성균관대학교 Unique Origin Unique Future

Carcinoid Tumor

-with emphasis on gastric carcinoid

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2009. 5. 9. 2009년 대한 *Helicobacter* 및 상부위장관 연구학회 춘계심포지엄

Types of GI neuroendocrine cells

- at least thirteen types

Cell type	Localisation	Products	Factors that regulate secretion
D	Gastrointestinal tract	Somatostatin	Hormones, neural factors, and acid
Enterochromaffin	Gastrointestinal tract	Serotonin, substance P, guanylin, and motilin	Luminal factors, hormones, and neural factors
Enterochromaffin like	Stomach	Histamine	Hormones, gastrin, and neural factors
G	Stomach and duodenum	Gastrin	Amino acids, neural factors, and acid
Gr	Gastrointestinal tract	Ghrelin	Luminal factors and hormones
I	Duodenum	Cholecystokinin, gastrin, etc	Lipids and neural factors
K	Duodenum and jejunum	Gastric inhibitory polypeptide	Nutrients and hormones
L	Small intestine	Glucagon like peptide, peptide YY, and neurotensin/CT	Glucose and hormones
Motilin	Duodenum	Motilin	Neural factors and luminal factors
N	Small intestine	Neurotensin	Lipids
S	Duodenum	Secretin	Acid
VIP	Gastrointestinal tract	Vasoactive intestinal peptide	Neural
X	Stomach	Amylin	Not defined

Table 1: Types of gastrointestinal neuroendocrine cells and luminal, paracrine, neural, and hormonal factors that regulate secretion of their bioactive products

Modlin. Lancet Oncol 2008;9:61-72

Classic definition of ***carcinoid tumors***

- Carcinoid tumors are classically defined as ***low-grade, potentially malignant, epithelial neoplasms showing NE differentiation***.
- The term encompasses wide spectrum of neoplasms that ***originate from various NE cells***.

Frnoglio-Preiser ed. GI Patholgoy. 3rd ed (2008). p1099-1160

WHO classification of NE tumors

- ***Well-differentiated endocrine tumors***
- Well-differentiated endocrine carcinomas
- Poorly differentiated endocrine carcinomas
- Mixed endocrine-exocrine tumorr (such as adenocardinoids)
- Rare neuroendocrinelike lesions

Frnoglio-Preiser ed. GI Patholgoy. 3rd ed (2008). p1099-1160

INCREASING neuroendocrine tumors

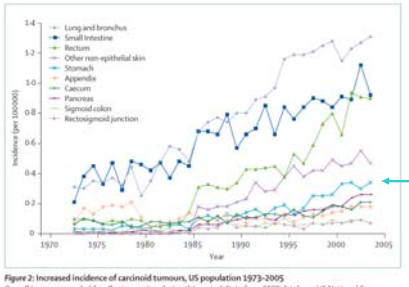


Figure 2: Increased incidence of carcinoid tumours, US population 1973-2005
Overall increase recorded for all primary sites during this period. Data from SEER database, US National Cancer Institute.

Modlin. Lancet Oncol 2008;9:61-72

Unpredictable behavior of carcinoid

Table 1 10 mm 이하의 직장 유암종 전이례(논문보고에서)

저자명	발표 연도	종양크기 (mm)	종양탈출	림프절	맥관침습	전이	
						림프절	간
片岡ら[9]	1983	9	+	sm	+	+	−
桜生ら[10]	1987	8	−	sm	+	+	−
曽我ら[11]	1991	10	+	sm	?	−	+
曽我ら[12]	1991	10	+	sm	?	−	+
荒畑ら[13]	1992	7	+	sm	+	+	−
太田ら[14]	1993	7	+	sm	+	+	−
前田ら[15]	1993	9	+	sm	−	+	+
反町ら[16]	1994	7	+	sm	−	−	+
Akamo ら[17]	1996	10	−	sm	?	+	−
丸山ら[18]	1997	5	−	sm	+	+	−
永野ら[19]	1999	10	+	sm	+	+	−
永野ら[20]	1999	8	+	sm	+	+	−
飯塚ら[21]	2000	10	+	sm	+	+	−
斉藤ら[22]	2001	9	+	sm	+	+	−
伊神ら[23]	2002	10	+	mp	+	+	−
富永ら[24]	2002	6	−	sm	+	+	+
福田ら[25]	2002	10	+	sm	+	−	+
野崎ら[26]	2002	10	−	mp	?	+	−
奥石ら[27]	2003	8	−	sm	+	+	−
川村ら[28]	2004	10	+	sm	−	−	+
川村ら[29]	2004	9	+	sm	−	+	−

