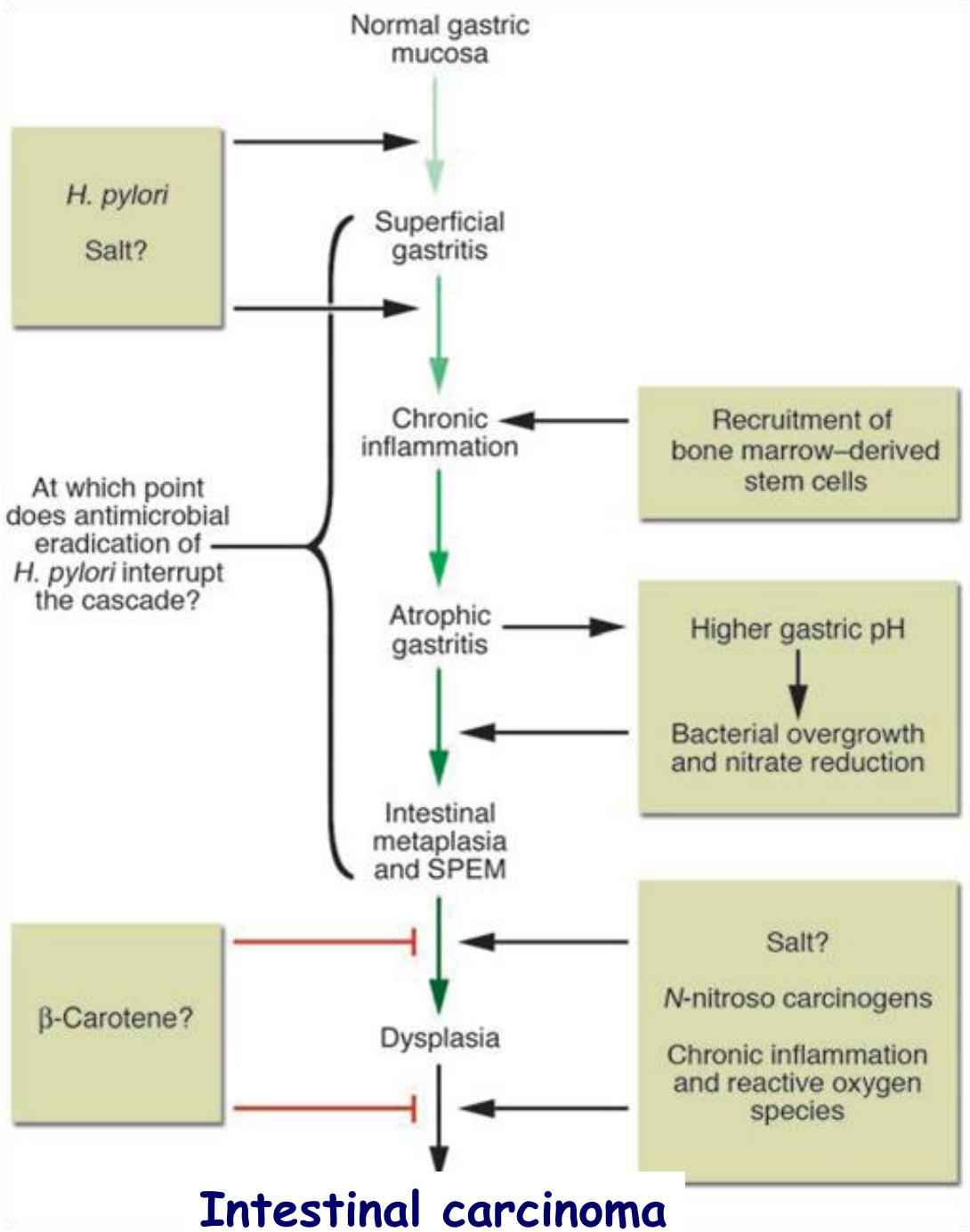
PRE-NEOPLASTIC AND NEOPLASIC LESIONS OF THE STOMACH

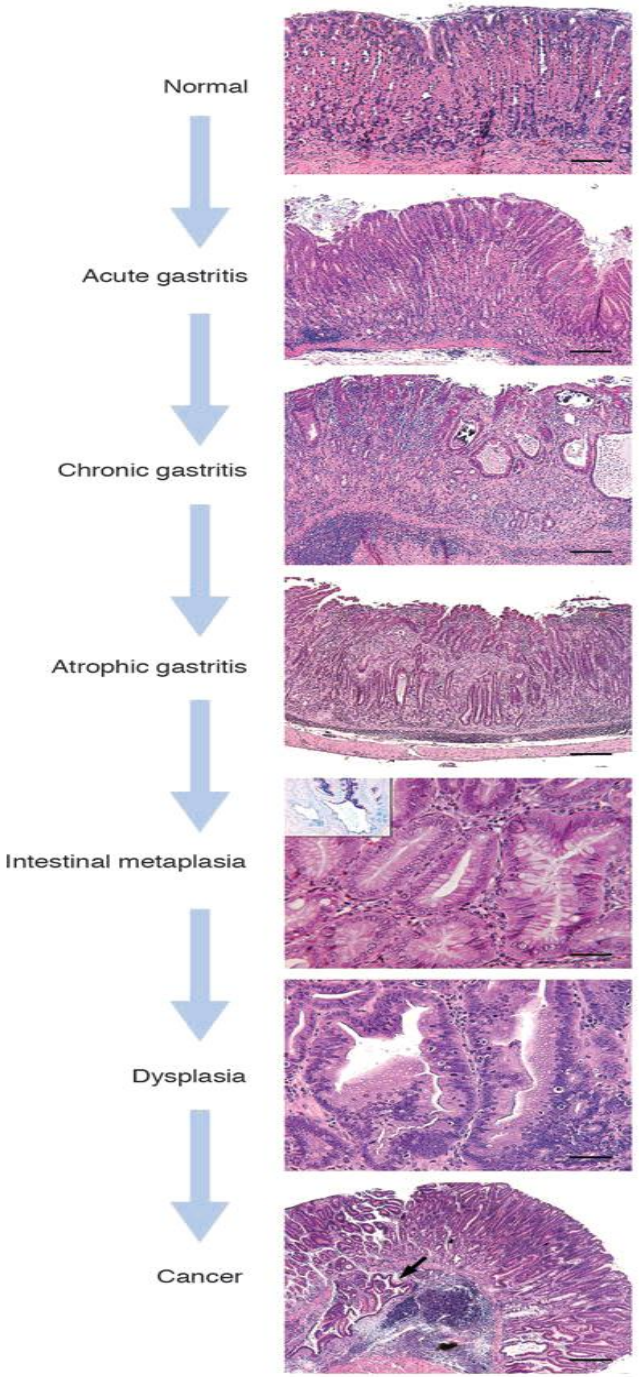
Luca Saragoni

U.O.Anatomia Patologica

Forlì



Intestinal carcinoma



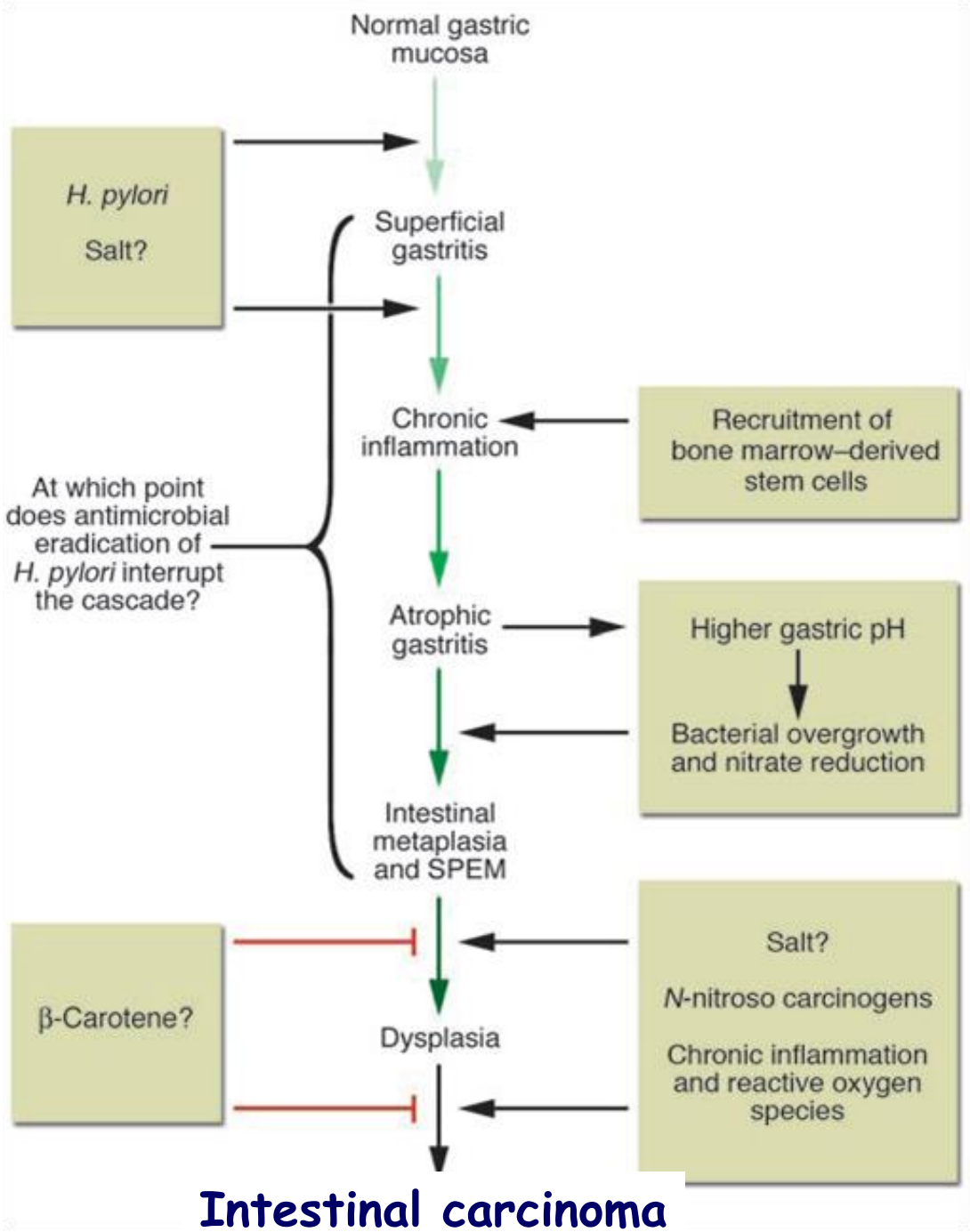
Histologic classifications

To standardize histologic diagnosis

Increase of inter-observer agreement

Better communication between pathologists and clinicians

Therapeutic management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H. pylori
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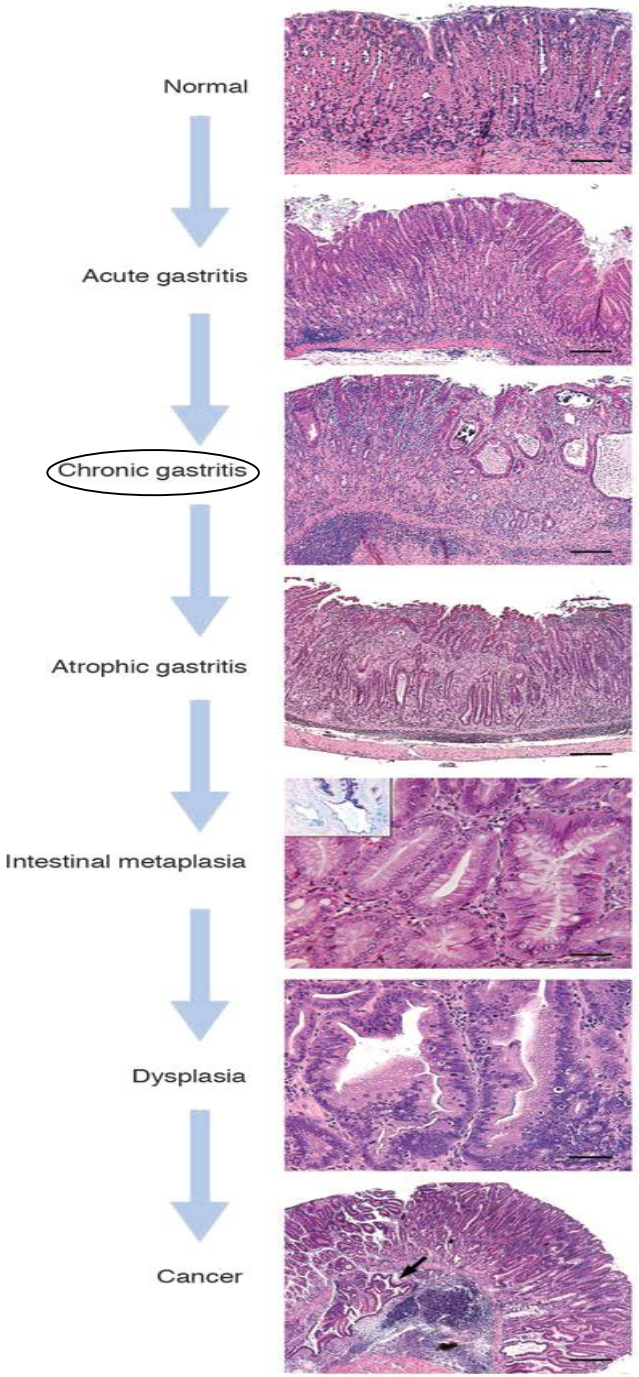
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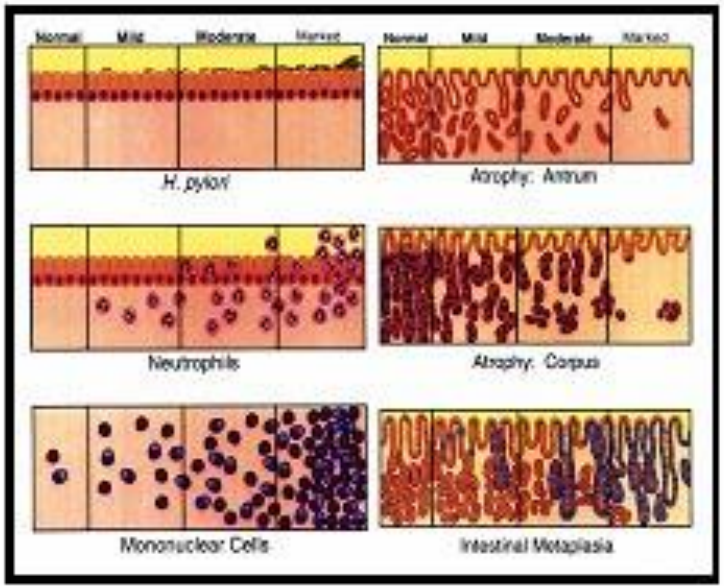
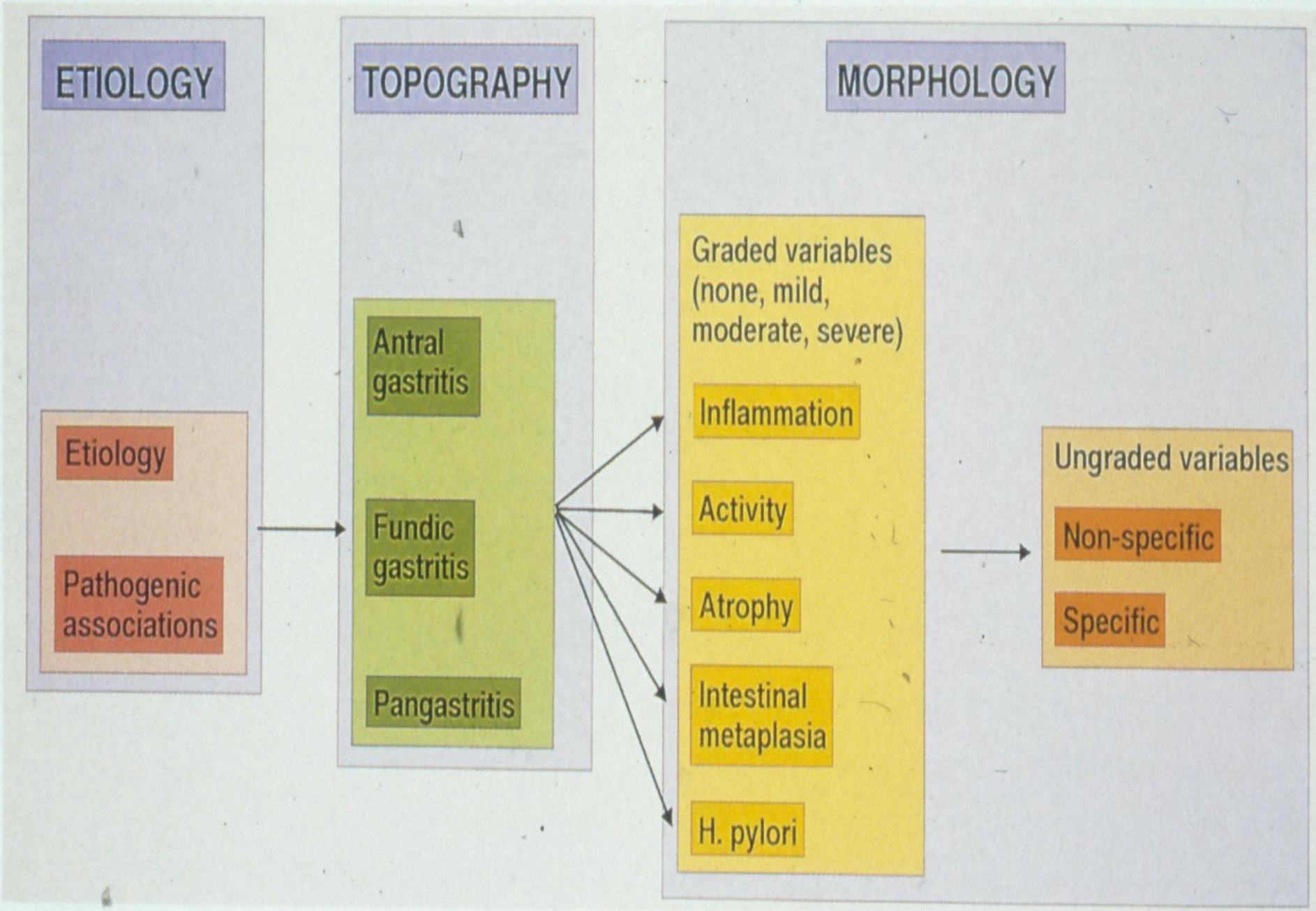
Acute gastritis
Chronic gastritis
Atrophic gastritis
Intestinal metaplasia
Dysplasia
Cancer

Houston Gastritis Workshop 1994



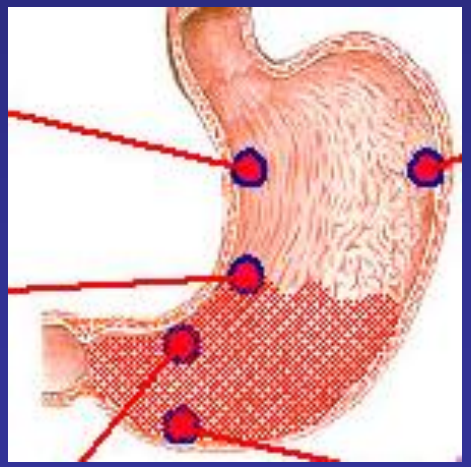
Updated Sydney System
Visual Analogue Scale

Dixon et al, Am J Surg Pathol 1996, 20:1161


ETIOLOGY
TOPOGRAPHY
MORPHOLOGY
Etiology
Pathogenic associations
Antral gastritis
Fundic gastritis
Pangastritis
Graded variables (none, mild, moderate, severe)
Inflammation
Activity
Atrophy
Intestinal metaplasia
H. pylori
Ungraded variables
Non-specific
Specific

Sampling

- Two biopsies from the distal antrum
- Two biopsies from the proximal corpus
- One from incisura angularis

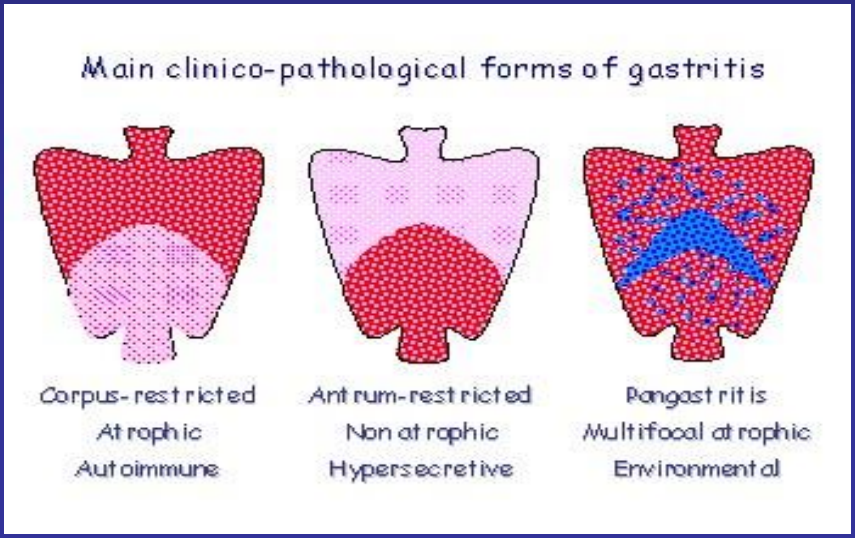


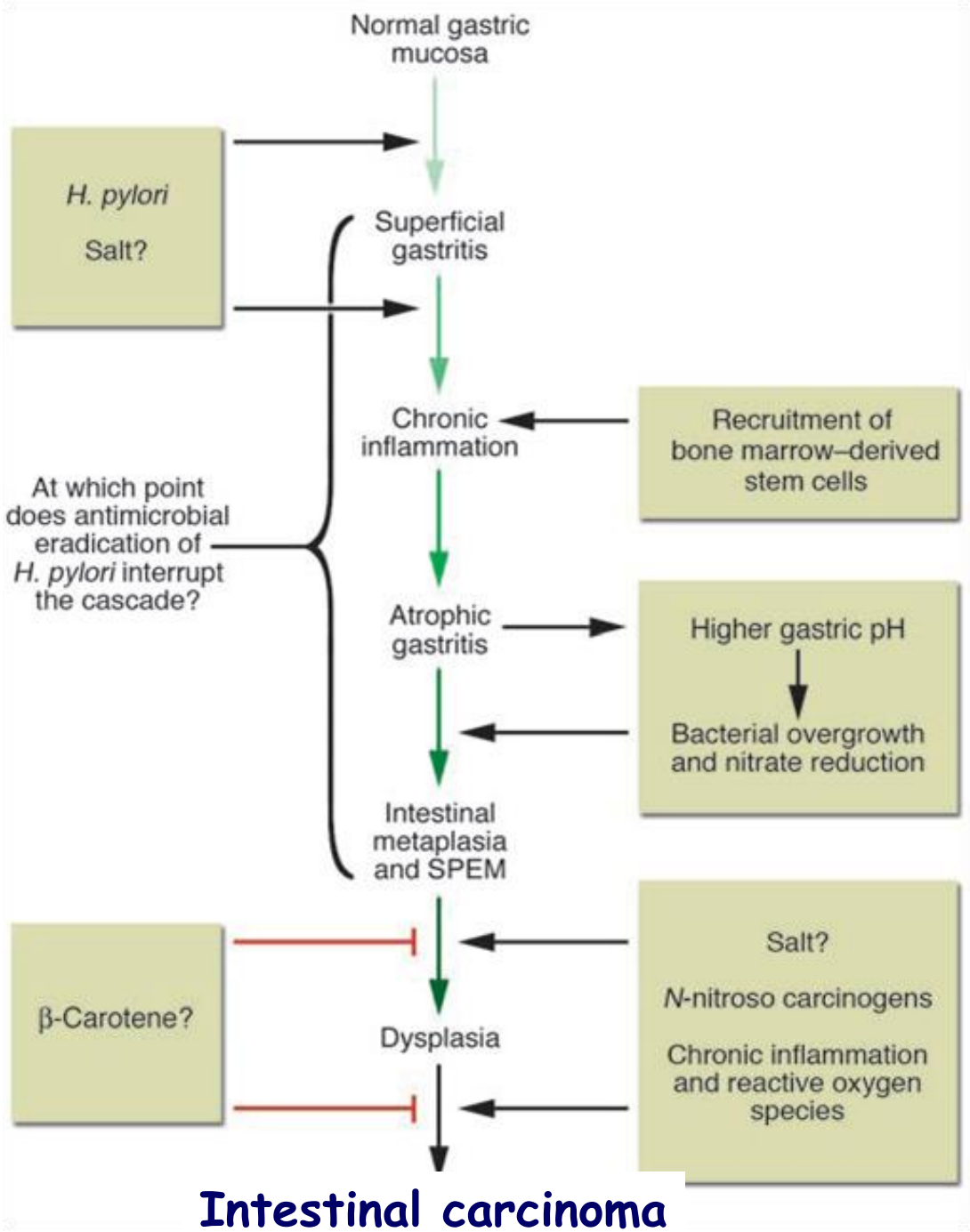
Extension of elementary lesions in each compartment

Patterns of gastritis

H.p. chronic gastritis, active, antrum - predominant
active chronic gastritis
corpus-restricted chronic atrophic gastritis (probably autoimmune)
H.p. associated multifocal atrophic gastritis, etc.

Different level of risk

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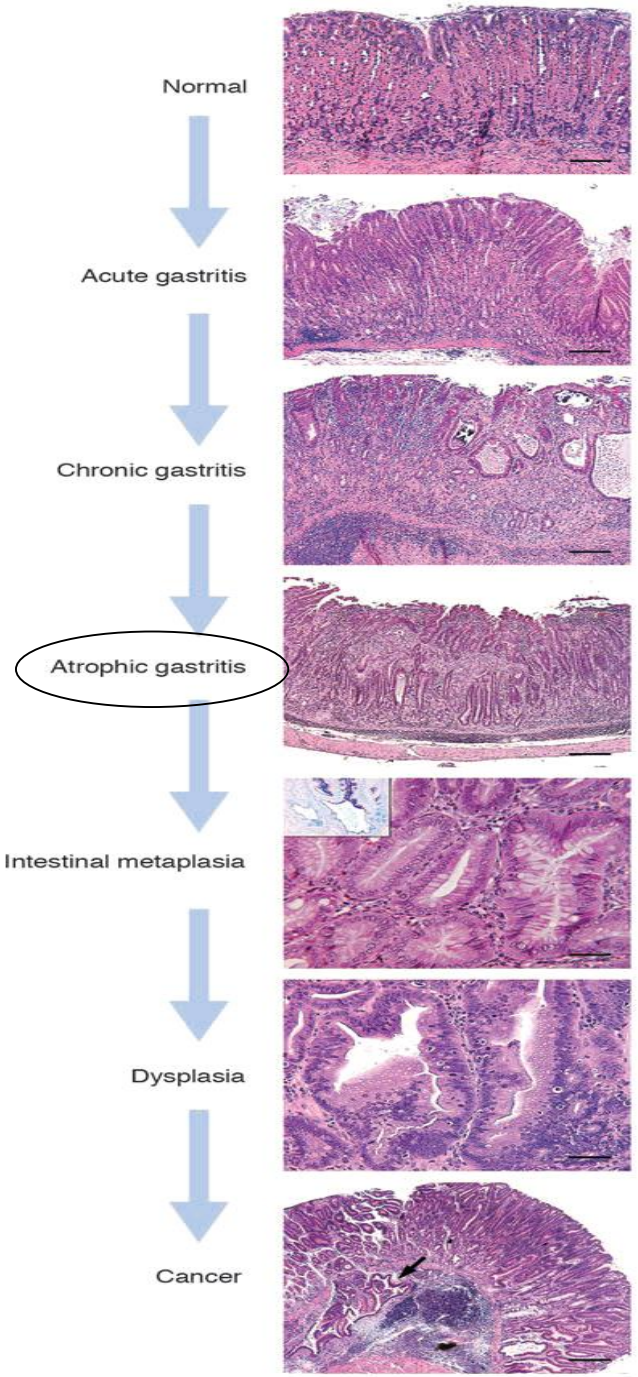
Normal
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Chronic gastritis
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Dysplasia
Cancer

Atrophy club

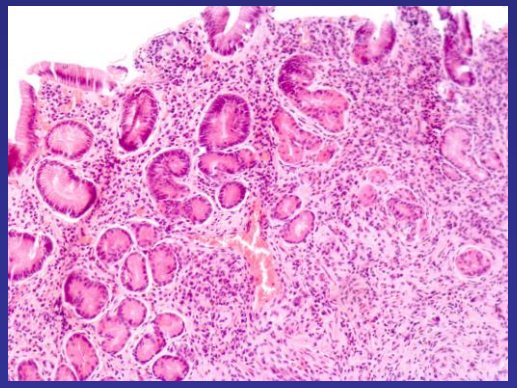
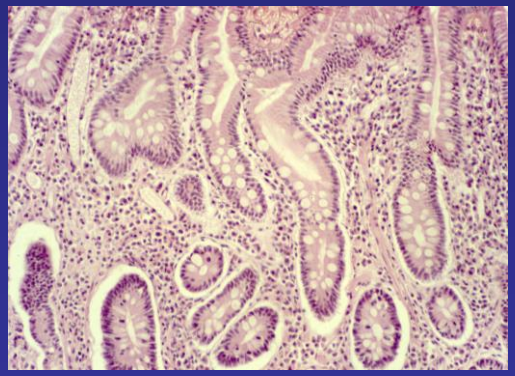
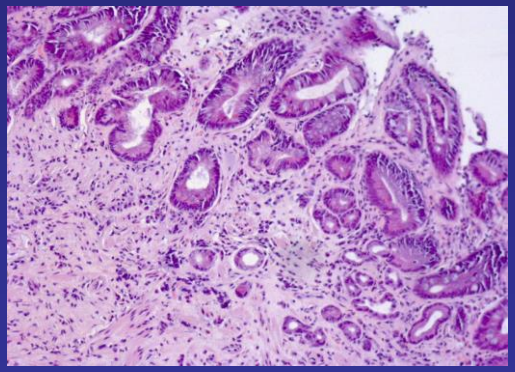
Gastric mucosal atrophy: interobserver consistency using new criteria for classification and grading

M. Rugge, P. Correa, M. F. Dixon, R. Fiocca, T. Hattori, J. Lechago, G. Leandr
A. B. Price, P. Sipponen, E. Solcia, H. Watanabe & R. M. Genta

Aliment Pharmacol Ther 2002; 16: 1249–1259.

