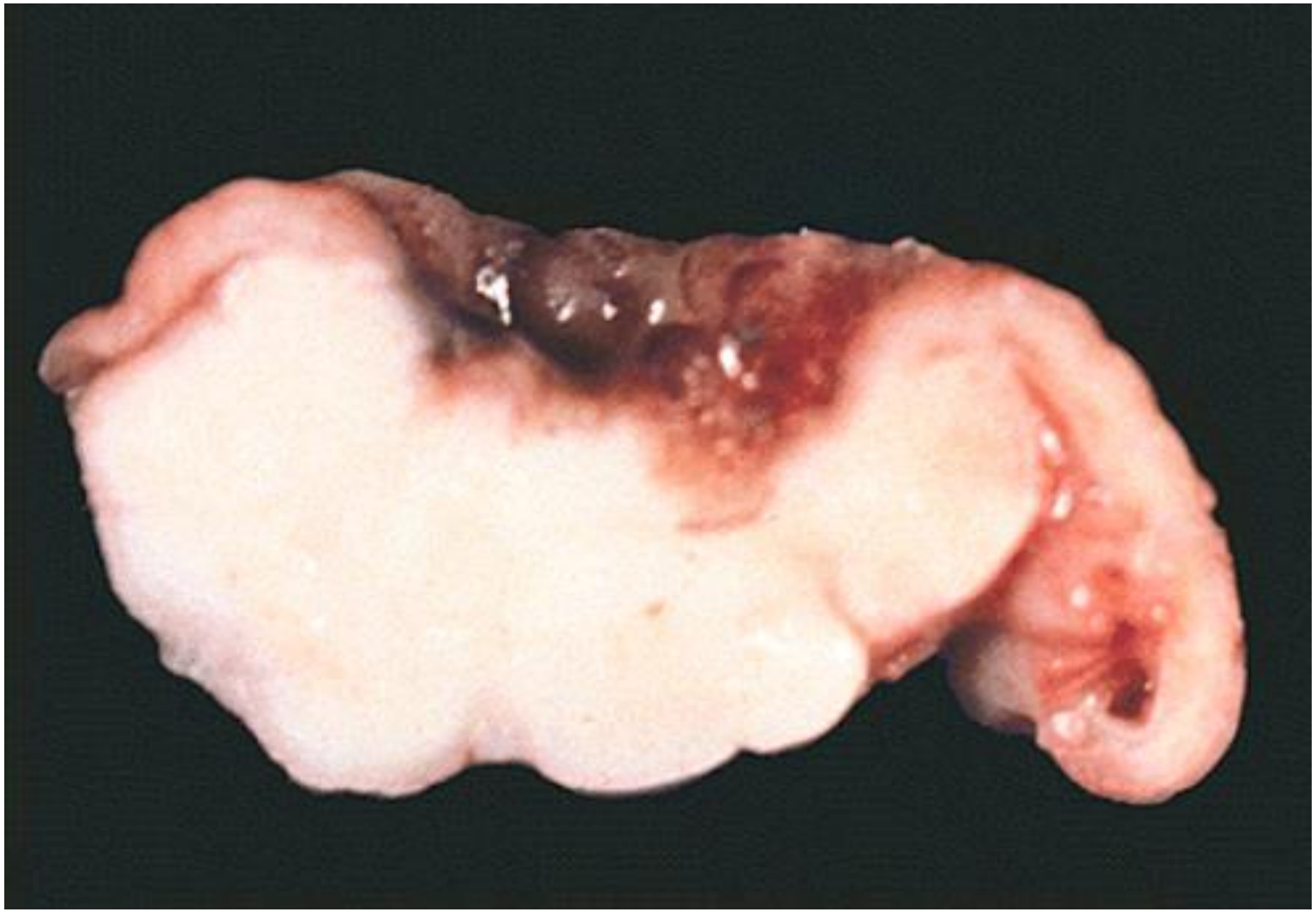
Neuroendocrine tumor

2018/01/02 Topic review

김태세



<Gastric carcinoid>
From Lewin KJ, Appelman HD. Tumors of the esophagus and stomach. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 18, 1996, Washington, DC. Armed Forces Institute of Pathology.

Definition

- Neoplasms arising from cells throughout the diffuse endocrine system (NCCN guideline)

- 병리적으로 풍부한 neurosecretory granule을 가짐

Epidemiology

- The age-adjusted incidence rate increased 6.4-fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000)

- Incidence rates in the SEER 18 registry grouping (2000-2012)
  - 3.56 per 100 000 in gastroenteropancreatic sites
  - 1.49 per 100 000 in the lung
  - 0.84 per 100 000 in NETs with an unknown primary site.

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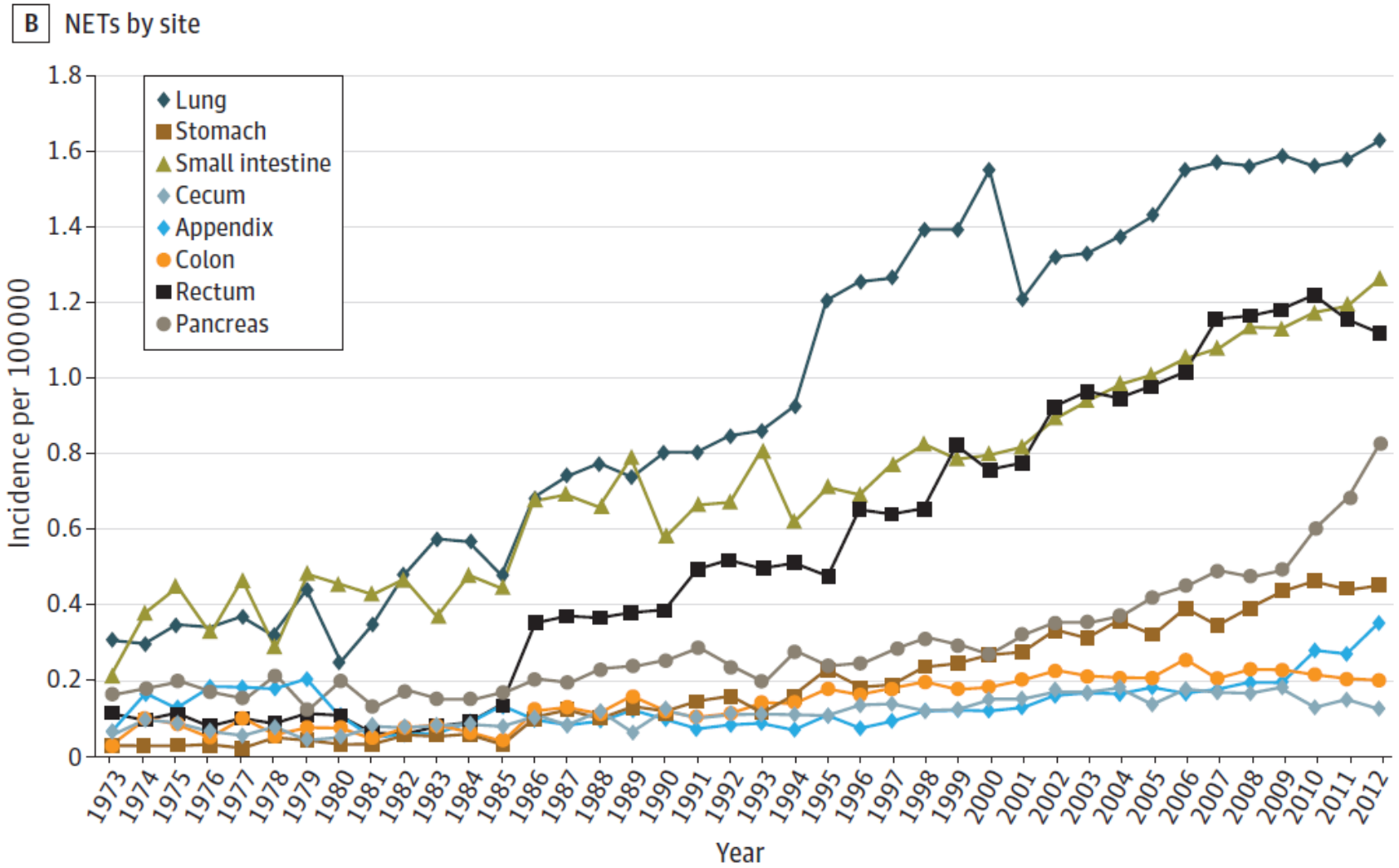
Epidemiology



