Management of gastric neuroendocrine tumors: a review

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Introduction

- Gastric neuroendocrine tumors (G-NET) : are rare tumors arising from enterochromaffin-like(ECL) cells of the gastric oxyntic mucosa

- Well-differentiated NET
- Poorly differentiated NET
- Poorly differentiated NEC
- Mixed neuroendocrine non-neuroendocrine neoplasmas(MiNEN)

- G-NET : 2.0% of all NET, 10% of all gastroenteropancreatic NET

- Clinical presentation of G-NET is not specific

Types

- WHO in 2019, classified based on their morphologic characteristics, behavior, and pathogenesis
  - **Histamine-producing ECL-cell NET : Majority of G-NET**
  - Somatostatin-producing D-cell NET
  - Gastrin-producing G-cell NET
  - Serotonin-producing enterochromaffin(EC) cell NET

- Type 1 : autoimmune gastritis(AIG)
- Type 2 : MEN1 & Zollinger-Ellison syndrome(ZES)
- Type 3 : sporadically, usually with a unifocal lesion

Rindi classification

Distinctive characteristics of different types of G-NET.

	Type 1	**Type 2**	**Type 3**
% among G-NET	80%-90%	5%-7%	10%-15%
Association with	Atrophic gastritis	MEN1-gastrinomas	-
Gastrin levels	Elevated	Elevated	Normal
Gastric pH	High	Low	Normal
Tumor size	<1cm	<2cm	>2cm
Number of tumors	Multifocal	Multifocal	Solitary
Sex predominance	Female	Equal	Male
Risk of metastasis	1-3%	10-30%	50%
Prognosis	Excellent	Very Good	Poor

Evolution of Nomenclature and staging

- WHO in 2010 : G3 was used to define poorly differentiated NEC. (consider Ki-67, Mitotic rate)
- WHO in 2019 : WD (G1, G2, G3), PD (small-cell and large-cell NEC)

Classification of gastroenteropancreatic neuronendocrine neoplasms (WHO, 2019) [4].

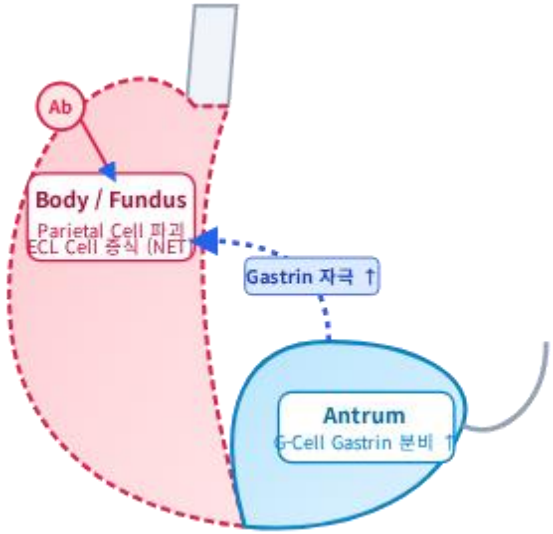
Terminology	Differentiation	Grade	Ki-67 index	Mitotic rate (mitoses/10HPF)
G1 NET	Well differentiated	Low	<3%	<2
G2 NET		Intermediate	3-20%	2-20
G3 NET		High	>20%	>20
NEC	Poorly differentiated	High	>20%	>20

→ Synaptophysic & chromogranin A (+)

→ Synaptophysic & chromogranin A (-) (~25%)
→ P53, RB1 gene mutation

In cases of disparity between Ki-67 index and mitotic rate, the result that indicates a higher grade tumor should be selected.

Type 1 G-NET



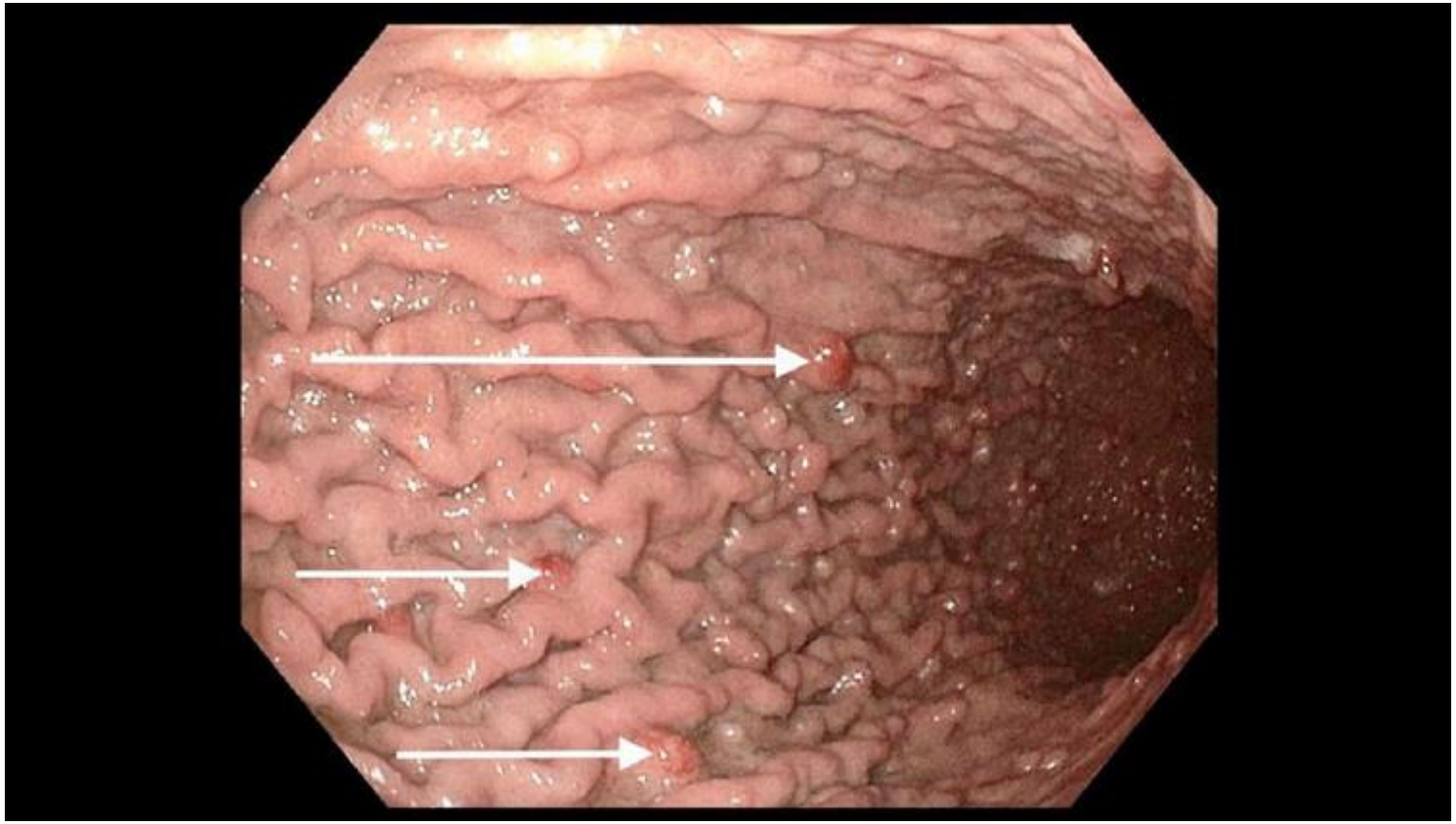
- 80-90% of all G-NET
- M:F = 0.4:1

- Associated with chronic AIG : anti-parietal cell Ab → achlorhydria, Intrinsic factor(IF) ↓ → gastrin ↑
  → hyperplasia of ECL cells → dysplasia or NET

- H. pylori infection is described as another etiologic factor for development of type 1 G-NET.

- Excellent prognosis; 5-year overall survival reaches 100%

Type 1 G-NET



Type 1 G-NET

- **<u>Presentation and histologic evaluation</u>**
- Multiple, rarely metastasis(1-3%)
- Low or intermediated grade monomorphic cells with round nuclei
- ECL-cell hyperplasia, dysplasia and absence of parietal cells

- **<u>Diagnosis and work-up</u>**
- Endoscopy with gastric polypectomy/biopsy, serum gastrin
  - High gastric pH, Presence of anti-parietal cell and anti-IF Ab, low serum B12 → support the diagnosis type 1
  - PPI may falsely elevated gastrin level; should cessation for at least 1 week
- EUS for >1cm to identify depth of invasion and involvement of regional LNs
- CT & MRI is only recommended in the presence of tumors >2cm
- 68Ga-Dotatate PET-CT should only be considered with high risk or advanced disease

Type 1 G-NET

- **Treatment and follow-up**
- Endoscopic resection of the most prominent tumor & observation <1cm
- Wedge resection
  - Beyond SM layer
  - ≥2cm
  - Lymph node involvement
  - Recurrent tumor
  - More than six polyps
- Antrectomy for remove the source of gastrin → regression of type 1 G-NET
  - Selectively in symptomatic patients with multifocal disease
- Total gastrectomy
  - Extensive fundal disease or widespread recurrence not amenable to endoscopic resection
- Somatostatin analogue : G-cell → reduce serum gastrin by negative feedback
  - Recurrence following endoscopic resection or multiple lesions not amenable to endoscopic resection
- Netazepide – gastrin/cholecystokinin-2 receptor antagonist
  - Large scale randomized trials are required to validate its effectiveness