Gastric mucosal atrophy is defined as the loss of appropriate glands

- vanishing of glands associated with fibrotic expansion of the lamina propria
- metaplastic replacement of the native glands
  intestinal metaplasia
  pseudopyloric metaplasia

Staging gastritis: an international proposal

Rugge M, Genta RM, OLGA Group

Gastroenterology 2005; 129: 1807-1808

Operative Link for Gastritis Assessment (OLGA)

OLGA Staging System

Immediate assessment of the severity of the atrophic gastritis

Prediction of the risk of gastric cancer depending on the extent of the atrophy and intestinal metaplasia

The stage of gastritis is obtained by combining the extent of atrophy scored histologically with the topography of atrophy identified by the multiple biopsies

Atrophy Score		Corpus			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
Antrum	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

Identification of a small group of patients candidated to the survaillance programs

Stage 0 - I ⇒ absent risk

Stage II ⇒ low risk

Stages III - IV (multifocal atrophic gastritis) ⇒ high risk

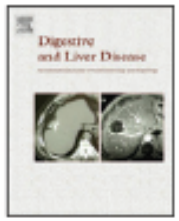
Gastric ulcer
High incidence areas

Digestive and Liver Disease 43S (2011) S373–S384

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

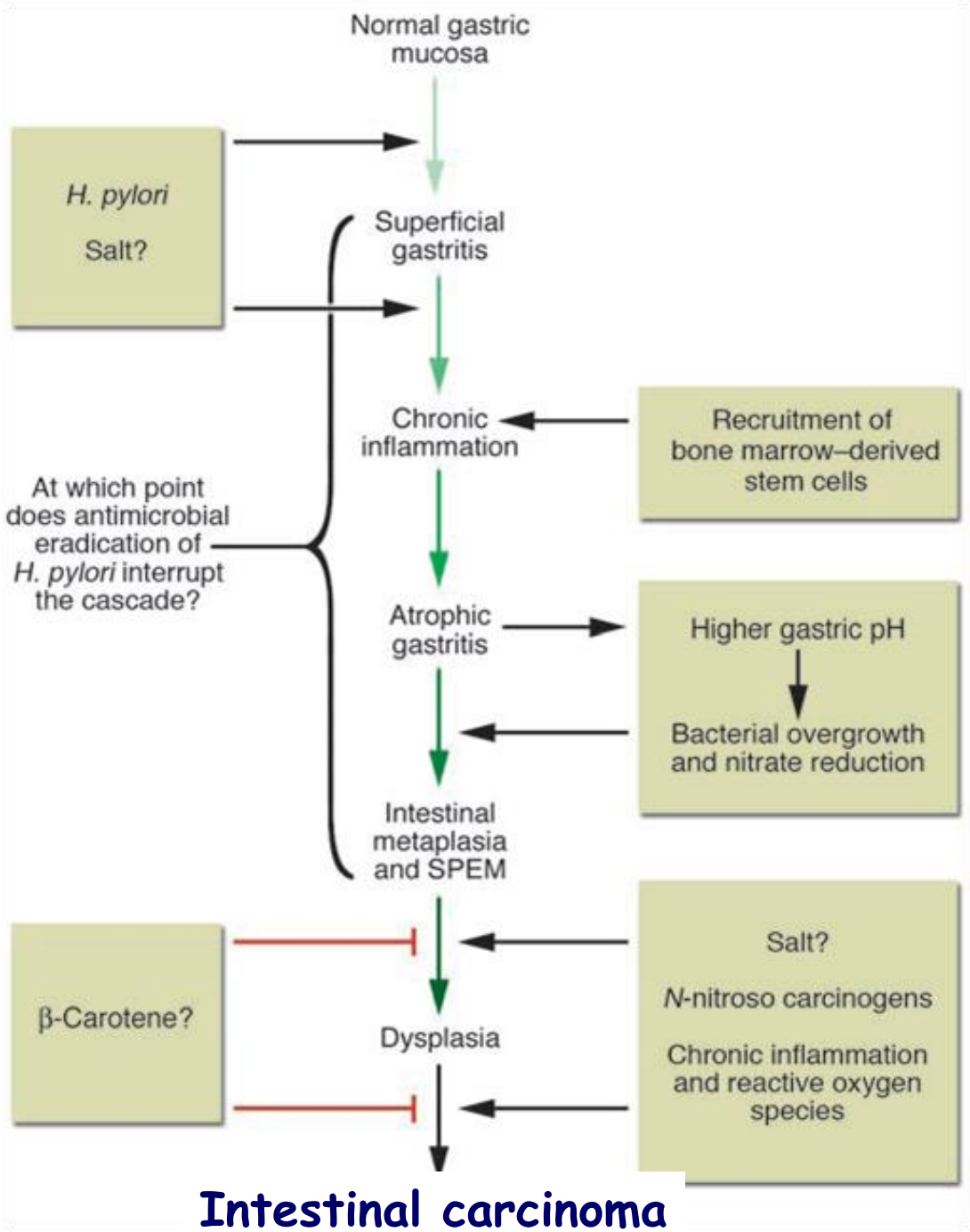


Gastritis: The histology report

Massimo Rugge[a,b,*], Gianmaria Pennelli[a], Emanuela Pilozzi[c], Matteo Fassan[a], Giuseppe Ingravallo[d], Valentina M. Russo[e], Francesco Di Mario[f]

On behalf of the "Gruppo Italiano Patologi Apparato Digerente (GIPAD)" and of the "Società Italiana di Anatomia Patologica e Citopatologia Diagnostica"/International Academy of Pathology, Italian division (SIAPEC/IAP)

[a] *Department of Medical Diagnostic Sciences & Special Therapies (Surgical Pathology & Cytopathology Section), University of Padova, Padova, Italy*
[b] *Istituto Oncologico del Veneto IOV-IRCCS, Padova, Italy*
[c] *Department of Pathology, University of Roma La Sapienza, Roma, Italy*
[d] *Department of Pathological Anatomy, University of Bari, Bari, Italy*
[e] *Department of Pathological Anatomy, Garibaldi Hospital Catania, Italy*
[f] *Department of Gastroenterology, University of Parma, Parma, Italy*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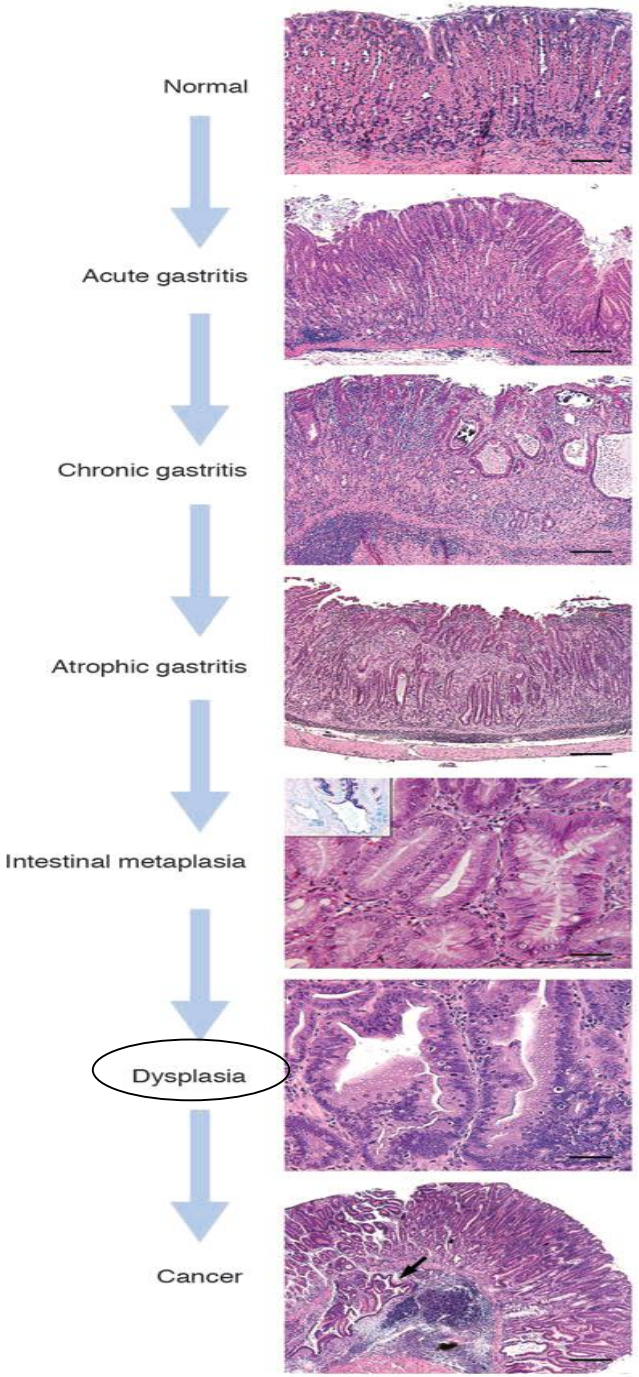
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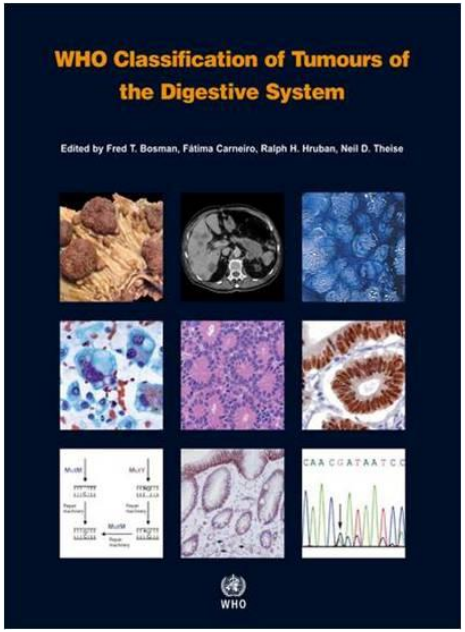
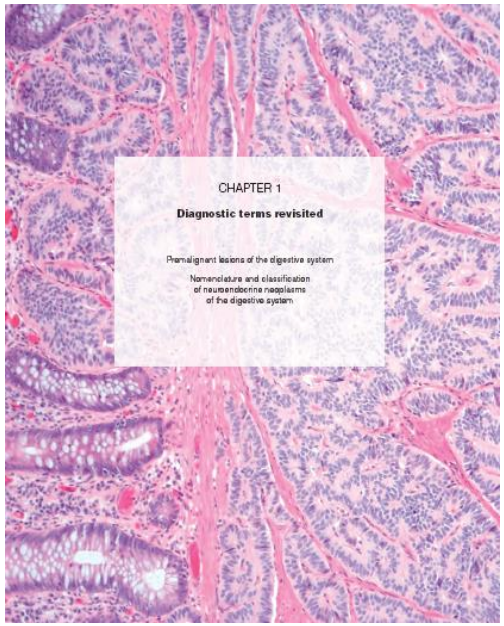
Gastric dysplasia - WHO classification (2010)





R.D. Odze
R.H. Riddell
F.T. Bosman
F. Carneiro
J.-F. Fléjou
K. Geboes
R.M. Genta
T. Hattori
R.H.Hruban
J.H. van Krieken
G.Y. Lauwers
G.J.A. Offerhaus
M. Rugge
M. Shimizu
T. Shimoda
N.D. Theise
M. Vieth

Odze RD *et al*. Premalignant lesions of the digestive system. *In*: WHO Classification of Tumours of the Digestive System, Fouth Edition. Bosman FT, Carneiro F, Hruban RH and Theise ND (eds), IARC Press: Lyon, 2010; Pp 10-12.

Recognizing that the terminology of dysplasia is entrenched in the European and particularly North-American literature, as well as in clinical practice, WHO considers that "intraepithelial neoplasia" and "dysplasia" should be considered as synonymous terms. The following categories should thus be considered:

- Negative for intraepithelial neoplasia /dysplasia*
- Indefinite for intraepithelial neoplasia /dysplasia

- Low -grade intraepithelial neoplasia/dysplasia
- High-grade intraepithelial neoplasia/dysplasia

- Intramucosal invasive neoplasia/intramucosal carcinoma

---

*In stomach, and as far as these guidelines is concerned, *category 1* includes lesions such as atrophic chronic gastritis and intestinal metaplasia.

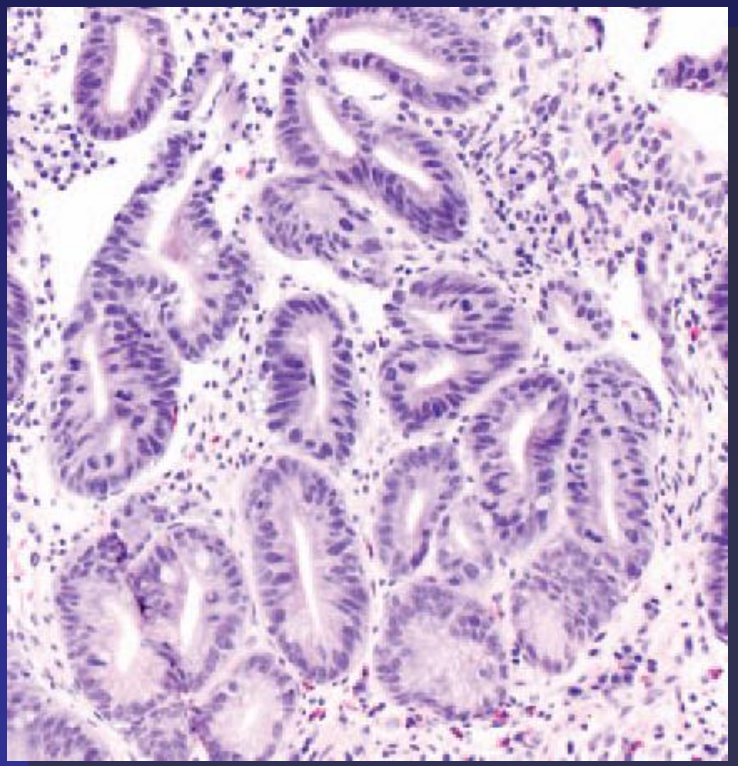
WHO – 4th Edition, 2010

Indefinite for intra-epithelial neoplasia/dysplasia

The use of this category is favoured where there is doubt as to whether a lesion is neoplastic or non-neoplastic (i.e. reactive or regenerative), particularly in small biopsies exhibiting inflammation.

This term represents a pragmatic solution to an ambiguous morphological pattern but it is not a final diagnosis.

It should not be seen as a diagnostic failure, but, rather, as the response to a real practical issue.



WHO classification of tumors of the digestive system 2010

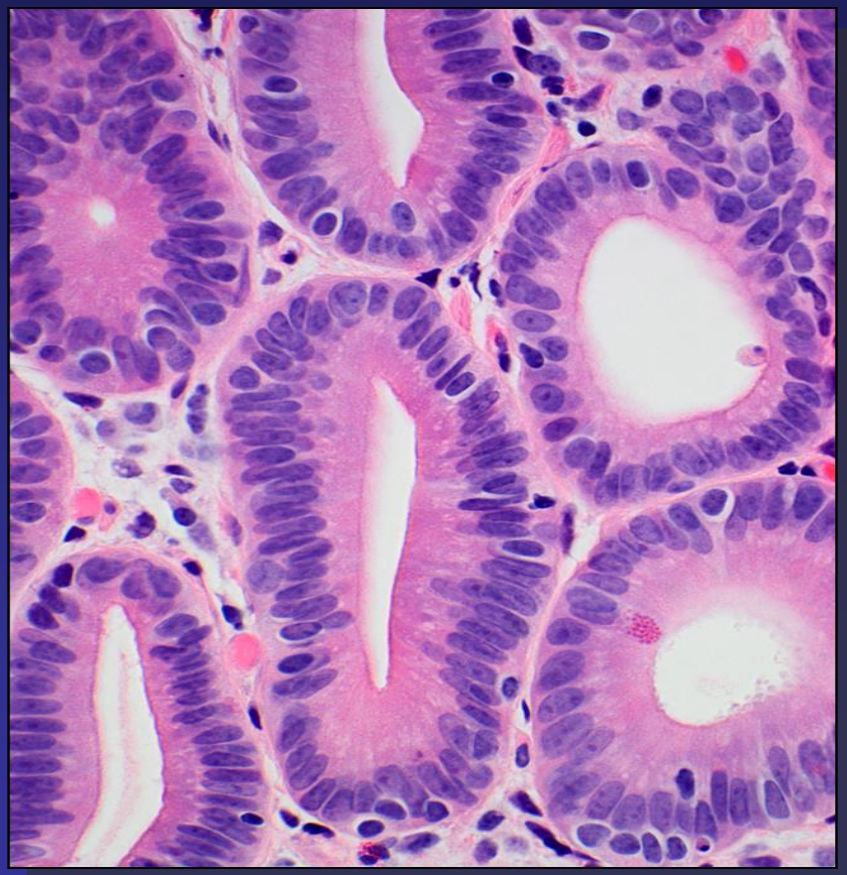
Low-grade intra-epithelial neoplasia/dysplasia

Minimal architectural disarray

Mild/moderate cytological atypia

Nuclei are elongated, polarised, basally located

Mitotic activity is mild/moderate



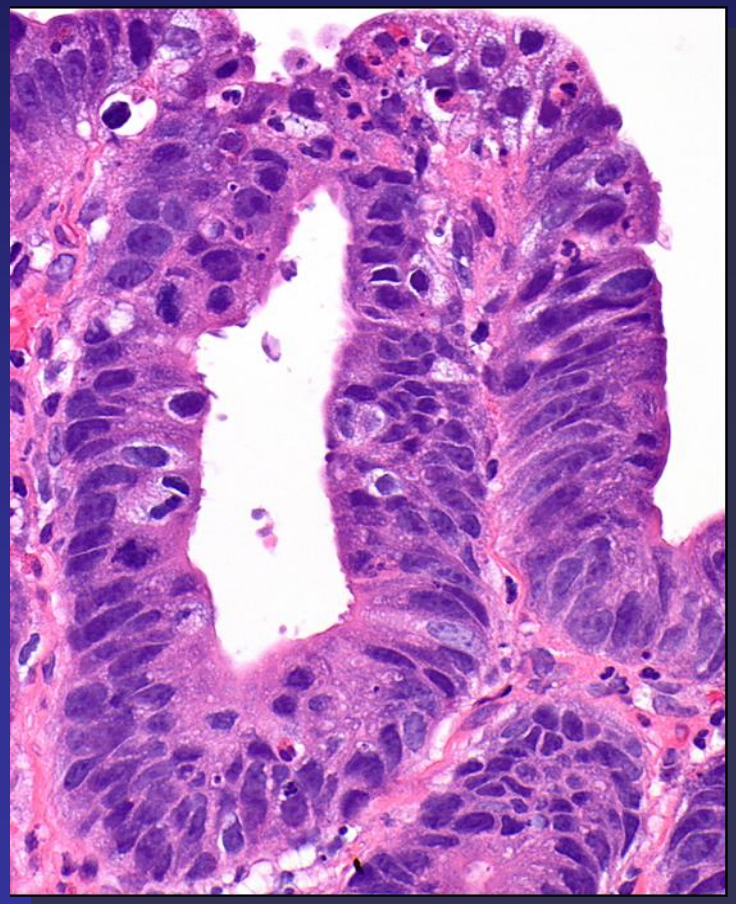
High-grade intra-epithelial neoplasia/dysplasia

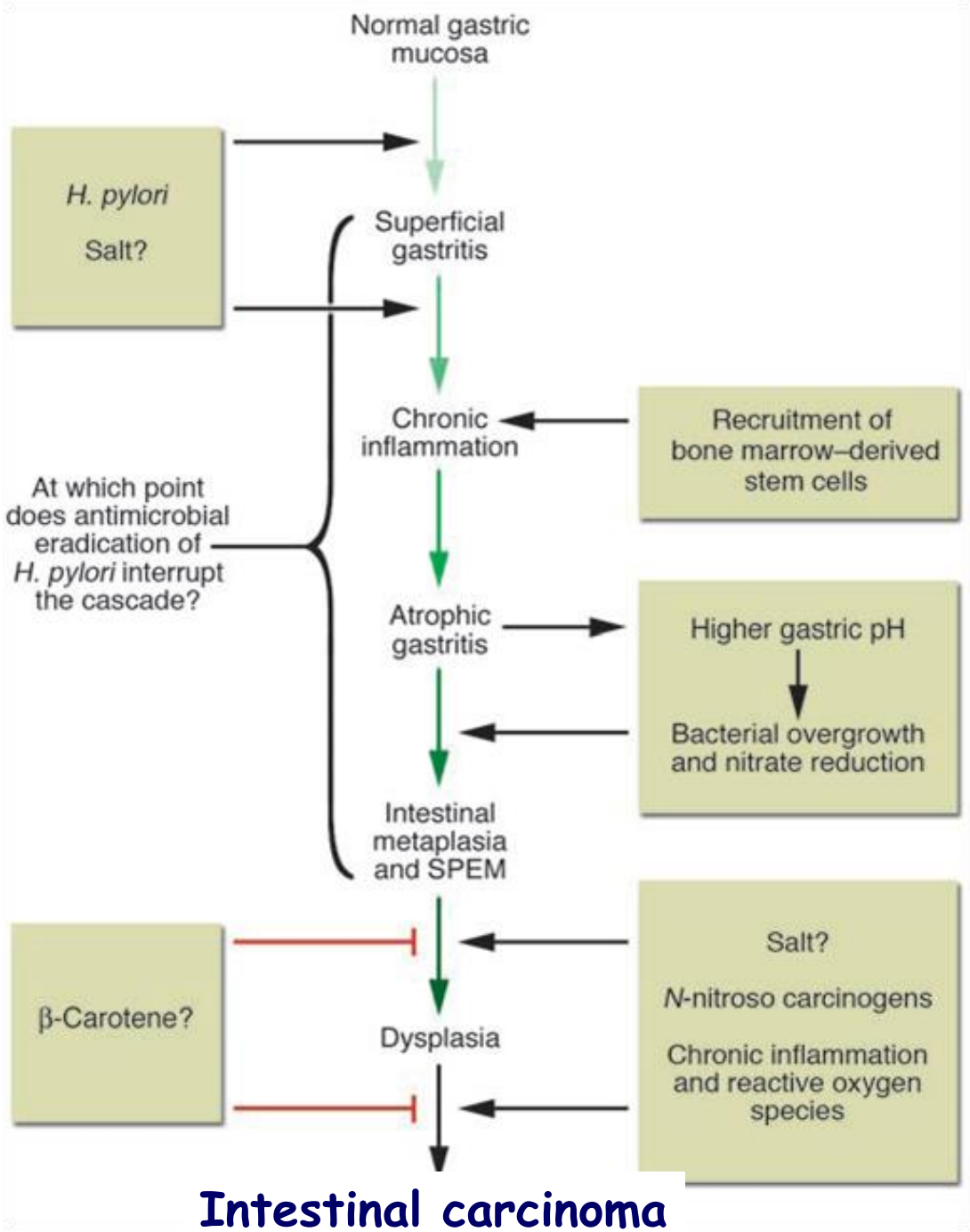
Pronounced architectural disarray

High nucleus/cytoplasm ratio

Numerous mitoses, often atypical

Nuclei frequently extend towards the luminal half of the gland

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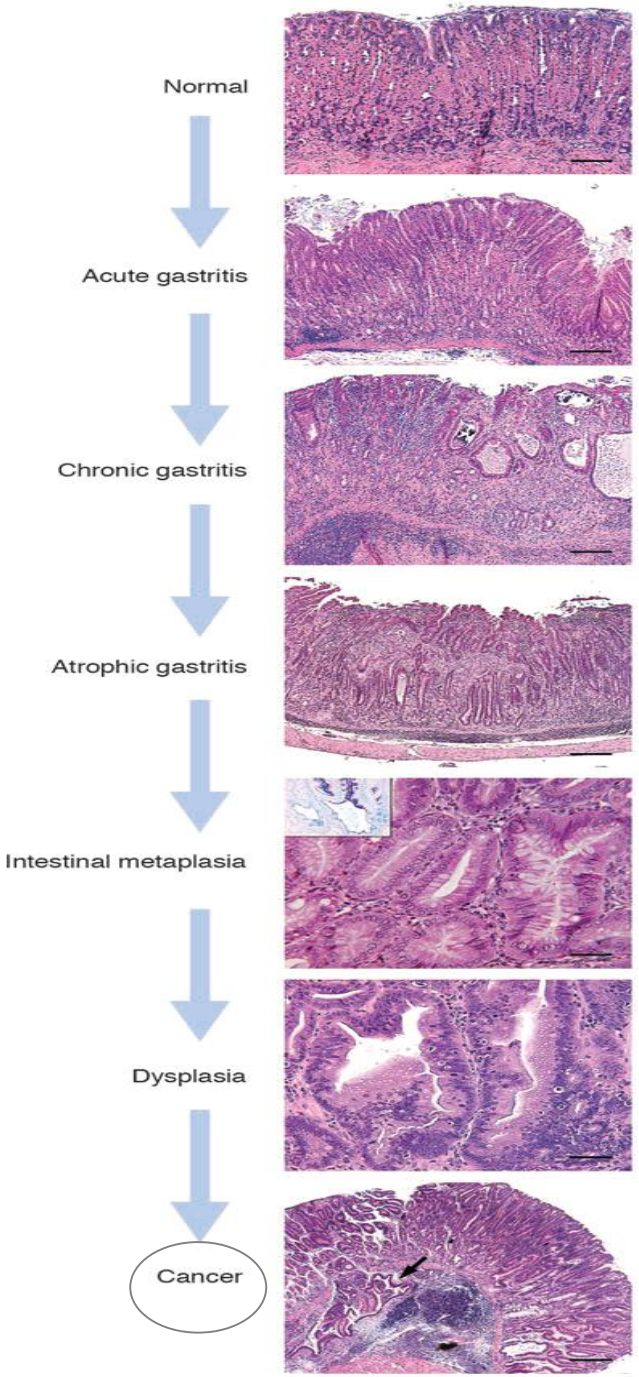
Normal
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Atrophic gastritis
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Dysplasia
Cancer

Intramucosal carcinoma

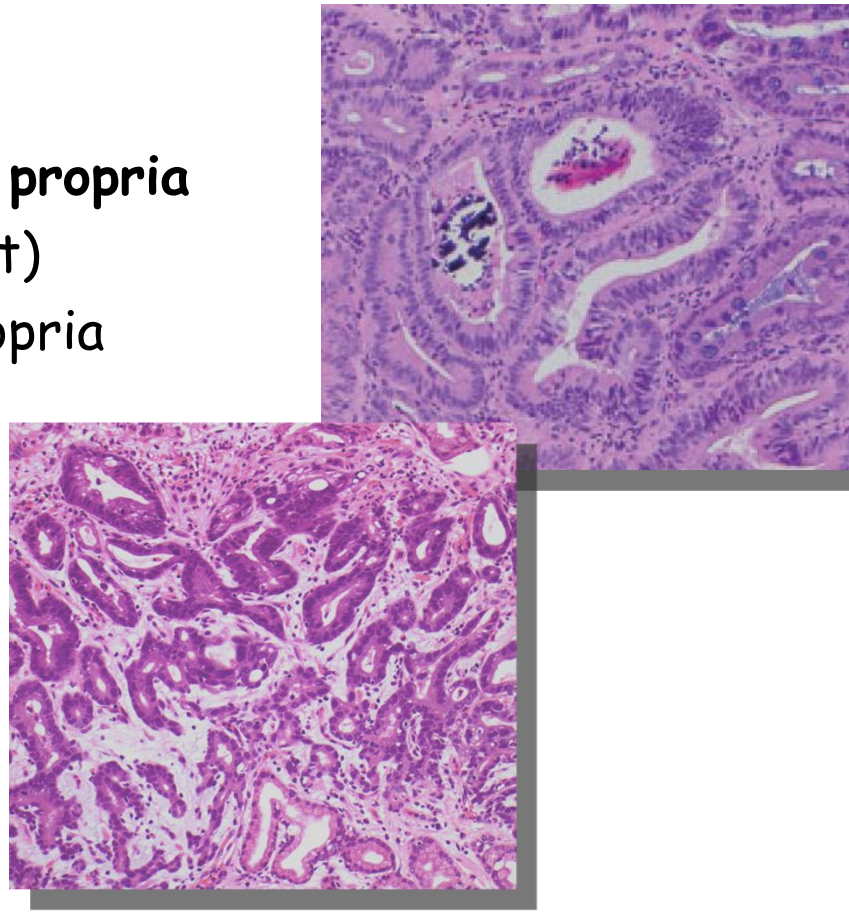
Defines carcinoma that invades lamina propria

Desmoplastic changes (minimal or absent)

Single infiltrating cells in the lamina propria

Distinct structural anomalies, such as

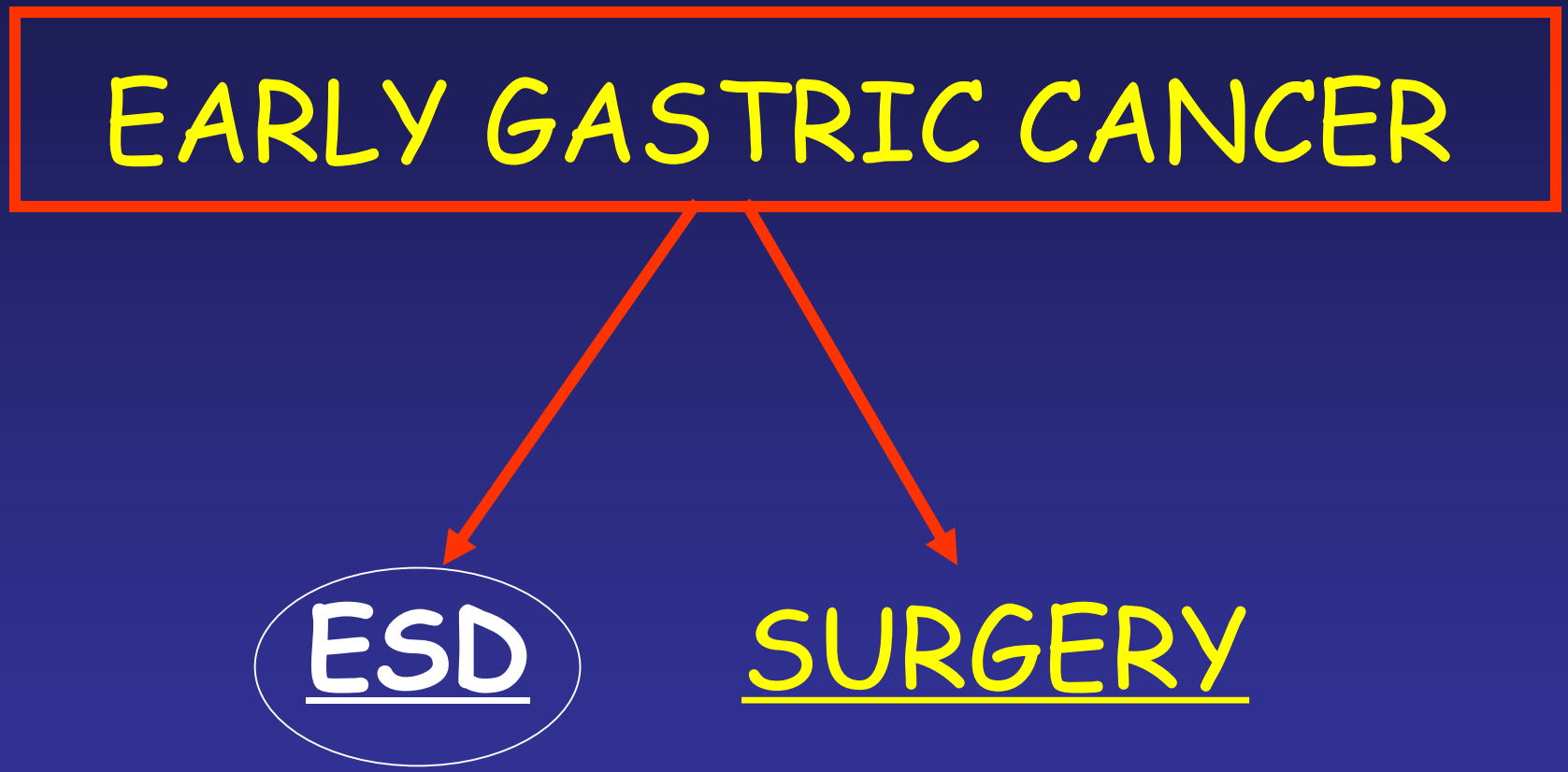
- marked glandular crowding
- excessive branching
- budding
- intraluminal necrotic debris



WHO classification of tumors of the digestive system 2010

DEFINITION OF EGC (MURAKAMI, 1971)

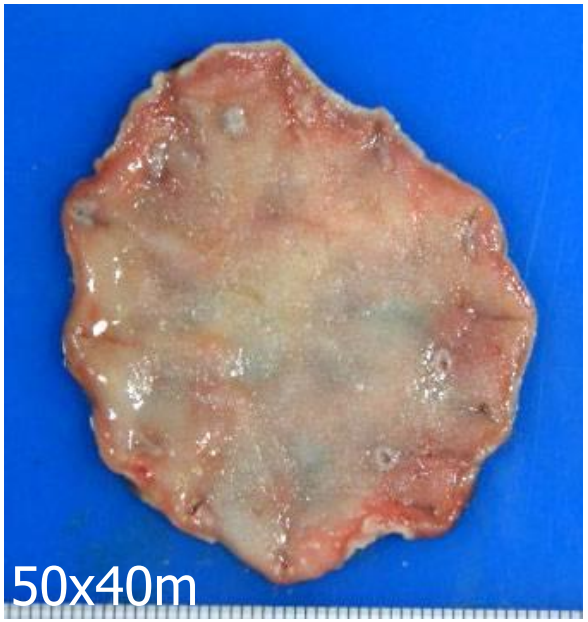
A TUMOUR WHICH INVADES MUCOSA AND/OR SUBMUCOSA, REGARDLESS OF LYMPH NODE STATUS

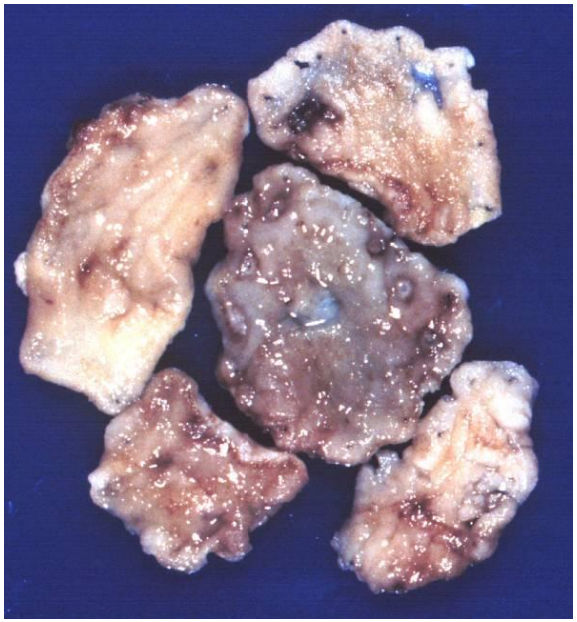

EARLY GASTRIC CANCER
ESD
SURGERY

DIAGNOSIS AND THERAPY

- High Grade Intra-epithelial Neoplasia/Dysplasia
- Intra-Mucosal Carcinoma (Early Gastric Cancer)
- Endoscopist
- Endoscopic Submucosal Resection (ESD)
- Pathologist

ESD vs EMR





Pictures from T Sano, Tokyo

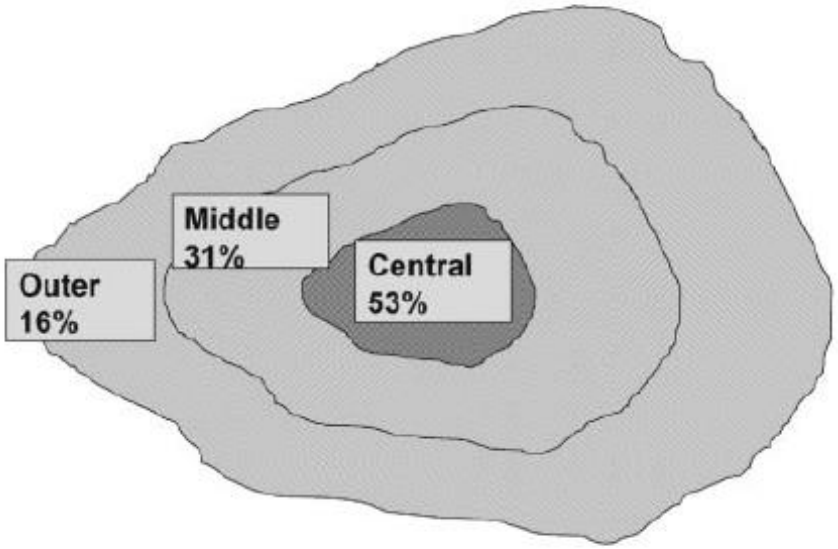
92% En bloc
82% R0
<1% recurrence
4% perforation

48% Piecemeal
42% R0
6% recurrence
<1% perforation

Meta-analysis by Lian J et al Gastrointestinal Endoscopy 76: 763-770, 2012

Piecemeal resection may impact on accurate tumour depth assessment.

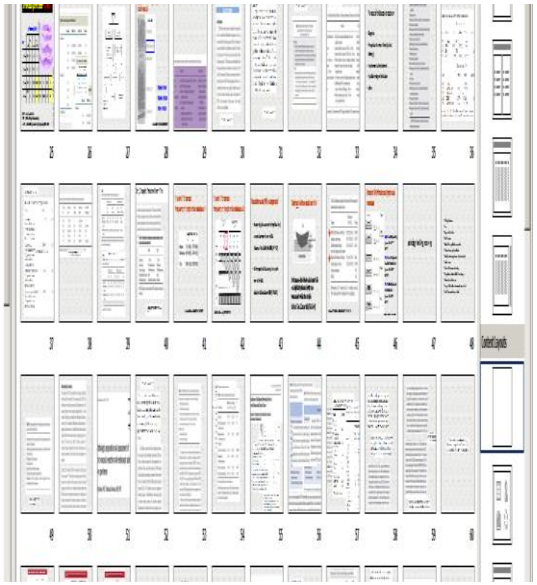
Characteristics	Number	Central	Middle	Outer	*P**
Macro type					
Raised	66	35	23	8	0.967
Depressed	129	68	37	24	
Tumor size (mm)					
≤20	93	47	25	21	0.542
>20	102	56	35	11	
Ulcer finding					
No	122	65	35	22	0.868
Yes	73	38	25	10	
Location					
U	37	22	13	2	0.105
M	99	57	23	19	
L	59	24	24	11	
ly–v					
No	162	86	46	30	0.869
Yes	33	17	14	2	
Histological type					
Well	162	84	47	31	0.156
Mod	30	18	11	1	
Pap	3	1	2	0	
Total	195	103	60	32	

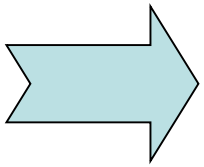


True tumour depth can only be assessed if the entire lesion is resected in one piece and there are no burn effects inside the lesion.