JAMA Oncol. 2017;3(10):1335-1342

Etiology

- Most are sporadic
  - Risk factors are poorly understood

- Some are due to inherited genetic syndromes
  - MEN1: *menin* gene
  - MEN2: *RET* protooncogene
  - Von Hippel-Lindau disease, tuberous sclerosis, neurofibromatosis

Classification

- Site of origin
- Stage
- Histologic characteristics

Staging system

- Separate TNM staging systems according to tumor site
  - Stomach, duodenum/ampulla/jejunum/ileum, colon/rectum, appendix
  - Lung: same with lung carcinoma
  - Pancreas: same as for exocrine pancreatic carcinoma

- ENETS proposal vs AJCC 2010 edition
  - ENET: PD-NET → same as WD-NET
  - AJCC: PD-NET → same as adenocarcinoma
  - Different T stage definitions for WD-NET except for pancreas

- NET of unknown primary → stage IV

Staging system

Stomach

TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ/dysplasia (tumor size less than 0.5 mm), confined to mucosa
T1 Tumor invades lamina propria or submucosa and 1 cm or less in size
T2 Tumor invades muscularis propria or more than 1 cm in size
T3 Tumor penetrates subserosa
T4 Tumor invades visceral peritoneum (serosal) or other organs or adjacent structures
For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastases (M)

M0 No distant metastases
M1 Distant metastasis

Duodenum/Ampulla/Jejunum/Ileum

TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor invades lamina propria or submucosa and size 1 cm or less* (small intestinal tumors); tumor 1 cm or less (ampullary tumors)
T2 Tumor invades muscularis propria or size > 1 cm (small intestinal tumors); tumor > 1 cm (ampullary tumors)
T3 Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into non-peritonealized tissues
T4 Tumor invades visceral peritoneum (serosa) or invades other organs
For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastases (M)

M0 No distant metastases
M1 Distant metastasis

* Note: Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma.

Staging system

Colon or Rectum

TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades lamina propria or submucosa and size 2 cm or less
T1a	Tumor size less than 1 cm in greatest dimension
T1b	Tumor size 1–2 cm in greatest dimension
T2	Tumor invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4	Tumor invades peritoneum or other organs For any T, add (m) for multiple tumors

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Staging system

Pancreatic

TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

* This also includes the "PanInIII" classification.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Staging system

Appendiceal Carcinoid

TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension
T1a	Tumor 1 cm or less in greatest dimension
T1b	Tumor more than 1 cm but not more than 2 cm
T2	Tumor more than 2 cm but not more than 4 cm or with extension to the cecum
T3	Tumor more than 4 cm or with extension to the ileum
T4	Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle*

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage I	T1	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

pTNM Pathologic Classification. The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 does not exist as a category.

pN0. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

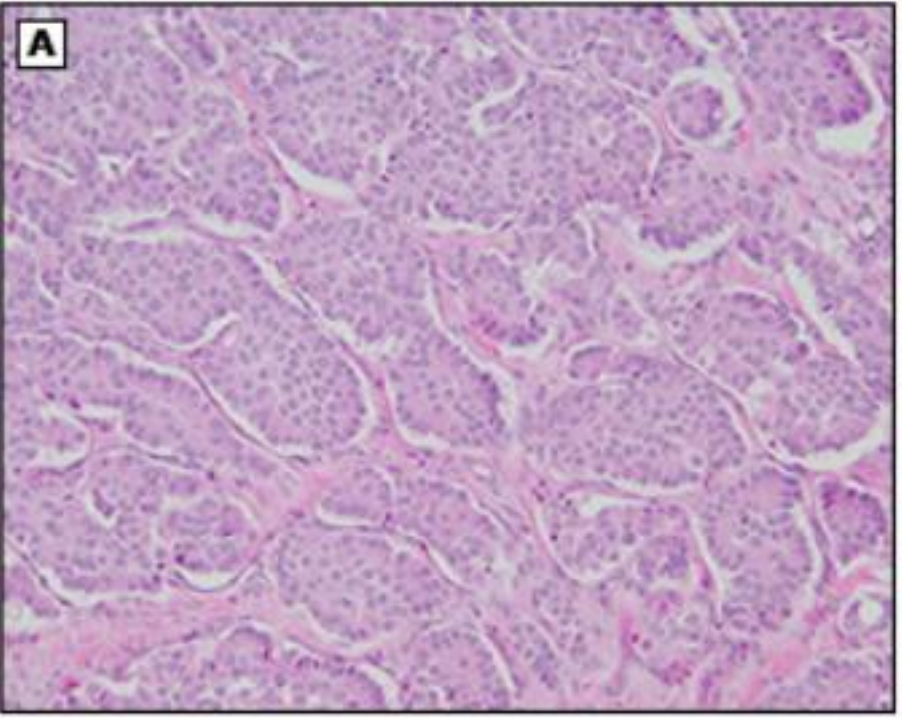
Note: Tumor that is adherent to other organs or structures, grossly, is classified cT4. However, if no tumor is present in the adhesion, microscopically, the classification should be classified pT1-3 depending on the anatomical depth of wall invasion.

