# Oesophageal malignancy - classification and assessment

Marco Novelli

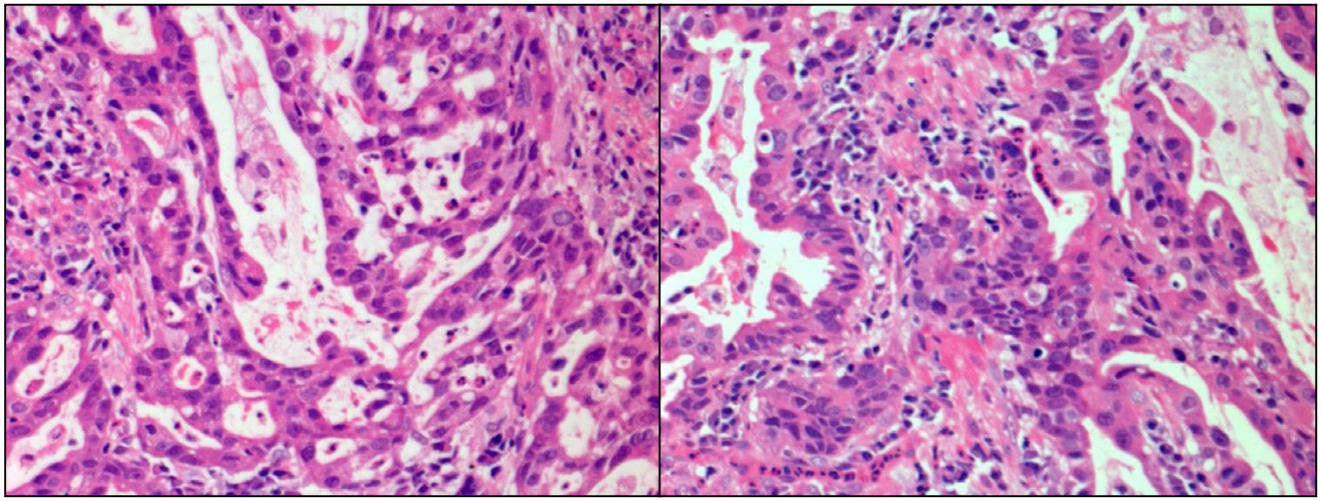
# Overview

- Types of oesophagogastric carcinoma.
- RCPath upper GI datasets.
- Endoscopic mucosal resections (EMRs)
- Use of immunostaining in oesophageal biopsies and EMRs

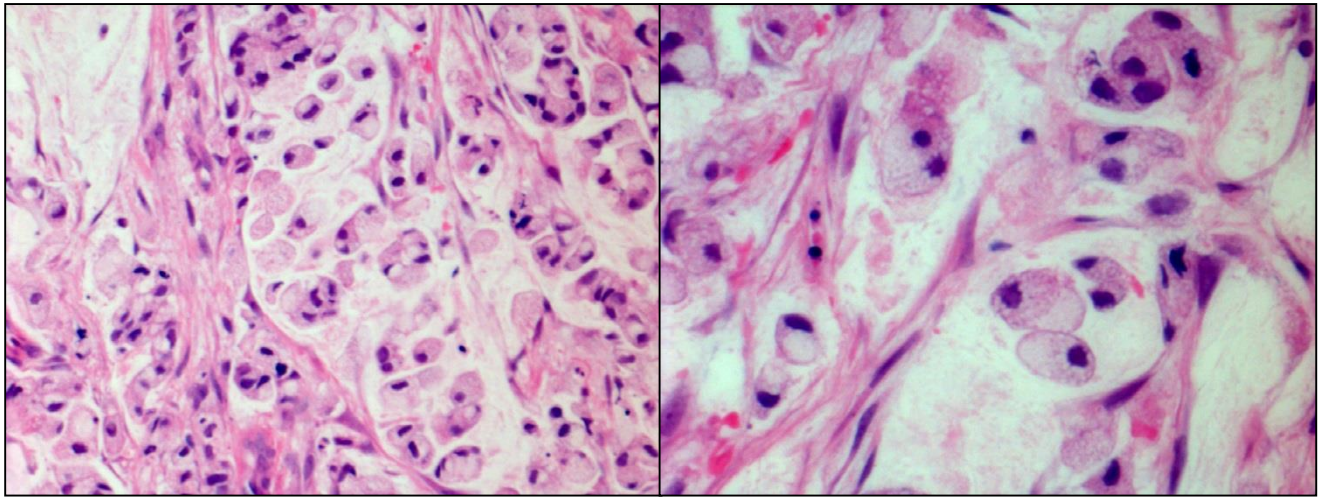
# Oesophagogastric carcinoma types

- Squamous cell carcinoma
- Adenocarcinoma
  - Commonest type (tubular, papillary, mucinous, other).
  - Lauren classification: intestinal / diffuse / mixed.
- Medullary / Lymphocyte-rich / Lymphoepithelial
  - Microsatellite unstable.
  - EBV.
- Hepatoid carcinoma – very rare.
- Adenosquamous – rare.
- Others – rare

# Gastric carcinoma - Lauren classification

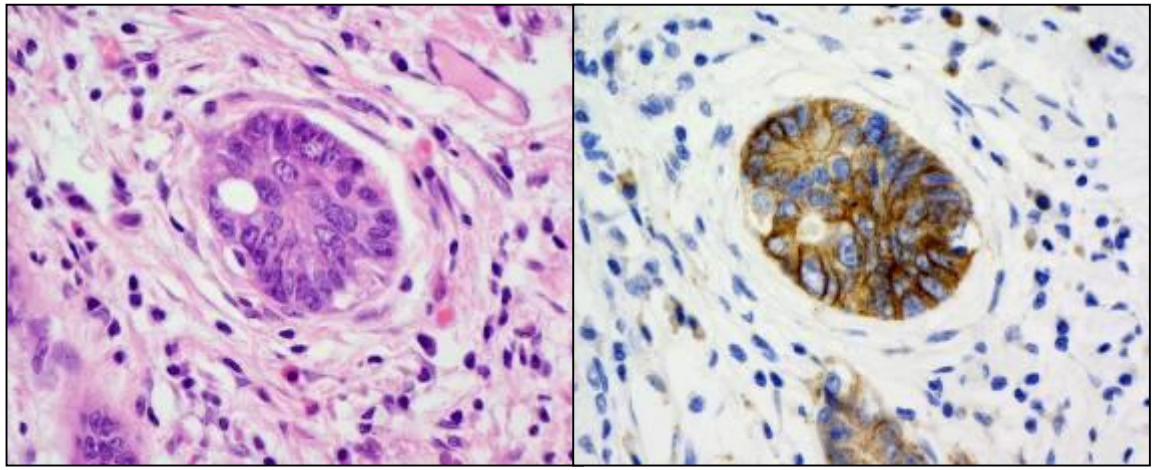


Intestinal type
(54%)

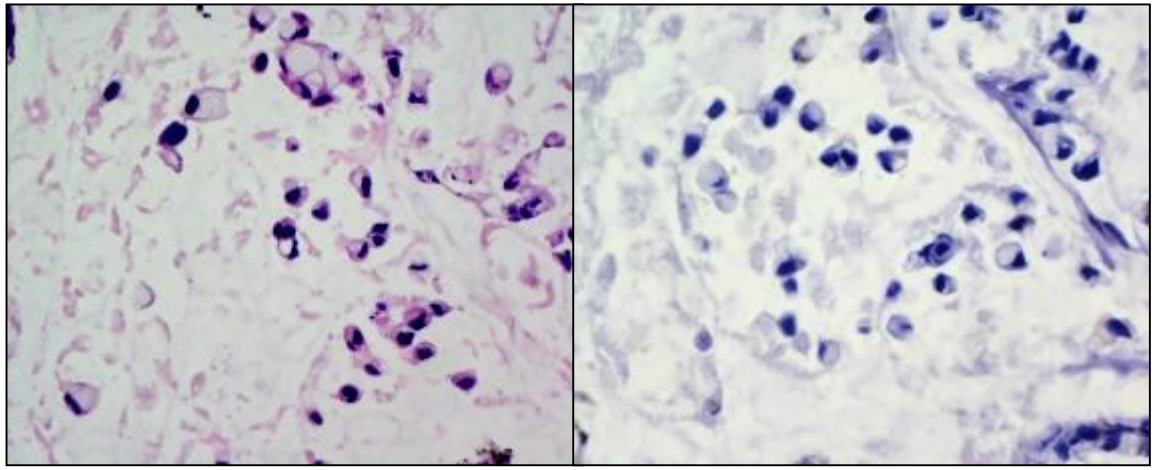


Diffuse type
(32%)

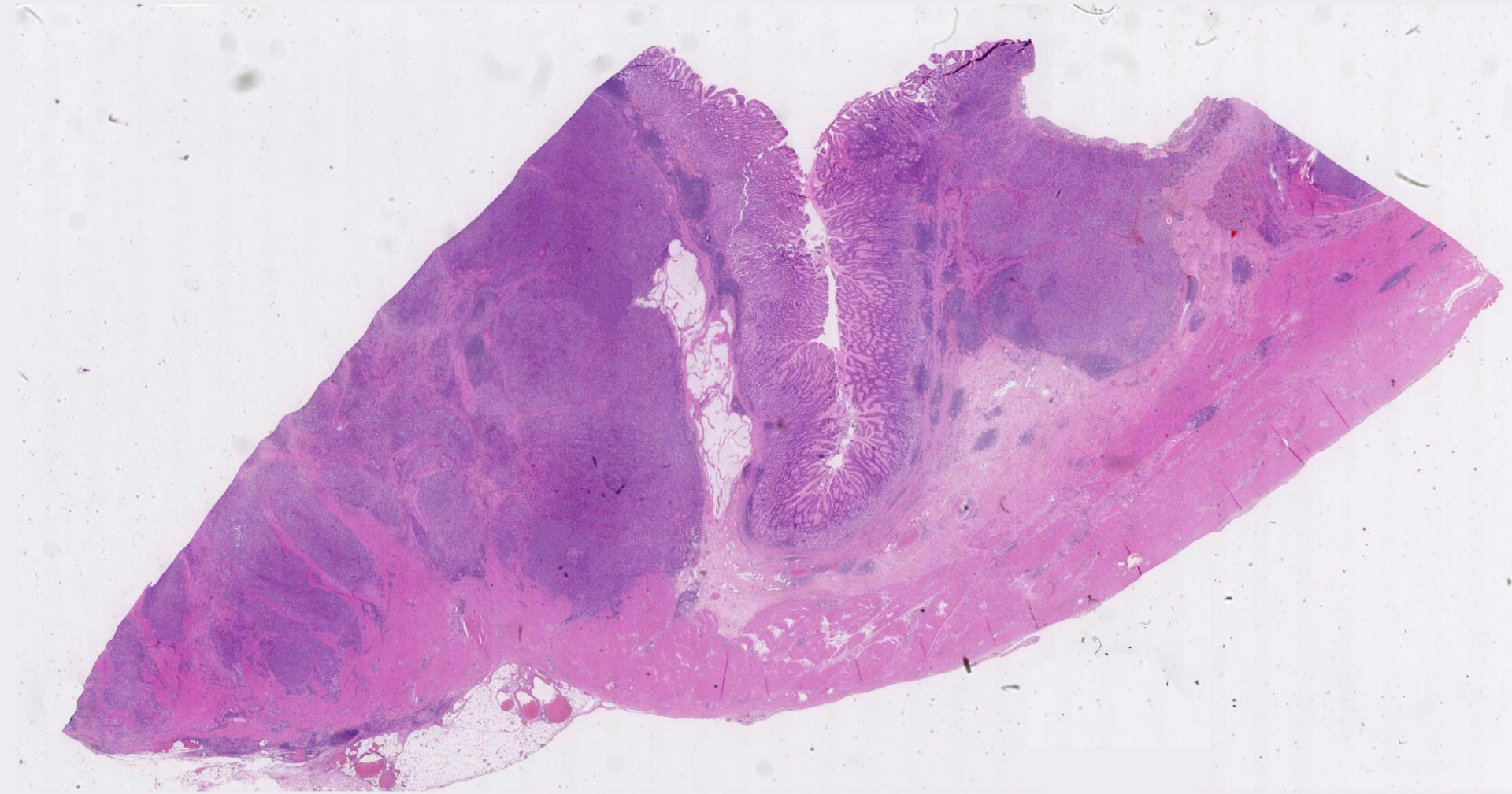
# HER2 staining and gastric carcinoma phenotype

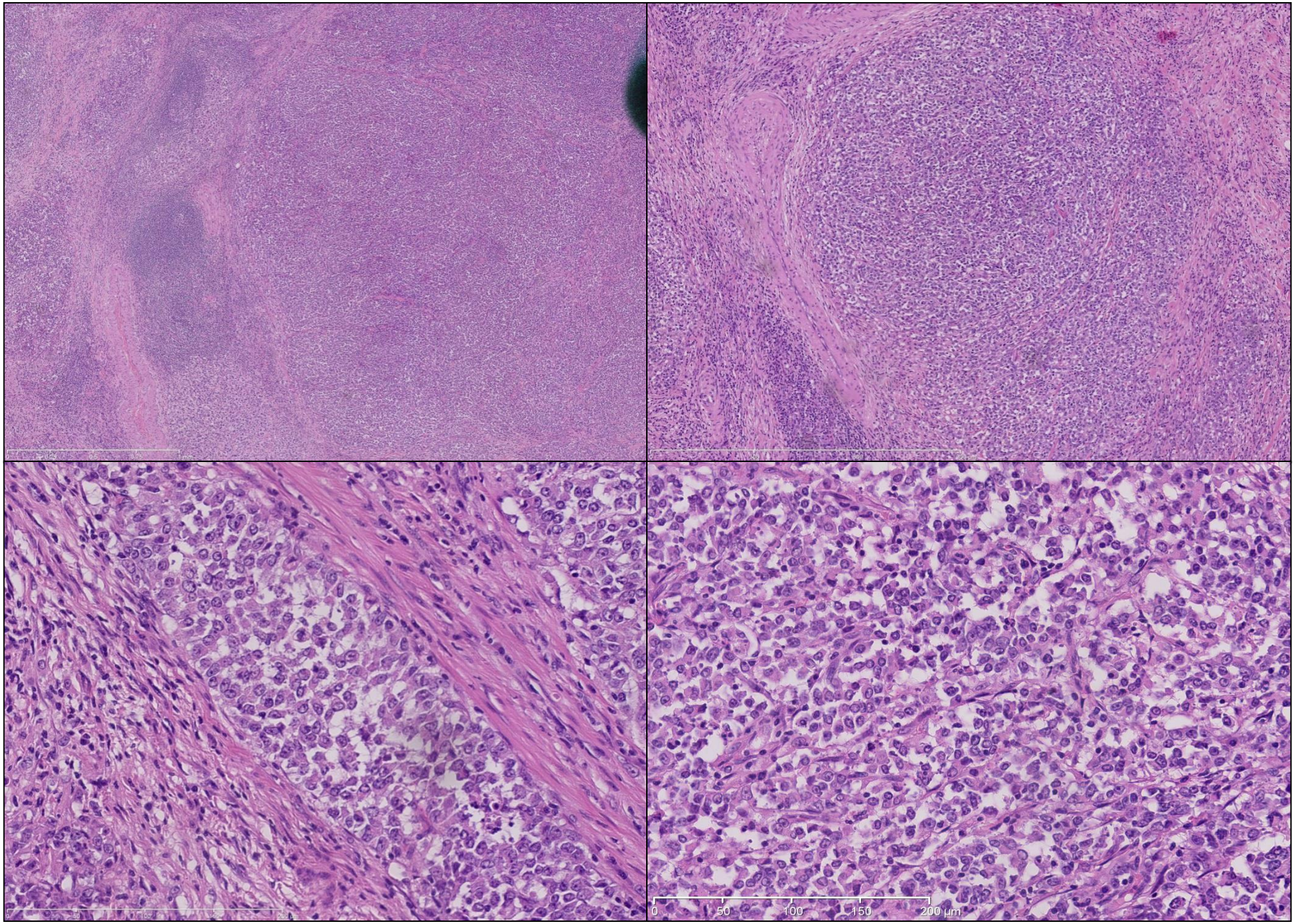


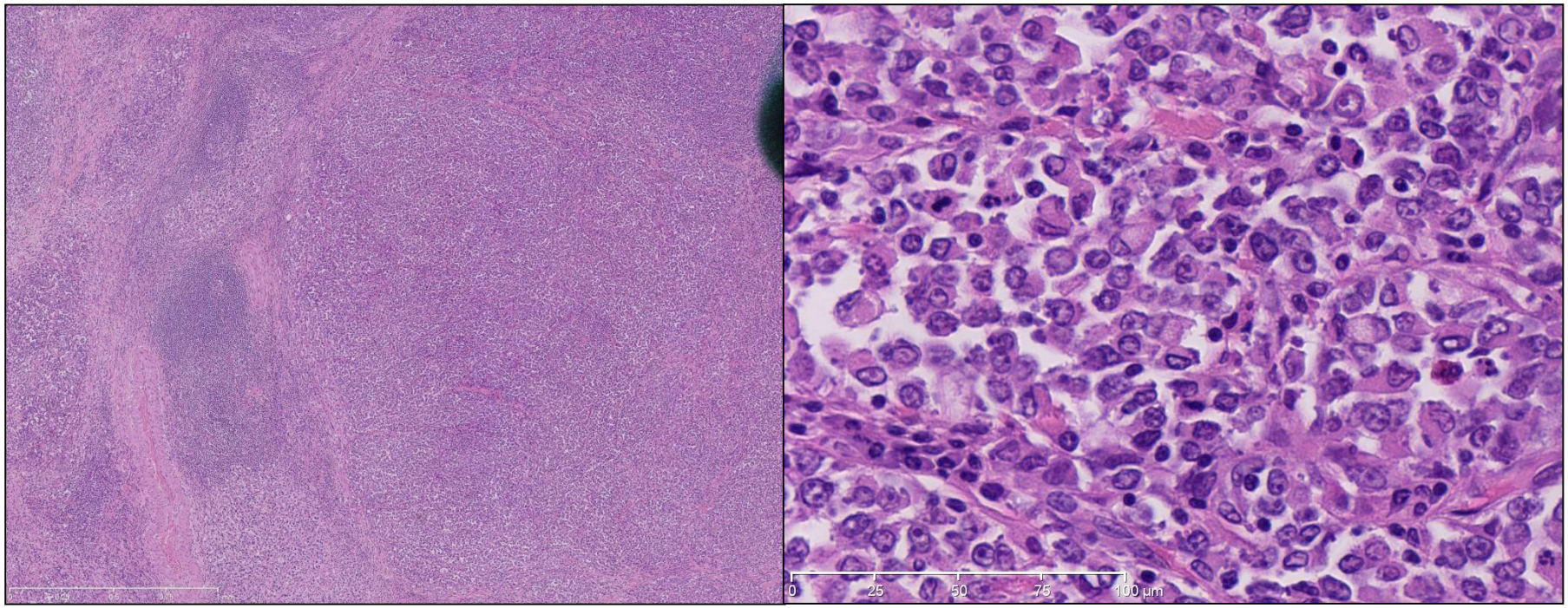
- Intestinal type
  33.4% +ve



- Diffuse type
  5.5% +ve




0
50
100
150
200 µm

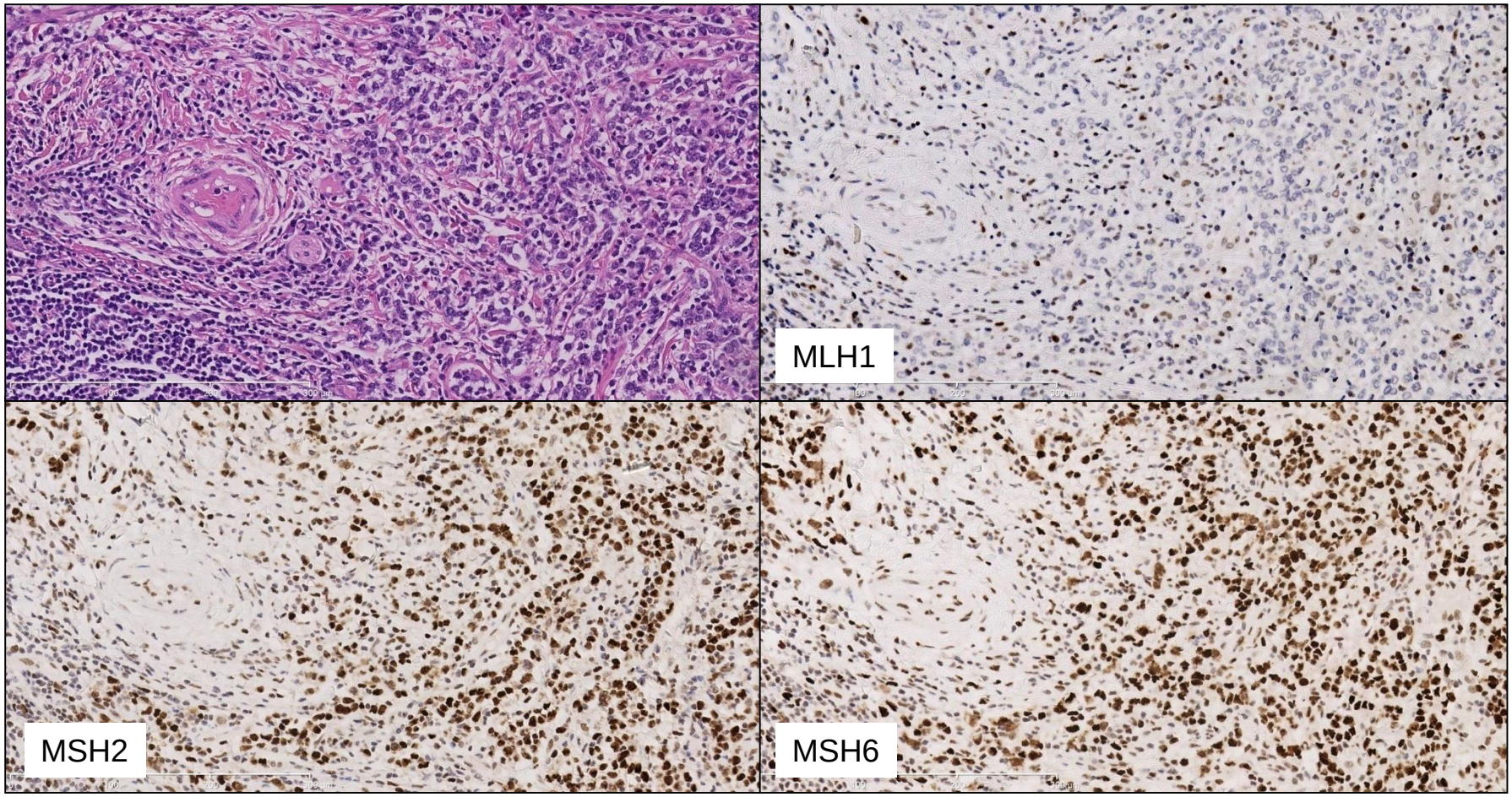



Medullary carcinoma.

