Sharing the Experience of GEP-NEN based on KSGC Multicenter Study

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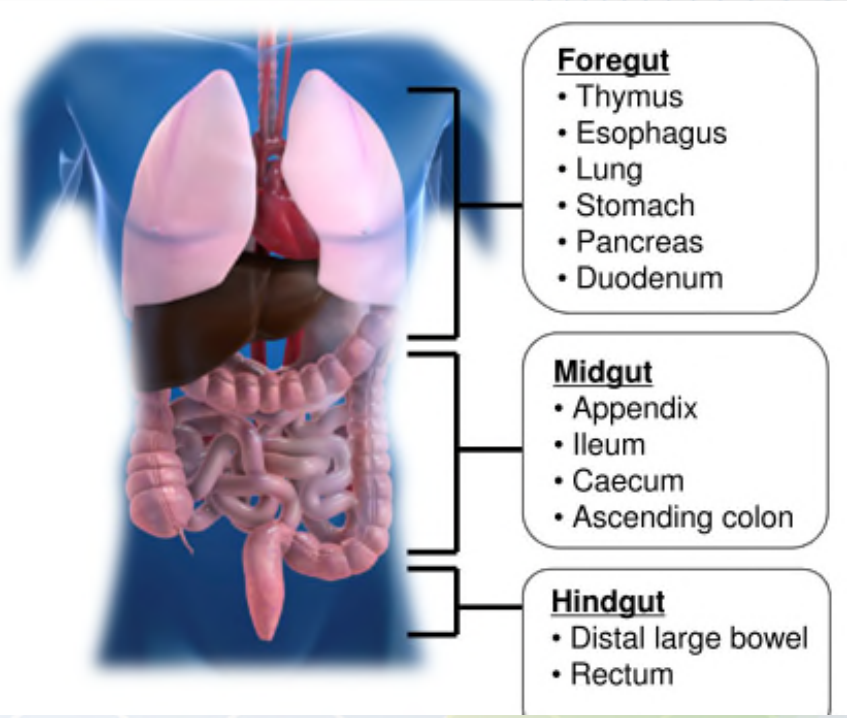
* The author has nothing to declare.

Contents

- Introduction
  - Korean retrospective GEP-NET registry
- Korean multicenter study
  - Epidemiology and clinical manifestation according to different sites
  - Therapeutic outcomes and introduction of novel therapeutic approach in Korea
- Current situation & future direction

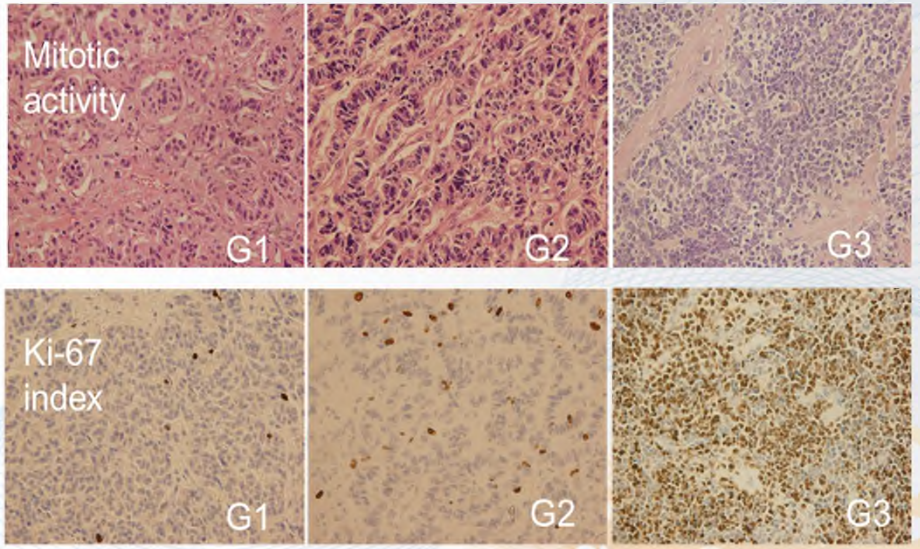
Neuroendocrine neoplasm

- Epithelial neoplasms with predominant neuroendocrine differentiation
- Relatively rare & not familiar disease
- Several terms with confusion
- Heterogenous group of cancers
- Diverse disease with different prognosis
- Classification
  - Site and embryonic origin
  - Functional status
  - Hereditary disease; MEN-1, MEN-2, VHLS



NEN classification

- Histologic grades : WHO 2010 → 2017
- Attempting to stratify patients into different prognostic groups
- Low grade (G1), intermediate grade (G2), and high grade (G3) NET vs. G3 NEC
- Based on cell morphology and proliferation rate using mitotic index and Ki-67 index



Grade (WHO 2017)	Ki-67 index	Mitoses/10 hpfs
Neuroendocrine tumor G1	<3 %	< 2/10 HPF
Neuroendocrine tumor G2	3-20 %	2-20/10 HPF
Neuroendocrine tumor G3	>20 %	>20/10 HPF
Neuroendocrine carcinoma G3 (small, large cell type)	>20 %	>20/10 HPF
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

History of GEP-NEN research

대한소화기암학회

➢The Korean Society of Gastrointestinal Cancer,

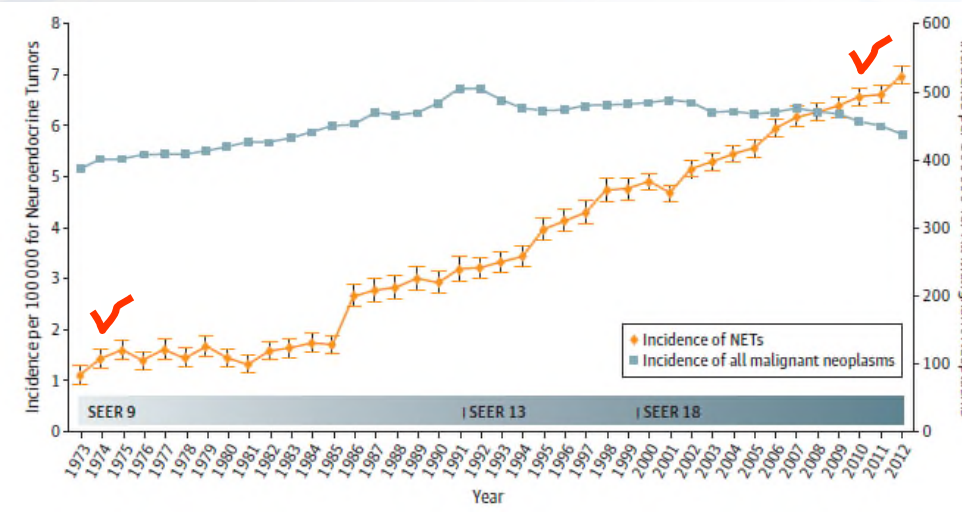
Council of the Neuroendocrine Tumor Research