Type 1 G-NET

- **Treatment and follow-up**
- 57 patients with surveillance study, progressed in 30%
- The higher serum gastrin levels in progressed patients
- 50% of patients with disease progression required re-interventions with a median follow up of 22 months after the first intervention

Type 2 G-NET

- Gastrinoma, ectopic gastrin producing G-cell neoplasma – duodenum or pancreas
- Elevated serum gastrin (>1000 pg/ml), low gastric pH
- Associated with MEN-1, ZES
- 10-30% metastasis
- 5-year overall survival : 60-90%

Type 2 G-NET

- **Presentation and histologic evaluation**
- Multiple tumors in fundus/body, <2cm
- Symptom associated with ZES; abdominal pain, peptic ulcers, secretory diarrhea
- Parietal cell hyperplasia, hypertrophy with the presence of monomorphic cells with extracellular mucoid-like material and formation of enlarged trabeculae and ribbons

- **Diagnosis and work-up**
- Endoscopy with gastric polypectomy/biopsy, serum gastrin & chromogranin A
- EUS may be considered
- CT or MRI – assess the location of the gastrinoma & evaluate metastatic disease
- 68Ga-Dotatate PET-CT is useful study; stage IV disease & receptor + → benefit from systemic therapy
- Genetic work-up – who meeting clinical criteria for MEN-1

Type 2 G-NET

- **Treatment and follow-up**
- Surgical resection of the primary gastrinoma → regression of Type 2 G-NET
- Metastatic disease or multifocal gastrinomas
  - Endoscopic resection of the most prominent G-NET & observation
- Somatostatin analogue for symptom or disease control
  - Netazepide has not been validated in type 2 G-NETs
- High dose PPIs
- Following resection, imaging surveillance should continue for at least 10 years

- **In MEN1** → resection of primary gastrinoma is recommended in larger than 2cm
- Medical Mx. Of hypergastrinemia is the mainstay of therapy
- Multiplicity of tumors, extra-pancreatic location, co-existent metastatic disease, low chance of surgical cure.

Type 3 G-NET

- 10-15% of G-NET
- Sporadically, non-gastrin dependent
- M:F 2.8:1

- 5-year overall survival : <50%
- Worse overall survival
  - Tumor size >2cm
  - Angio-lymphatic invasion
  - Invasion of gastric wall
  - Distant metastasis

Type 3 G-NET

- **Presentation and histologic evaluation**
- Single, large(usually >2cm)
- 50% distant metastases at the time of diagnosis

- **Diagnosis and work-up**
- Endoscopy with biopsy,
- EUS may be considered to determine T-stage, especially for smaller tumors
- CT or MRI
- 68Ga-Dotatate PET-CT

Type 3 G-NET

- **<u>Treatment and follow-up</u>**
- Radical resection with regional lymphadenectomy ← non-metastatic lesions, >2cm
- Wedge resection ← 1-2cm, low-grade type 3 G-NET
- Endoscopic resection ← Small and low-grade type 3 G-NET

- A study by MIN *et al.*
- 32 patients with type 3 G-NETs → 22 patients with grade 1 G-NET without lymphovascular invasion
- Wedge or endoscopic resection, median follow up of 59 months
  - Tumor size >1.5cm developed recurrence
  - No patients with a grade 1 NET & ≤ 1.5cm developed recurrence

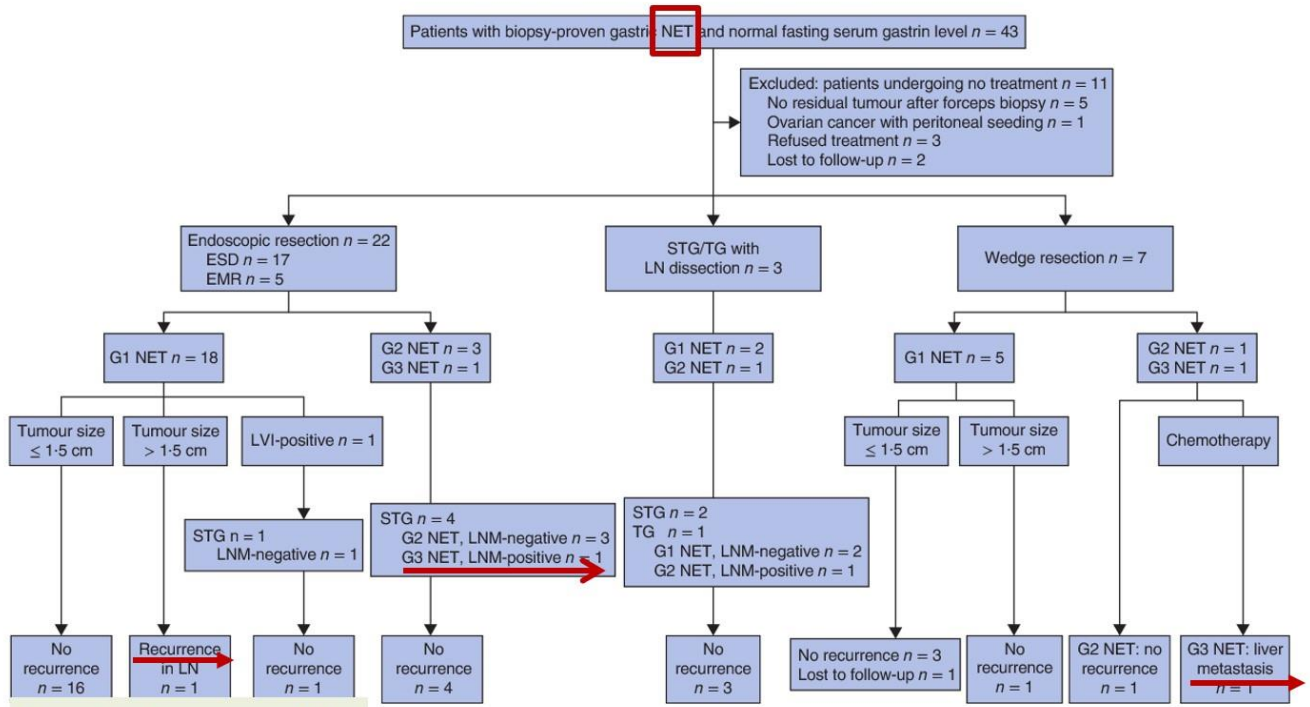
- Higher tumor grade and presence of nodal or distant metastases was associated with worse survival

- Imaging surveillance should continue for at least 10 years

Type 3 G-NET

- **<u>Treatment and follow-up</u>**

- In ESGE guidelines, Endoscopic resection may be indicated for tumors smaller than 2.0 cm
- In ENETS guidelines, Endoscopic resection may be considered for tumors < 1.0 cm (grade 1 or 2, mucosa or superficial submucosa invasion < 0.5 mm)
- National Comprehensive Cancer Network (NCCN) guidelines stated that ER should be reserved for small (< 1.0 cm), superficial, and low-grade tumors.



Case in the next slide

tumour (NET) and a normal fasting serum gastrin level. ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; STG, subtotal gastrectomy; TG, total gastrectomy; LN, lymph node; LVI, lymphovascular invasion; LNM, lymph node metastasis

Min BH (SMC). Br J Surg 2018;105:1480

Grade 3 G-NET and NEC

- High-grade neuroendocrine neoplasms
- Extremely rare, 0.5% of all malignant gastric neoplasms
- Paucity of literature regarding the workup and management of high grade gastric NENs

Grade 3 G-NET and NEC

- **<u>Diagnosis and work-up</u>**
- Endoscopy with biopsy, immunohistochemistry is crucial to determine neuroendocrine differentiation and confirm the high-grade nature of the tumor

- G3 : well-differentiated or moderately differentiated
- NEC : poorly-differentiated, nearly identical to gastric ADC

- EUS provides valuable information on tumor depth and regional lymph node involvement
- CT or MRI – essential
- 68Ga-Dotatate PET-CT
  - Benefit from systemic therapy
  - The more high grade, the higher FDG uptake
  - The degree of FDG uptake is correlated with prognosis
- Brain imaging – Symptomatic or high burden of systemic disease

Grade 3 G-NET and NEC

- **<u>Treatment and follow-up</u>**
- Grade 3 G-NET
  - Surgery with lymphadenectomy
  - No consensus about definitive, neoadjuvant, adjuvant CTx, RTx
- NEC
  - Surgery
  - Neoadjuvant CTx or adjuvant CTx
- Post operative surveillance with imaging studies : every 3 months for 3 years, and then every 6-12 months for at least 10 years

Table 1. World Health Organization 2010 Classification and Suggested Grading of Neuroendocrine Neoplasms of the Digestive System

Classification	Grading		
	Grade	Mitotic count (per 10 HPF)	Ki-67 index, %
NET	G1[a]	<2	≤2
NET	G2[b]	2-20	3-20
NEC	G3[c]	>20	>20

Adapted from Rindi et al. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 13. with the permission of the publisher.[3]
HPF, high power field; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.
[a]G1, low-grade tumors; [b]G2, intermediate-grade tumors; [c]G3, high-grade tumors.