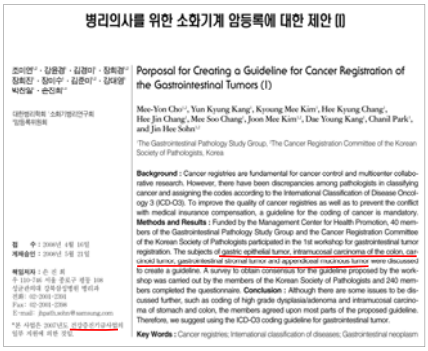
Hirata. Stomach Intest 2005;40:172-183

암보험, 중증질환등록사업 등의 혼선

일반인, 보험회사, 공무원, 의료진 등이 모두 인정하고 공감하는 공통된 진단 기준 및 코딩 기준이 필요하다고 생각된다

http://k.daum.net/qna/view.html?qid=2gVls

병리의사를 위한 소화기계 암등록에 대한 제안 (I)



Porposal for Creating a Guideline for Cancer Registration of the Gastrointestinal Tumors (I)

조미연. 대한병리학회지 2008;42:140-150

Biologic behavior codes of ICD-O3

Code	Disease
/0	Benign
/1	Uncertain whether benign or malignant Borderline malignancy Low malignant potential Uncertain malignant potential
/2	Carcinoma in-situ Intraepithelial Noninfiltrating Noninvasive
/3	Malignant, primary site
/6	Malignant, metastatic site Malignant, secondary site
/9	Malignant, uncertain whether primary or metastatic site

조미연. 대한병리학회지 2008;42:140-150

Results of survey

- pathologists' opinion for coding of carcinoid

Table 7. Results of questionnaire for ICD-O3 code of gastrointestinal carcinoid tumor

Organ or subject	Diagnosis	ICD-O3 code (n=240)					
		0	1	2	3	6	NA
Carcinoid tumour							
	All except appendix and rectum	2	6	8	210		14
Appendix	Carcinoid tumor (=well differentiated neuroendocrine tumor: Size < 1 cm, no invasion)	3	210	7	14		
	Carcinoid tumor (=well differentiated neuroendocrine carcinoma: Any size, Mesoappendix invasion, metastasis, angioinvasion)		2	2	235		1
Rectum	Carcinoid tumor (=well differentiated neuroendocrine tumor: Size < 1 cm, no invasion)	2	213	7	17		1
	Carcinoid tumor (=well differentiated neuroendocrine carcinoma: Any size, Muscle invasion, angioinvasion, node or distant metastasis)		2	3	234		1
Pancreas	Well differentiated endocrine tumor	1	220	6	11		2
	Well differentiated endocrine tumor		*192*	*19*	*27*		*2*

NA, no answer.

조미연. 대한병리학회지 2008;42:140-150

Carcinoid의 biologic behavior code

- 우연히 발견된 크기가 작은 종양이라 하더라도 악성 종양의 가능성을 가지고 있으므로 적어도 /1 이상의 행태코드를 부여하는 것에 대해 의견을 모았다.
- WHO 분류에서 보는 바와 같이 1등급에 해당하는 종양의 경우 양성에 가까우므로 모든 carcinoid 종양에 /3을 부여하는 것은 적당하지 않다고 의견을 모았다.