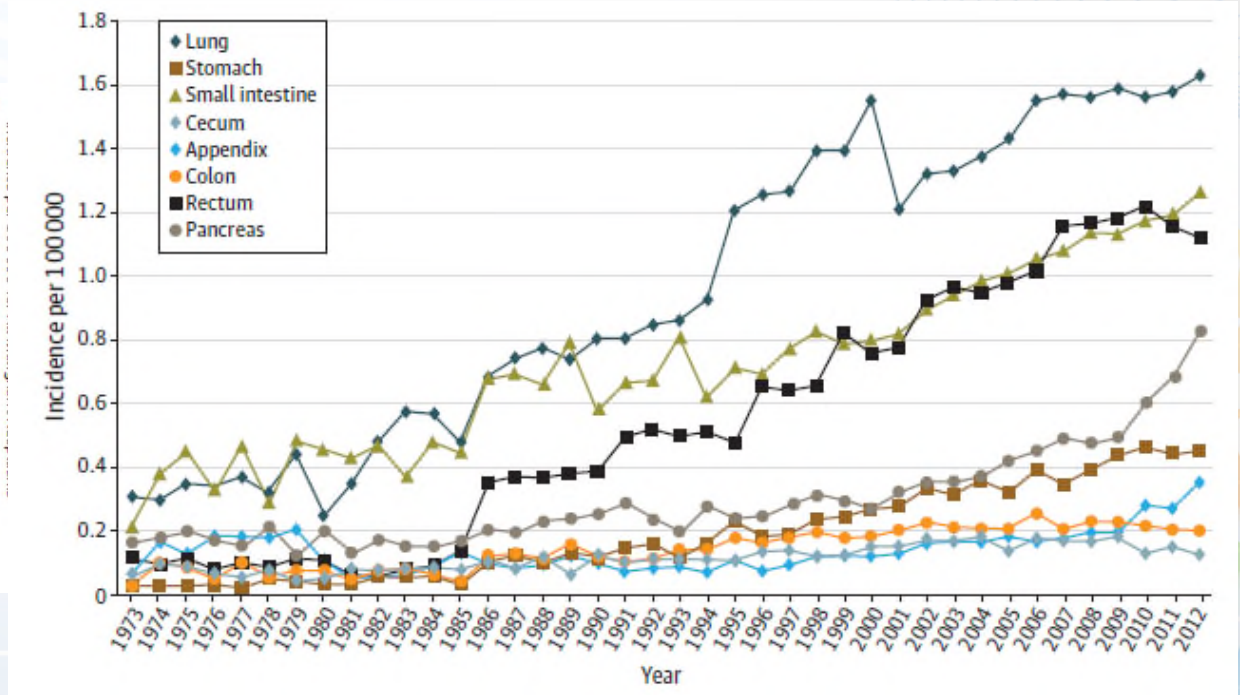
➢History of GEP-NET research in KSGC

- Publication of the Korean textbook of "Gastroenteropancreatic Neuroendocrine Tumor" (52 authors, 1st ed. 2012)
- Korean GEP-NET tumor registry (KGNTR, 2002-2012)
  - Esophageal NET (BMC Cancer. 2014 7;14:569)
  - pNET (Pancreas. 2016 45(7):941-6.)
  - Biliary NET (Scand J Gastroenterol. 2017 52(4):437-441)
  - Everlimus in pNETs (Cancer Chemother Pharmacol. 2017 80(4):799-805)
  - Gastric NET (Journal of Digestive Cancer Reports. 2017 5(2):86-90)

Incidence of GEP-NET (US SEER Data)

64,971 US GEP-NETs (1973-2012)



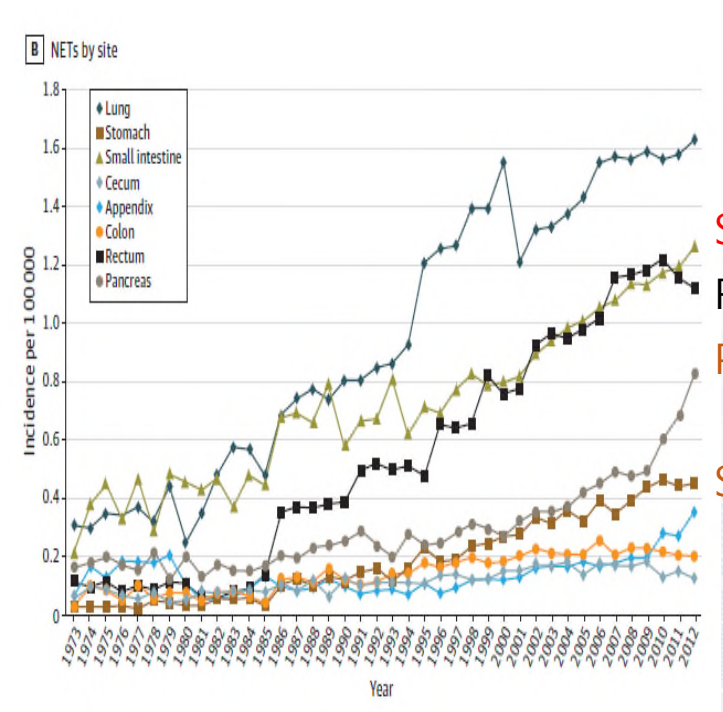


Dasari, Yao JC et al. JAMA oncol 2017

Distribution according to primary site (KGNTR)

대한소화기암학회

US SEER data GEP-NETs (1973-2012)