Table 2. Therapy of Gastric Neuroendocrine Neoplasms

	No risk factors (for metastatic disease)		Risk factors[a]
Size	≤1 cm	1-2 cm	-
Type 1	Surveillance[b] optionally EMR	EMR followed by surveillance	Surgery[c]
Type 2	Surveillance[b]	EMR followed by surveillance	Surgery[c]
Type 3	EMR	Surgery	Surgery[c]
Type 4	-	-	Surgery[d]

Adapted from Scherübl et al. World J Gastrointest Endosc 2011;3:133-139.[17]
EMR, endoscopic mucosal resection.
[a]Risk factors for metastatic disease are angioinvasion or G2-G3 histological grading or infiltration of the muscularis propria or tumor size > 2 cm; [b]Somatostatin analogs are being tested in ongoing clinical trials, they should not be used except in clinical trials; [c]Followed by endoscopic surveillance of the gastric remnant. Adjuvant (medical) therapy is not established in NET/carcinoid disease; [d]Surgery in localized type 4 gastric/d neuroendocrine carcinoma (NEC) disease (or systemic cytoreductive chemotherapy in advanced type 4 gastric NEC disease). Type 4 gastric NECs are never benign, they areneuroendocrine carcinomas.

Metastatic G-NET

- If complete resection is possible → should undergo resection of the primary tumor and metastatectomy

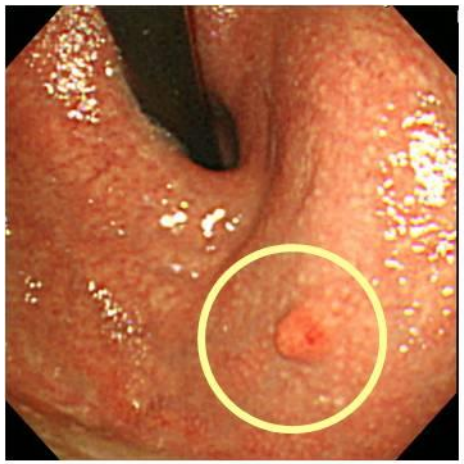
- Asymptomatic and the disease burden is low → Observation with serial imaging
  → Somatostatin analogs (somatostatin receptor positive tumors)

- Symptomatic from the primary tumor → debulking or resection of the primary tumor

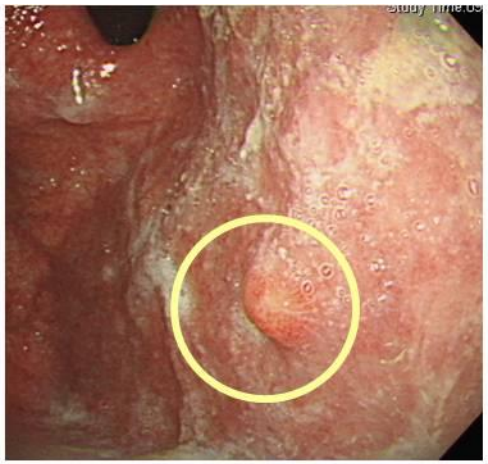
- Unresectable or significant disease burden
- Somatostatin analogs : first-line
- Peptide Receptor Radionuclide Therapy (PRRT), if significant uptake on Dotatate PET-CT
  - Molecular therapy that combines a somatostatin analog with a radionuclide and targets somatostatin receptor positive tumors
- Cytotoxic CTx : controversial and may be considered in patients with progressive disease.
- Liver-directed therapy : surgical resection, hepatic arterial embolization and ablation for control of liver metastases. Symptomatic bone metastases : palliative RTx

Endotoday 증례

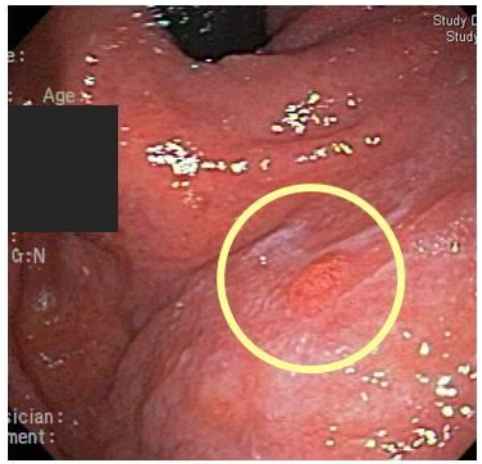
증례 1: Type 1 G-NET



gastrin = 692 pg/ml



gastrin = 404 pg/ml



gastrin = 208 pg/ml

경과관찰

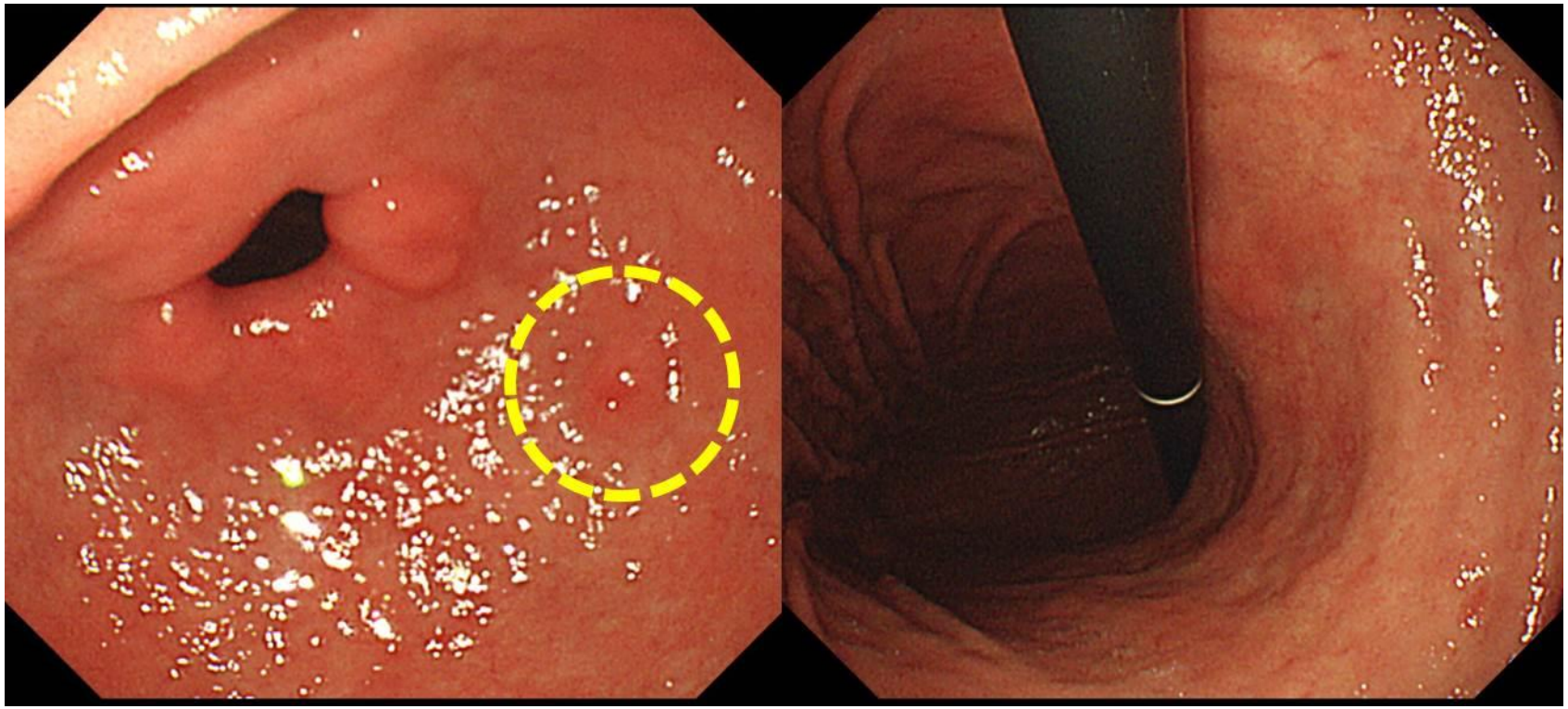
증례 2: Rindi 분류가 애매한 경우

- Atrophic gastritis를 중요시 할 것인가? Gatrin level을 중요시 할 것인가?

증례 2: Rindi 분류가 애매한 경우

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- 대장암 수술 후 경과관찰 중인 분에서 우연히 발견된 NET



증례 2: Rindi 분류가 애매한 경우

- Atrophic gastritis를 중요시 할 것인가? Gatrin level을 중요시 할 것인가?

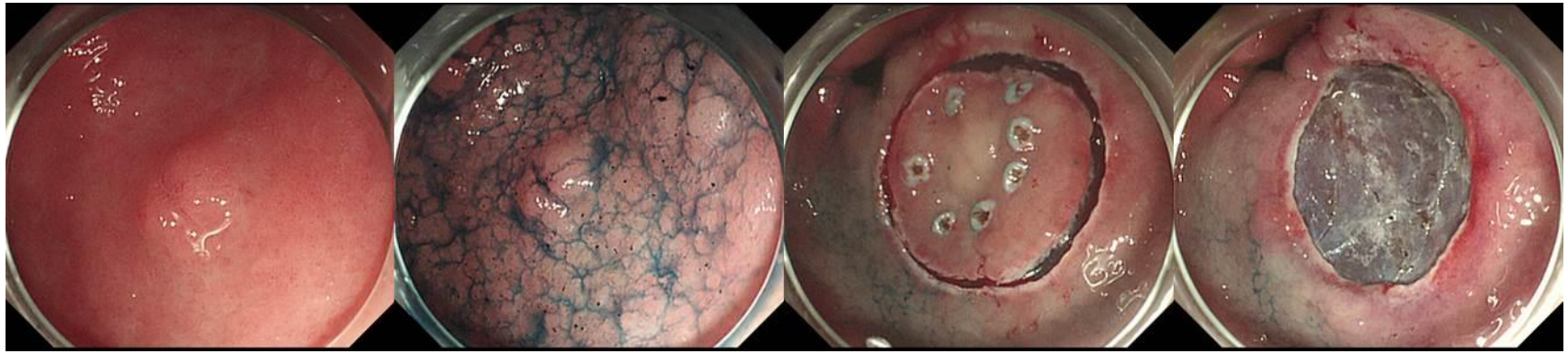
- 대장암 수술 후 경과관찰 중인 분에서 우연히 발견된 NET
- 0.3cm, NET-WD
- Atrophic metaplstic gastritis
- Gastrin – normal

- Type 1 → observation ± HPE
- Type 3 → endoscopic resection

증례 2: Rindi 분류가 애매한 경우

- Atrophic gastritis를 중요시 할 것인가? Gatrin level을 중요시 할 것인가?