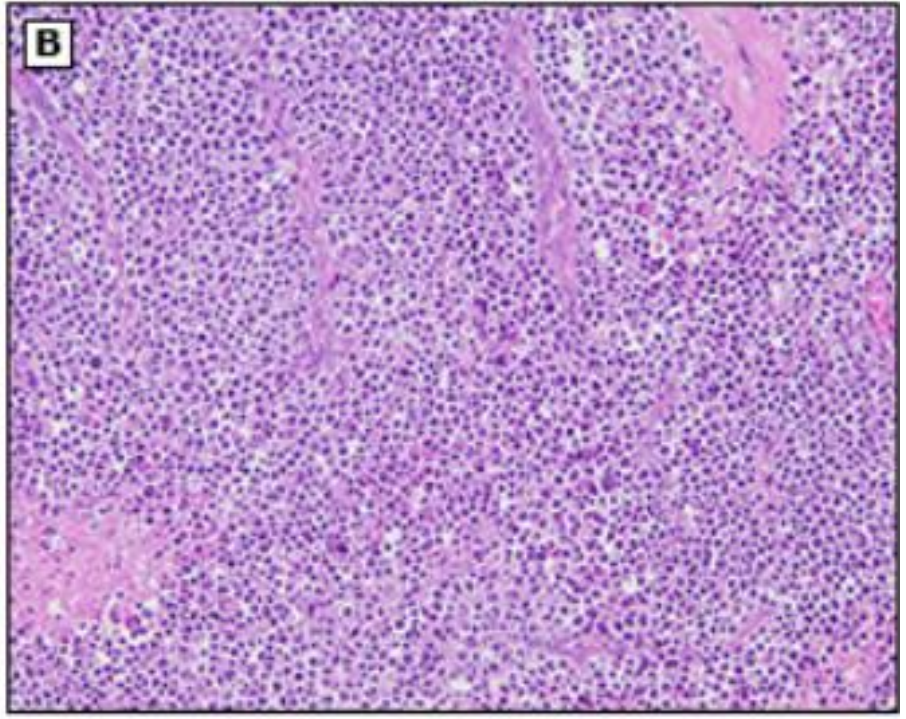
*Penetration of the mesoappendix does not seem to be as important a prognostic factor as the size of the primary tumor and is not separately categorized.

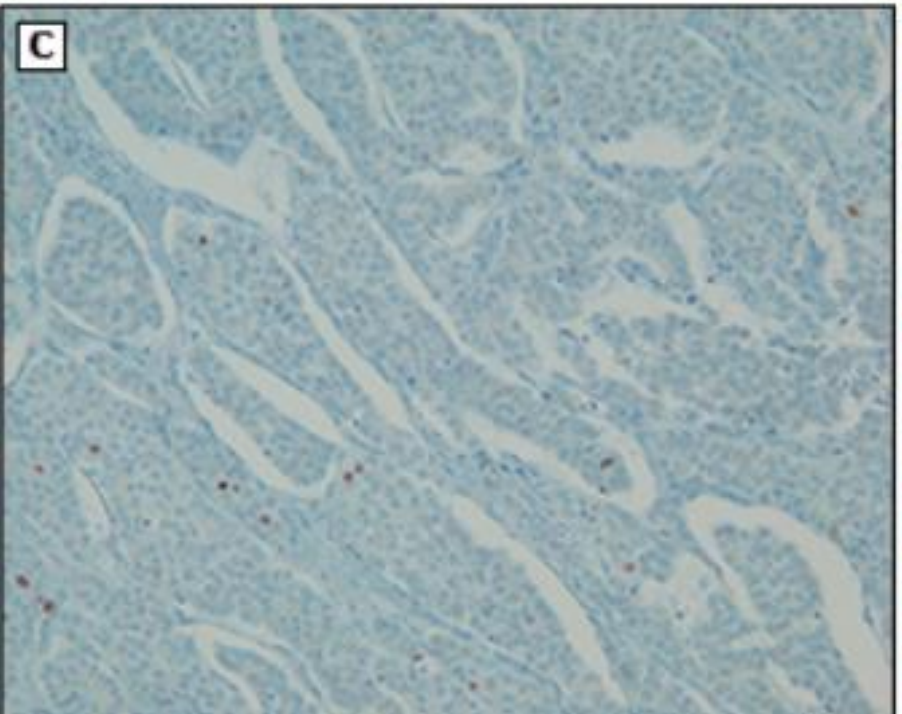
Histology: two major categories

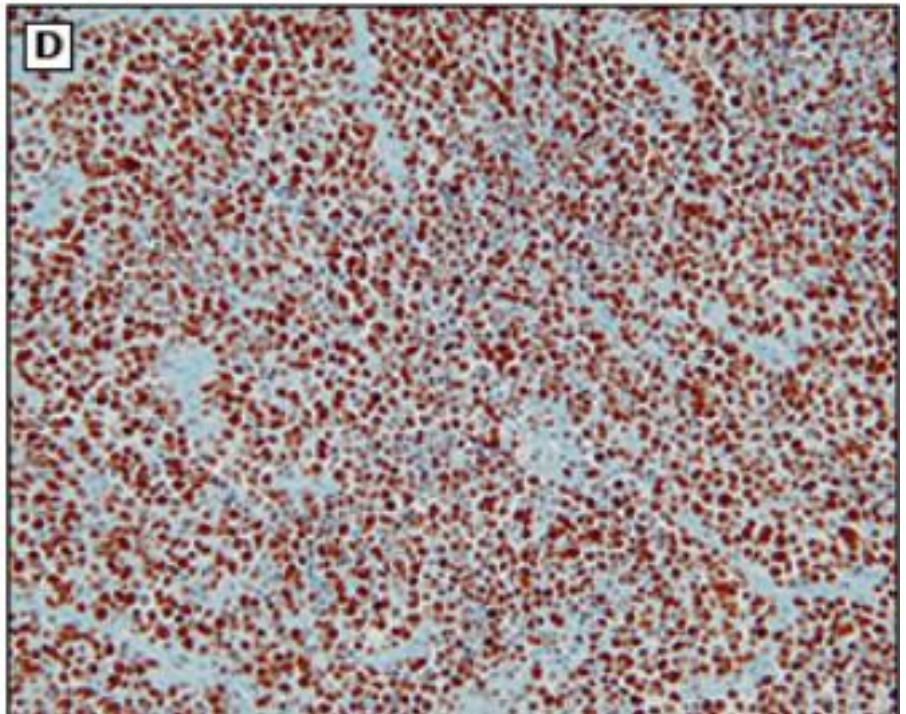
- Well-differentiated neuroendocrine tumors
  - Traditionally referred to as carcinoid and pancreatic islet tumors
  - Better prognosis (5 year overall survival = 67%)
  - Not a homogeneous group → variable clinical course

- Poorly differentiated neuroendocrine carcinomas
  - High grade carcinoma resembling small cell or large cell neuroendocrine carcinoma of the lung
  - Rapid clinical course









<Well-differentiated NET>
- H&E stain (A)
: Nearly no mitotic activity
- Ki67 labeling index (C)
: <1%, low proliferative rate

<Poorly-differentiated NET>
- H&E stain (B)
: Numerous mitosis
: Tumor necrosis
- Ki67 labeling index (D)
: >80%, high proliferative rate

Histologic grading scheme

Grade	Definition
GX	Grade cannot be assessed
G1	Mitotic count (per 10 HPF)* <2 and Ki-67 index (%)¶ <3
G2	Mitotic count (per 10 HPF) = 2 to 20 or Ki-67 index (%)¶ = 3 to 20
G3	Mitotic count (per 10 HPF) >20 or Ki-67 index (%)¶ >20

* 10 HPF = 2 mm^2; at least 50 HPFs (at 40 times magnification) must be evaluated in areas of highest mitotic density in order to adhere to WHO 2010 criteria.
¶ MIB1 antibody; % of 500 to 2000 tumor cells in areas of highest nuclear labeling.

