

Session IV. 헬리코박터와 위종양

헬리코박터 음성 및 헬리코박터 제균치료 후 위암

건국대학교 의과대학 내과학교실

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[CURRICULUM VITAE]

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H. pylori-negative gastric cancers & gastric cancers after eradication

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H. pylori-negative vs. *H. pylori*-naïve

H. pylori-negative

Individuals with past infection

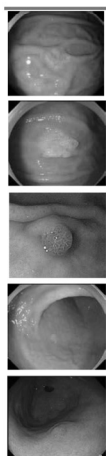
- After *H. pylori* eradication therapy
- Unintended eradication
- Spontaneous regression of *H. pylori*

H. pylori-naïve
(never been infected)

H. pylori-naïve cancers

Ono et al. Digestion 2012;86:59-65	0.42% (1 / 240)
Yamada et al. Digestion 2018;98:127-34	2.40% (16 / 666)
Kim et al. Gut Liver 2016;10:212-9	3.97% (28 / 705)
Yoon et al. Helicobacter 2011;16:382-8	5.42% (34 / 627)
Kotani et al. J Gastroenterol 2024;59:1-10	5.57% (63 / 1,131)

H. pylori-negative cancers



Adenocarcinoma of fundic gland-type

Flat foveolar-type tumor

Raspberry-like foveolar-type tumor

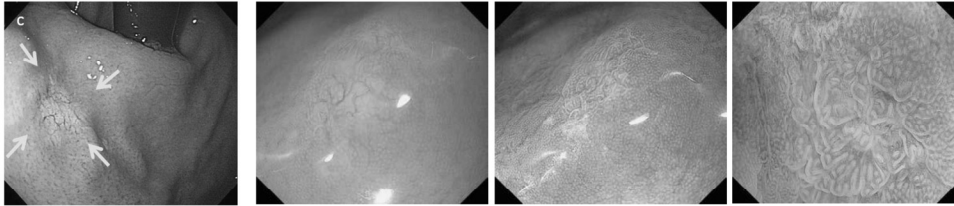
Signet ring cell carcinoma

Pyloric gland tumor
(Intestinal-type gastric dysplasia)

Stomach and Intestine 2024;59:829-39

- Cardiac cancers
- Autoimmune gastritis-related cancers
- Epstein Barr virus-related cancers
- Cancers induced by bile reflux
- Genetic diseases:
 - ① Hereditary diffuse gastric cancer
 - ② Familial adenomatous polyposis
 - ③ Gastric adenocarcinoma and proximal polyposis of the stomach
 - ④ Familial intestinal gastric cancer
 - ⑤ Li-Fraumeni syndrome
 - ⑥ Peutz-Jeghers syndrome
 - ⑦ Hereditary non-polyposis colorectal cancer

1. Adenocarcinoma of the fundic gland type



- Oxyntic gland adenocarcinoma covered by foveolar epithelium (no demarcation line)
- White subepithelial tumor with irregular vasculatures and dilated gastric pits
- Chief cell-predominant: MUC6 (+), PG I (+), H⁺/K⁺-ATPase (+)
- Some (12-43%) show guanine nucleotide binding protein alpha-stimulating complex (GNAS) mutation

Jap J Gastroenterol Endosc 2016;58:1492-503, Stomach and Intestine 2024 ;59:673-86

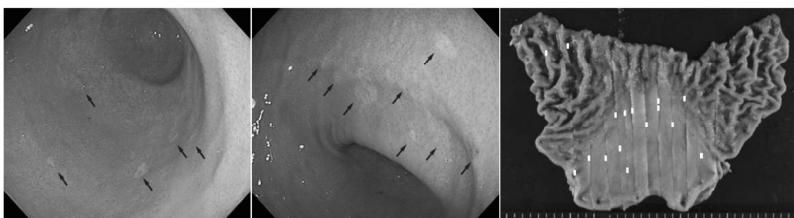
2. Signet ring cell carcinoma (SRCC)



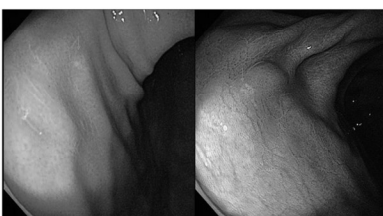
Stomach and Intestine 2023;58:1669-78, 2018;53:658-70, 2016;51:622-33