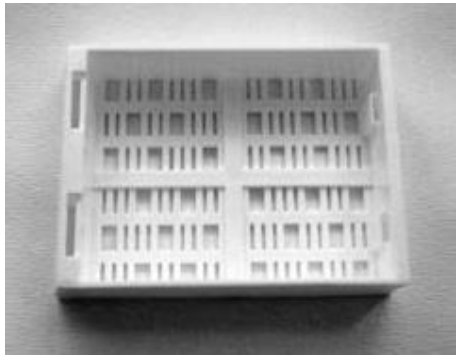
Jpn J Clin Oncol 2005;35(10)587–590

From endoscopist to pathologist



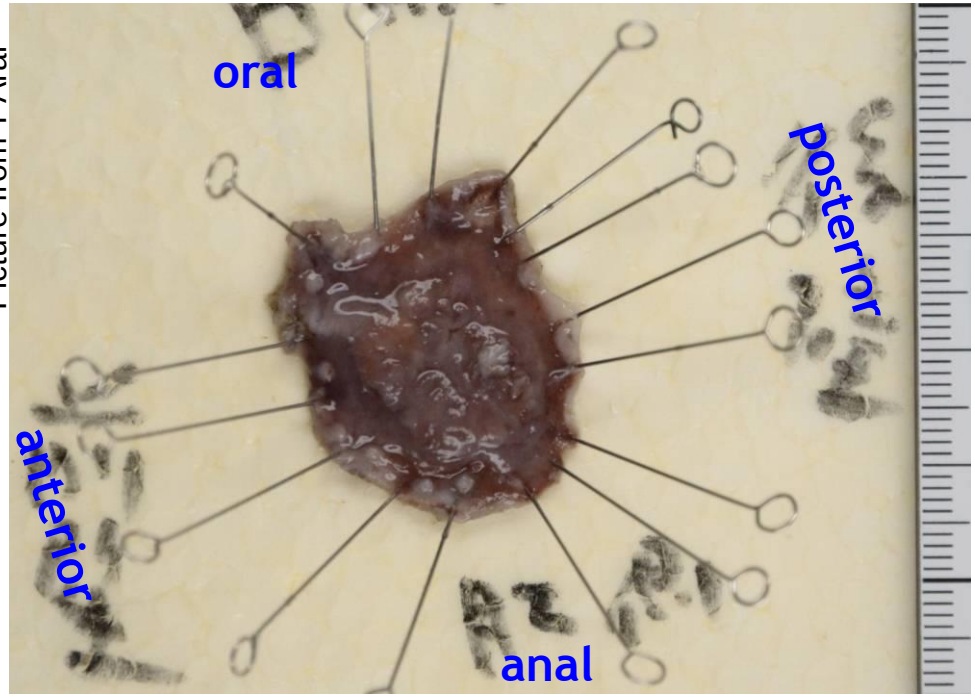


Prevent curling up of small specimens

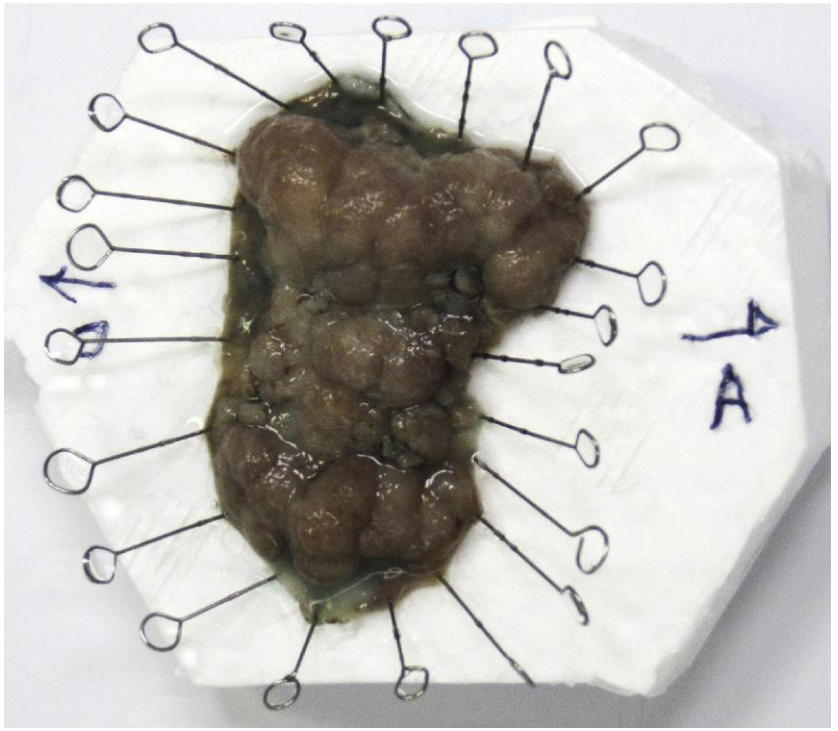


Place specimen in between ‘histology sponges’ regular size cassette or megablock cassette.

Specimen pinned out by endoscopist



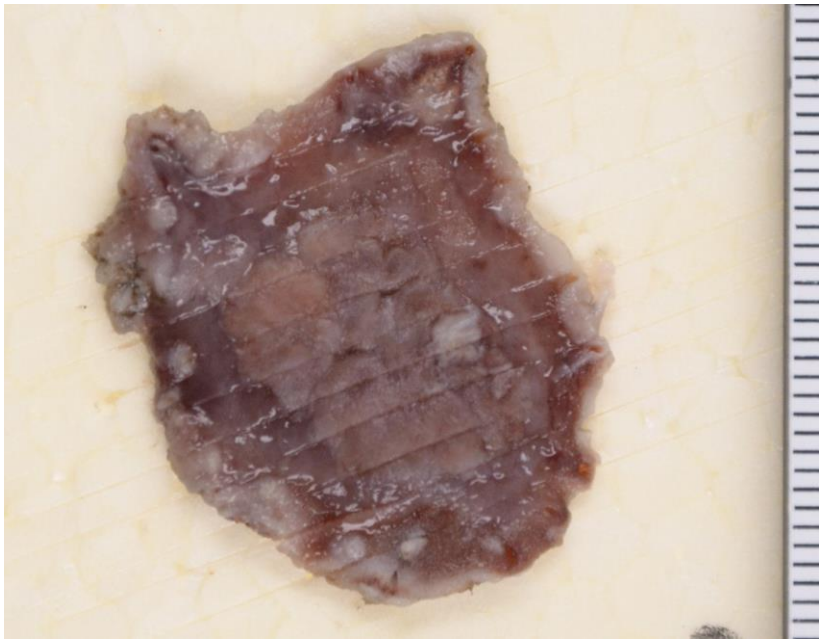
Picture from T Arai



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

The larger the specimen the more important it becomes that the specimen is pinned out and ‘orientated’ to facilitate repeat EMR/ESD for positive lateral margins.

Macroscopic description

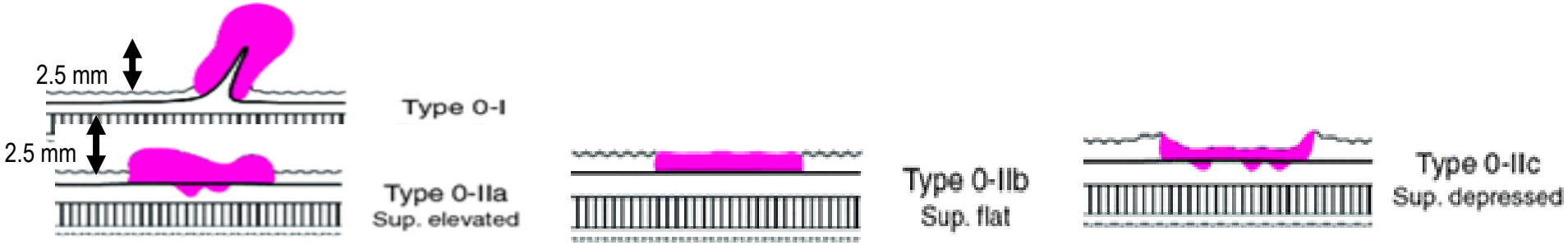


Photograph (optional)

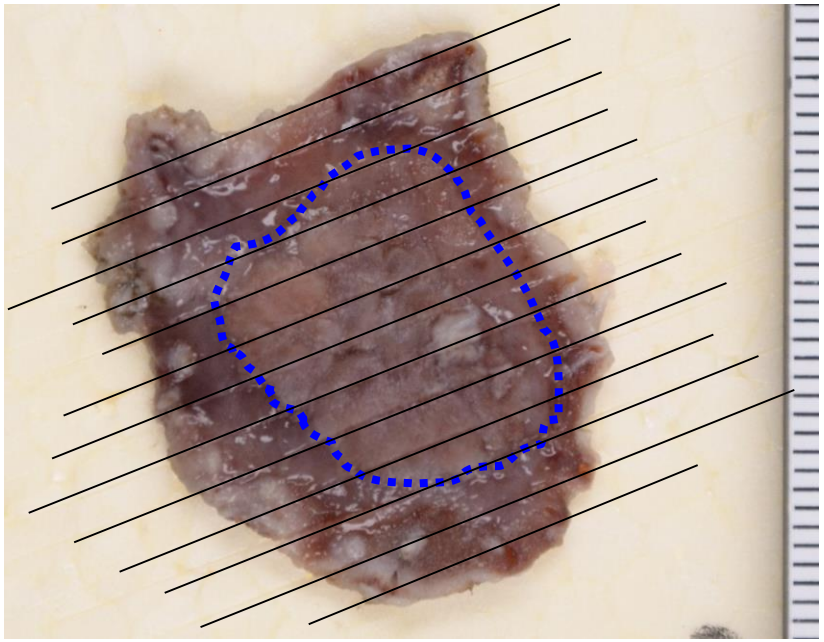
Measurements:
- Specimen in 3 dimensions
- Lesion incl. distance to margin

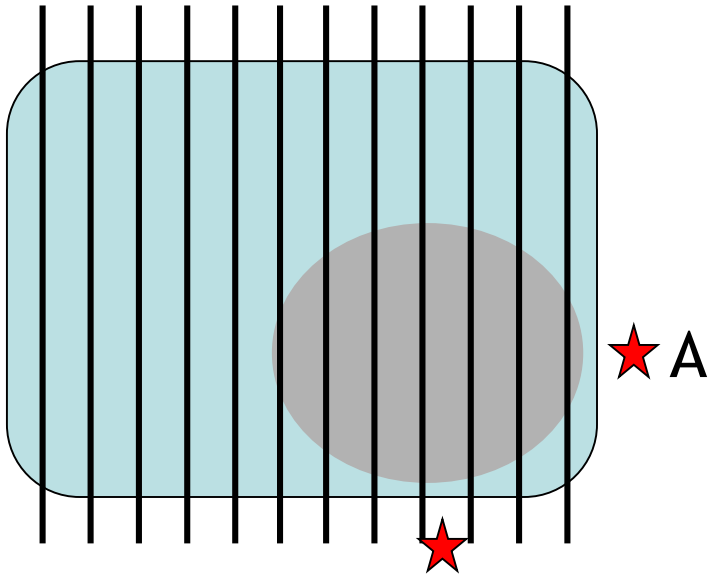
Determine macroscopic type
if not provided by endoscopist
(Paris classification)

Ink deep margin (optional)



Cutting the specimen





2 to max 3mm wide sections

Direction optimised to demonstrate distance to lateral margin.

If lesion in the centre, then cut perpendicular to longest axis.

Block out sections systematically from ‘one end to the other’ and ask to be cut ‘on edge’.

If lesion close to two lateral margins, then position section (A) ‘flat’ to cut from the margin towards the lesion.

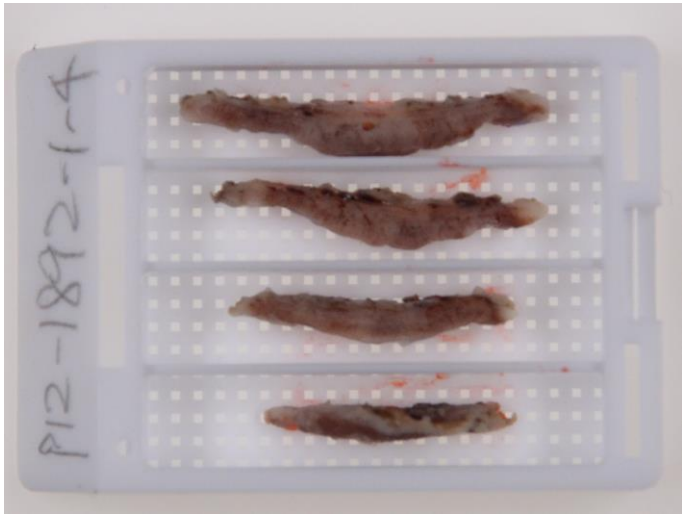
Processing the specimen

Mojtahed A et al

3 sections in a ‘half width megablock’
> ideal for large ESDs

(Note: this type of cassette is currently not available in the EU)

Another option by M Vieth from Bayreuth



Regular size cassette with dividers

Histological evaluation – Resection margin

1. **Deep (vertical) margin**
   VM0 – not involved (measure distance to margin)
   VM1 – involved VMx – cannot be assessed

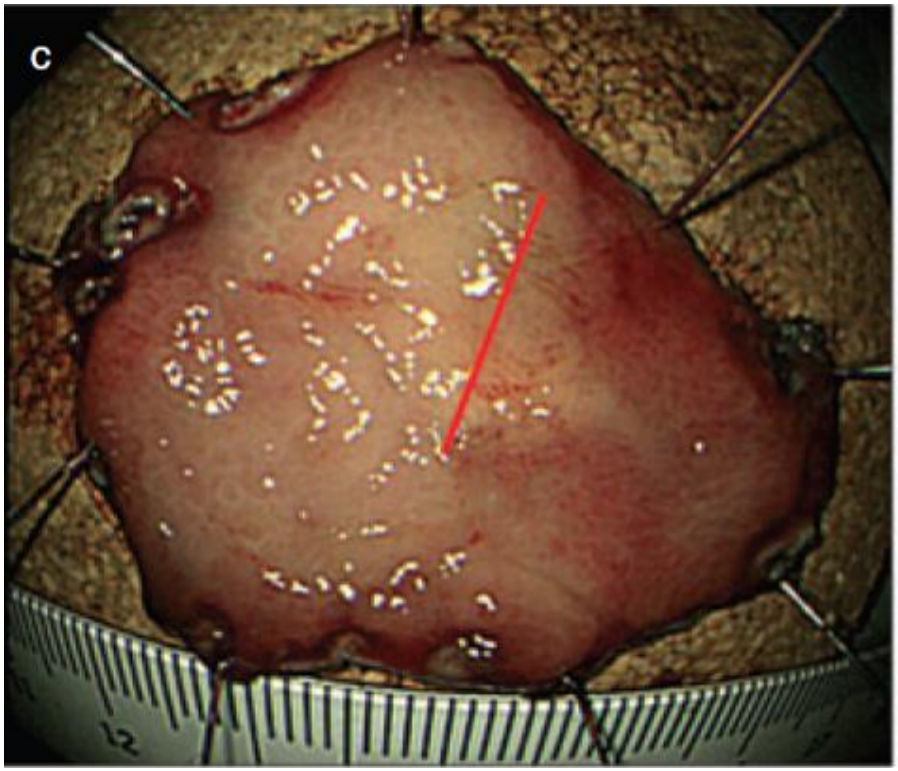
2. **Lateral (horizontal) margin**
   HM0 – not involved (measure distance to margin)
   = No cancer in first and last section. No cancer at both sides of all other sections.

   HM1 – involved.
   Record number of sections with HM.
   If one section HM1 > no further treatment,
   if more than 1 section positive > immediate repeat EMR/ESD

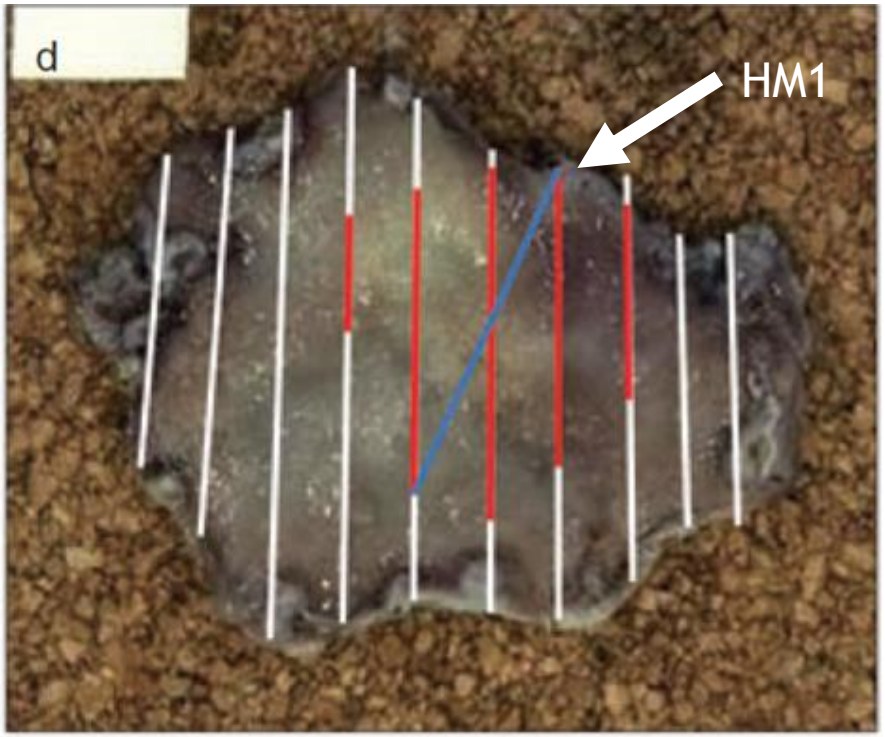
   HMx – cannot be assessed

Histological evaluation – Size of tumour

Size of the tumour needs to be confirmed on histology as size may be underestimated on macroscopy



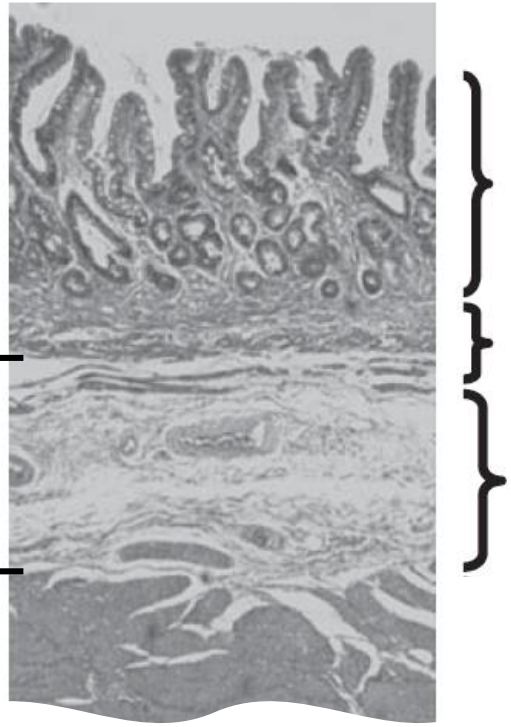
Max tumour diameter (macro): 15mm (red line)



Max tumour diameter (micro): 23mm (blue line), also R1 (HM)

Digestive Endoscopy (2010) **22**, 112–118

Histological evaluation – Depth of invasion ‘extended’ TNM classification



pT1a

pT1b

pT2

M — m1 (in situ/HGD)

M — m2 (lamina propria)

MM — m3

SM — sm1 (≤ 500 µm; SCC: ≤ 200 µm)

SM — sm2 (> 500 µm; SCC: > 200 µm)

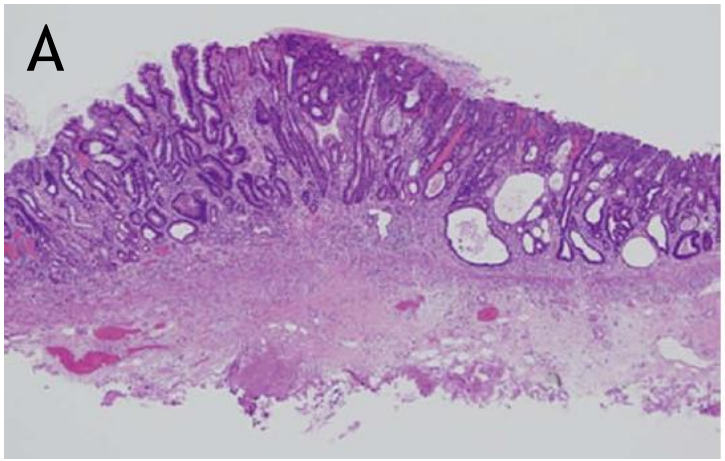
Alternatively proposed:
sm1: (1/3), sm2: (2/3), sm3: (3/3)

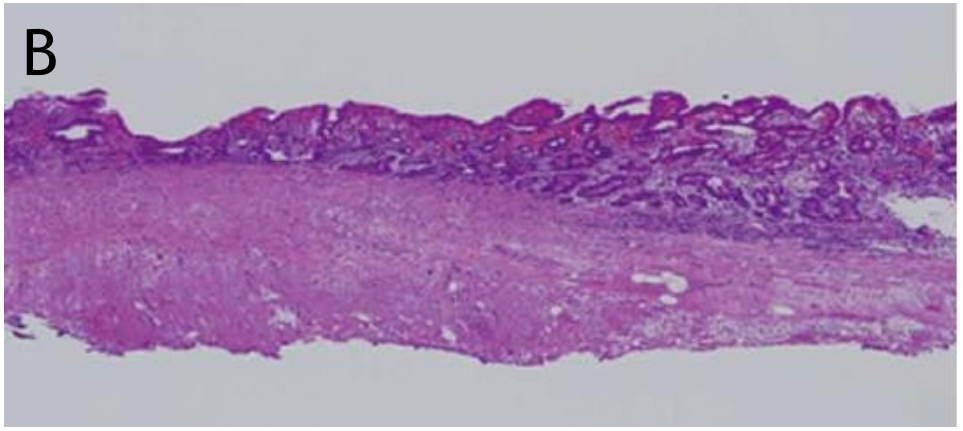
Notes:
Depth of invasion is only assessed if the deep margin is negative.
Always provide absolute measurement from muscularis mucosae.

Histological evaluation – Ulceration/scar

UL(-): intratumoral ulcer or ulcer scar is absent

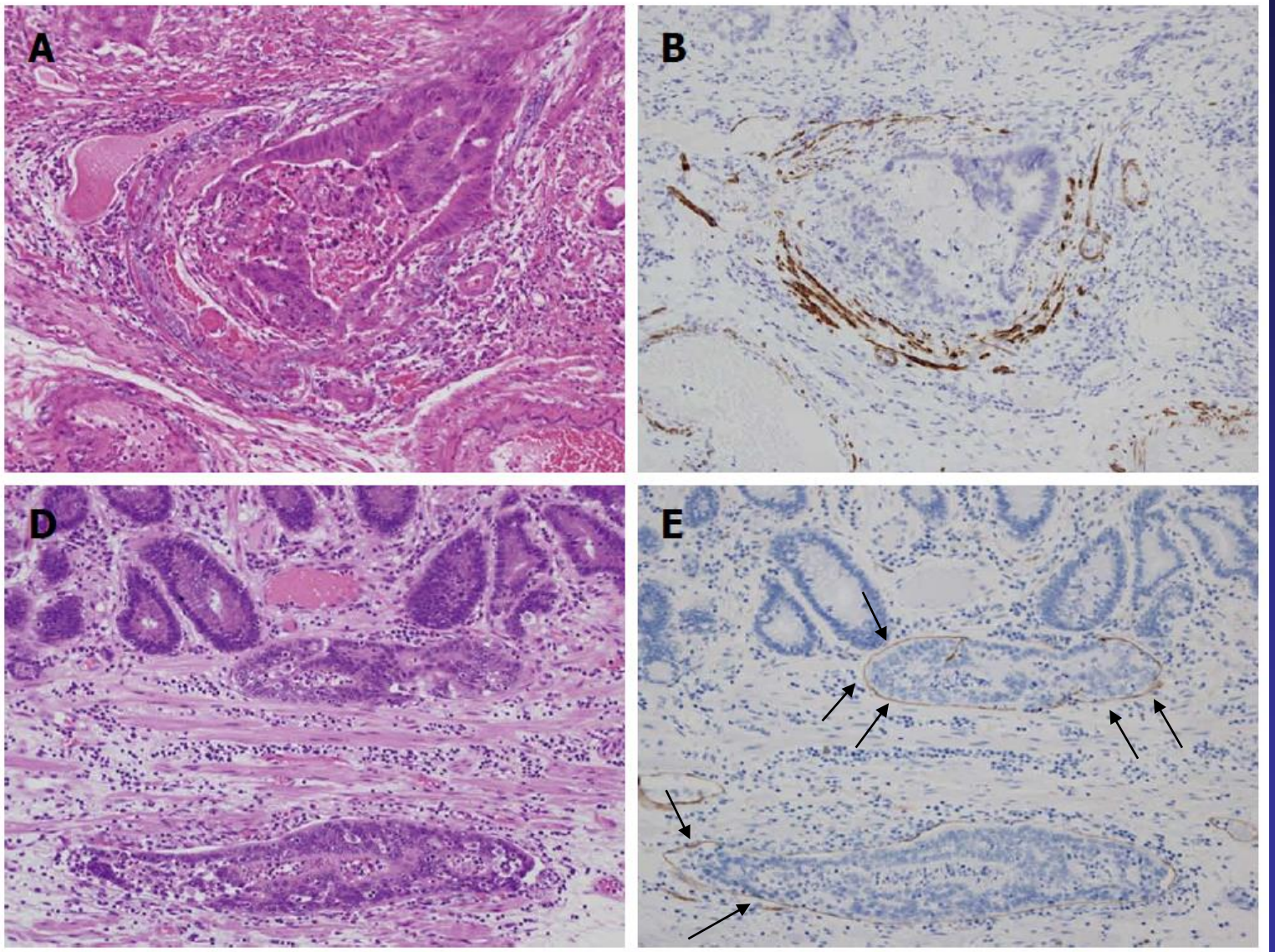
UL(+): intratumoral ulcer or ulcer scar is present





Challenge:
Scarring due to biopsy (A: usually small and circumscribed) vs. scarring after ulceration (B: usually expansive lesion).
Only scar due to tumour ulceration counts!

Histological evaluation – Lymphovascular invasion



Desmin for smooth muscle in the vessel wall

CD31/34 for endothelial cells

D2-40 for lymphatic endothelial cells

Curative resection (standard criteria)

- en-bloc resection of lesion
- tumour size ≤ 2cm
- Intestinal differentiated type
- intramucosal
- negative resection margins (HM0, VM0)
- no lymphovascular invasion (L0, V0)
- no ulcer or ulcer scar (UL-)

ESD Curative resection (GIRCG Guidelines)
Standard Criteria of Japanese Gastric Cancer Association

Gastric Cancer
DOI 10.1007/s10120-011-0042-4

SPECIAL ARTICLE

Japanese gastric cancer treatment guidelines 2010 (ver. 3)

Japanese Gastric Cancer Association

Gastric Cancer
DOI 10.1007/s10120-016-0615-3

SPECIAL ARTICLE

The Italian Research Group for Gastric Cancer (GIRCG) guidelines for gastric cancer staging and treatment: 2015

Giovanni De Manzoni[1] · Daniele Marrelli[1] · Gian Luca Baiocchi[1] · Paolo Morgagni[1] · Luca Saragoni[1] · Maurizio Degiuli[1] · Annibale Donini[1] ·

- Tumour size ≤ 2cm
- Intestinal differentiated type
- intramucosal
- negative resection margins (HM0, VM0)
- no lymphovascular invasion (L0, V0)
- no intratumoral ulcer or ulcer scar (UL-)

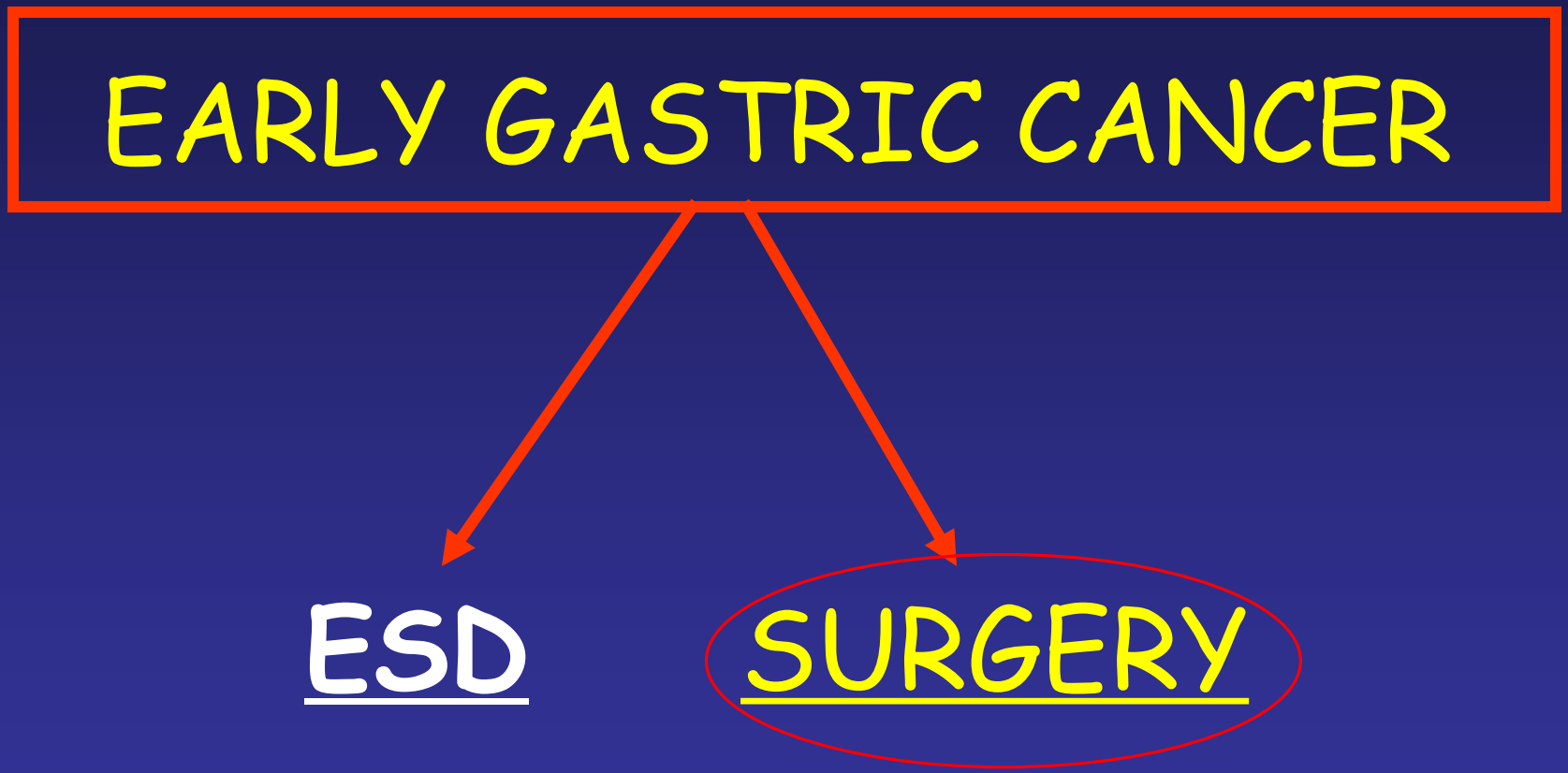
Frequency of lymph node metastases
Mucosal and submucosal gastric cancer

			pT1a		pT1b	
Author	**Year**	**Origin**	**n**	**% LNM**	**n**	**% LNM**
Folli et al[32]	1995	Italy	117	4	106	23
Hayes et al[33]	1996	Germany	14	21	14	64
Bösing et al[19]	1998	Germany	33	9	24	17
Popiela et al[22]	2002	Poland	113	6	125	21
Roviello et al[28]	2006	Italy	330	5	322	24
Hölscher et al	2009	Germany	47	11	79	25
		Europe	654	6.5	670	23.9
Kitamura et al[34]	1997	Japan	326	1	308	16
Tachibana et al[20]	1999	Japan	59	2	41	32
Skoropad et al[35]	2005	Russia	60	0	89	20
Nasu et al[36]	2006	Japan	169	5	118	24
Ishikawa et al[37]	2007	Japan	156	4	122	23
Xu et al[38]	2007	China	152	6	170	22
Ha et al[39]	2008	Korea	847	2	673	23
Park et al[4]	2008	Korea	118	3	116	22
Ye et al[5]	2008	Korea	339	3	252	27
		Asia	2226	2.7	1889	22.1
Total		All	2880	3.2	2559	22.5

(*Ann Surg* 2009;250: 791–797)

Minimum items for EMR/ESD pathology report

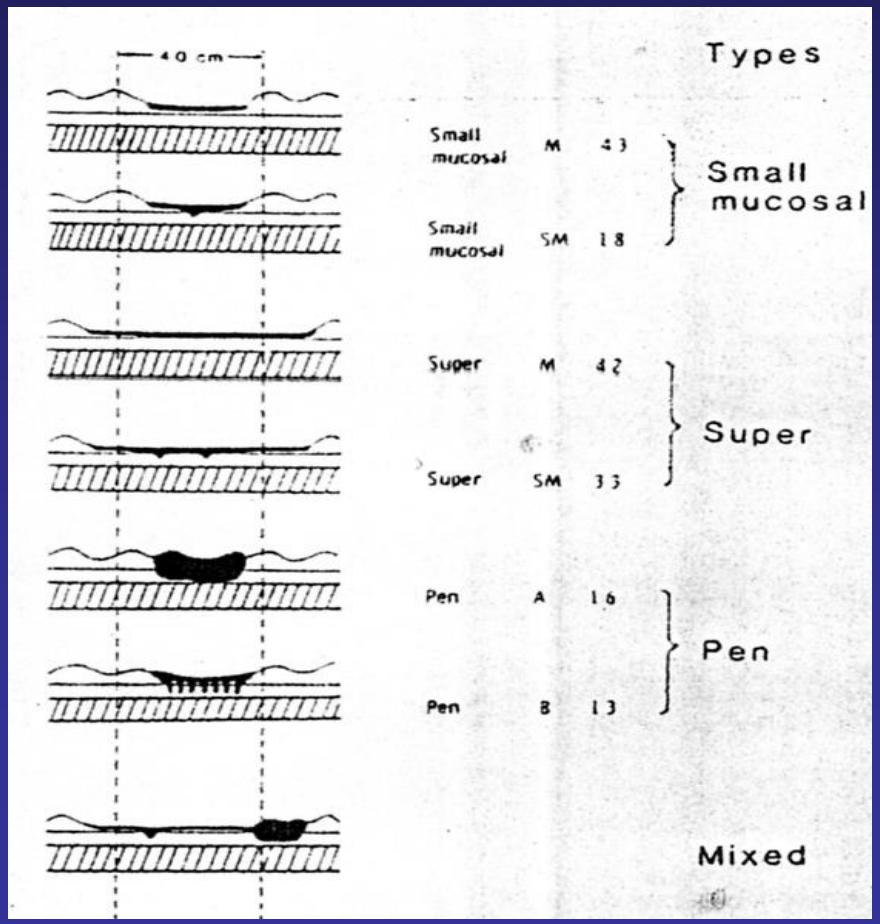
- Number of specimens (en bloc vs. piecemeal resection)
- Size of the specimen, size of the lesion (macro/micro)
- Macroscopic tumour type (Paris classification)
- Histological tumour type (different. vs. undifferent.)
- Depth of invasion
- Presence of intratumoral ulcer
- Presence of lymphovascular invasion
- Resection margin status (deep and lateral, distance)
- Curative resection (yes/no)