조미연. 대한병리학회지 2008;42:140-150

내과의사의 입장에서 바라본 소화기 병리연구회 방안의 제한점

- Gastric carcinoid가 혈청 gastrin치, 타장기의 동반질환 등에 따라 몇 가지 subtype으로 나누어지는 점이 반영되지 못함.
- 내시경 검사에서 우연히 발견되는 (multiple) small carcinoid(s)에 대한 언급이 없음.
- 실제 임상에서 gastric carcinoid의 coding reference로 사용하기에는 애매한 기준이다.

Pathogenesis of gastric carcinoid

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Most commonly ECL cells in the fundus and G cells in the antrum

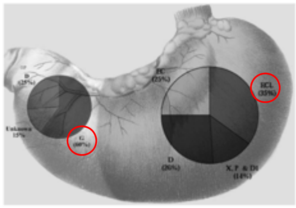

Fig. 4. Different endocrine cell types and their relative frequency in the fundus of the human stomach. A cartoon of the endocrine cells of the fundus. Communication between the antrum and the fundus is mediated via a classical hormonal mechanism, with laminal pH regulating gastrin secretion from G-cells and activation of gastrin/CCK_B receptors on the ECL cell. The relationship between these two cell types is pivotal in the positive regulation of acid secretion. D cells (which also occur in the antrum) secrete somatostatin, which is responsible for inhibition of ECL secretion of histamine, and this cell type thus plays an important negative regulatory role in acid secretion. The function of other neuroendocrine cells of the fundus (EC, X, P and D_1) remains unknown.

Modlin. Surg Oncol 2003;12:153-172

Histologic development of carcinoid

Histologic pattern	Definition
Simple hyperplasia	Increase in single cells in glands
Linear hyperplasia	Forms of chains of five or more endocrine cells and equals two chains per millimeter
Micronodular hyperplasia	Nodules of endocrine cells with more than five endocrine cells in glands or crypts that do not exceed the diameter of the gastric glands
Adenomatoid hyperplasia	The presence of five or more coalescing nodules
Dysplasia	Enlargement and fusion of ECL nodules measuring ***< 0.5 mm in diameter.*** These contain relatively atypical cells and may have microinvasion or newly formed stroma
Intramucosal or invasive ***carcionids***	Endocrine cell growths ***measuring > 0.5 mm or invading submucosa***

Frnoglio-Preiser ed. GI Patholgoy. 3rd ed. p1099-1160

Inter-observer variation 문제가 가능

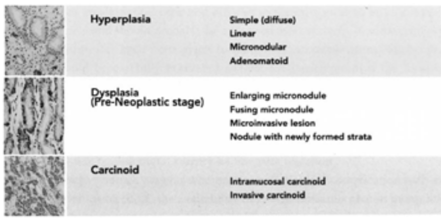

Fig. 8. A histo-pathological grading system for the evaluation of ECL cell proliferation.

Modlin. Surg Oncol 2003;12:153-172

Regulation of ECL cells

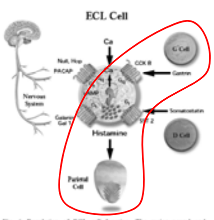

Fig. 6. Regulation of ECL cell function. The major neural and endocrine regulators of ECL cell histamine release. Antral G cells produce gastrin, which drives histamine secretion via activation of CCK_B receptors that is coupled to intracellular G_q proteins. Histamine release is coupled with Calcium (Ca) influx into the cell and its release from intracellular stores. PACAP functions as the dominant neural regulator and is coupled to histamine release and calcium flux via the Null and Hop variants of the PACAP receptor and G_s and G_q proteins. Galanin is the negative neural regulator of this cell and its inhibitory effects are mediated via activation of GAL1 and G_i. Fundic somatostatin from D cells inhibits ECL cell histamine release via activation of somatostatin subtype 2 receptor and G_i. Overall, the ECL cell functions as the pivotal cell in regulation of acid secretion, both by its production of histamine and through modulation by gastrin of the functional parietal cell mass.