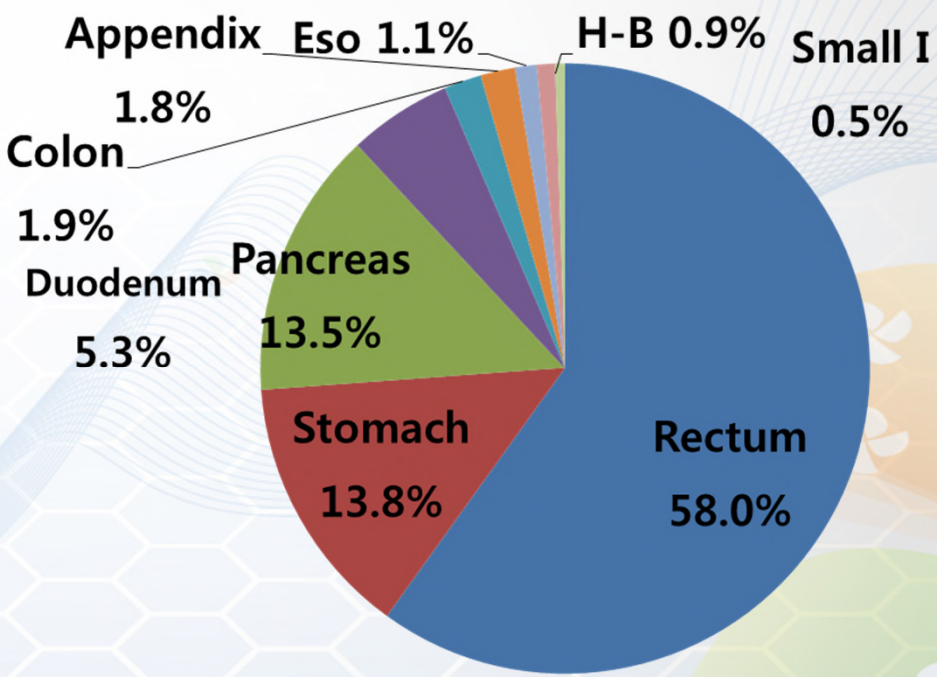
Small intestine

Rectum

Pancreas

Stomach

2,345 Korea GEP-NETs from KGNTR

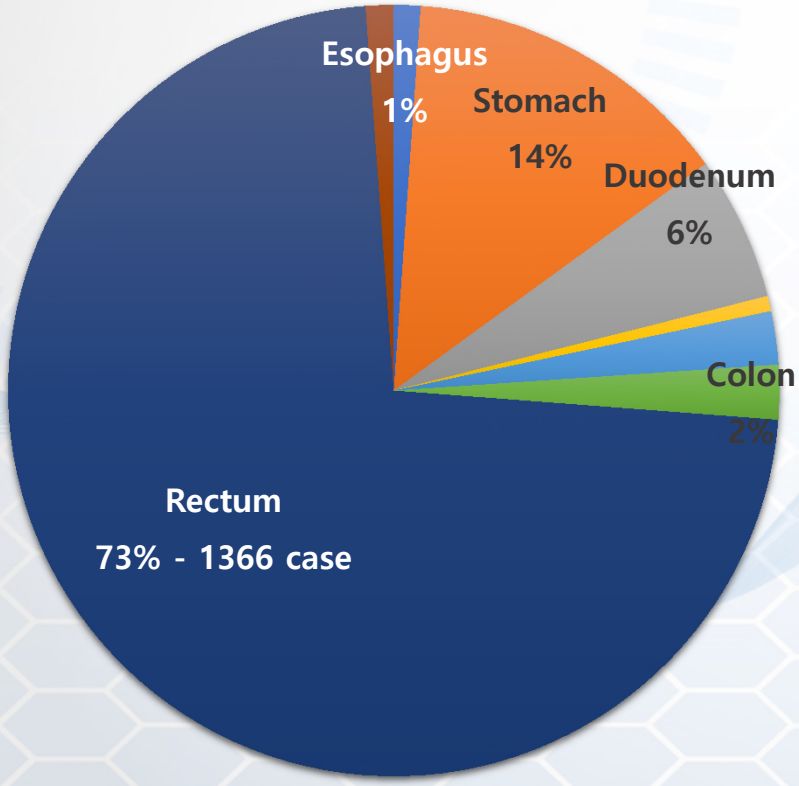


Lawrence B et al. Endocrinol Metab Clin North Am 2011.
Lee WJ et al. IKSGC 2013 (abstract)

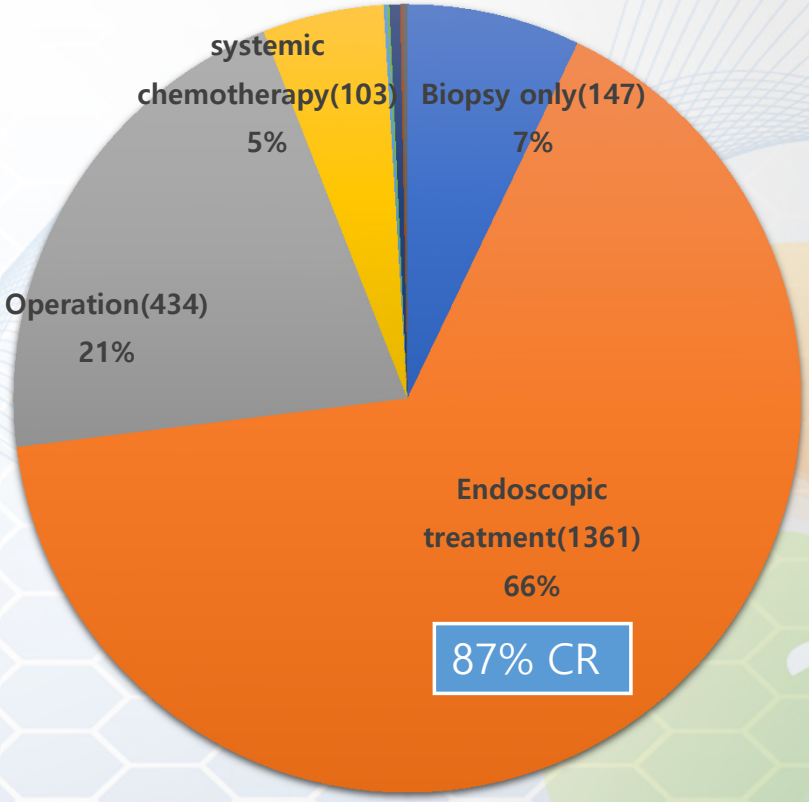
Gastrointestinal NET

대한소화기암학회

- 25 hospital, 2037 patients



Treatment modality & outcomes



Esophageal NET

대한소화기암학회

- 26 cases of esophageal NET
- Characteristics
  - Site: lower third of esophagus (76.9%), size : 2.34 cm
  - P/D 38.5% , W/D 11.5%
  - Regional LN metastasis: 57.7%
  - Endoscopic treatment: only 3 small cases (< 1.0 cm)
- Advanced esophageal NET has unfavorable prognosis compared to other site GEP-NETs