- 대장암 수술 후 경과관찰 중인 분에서 우연히 발견된 NET



증례 2: Rindi 분류가 애매한 경우

Endotoday style

Personal approach to gastric NEN (2019)

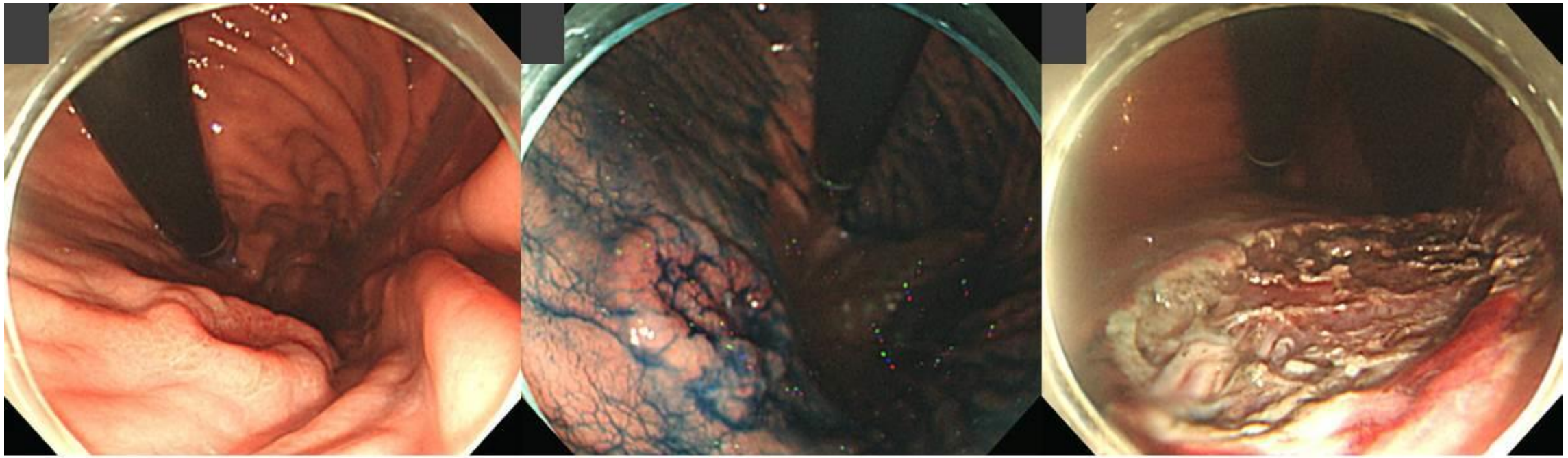
Classification	High gastrin	Normal gastrin
WD-NET G1	Observation (small, signle or multiple) EMR/ESD (small, 1-3) Wedge resection (large)	EMR/ESD (small) Wedge resection (small) Gastrectomy + D2 (large)
WD-NET G2	EMR/ESD +/- additional surgery (?) Wedge resection +/- additional lymph node dissection (?)	Gastrectomy + D2
WD-NET G3	Gastrectomy + D2	Gastrectomy + D2
P-D NEC	Gastrectomy + D2	Gastrectomy + D2

증례 3: Type 3 G-NET

- 50대 여성. Gastrin 23.5, 수술 권유하였으나 내시경치료 원하여 ESD.

증례 3: Type 3 G-NET

- 50대 여성. Gastrin 23.5, 수술 권유하였으나 내시경치료 원하여 ESD.



증례 3: Type 3 G-NET

- 50대 여성. Gastrin 23.5, 수술 권유하였으나 내시경치료 원하여 ESD.
-
  Stomach, high body, posterior, endoscopic submucosal dissection:
  WELL DIFFERENTIATED ENDOCRINE TUMOR (CARCINOID TUMOR):
  1) size: 1.6x1.5 cm
  2) confined to mucosa/submucosa
  3) lymphovascular invasion: not identified
  4) mitosis: 0/10 HPFs
  5) negative resection margins
  Chromogranin : Strong positive
  Synaptophysin: Positive
  Ki-67 : Positive in less than 1% of tumor cells

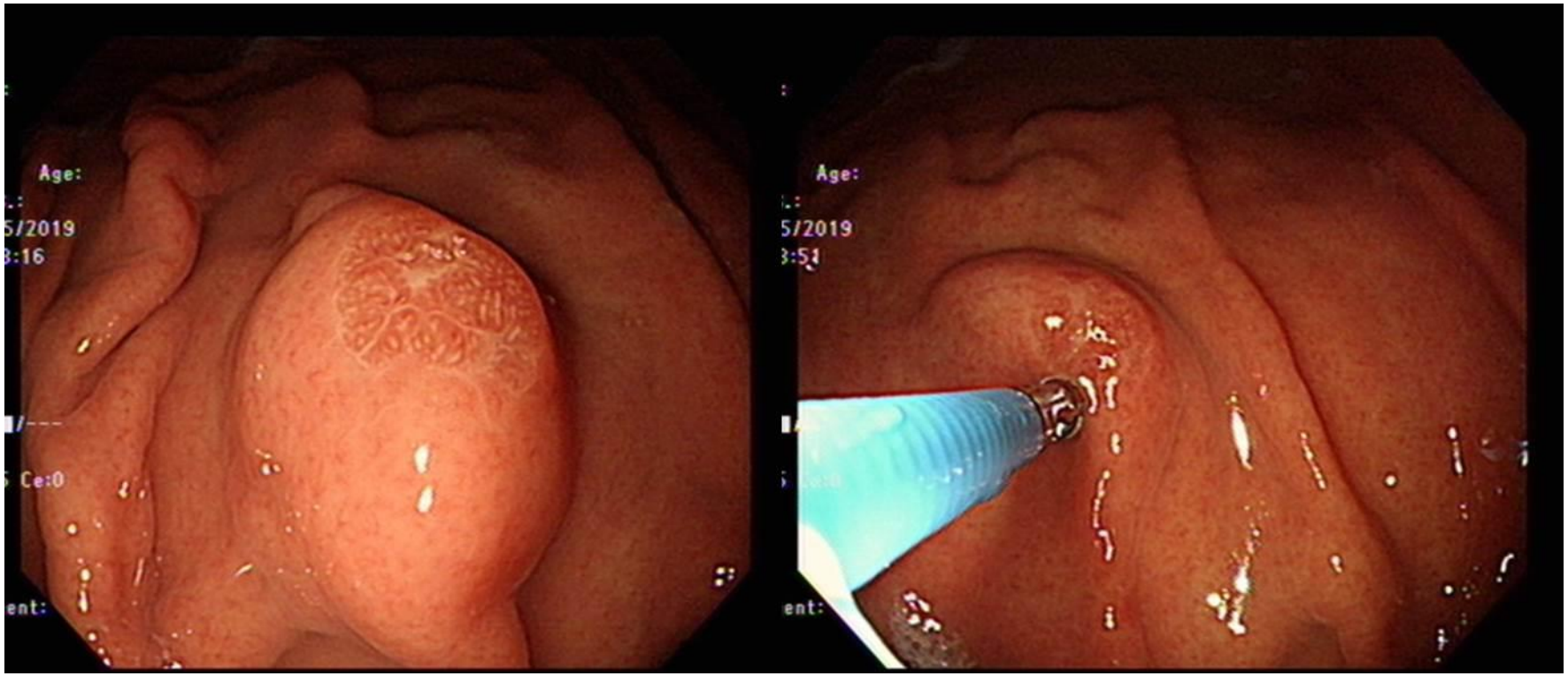
증례 3: Type 3 G-NET



임상상 및 내시경 소견

외부 병원 건진 내시경에서 발견된 신경내분비 종양(조직검사 결과: carcinoid tumor)의 치료를 위하여 의뢰되었다. 혈청 가스트린은 23.5 pg/mL 였다. 수술적 치료를 권하였으나 환자는 내시경절제술을 원하여, ESD를 시행하였다 **(사진 A 하단)**. 병리결과는 well differentiated neuroendocrine tumor (carcinoid tumor), 1.6×1.5 cm, confined to mucosal and submucosa, mitosis: 0/10 HPFs, Ki-67: positive in less than 1% of tumor cells이었다. 11년 후 연고지에서 시행한 내시경검사에서 ESD 반흔 주위로 발적과 융기부가 발견되었고, 조직검사에서 well differentiated neuroendocrine tumor가 확인되어 다시 의뢰되었다**(사진 B)**. CT에서 위체상부 소만과 맞닿은 3×2.5 cm 림프절이 관찰되었고, 68Ga-DOTATATE PET에서 강하게 uptake 되었다**(사진 B 하단)**.