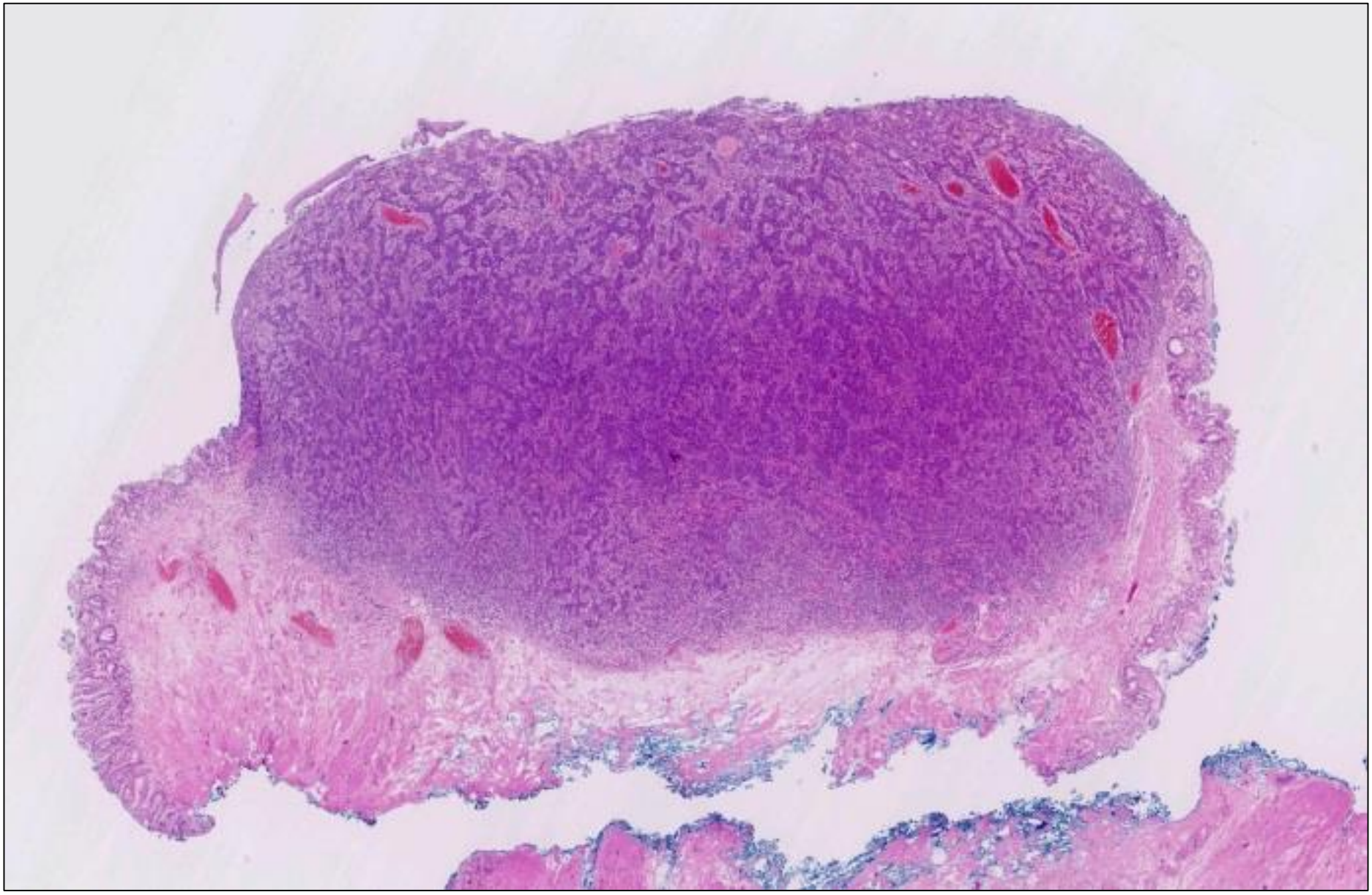
Lymphoepithelioma-like carcinoma.

Gastric adenocarcinoma with lymphoid stroma.

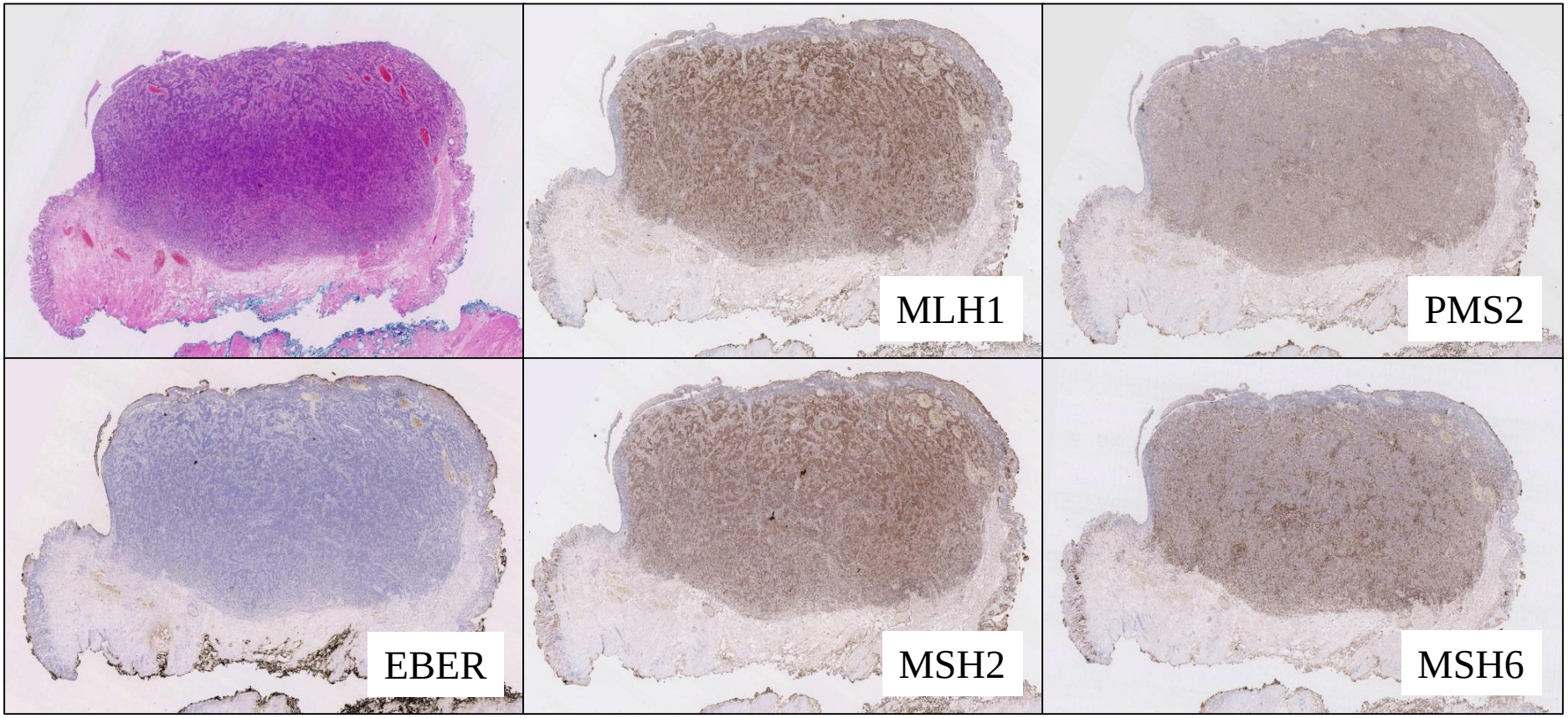
→ MSI sporadic, Lynch syndrome or EBV-associated.

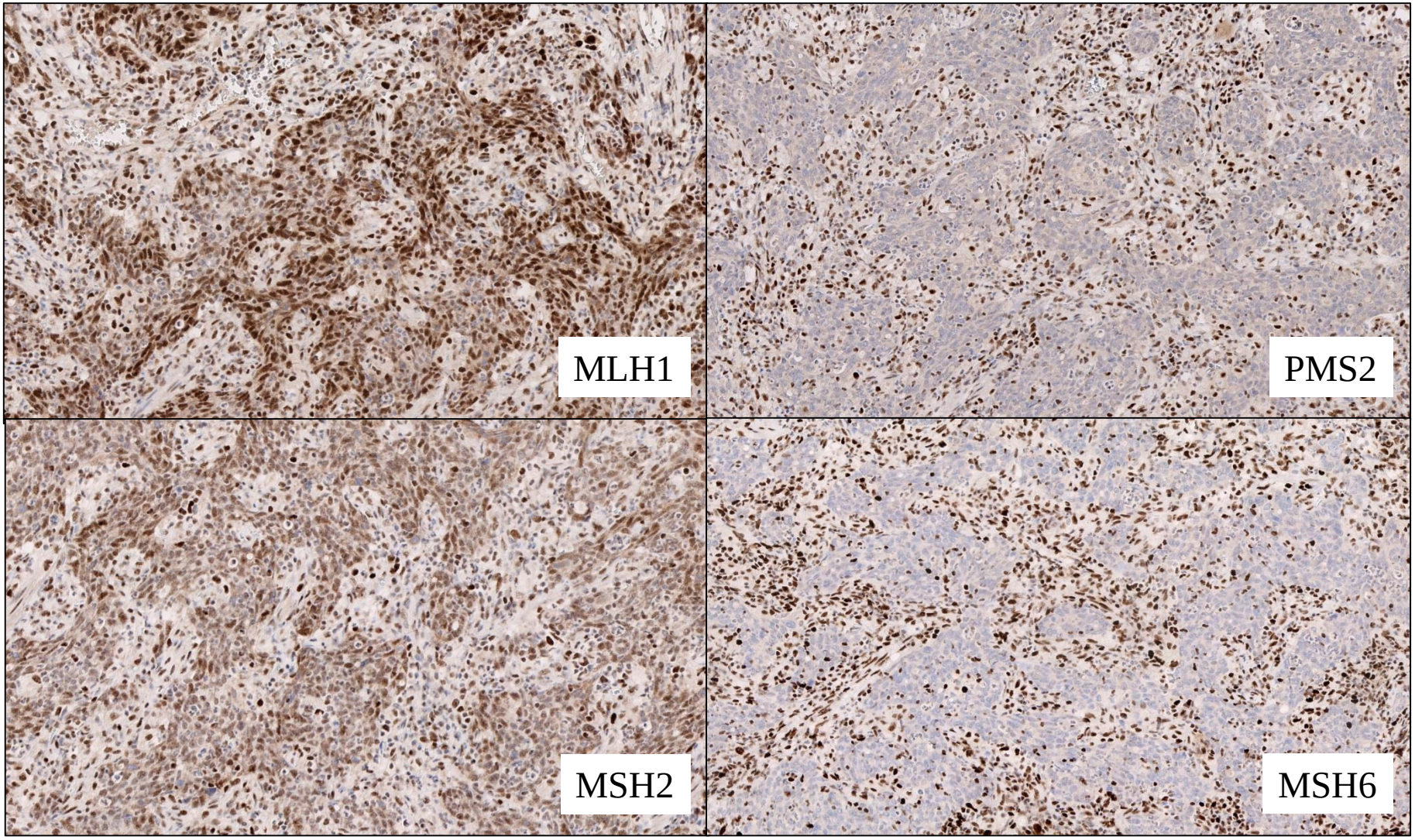


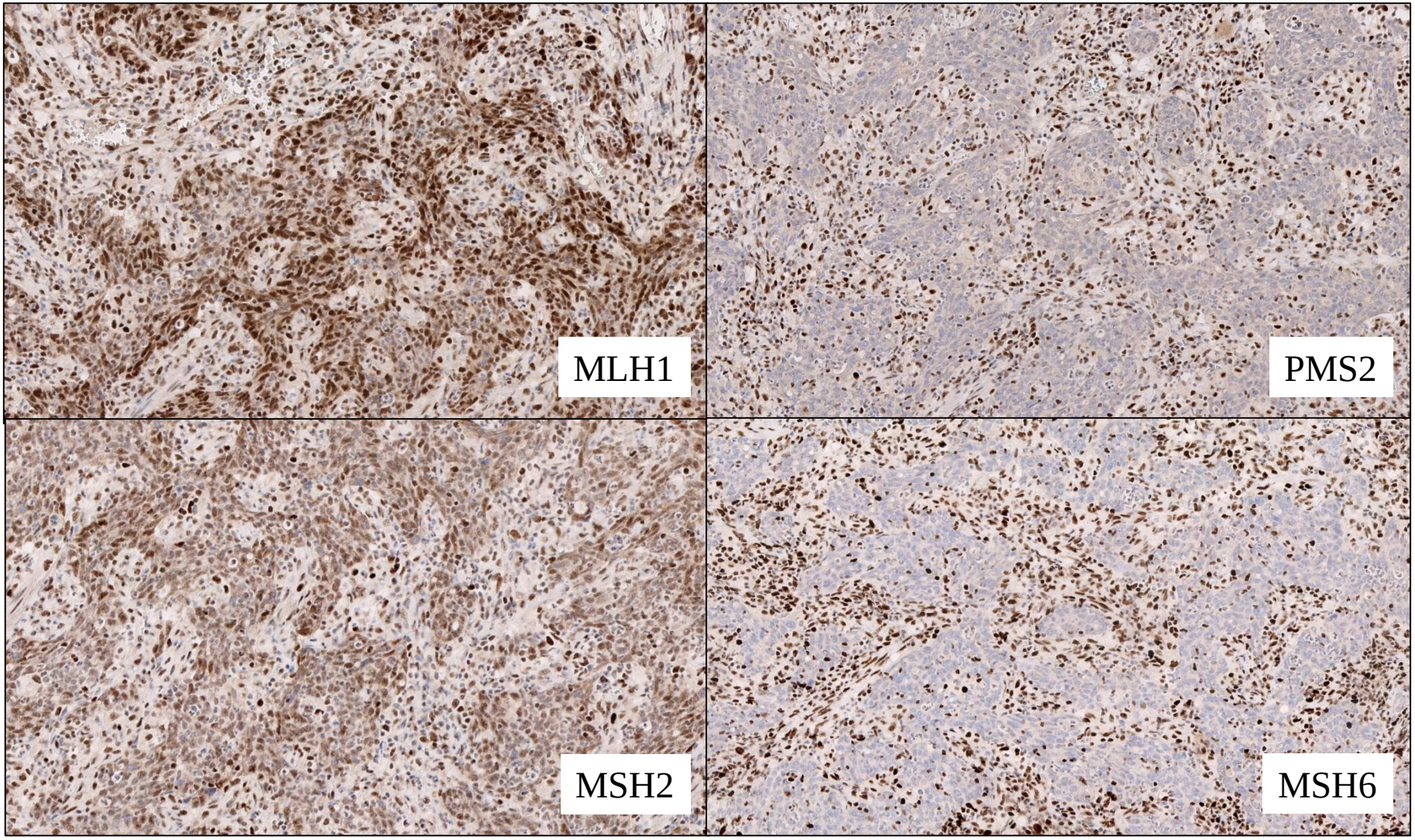

Loss MLH1 (+ PMS2) → MSI tumour (sporadic)



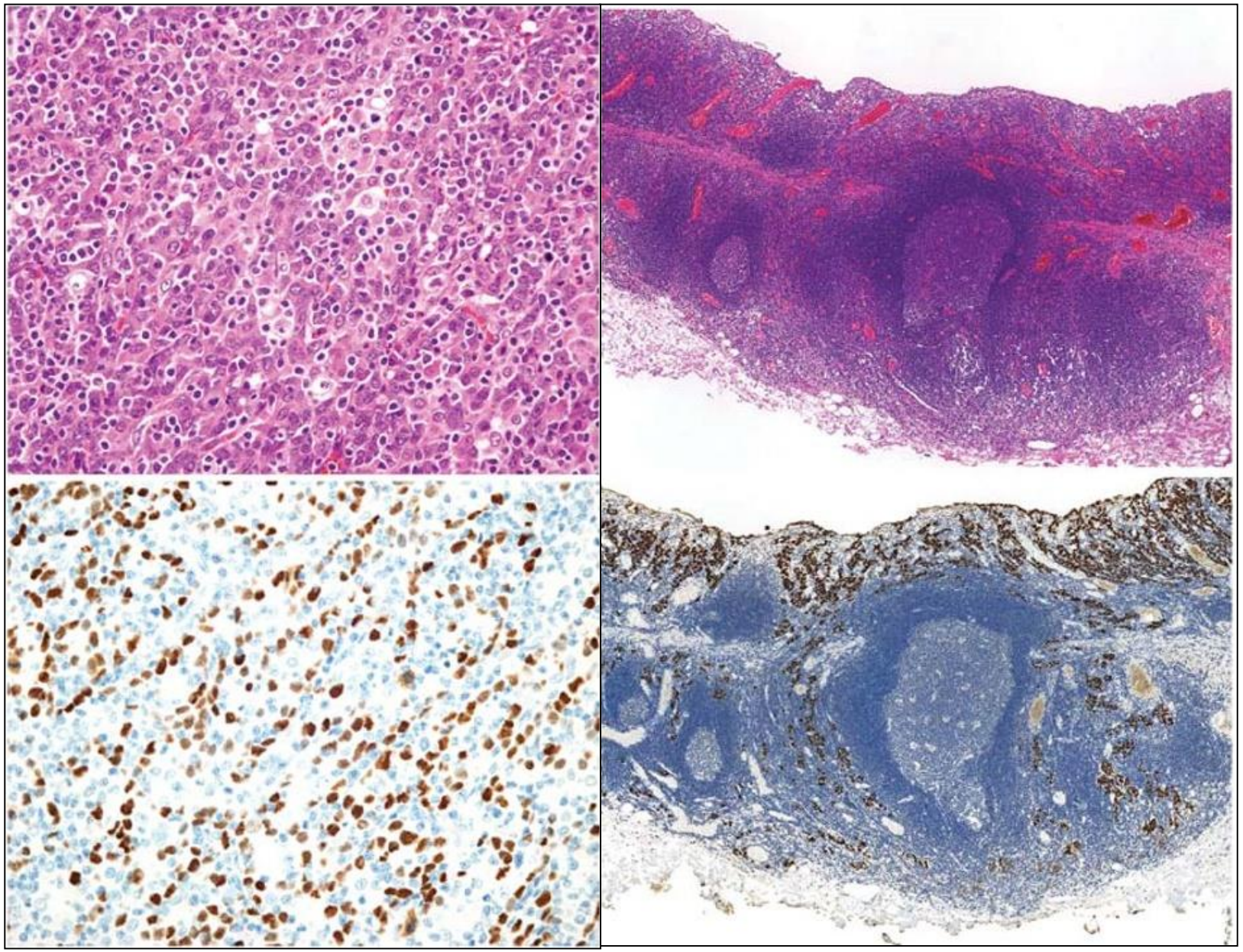
74 year old male - EMR oesophageal nodule


MLH1
PMS2
EBER
MSH2
MSH6


MLH1
PMS2
MSH2
MSH6

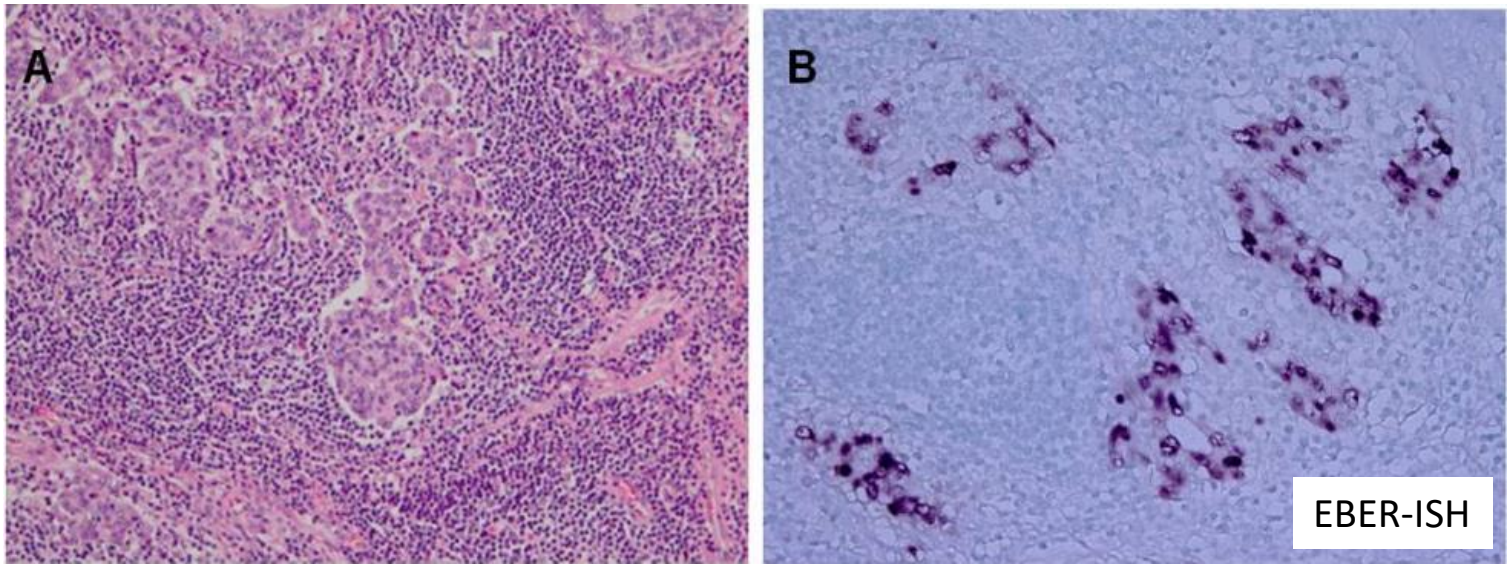



Loss of PMS2 and MSH6 expression → **Germline mutation of PMS2**
**LYNCH SYNDROME**



EBV – associated adenocarcinoma

# EBV – associated gastric adenocarcinoma

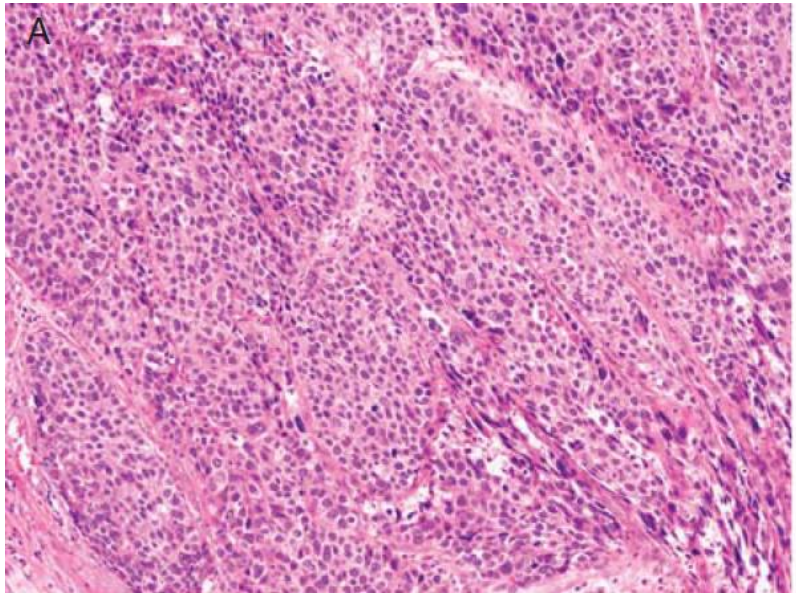



- 10% global gastric adenocarcinomas (18% USA and Germany, 4.3% China).
- Typically proximal stomach / non-antral.
- EBV seen in epithelial cells (not just lymphocytes).

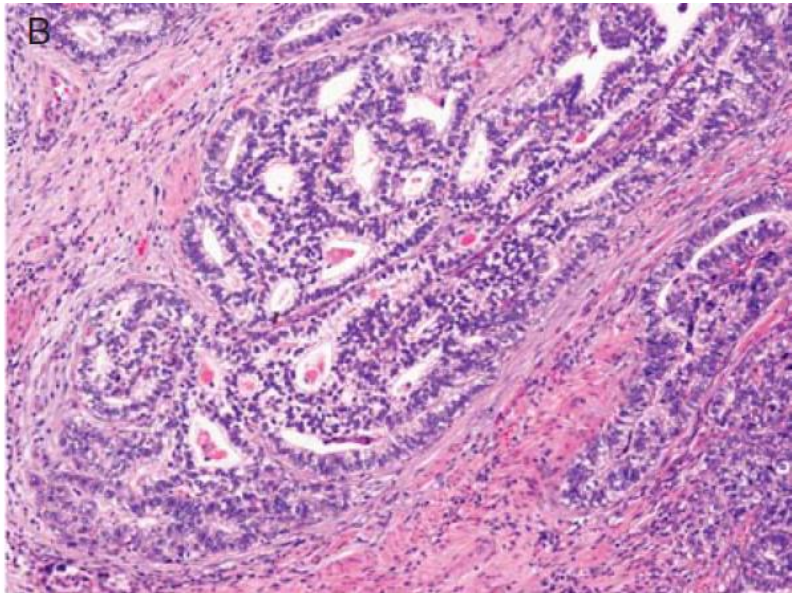
Epstein-Barr Virus (EBV)-associated gastric carcinoma. Iizasa H, Nanbo A, Nishikawa J, Jinushi M, Yoshiyama H. Viruses. 2012 Dec;4(12):3420-39.