Classification

- Very confusing & evolving

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor	1. Neuroendocrine tumor grade 1 (G1) (carcinoid)
	2. Well-differentiated endocrine carcinoma	2. Neuroendocrine tumor grade 2 (G2)
	3. Poorly differentiated endocrine carcinoma/small cell carcinoma	3. Neuroendocrine carcinoma (large cell or small type)
II. Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma	4. Mixed adenoneuroendocrine carcinoma
III. Mixed forms carcinoid adenocarcinoma		
IV. Pseudotumor lesions	5. Tumor-like lesions	Hyperplastic and preneoplastic lesions

Histologic classification

- Most NETs fall into 3 broad histologic categories
  - Well-differentiated, low-grade (G1)
  - Well-differentiated, intermediate-grade (G2)
  - Poorly differentiated, high-grade (G3)

- Still ongoing debate
  - Poorly differentiated NETs ≠ G3 NECs.
    - Morphologically well-differentiated, low mitotic index, high Ki-67?
  - Current WHO G3 category is heterogeneous
    - Clinical judgement is needed

Functionality and nomenclature

- Functioning NET are defined based upon clinical symptoms
  - If gastrin (+), Sx (-) → gastrinoma (X), gastrin secreting NET (O).

Tumor	Clinical presentation	Pancreatic localization	Malignancy
Insulinoma (insulin)	Whipple's triad	>97%	<10%
Gastrinoma (gastrin)	Zollinger-Ellison syndrome	25-60%	60-90%
VIPoma (Vasoactive intestinal polypeptide)	Verner-Morrison syndrome	>90%	40-70%
Glucagonoma (glucagon)	Glucagonoma syndrome	>95%	50-80%
Somatostatinoma	Somatostatinoma syndrome	55%	>70%

Jensen RT. Pancreatic endocrine tumors: Recent advances. Ann Oncol 1999; 10:170.
Ehehalt F, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. Oncologist 2009; 14:456.

Clinical manifestation

- Esophageal NET
- Gastric NET
- Pancreatic NET

Esophageal NET

- Frequently poorly differentiated and high grade
- Aggressive, diagnosed at advanced stage
- Endoscopy findings
  - Flat or exophytic lesion, frequently with central ulceration
  - Middle or lower third of esophagus
- EUS/CT/PET-CT for accurate staging
- 국소병기 → 수술, 진행병기 → 항암치료
  - If localized & < 2cm → Endoscopic resection 했다는 보고도 있음

Gastric NET

- 3 subtypes
  - Type 1: most common(80%), chronic autoimmune atrophic gastritis related hypergastrinemia, indolent manner
  - Type 2: gastrin secreting tumor induced hypergastrinemia (MEN1, Zollinger-Ellison syndrome)
  - Type 3: high grade, poor differentiation, aggressive behavior

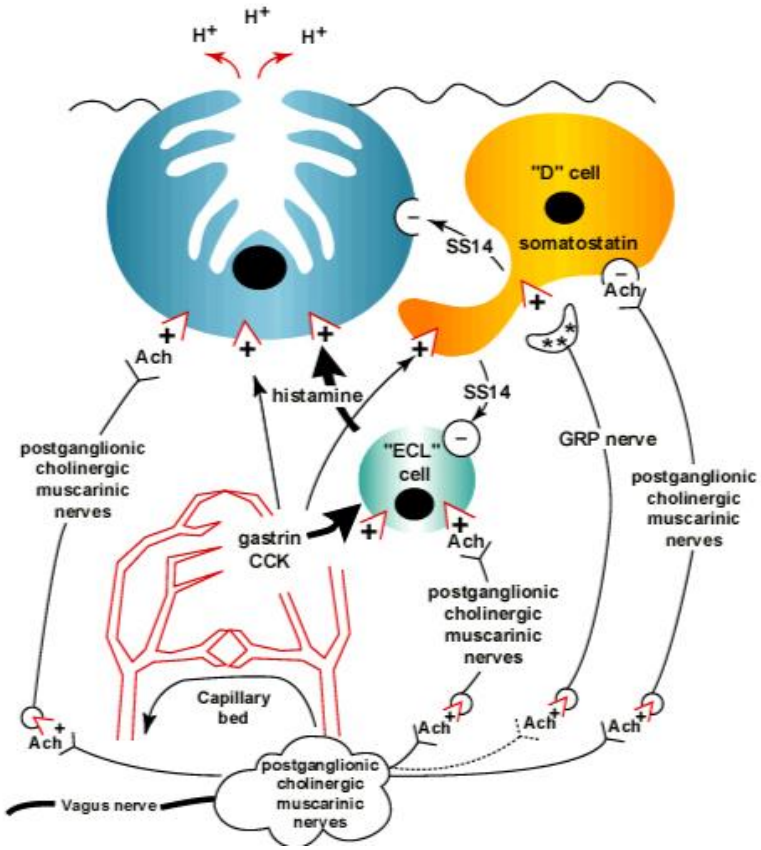
Type 1 gastric NET

- Auto-antibodies to either intrinsic factor or parietal cells

→ gastric achlorhydria → hypergastrinemia

→ enterochromaffin-like cell proliferation

→ type 1 gastric NET



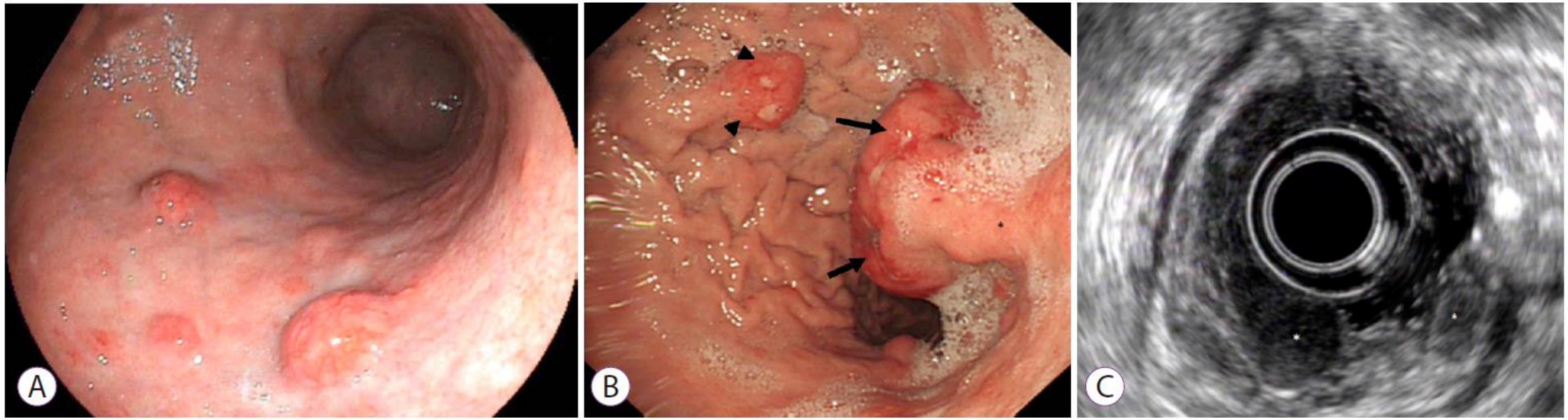
Modified from: Soll AH, Berglindh T. Receptors regulating acid secretory function. In: Physiology of the Gastrointestinal Tract, volume 1, Johnson LR, Christensen MJ, Jackson ED, et al (Eds), Raven Press, New York 1994. p.11.