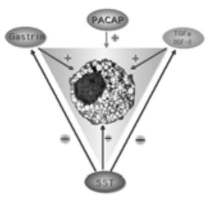

Fig. 7. Regulators of ECL cell proliferation. Cartoon of an isolated ECL cell (center) demonstrating the variety of peptide agonists that regulate DNA synthesis and cell proliferation. Agents that promote proliferation include hormonal gastrin, neural PACAP, and the growth factors TGF-α (autocrine) and IGF-1 (paracrine). Inhibition of proliferation is via the paracrine or neurocrine effects of somatostatin, which functions indirectly by decreasing antral release of gastrin and directly by inhibiting ECL cell proliferation through an ECL cell somatostatin subtype 2 receptor.

Modlin. Surg Oncol 2003;12:153-172

Types of gastric carcinoid tumors

- modification of the Rindi classification (Gastroenterology 1993;104:994)

Type I	ECL cell tumors associated with chronic atrophic gastritis[a]
Type II	ECL cell tumors associated with combined MEN-A and Zollinger-Ellison syndrome[a]
Type III	Sporadic ECL tumors
Type IV	***Non-ECL tumors*** (gastrin-, serotonin-, and ACTH-secreting tumors)
Type V	ECL tumors associated with achlorhydria and parietal cell hyperplasia[a]

[a]Hypergastrinemic state

Frnoglio-Preiser ed. GI Patholgoy. 3rd ed. p1099-1160

Characteristics of gastric carcinoids

	Type I	Type II	Type III
Tumor site	fundus	fundus	Antrum or fundus
Numbers	Usually multicentric, polypoid	Usually multicentric	Single, solitary
Size	< 1 - 2 cm	< 1 - 2 cm	2 – 5 cm
Behavior	Slow growth; rarely metastasizes	Slow growth; may metastasize	Relatively aggressive, frequent metastases to regional nodes (55%) and liver (24%)
Gastrin	Elevated	Elevated	Normal

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Management of gastric carcinoid

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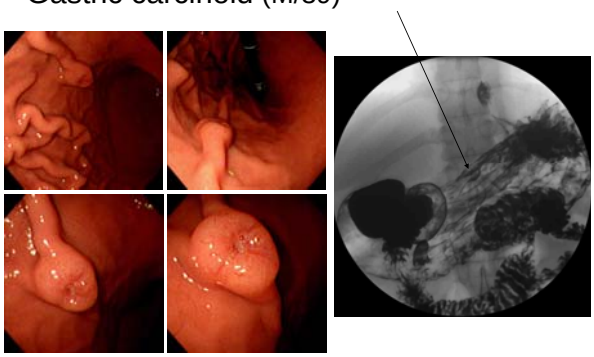
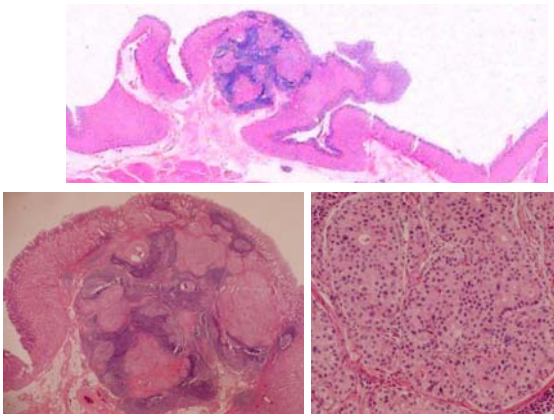
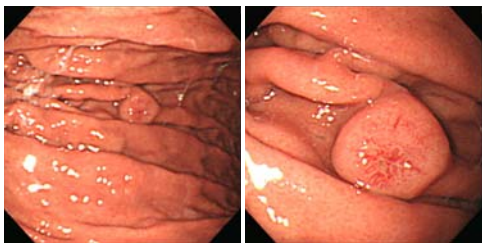
Gastric carcinoid (M/39)