EARLY GASTRIC CANCER
ESD
SURGERY

HISTOLOGY REPORT (EARLY GASTRIC CANCER)

- Histotype (Classifications of Lauren and WHO)
- Histological grade (WHO)
- Depth of neoplastic infiltration (pT)
- Pattern of invasion (Kodama's classification)
- Presence/absence of lymphovascular invasion
- Margins status
- Total number of examined lymph nodes
- Number of metastatic lymph nodes over the total number of examined nodes (ratio)
- Staging according to pTNM (8th Edition)
- Topography of lymph node stations (Maruyama's classification)

EARLY GASTRIC CANCER SURGICAL SPECIMENS



Kodama

(growth patterns of EGC)

5 AND 10-YEAR CUMULATIVE INCIDENCE FOR GASTRIC CANCER SPECIFIC MORTALITY FOR KODAMA'S TYPES (GIRCG study Saragoni L et al The Oncologist 2018; 23 : 1-7)

	No. pts	No. events	5-Year % (95% CI)	10-Year % (95% CI)	p value (logrank)
Kodama					
Small mucosal M	530	34	3 (0-19)	5 (3-8)	
Small mucosal SM	140	13	6 (1-10)	8 (2-13)	
Super mucosal M	37	1	0	5 (0-14)	
Super mucosal SM	41	4	5 (0-10)	8 (0-17)	
PEN B	85	5	4 (0-9)	7 (1-14)	
PEN A	230	39	14 (9-19)	22 (16-28)	<0.0001

MULTIVARIABLE ANALYSIS

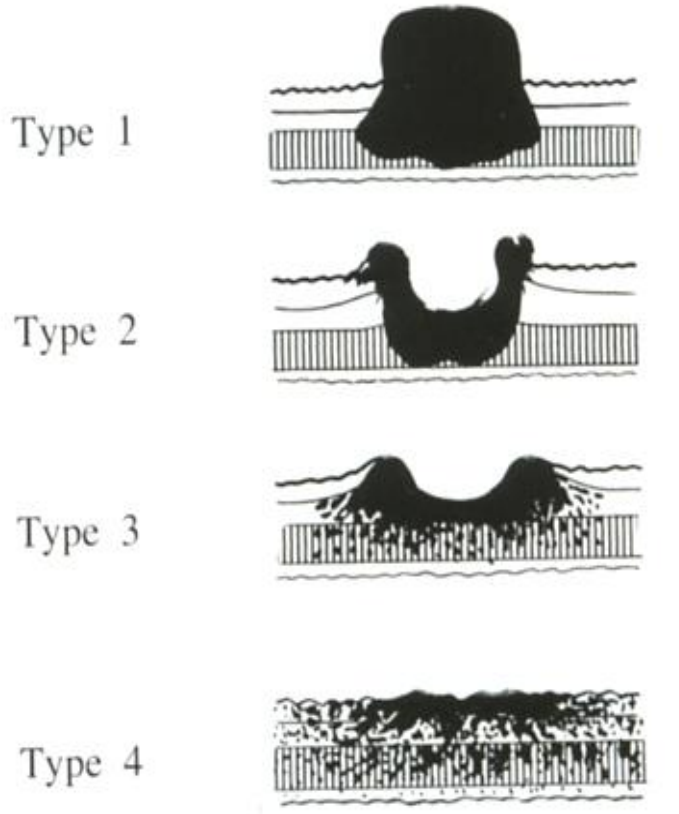
Adjusted Hazard Ratio for gastric cancer-related death
(Fine and Gray method)

	HR (95% IC)	p
Size		
</=2cm	1.00	0.015
>2cm	1.44 (1.07-1.94)	
Kodama		
Not PEN A	1.00	0.008
PEN A	1.73 (1.15-2.61)	
Nodes		
Negative	1.00	<0.0001
Positive	2.28 (1.61-3.21)	

DISTRIBUTION OF LYMPH NODE METASTASES

	N-Patients N. (%)	N+Patients N. (%)	p value
Kodama			
PEN A	157 (17.4)	70 (44.9)	**<0.0001**
Not PEN A	744 (82.6)	86 (55.1)	
Histotypes (Lauren)			
Intestinal	679 (75.0)	73 (46.8)	**<0.0001**
Diffuse	226 (25.0)	83 (53.2)	
Depth			
Mucosal	597 (66.5)	48 (31.4)	**<0.0001**
Submucosal	301 (33.5)	105(68.6)	
Size.			
</= 2 cm	536 (59.8)	69 (43.9)	**<0.0001**
> 2 cm	360 (40.2)	88 (56.1)	

Advanced Carcinoma



Borrmann

Type 1 polypoid

Type 2 ulcerated with raised margins

Type 3 ulcerated infiltrating the surrounding wall

Type 4 diffusely infiltrating (linite plastica)

HISTOLOGY REPORT

- Histotype (Classifications of Lauren and WHO)
- Histological grade (WHO)
- Depth of infiltration (pT)
- Presence/absence of lymphovascular invasion
- Margins status
- Total number of examined lymph nodes
- Number of metastatic lymph nodes over the total nodes examined (ratio)
- Staging according to pTNM (8th Edition)
- Lymph nodes topography (Japanese classification of Maruyama)

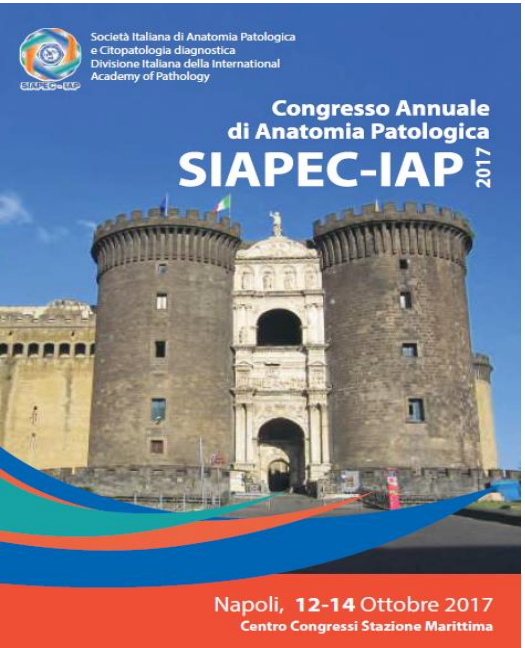
EUROPEN CHAPTER IGCA

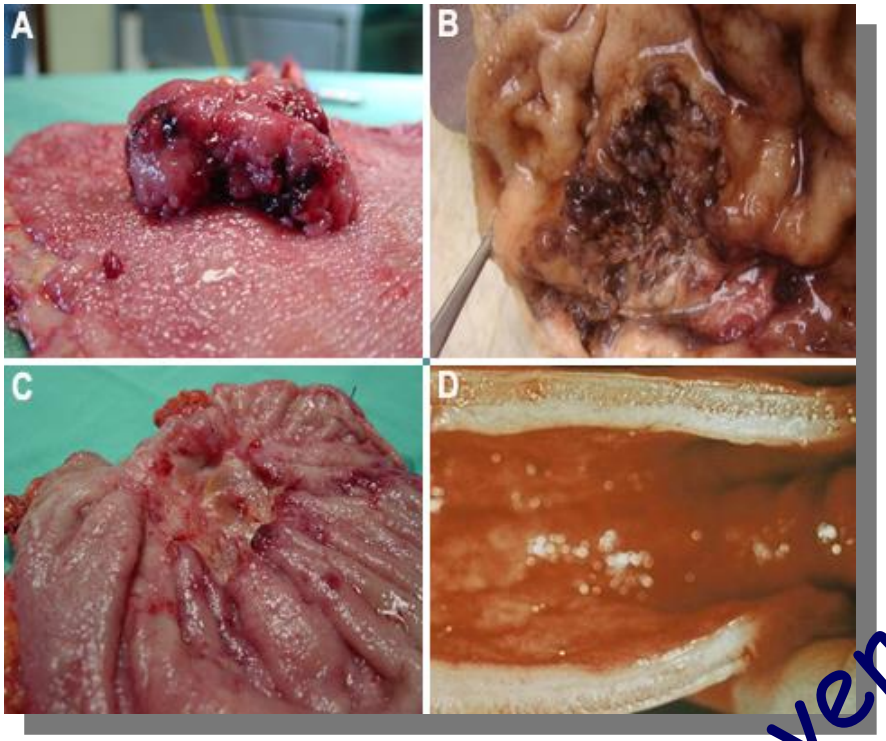
VERONA WORKSHOP ON SIGNET RING CELL GASTRIC ADENOCARCINOMA

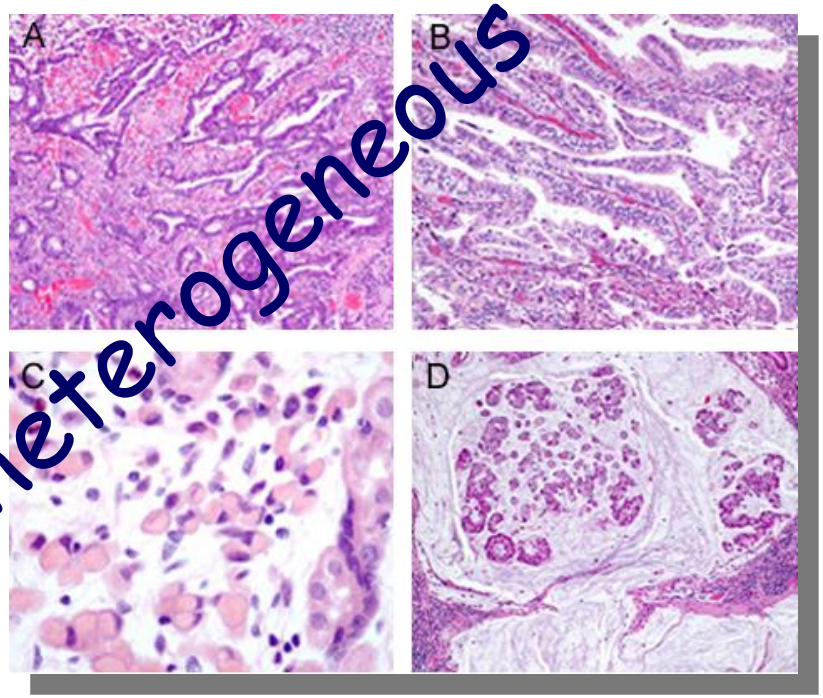
17TH MARCH 2017

Molecular characterization of gastric cancer with an emphasis on poorly cohesive/SRC carcinomas

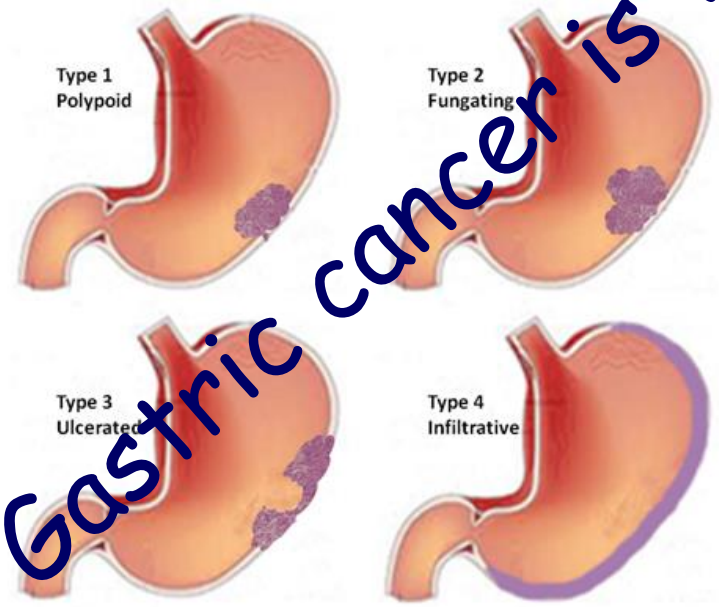
How to set up the biological research in this field?

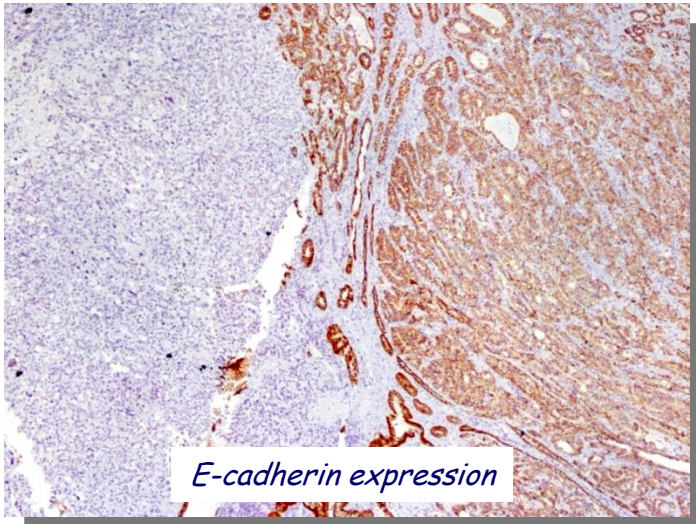






Gastric cancer is very heterogeneous





Gastric carcinoma

4-1-02 - ICD-O Code

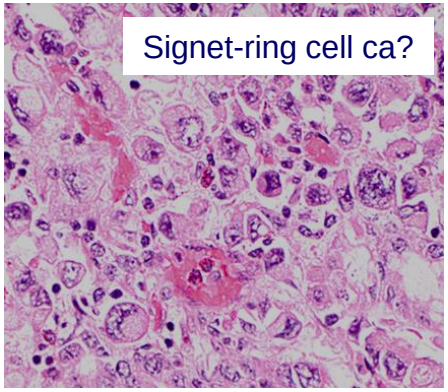
Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3

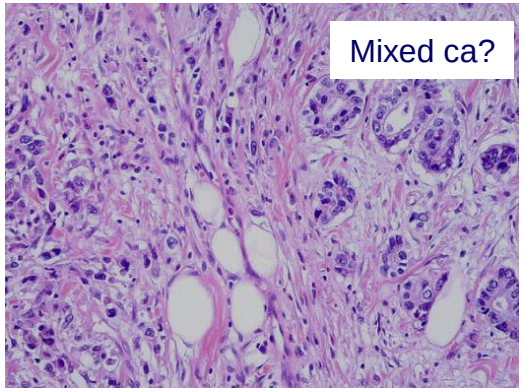
WHO – 3rd Edition, 2000

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3

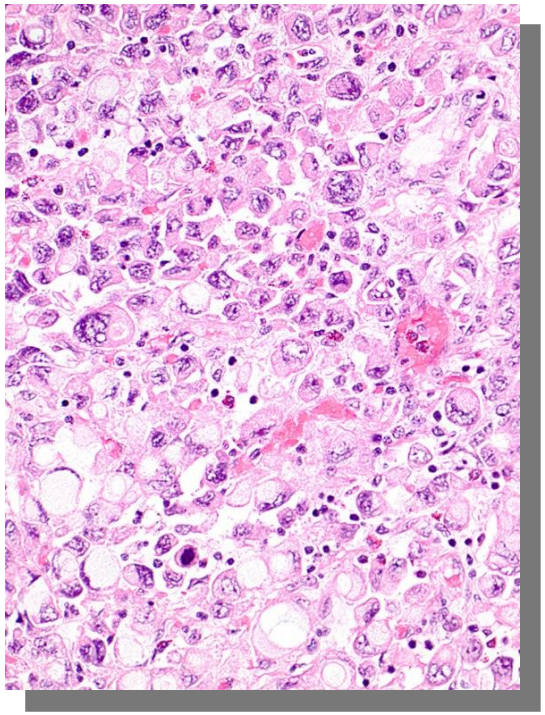
WHO – 3rd Edition, 2000

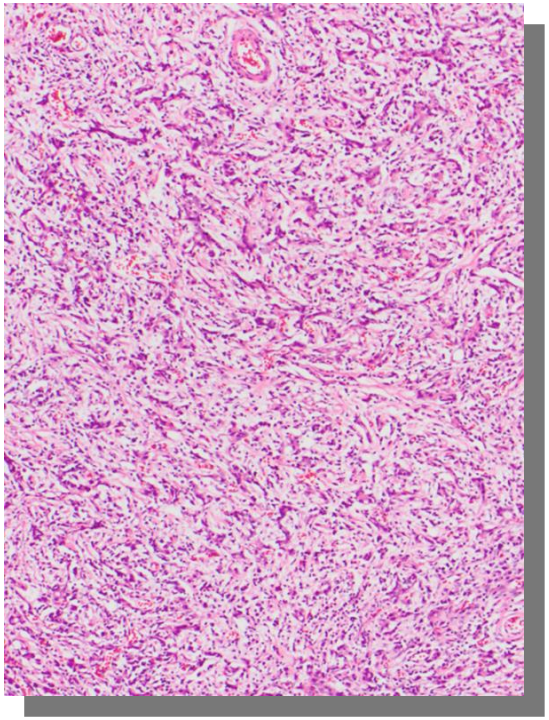
Shortcomings:

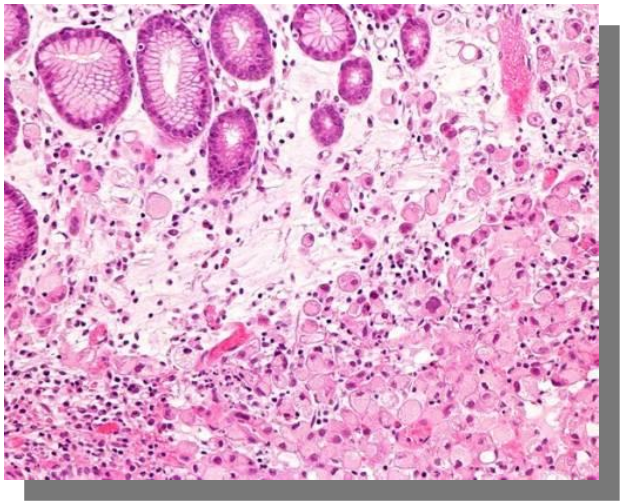


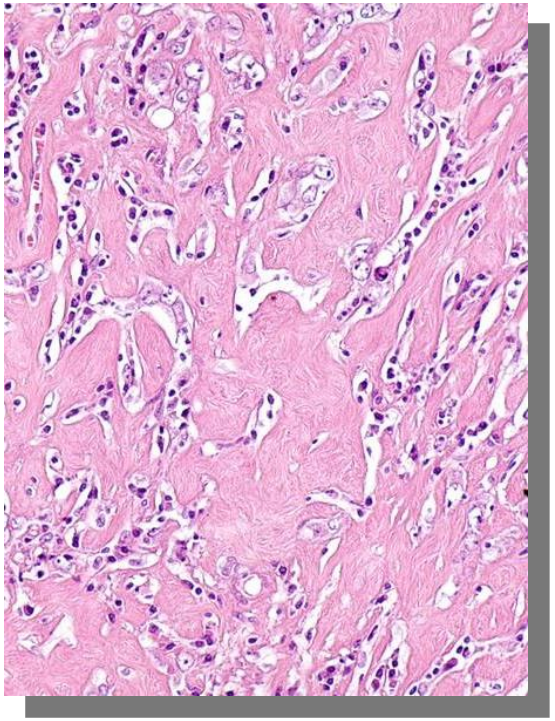


Signet-ring cell carcinoma

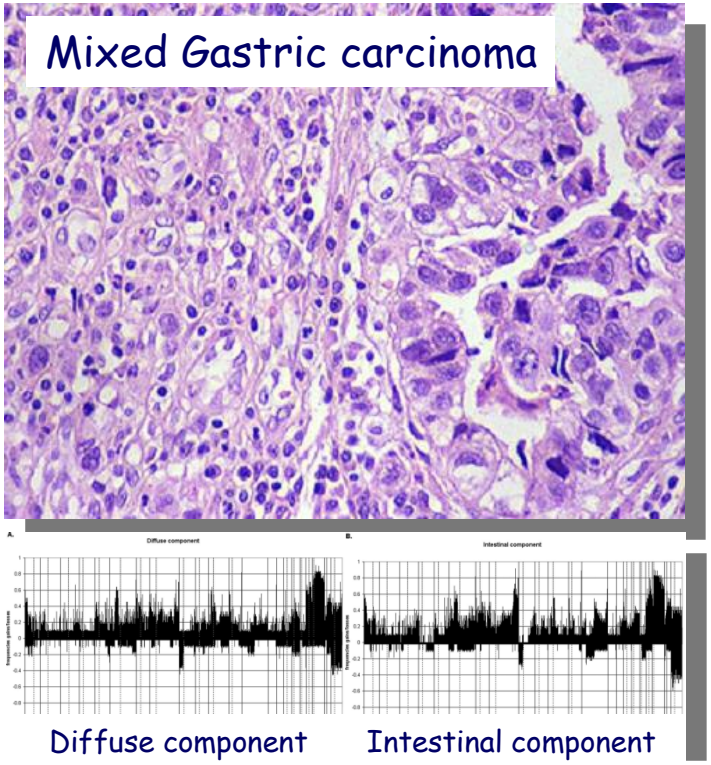






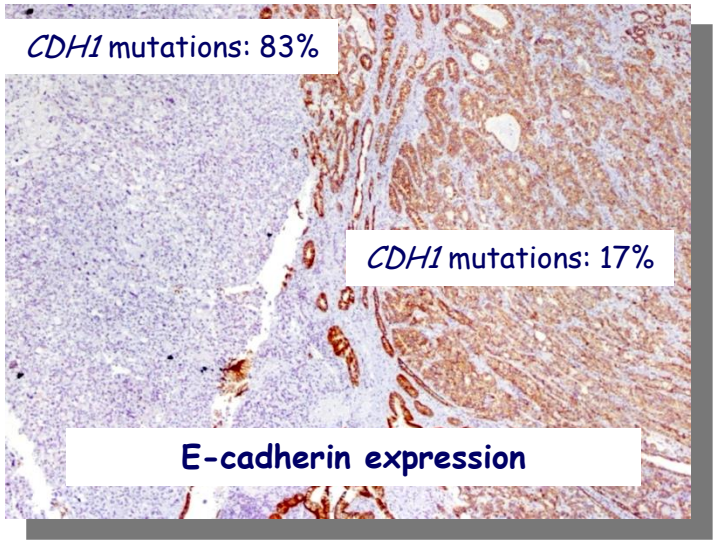


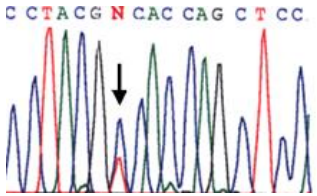
Signet-ring cell carcinoma
without signet-ring cells…



Diffuse component Intestinal component

Laser microdissection



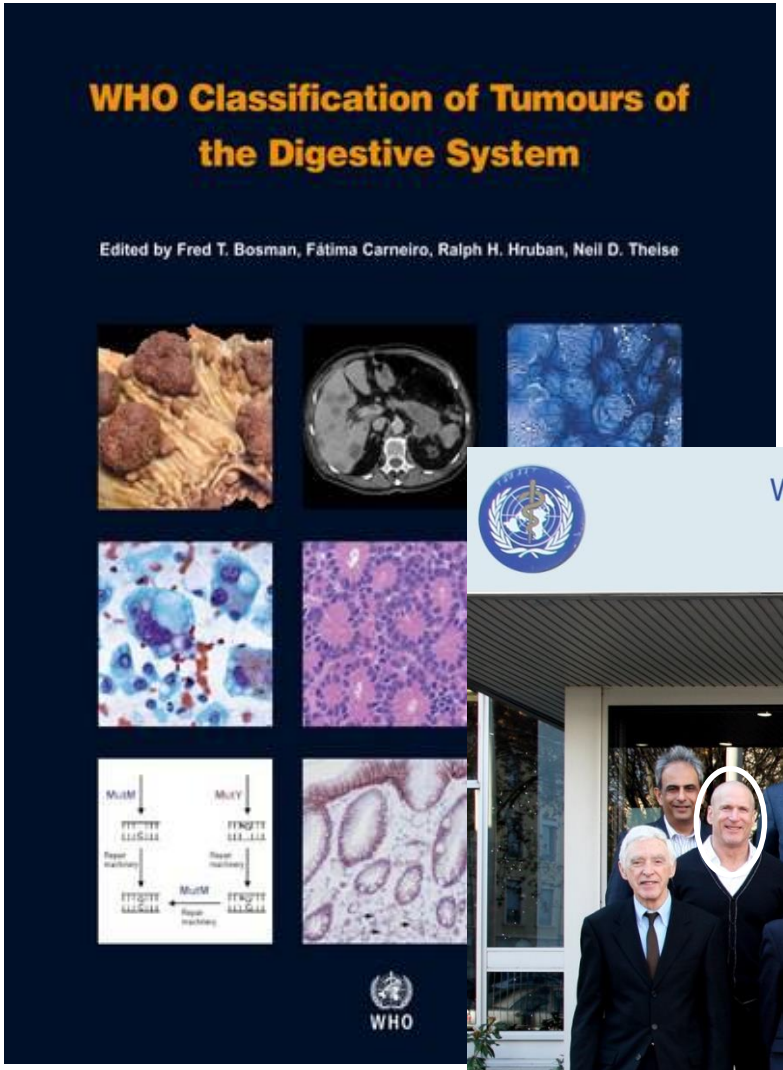


CDH1 mutations

E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas

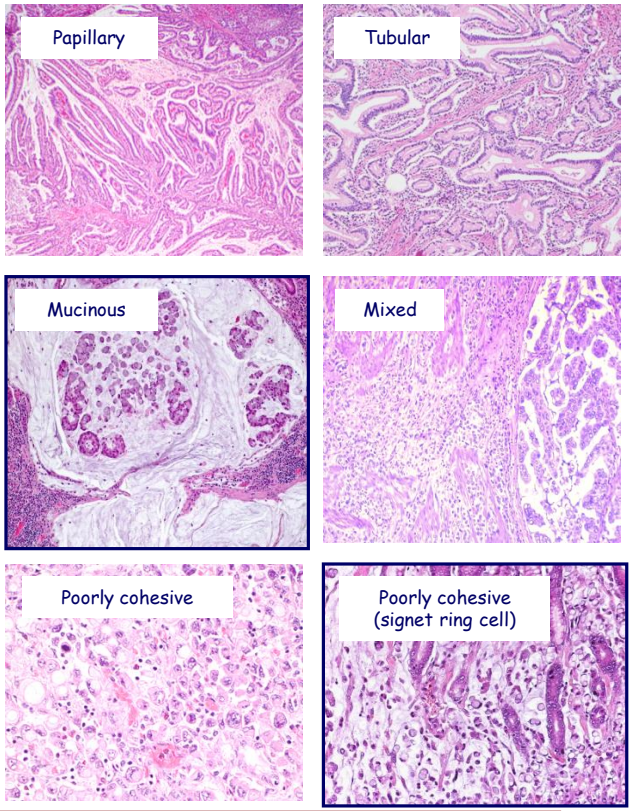
Machado J *et al*: Lab Invest 79: 459, 1999
Carvalho B et al: Cellular Oncology 28:283, 2006

Park SY *et al*: **Mixed-type gastric cancer and its association with high-frequency CpG island hypermethylation.** *Virchows Archiv* 456, 2010


WHO Classification of Tumours of the Digestive System
Edited by Fred T. Bosman, Fátima Carneiro, Ralph H. Hruban, Neil D. Theise
MutM
MutY
MutM
WHO


WHO Classification of Tumours of the Digestive System
Consensus and Editorial meeting
IARC, Lyon, 10-12 December 2009

WHO – 4th Edition, 2010

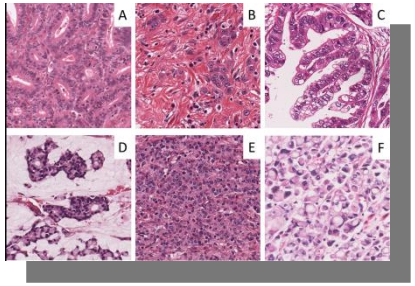


4-1 Gastric carcinoma

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori

4-1-02 - ICD-O Code

Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Poorly cohesive carcinoma (Signet-ring cell carcinoma and other variants)	8490/3
Mixed carcinoma	8255/3



Classification of gastric cancer

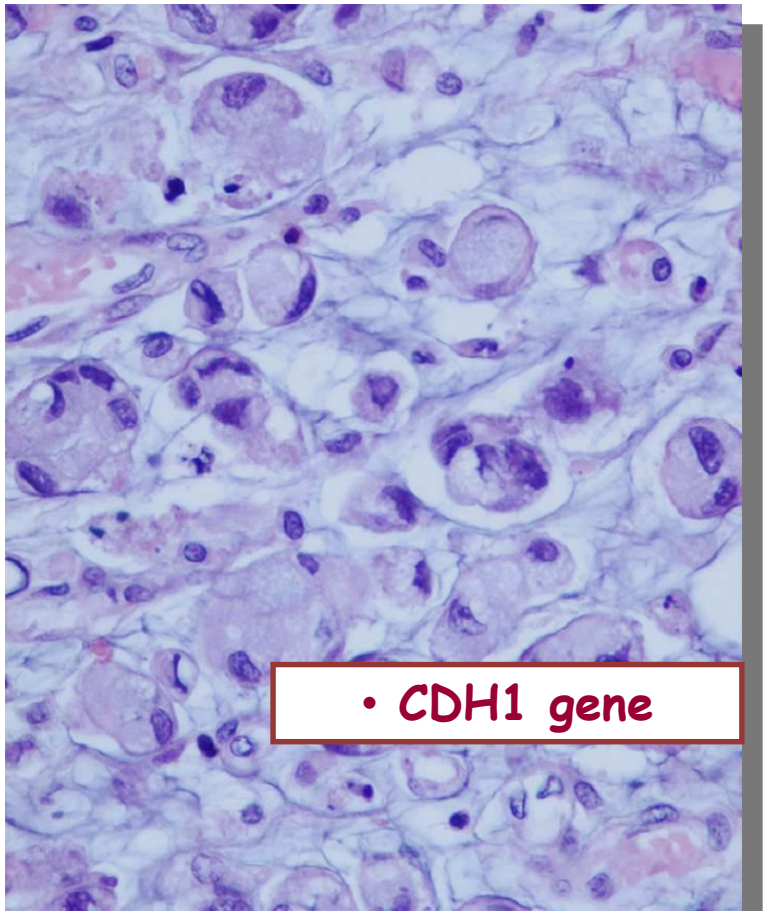
Laurén classification	World Health Organization 2010	Japanese classification 2011	Nakamura classification
Intestinal type	Papillary Tubular	Papillary Tubular 1	Differentiated type
	Mucinous	Tubular 2 Mucinous	Undifferentiated type
Diffuse type	Poorly cohesive, including signet ring cell carcinoma and other variants	Signet ring cell Poorly differentiated, non-solid type	
Mixed (intestinal and diffuse type)	Mixed type (tubular/papillary and poorly cohesive/signet ring)	-	-
Indeterminate type	Undifferentiated Adenosquamous Medullary Hepatoid	Poorly differentiated, solid type	Undifferentiated type

Carneiro F, Grabsch H: **Pathogenesis of gastric cancer**. *In*: Minimally Invasive Foregut Surgery for Malignancy: Principles and Practice. Steven N Hochwald and Moshim Kukar (eds). Springer 2015, pp 61-72. ISBN: 978-3-319-09341-3

Tubulo-papillary ca. (WHO)
"Intestinal" carcinoma (Lauren)

- Elderly patients, mainly males
- Decreasing incidence everywhere
- Blood-born metastases

Poorly cohesive/signet ring ca. (WHO)
"Diffuse" carcinoma (Lauren)



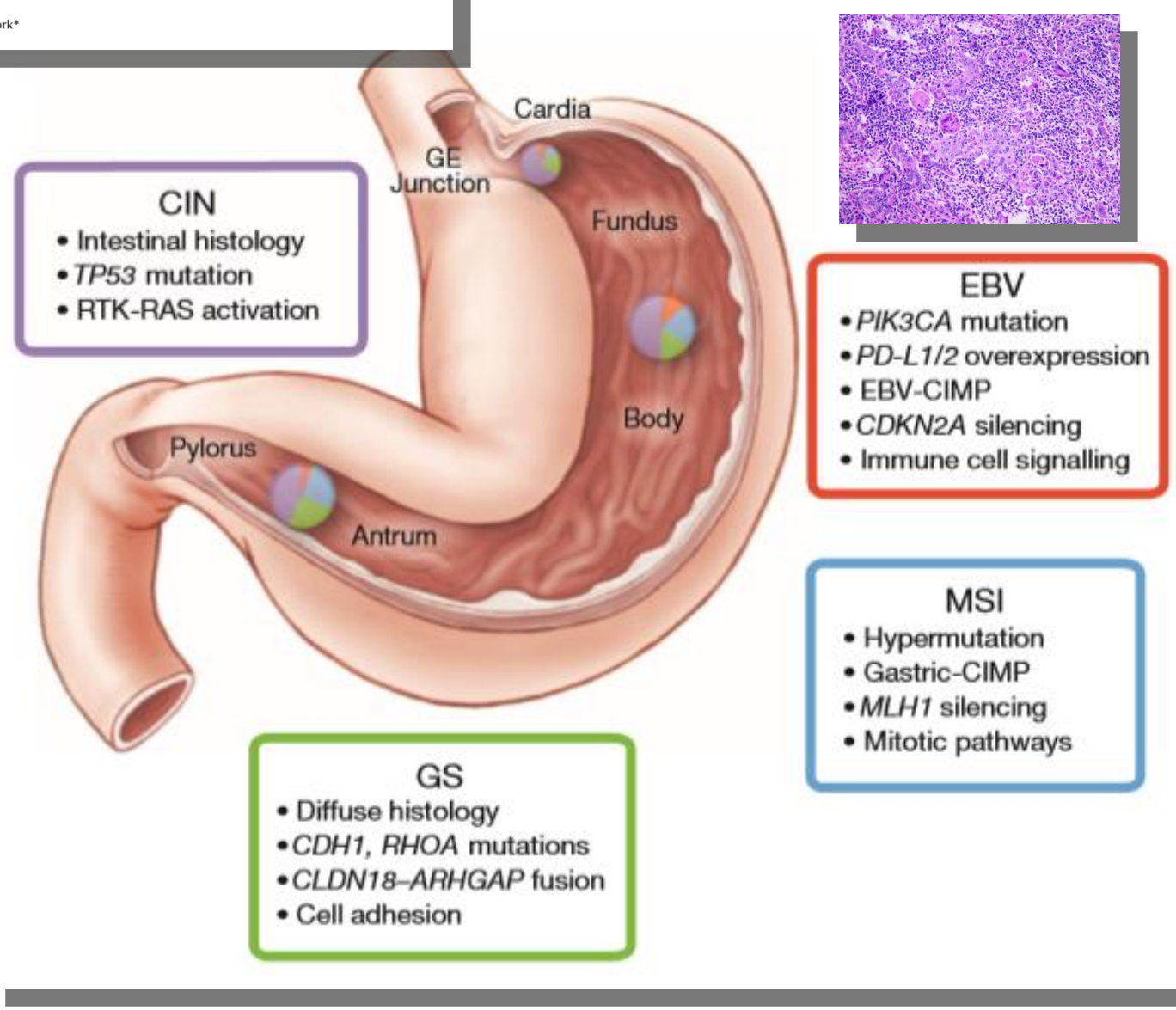
- Young patients, mainly females
- Familial/hereditary conditioning
- Dissemination to the peritoneum

ARTICLE

OPEN
doi:10.1038/nature13480

Comprehensive molecular characterization of gastric adenocarcinoma

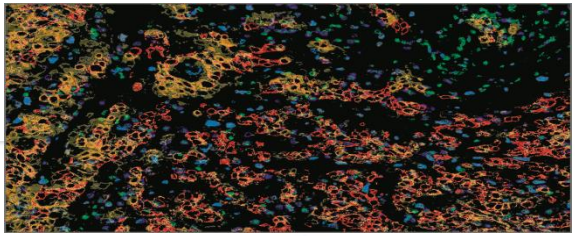
The Cancer Genome Atlas Research Network*

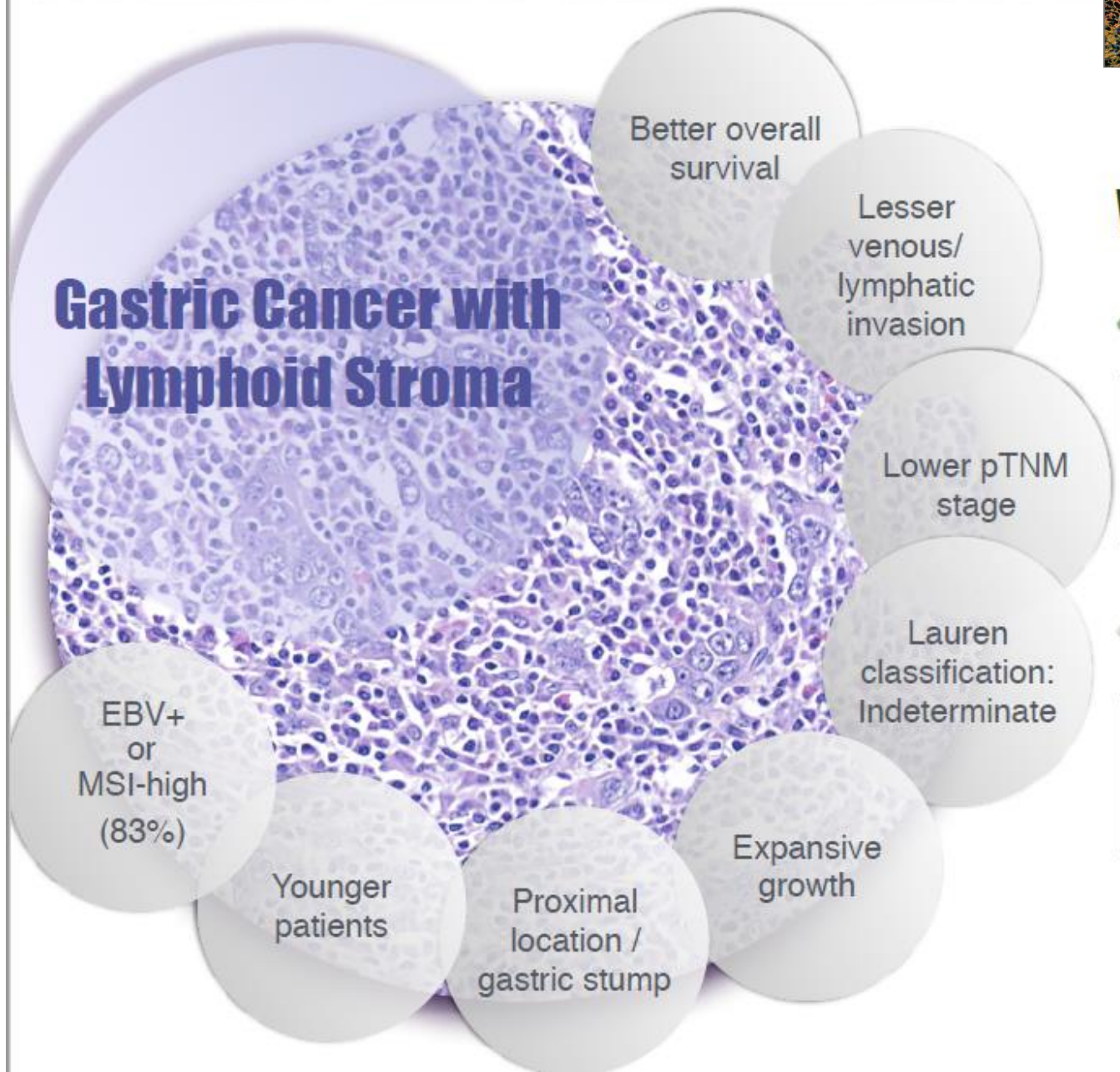


The Cancer Genome Atlas (TCGA) project; Nature 2014

Gastric carcinoma with lymphoid stroma

in the era of the immune context and immunotherapies





What is new?

