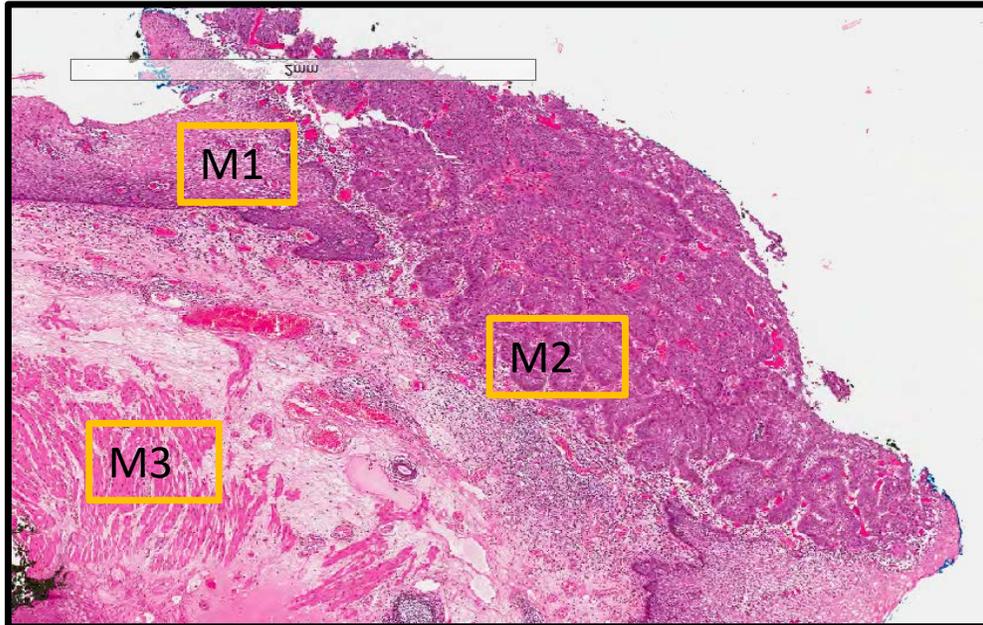
T1a: invading into deep mm (M4)



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

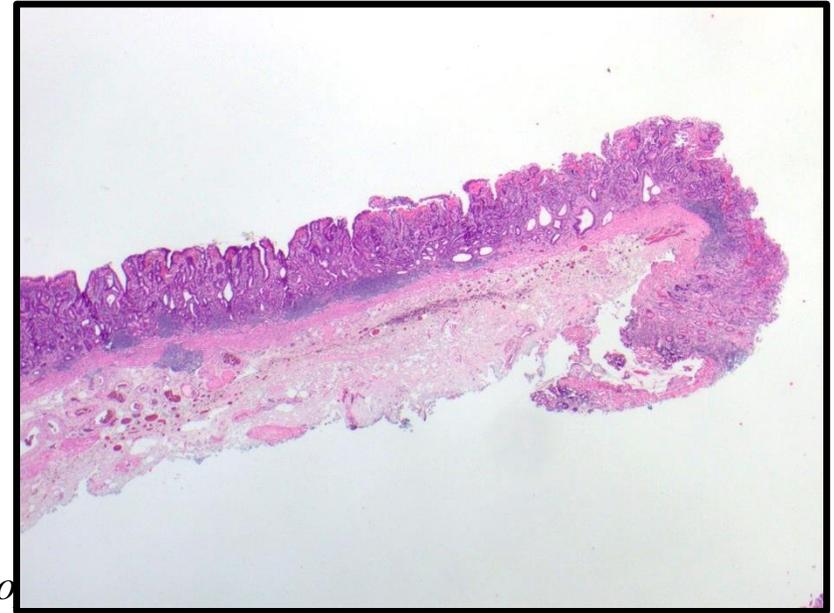


Depth of invasion		Esophagus	
		Adenocarcinoma	SCC
Mucosa :T1a		0-2%	0-5%
Submucosa: T1b	Overall	26%	45%
	Sm1	10-2% (500 μm)	24%(≤200 μm)
	Sm2	21%	37%
	Sm3	49%	48%