# Hepatoid gastric adenocarcinoma

- Approximately 3% gastric adenocarcinomas.
- Very aggressive clinical course.
- Produce AFP and can mimic hepatocellular carcinoma histologically.

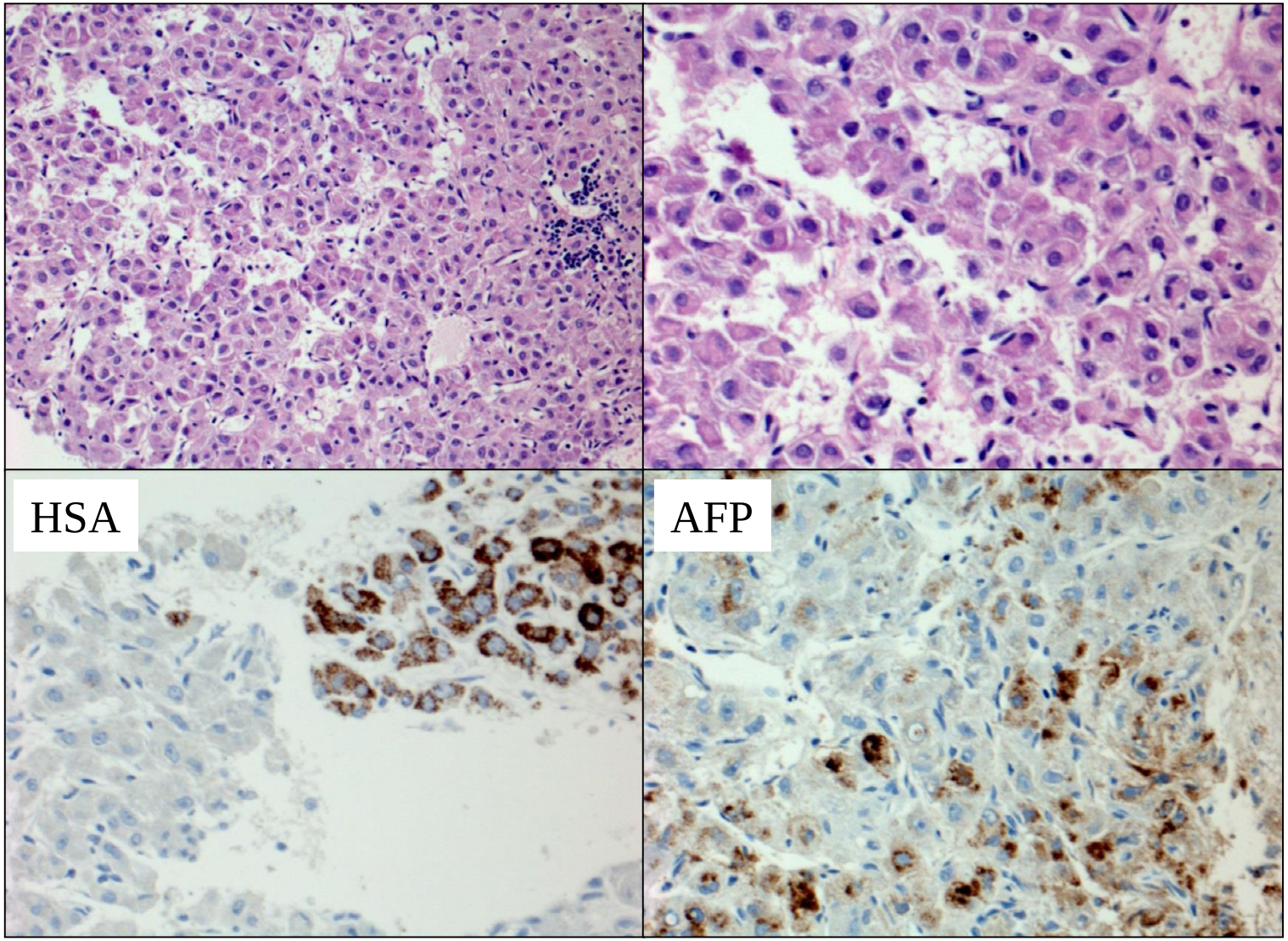



Hepatoid pattern




Clear cell tubular pattern

Ushiku T1, Shinozaki A, Shibahara J, Iwasaki Y, Tateishi Y, Funata N, Fukayama M. SALL4 represents fetal gut differentiation of gastric cancer, and is diagnostically useful in distinguishing hepatoid gastric carcinoma from hepatocellular carcinoma. Am J Surg Pathol. 2010 Apr;34(4):533-40.




Omental biopsy

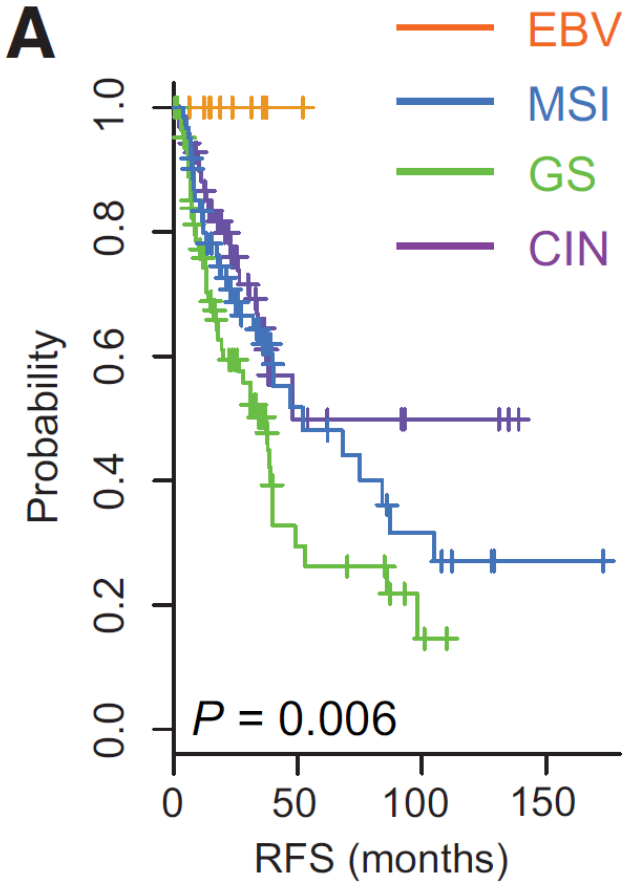
Biology of Human Tumors

Clinical Cancer Research

# Clinical Significance of Four Molecular Subtypes of Gastric Cancer Identified by The Cancer Genome Atlas Project

Bo Hwa Sohn[1], Jun-Eul Hwang[2], Hee-Jin Jang[1,3], Hyun-Sung Lee[3], Sang Cheul Oh[4],

- Divide gastric carcinoma into 4 types:
  - EBV-associated
  - MSI
  - Genomically stable
  - Chromosomal instability.
- CIN best response to adjuvant chemotherapy. GS worse.



CANCER BIOMARKERS

# Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3]* Kellie N. Smith,[1,3]* Hao Wang,[3]*
Bjarne R. Bartlett,[2,4]* Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3]
Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3]
Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8]
Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11]
Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3]
Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12]
Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3]
Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3]
Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15]
Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡

Le *et al.*, *Science* **357**, 409–413 (2017) 28 July 2017

- 12 different tumour types
  - Radiological responses 53%
  - Complete response 21%

- Ampulla of Vater
- Cholangiocarcinoma
- Colorectal
- Endometrial cancer
- Gastroesophageal
- Neuroendocrine
- Osteosarcoma
- Pancreas
- Prostate
- Small Intestine
- Thyroid
- Unknown Primary

# Oesophagogastric adenocarcinoma

- EBV-associated tumours said to have a better prognosis.
- Hepatoid gastric adenocarcinoma said to have a poor prognosis
- CIN tumours said to respond best to adjuvant therapy.
- MSI tumours may respond to PD-L1 therapy.
- Approx 20% will be HER2+ve.

# RCPath Upper GI Datasets

# RCPath Upper GI Datasets

- Oesophageal and gastric datasets will be combined.
- Written > 1 year ago but publication has been delayed to allow for TNM8.
- Has been updated for TNM8 with early 2018 expected date of implementation.
- Changes in TNM8 mostly concern OGJ tumours

# Oesophagogastric changes in TNM7

- Oesophagus:
  - T1 and T4 have been subdivided.
  - N has been subdivided N1, N2
- Stomach
  - T2a and T2b were changed into T2 (muscularis propria) and T3 (subserosa)

  → Stomach and oesophagus aligned
- Oesophagogastric junction tumours
  - Changes to classification

# Oesophagus 7th edition

## TNM definitions: AJCC = UICC

| | |
|---|---|
| Tis | Carcinoma in situ /High-grade dysplasia |
| T1 | lamina propria or submucosa |
| | T1a lamina propria or muscularis mucosae |
| | T1b submucosa |
| T2 | muscularis propria |
| T3 | adventitia |
| T4 | adjacent structures |
| | T4a pleura, pericardium, diaphragm, or adjacent peritoneum |
| | T4b other adjacent structures, e.g. aorta, vertebral body, trachea |

| | |
|---|---|
| N0 | No regional lymph node metastasis |
| N1 | 1 to 2 regional lymph nodes |
| N2 | 3 to 6 |
| N3 | >6 |

[N1 was site dependent]

M - Distant Metastasis

| | |
|---|---|
| M1 | Distant metastasis |

[M1a,b were site dependent]

Changes from 6th edition

# OGJ tumours

- Siewert classification
- Gastric versus oesophageal dataset?

Leading article

# Classification of adenocarcinoma of the oesophagogastric junction

J. R. Siewert
H. J. Stein

"We have defined and described adenocarcinomas of the oesophagogastric junction as tumours that have their centre within 5 cm proximal and distal of the anatomical cardia and have differentiated the following three distinct tumour entities within this area[1,3]:"

| | |
|---|---|
| Type I tumour | Adenocarcinoma of the distal oesophagus which usually arises from an area with specialized intestinal metaplasia of the oesophagus (i.e. Barrett's oesophagus) and which may infiltrate the oesophagogastric junction from above. |
| Type II tumour | True carcinoma of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the oesophagogastric junction; this entity is also often referred to as 'junctional carcinoma'. |
| Type III tumour | Subcardial gastric carcinoma which infiltrates the oesophagogastric junction and distal oesophagus from below. |

*British Journal of Surgery* 1998, 85, 1457–1459

Leading article

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|---|---|
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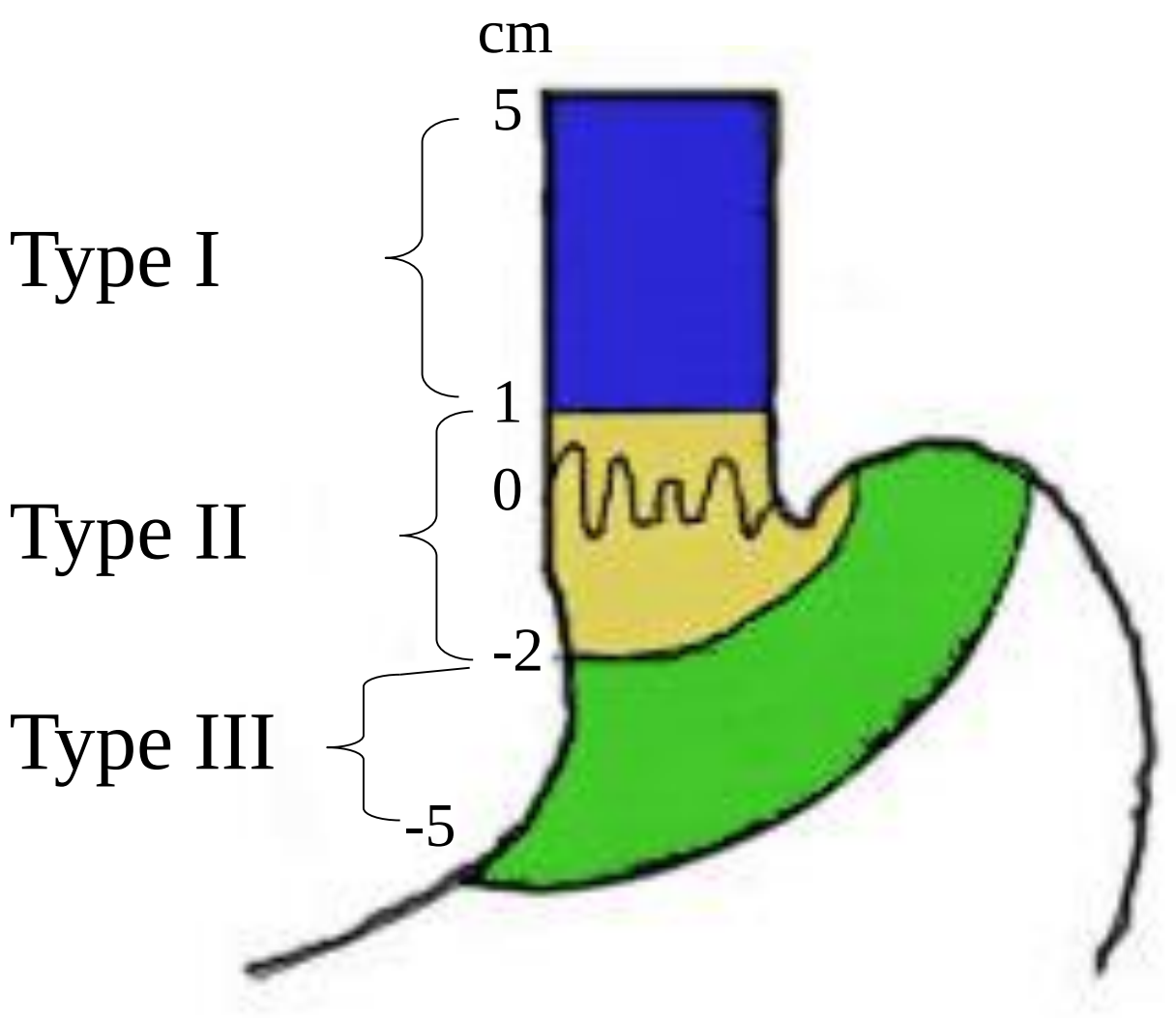
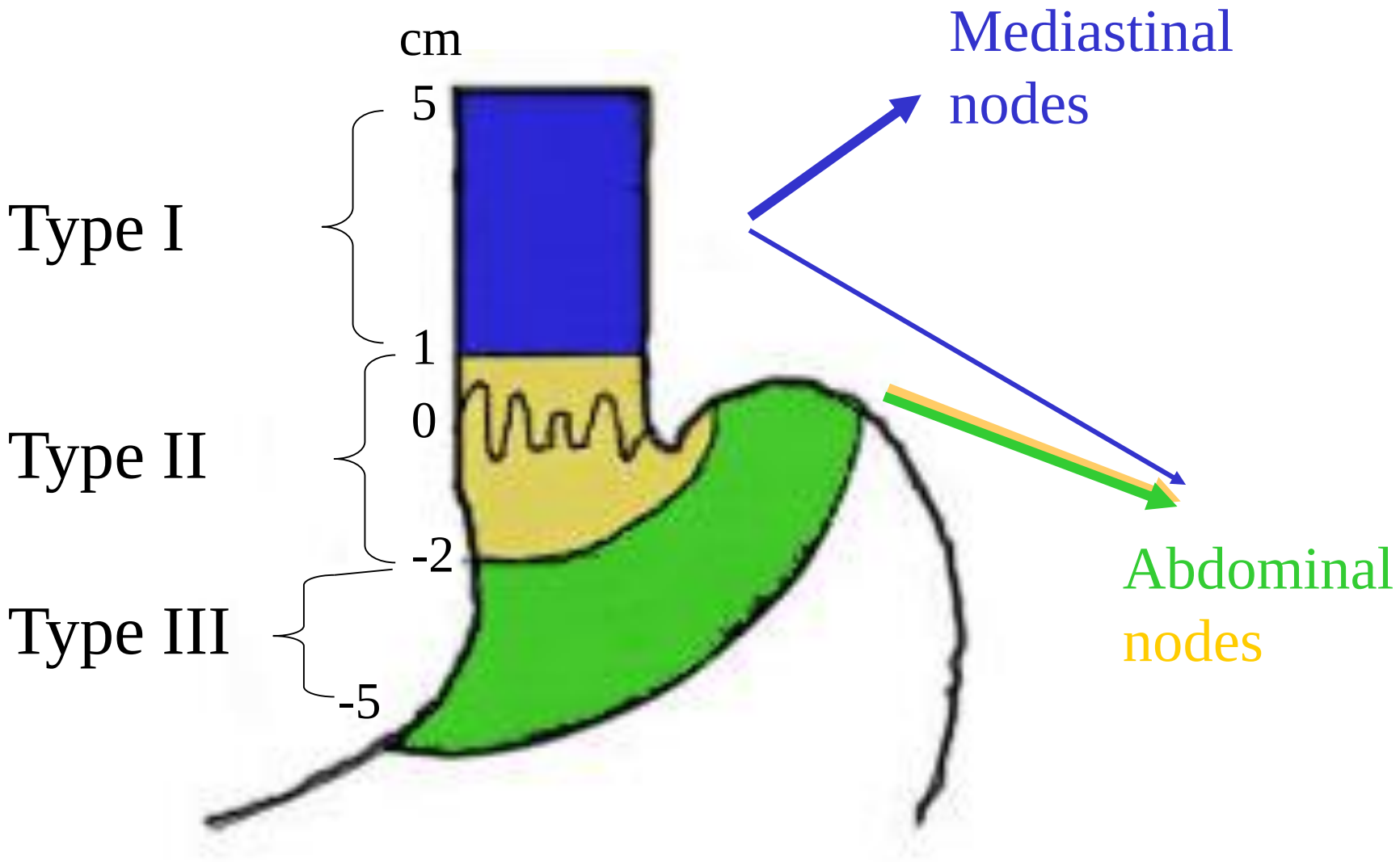
*British Journal of Surgery* 1998, 85, 1457–1459