증례 4: Type 3 G-NET

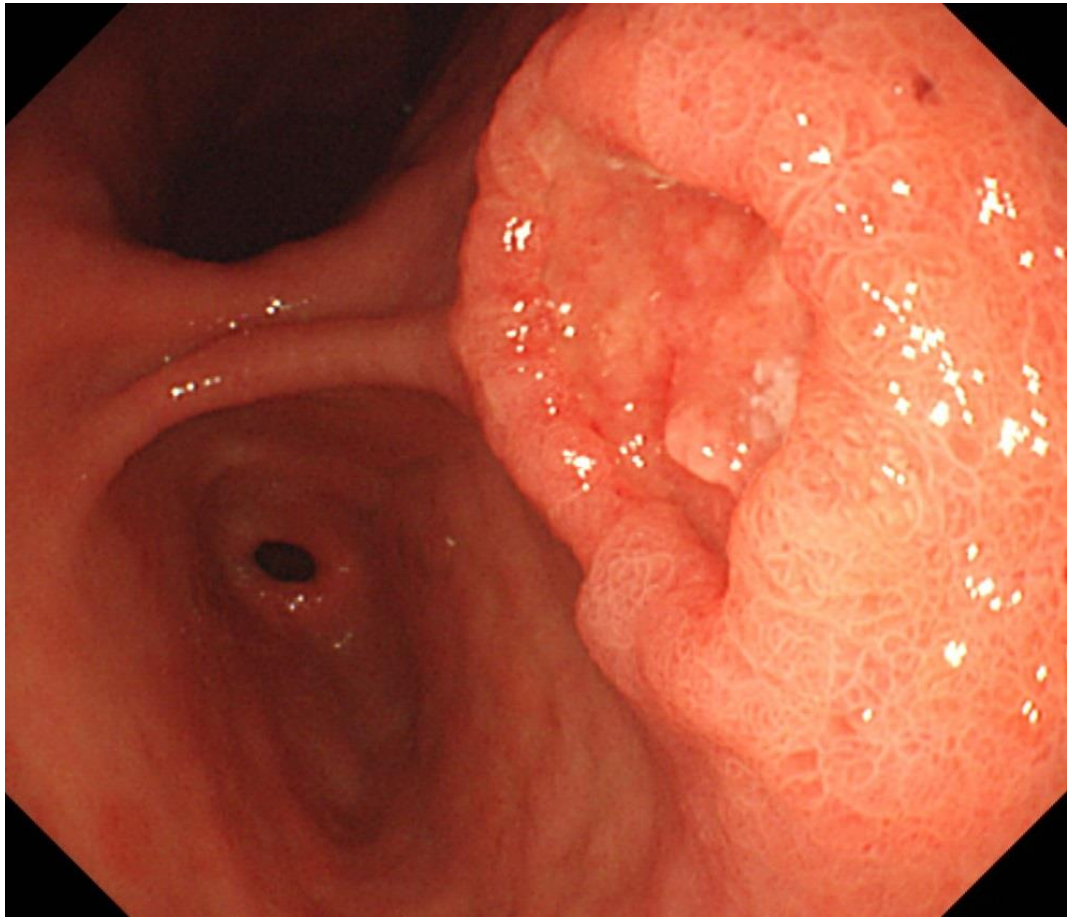


Serum gastrin 41.9

Stomach, laparoscopic wedge resection

- 1. Name of Procedure: laparoscopic wedge resection
  2. Site of Tumor: Stomach (high body, greater curvature)
  3. Diagnosis: Neuroendocrine tumor
  4. WHO classification(2010): Well-differentiated Neuroendocrine tumor (G1)
  5. Multiplicity: Single
  6. Size: 1.7x1.5 cm
  7. Extent: Mucosa and submucosa
  8. Grading: Mitotic Count(/10HPF): 0-1, Ki-67 labeling index: G1: <3%
  9. Immunohistochemical Stains:
  1) Synaptophysin : Positive
  2) Chromogranin A: Positive
  10. Lymphovascular invasion: Not identified
  11. Perineural invasion: Not identified
  12. Lymph node metastasis: not evaluated
  13. Resection Margins: Negative, Safety margin : 1.5 cm

증례 5: Neuroendocrine carcinoma



증례 5: Neuroendocrine carcinoma

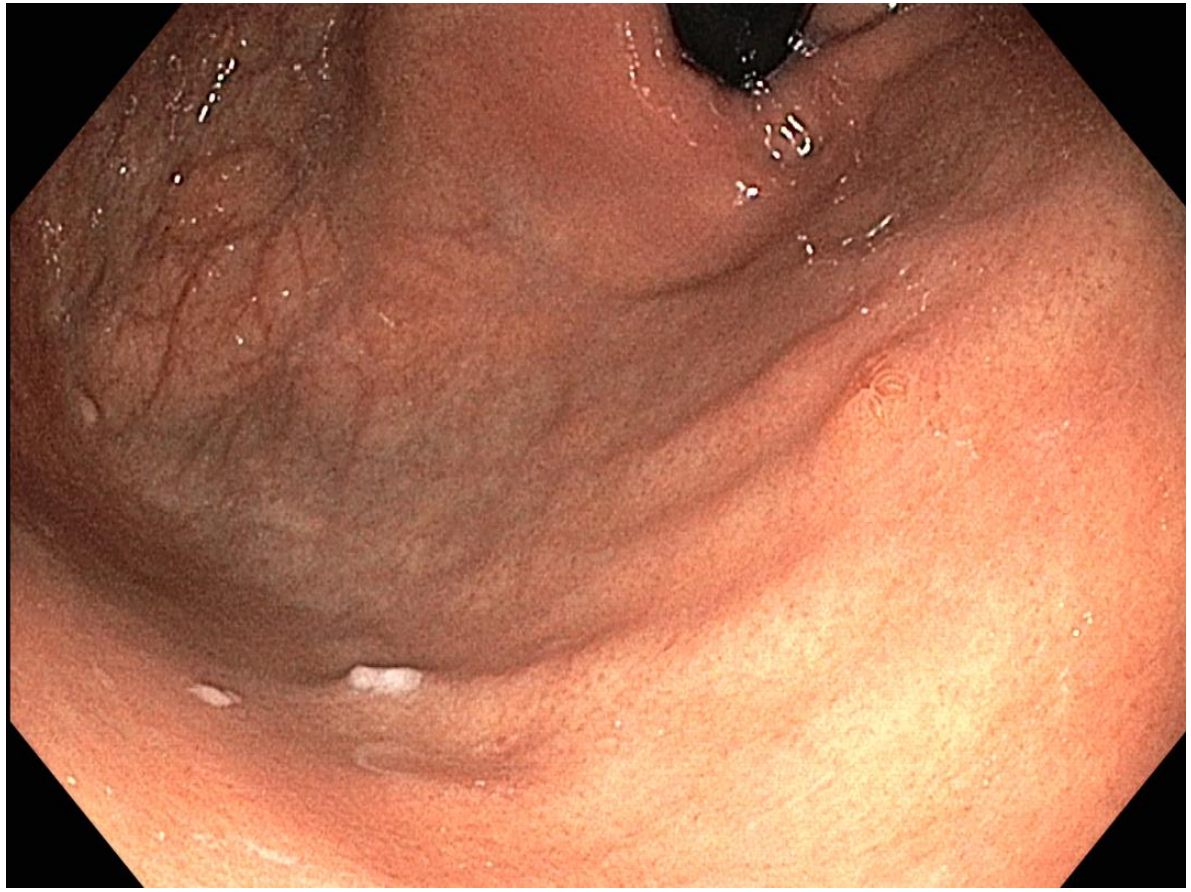
- Poorly-differentiated neuroendocrine carcinoma (G3)
  1. Name of Procedure: Organ resection+Node dissection (specify: subtotal gastrectomy)
  2. Site of Tumor: Stomach (Antrum and pylorus)
  3. Diagnosis: Neuroendocrine carcinoma
  4. WHO classification(2010): Neuroendocrine carcinoma
  5. Multiplicity: Single
  6. Size: 2.5x1.8 cm
  7. Extent: Mucosa and submucosa (pT1b)
  8. Grading: Mitotic Count: >20/10HPF, Ki-67 labeling index: G3>20%
  9. Immunohistochemical Stains: 1. Synaptophysin : Positive 2. Chromogranin A: Positive OPTIONAL : CD56 (+)
  10. Lymphovascular invasion: Present (intra- and extramural)
  11. Perineural invasion: Present
  12. Lymph node metastasis: metastasis to 6 out of 71 regional lymph nodes (pN2) (perinodal extension: absent) (6/71: "1", 0/9; "3", 4/19; "4", 1/3; "4sb", 0/5; "5", 0/0; "6", 0/5; "7", 0/6; "8a", 1/3; "9", 0/8; "11p", 0/9; "12a", 0/3; "11d", 0/1)
  13. Resection Margins: Negative Safety margin : proximal, 4 cm; distal, 2.8 cm
  14. AJCC stage by 7th edition: pT1b N2