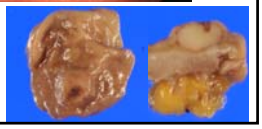


Gastric carcinoid (M/52)

- gastrin 48.2 pg/ml



Wedge resection
well differentiated neuroendocrine tumor
0.8x0.8cm, mitosis: 0/10 HPFs, confined to submucosa
Synaptophysin (+), Chromogranin (+)



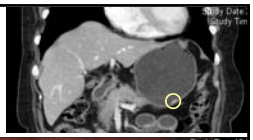
Gastric carcinoid with hypergastrinemia

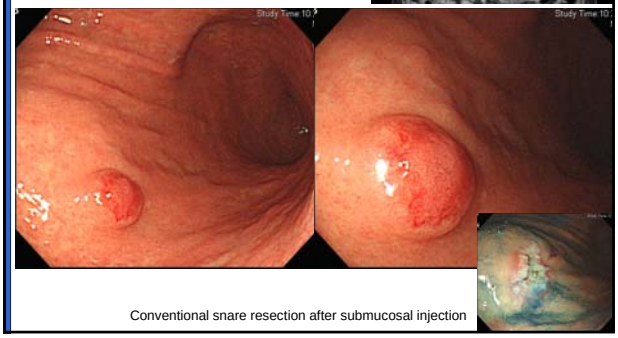
Lesions < 1 cm < 3-5 in number	Lesions > 1 cm > 3-5 in number
Endoscopic polypectomy	***Antrectomy and local excision***
Endoscopic surveillance at 6 month intervals	Endoscopic surveillance at 6 month intervals
Recurrence	Recurrence
? ***Antrectomy and local excision***	Completion gastrectomy

Modlin. Surg Oncol 2003;12:153-172

Gastric carcinoid (F/63)

- serum gastrin = 390 pg/ml

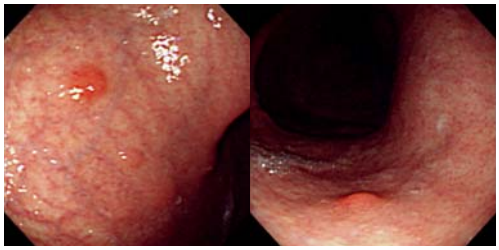




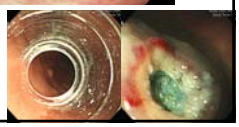
Conventional snare resection after submucosal injection

건진발견 carcinoid (F/56)

- gastrin 290 pg/ml

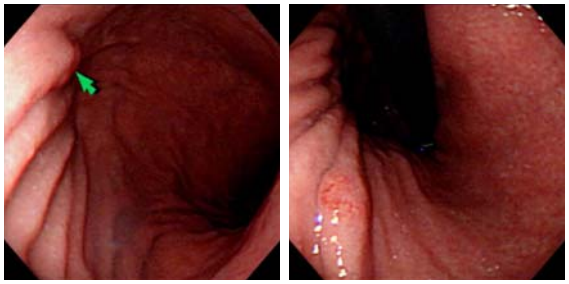


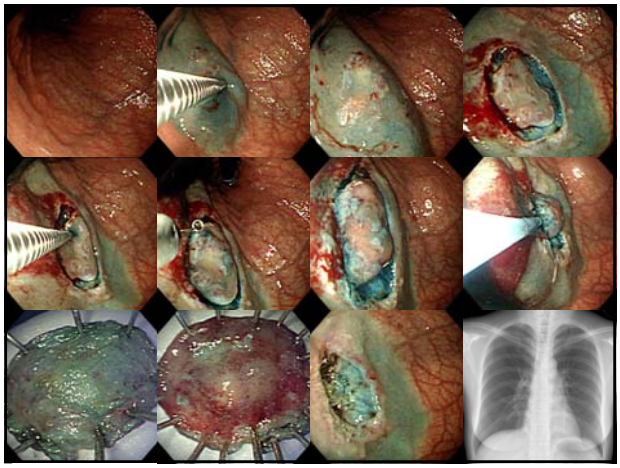
Cap-EMR
0.4x0.2 cm
Focal submucosal extension
Negative margins