- Cancers at the border of oxyntic and pyloric glands
- Small (<2 cm) and pale IIb: better prognosis than *H. pylori*-infected SRCCs
- Most (67%) show cadherin-1 (CDH1) mutation
- Related to hereditary diffuse gastric cancer syndrome

Hereditary diffuse gastric cancer syndrome



Stomach and Intestine
2020;55:1146-9

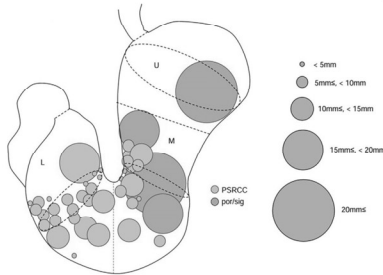


- Family history of SRCC
- CDH1 mutation (+)

Jap J Gastroenterol Endosc 2018;60:1450-63

H. pylori-naive undifferentiated gastric cancers in Japan – a multicenter study at 12 centers

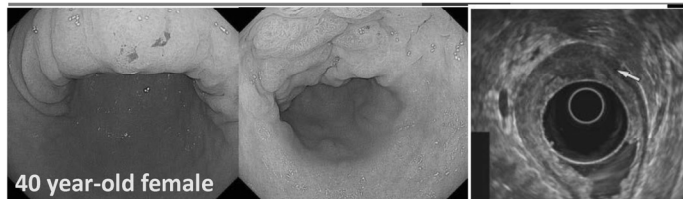
- Among 222,656 individuals, 35 (0.020%) pure SRCC (PSRCC) and 7 (0.003%) mixed SRCC and poorly-differentiated adenocarcinoma (por/sig) were identified.



	PSRCC	por/sig	p value
Patient background			
n	34	7	
Age (years)	54.2±1.6	47±8.4	0.137
Sex (male) (%)	23 (67.6)	3 (42.9)	0.390
Family history of gastric cancer (%)	1 (2.9)	1 (14.3)	0.316
History of gastric cancer (%)	1 (2.9)	0 (0)	1.000
Smoking history (%)	18 (52.9)	3 (42.9)	0.697
Acid-suppressive medication usage (%)	8 (23.5)	0 (0)	0.310
Lesion characteristics			
n	35	7	
Size (mm)	6.7±3.7	20.6±16.6	0.088
Location (U : M : L)	0 : 14 : 21	1 : 4 : 2	0.040
Location (Gre : Less : Ant : Post)	7 : 13 : 10 : 5	4 : 2 : 0 : 1	0.162
Depth of invasion (pT1a : pT1b1 : pT1b2 : pT2)	35 : 0 : 0 : 0	2 : 1 : 2 : 2	<0.001
Vascular invasion (%)	0 (0)	2 (28.6)	0.024
Lymph node metastasis (%)	0 (0)	0 (0)	1.000
Treatment method (ER : ER following surgery : Surgery)	35 : 0 : 0	3 : 3 : 1	<0.001

Kemmoto Y, et al. Intern Med 2025; Epub ahead of print

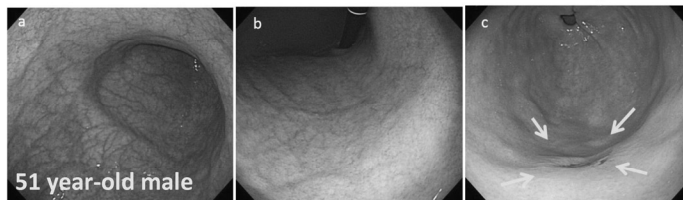
Atypical SRCCs in *H. pylori*-naive patients



40 year-old female

Stomach and Intestine 2025;60:494-508

- pT4aN2M0 AGC B5
- 90 × 80mm
- SRCC mixed with poorly-differentiated adenocarcinoma



51 year-old male

Jap J Gastroenterol Endosc 2016;58:1492-503

- SRCC in the antrum
- Pan-atrophy in corpus
- Pernicious anemia
- 25% develops gastric cancer after age of 50