Type 1 gastric NET

- Anemia work-up 하면서 발견되기도 함
- Serum gastrin level, serum B12, serum chromogranin A
- Anti parietal cell or IF antibodies
- Thyroid function test
  - Risk of developing subclinical or clinical hypothyroidism

- 내시경 소견
  - Multiple polyps or nodules (<1 to 2 cm) in fundus & body
  - Reduced or flattened gastric folds
  - Low volume gastric acid/mucus pool.

Type 1 gastric NET



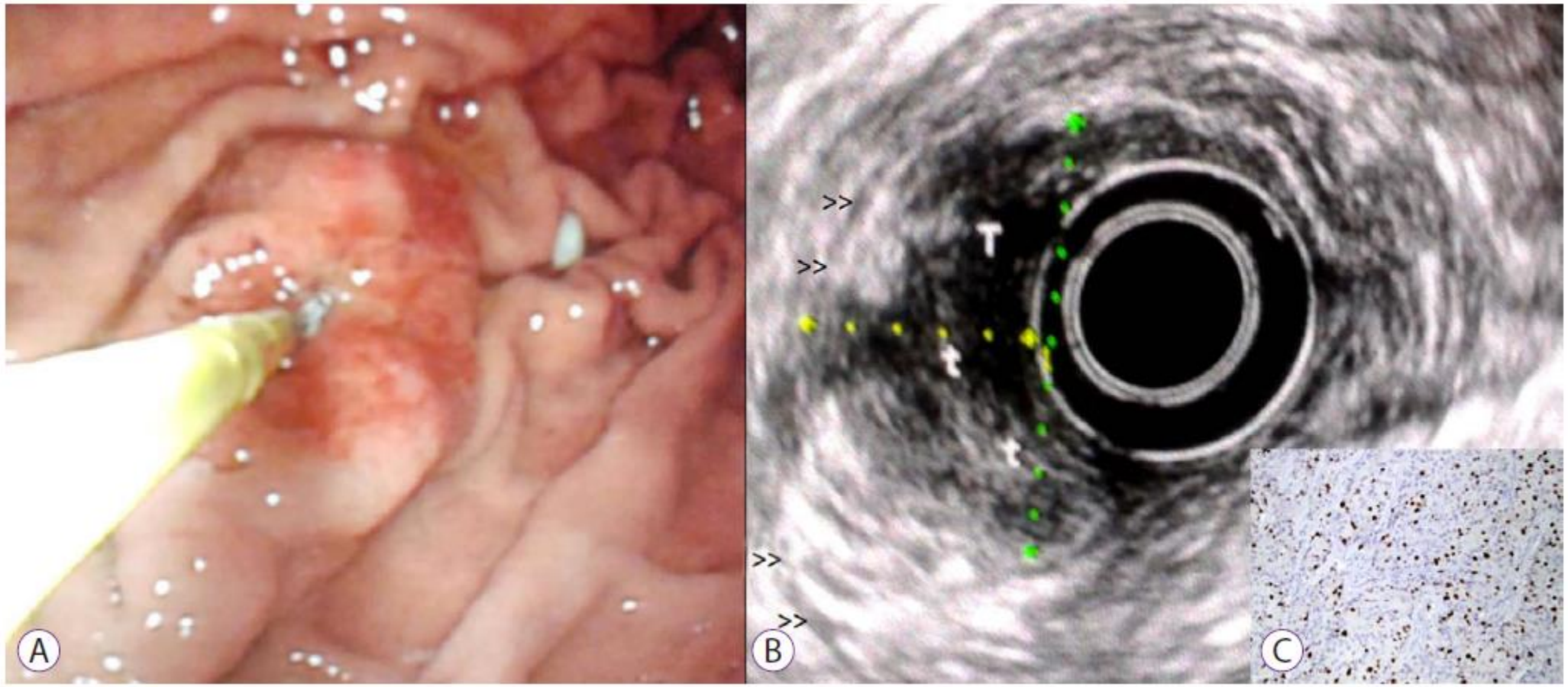
Type 2 gastric NET

- Rare (5-6% of gastric NETs)
- Zollinger-Ellison syndrome
  - Severe abdominal pain, multiple gastric & duodenal ulcers
  - Watery diarrhea due to excessive gastric acid production
  - Associated with autosomal dominant MEN-1 syndrome
- Hypertrophied gastric folds
- Large mucous acid pools
- Multiple ulcers

Type 3 gastric NET

- Normal gastrin level
- Usually occur singly and may be large, up to 2 to 3 cm
- Gastric antrum

Type 3 gastric NET



Pancreatic NETs

- Peak incidence between age 40 and 69 years
- 22% of pancreatic NETs have hormonal symptoms
  - 70% insulinomas, 15% glucagonomas, 10% gastrinomas and somatostatinomas, 5% VIPomas
- Hormone 검사는 증상 있을 때에만 시행 (routine 아님)
  - Insulinoma: hypoglycemia
  - Gastrinoma: recurrent peptic ulcer
  - Glucagonoma: DM, migratory necrolytic erythema
  - Somatostatinoma: DM, diarrhea/steatorrhea
  - VIPoma: watery diarrhea, hypokalemia, achlorhydria

Pancreatic NETs

- Evaluation
  - Gastrinoma: PPI 1주 중단한 후 fasting serum gastrin level 10배 이상 상승 및 gastric pH 2 미만일 경우 gastrinoma로 진단
  - Insulinoma: serum insulin > 3 mcIU/mL, pro-insulin ≥ 5 pmol/L, C-peptide ≥ 0.6 ng/mL, fasting blood glucose < 55 mg/dL

Treatment

1) Tumor size
2) Anatomic location of the primary tumor
3) Clinical status

Locoregional disease

- 수술이 가능하다면 수술적 절제가 주된 치료이다.