RESEARCH ARTICLE Open Access

The clinical features and treatment modality of esophageal neuroendocrine tumors: a multicenter study in Korea

Chang Geun Lee[1], Yun Jeong Lim[1*], Seun Ja Park[2], Byung Ik Jang[3], Seok Reyol Choi[4], Jae Kwang Kim[5], Yong-Tae Kim[6], Joo Young Cho[7], Chang Hun Yang[1], Hoon Jai Chun[8], Si Young Song[9] and Neuroendocrine tumor study group

Abstract

Background: Neuroendocrine tumors (NETs) of the esophagus are extremely rare, and few cases have been reported worldwide. Thus, a comprehensive nationwide study is needed to understand the characteristics of and treatment strategy for esophageal NETs.

Methods: We collected data on esophageal NET patients from 25 hospitals in Korea from 2002–2012. The incidence, location, clinical symptoms, histopathology, treatment response, and the biochemical, radiologic and endoscopic characteristics of esophageal NETs were surveyed.

Results: Among 2,037 NETs arising in different gastrointestinal sites, esophageal NETs were found in 26 cases (1.3%). The mean patient age was 60.12 ± 9.30 years with a 4:1 male predominance. In endoscopic findings, 76.9% (20/26) of NETs were located in the lower third of the esophagus and the mean size was 2.34 ± 1.63 cm. At diagnosis, more than half the patients (15/26, 57.7%) had regional lymph node metastasis or widespread metastasis. Endoscopic resection was conducted in three cases, and in all three of them, lymph node metastasis was not found and tumor size was below 1.0 cm. All tumors were completely removable through endoscopic procedures and there was no recurrence during the follow-up period. Eighteen other patients received an operation, chemotherapy or both. Among them, nine patients (50.0%) expired because of the progression of their cancer or post-operative complications. In Kaplan-Meier survival analysis, only tumor size (more than 2.0 cm) showed prognostic significance ($P = 0.045$).

Conclusions: Despite the general assumption that gastrointestinal NETs are benign and slow-growing tumors, the prognosis of advanced esophageal NETs is not favorable.

Keywords: Esophagus, Neuroendocrine tumor, Treatment, Prognosis

Lee CG, Lim YJ et al. BMC cancer 2014

Gastric NET

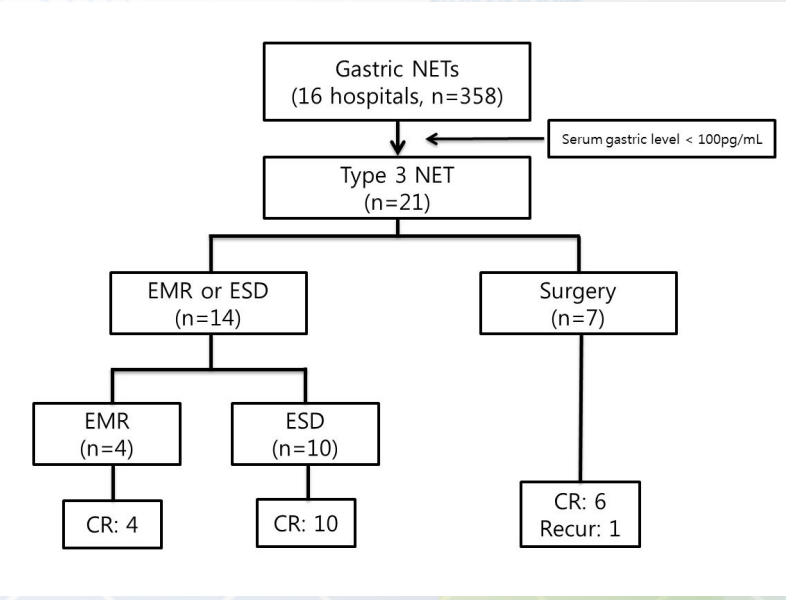
대한소화기암학회

- Type 3 gastric NET (n=21)
  - TG vs. endoscopic treatment
  - Site : body (85.7%), size (9.5mm)
  - WHO 2010 G1 (61.9%) G2 (33.4%), G3 (1%)
- Endoscopic treatment
  - Small sized type 3 gastric NET (n=14)
  - no recurrence (median fu 27 months)
- Endoscopic treatment can be an alternative safe modality in selected cases of type 3 gastric NET.