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

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

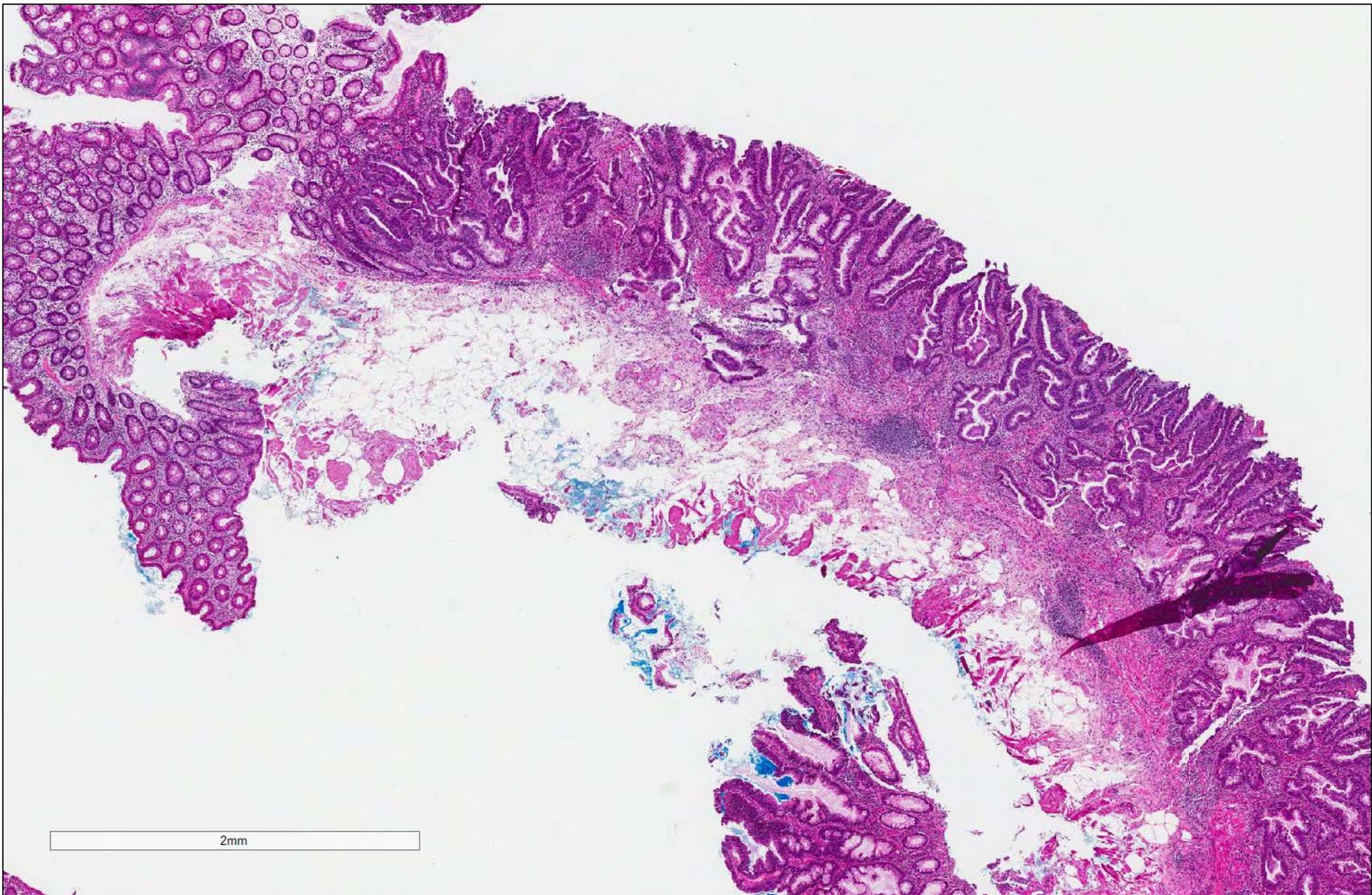
Low risk submucosal invasive cancer (LR –SMIC)

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%
	Sm3	49%	48%	26%	pT1: 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.