Tumour immune microenvironment

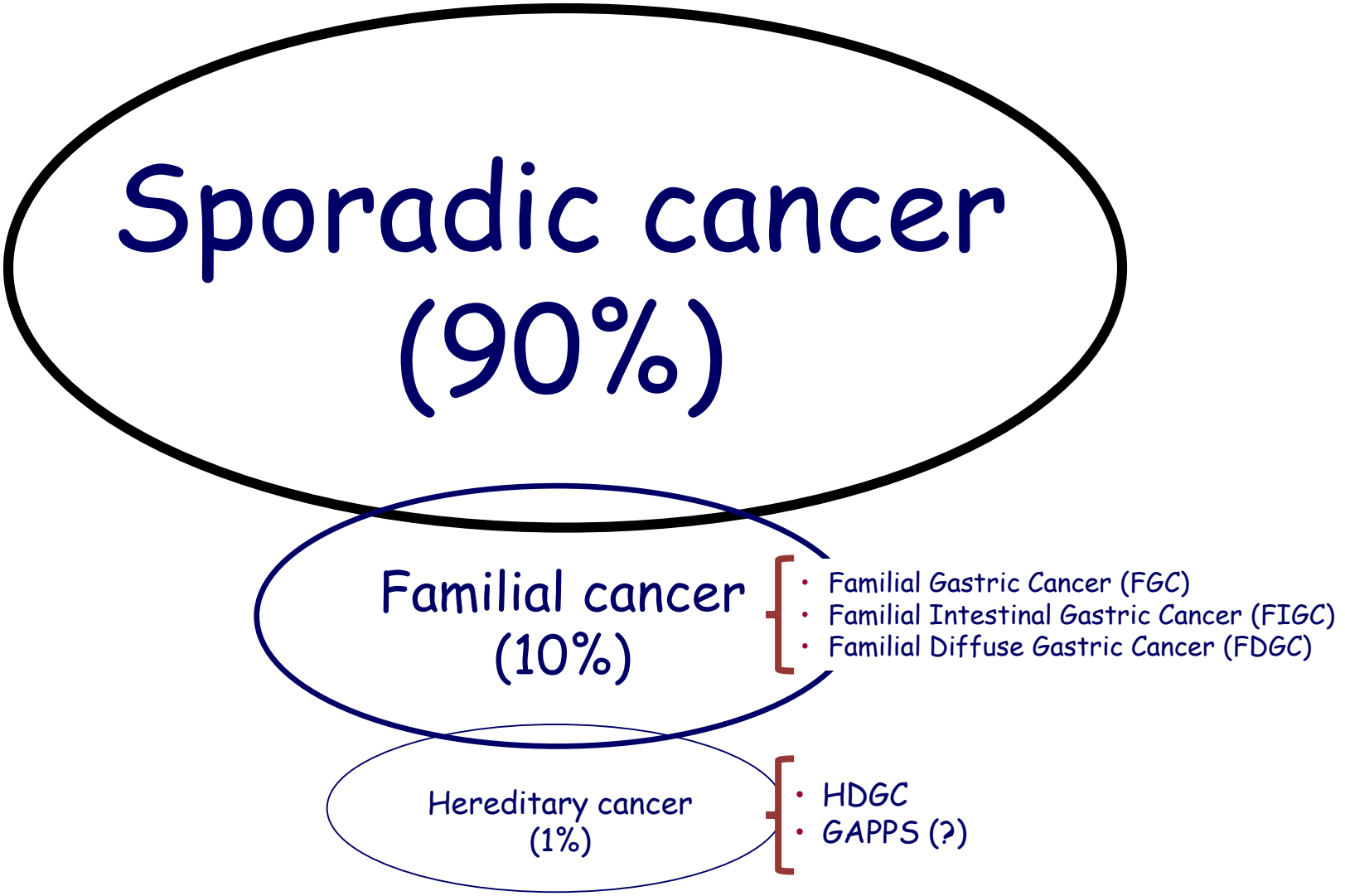
CD8/CD3R significantly associated with EBV infection; CD3 density associated with PD-L1 expression

PD-L1/PD-1 immune inhibitory checkpoint

PD-L1 expression/ amplification frequent and restricted to EBV+ and MSI-H GCLS

Targeted therapies?

Gastric cancer



New Chapter on:

Hereditary diffuse gastric cancer

F. Carneiro
A. Charlton
D.G. Huntsman

Definition

Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant cancer-susceptibility syndrome that is characterized by signet-ring cell (diffuse) gastric cancer and lobular breast cancer. The genetic basis for this syndrome was discovered in 1998 by Guilford *et al.* [1081], who identified germline mutations of the E-cadherin (*CDH1*) gene (MIM No. 192090) by linkage analysis and mutation screening in three Maori kindreds with multigenerational, diffuse gastric cancer in New Zealand.

MIM No.: 137215

Diagnostic criteria

In families with an aggregation of gastric cancer, the histopathology of the tumours is often unknown; these cases are designated as familial gastric cancer (FGC). When the histopathological type of one or more gastric cancers is known, discrete syndromes/diseases can be diagnosed; these include HDGC, familial diffuse gastric cancer (FDGC) and familial intestinal gastric cancer (FIGC) [397].

On the basis of clinical criteria, the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 defined families with the HDGC syndrome as those fulfilling one of the following features: (1) two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one being diagnosed before the age of 50 years; or (2) three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of diagnosis [397]. Women in these families also have an elevated risk of lobular breast cancer [341, 1501, 1513, 2855, 3136]. IGCLC criteria for genetic testing, updated in 2009 [871] are shown in Table 4.2.01. An alternative genetically-based nomenclature, proposed by the New Zealand group, in which the term "HDGC" is restricted to families with germline mutations in the *CDH1* gene [1091, 1092]. The IGCLC definition for HDGC will be used for the remainder of this section [871].

Epidemiology

The vast majority of gastric cancers are sporadic, but approximately 1–3% result from an inherited predisposition [870, 2396, 2439].

The prevalence of HDGC is uncertain, partly due to the recent identification of this syndrome. In a review of 439 families with aggregation of gastric cancer [2395], *CDH1* mutations were preferentially observed in families fulfilling the clinical criteria for HDGC (36.4%). In FDGC, the frequency of germline mutations in *CDH1* was much lower (12.5%) [2395]. *CDH1* mutations have not been found in families with weaker histories of gastric cancer; however, mutation rates of up to 10% have been described in individuals with no family history but DGC diagnosed at less than age 35 years, from populations with a low incidence of gastric cancer [1501, 3136]. There are striking population-specific differences regarding the fraction of families with aggregation of gastric cancer and frequency of *CDH1* germline mutations. In countries with a low incidence of gastric cancer, the frequency of germline alterations in the *CDH1* gene is > 40%, while in countries with a moderate or high incidence of gastric cancer, the frequency of alterations in *CDH1* is about 20% [2396]. These observations in moderate- or high-incidence countries are probably related to clustering of gastric cancer attributable to environmental risk factors (lifestyle, diet) and/or variation in genes conferring a weak susceptibility [2396].

Localization

Most index cases with HDGC present with cancers that are indistinguishable from sporadic diffuse gastric cancer, often with linitis plastica, which can involve all topographic regions within the stomach. Systematic complete mapping of total gastrectomies from asymptomatic carriers

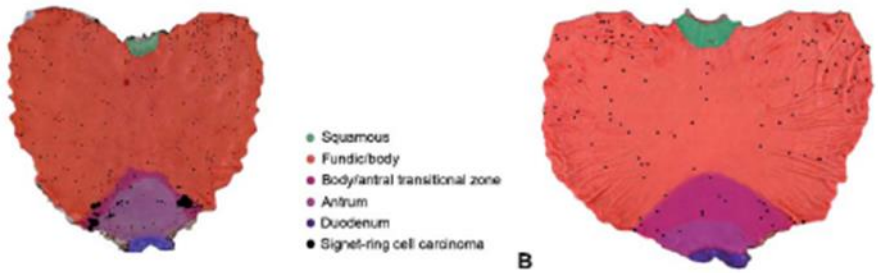
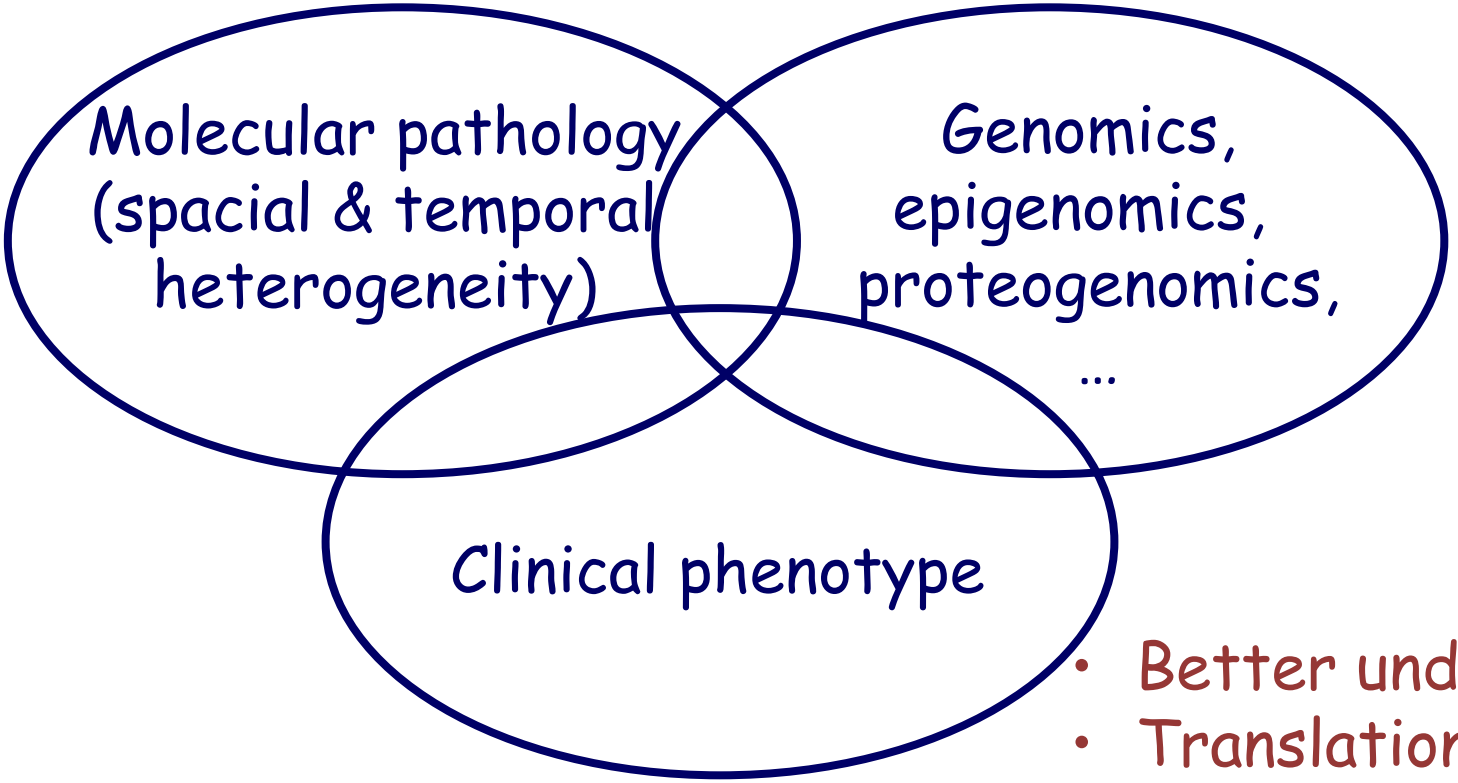


Fig. 4.2.01 Mapping of gastric mucosal zones (semi-opaque colours) and location of foci of stage T1a signet-ring cell (diffuse) carcinoma (black circles) on photos of two stomachs. Adapted from Charlton *et al.* (493). A Asymptomatic *CDH1*-mutation carrier, aged 15 years; the map indicates the location of 318 foci and mucosal zones. B Asymptomatic *CDH1*-mutation carrier, aged 19 years, from the same family; the map indicates the location of 115 foci and mucosal zones.

WHO – 4th Edition, 2010

Integrated Molecular Pathology (Integromics framework)



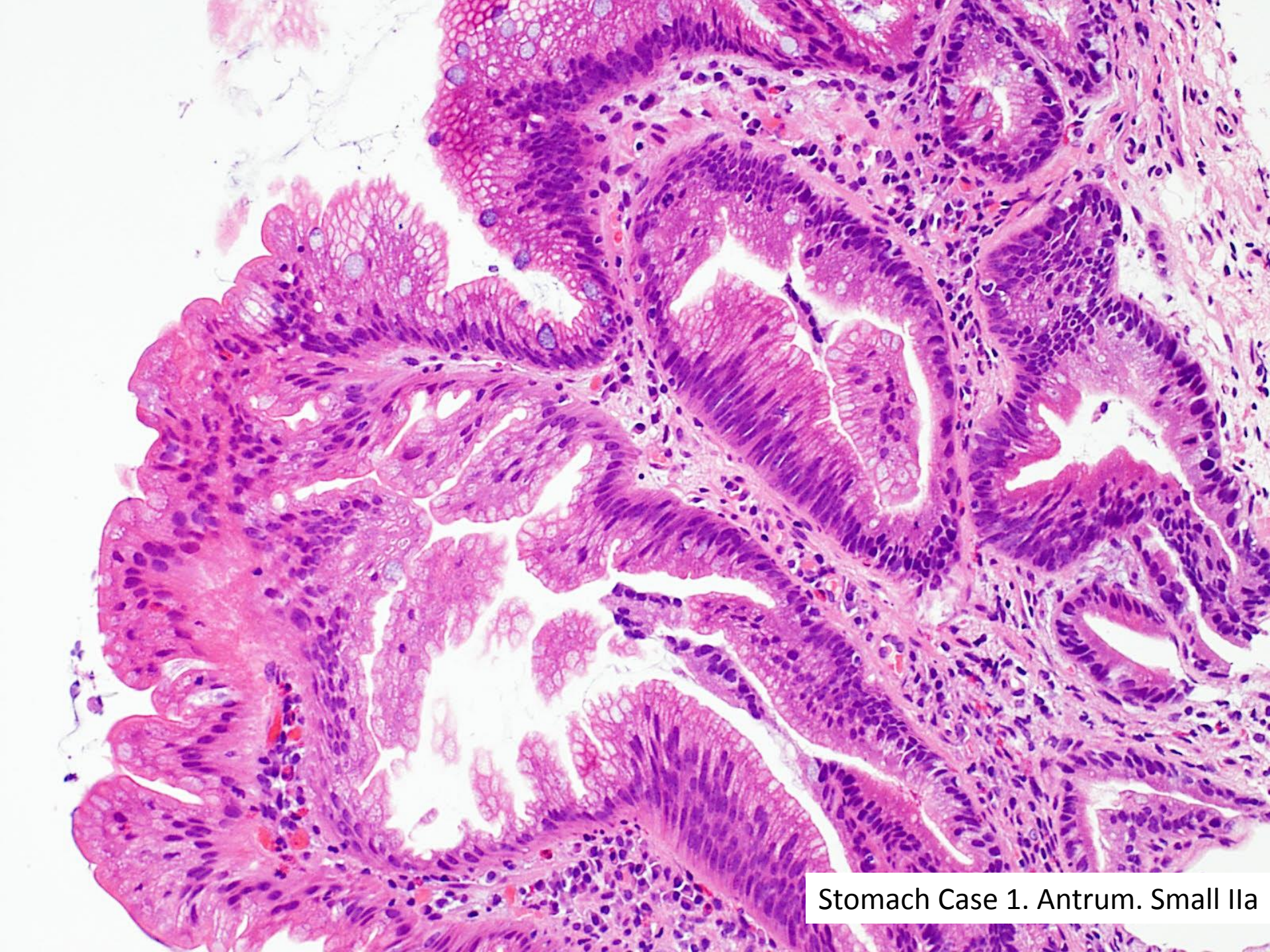
- Better understanding
- Translation to clinics

- Lloyd M et al: Pathology to enhance precision medicine in oncology: Lessons from landscape ecology. Adv Anat Pathol 22: 267, 2015
- Salto-Tellez M & Kennedy M:Integrated molecular pathology: the Belfast model. Drug Discovery Today 20: 1451, 2015

ALCUNI CASI....

Stomach Case 1. Antrum. Small IIa lesion biopsy

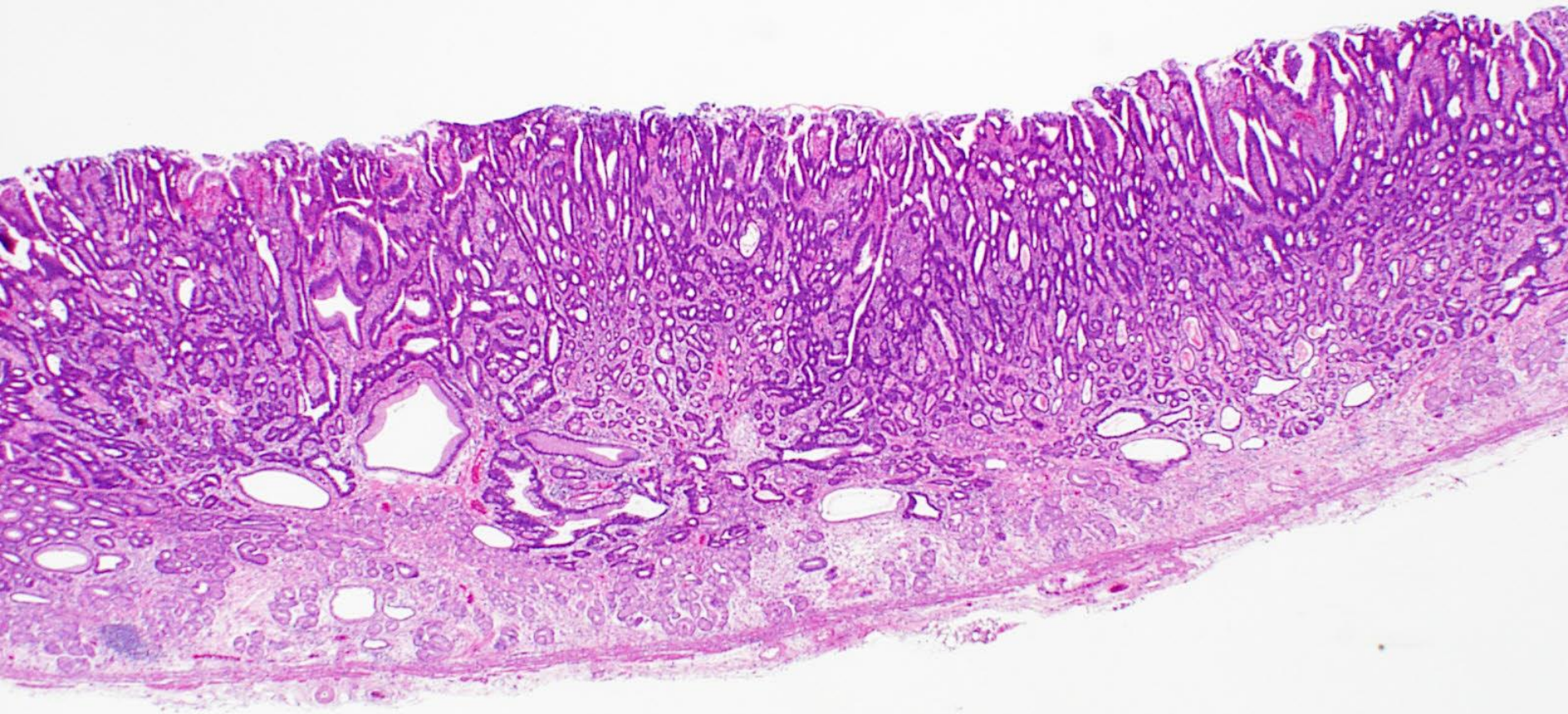
Stomach Case 1. Antrum. Small IIa



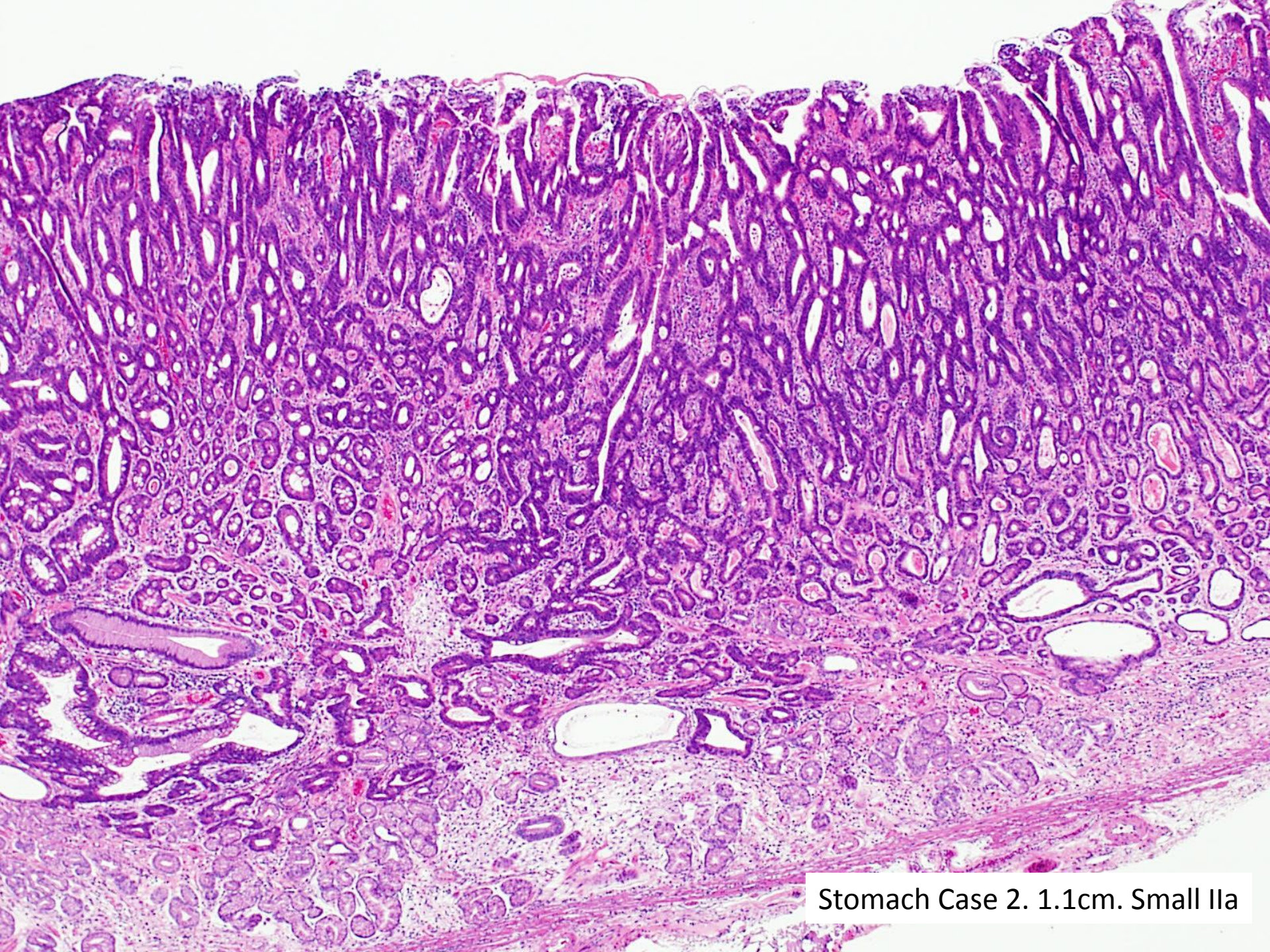
Stomach Case 1. Antrum. Small IIa

DIAGNOSI ISTOLOGICA

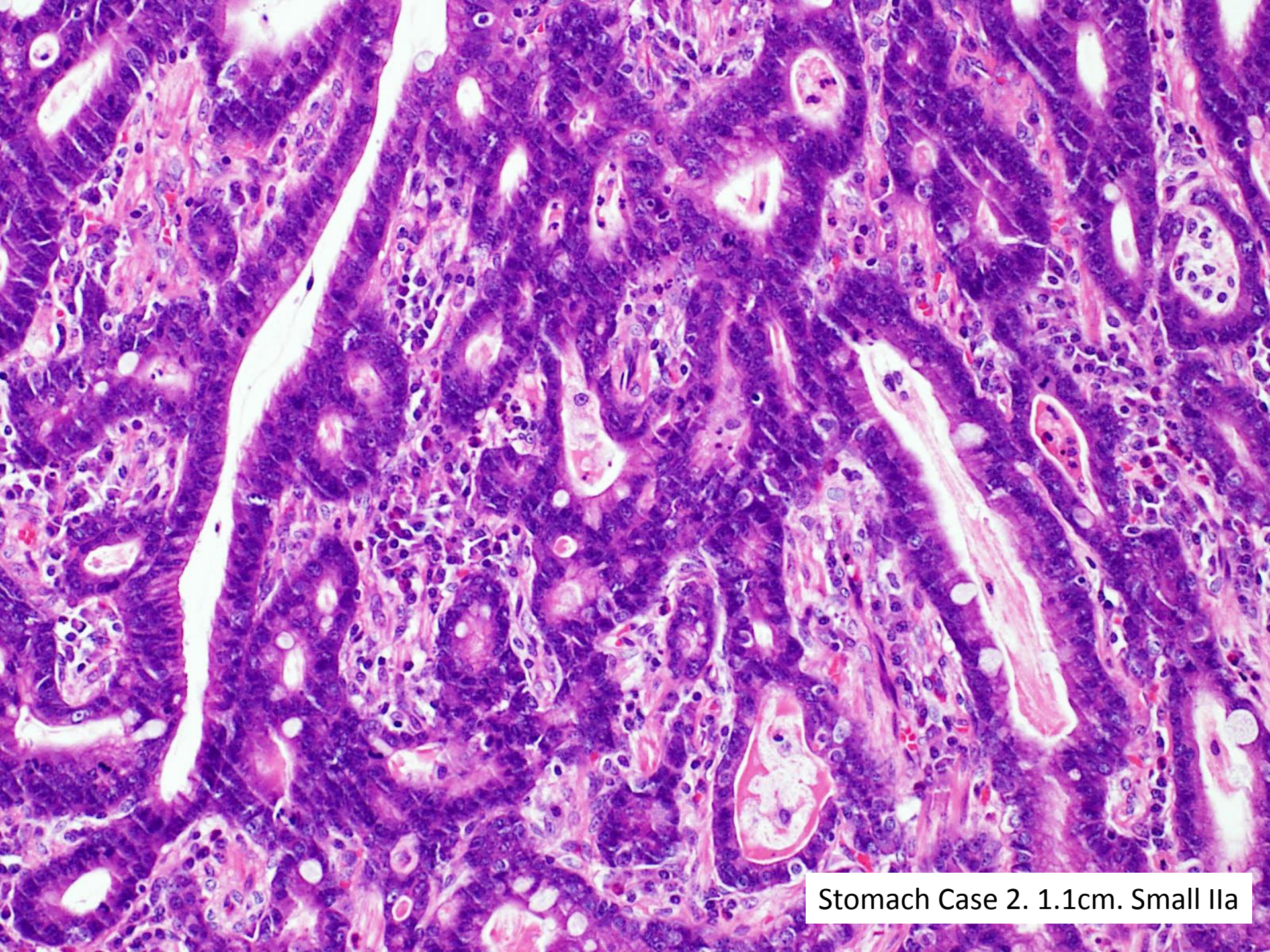
NEGATIVO PER NEOPLASIA INTRA-EPITELIALE/DISPLASIA (METAPLASIA INTESTINALE)