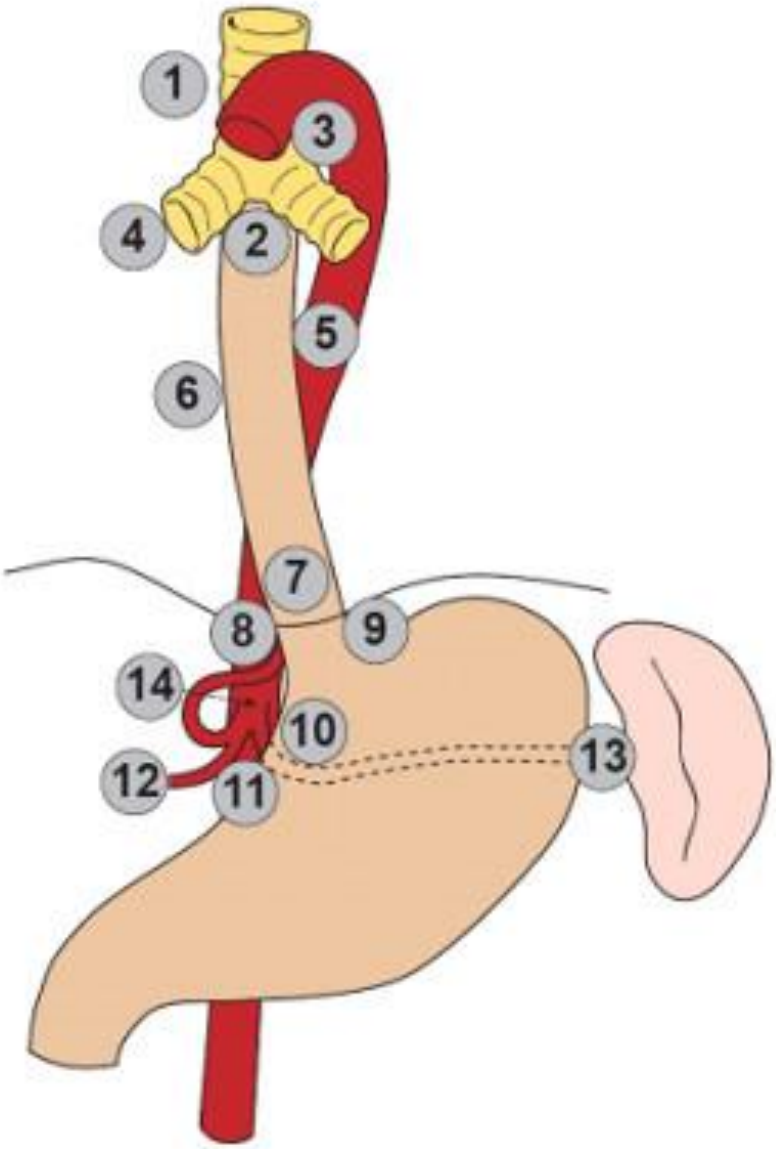
# Siewert Classification of OGJ Tumours



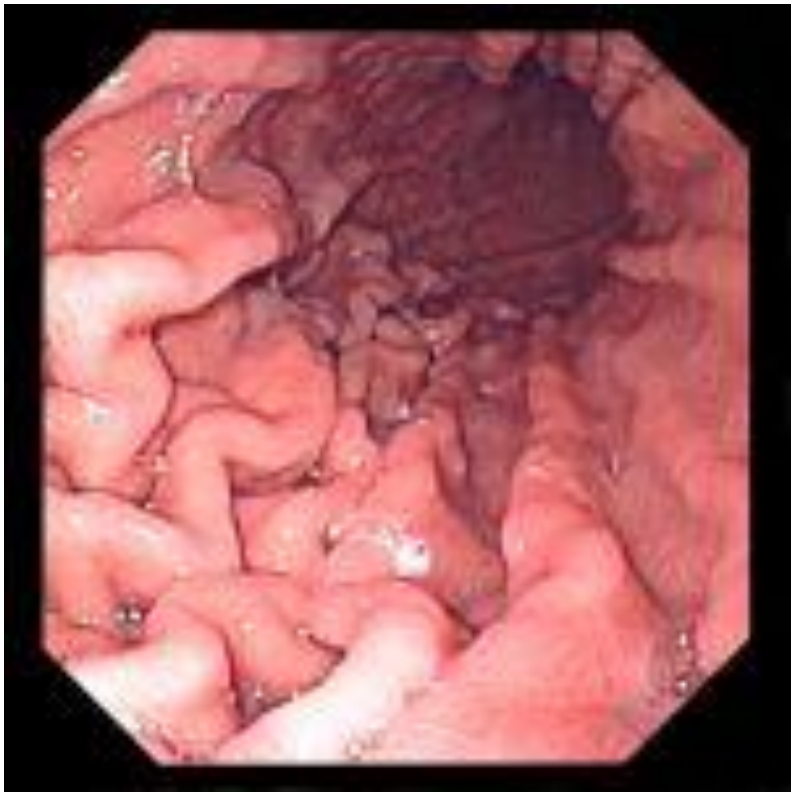
# Siewert Classification of OGJ Tumours



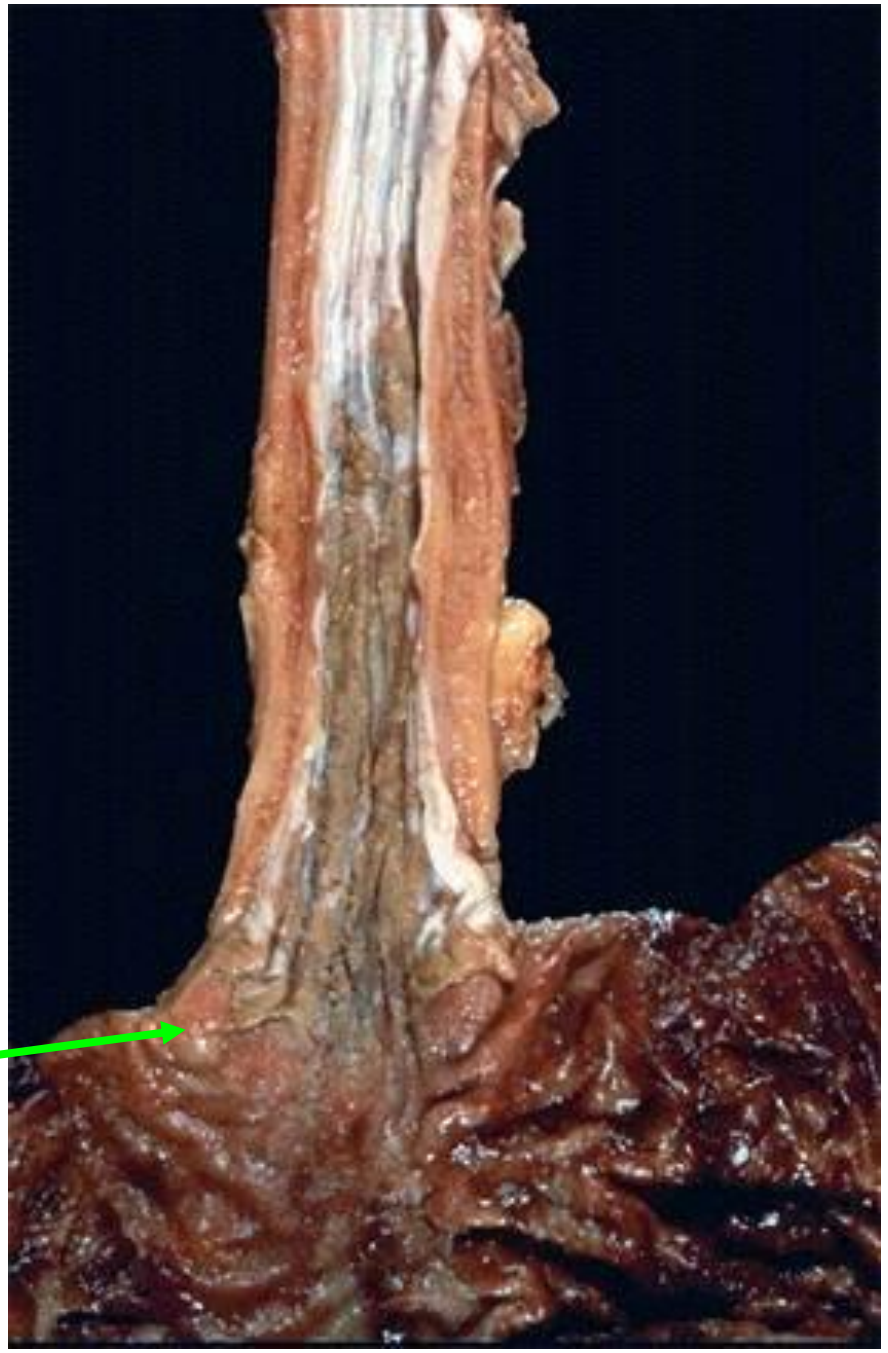
| SIEWERT TYPE | I | II | III |
|---|---|---|---|
| **Mediastinal stations** | | | |
| 1. Paratracheal | 4% | 0% | - |
| 2. Carinal | 10% | 0% | - |
| 3. Left bronchial | 15% | 0% | - |
| 4. Right bronchial | 19% | 0% | - |
| 5. Para-aortic | 20% | 2% | - |
| 6. Middle and | | | |
| 7. lower paraoesophageal | 55% | 5% | 3% |
| **Abdominal stations** | | | |
| 8. Right paracardial | 41% | 46% | - |
| 9. Left paracardial | 32% | 50% | - |
| 10. Left gastric | 60% | 65% | 24% |
| 11. Lesser curve | 14% | 65% | 41% |
| 12. Common hepatic | 3% | 16% | 17% |
| 13. Splenic artery | 6% | 30% | 28% |
| 14. Coeliac axis | 5% | 30% | - |



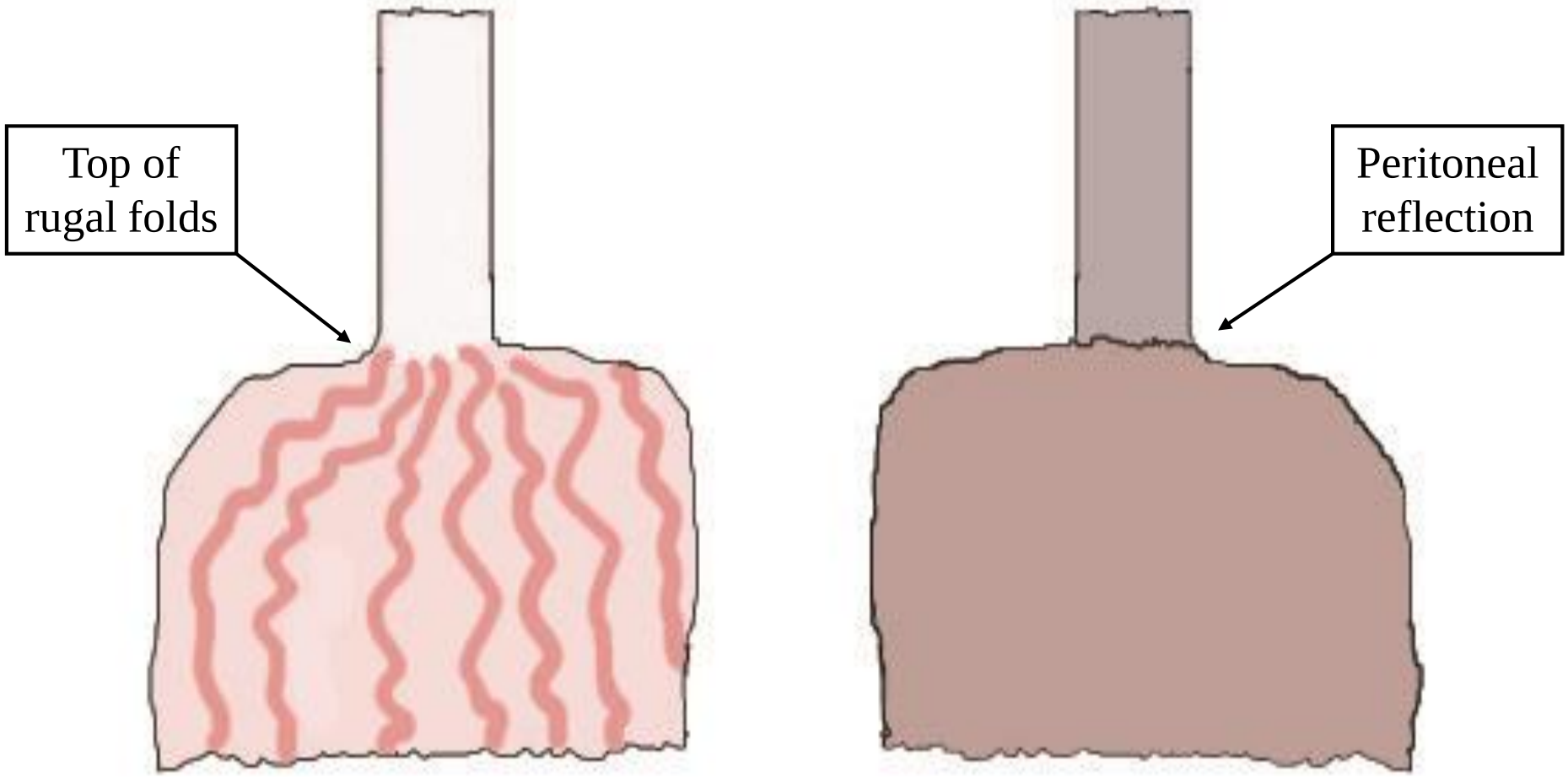
Gastric versus oesophageal dataset?



OG Junction

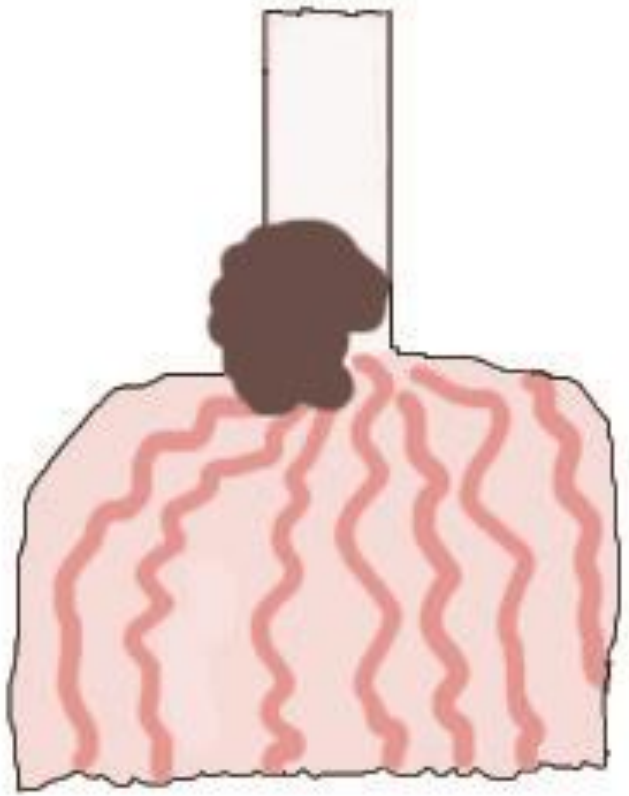


# Oesophagogastric junction

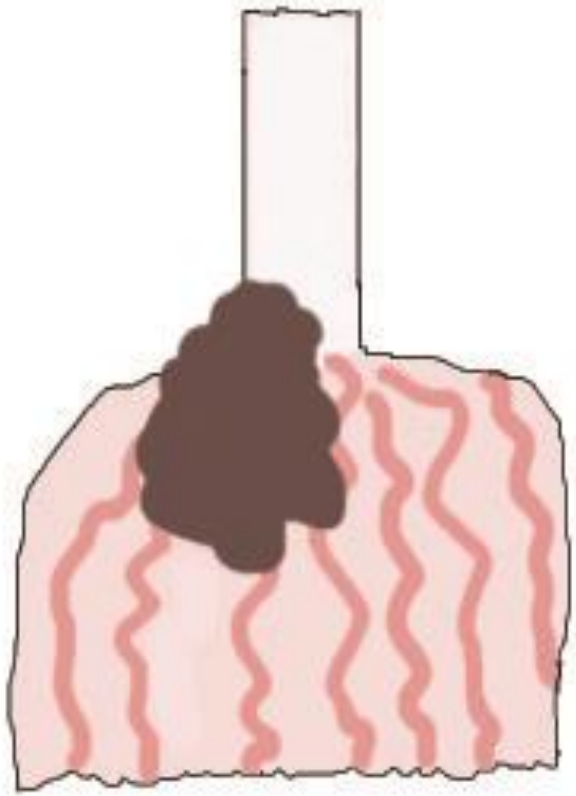



Mucosal aspect

Serosal aspect



> 50% tumour in oesophagus



> 50% tumour in stomach

Oesophageal dataset

Gastric dataset

TNM6

# TNM-7
# Oesophagogastric junction tumours

A tumour the epicenter of which is within 5 cm of the esophagogastric junction and also extends into the oesophagus is classified and staged according to the **oesophageal** scheme

All other tumours with an epicenter in the stomach greater than 5 cm from the oesophagogastric junction or those within 5 cm of the EGJ *without* extension into the oesophagus are staged using the **gastric** carcinoma scheme

# TNM-7
# Oesophagogastric junction tumours

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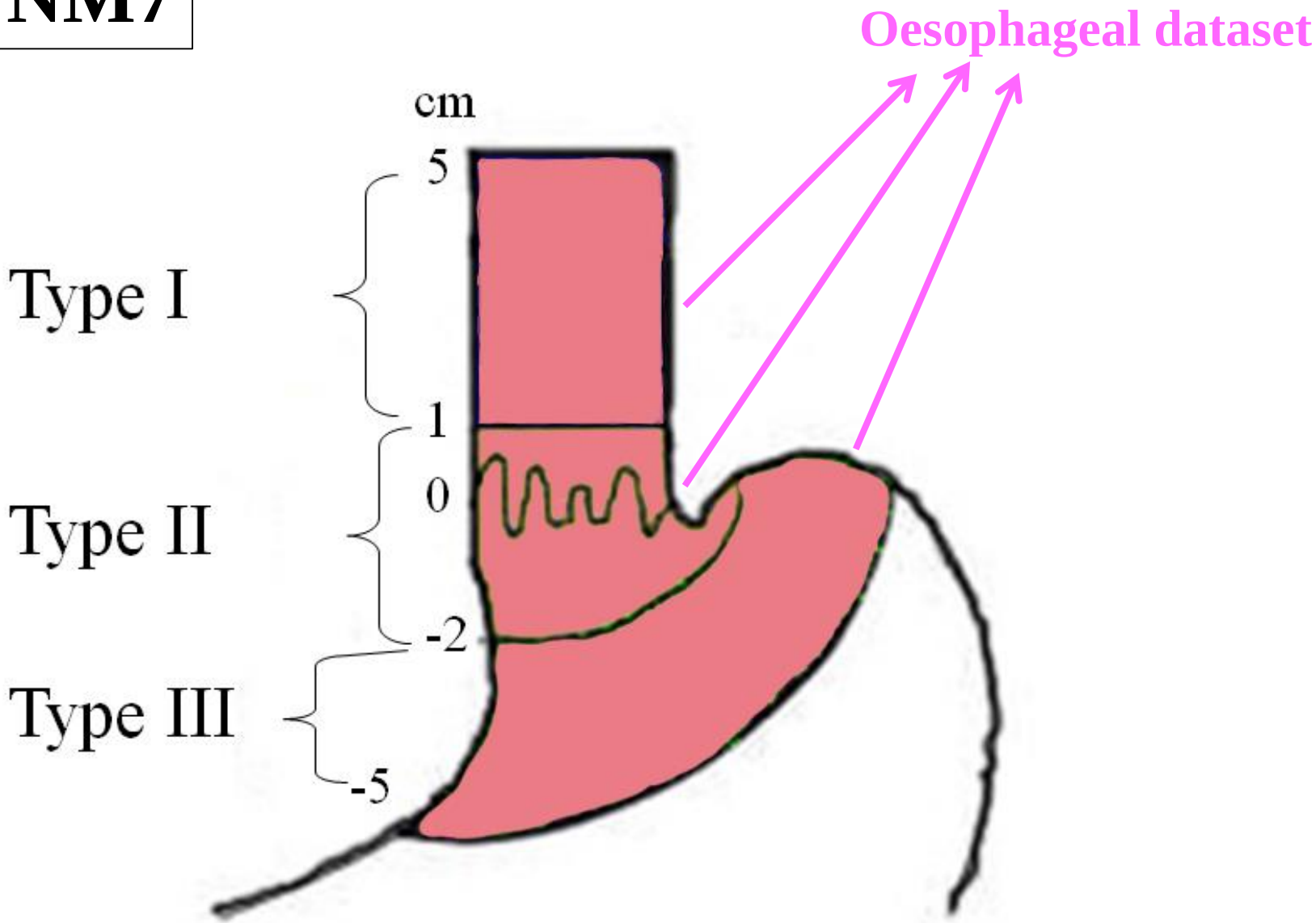
All other tumours with an epicenter in the stomach greater than 5 cm from the oesophagogastric junction or those within 5 cm of the EGJ *without* extension into the oesophagus are staged using the **gastric** carcinoma scheme

→ Most tumours which involve the OGJ are classified under oesophageal dataset in TNM7

# TNM7

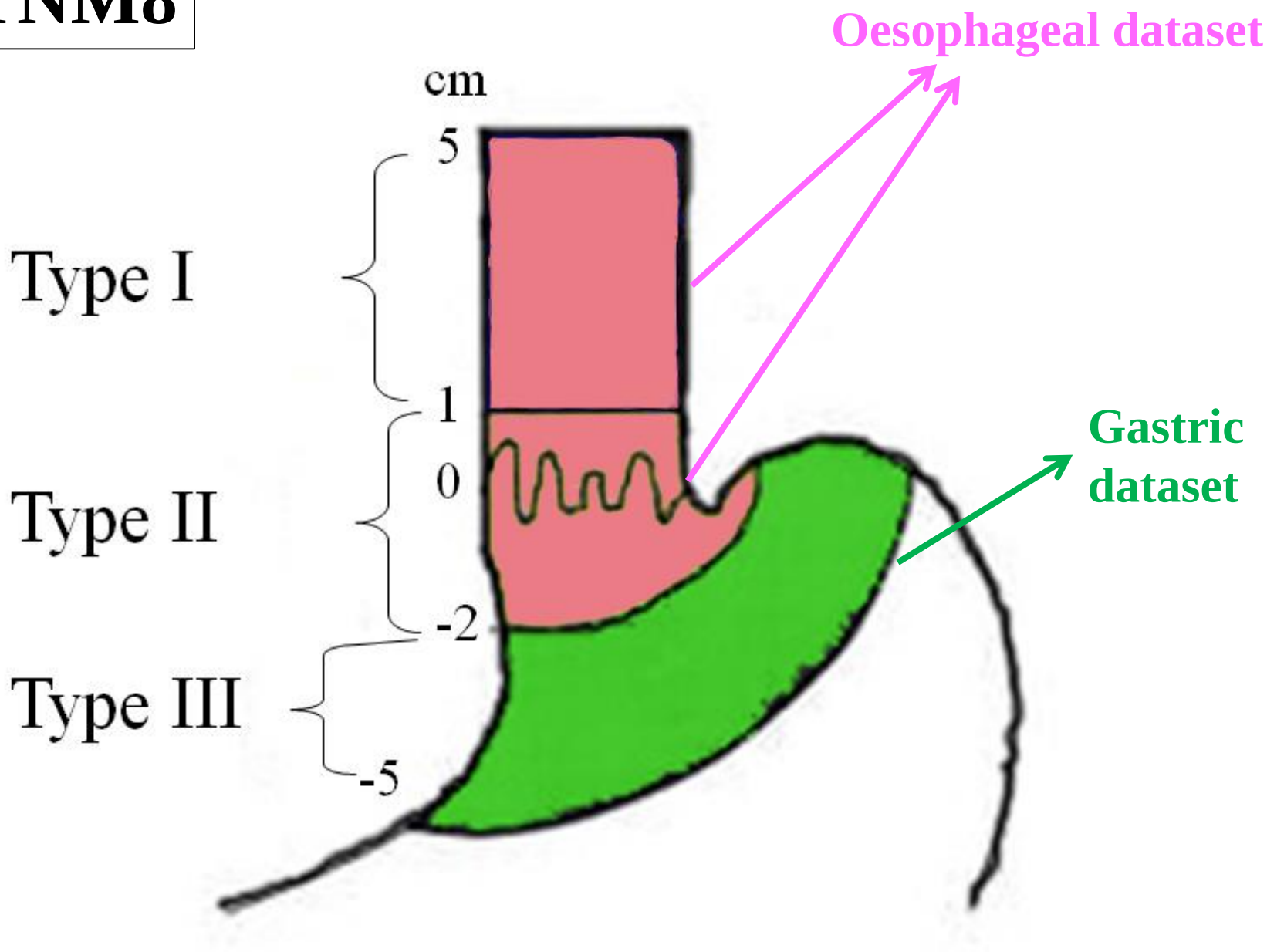


# TNM-8 Oesphagogastric Junction

**Oesophagus and Gastric Carcinomas**

- **A tumour the epicenter of which is within 2 cm of the oesophagogastric junction and also extends into the oesophagus is classified and staged using the oesophageal scheme. Cancers involving the oesophagogastric junction (OGJ) whose epicenter is within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as oesophageal**
- **Cancers whose epicenter is more than 2 cm distal from the OGJ will be staged using the Stomach Cancer TNM and Stage even if the OGJ is involved.**

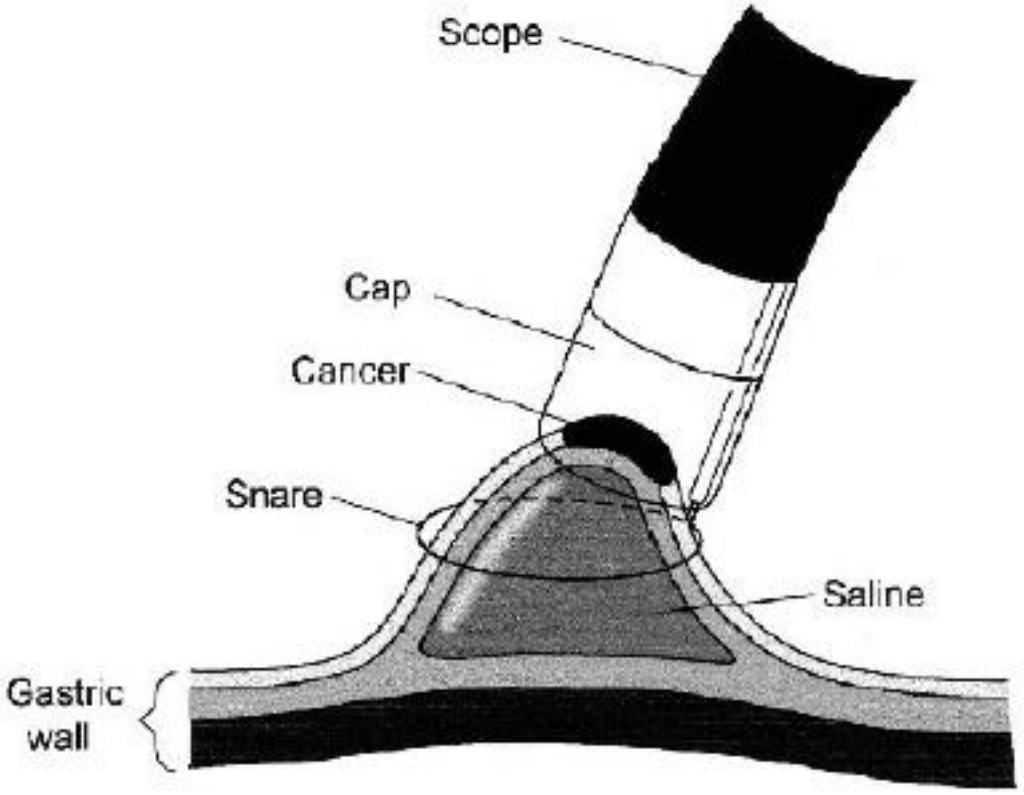
# TNM8


Oesophageal dataset
cm
5
1
0
-2
-5
Type I
Type II
Type III
Gastric dataset

# Endoscopic mucosal resection

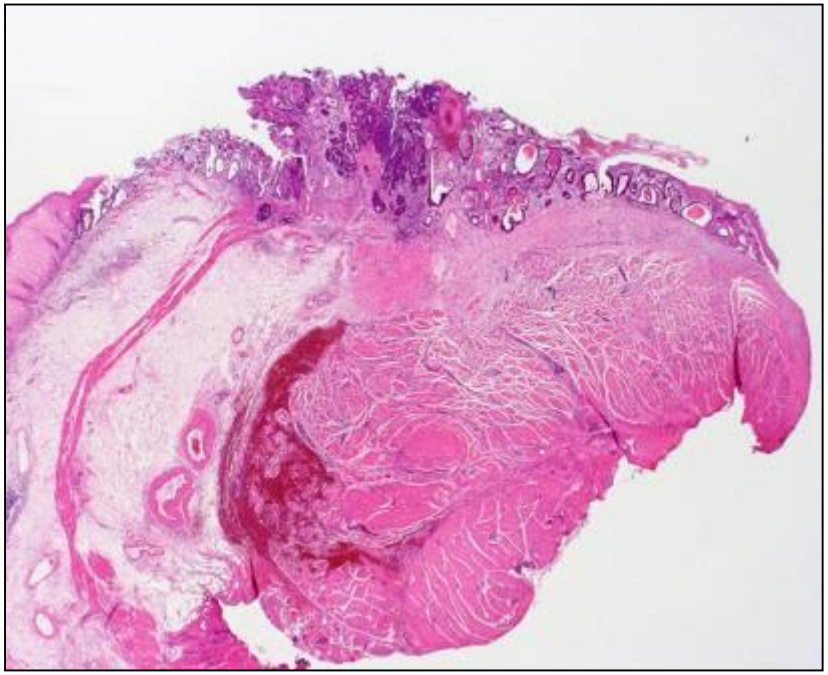
# Endoscopic mucosal resection (EMR) + Endoscopic submucosal dissection (ESD)

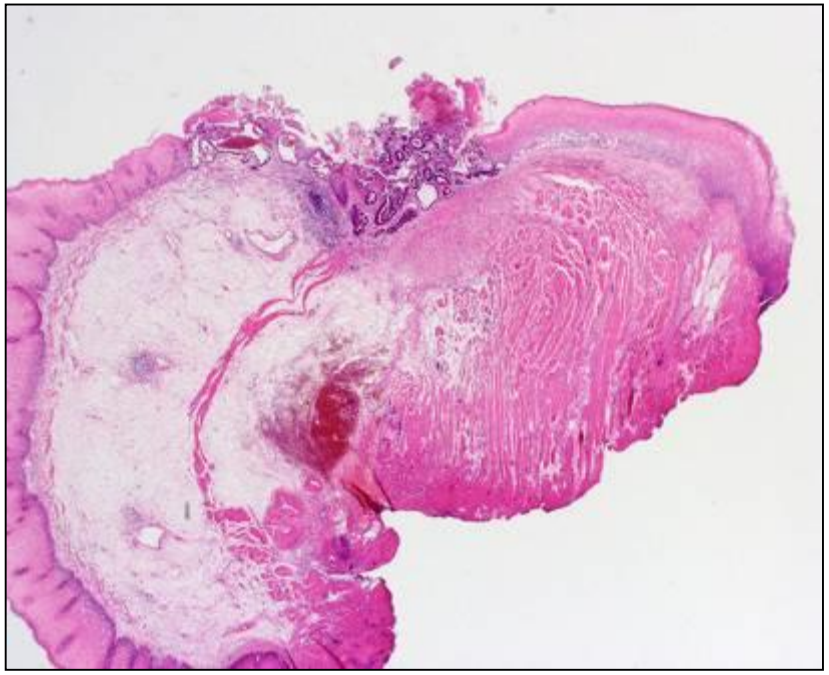
- Currently - EMRs for oesophagus.
  ESDs for stomach.
- EMR - Accurate staging and debulking.
  RFA/Cryo for removing dysplasia.
- Now main treatment for intramucosal and SM1 disease. (SM2 disease at UCL!)
- Becoming increasingly clinically important.
- Accurate staging crucial for management.