Gastric adenocarcinomas in autoimmune gastritis



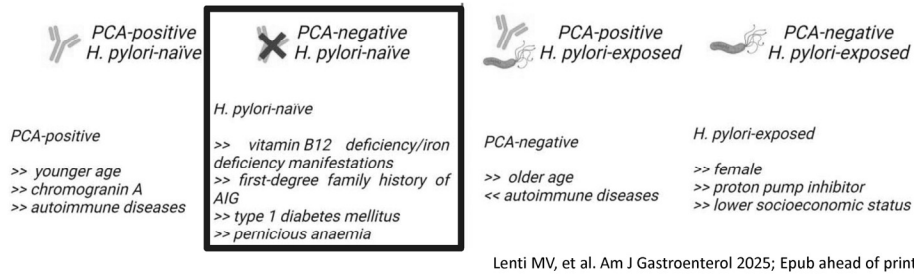
SRCC with poorly-diff. adenocarcinoma

AIG patients with gastric adenocarcinoma	<i>H. pylori</i> -naive	With past or current <i>H. pylori</i> infection
Number of patients	18 (25 cancers)	47 (72 cancers)
Age	70 (63–74) years	75 (62–79) years
Lauren's diffuse-type	28.0%	8.3%
Location of cancer	Upper and middle stomach	Lower stomach

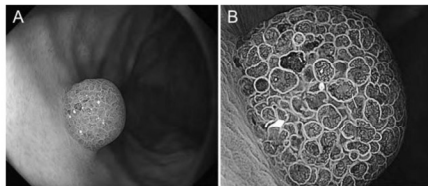
Takasu A, et al. Gastric Cancer 2025; Epub ahead of print
Cureus 2024;16:e66910

Gastric neuroendocrine tumors (NET) in AIG

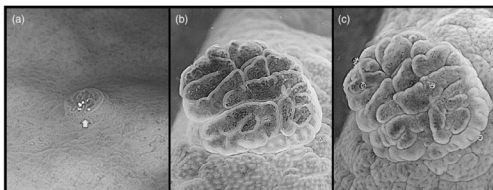
- 1,598 AIG patients (median follow-up: 89 months)
- Gastric adenocarcinoma: 0.12 per 100 person/year
- Gastric NET: 1.22 per 100 person/year
- **Risk factor for NET:** vitamin B12 or iron deficiency (HR=16.44)



3. Raspberry-like foveolar-type cancer



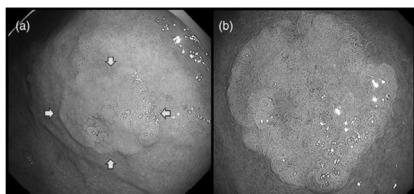
Kotani S, et al. Histology and Histopathology 2025; Epub ahead of print



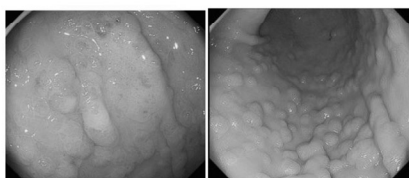
Dig Endosc 2025; 37: 611–628

- Adenoma outside Japan
- <1 cm red lsp
- Gyrus-like microstructure with irregular papillary structure
- Irregular capillaries with well-vascularized stroma
- MUC5AC (+)
- All show Kruppel-like factor 4 (KLF4) mutation

4. Flat foveolar-type cancer



Dig Endosc 2025;37:611-28

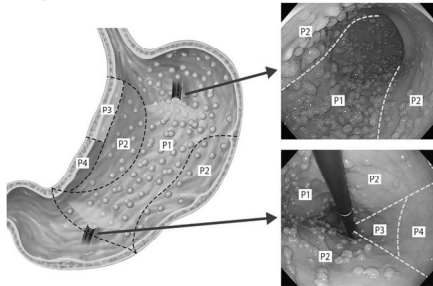


Jap J Gastroenterol Endosc 2018;60:1450-63

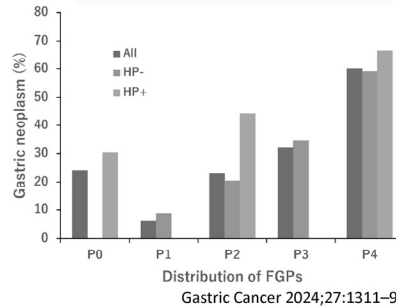
- Adenoma outside Japan
 - 3-5 cm
 - White and flat
 - Upper and middle layer of lamina propria
 - MUC5AC (+)
 - All show adenomatous polyposis coli (APC) and K-ras mutations
1. Familial adenomatous polyposis (FAP)
 2. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

Distribution of fundic gland polyps and risk of *H. pylori*-naive cancers in FAP patients

- **P0:** No fundic gland polyp
- **P1:** fundus or greater curvature of the body
- **P2:** greater curvature to the anterior or posterior wall of the body
- **P3:** involving the lesser curvature of the body and localized to the proximal half of the distance between the cardia and angle
- **P4:** spreading from P3 to the anal side of the lesser curvature



Cancers increased from P0 to P4 (odds ratio=14.1) only in *Hp*-naive FAP patients.