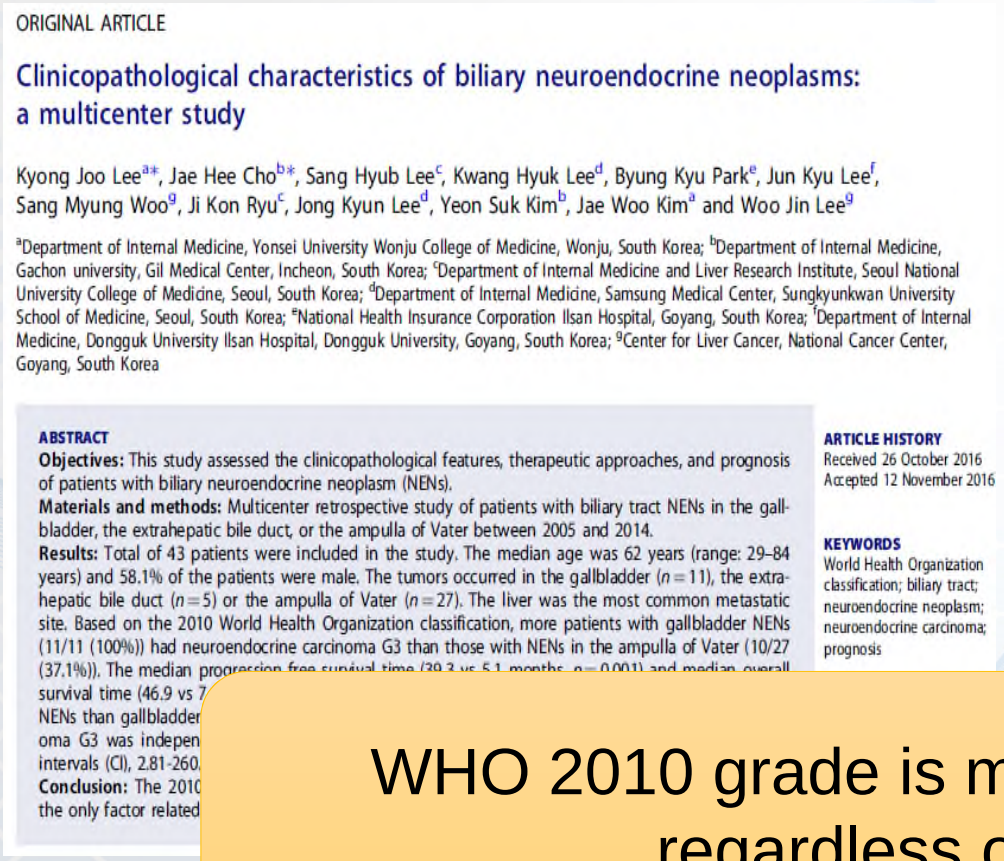
ORIGINAL ARTICLE
Journal of Digestive Cancer Reports 5(2):86-90, 2017
ISSN 2288-1581
http://www.gicancer.or.kr

Type 3 Gastric Neuroendocrine Neoplasm Clinical Features: A Multicenter Study in Korea

Kyong Joo Lee[1], Hee Man Kim[1], Sang Kil Lee[2], Ho Sun Choi[3], Jie-Hyun Kim[4], Seun Ja Park[5], Sung Chul Park[6], Byung Ik Jang[7], Jin Tae Jung[8], Tae Joo Jeon[9], Jong Hun Lee[10], Jae Kyu Sung[11], Semi Park[12], Yoon Jae Kim[13], Jae Hee Cho[13]



Biliary NET



ORIGINAL ARTICLE

Clinicopathological characteristics of biliary neuroendocrine neoplasms: a multicenter study

Kyong Joo Lee[a*], Jae Hee Cho[b*], Sang Hyub Lee[c], Kwang Hyuk Lee[d], Byung Kyu Park[e], Jun Kyu Lee[f], Sang Myung Woo[g], Ji Kon Ryu[c], Jong Kyun Lee[d], Yeon Suk Kim[b], Jae Woo Kim[a] and Woo Jin Lee[g]

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ABSTRACT

Objectives: This study assessed the clinicopathological features, therapeutic approaches, and prognosis of patients with biliary neuroendocrine neoplasm (NENs).

Materials and methods: Multicenter retrospective study of patients with biliary tract NENs in the gallbladder, the extrahepatic bile duct, or the ampulla of Vater between 2005 and 2014.

Results: Total of 43 patients were included in the study. The median age was 62 years (range: 29–84 years) and 58.1% of the patients were male. The tumors occurred in the gallbladder ($n = 11$), the extrahepatic bile duct ($n = 5$) or the ampulla of Vater ($n = 27$). The liver was the most common metastatic site. Based on the 2010 World Health Organization classification, more patients with gallbladder NENs (11/11 (100%)) had neuroendocrine carcinoma G3 than those with NENs in the ampulla of Vater (10/27 (37.1%)). The median progression-free survival time (39.3 vs 5.1 months, $p = 0.001$) and median overall survival time (46.9 vs 7
NENs than gallbladder
oma G3 was indepen
intervals (CI), 2.81-260.
Conclusion: The 2010
the only factor related

ARTICLE HISTORY
Received 26 October 2016
Accepted 12 November 2016

KEYWORDS
World Health Organization classification; biliary tract; neuroendocrine neoplasm; neuroendocrine carcinoma; prognosis

- Biliary NET
  - 43 cases from 7 institutes
  - GB (n=11), EHBD (n=5), AoV (n=27)
- Poor prognostic factor after univariate analysis
  - GB > AoV + EHBD
  - Metastasis
  - WHO grade 3
  - No chemotherapy
- Biliary WHO grade 3 was the only significant

WHO 2010 grade is most important prognostic factor regardless of site and metastasis

Lee KJ, Cho JH, et al. Scand J gastro 2017

Pancreas NET

대한소화기암학회

- US SEER data
  - 11.5% of GEP-NET (29,664 cases, 1973-2007)
  - Lowest 5 year survival (37.6%) (Rectal NET 88.5%)
- Taiwan multicenter study
  - 6% of GEP-NET (2,187 cases, 1996-2008)
- Korean multicenter study
  - 13.5% of GEP-NET (2,354 cases, 2002-2012)

	n= 299
Follow-up duration, median months (range)	Not available
Progression free survival (PFS), median months (95% C.I.)	91.0 (78.8 – 103.2)

n= 317	
Median age, year (IQR)	56 (47 – 65)
Sex, n (%)	
M /F	162 / 155
Family history of NET	4 (1.3 %)
Function	
Non-functioning tumor	174 (78.7 %)
Functioning tumor	47 (21.3 %)
Insulinoma	33 (14.9 %)
Gastrinoma	2 (0.9%)
Somotostatinoma	4 (1.8%)
Glucagonoma	3 (1.4%)
Others	5 (2.3%)

Lawrence B, et al. Endocrinol Metab Clin North Am 2011
Tsai HJ et al. PLoS one 2013