# EMR Technique

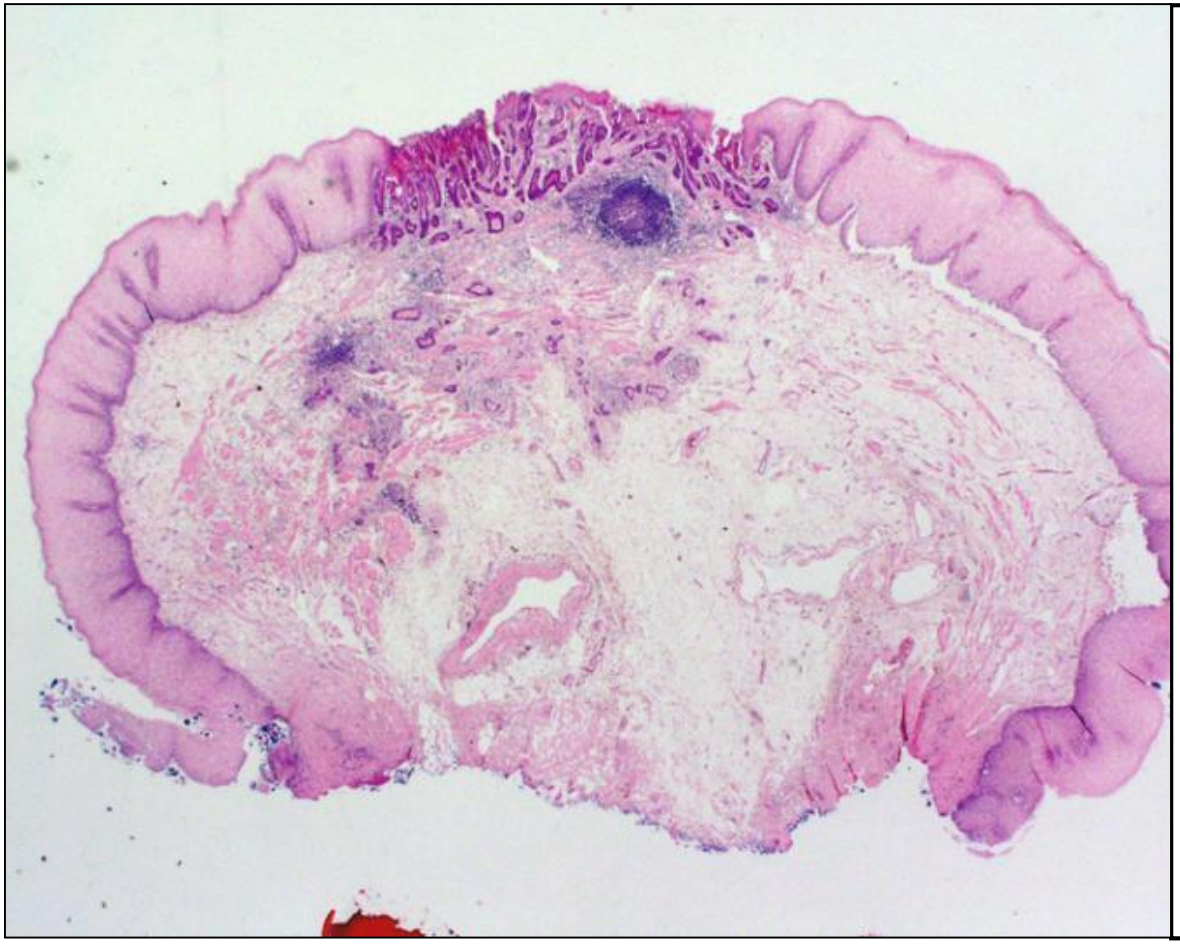
# Endoscopic mucosal resection (EMR)





- Usually diathermy artefact – no need to ink.
- Often multiple with dysplasia at circumferential margins.
- Orientation and exact site usually unknown.
- Diagnostic and “debulking” procedure!

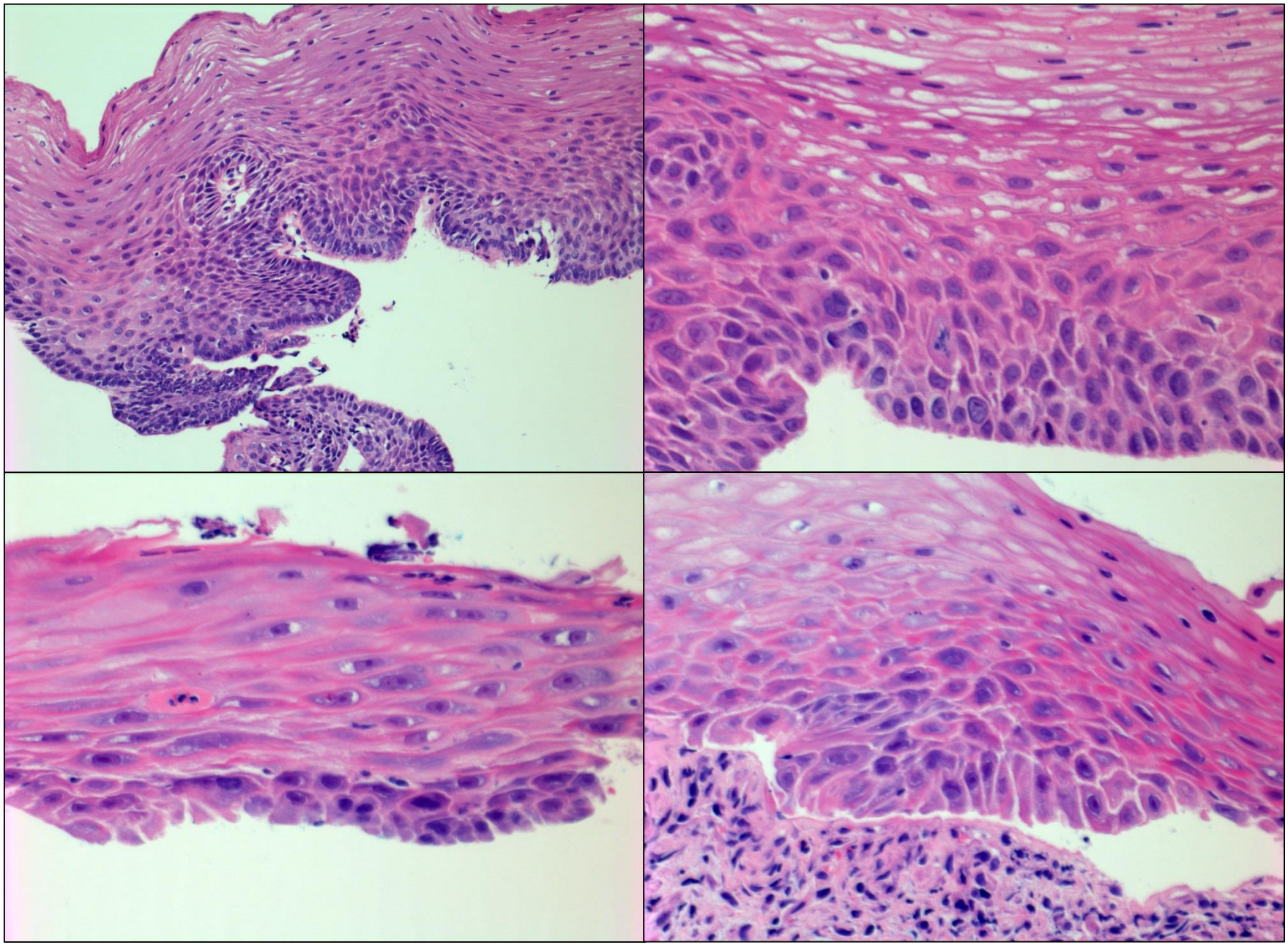
# Endoscopic mucosal resection (EMR)



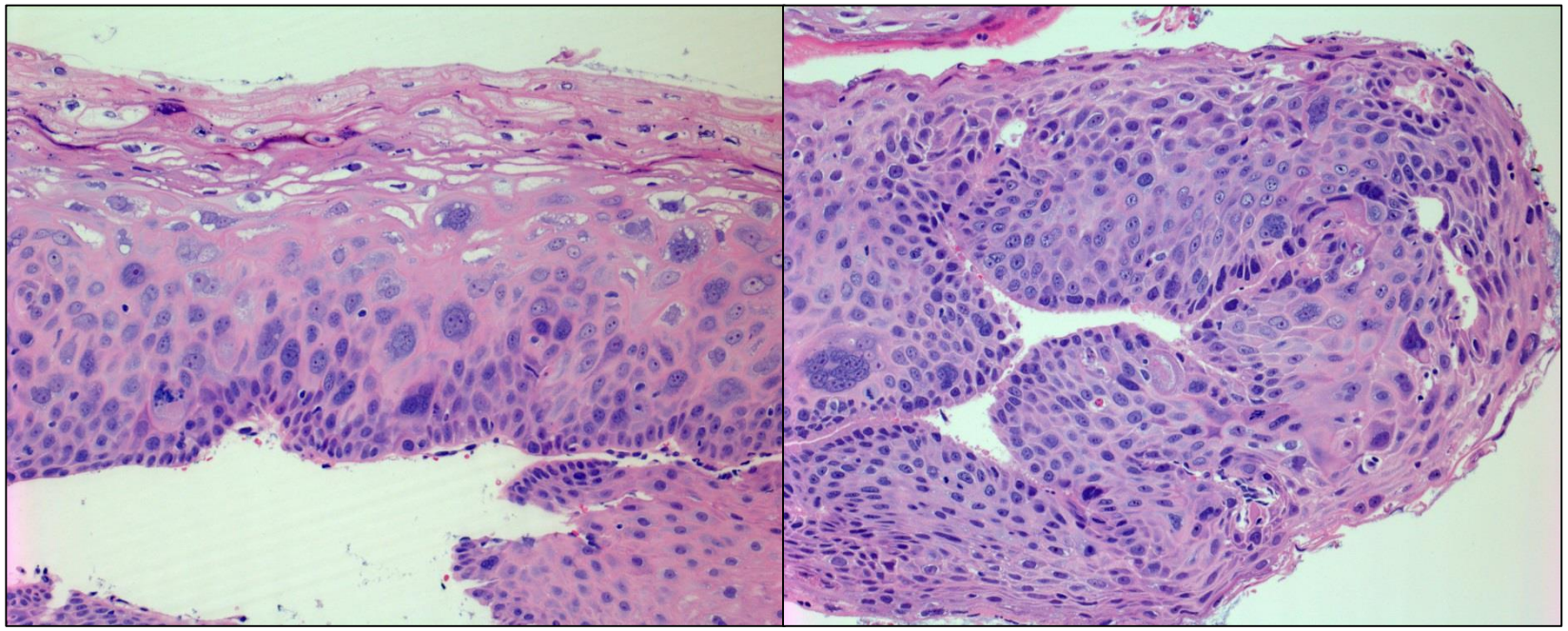
- Diagnosis of dysplasia/IMC/ invasive.
- Stage lesion.
- Circumferential margins.
- Deep resection margin.