Locoregional disease

- Gastric neuroendocrine tumors
  - Type 1 (atrophic gastritis)
    - Indolent, metastases rate < 5%
    - Annual endoscopic surveillance and endoscopic resection of prominent tumors
    - Consider antrectomy if tumors increase in size or number
  - Type 2 (gastrinoma)
    - Resection
    - High dose PPI
  - Type 3 (sporadic)
    - Aggressive
    - Radical resection and regional lymphadenectomy
    - If LN metastases (-) in EUS → consider wedge resection
    - Endoscopic resection reserved for small (<1cm), superficial, low-grade tumors

Locoregional disease

- Duodenum
  - Endoscopic resection, if feasible
  - Local excision or pancreatoduodenectomy are other options
- Jejunum, ileum, colon
  - Surgical resection with regional lymphadenectomy
  - Multiple synchronous lesions may be present

Locoregional disease

- Appendix
  - Mostly found incidentally during appendectomy for appendicitis
  - Mostly well-differentiated, 2 cm or smaller, confined to the appendix
    - Simple appendectomy is sufficient in such cases
  - More aggressive treatment may be needed when
    - Lymphovascular invasion
    - Mesoappendiceal invasion
    - Atypical histologic features
  - Incomplete resection or > 2cm → re-exploration with right hemicolectomy

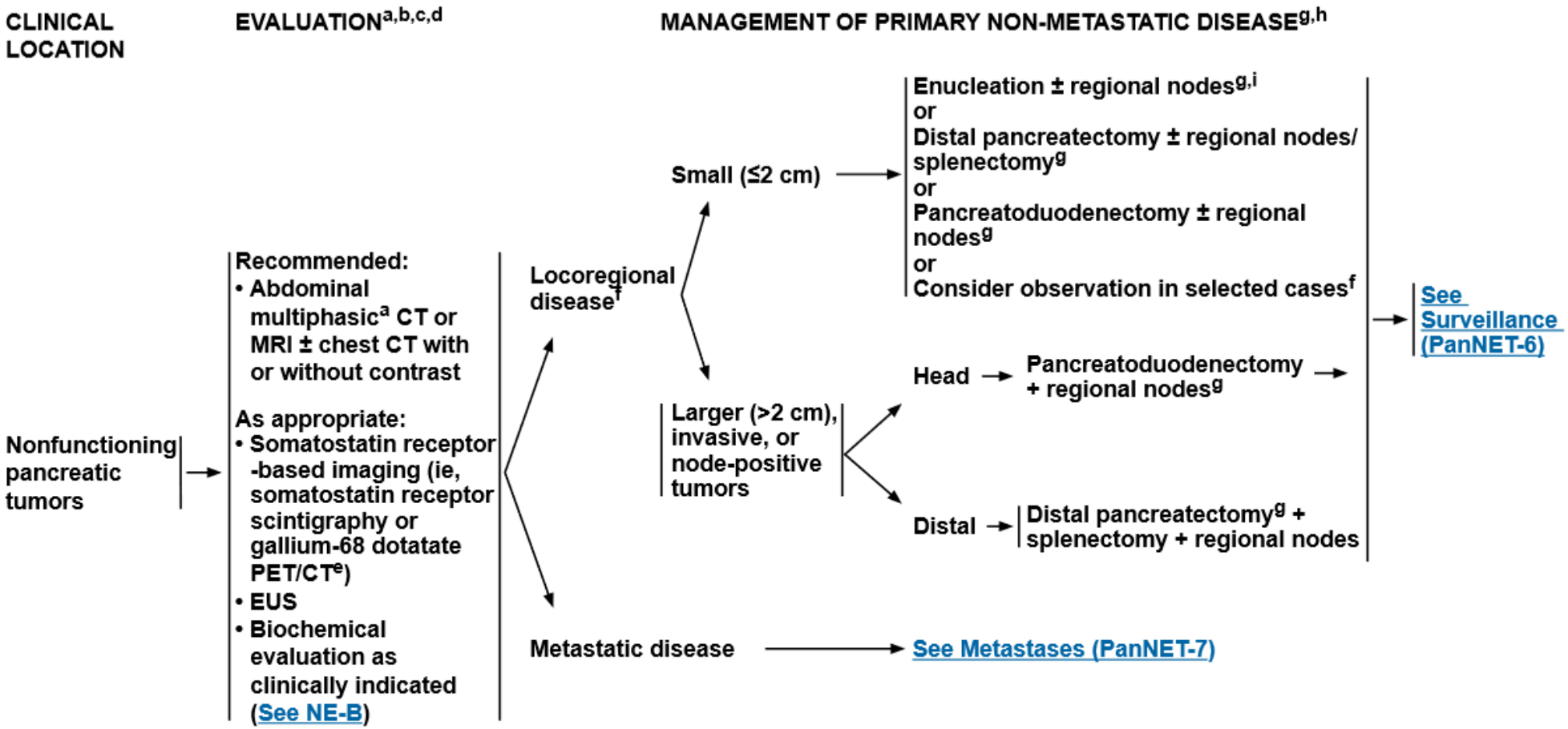
Locoregional disease

- Rectum
  - < 1 cm → endoscopic resection
  - ≤ 2 cm & T1 → endoscopic or transanal excision
  - > 2 cm or T2-T4 or LN metastases → low anterior resection or abdominoperineal resection

Locoregional disease

- Pancreatic NET
  - Resection when possible
  - Any symptoms of hormonal excess must be treated
    - Octreotide or lanreotide
      - Insulinoma에서는 사용에 주의할 것 (counterregulatory hormone suppression)
      - 심각한 hypoglycemia 발생할 수 있음

Locoregional disease



Follow-up schedule

- Jejunum/ileum/colon, duodenum, rectum, type 3 gastric neuroendocrine tumors
  - 3 to 12 months after resection, then every 6 to 12 months for up to 10 years
  - Rectum < 1 cm → no follow up
  - Appendix < 2 cm → no follow up or 1 year follow up
- Type 1 or 2 gastric NET
  - 6 to 12 months endoscopy f/u for 3 years and annually thereafter

Unresectable disease

- Evaluation
  - Baseline imaging with CT or MRI
  - Somatostatin receptor based imaging recommended
    - 특히 octreotide or lanreotide 고려하고 있을 때
  - Baseline chromogranin A or 24 hour urine 5-HIAA 측정도 고려
    - 특히 carcinoid syndrome 의심 시 24hr urine 5-HIAA 측정

Unresectable disease

- Somatostatin analogs
  - Control of symptoms and tumor growth
    - Long acting release octreotide 20 to 30mg IM every 4 weeks
    - Short acting octreotide (150-250mcg SC 3 tid) added for rapid relief
    - Lanreotide has similar mechanisms but SC injection

Somatostatin analog therapy

- Standard treatment for metastatic NETs
- Somatostatin binds to somatostatin receptors(types 1-5, most commonly type 2), overexpressed in the tumor tissue
- Somatostatin has

1) Inhibitory effects on exocrine & endocrine secretion
2) Gastrointestinal motility ↓, GB contraction ↓, GI blood flow ↓

Somatostatin analog therapy

- Recommended dosage
  - Long acting release (LAR): 20-30mg by I.M. every 4 weeks
  - Rescue dose of short acting octreotide to control breakthrough symptoms: 2-3 times/day S.C., up to 1mg/day
  - Lanreotides: 120mg S.C. every 28 days
- Side effects
  - Cholelithiasis and biliary sludge in up to 50% in long term use