64/F

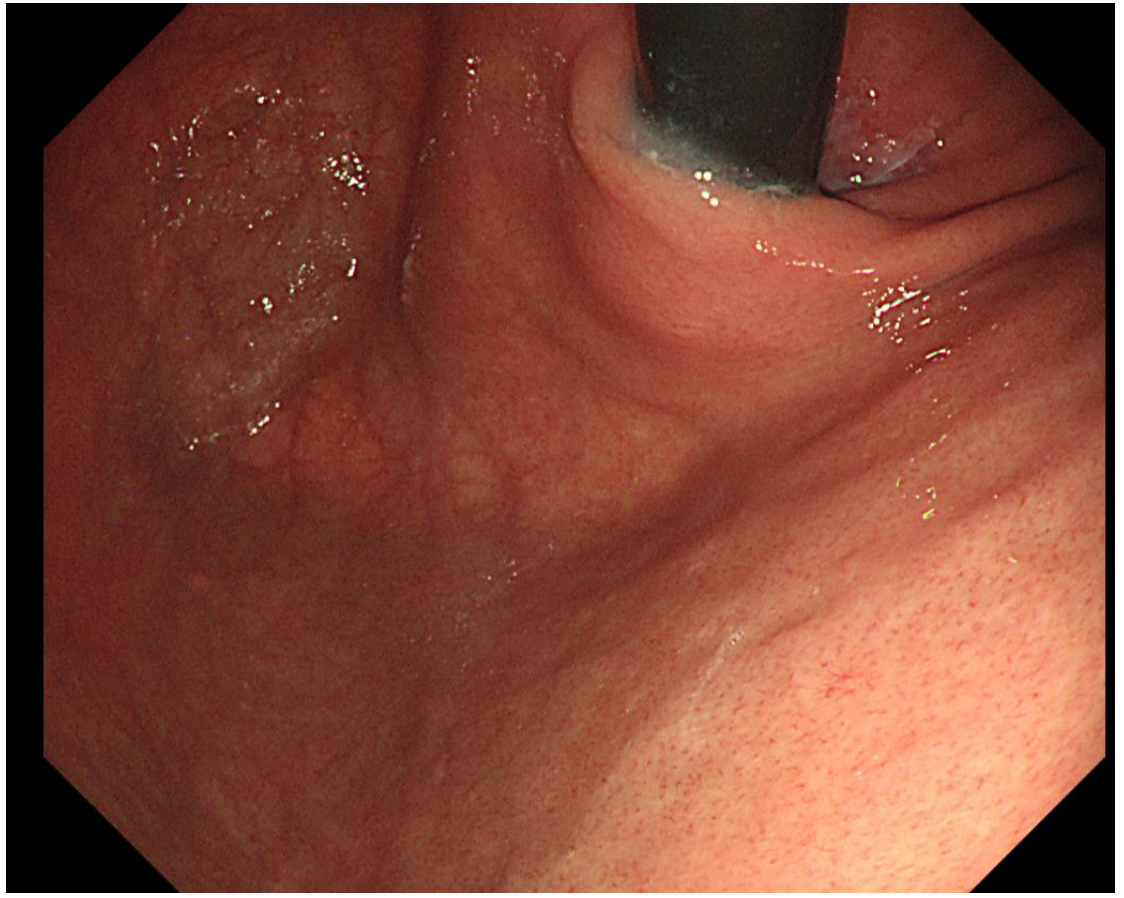
- C.C : NET, G1

- P.I : 신물이 올라오는 증상 이외 다른 상부위장관 증상 없으나 검진 내시경에서 NET, G1 소견 있어 본원 외과 외래 내원함.

외부 EGD



본원 EGD



Stomach, upper body, anterior wall, biopsy:

. Well differentiated neuroendocrine tumor (G1)

Gastrin : 79.7 pg/mL

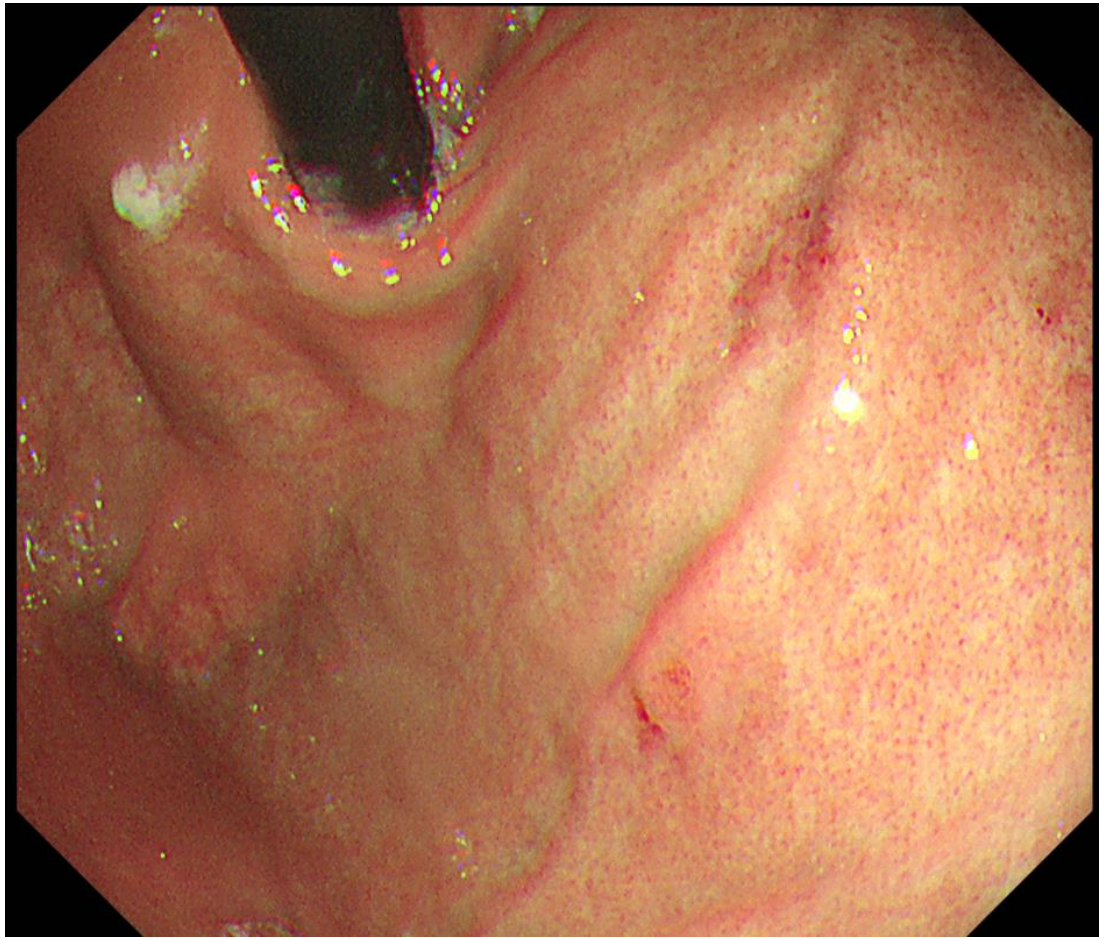
Stomach, #1x1 : Anterior wall of high body, biopsy :

. Chronic gastritis, inactive
. No H. pylori identified.