# Squamous dysplasia

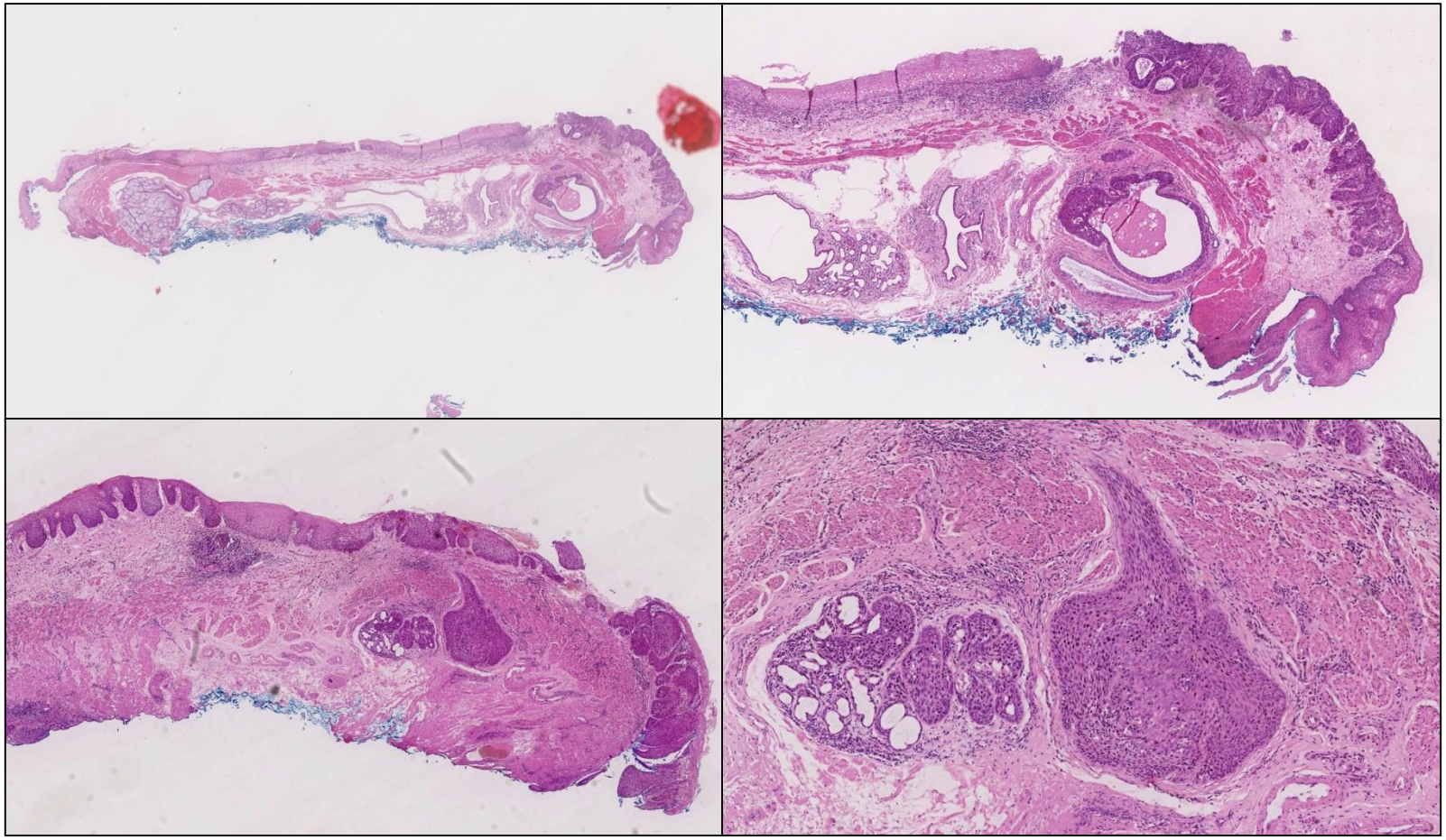
# Low grade squamous dysplasia



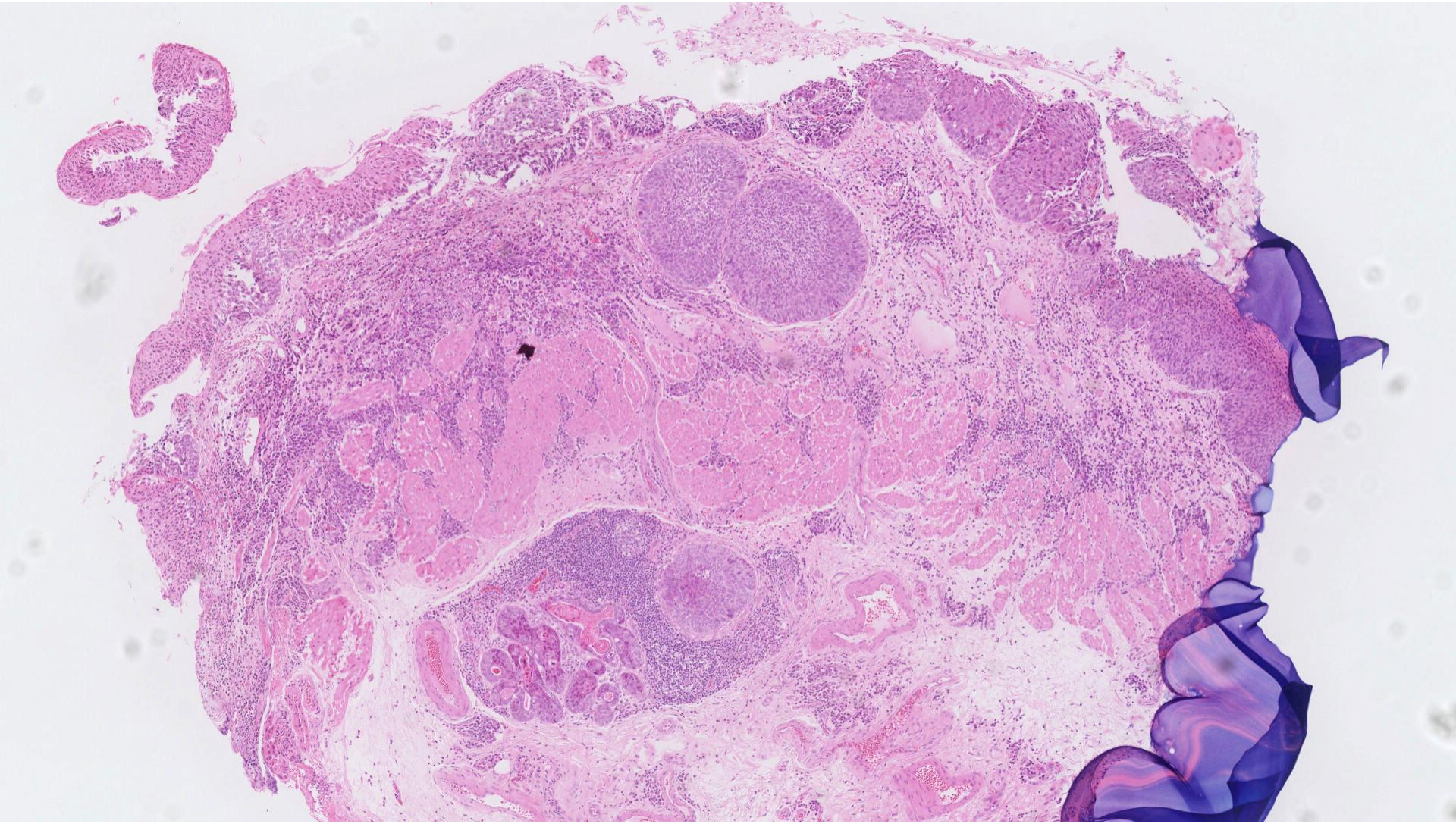
# High grade squamous dysplasia

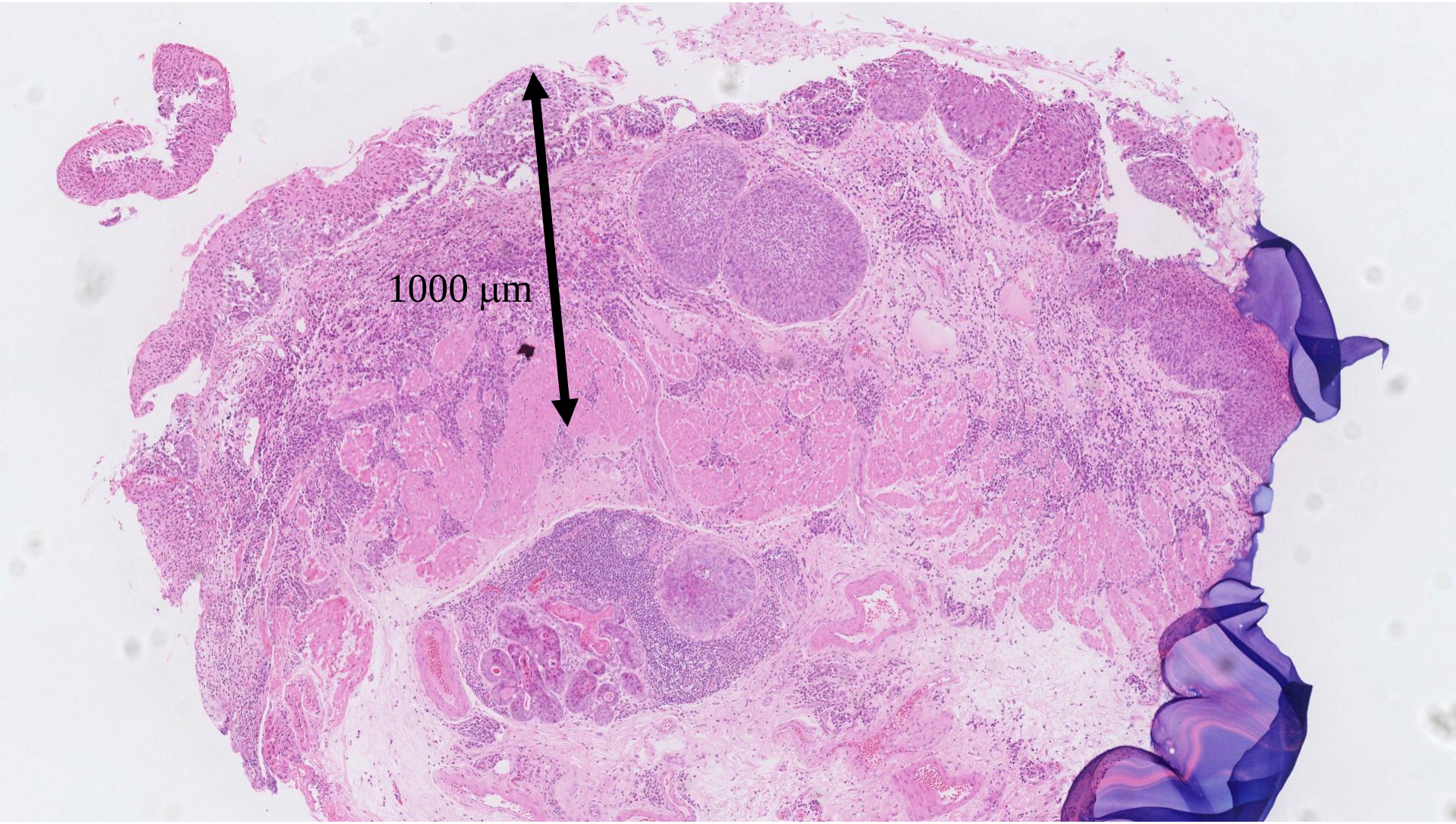


# Colonisation of submucosal glands by squamous dysplasia

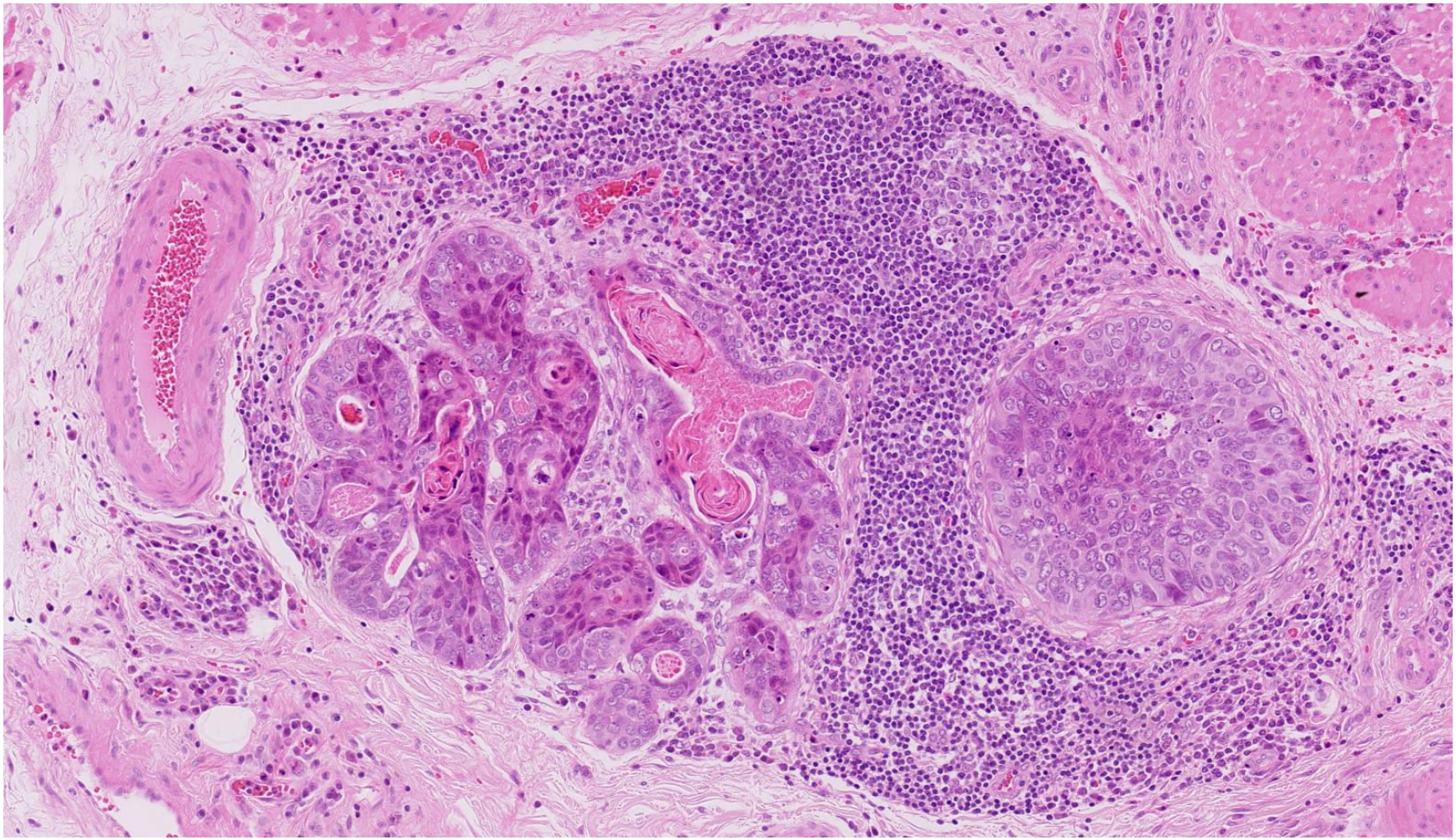


Squamous dysplasia often extends into submucosal glands.






Radiofrequency ablation works to a depth of 500 microns

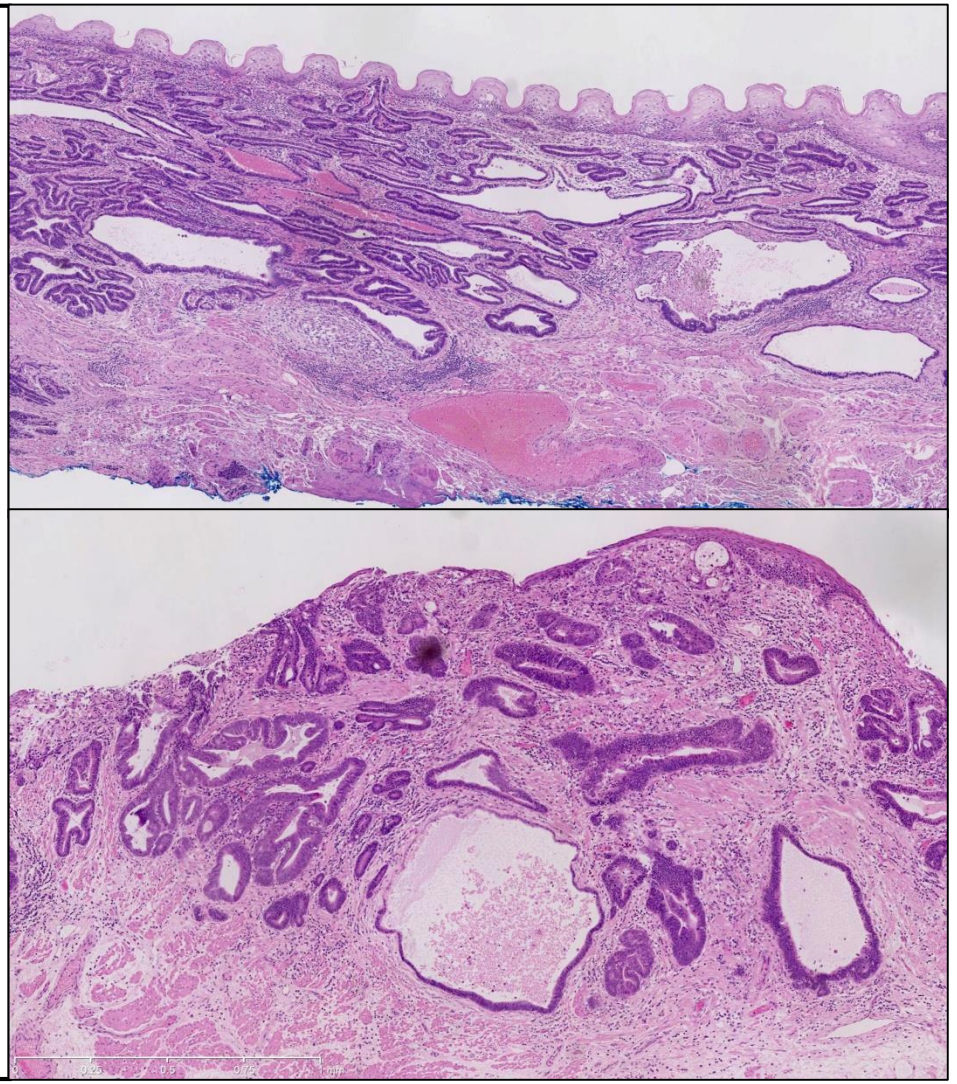


Colonisation of submucosal glands by high grade squamous dysplasia

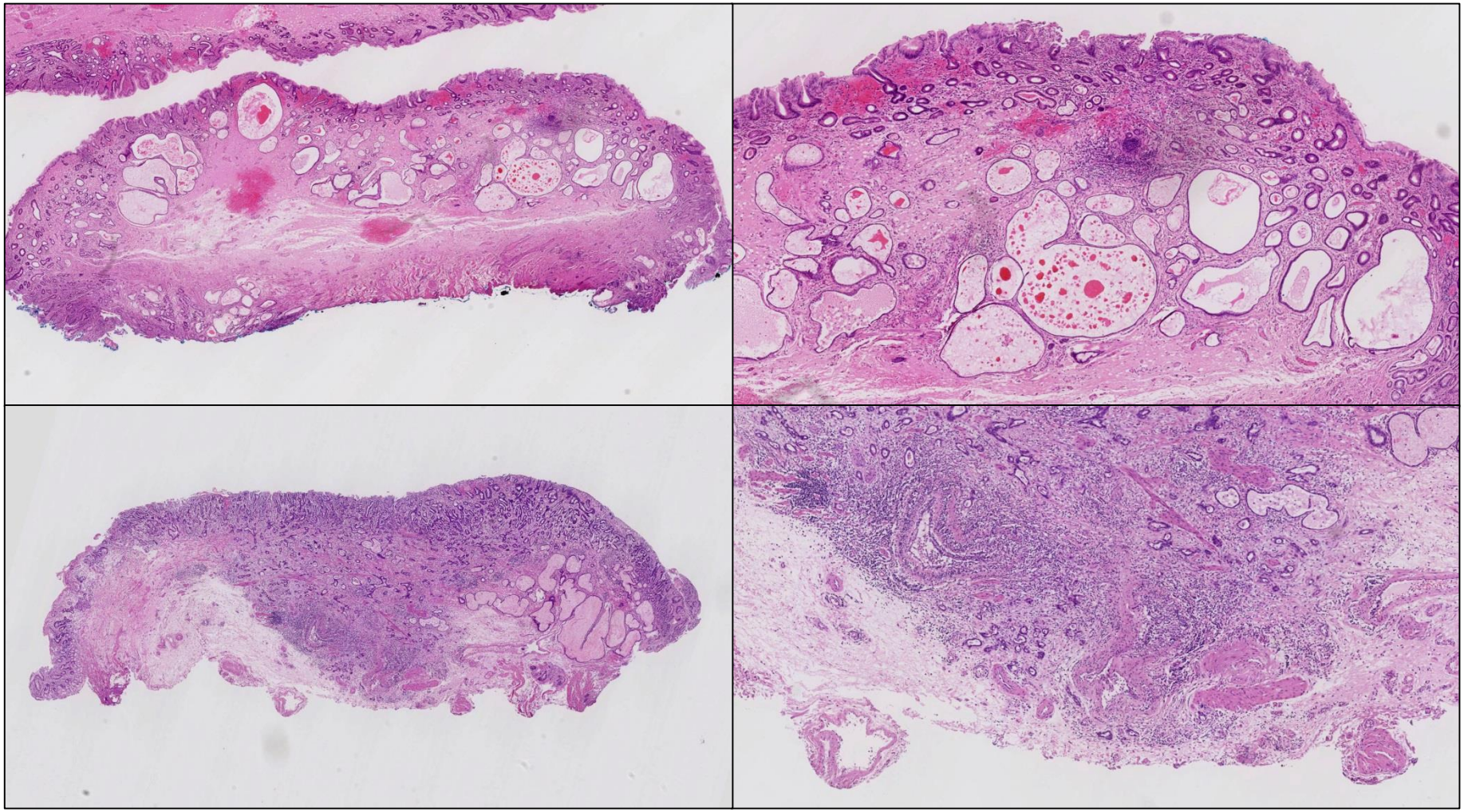
→ RFA not usually used for squamous dysplasia

# Intramucosal adenocarcinoma

- Poor agreement between histopathologists.
- Clinicians keen to separate HGD from IMA.
- Need for criteria for well/moderately differentiated lesions.
- Consensus - architectural change with horizontal rather than vertical orientation of glands.



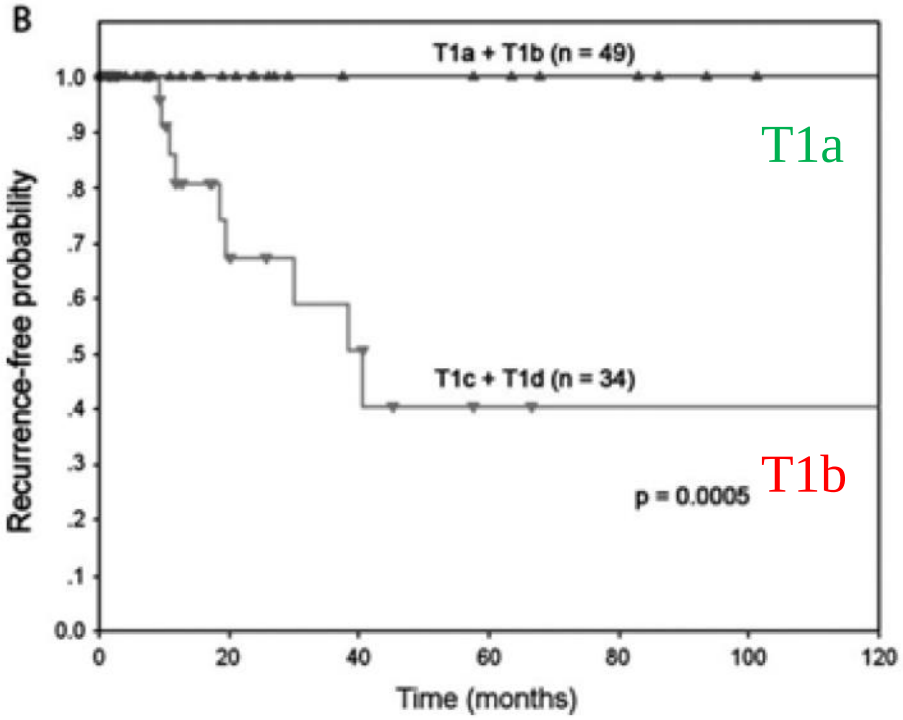
# Beware dilated bland glands – usually IMA!

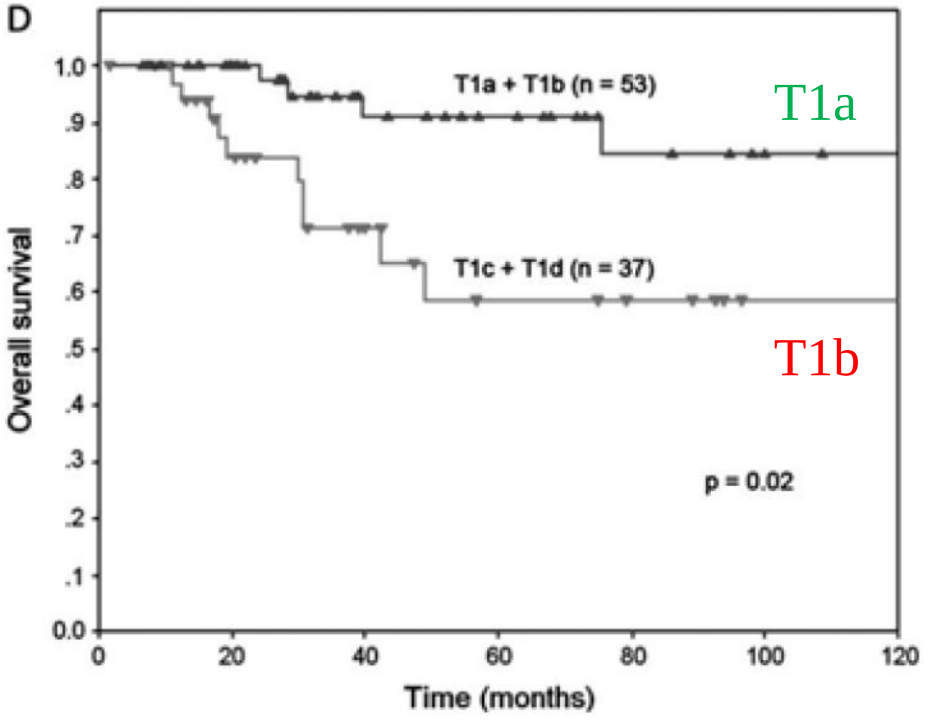


# Oesophageal adenocarcinoma T staging, TNM7

| **Primary tumor (T)** | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | High-grade dysplasia |
| T1 | Tumor invades lamina propria, muscularis mucosae, or submucosa |
| T1a | Tumor invades lamina propria or muscularis mucosae |
| T1b | Tumor invades submucosa |
| T2 | Tumor invades muscularis propria |
| T3 | Tumor invades adventitia |
| T4 | Tumor invades adjacent structures |
| T4a | Resectable tumor invading pleura, pericardium, or diaphragm |
| T4b | Unresectable tumor invading other adjacent structures, such as the aorta, vertebral body, and trachea |

# Significance of the Depth of Tumor Invasion and Lymph Node Metastasis in Superficially Invasive (T1) Esophageal Adenocarcinoma




T1a – lamina propria. T1b – muscularis mucosae. T1c – superficial submucosa. T1d – deep submucosa.

Liu L *et al*. Am J Surg Pathol. 2005 Aug;29(8):1079-85.

# Staging of mucosal invasion I

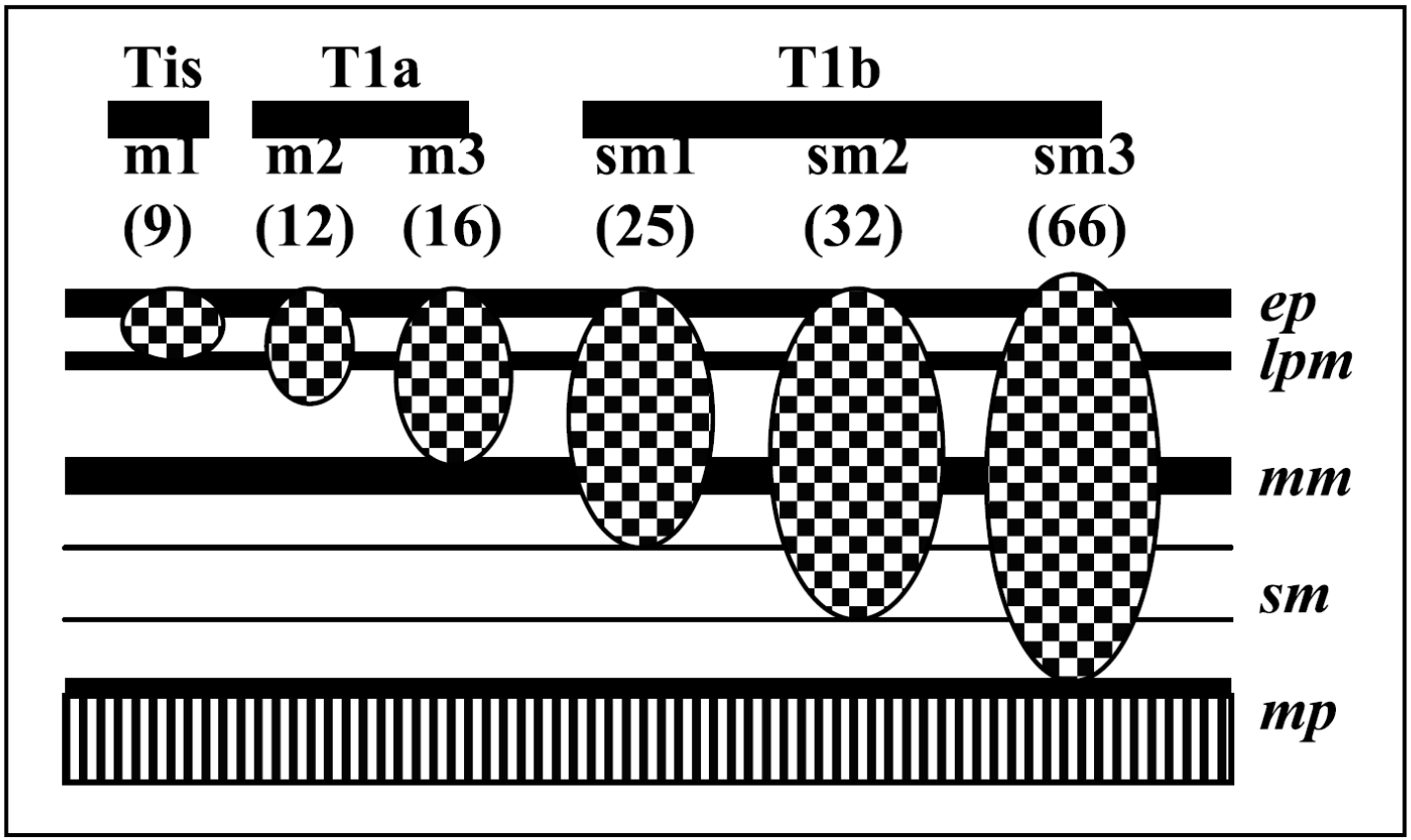



Fig. 1. Subclassification of the depth of superficial esophageal cancer (number of patients). ep, carcinoma in situ; lpm, lamina propria mucosa, mm, muscularis mucosa; m, mucosa; sm, submucosa; mp, muscularis propria.