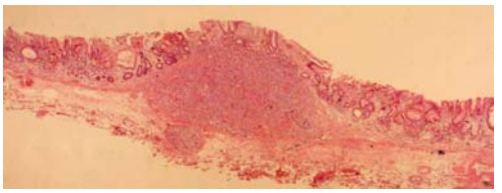


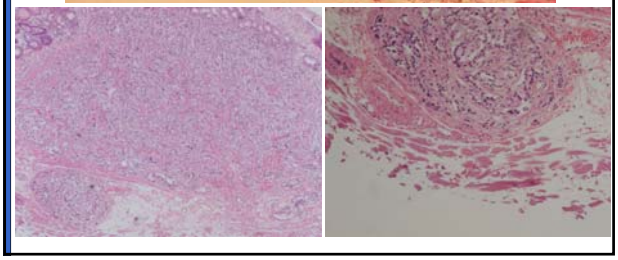
Gastric carcinoid (F/41)

- serum gastrin: 650 pg/ml









우연히 발견된 작은 carcinoid(s)를 반드시 모두 절제해야 하는가?

Gastric carcinoid with hypergastrinemia

Lesions < 1 cm < 3-5 in number	Lesions > 1 cm > 3-5 in number
? ***Endoscopic polypectomy***	Antrectomy and local excision

Modlin. Surg Oncol 2003;12:153-172

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Digestive and Liver Disease
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www.elsevier.com/locate/dld

Alimentary Tract

Long-term endoscopic and clinical follow-up of untreated type 1 gastric neuroendocrine tumours

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Abstract

Background and aims. Type 1 gastric neuroendocrine tumour surveillance and treatment are a matter of debate. Endoscopic, or surgical, resection and chronic somatostatin analog therapy have been proposed. Based on the favourable behaviour of this neoplasm, we performed an endoscopic and clinical follow-up in 11 patients affected by type 1 gastric neuroendocrine tumours, avoiding any specific treatment.

Methods. Between 1994 and 2006, we prospectively recorded the data of 11 untreated patients with type 1 gastric neuroendocrine tumours who underwent an endoscopic and clinical follow-up. All the patients were also evaluated by means of an abdominal computed tomography scan, somatostatin receptor scintigraphy and blood tests.

Results. During the follow-up (median 54 months, range 9–136), the endoscopic picture of 4 (36%) out of 11 patients changed in terms of increased number of lesions. In none of the cases were detected any lesions that exceeded 10 mm in diameter, and none of the patients demonstrated any evidence of local or distant metastases.

Conclusions. Our data confirm the literature data of the indolent behaviour of type 1 gastric neuroendocrine tumours and suggest that a careful endoscopic follow-up, without any treatment, might represent a reasonable and safe option in selected patients.

Keywords: Endoscopy; Type 1 gastric neuroendocrine tumour

Ravizza D. DLD 2007;39:537-543

Clinical and surveillance data of 11 patients with type 1 gastric neuroendocrine tumours

Case	Age/sex	APCA	Hb (g/dl)	Vitamin B12 (pg/ml)	Gastrin (pg/ml)	CgA (U/l)	5 HIAA (mg/24 h)	Follow-up (mo)	Metastases*
1	66/female	1:160	14	278	1953	92	3.5	20	Not detected
2	53/male	1:40	12	333[a]	693	37	3.9	136	Not detected
3	62/female	<1:20	12	429	787	183	3.2	12	Not detected
4	53/male	1:80	14	110	509	92	2.2	53	Not detected
5	56/male	1:80	17	60	795	22	3.5	62	Not detected
6	63/female	1:80	14	50	370	272	3	9	Not detected
7	68/female	1:160	12	207	1000	43	2	56	Not detected
8	69/male	<1:20	14	320[a]	6110	106	3	54	Not detected
9	63/female	1:80	11	108	1000	194	2	56	Not detected
10	45/male	1:80	12	60	1000	56	3	30	Not detected
11	72/male	1:20	15	686	1000	17	3	71	Not detected