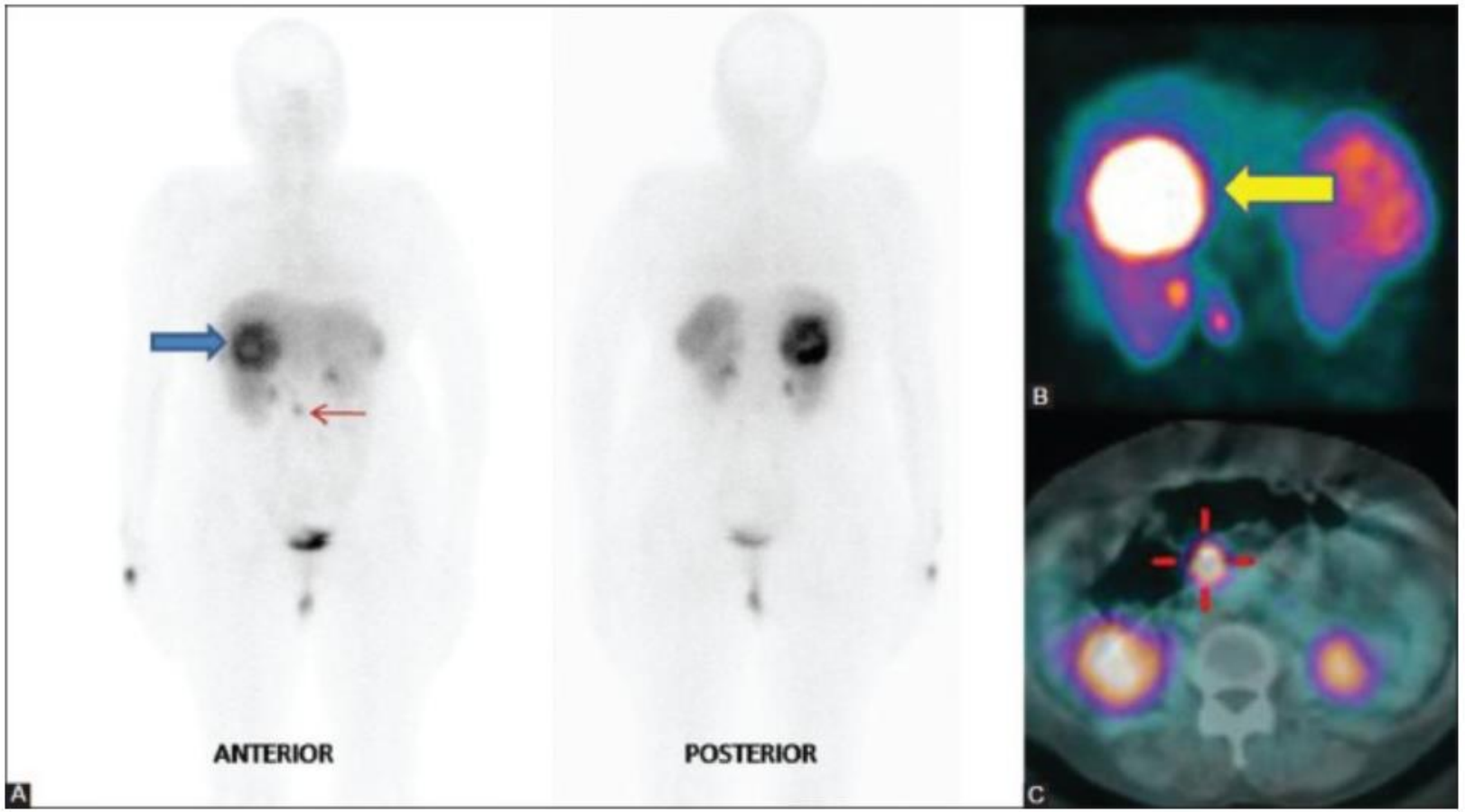
  → Consider prophylactic cholecystectomy (특히 수술 계획 있는 환자)
  - Abdominal cramps, diarrhea, nausea, hypoglycemia

Somatostatin receptor scintigraphy

- Radiolabeled somatostatin analog (111In)
  → bind to somatostatin receptor
  → imaged via positron emission tomography scanning
  → should be performed before analog therapy to confirm somatostatin receptor expression in vivo

- Receptor radiotherapy is not yet approved by the FDA

Somatostatin receptor scintigraphy



Indian J Radiol Imaging. 2012 Oct-Dec; 22(4): 267–275.

Unresectable disease

- Telotristat
  - When carcinoid syndrome is poorly controlled
  - Small molecule tryptophan hydroxylase inhibitor
  - Combination with somatostatin analogs
  - Decreases urinary 5-HIAA levels and frequency of bowel movements

Unresectable disease

- Resection of metastatic disease
  - Limited hepatic metastases → hepatectomy with curative intent
  - Non-curative debulking surgery in symptomatic patients

- 수술 예정인데 향후 octreotide 또는 lanreotide 장기 투여의 계획이 있을 경우 prophylactic cholecystectomy를 고려한다.

Unresectable disease

- Liver directed therapies
  - 가장 흔한 전이 장기이며 예후에 중요
  - Unresectable, hepatic-predominant, progressive disease인 경우 생명 연장 및 증상 완화 목적으로 시행
  - Intraarterial bland embolization, cheomoembolization, radioembolization, radiofrequency ablation, cryoablation
    - 치료 방법끼리 비교한 randomized trials 없음
  - Unresectable liver metastases and no unresectable extrahepatic disease → consider liver transplantation

Systemic cytotoxic chemotherapy

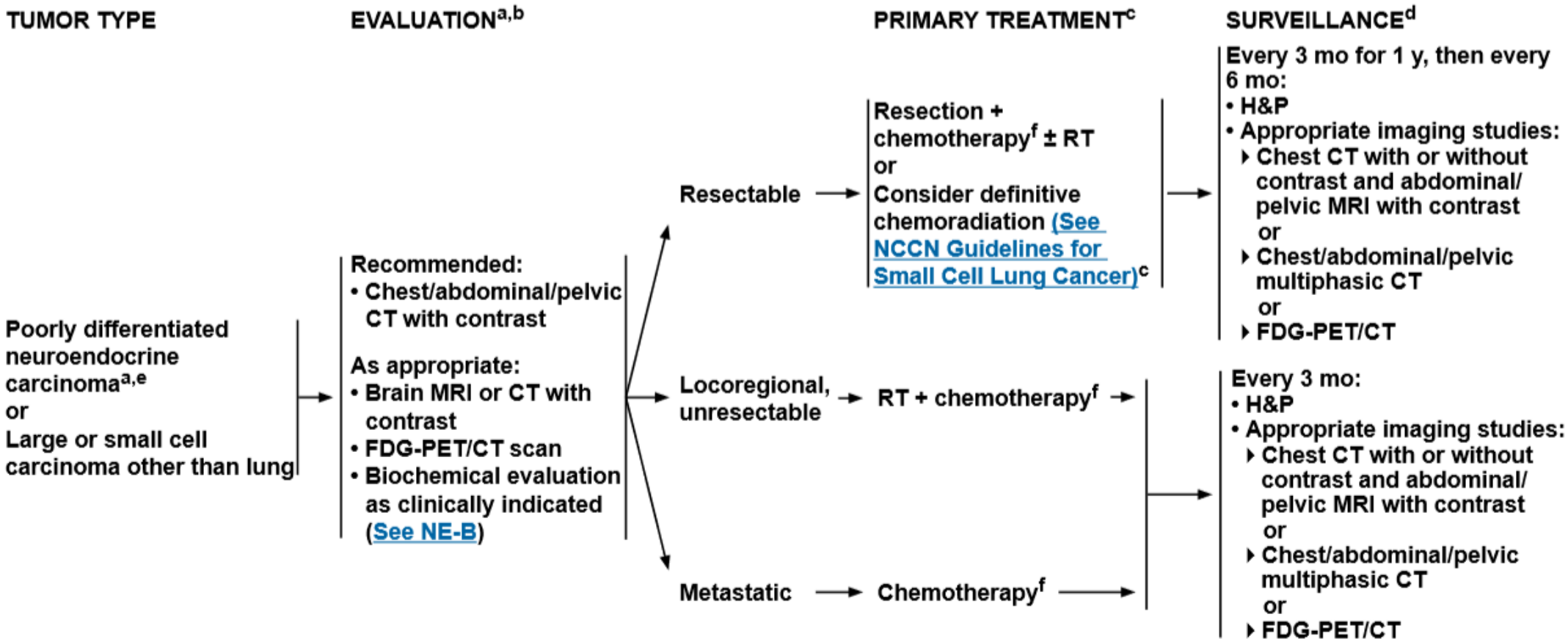
- Reserved for rapidly progressive disease (high grade NETs)
  → Treat like small cell lung cancer (platinum based doublet)
- Alkylating agents
  - Streptozocin for advanced pancreatic NETs (FDA approved in 1982)
    - Acceptable efficacy when used in combination with doxorubicin and fluorouracil (response rate, 39%; two-year PFS rate, 41%; two-year OS, 74%).