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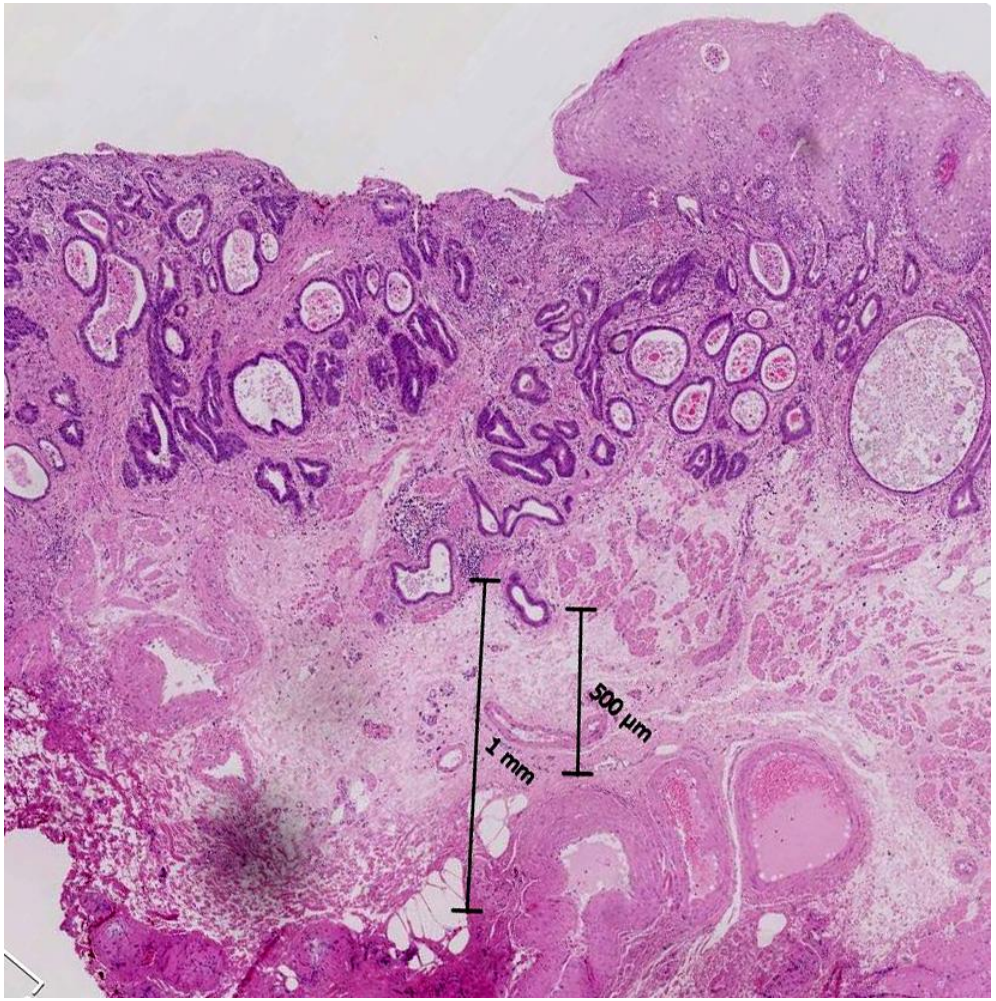
# Staging of submucosal disease

- Oesophagectomy specimens:
  - SM1 upper 1/3
  - SM2 middle 1/3
  - SM3 lower 1/3
- EMRs (adenocarcinoma)
  - SM1 < 500 um
  - SM2 > 500 - 1000 um
  - SM3 > 1000 um

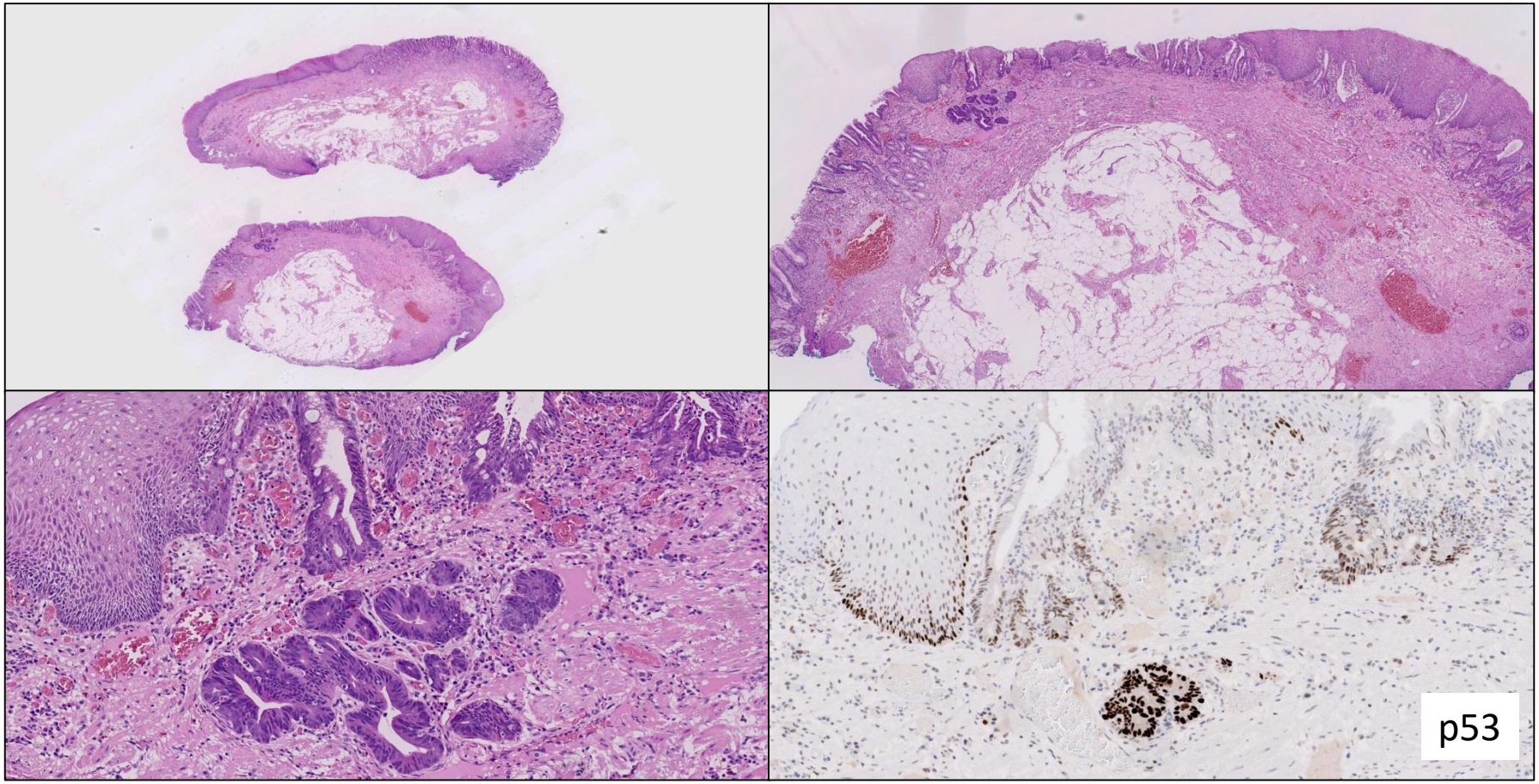


# Current Clinical Management

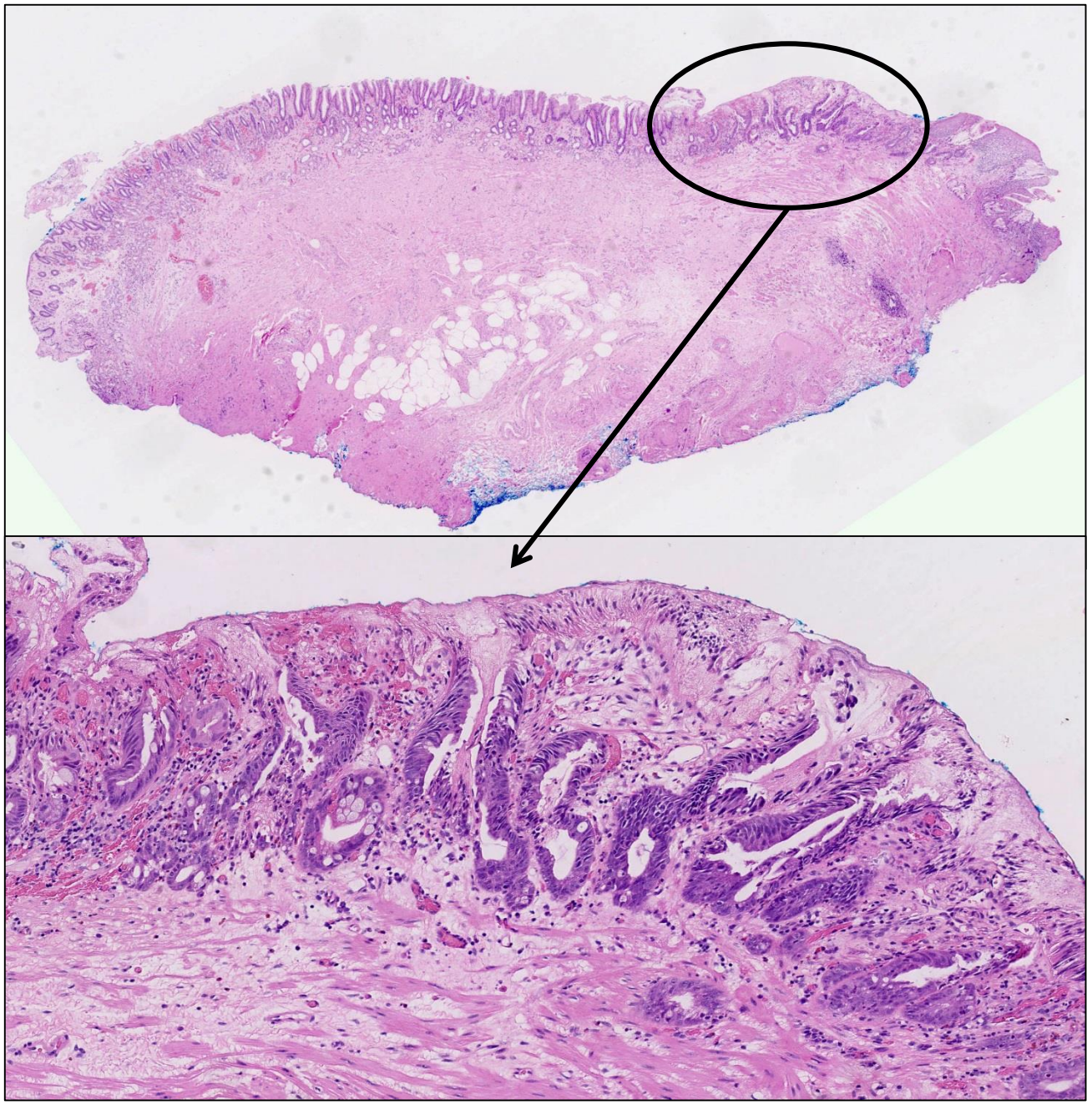
- Local therapy:
  - Well/moderately differentiated.
  - pT1a +/- pT1b, SM1.
  - Clear deep margin.
- Referral for surgery/chemoradiation
  - pT1b – poorly differentiated.
  - Lymphovascular invasion present.
  - Deep margin +ve.

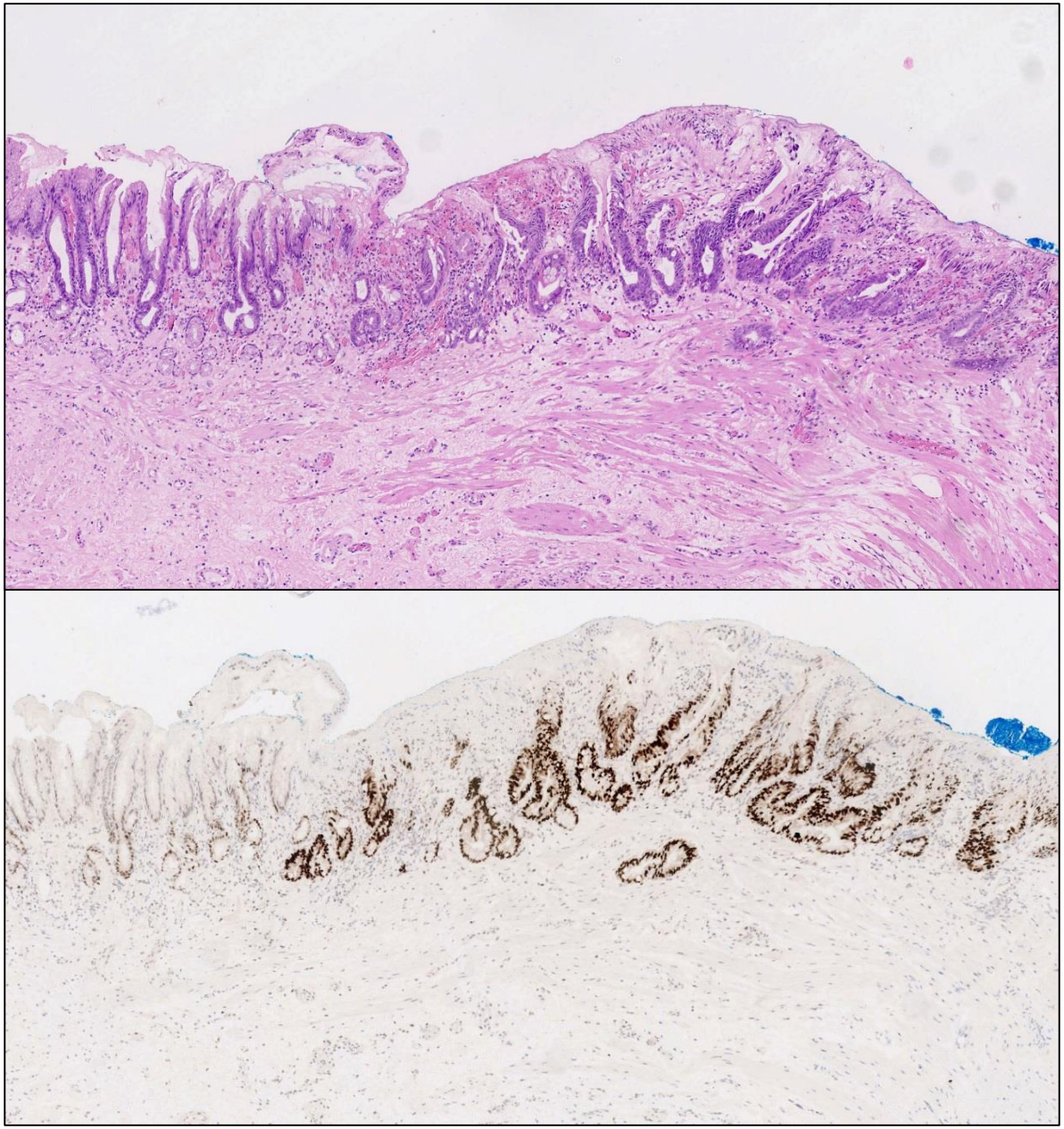
# Use of immunostaining in EMRs

# P53 to confirm dysplasia

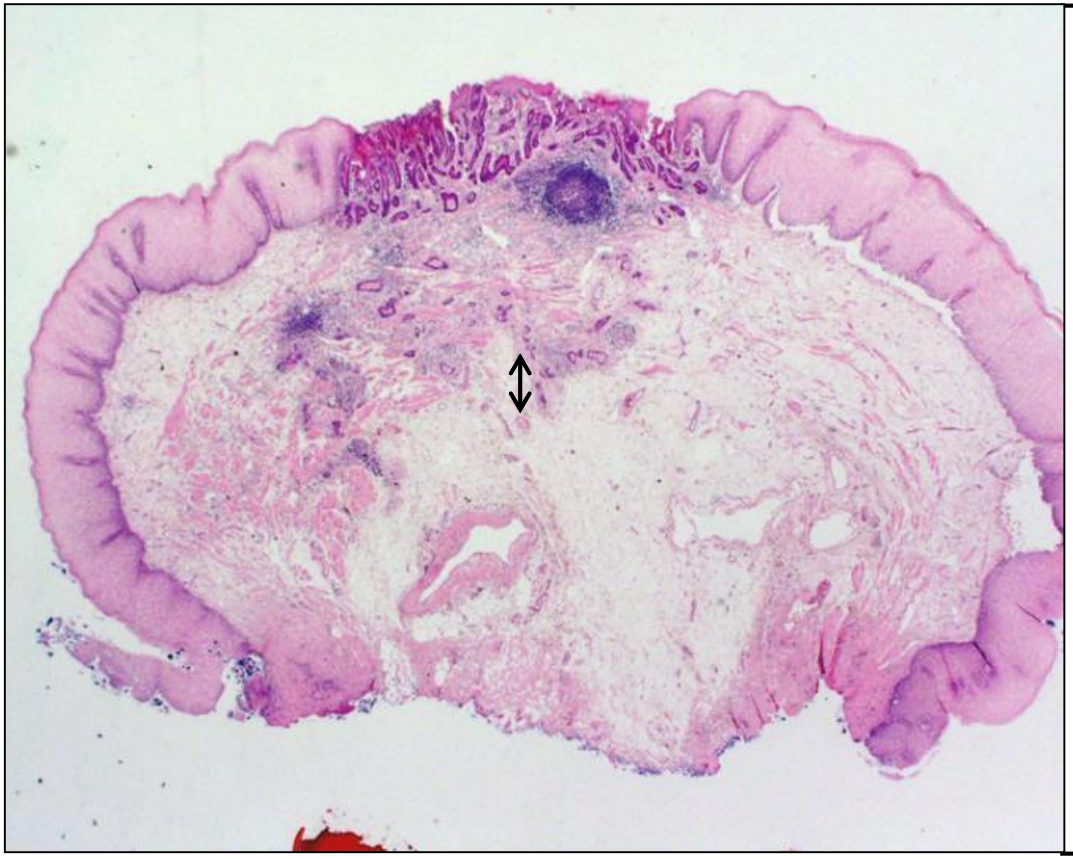



- Buried glands.
- Loss of surface epithelium.

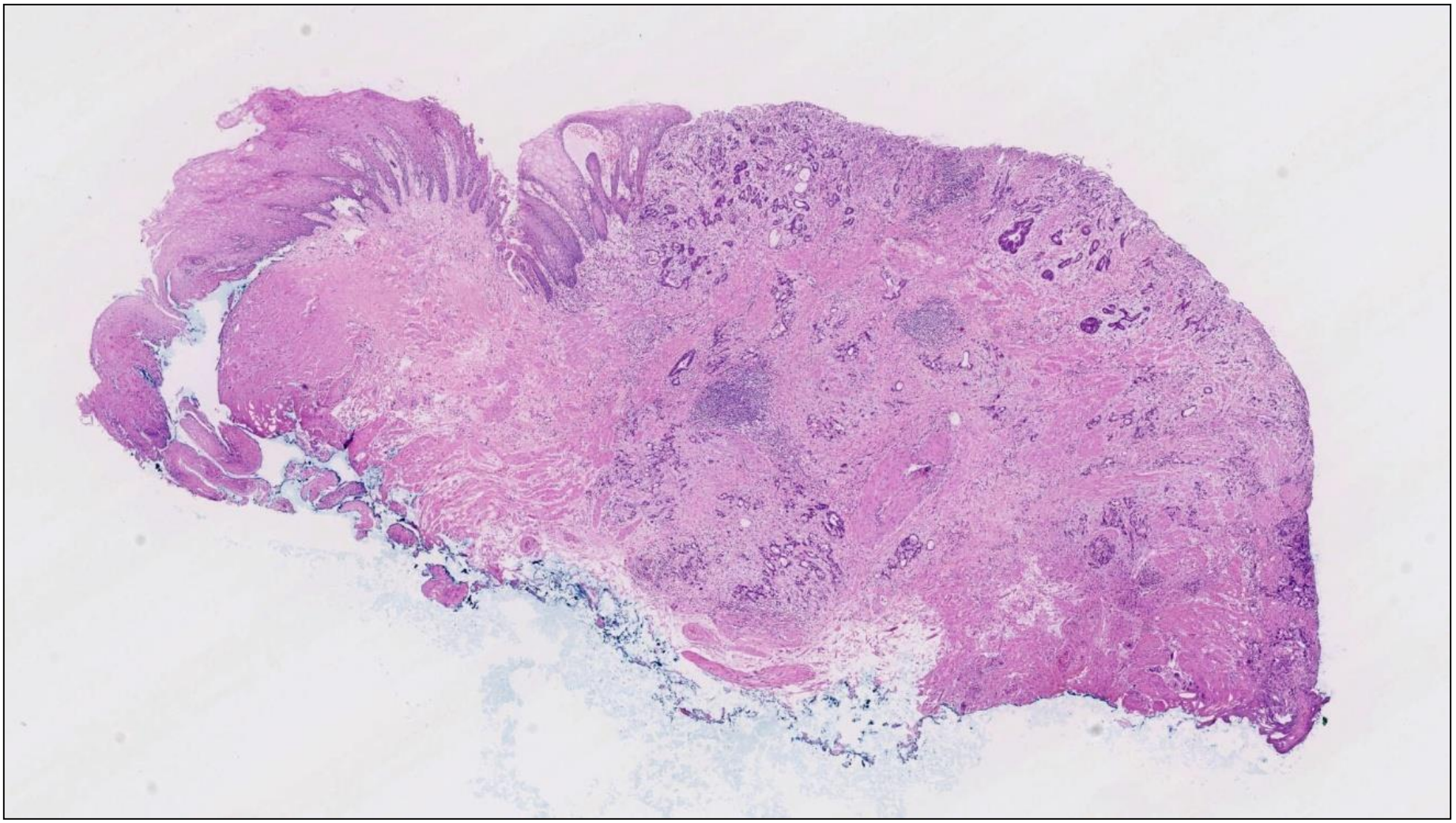




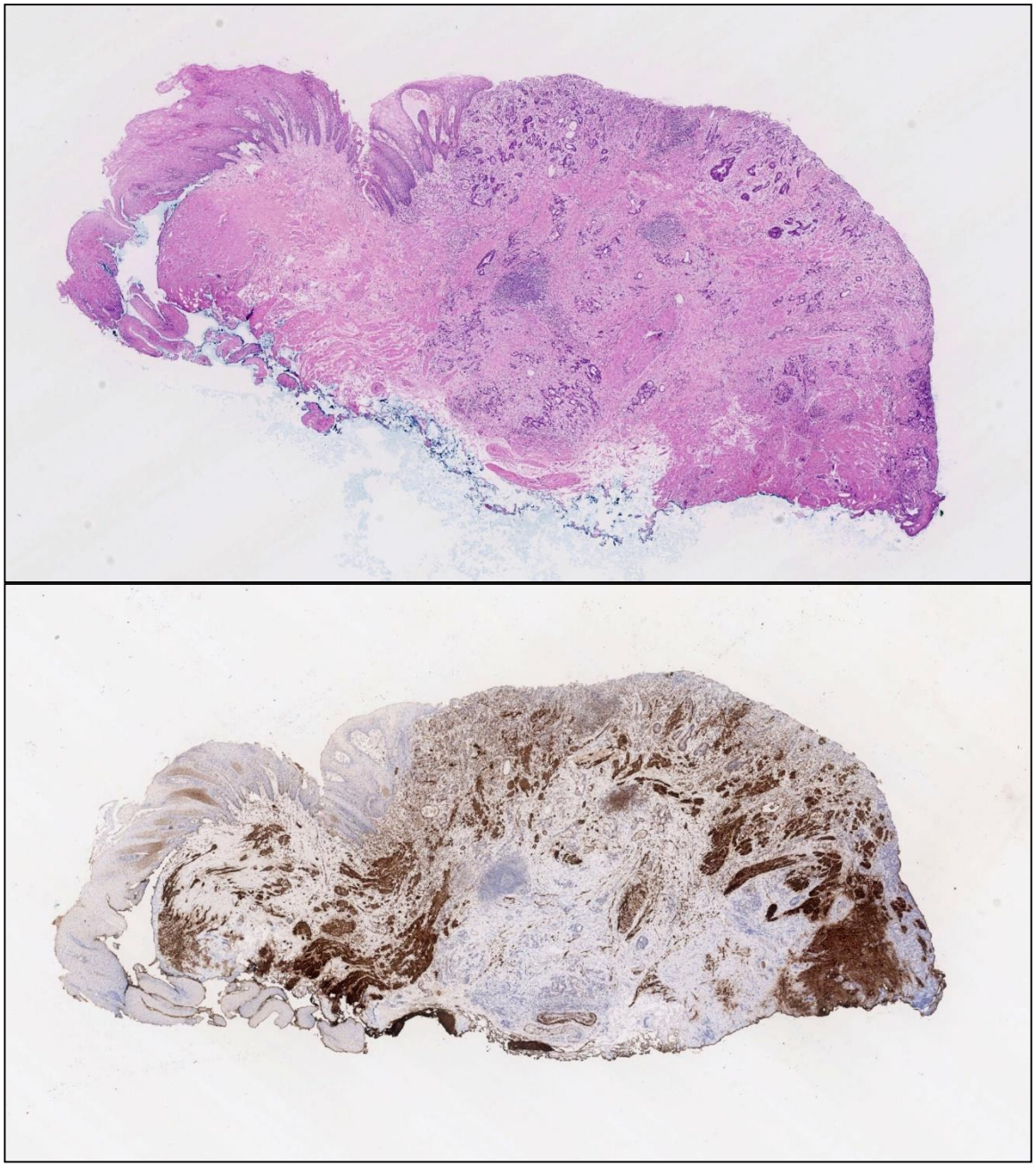
# Use of desmin staining in staging EMRs