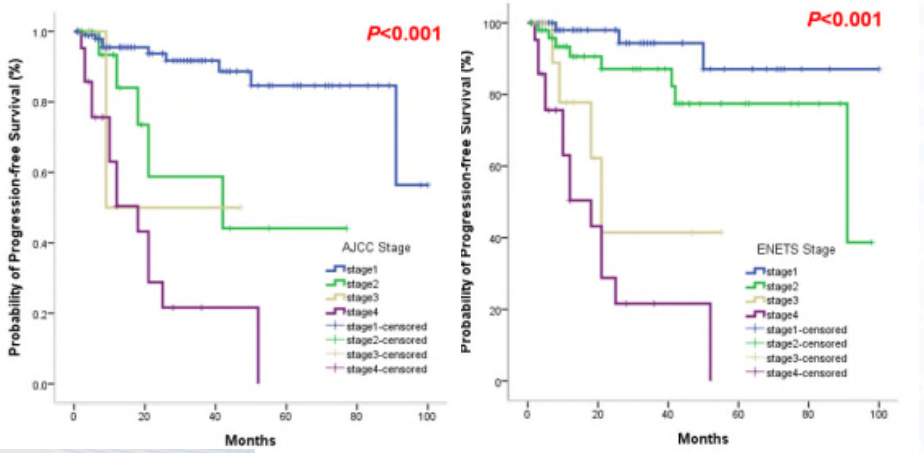
AJCC *vs.* ENETS *vs.* WHO 2010
(153 cases from 15 institutues)

ORIGINAL ARTICLE

Prognostic Validity of the American Joint Committee on Cancer and the European Neuroendocrine Tumors Staging Classifications for Pancreatic Neuroendocrine Tumors

A Retrospective Nationwide Multicenter Study in South Korea

Jae Hee Cho, MD, PhD, Ji Kon Ryu, MD, PhD,† Si Young Song, MD, PhD,‡ Jin-Hyeok Hwang, MD, PhD,§ Dong Ki Lee, MD, PhD,|| Sang Myung Woo, MD, PhD,¶ Young-Eun Joo, MD, PhD,# Seok Jeong, MD, PhD,** Seung-Ok Lee, MD, PhD,†† Byung Kyu Park, MD, PhD,‡‡ Young Koog Cheon, MD, PhD,§§ Jimin Han, MD, PhD,|||| Tae Nyeun Kim, MD, PhD,¶¶ Jun Kyu Lee, MD, PhD,## Sung-Hoon Moon, MD, PhD,*** Hyunjin Kim, MD, PhD,††† Eun Taek Park, MD, PhD,‡‡‡ Jae Chul Hwang, MD, PhD,§§§ Tae Hyeon Kim, MD, PhD,|||||| Tae Joo Jeon, MD, PhD,¶¶¶ Chang-Min Cho, MD, PhD,### Ho Soon Choi, MD, PhD,**** and Woo Jin Lee, MD, PhD¶*



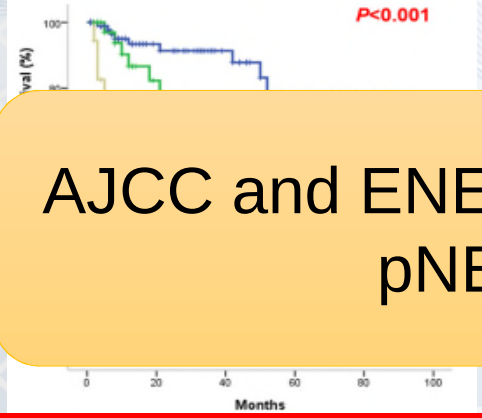


TABLE 3. Univariate and Multivariate Analysis of Prognostic Factors for pNETs

		Univariate Analysis			AJCC Multivariate Analysis			ENETS Multivariate Analysis		
	Mean Survival, mo	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
AJCC stage				<0.001			<0.001			
I	87									
II	47	4.64	1.51–14.23	0.007	2.87	0.83–9.89	0.096			
III	28	6.18	0.77–49.90	0.087	4.62	0.56–38.41	0.157			
IV	18	17.01	7.13–40.56	<0.001	10.23	3.66–25.56	<0.001			
ENETS stage				<0.001						<0.001
I	92									
II	79	2.86	0.76–10.86	0.122				2.37	0.62–9.01	0.205
III	32	10.35	2.30–46.64	0.002				5.30	1.07–26.38	0.042
IV	18	27.38	7.857–95.51	<0.001				15.37	3.88–60.91	<0.001
WHO				<0.001			0.074			0.062
Grade I	83									
Grade II	47	2.94	1.19–7.25	0.019	1.72	0.63–4.66	0.290	1.66	0.63–4.41	0.307
Grade III	21	12.55	5.12–30.79	<0.001	3.55	1.17–10.79	0.025	3.61	1.21–10.79	0.021
Age		1.02	0.99–1.05	0.315						
Sex										
Male	64									
Female	74	0.73	0.36–1.48	0.384						0.085

AJCC and ENETS TNM stages better reflect the prognosis of pNETs compared to WHO 2010 grade