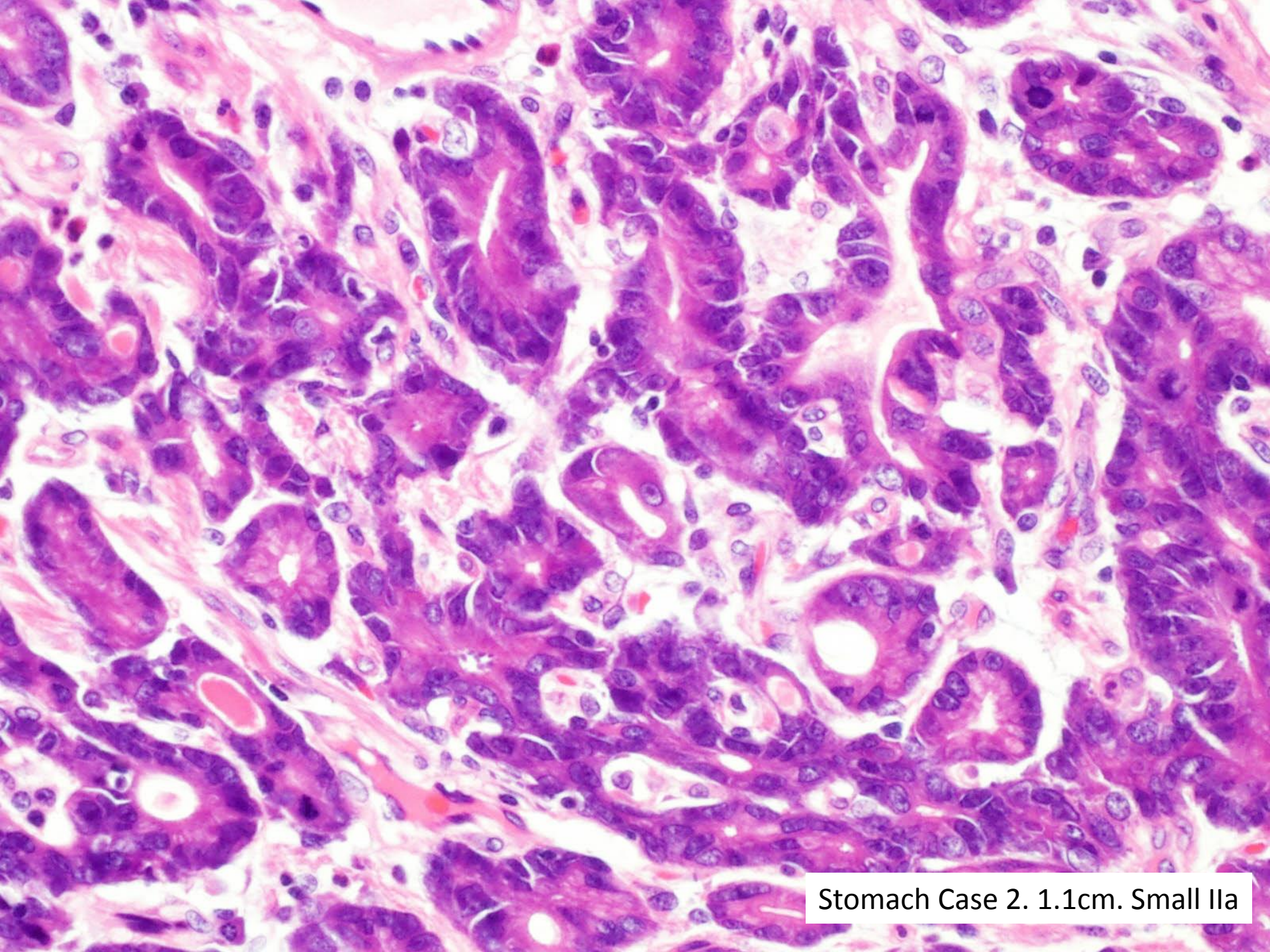


Stomach Case1. Antrum. Small IIa ESD



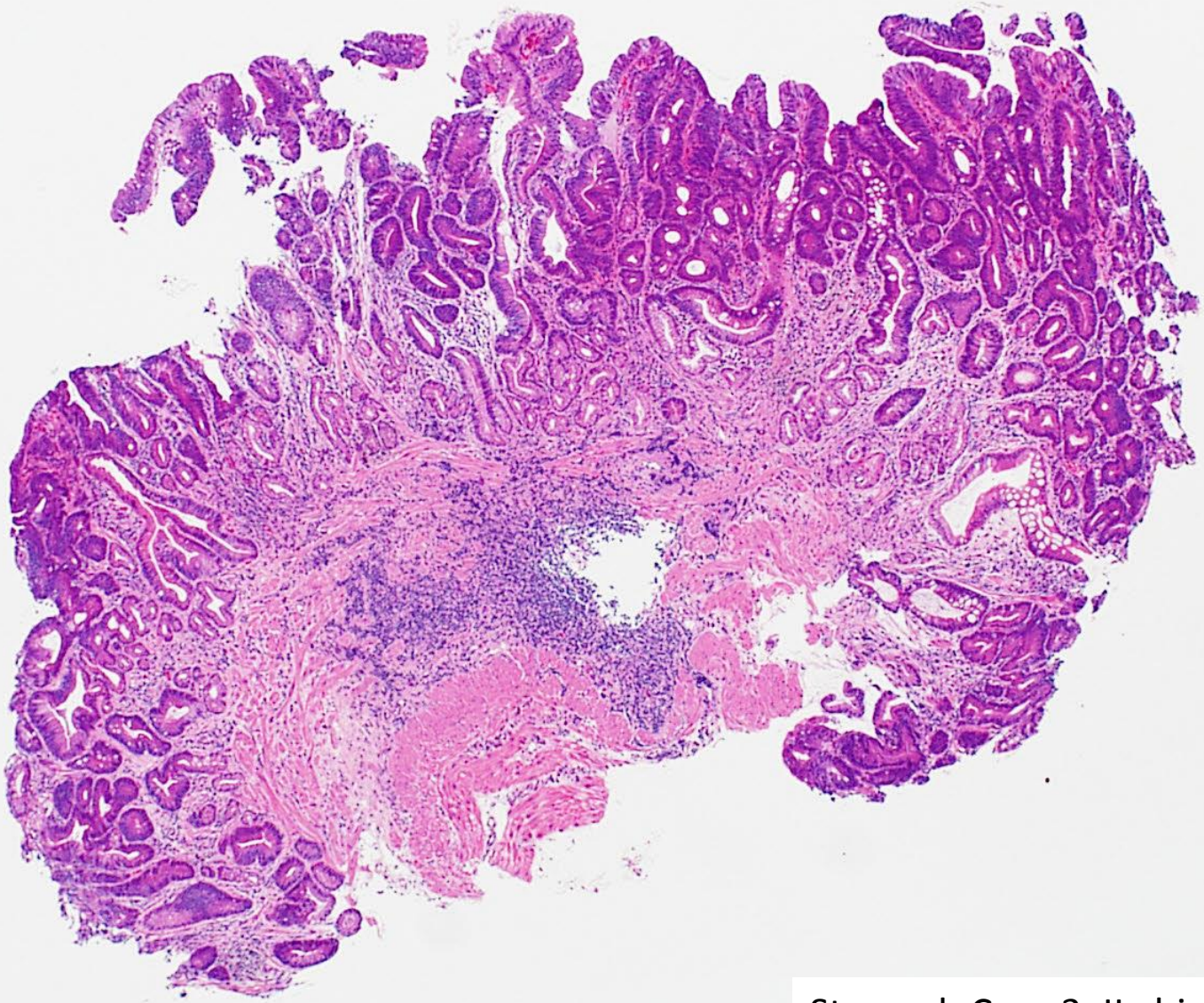
Stomach Case 2. 1.1cm. Small IIa


Stomach Case 2. 1.1cm. Small IIa

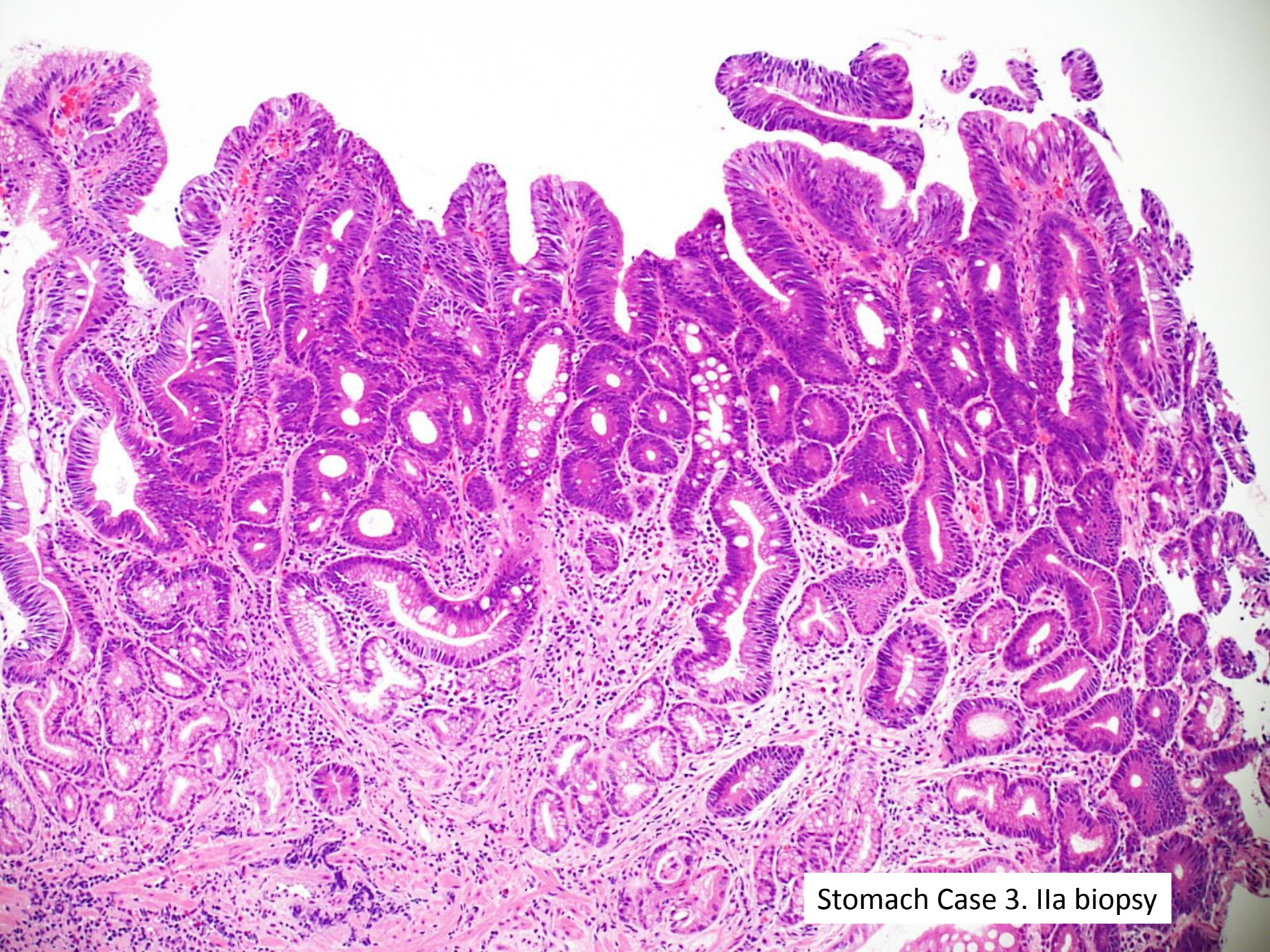

Stomach Case 2. 1.1cm. Small IIa

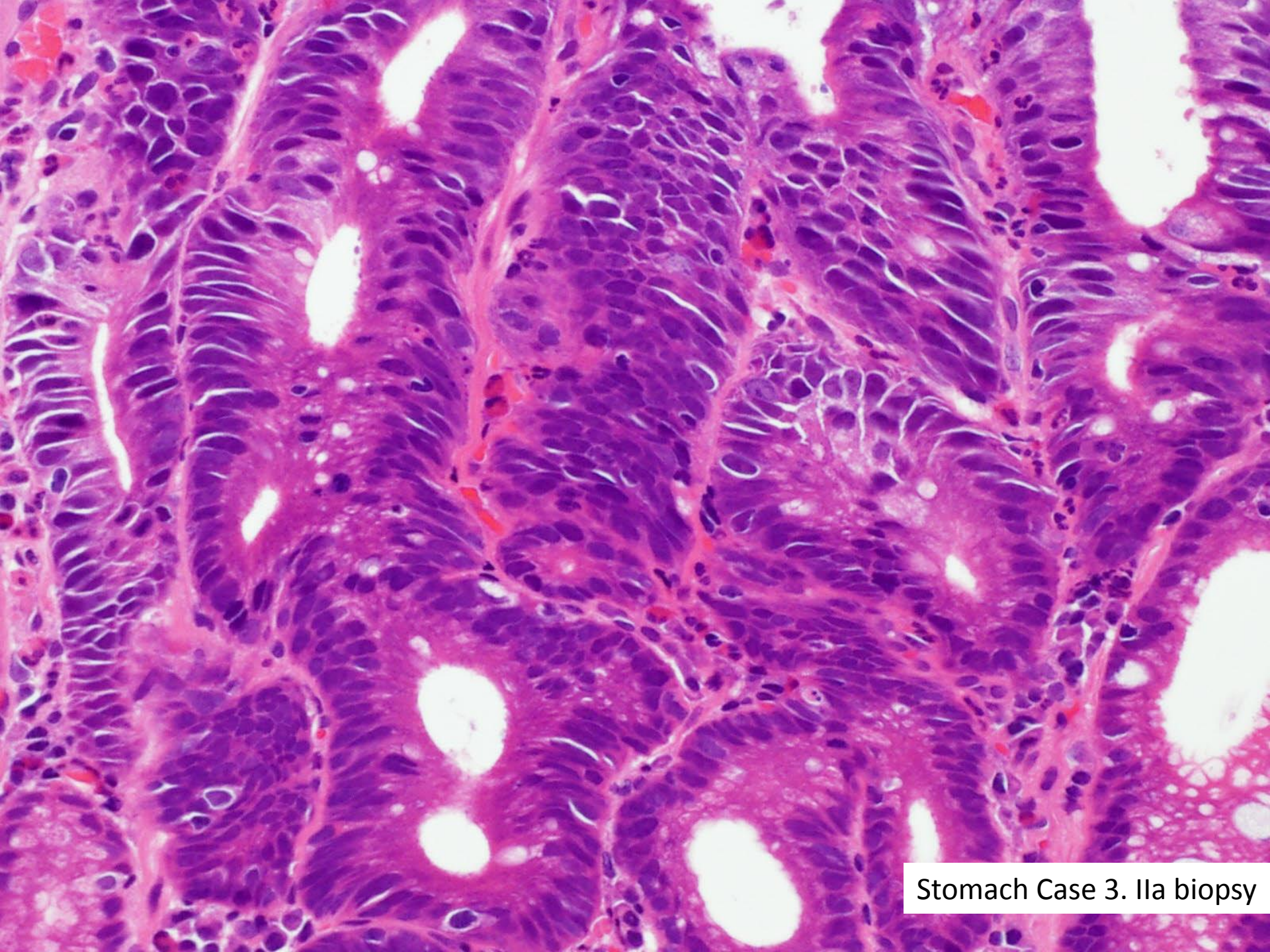
DIAGNOSI ISTOLOGICA

ADENOCARCINOMA INTRA-MUCOSO
(EARLY GASTRIC CANCER)



Stomach Case 3. IIa biopsy

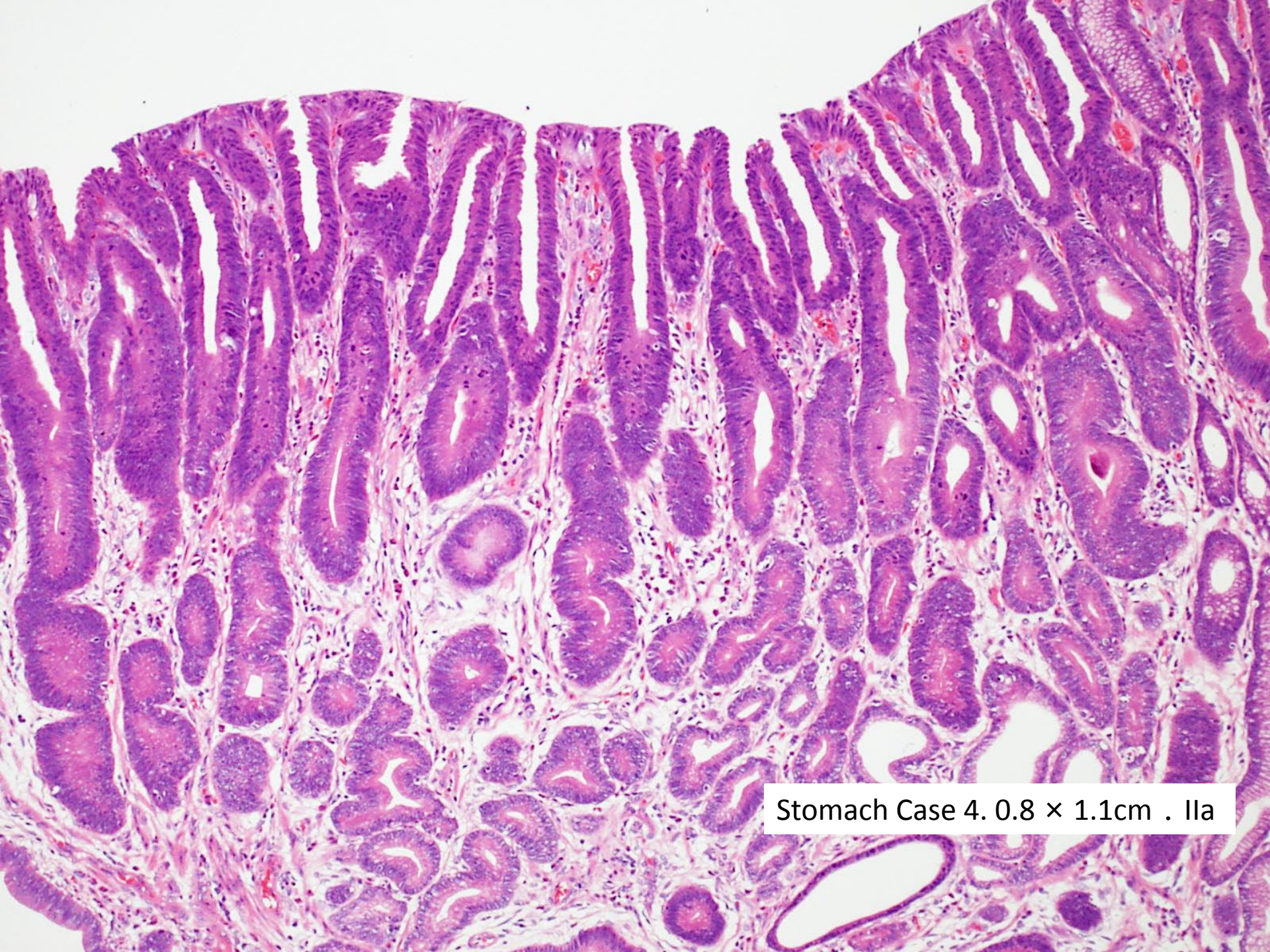

Stomach Case 3. IIa biopsy

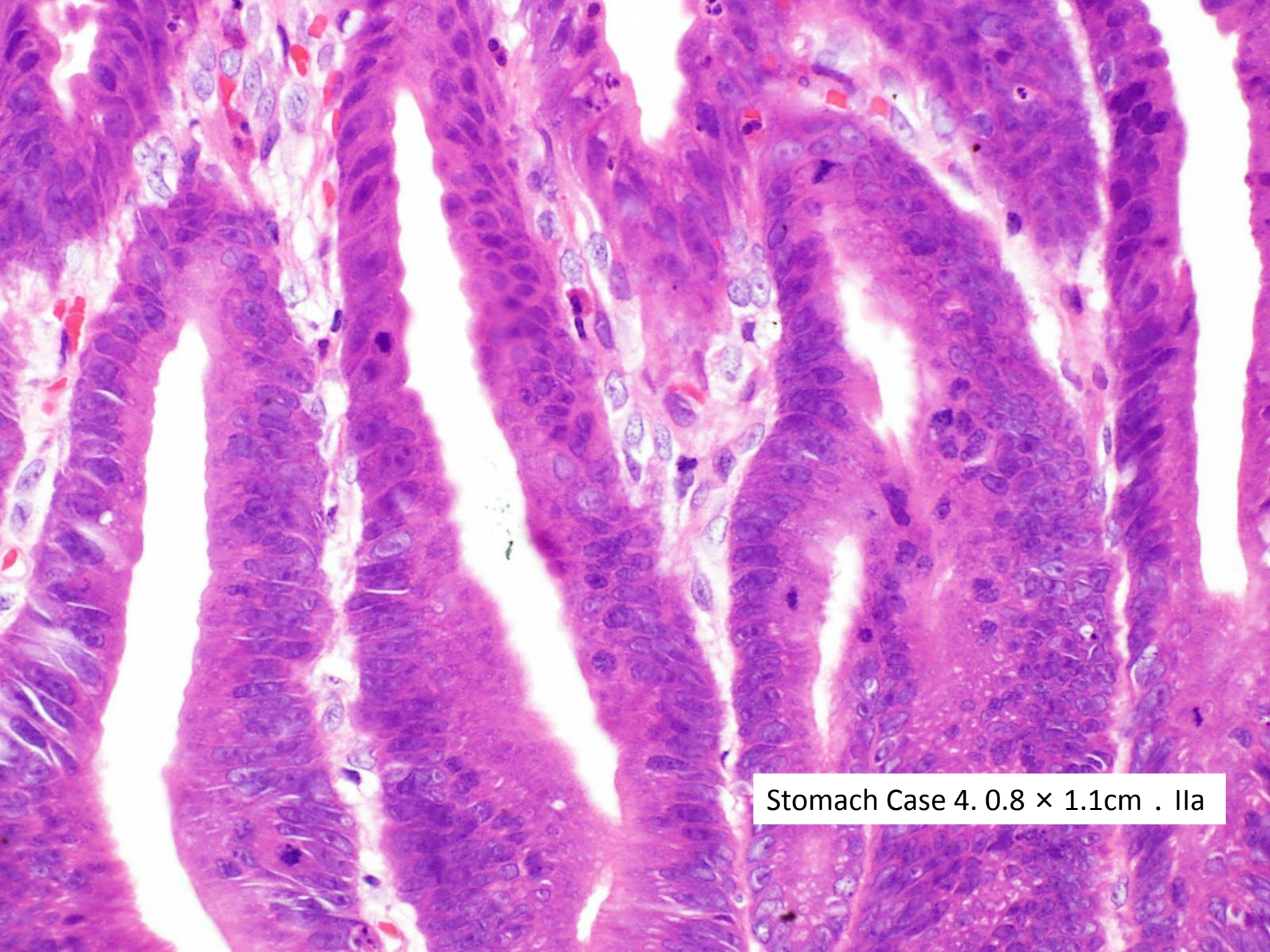

Stomach Case 3. IIa biopsy

DIAGNOSI ISTOLOGICA

NEOPLASIA INTRA-EPITELIALE DI BASSO GRADO/DISPLASIA EPITELIALE DI BASSO GRADO (DISPLASIA MODERATA)