Foveolar-type tumors after using acid suppressant

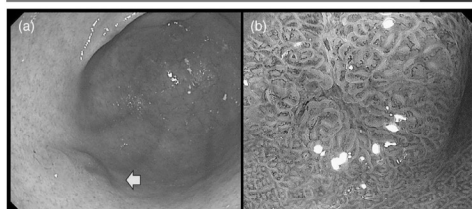


Gastric Cancer 2025;28:537-43

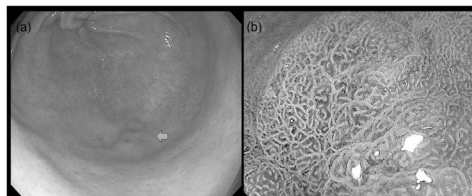
Multiple metachronous foveolar-type tumors

1. Recurrence after ESD in the greater curvature
2. New, de novo tumor in the lesser curvature

5. Pyloric gland cancer



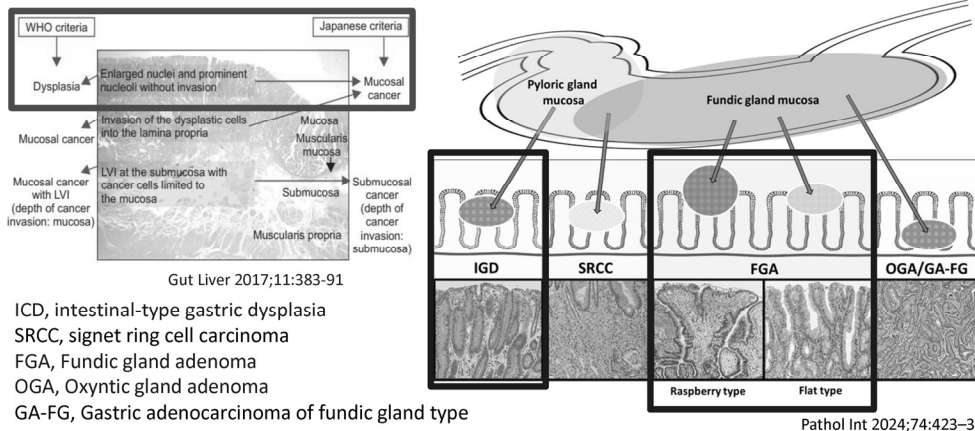
Dig Endosc 2025;37:611-28



Pathol Int 2024;74:423-37

- Adenoma outside Japan
- Intestinal-type gastric dysplasia
- Middle layer of the lamina propria
- Smaller size (<1 cm) than *Hp*-infected pyloric gland tumors
- CD10 (+), Cdx2 (+), p53 (+), Ki 67 (+)
- Most (75%) show APC mutation

Foveolar-type and pyloric gland cancers in Japan = Adenomas outside Japan



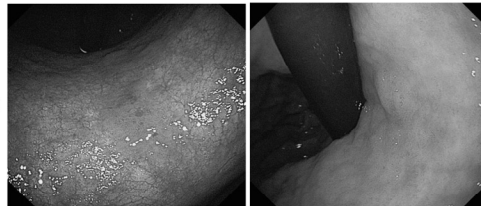
Gastric cancers after *H. pylori* eradication

Common findings:

- Gastritis-like cancer
- Well-differentiated adenocarcinoma
- Lauren's intestinal-type
- Small and slow growing

Risk factors:

- Advanced atrophy or IM
- Old age
- Male
- Use of acid suppressants



Stomach and Intestine 2016;51:750-8

Corpus atrophy (high-risk group)

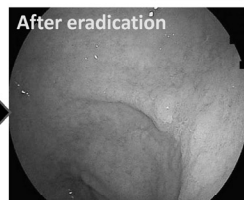
1. Gastroscopy: open-type atrophy

2. Microscopy: OLGA stage III/IV

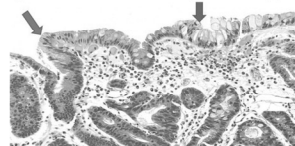
3. Pepsinogen assay

- ABC method: PG I ≤ 70 ng/mL & I/II ≤ 3
- GastroPanel: PG I < 30 ug/L or PG I < 50 ug/L & I/II < 3