Cho JH, Lee WJ et al. Pancreas. 2016

Contents

- Introduction
  - Korean retrospective GEP-NEN registry
- Korean multicenter study
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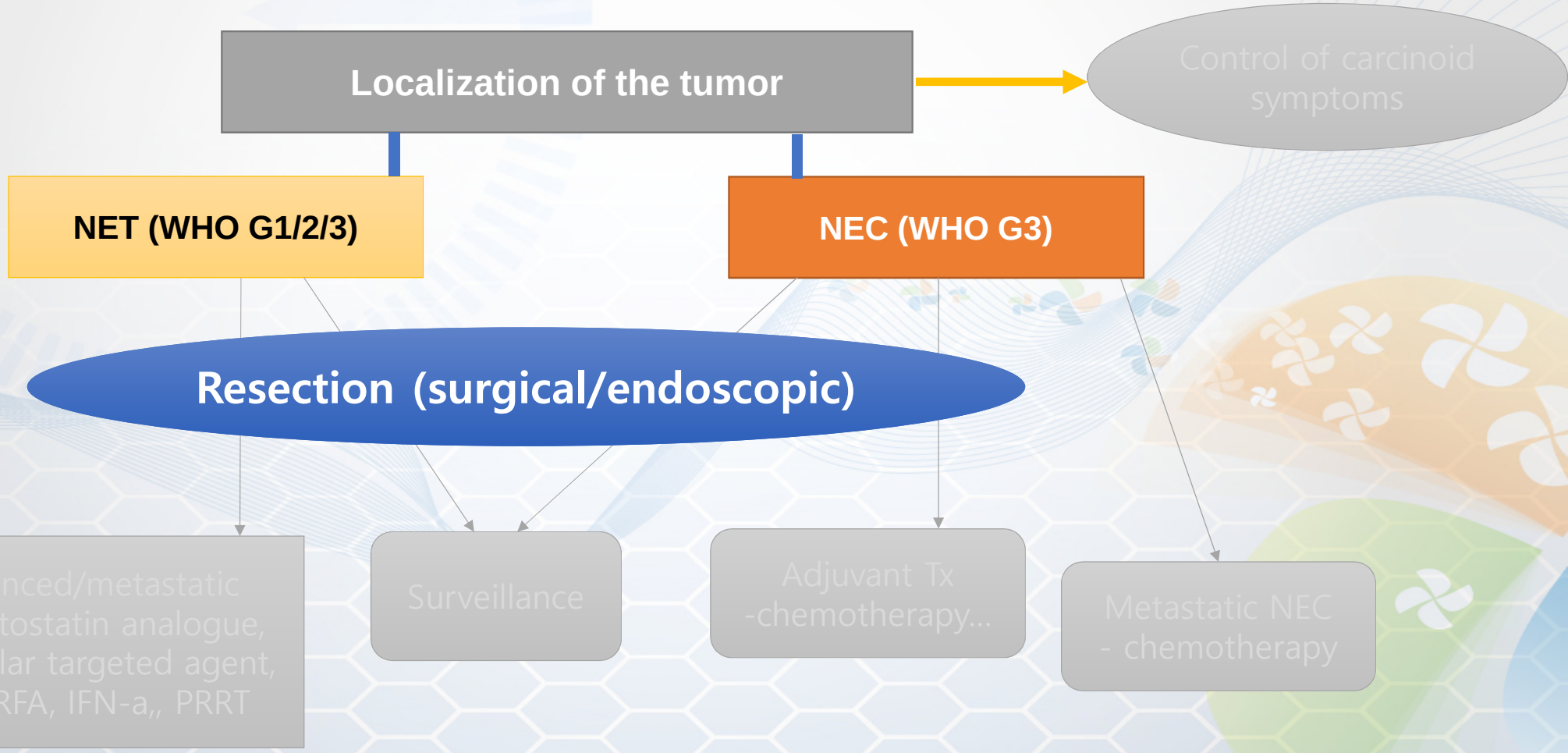
  - Therapeutic outcomes and introduction of novel therapeutic approach in Korea
- Current situation & future direction