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

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

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

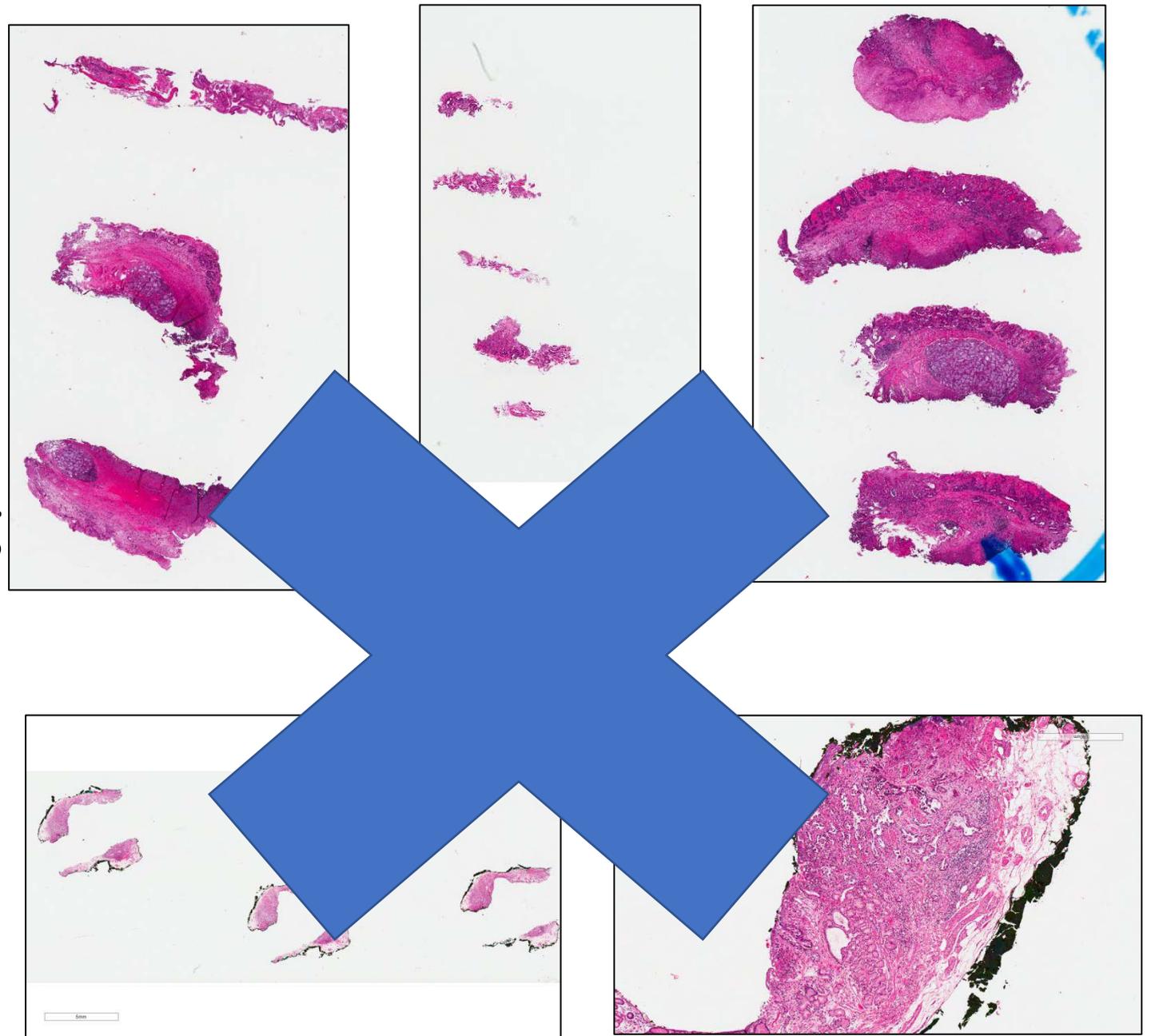
- Cytokeratin (AE1/AE3)- detection of single infiltrating cells
- Vascular markers: D2 40, CD31, ERG
- Desmin for mm
- **MMRP: Colon**, other GIT tumors....
- HER2 ?
- PDL1 ?

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