APCA, anti-parietal cells antibodies; Hb, haemoglobin; CgA, chromogranin A; 5-HIAA, 24-h urinary 5-hydroxyindolacetic acid; mo, months.
Normal values: APCA < 1:20; Hb 13.5–17.5 g/dl; vitamin B12 179–1162 pg/ml; gastrin 15–80 pg/ml; CgA 0–20 U/l; 5 HIAA 0.2–10 mg/24 h.
* Assessment performed by means of abdominal computed tomography scan and somatostatin receptor scintigraphy.
[a] Patient with ongoing replacement therapy with vitamin B12.

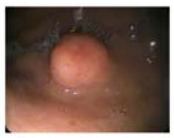


Fig. 2. Type 1 gastric neuroendocrine tumour described as polyp.

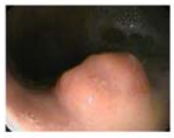


Fig. 4. Type 1 gastric neuroendocrine tumour described as submucosal lesion.

Ravizza D. DLD 2007;39:537-543

Endoscopic data of 11 patients with type 1 gastric neuroendocrine tumours

Case	No. of tumours per patient								Modification
	First observation				Last observation				
	1	2–5	6–10	>10	1	2–5	6–10	>10	
(a) Number of lesions at the first and the last endoscopic observations									
1		No lesion observed			X				*Changed*
2	X					X			*Changed*
3		No lesion observed			No lesion observed				Unchanged
4			X					X	*Changed*
5		Micropolyposis			Micropolyposis*				Unchanged
6		X			X				Unchanged
7		Micropolyposis			Micropolyposis				Unchanged
8			X			X			Unchanged
9		Micropolyposis			Micropolyposis				Unchanged
10	X				X				*Changed*
11		Micropolyposis			Micropolyposis*				Unchanged

Case	Tumour diameter								Modification
	First observation				Last observation				
	<5 mm		5–10 mm	>10 mm	<5 mm		5–10 mm	>10 mm	
(b) Size of the lesions at the first and the last endoscopic observations									
1	No lesion observed				X				*Changed***
2	X						X		*Changed**
3	No lesion observed				No lesion observed				Unchanged
4			X				X		Unchanged
5	Micropolyposis				Micropolyposis*				Unchanged
6	X				X				Unchanged
7	Micropolyposis				Micropolyposis				Unchanged
8			X				X		Unchanged
9	Micropolyposis				Micropolyposis				Unchanged
10		X					X		Unchanged
11	Micropolyposis				Micropolyposis*				Unchanged

Micropolyposis: presence of at least 15 polyps with a diameter equal to or less than 2 mm.
* Changed because a new lesion developed with a diameter more than 5 mm. The first observed lesion had a stable size (<5 mm) during the follow-up.
** Patients without any microscopic evidence of neuroendocrine tumour at last observation.
*** Changed because a new measurable lesion appeared.

Ravizza D. DLD 2007;39:537-543

Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours

A Consensus Statement on Behalf of the European Neuroendocrine Tumour Society (ENETS)

Type 1 is the most common NE neoplasm in the whole stomach with a relative incidence of 70–85%, and is frequently small, polypoid, often multiple and usually benign (WHO group 1). It is secondary to hypergastrinaemia, related to atrophic gastritis (also includes microcarcinoidosis) and is always associated with ECL-cell hyperplasia.

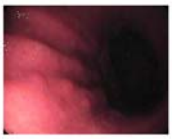


Fig. 1. Gastric micropolyposis.

Plockinger. Neuroendocrinology 2004;80:394-424
Figure: Ravizza D. DLD 2007;39:537-543

Endoscopic and Surgical Therapy [10]

1.1. Curative Therapy

Type 1 and 2 tumours (atrophic gastritis or MEN-1).