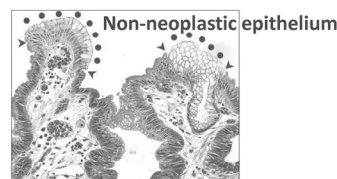
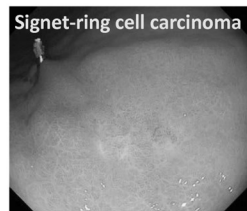
Gastritis-like cancers after eradication



Epithelium with low-grade atypia

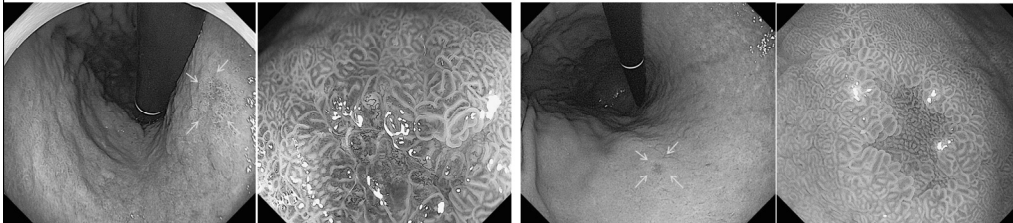


Gut Liver 2021;15:338-45



Stomach and Intestine 2018;53:672-96, 2016;51:742-9

Gastritis-like cancer vs. IM after eradication



Well-differentiated tubular adenocarcinoma

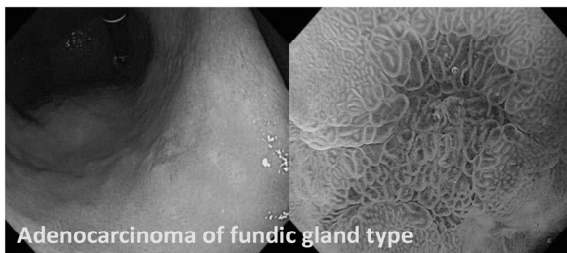
- Irregular microsurface pattern
- Irregular microvascular pattern
- Demarcation line (+)

IM (map-like redness)

- Regular microsurface pattern
- Regular microvascular pattern
- Demarcation line (+)

Gut Liver 2021;15:338-45

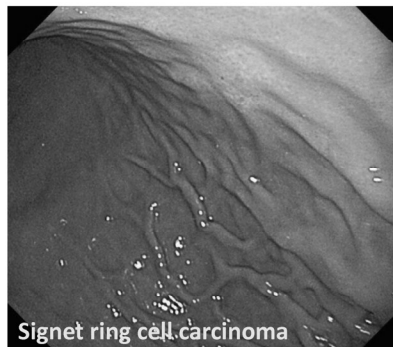
H. pylori-negative cancers after eradication



Adenocarcinoma of fundic gland type

Stomach and Intestine 2025;60:98-105

- Irregular microsurface pattern
- Regular microvascular pattern
- Demarcation line



Signet ring cell carcinoma

Stomach and Intestine 2016;51:750-8

Summary on *H. pylori*-negative cancers

- Most cancers occur in Hp-exposed stomachs.
- Only few are true Hp-naïve cancers.
- Some are induced by acid suppressant, iron deficiency, and vitamin B12 deficiency.

Hp-naïve cancers	Adenocarcinoma of the fundic gland type	Signet ring cell carcinoma	Raspberry-like foveolar-type cancer	Flat foveolar-type cancer	Pyloric gland cancer
Pathology	Oxyntic gland adenocarcinoma covered by foveolar epithelium	Cancer at the border of oxyntic and pyloric glands	Adenoma (dysplasia) outside Japan		
Gastroscopy	Subepithelial tumor	Small pale IIb	Small red Isp	3-5 cm white IIa	Small IIa or IIc
Gene mutations	GNAS (12-43%)	CDH1 (67%)	KLF4 (100%)	APC (100%), K-ras (100%)	APC (75%)

GNAS, guanine nucleotide binding protein alpha-stimulating complex; CDH1, cadherin-1; KLF4, Kruppel-like factor; APC, adenomatous polyposis coli