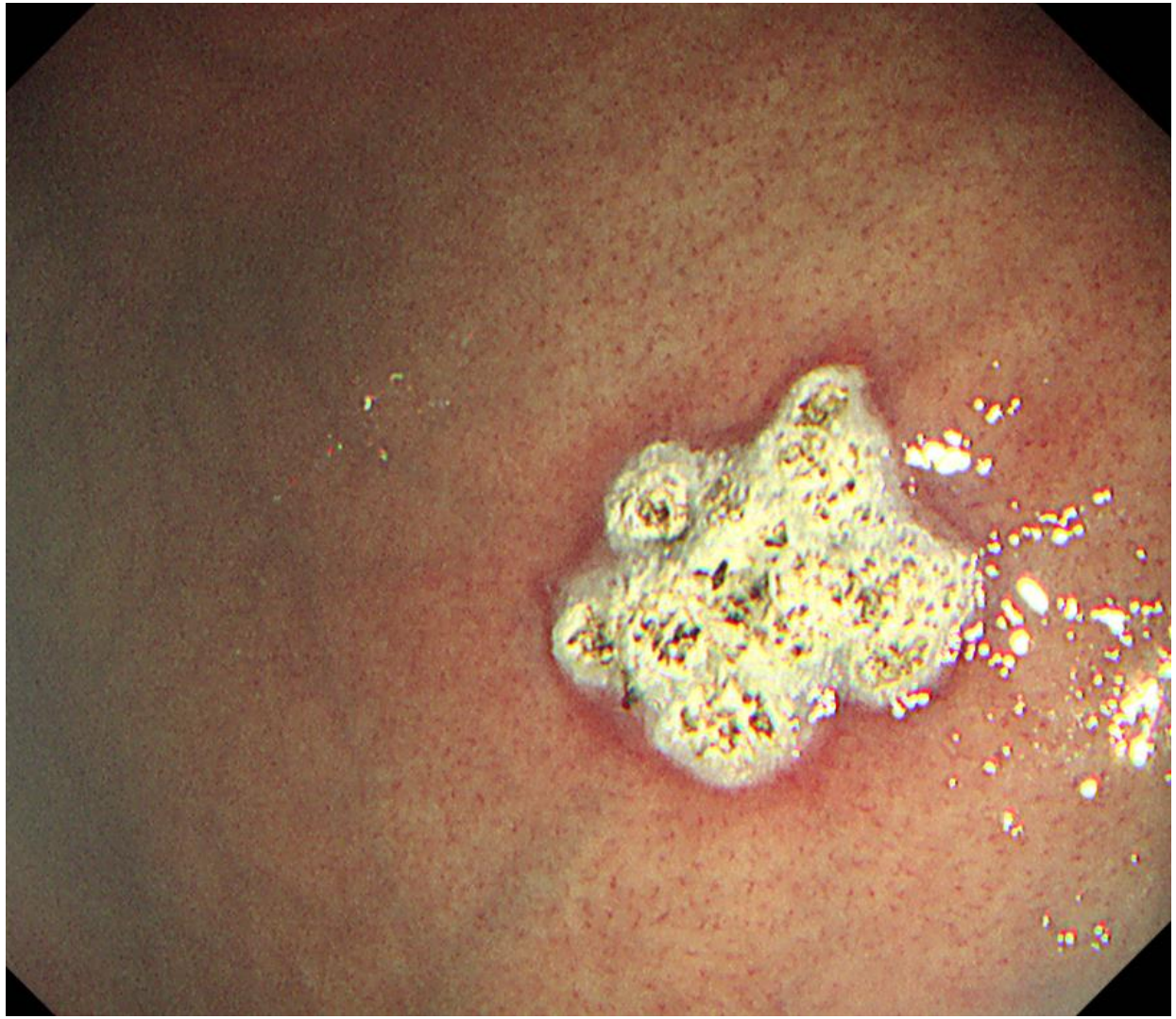
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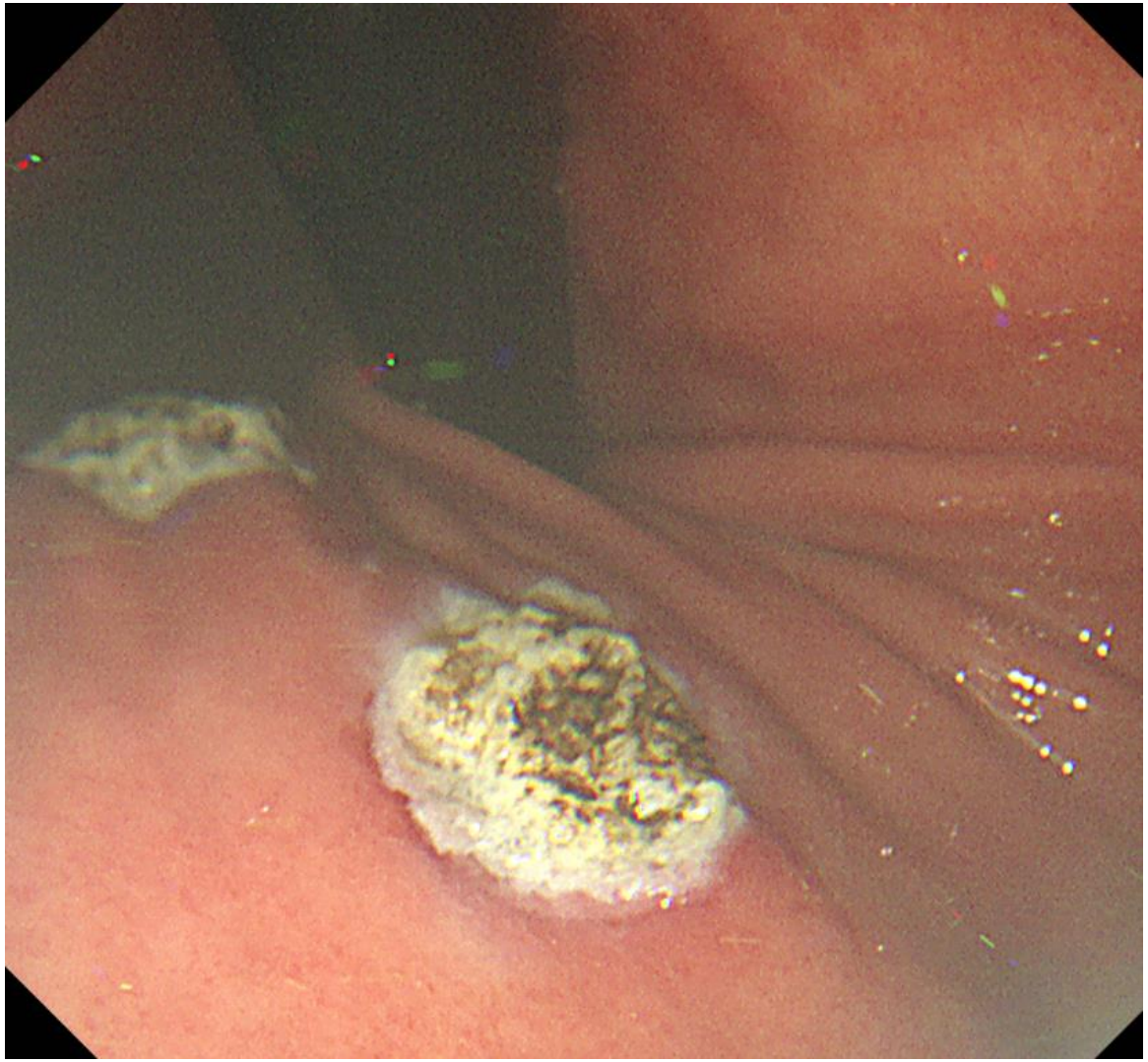
- IM1 plan

- 제거 되었을 가능성 있음
- OPD APC or EGD check (병소가 보이지 않으면 검사만 진행할 수 있음을 설명)