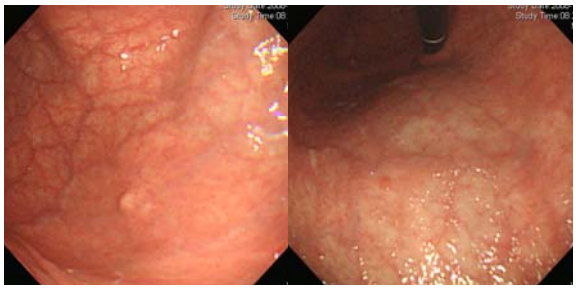
Polyps <1 cm in size: surveillance once per year; 1–6 polyps and >1 cm in size, endoscopic resection after EUS and surveillance; >6 polyps and >1 cm in size, extension to muscularis and/or repeated recurrences: alternatively surgical resection or antrectomy (reduces gastrin stimulation from antral G-cells).

Malignant development or recurrence despite local surgical resection: partial or total gastrectomy with lymph node dissection.

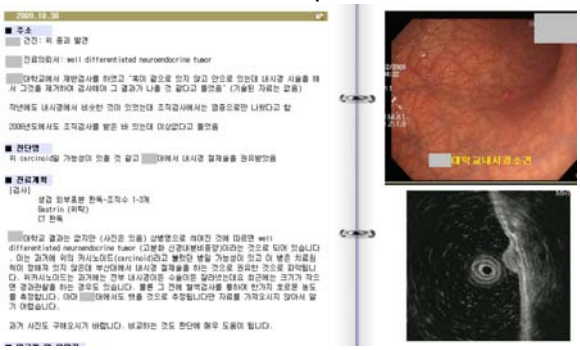
Type 3 and poorly differentiated tumours: partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Plockinger. Neuroendocrinology 2004;80:394-424

1994년부터 경과관찰중인
multiple gastric carcinoids (gastrin = 386)

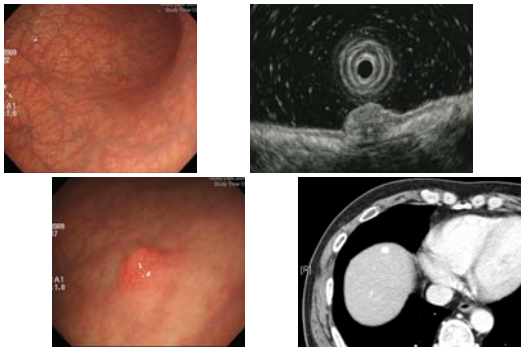


환자가 유암종의 follow-up을 원하게 된 사연

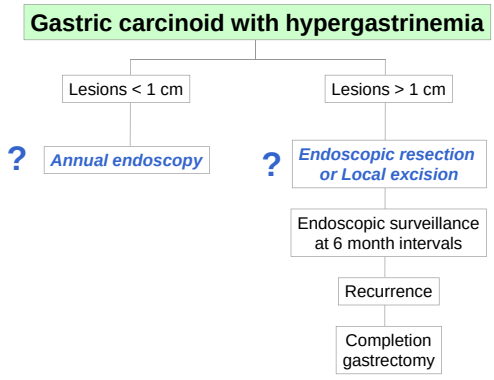


Bx: W/D neuroendocrine tumor

- Serum gastrin 373 pg/ml



Gastric carcinoid with hypergastrinemia



Unpublished personal opinion

Take home message

- Gastric carcinoid는 heterogeneous한 neuroendocrine cell tumor이다.
- 주로는 병소의 크기와 개수 및 hypergastrinemia 여부에 따라서 치료방침이 달라진다.
- 무증상 성인에서 발견되는 hypergastrinemia를 동반한 작은 gastric carcinoid(s)에 대하여 경과관찰을 고려할 수 있다.
- Gastric carcinoid의 biologic behavior에 대한 규명이 부족하므로 coding 작업은 미해결 과제이다.

2009. 5. 9. 2009년 대한 *Helicobacter* 및 상부위장관 연구학회 춘계심포지엄