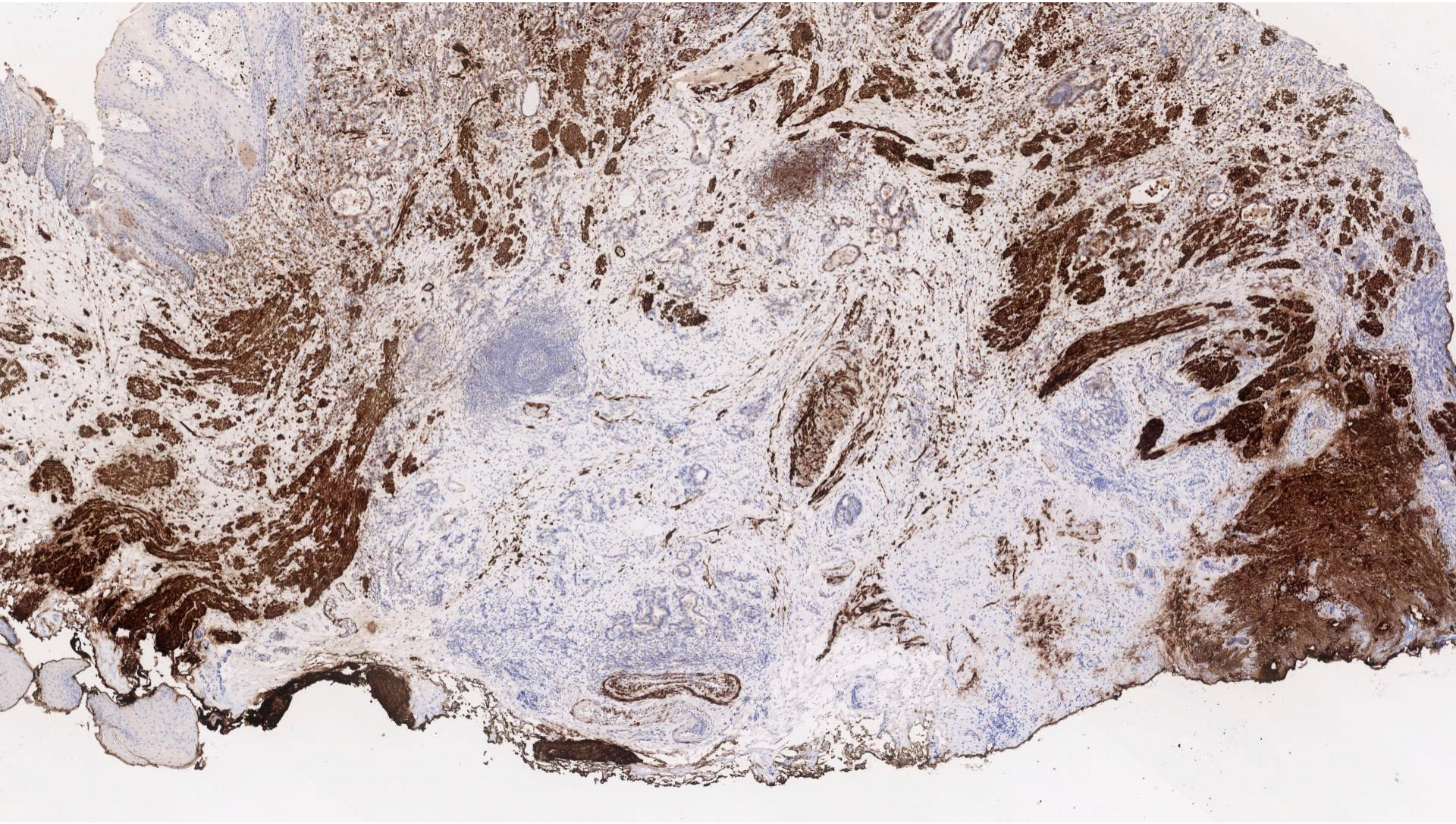
- Stage lesion.
  - Measure depth of invasion beyond muscularis mucosae.
  - Desmin staining can be very helpful in delineating the lower border of the muscularis mucosae

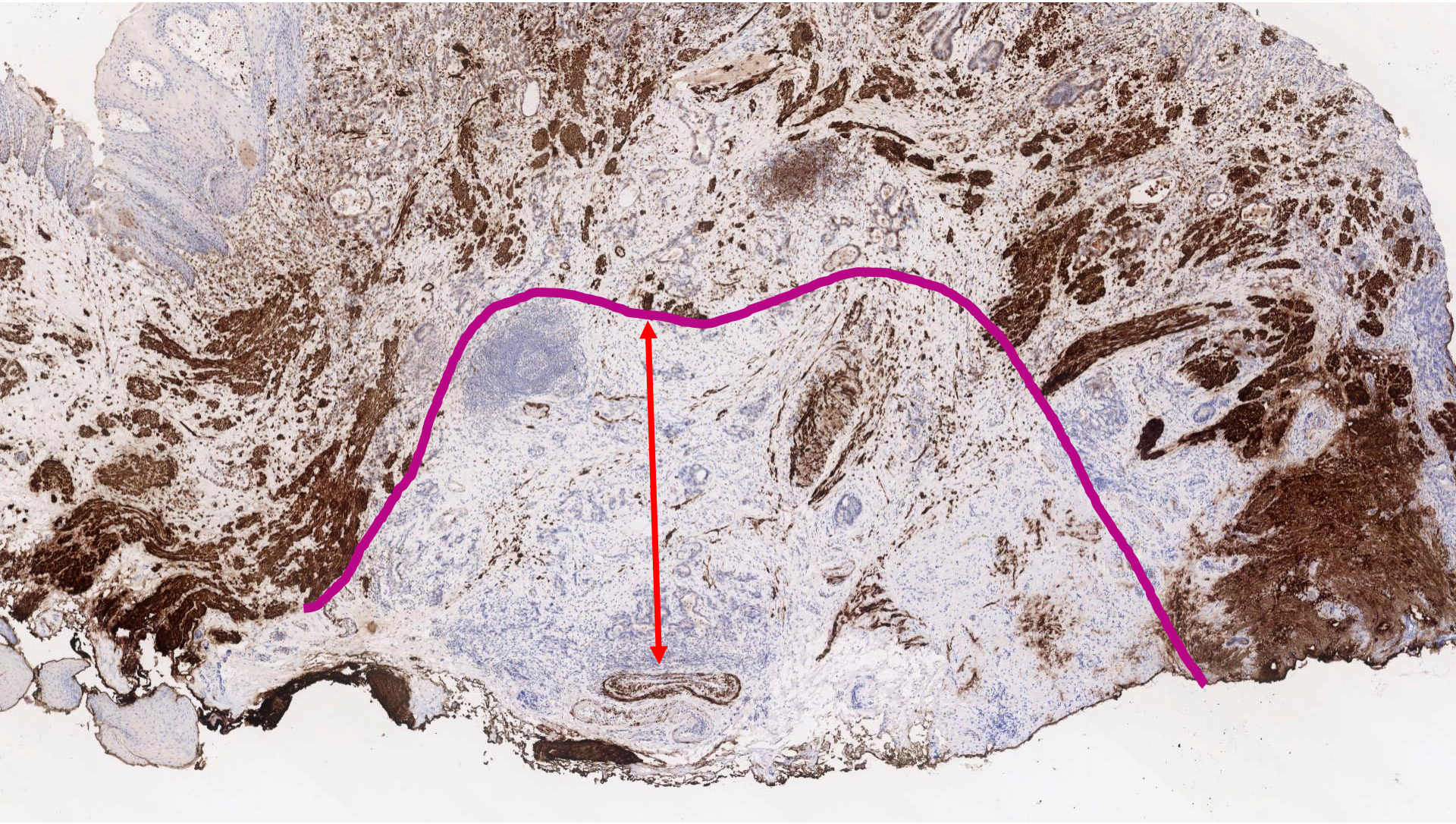


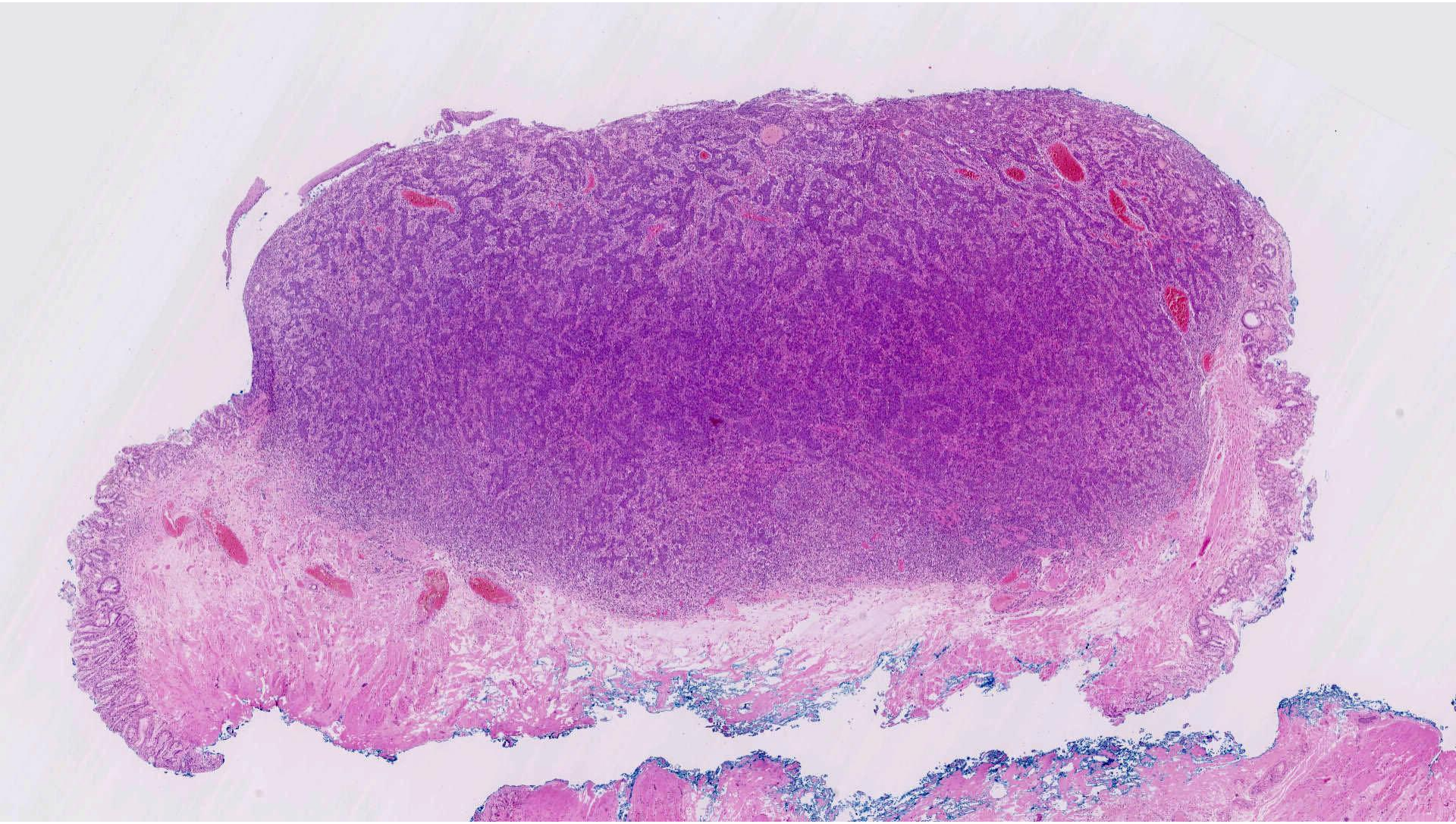
pT staging?

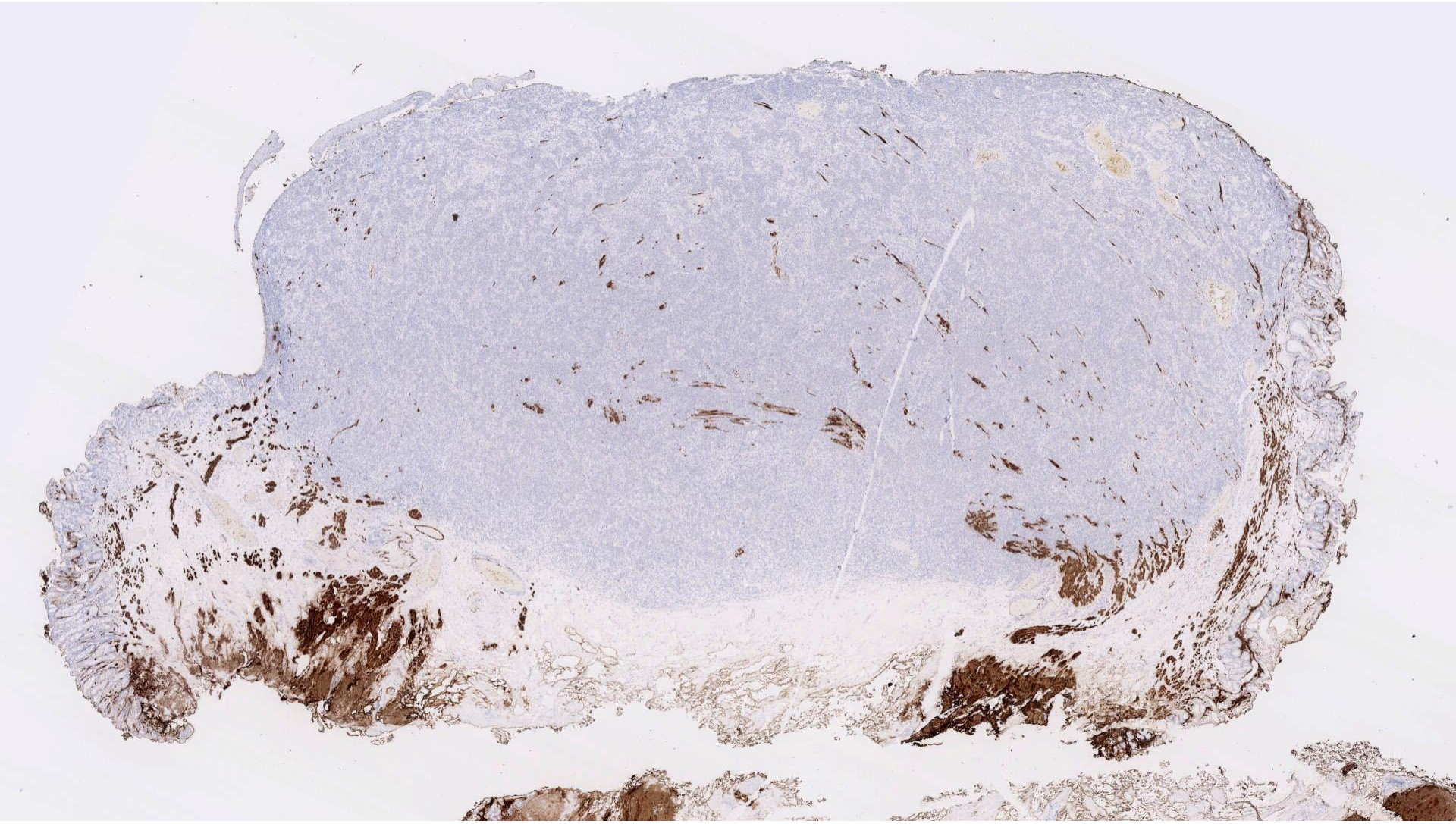


Desmin

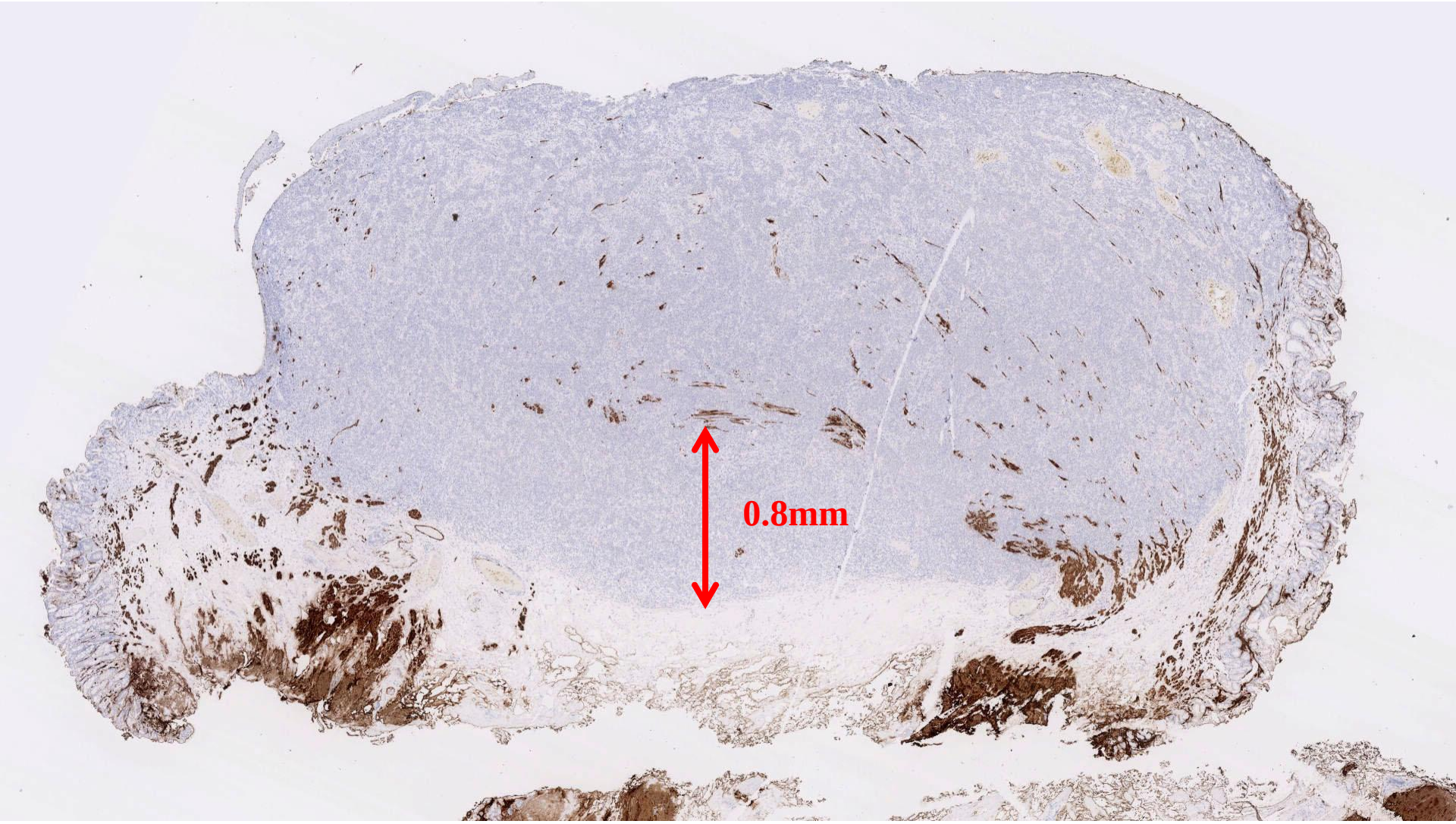








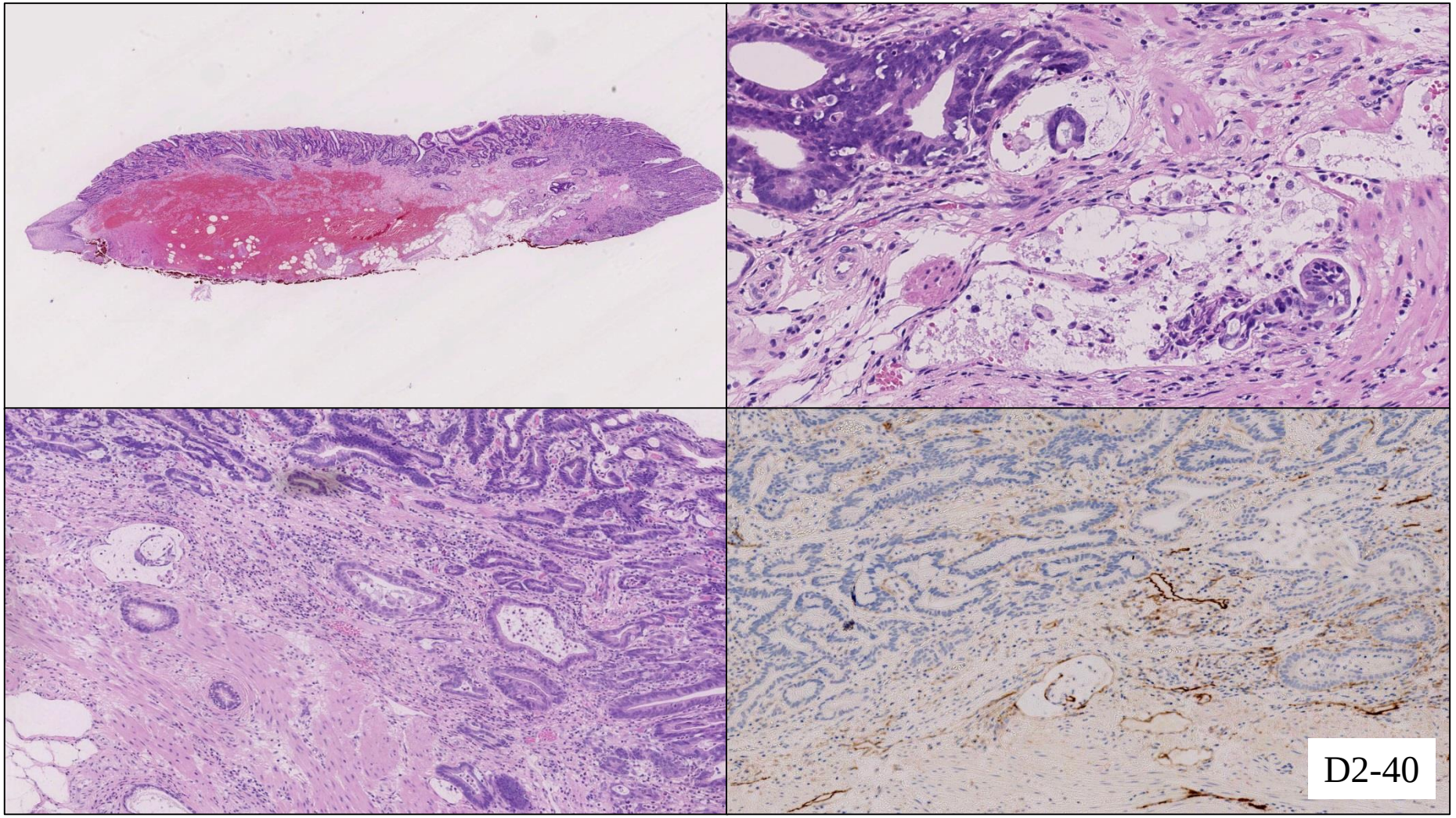
Desmin staining




0.8mm invasion beyond muscularis mucosae

→ pT1b, SM2

# D2-40 and CD31 for lymphovascular invasion



# EMRs and RFA

- Local therapy becoming mainstay of treatment for dysplasia / early adenocarcinoma in Barrett's.
- EMR for debulking and staging + RFA for eradication of flat / residual dysplasia (glandular).
- Rapidly changing field.
- Clinicopathological correlation very important.

# Thank you for your attention!