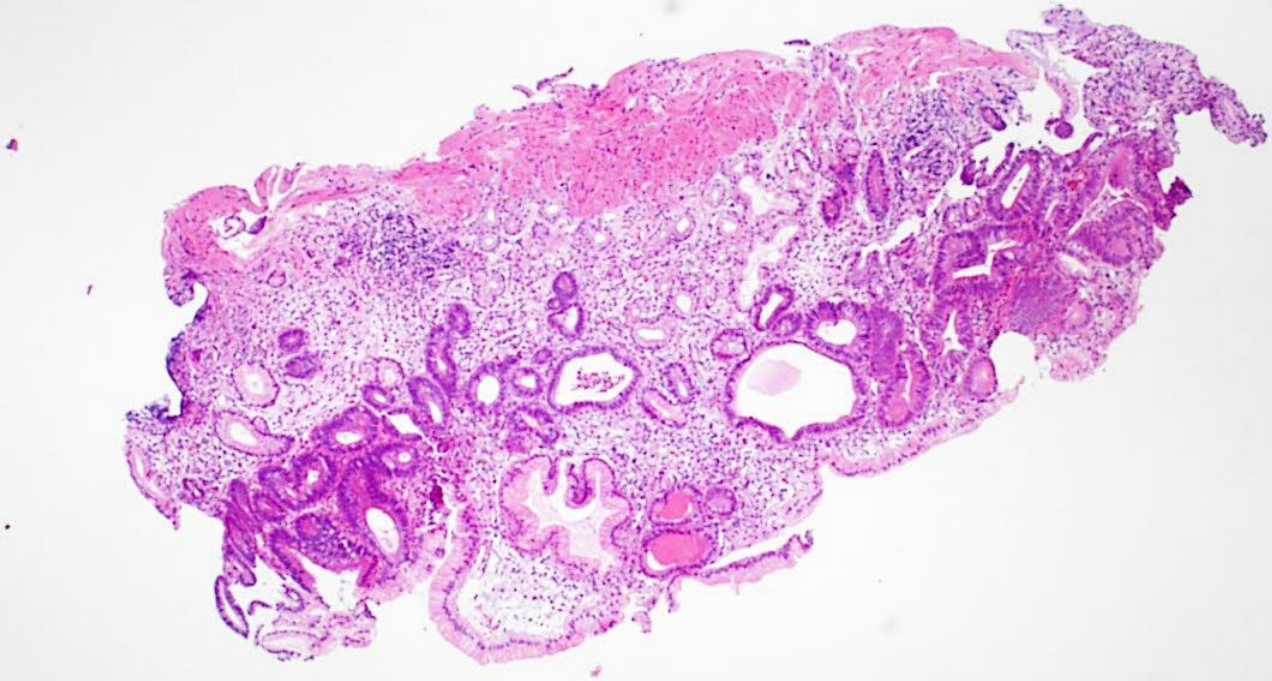
Stomach Case 4. 0.8 ×1.1cm ． IIa ESD


Stomach Case 4. 0.8 × 1.1cm ． IIa

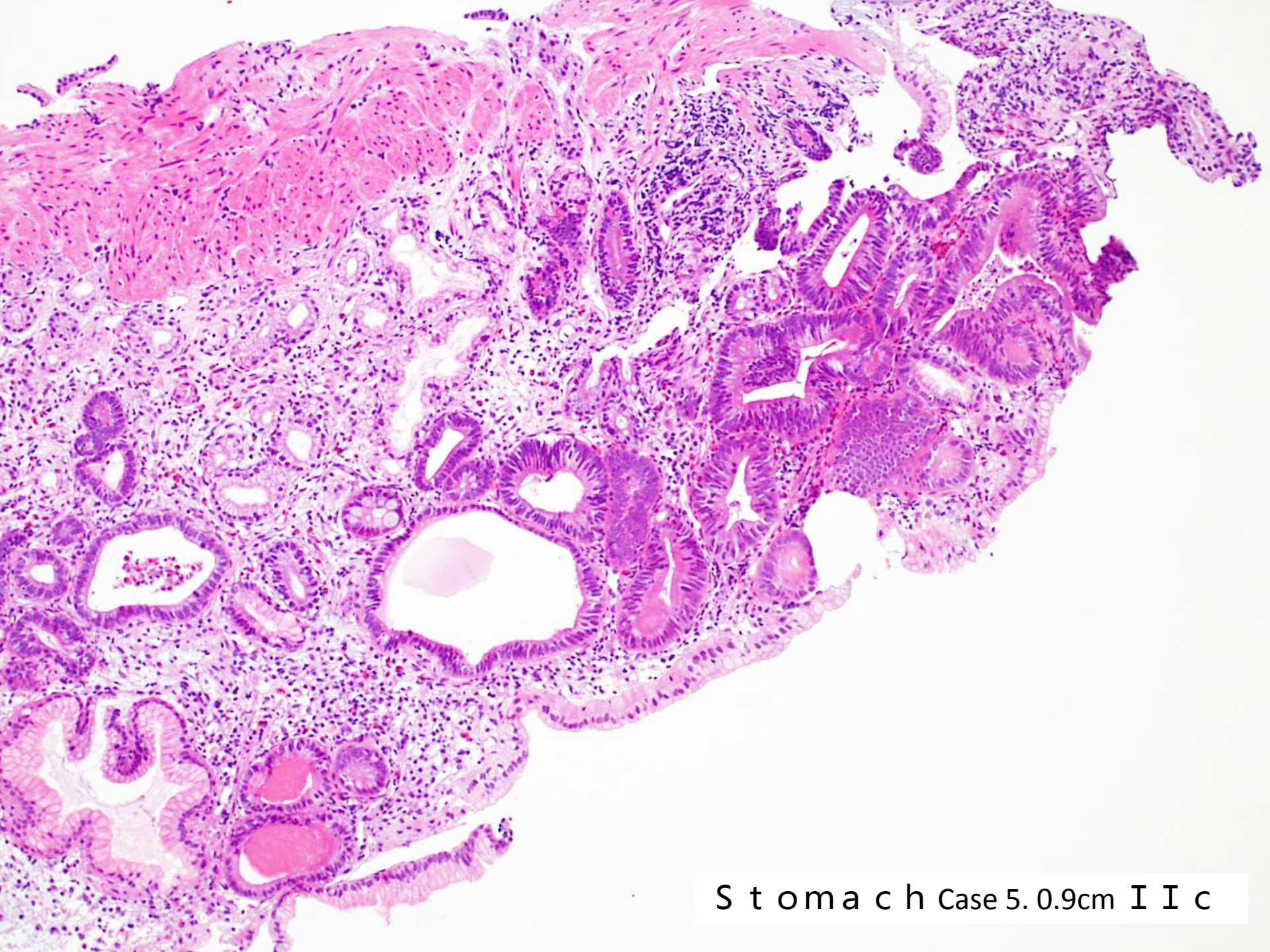

Stomach Case 4. 0.8 × 1.1cm ． IIa

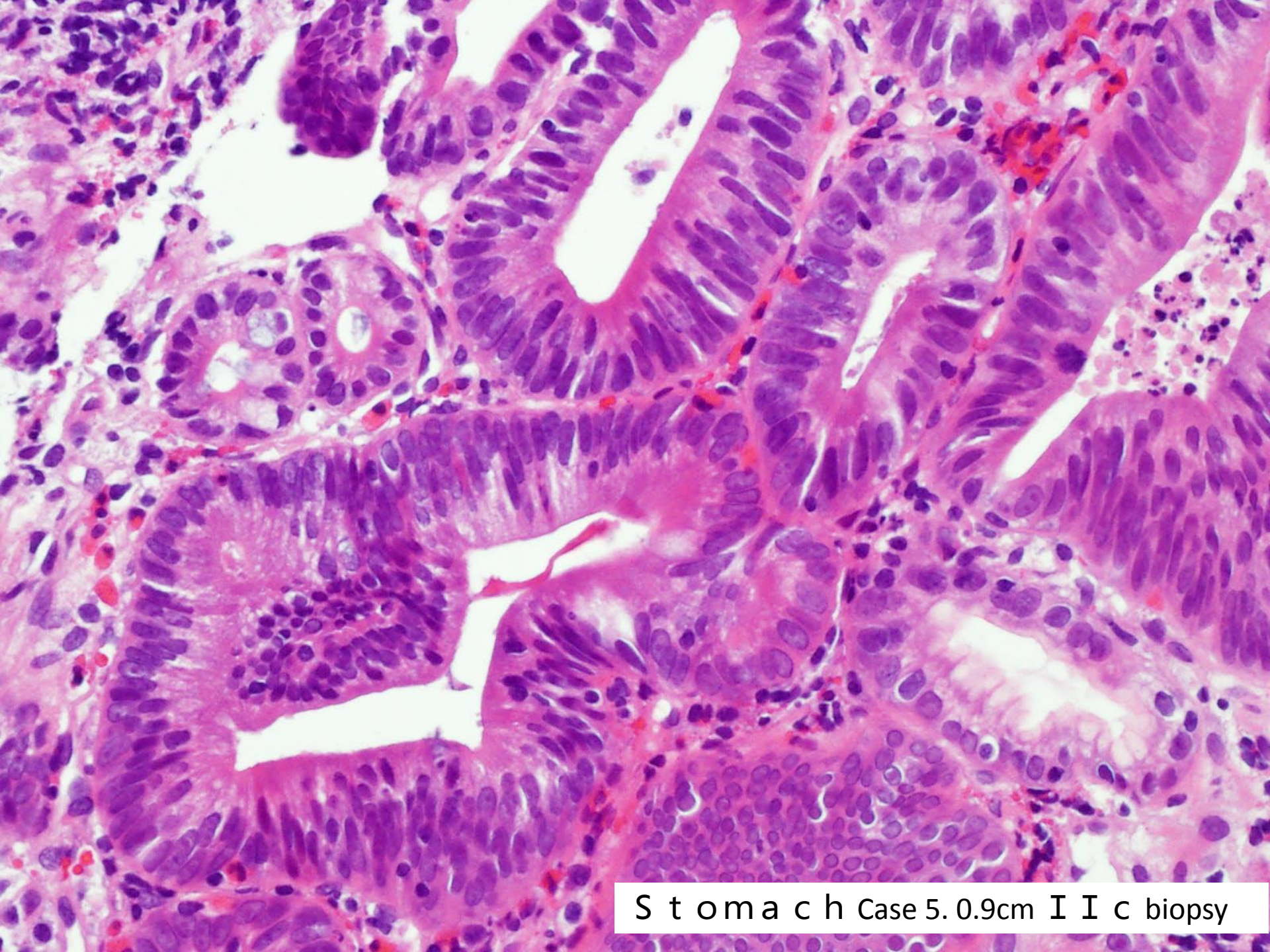
DIAGNOSI ISTOLOGICA

NEOPLASIA INTRA-EPITELIALE DI ALTO GRADO/DISPLASIA EPITELIALE DI ALTO GRADO



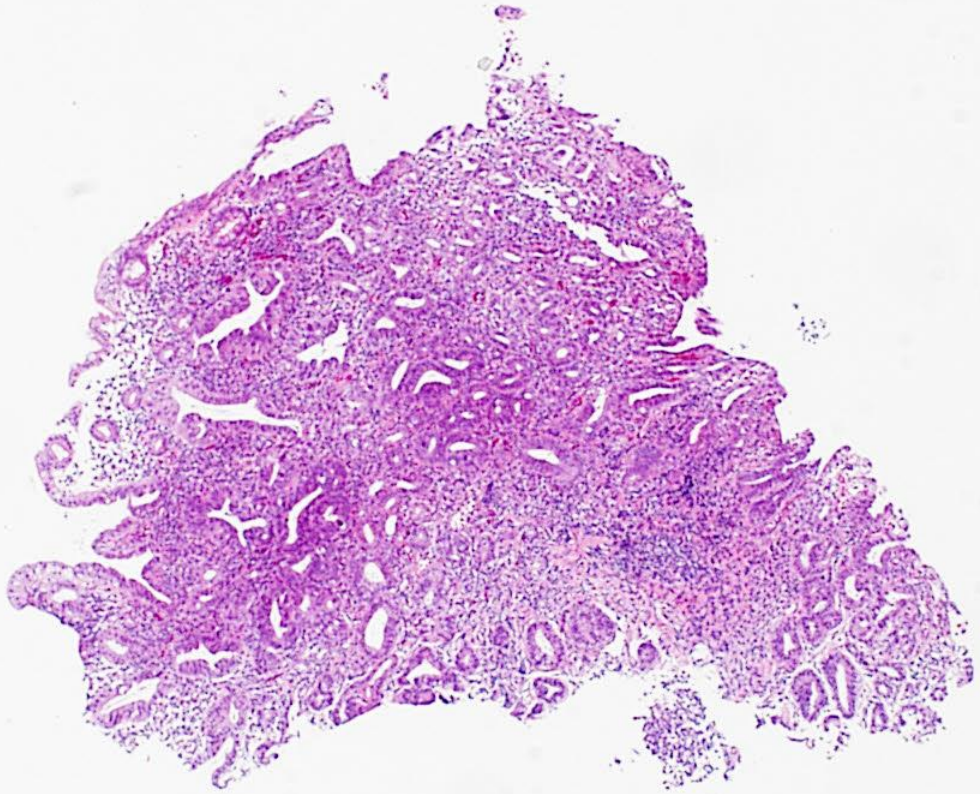
Stomach Case 5. 0.9cm IIc biopsy


S t o m a c h Case 5. 0.9cm I I c

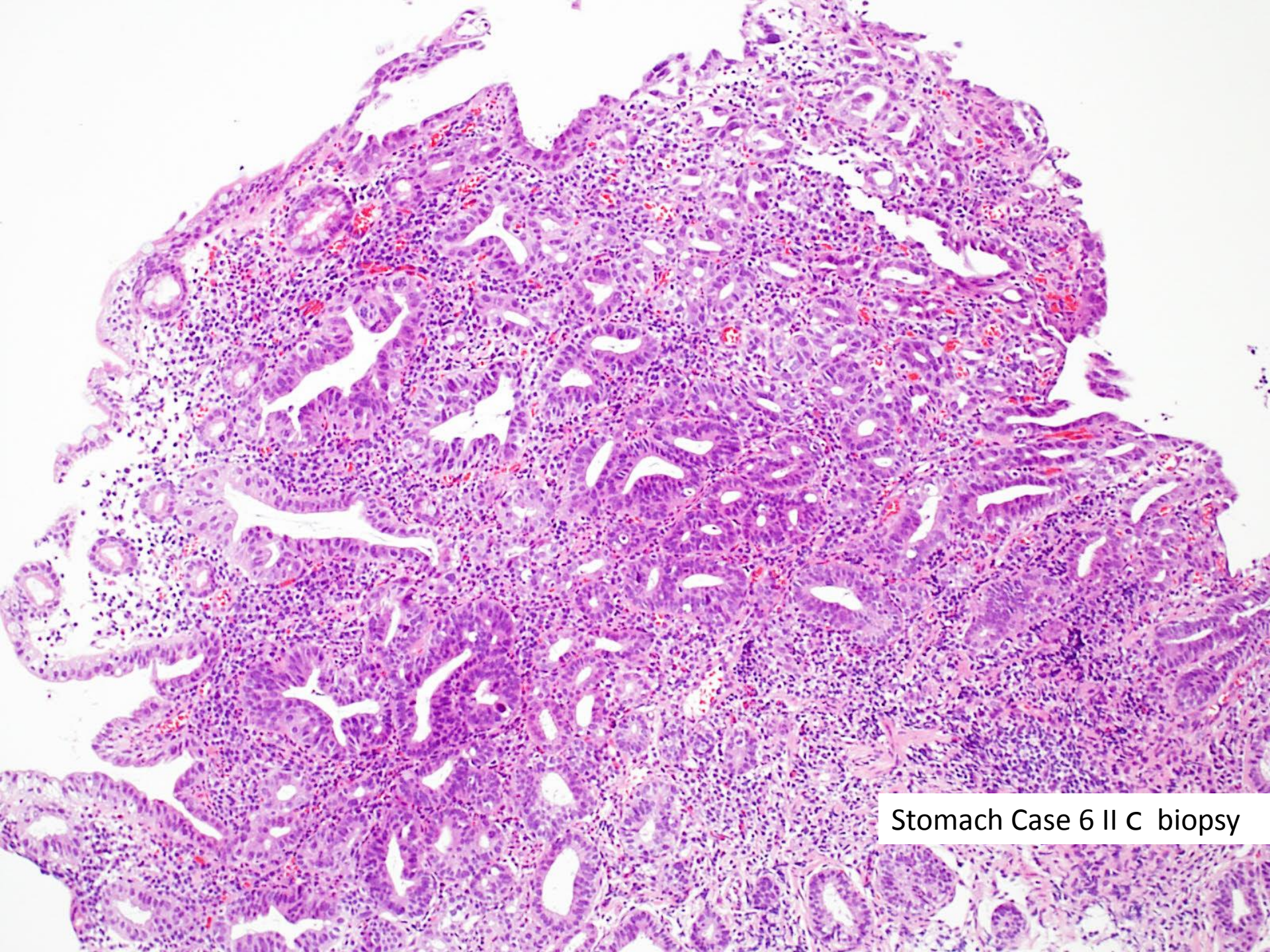

S t o m a c h Case 5. 0.9cm I I c biopsy

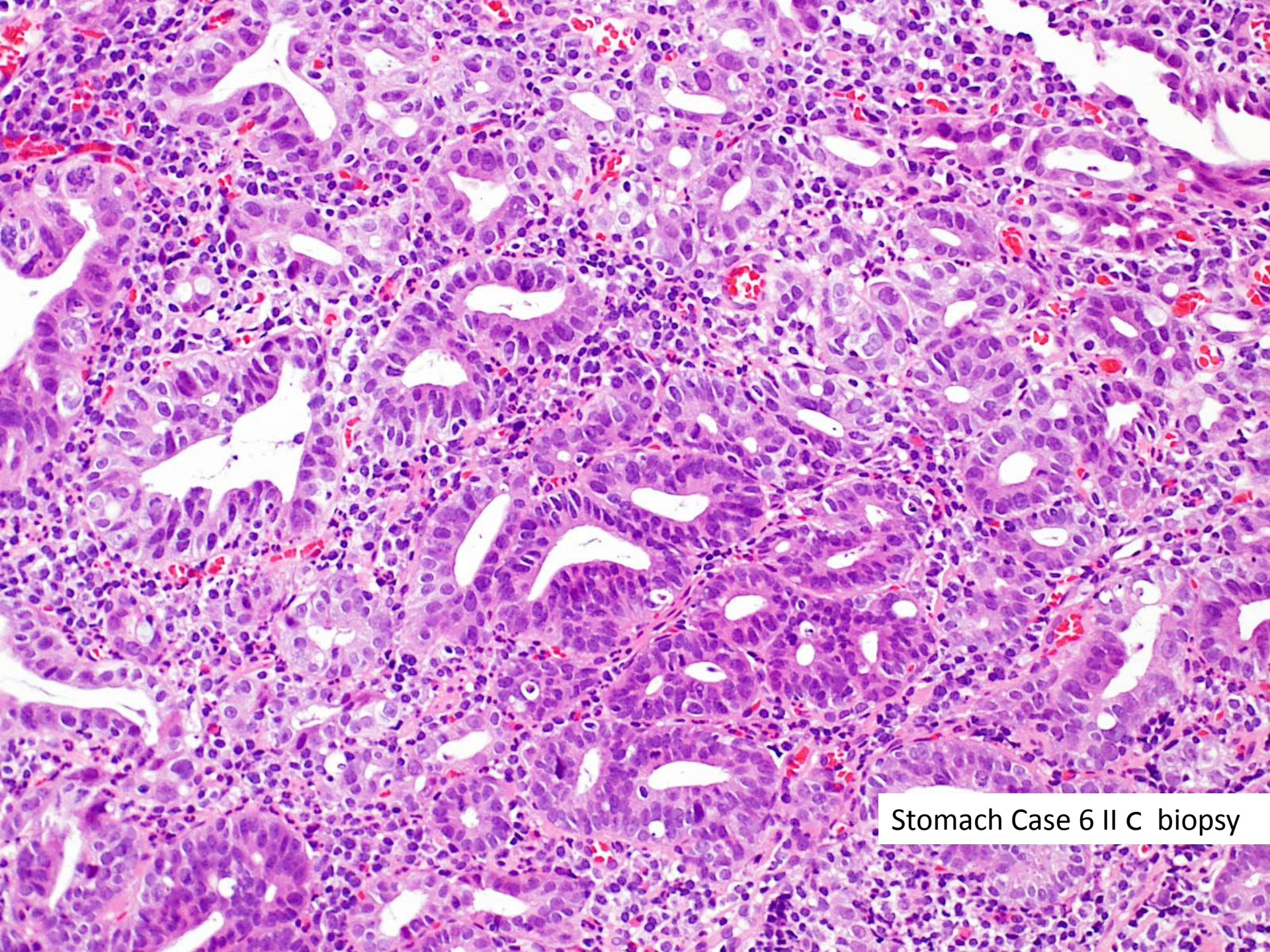
DIAGNOSI ISTOLOGICA

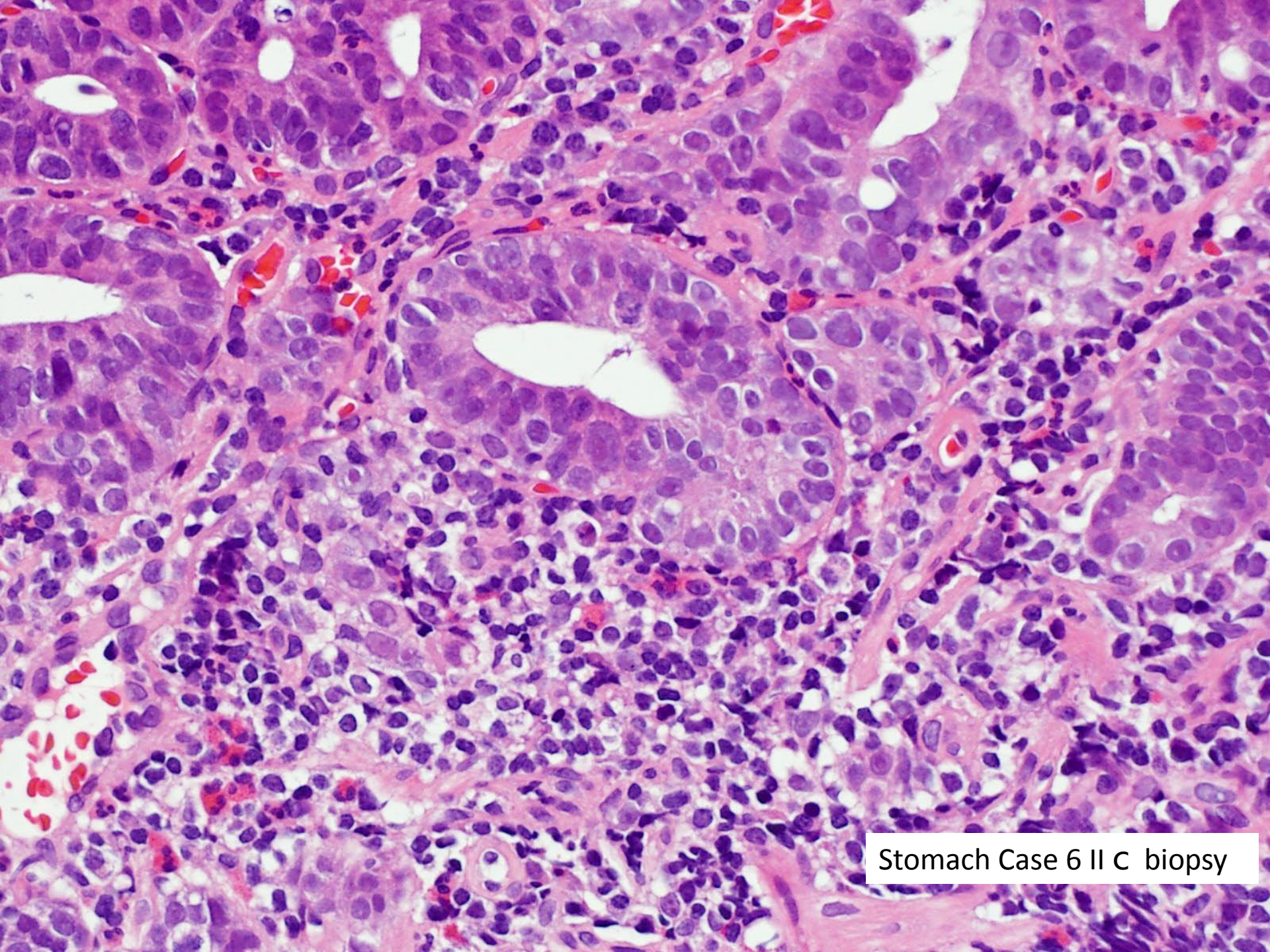
FRAMMENTO SUPERFICIALE DI ADENOCARCINOMA DI BASSO GRADO (G1)



Stomach Case 6 II C biopsy

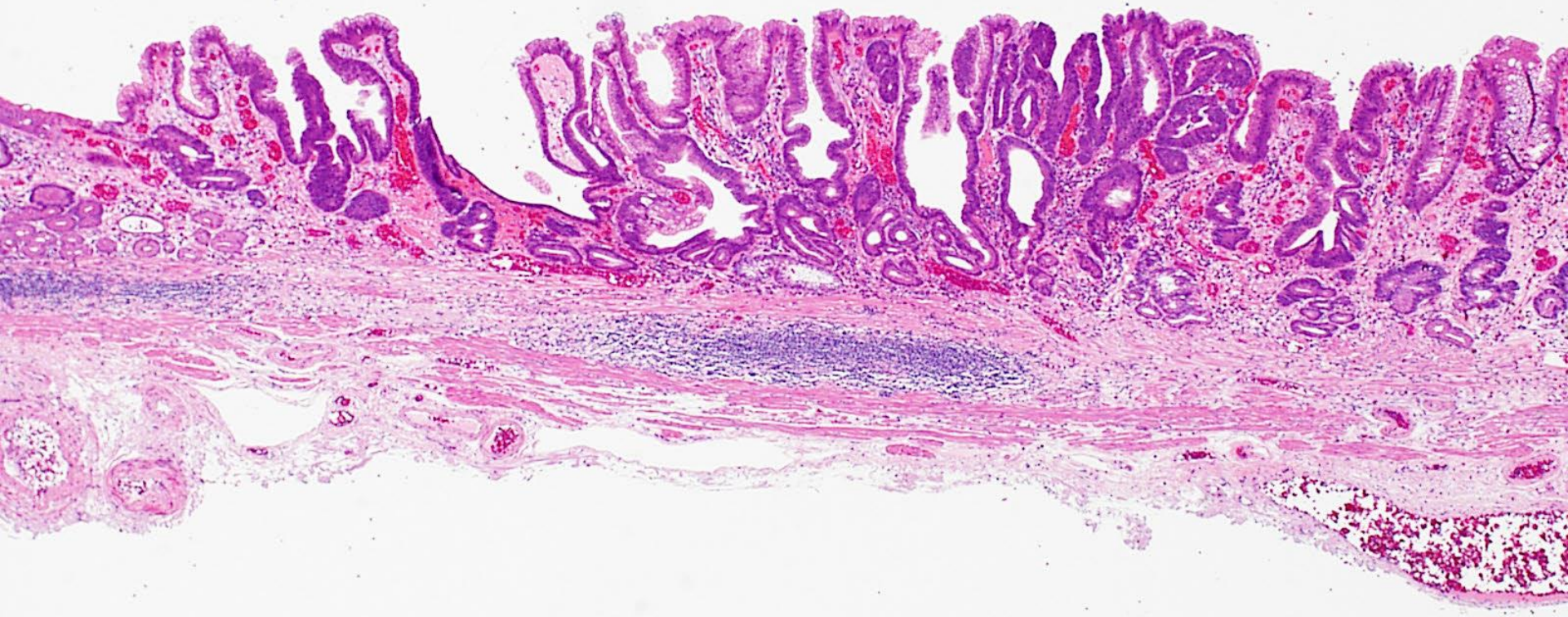

Stomach Case 6 II C biopsy


Stomach Case 6 II C biopsy


Stomach Case 6 II c biopsy

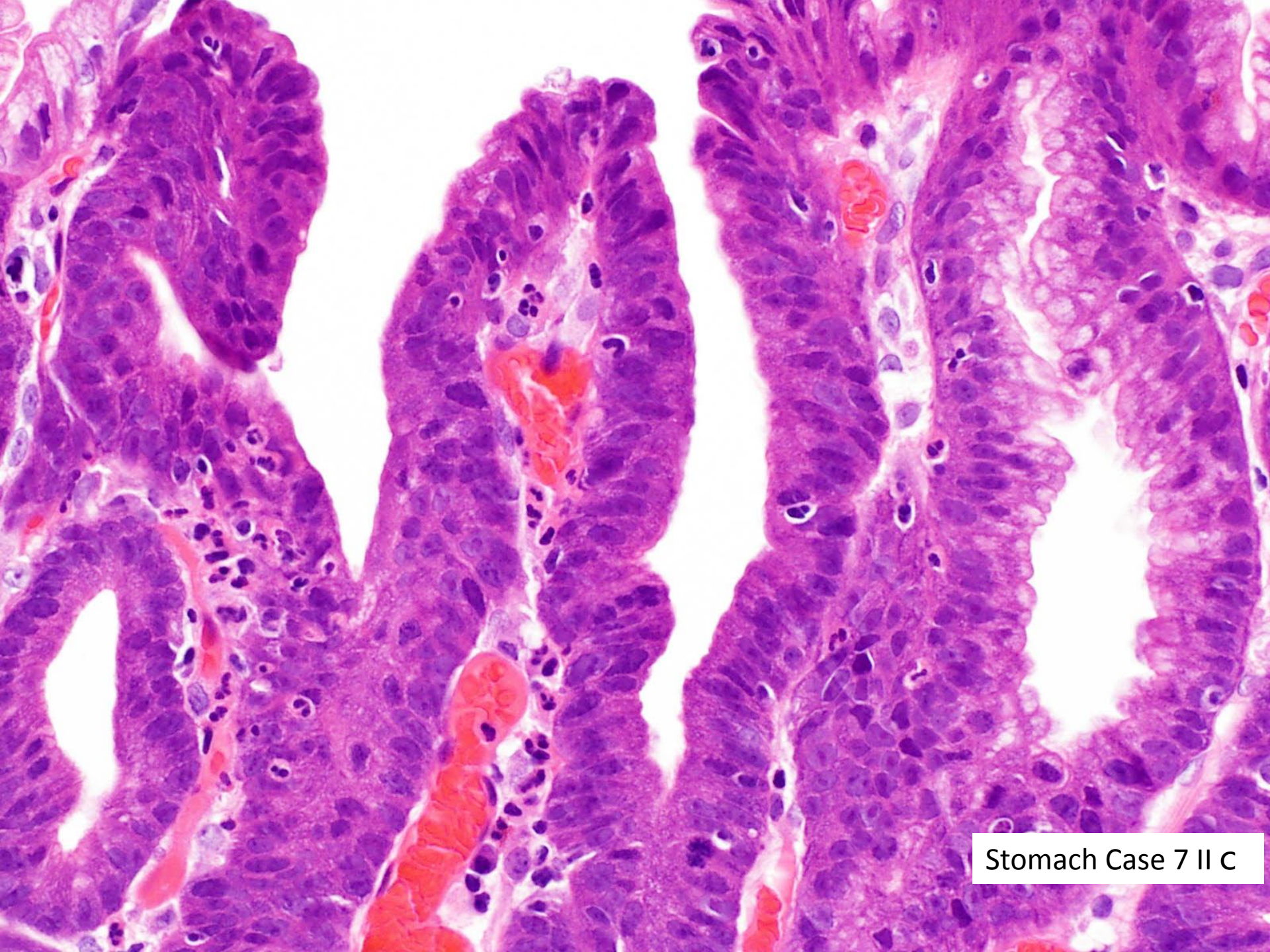
DIAGNOSI ISTOLOGICA

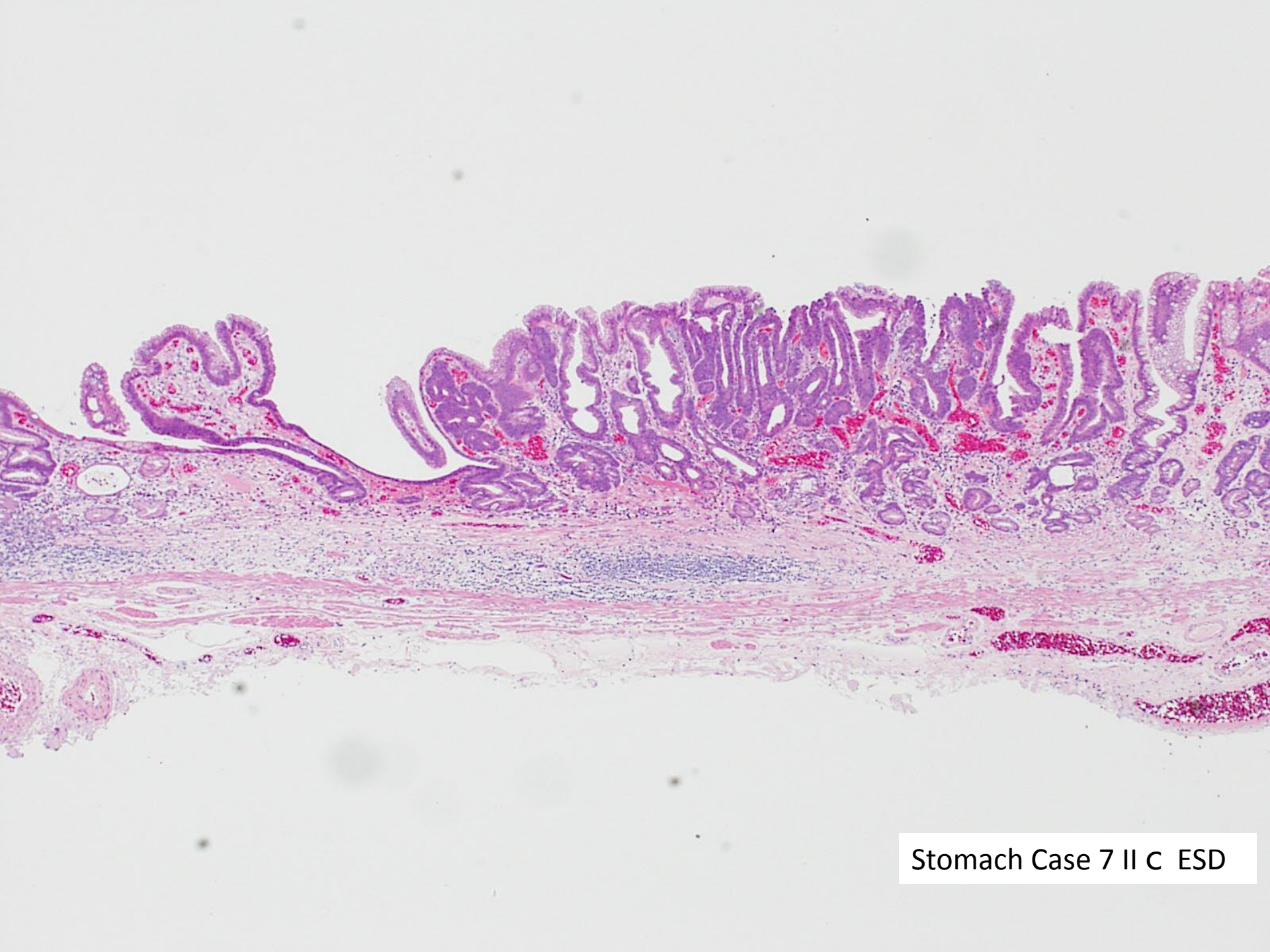
FRAMMENTO SUPERFICIALE DI ADENOCARCINOMA DI BASSO GRADO (G2)