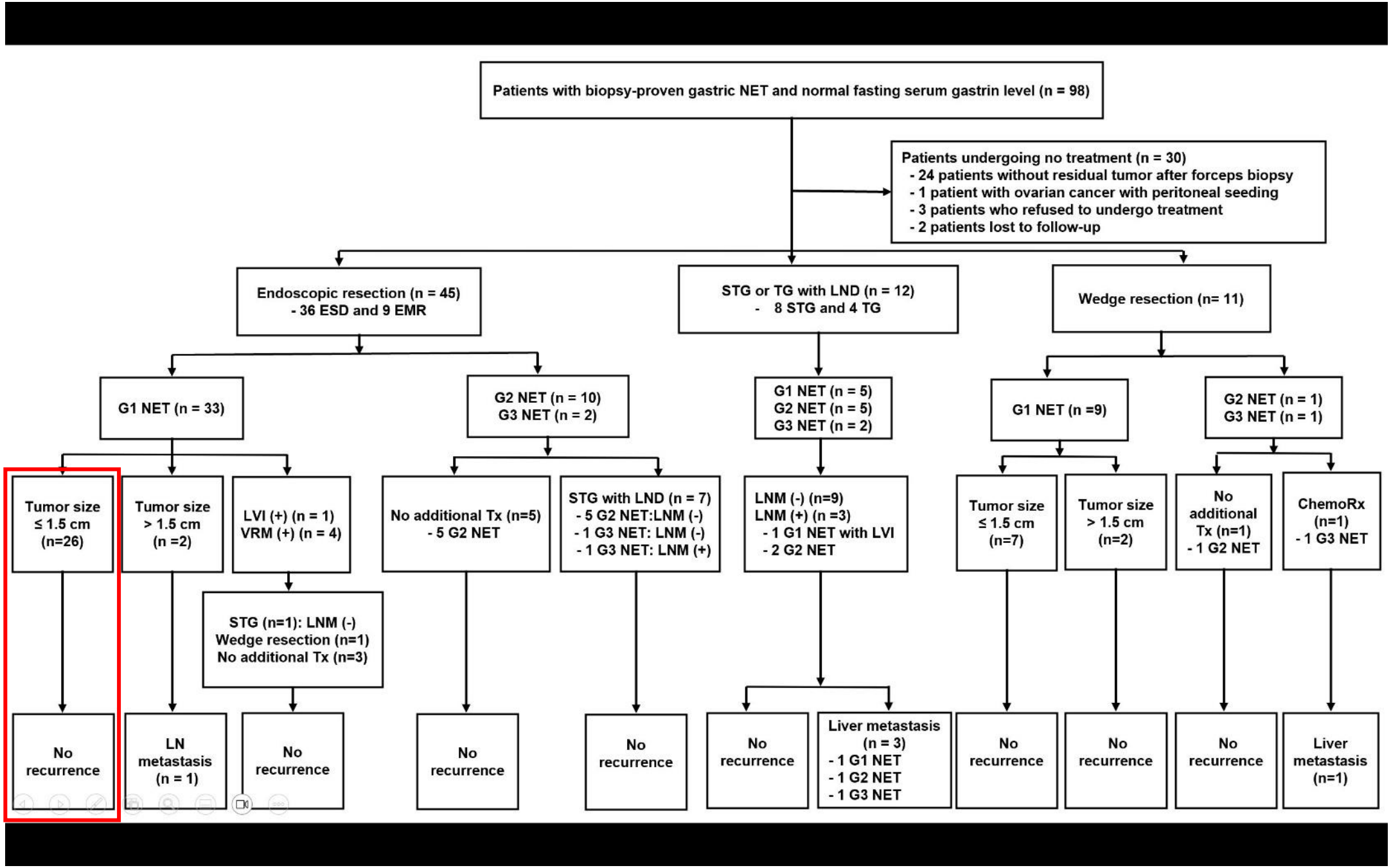


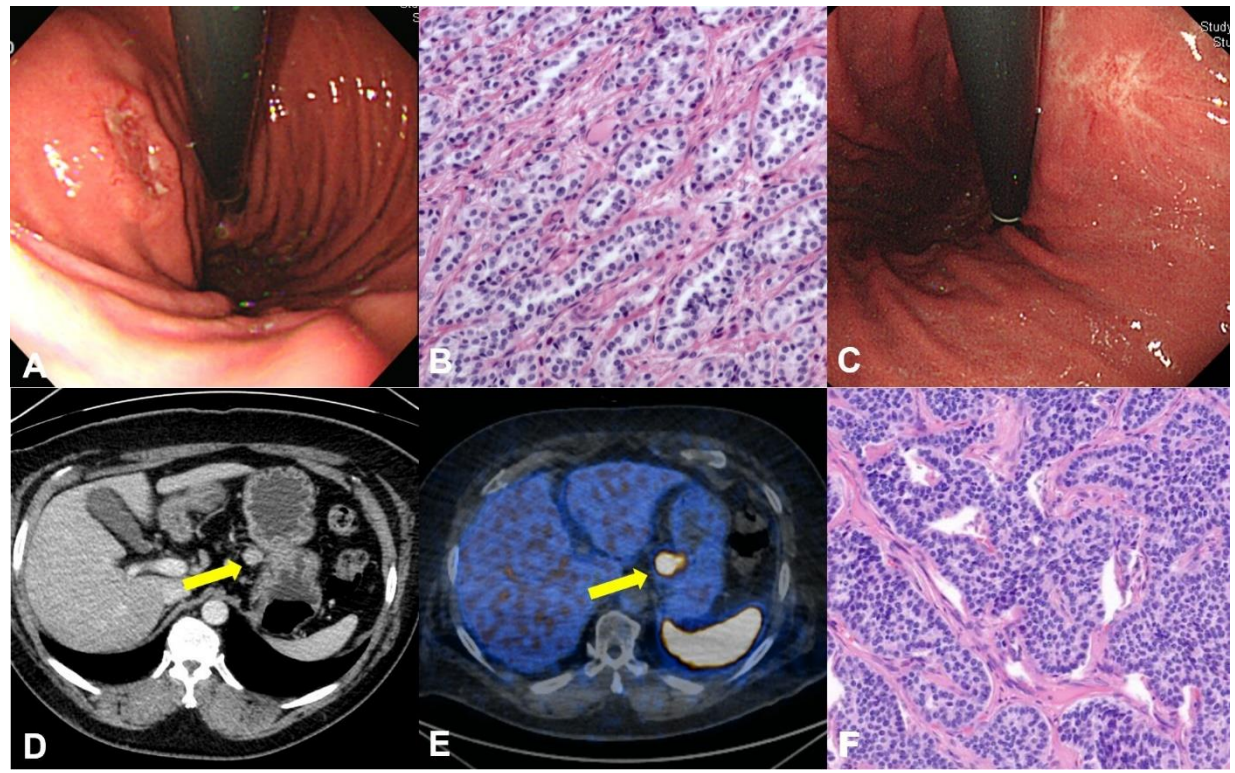




Long-term Outcomes of Endoscopic Resection for Type 3 Gastric Neuroendocrine Tumors

- **Background & Aims:** Long-term outcomes of endoscopic resection (ER) for type 3 gastric neuroendocrine tumors (NETs) remain unclear; therefore, recommended indications for ER vary between current guidelines. This study aimed to evaluate the long-term oncological outcomes and establish a robust indication for ER for type 3 gastric NETs.
- **Methods:** We retrospectively reviewed the database on 68 consecutive patients who underwent endoscopic or surgical resection for biopsy-proven type 3 gastric NET. Clinicopathological features and long-term outcomes following ER or surgical resection of type 3 NETs were evaluated.
- **Results:** Among 68 patients with type 3 gastric NET, grade 1, grade 2, and grade 3 NETs accounted for 69.1%, 23.5%, and 7.4% of total patients, respectively. Lymphovascular invasion rates were 36.4% for grade 2 NET and 100% for grade 3 NET, respectively. The median tumor size was 0.8 cm. During median 155 months (range, 29-240 months) of follow-up, no recurrence occurred in 26 patients undergoing ER for grade 1 type 3 NETs ≤ 1.5 cm without lymphovascular invasion. One patient had histologically proven NET recurrence in lymph node 68 months after ER for 1.6 cm-sized grade 1 tumor. In 33 patients undergoing ER as the initial treatment for grade 1 type 3 NETs, the 5-year overall and recurrence-free survival rates were 89.5% and 100%, respectively. There were no gastric NET-related deaths in these 33 patients during median 155 months (range, 25-240 months) of follow-up.
- **Conclusions:** Given this favorable long-term oncological outcomes, ER may be a valid treatment option for patients with grade 1 type 3 gastric NETs ≤ 1.5 cm without lymphovascular invasion.


Patients with biopsy-proven gastric NET and normal fasting serum gastrin level (n = 98)
Patients undergoing no treatment (n = 30)
- 24 patients without residual tumor after forceps biopsy
- 1 patient with ovarian cancer with peritoneal seeding
- 3 patients who refused to undergo treatment
- 2 patients lost to follow-up
Endoscopic resection (n = 45)
- 36 ESD and 9 EMR
STG or TG with LND (n = 12)
- 8 STG and 4 TG
Wedge resection (n= 11)
G1 NET (n = 33)
G2 NET (n = 10)
G3 NET (n = 2)
G1 NET (n = 5)
G2 NET (n = 5)
G3 NET (n = 2)
G1 NET (n =9)
G2 NET (n = 1)
G3 NET (n = 1)
Tumor size ≤ 1.5 cm (n=26)
Tumor size > 1.5 cm (n =2)
LVI (+) (n = 1)
VRM (+) (n = 4)
No additional Tx (n=5)
- 5 G2 NET
STG with LND (n = 7)
- 5 G2 NET:LNM (-)
- 1 G3 NET: LNM (-)
- 1 G3 NET: LNM (+)
LNM (-) (n=9)
LNM (+) (n =3)
- 1 G1 NET with LVI
- 2 G2 NET
Tumor size ≤ 1.5 cm (n=7)
Tumor size > 1.5 cm (n=2)
No additional Tx (n=1)
- 1 G2 NET
ChemoRx (n=1)
- 1 G3 NET
STG (n=1): LNM (-)
Wedge resection (n=1)
No additional Tx (n=3)
No recurrence
LN metastasis (n = 1)
No recurrence
No recurrence
No recurrence
No recurrence
Liver metastasis (n = 3)
- 1 G1 NET
- 1 G2 NET
- 1 G3 NET
No recurrence
No recurrence
No recurrence
No recurrence
Liver metastasis (n=1)


A
B
C
D
E
F

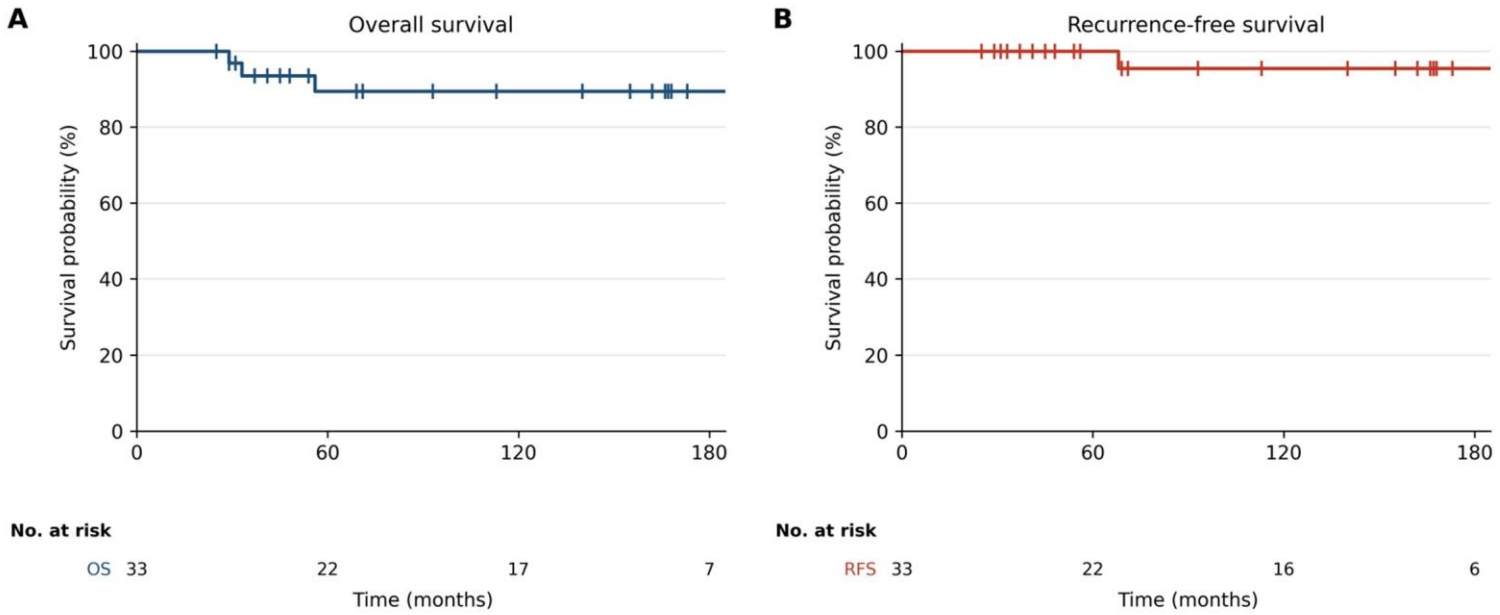


Figure 3 shows Kaplan-Meier curves for overall and recurrence-free survival for 33 patients undergoing ER as the initial treatment for grade 1 type 3 gastric NETs. The median follow-up duration was 155 months (range, 25-240 months). The 5-year overall and recurrence-free survival rates were 89.5% and 100%, respectively. There were no gastric NET-related deaths in these 33 patients with grade 1 NET during the follow-up period.

Reference

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