  - Temozolomide

    J Clin Oncol. 2004; 22:4762-71
    - A radiological response rate of 14%, a rate of stable disease of 53%, and a median time to progression of 7 months (range, 3–10 months) in 36 patients treated with single-agent temozolomide were observed.

      Clin Cancer Res. 2007; 13:2986-91.
- When other treatments have failed

Poorly differentiated NEC



Treatment summary

- Early stage & well-differentiated NETs
  → Surgery
- Locally advanced or metastatic disease
  → Somatostatin analog therapy
  → Debulking or palliative surgery
  → Liver directed therapies
- Poorly differentiated or high grade NETs
  → Cytotoxic systemic chemotherapy

Prognosis

- Primary tumor site is a major impact factor
  - Best median OS: rectum (24.6 years) and appendix (>30.0 years)
  - Worst median OS: pancreas (3.6 years) and lung (5.5 years)

- Histologic grade is an another major impact factors
  - Assigned based upon the mitotic rate or Ki-67 labeling index
  - G1 NET median OS → 16.2 years
  - G2 NET median OS → 8.3 years
  - G3/4 NET median OS → 10 months

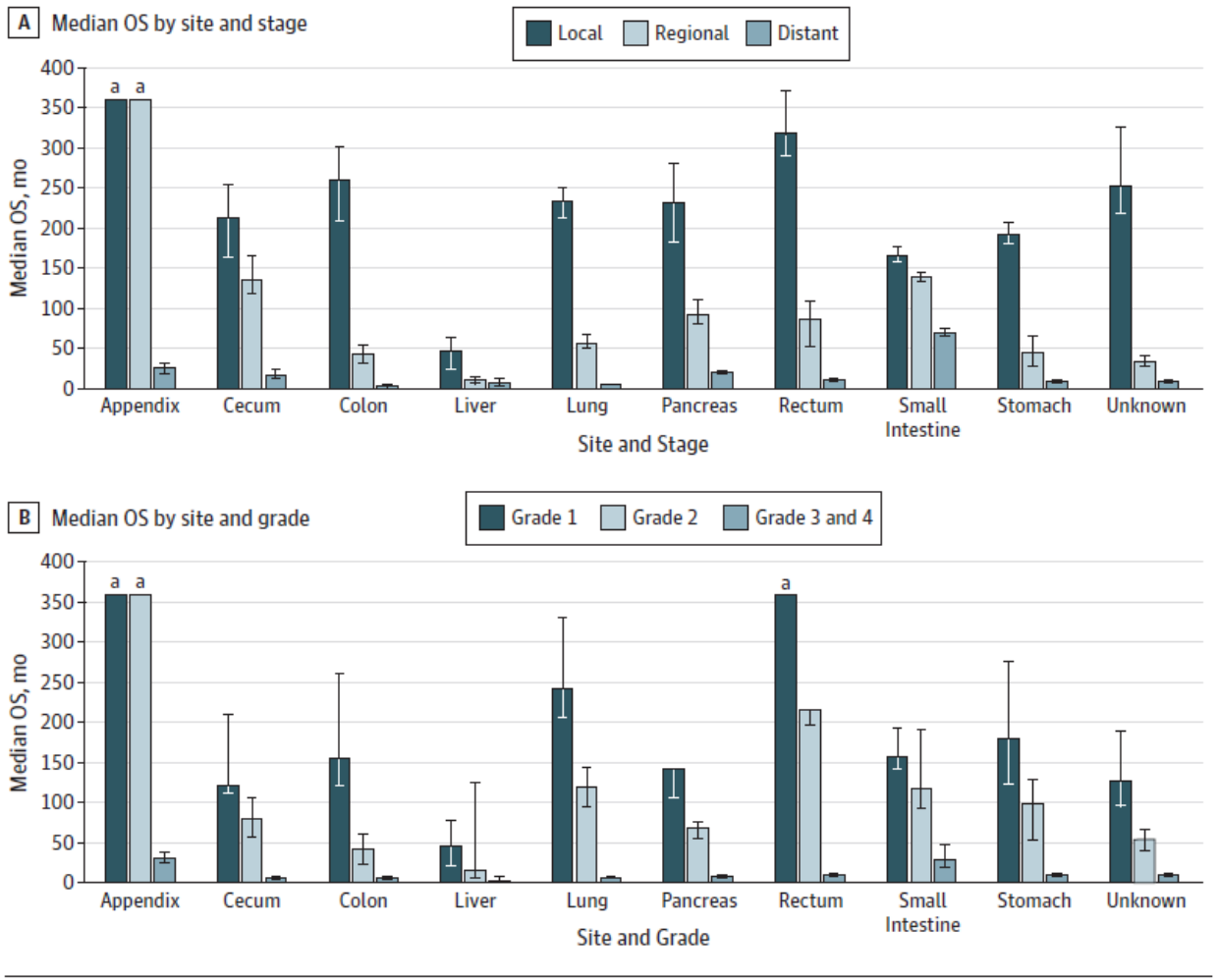
Prognosis

- The median OS time for all patients was 9.3 years (112months).

- Prognosis by stage (median OS)
  - Localized NETs → >30 years
  - Regional NETs → 10.2 years
  - Distant NETs → 12 months

Prognosis

Figure 3. Median Overall Survival (OS) of Neuroendocrine Tumors



A, Median OS of all patients included in study according to stage.
B, Median OS of all patients included in study according to grade. Error bars indicate 95% CI.

[a] Maximum follow-up time was 360 months.

JAMA Oncol. 2017;3(10):1335-1342

Prognosis

- SEER group multivariable analyses
  - Median 5-year OS rate varied significantly by stage, grade, age at diagnosis, primary site, and time period of diagnosis.

References

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- Am J Health-Syst Pharm. 2016; 73:1729-44.
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- 2017 NCCN guideline.

새해 복
많이 받개