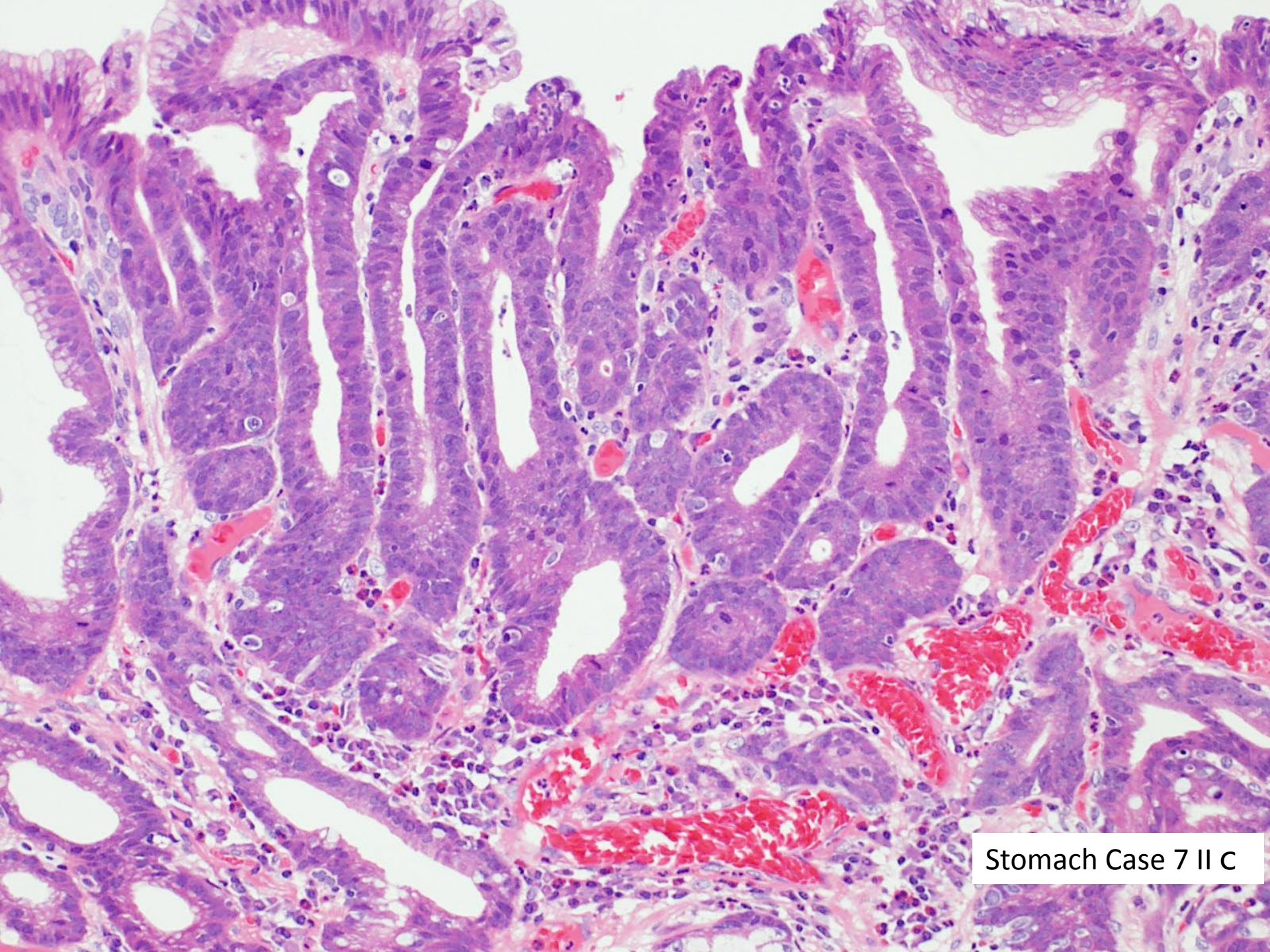
Stomach Case7 II b 4mm ESD

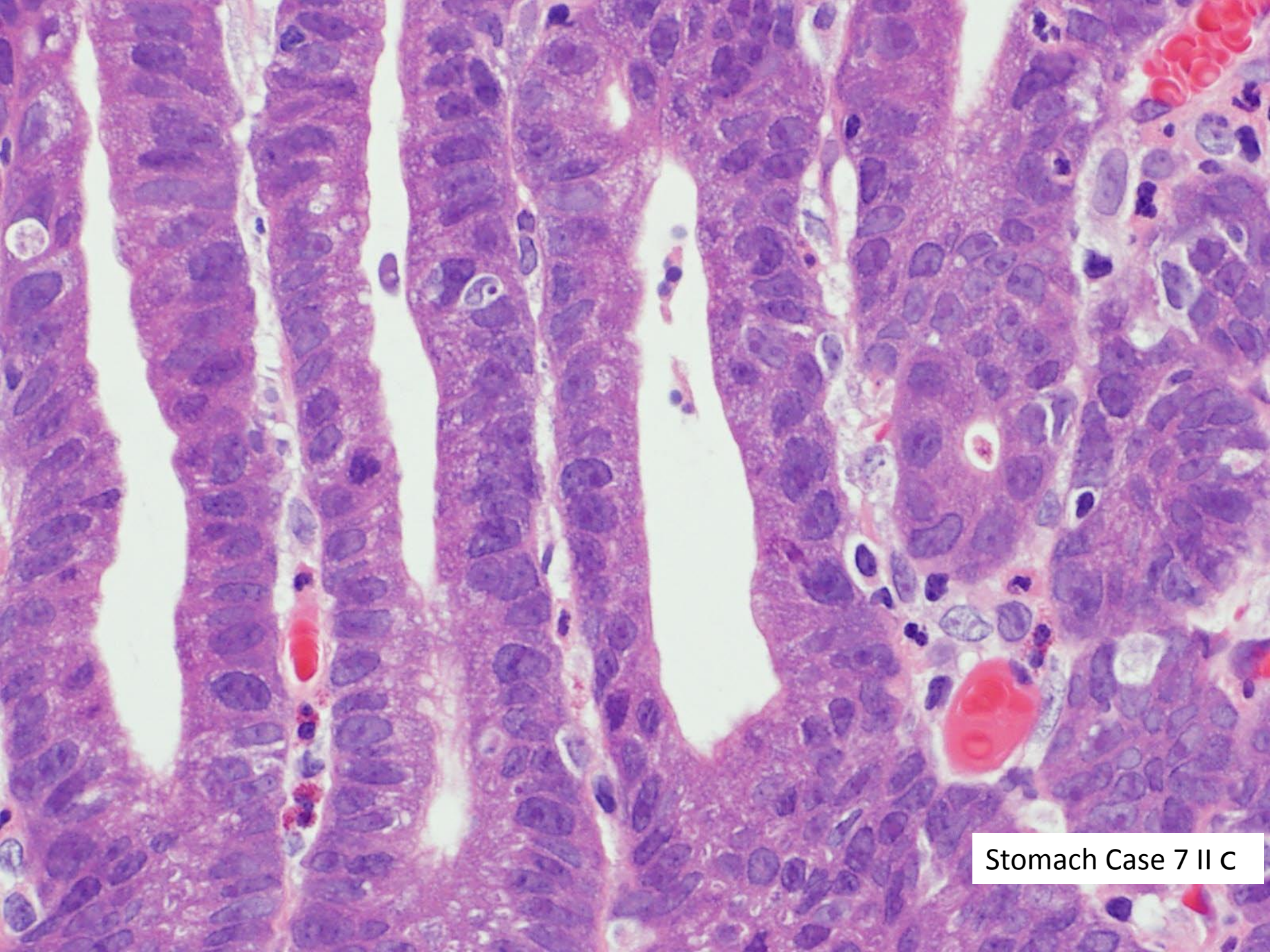

Stomach Case 7 II c


Stomach Case 7 II c



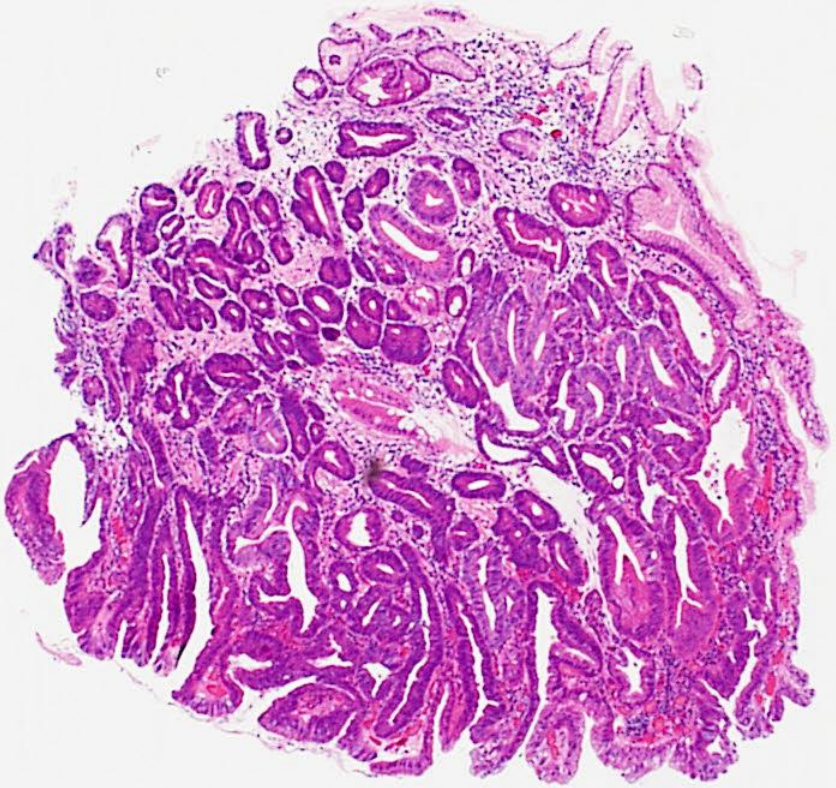
Stomach Case 7 II c ESD


Stomach Case 7 II c

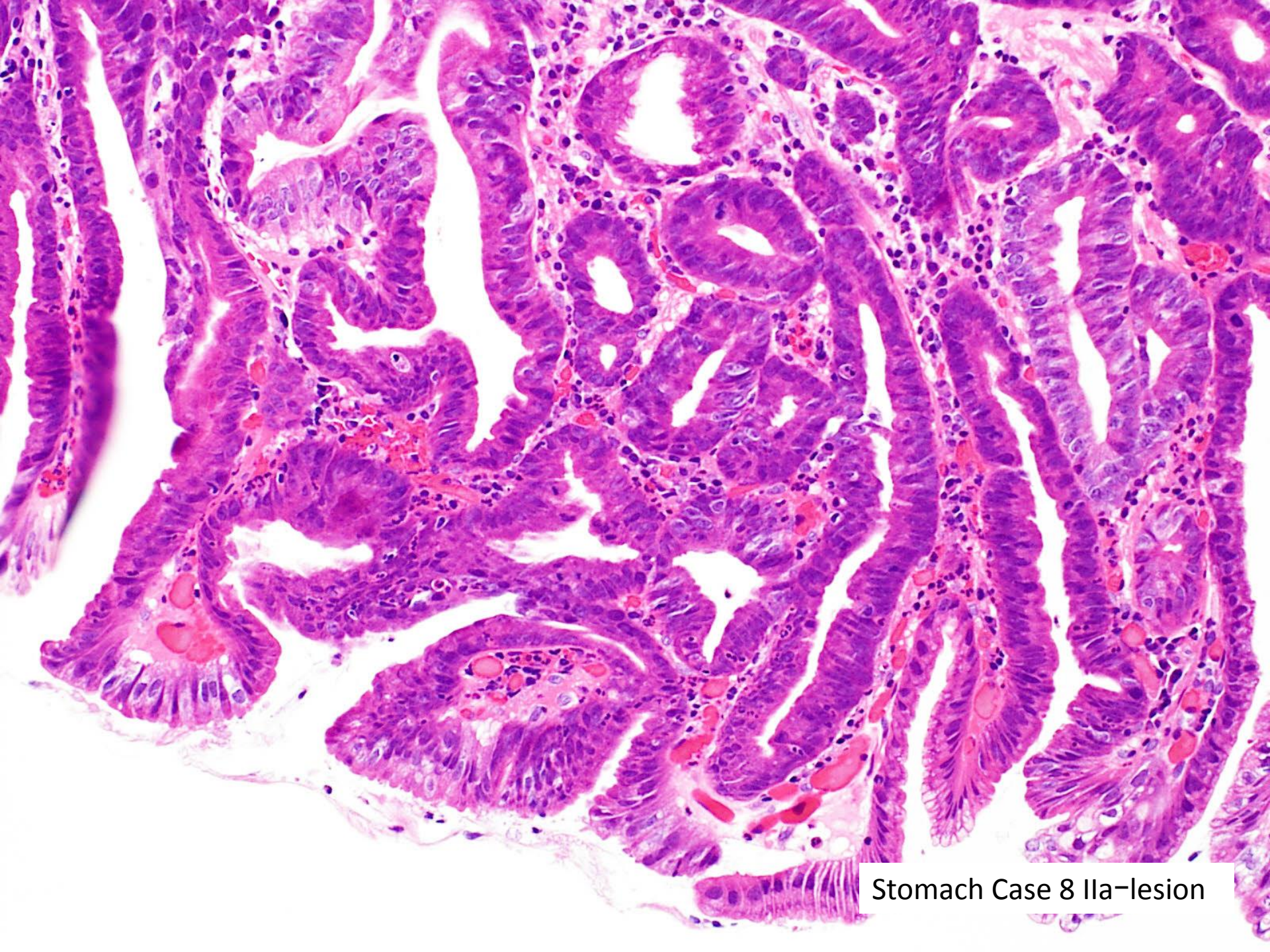

Stomach Case 7 II c

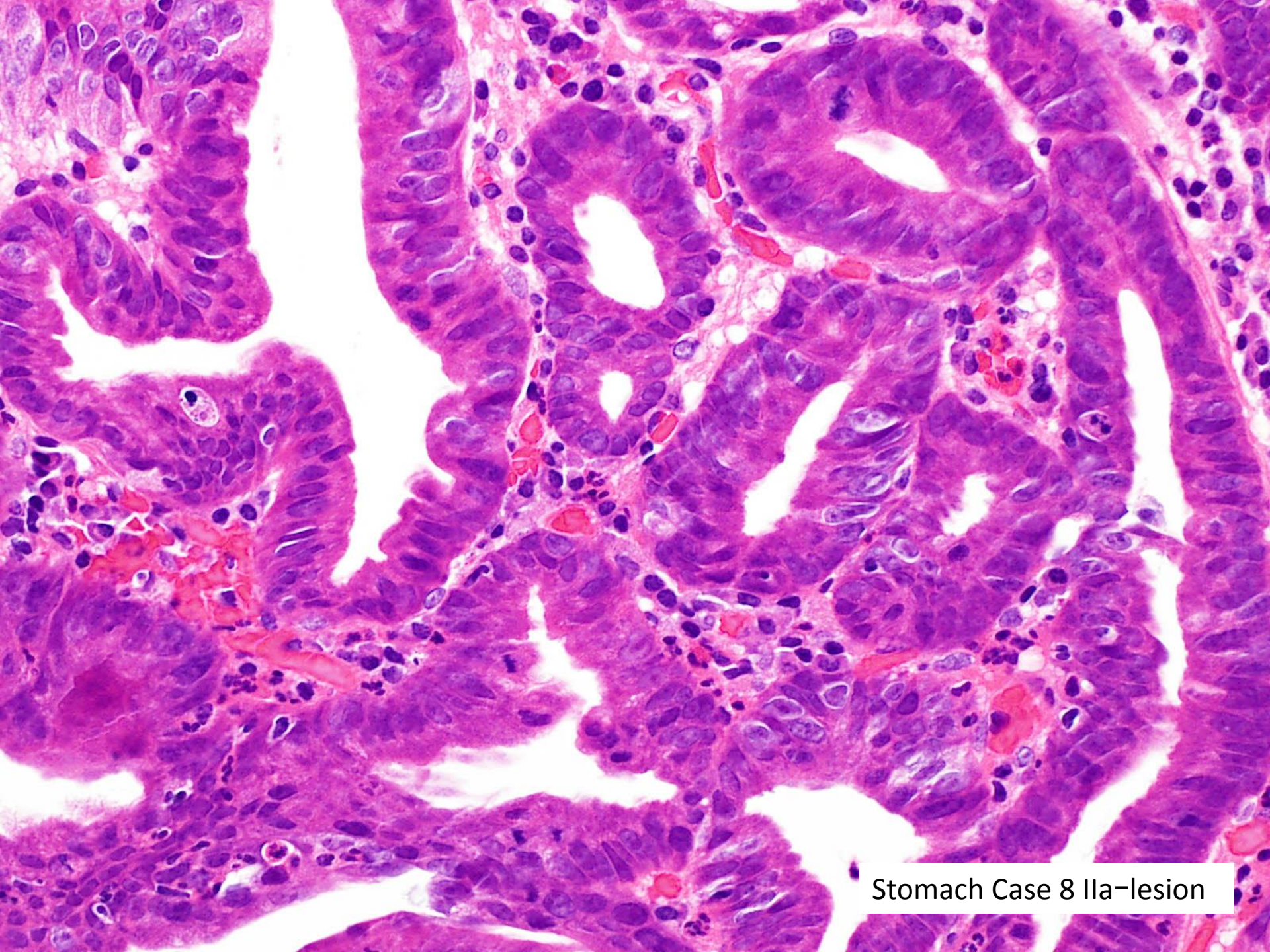
DIAGNOSI ISTOLOGICA

NEOPLASIA INTRA-EPITELIALE DI ALTO GRADO/DISPLASIA EPITELIALE DI ALTO GRADO



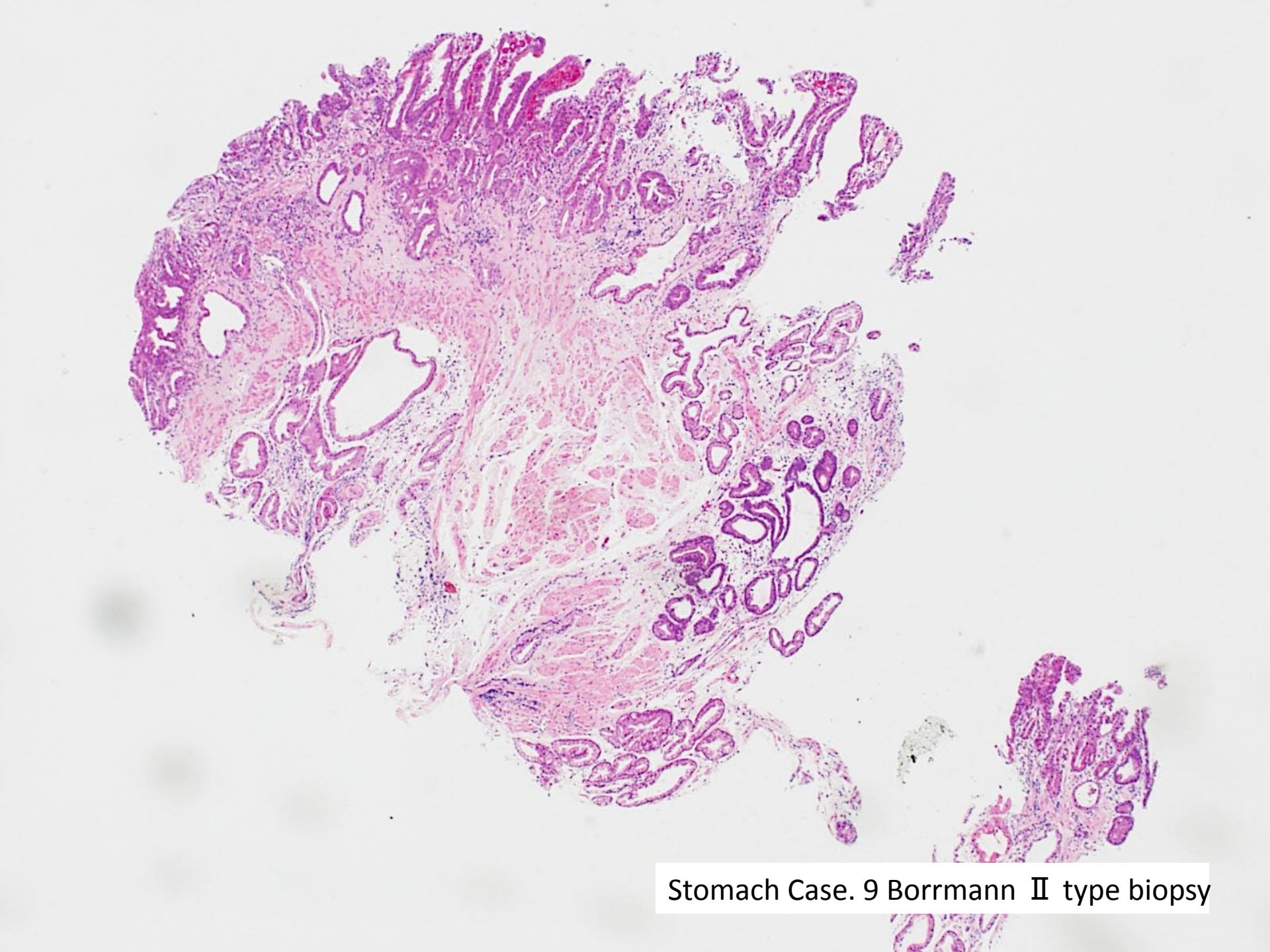
Stomach Case 8 IIa−lesion


Stomach Case 8 IIa−lesion

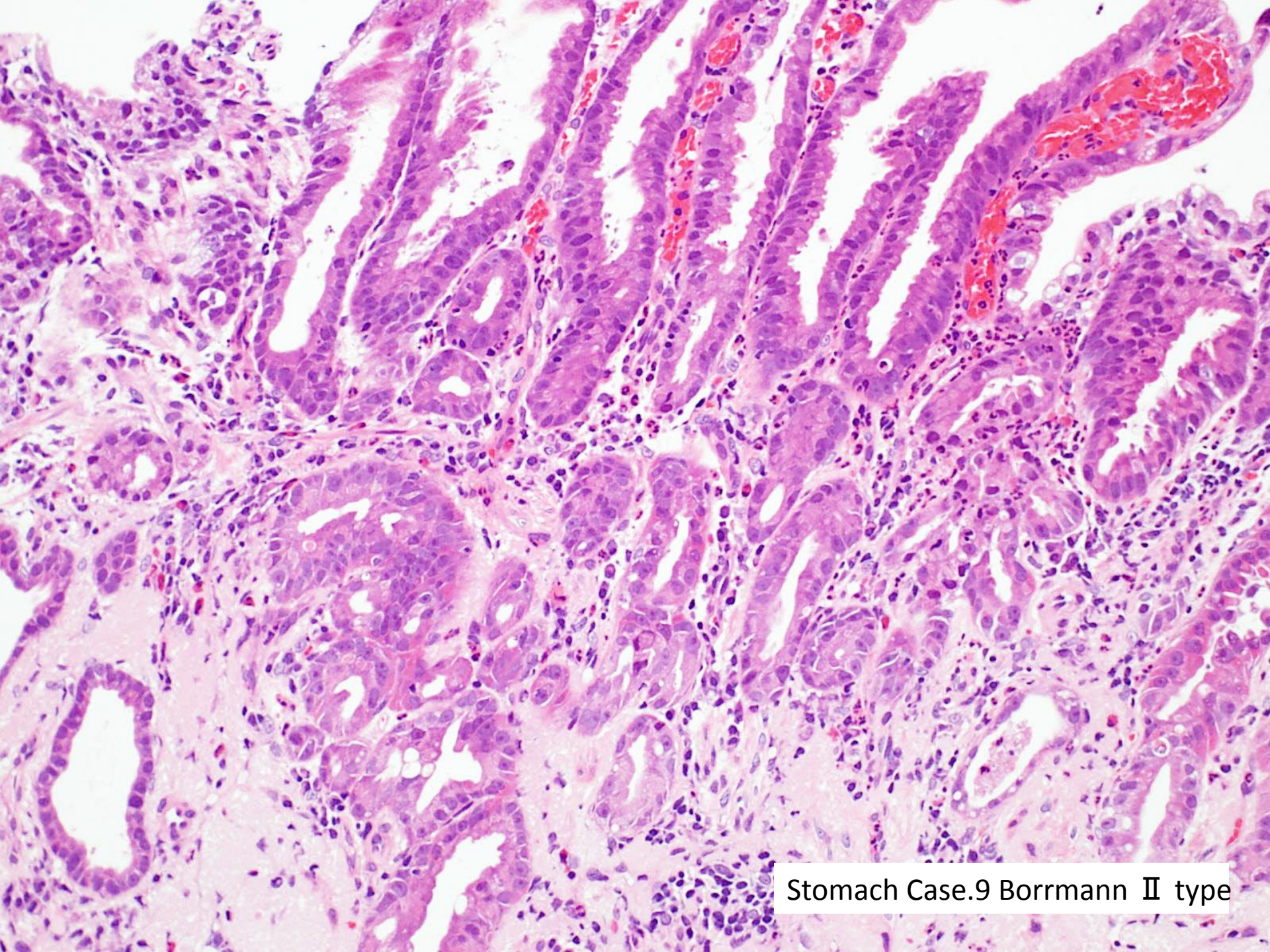

Stomach Case 8 IIa−lesion

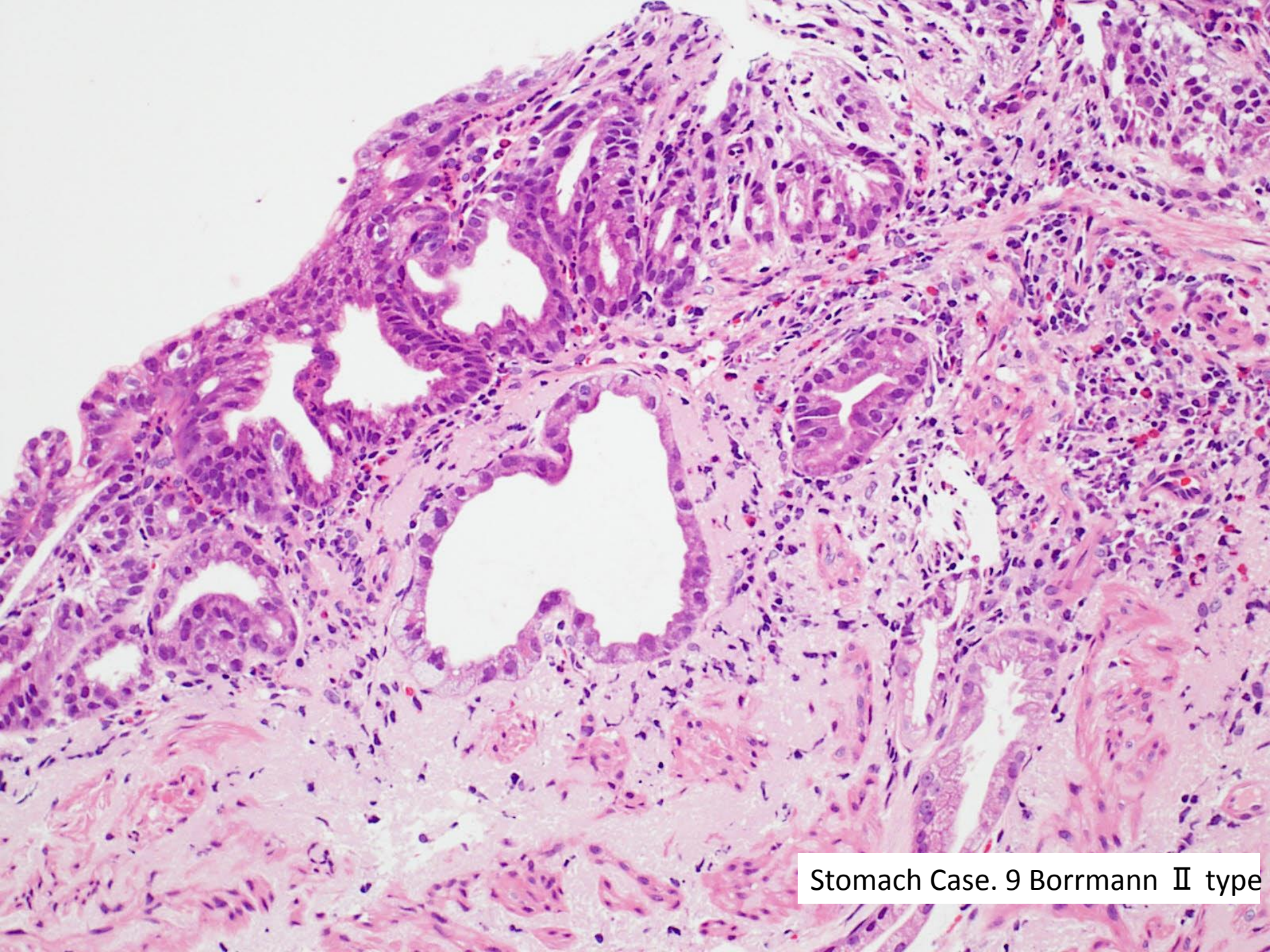
DIAGNOSI ISTOLOGICA

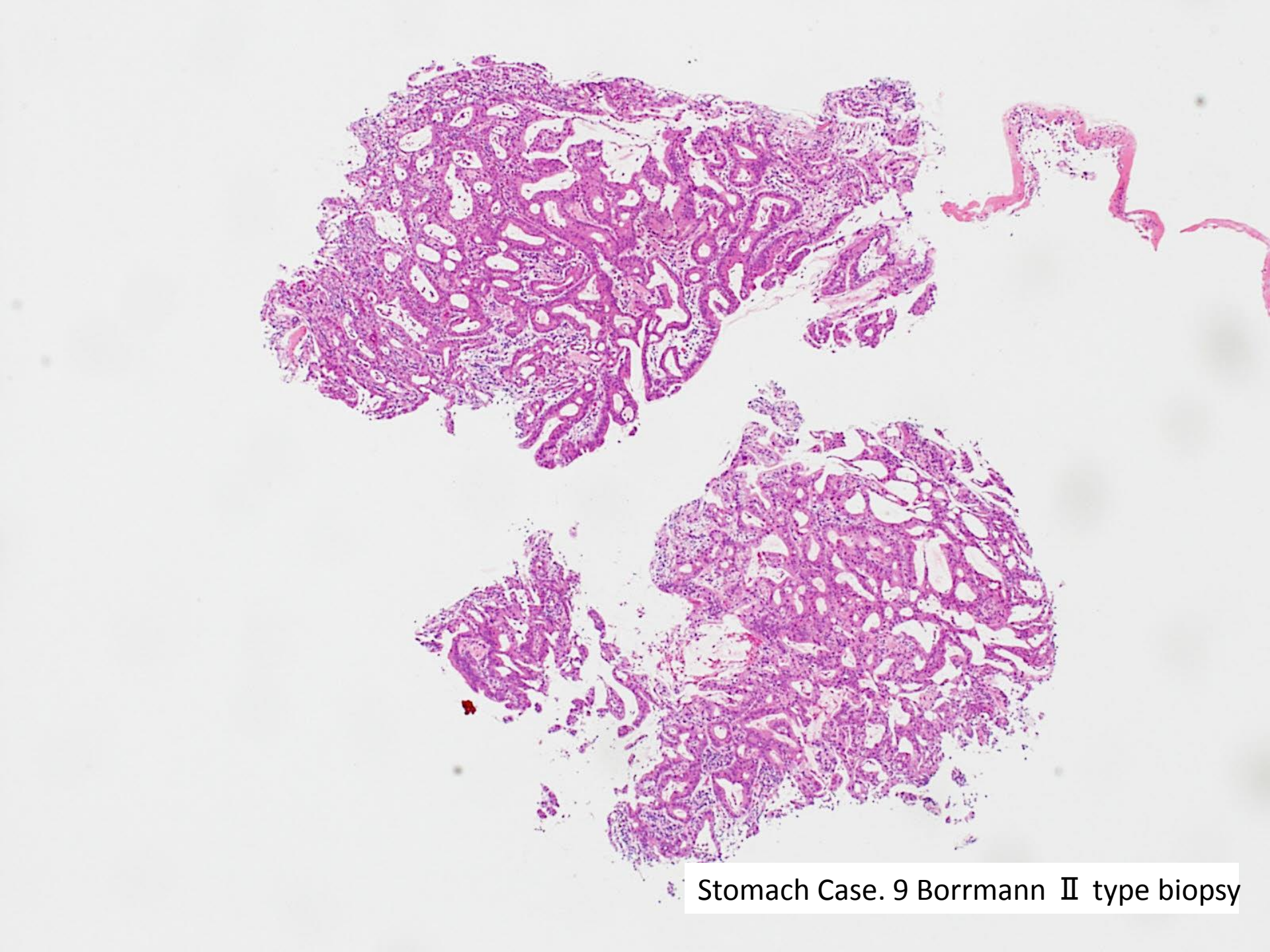
FRAMMENTO SUPERFICIALE DI ADENOCARCINOMA (G1)



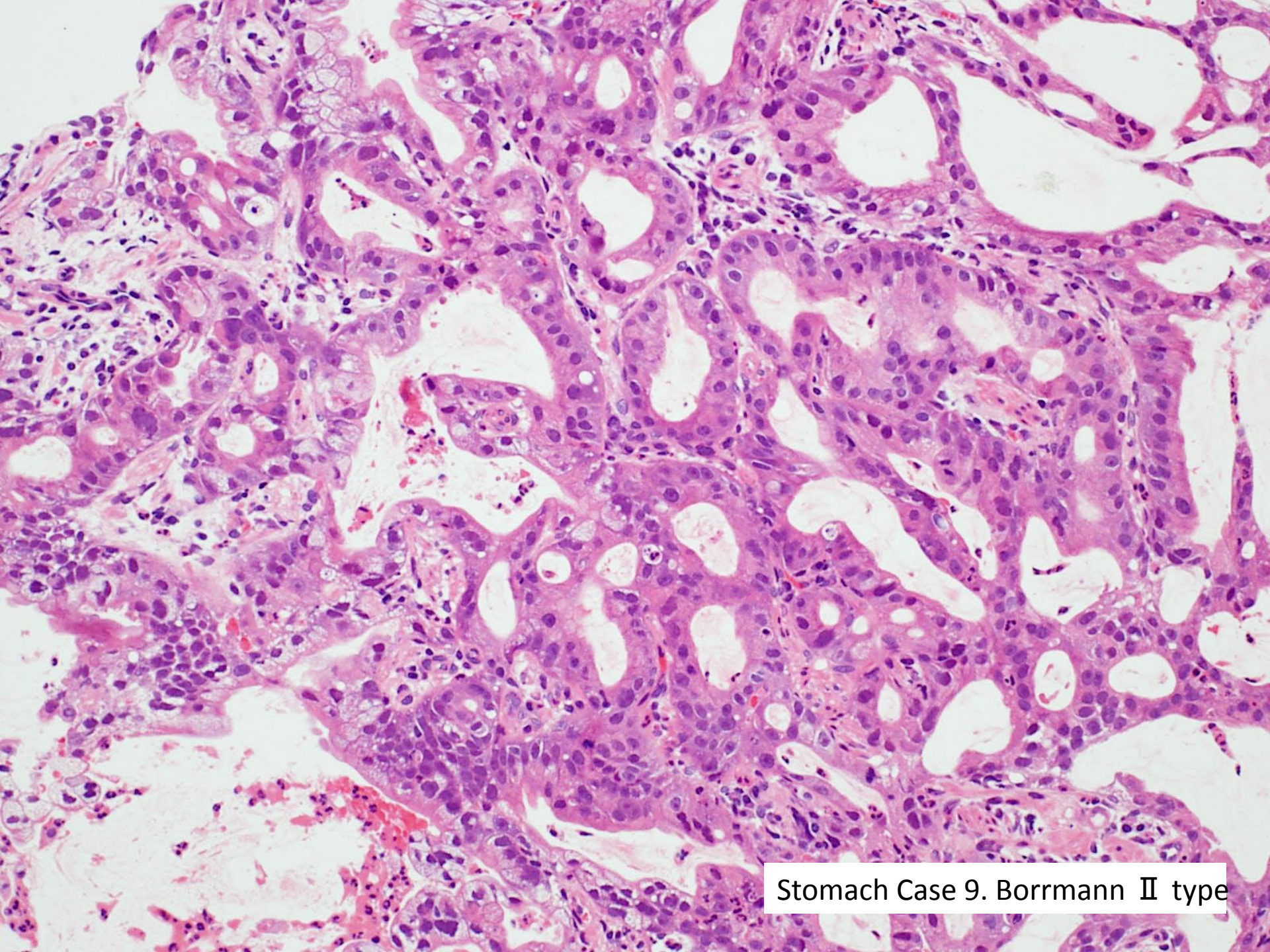
Stomach Case. 9 Borrmann Ⅱ type biopsy


Stomach Case.9 Borrmann Ⅱ type


Stomach Case. 9 Borrmann Ⅱ type

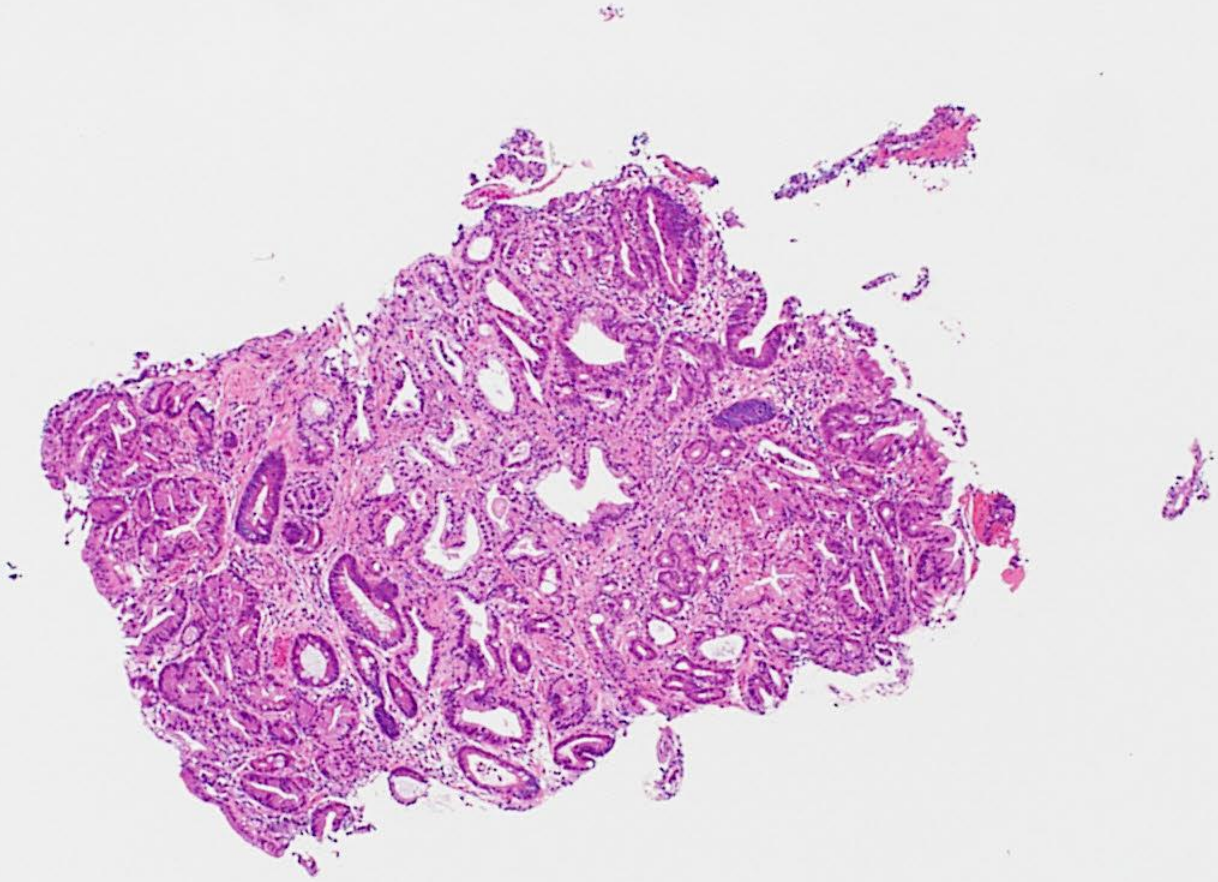


Stomach Case. 9 Borrmann Ⅱ type biopsy

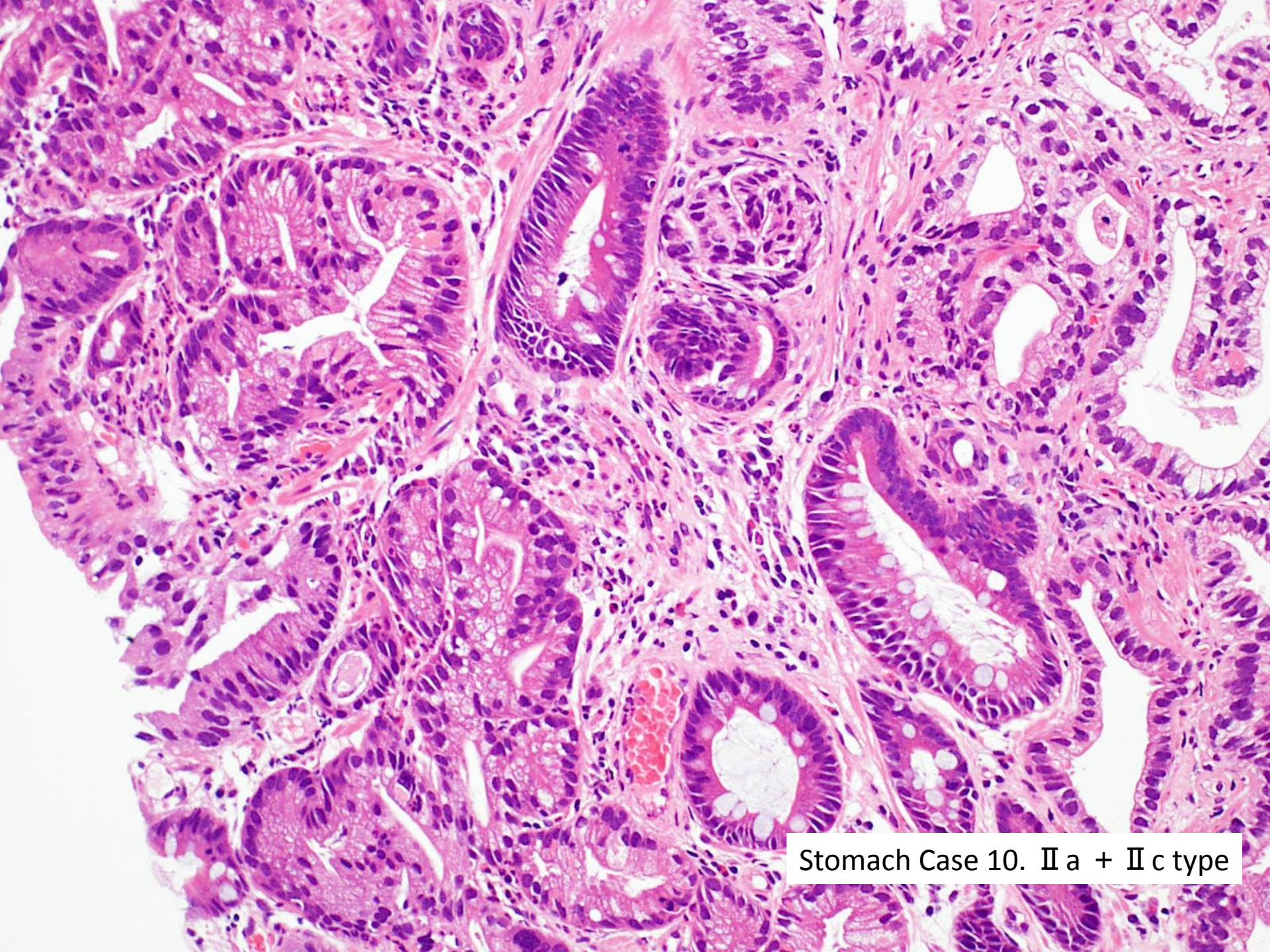

Stomach Case 9. Borrmann Ⅱ type

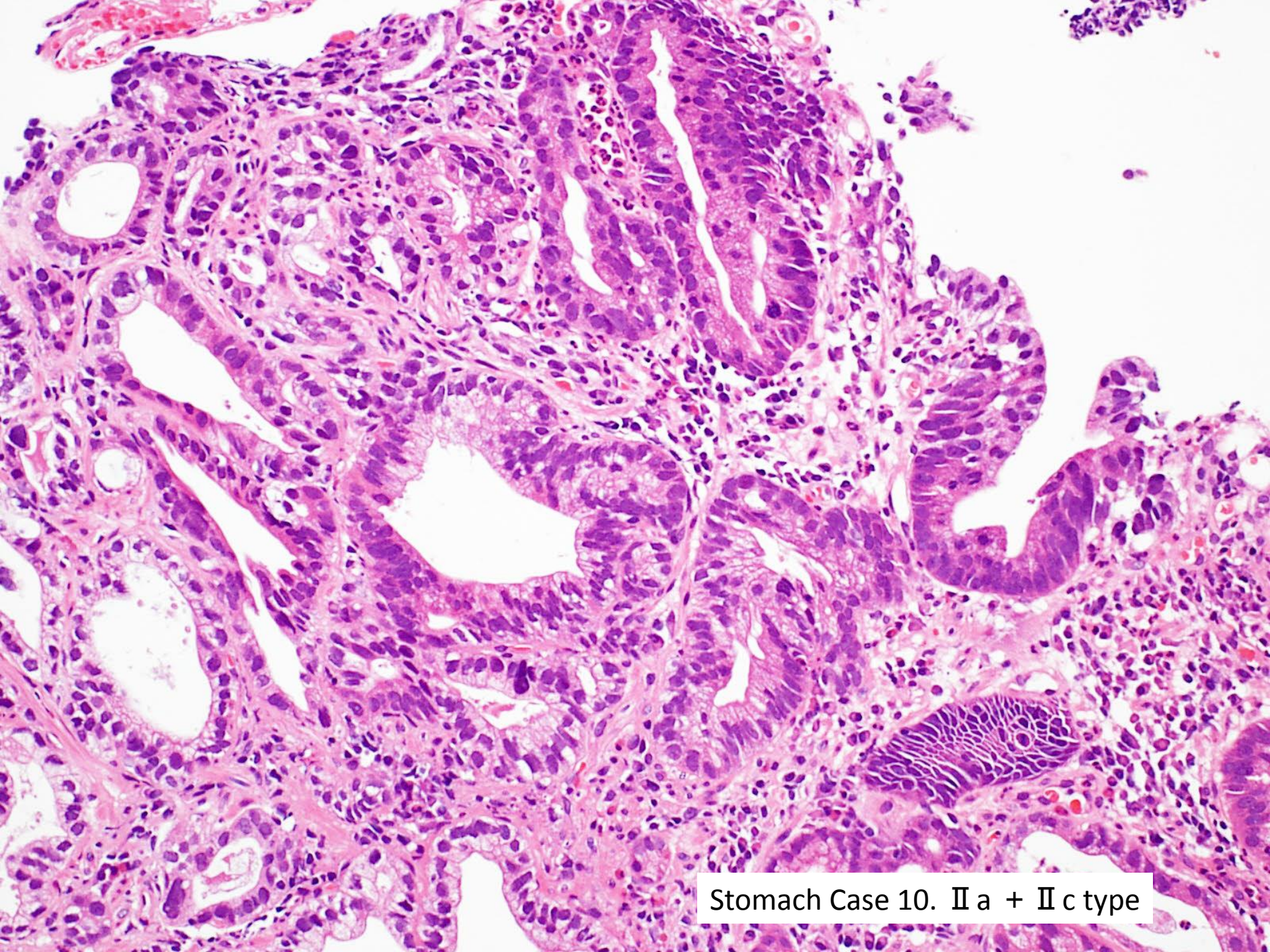
DIAGNOSI ISTOLOGICA

FRAMMENTI SUPERFICIALI DI ADENOCARCINOMA



Stomach Case 10. Ⅱa + Ⅱc type biopsy


Stomach Case 10. Ⅱa + Ⅱc type


Stomach Case 10. Ⅱa + Ⅱc type

DIAGNOSI ISTOLOGICA

FRAMMENTO SUPERFICIALE DI ADENOCARCINOMA

GRAZIE PER LA VOSTRA ATTENZIONE E PARTECIPAZIONE

Luca Saragoni

TEL: 0543 731702

MAIL: luca.saragoni@auslromagna.it