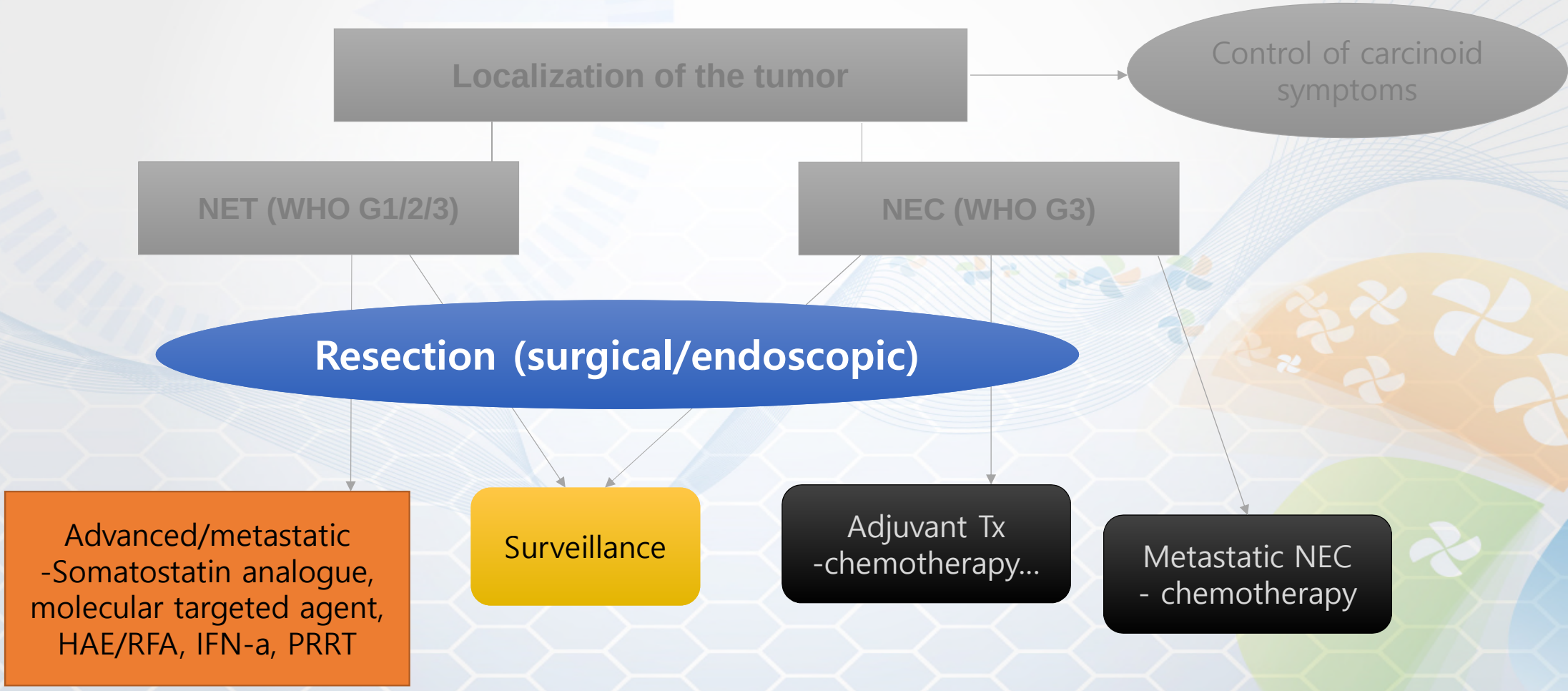
Overview of treatment algorithm



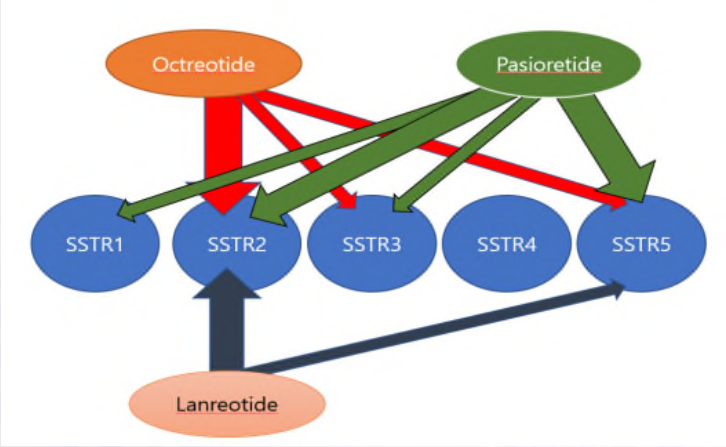
Management of GEP-NEN

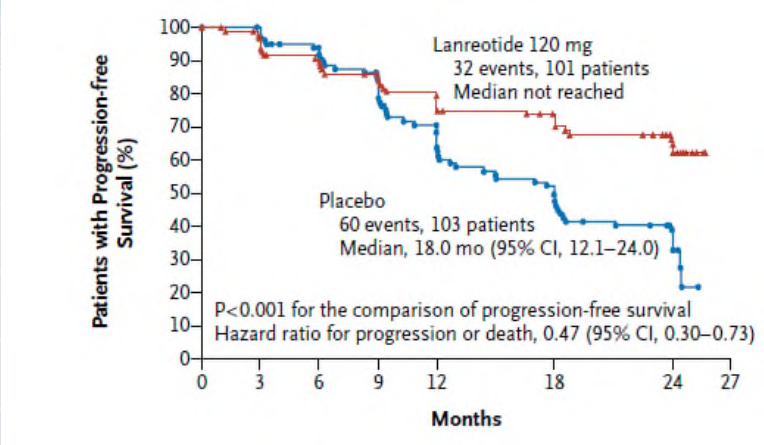
Site	Criteria	Management		
Appendix	≤ 2 cm and confined to the appendix >2 cm, Incomplete resection (nodes, margin)	Simple appendectomy Re-exploration, Rt hemicolectomy		Simple appendectomy Re-exploration, Right hemicolectomy
Small bowel	Irrespective of size	En-bloc bowel resection with regional lympadenectomy		
Duodenum	Locoreginal disease (noninvasive or invasive)	Endoscopic resection Local excision (Transduodenal) Pancreaticoduodenectomy		
Colon	Irrespective of size	Partial colectomy and regional lymphadenectomy		
Rectum	≤ 1cm incidental tumors All other rectal tumors	Completely resected Endorectal MRI or EUS (T1 vs T2-4)	No additional f/u ≤ 2cm >2cm	No additional f/u T1: Transanal or endoscopic resection T2: LAR, APR
Stomach	Type 1 (atrophic gastritis, Gastrin↑) Type 2 (Gastrin↑), Zollinger Ellison Type 3 (Gastrin NL)	Endoscopic resection, antrectomy Endoscopic or surgical resection Radical gastric resection with lymphadenectomy Consider endoscopic or surgical wedge resction (EUS no LN)		
Pancreas	Nonfunctional Functional	Surgical resection, symptomatic treatment		

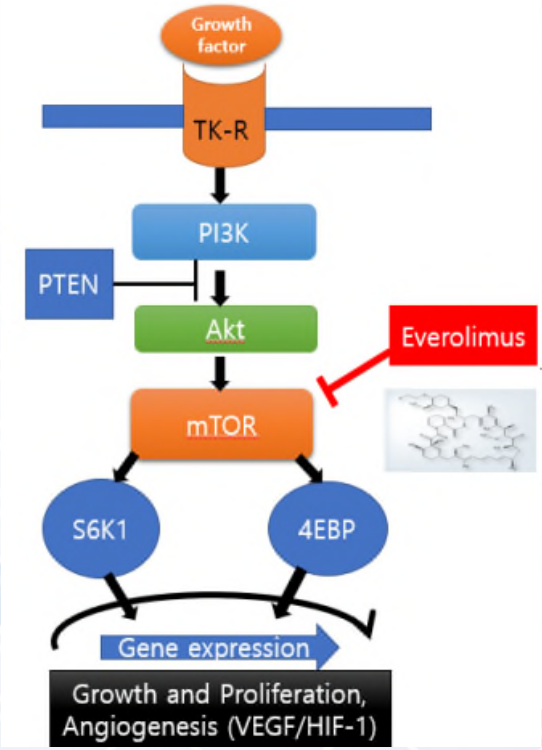
Overview of treatment algorithm

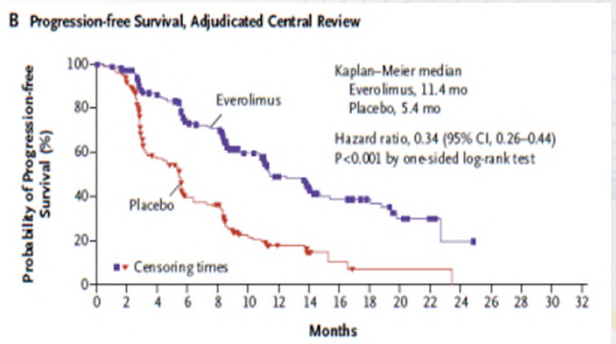


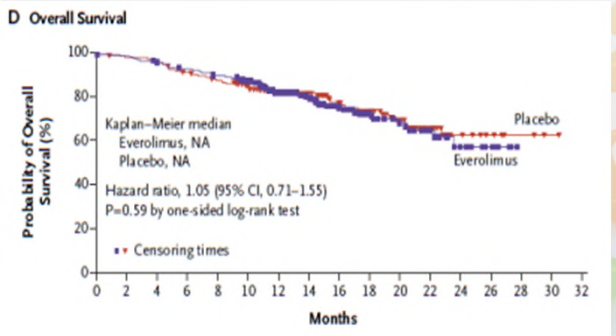
Somatostatin analogue / molecular targeted agent











Korean experience of everolimus for pNET

대한소화기암학회

Cancer Chemother Pharmacol (2017) 80:799–805
DOI 10.1007/s00280-017-3421-7

CrossMark

ORIGINAL ARTICLE

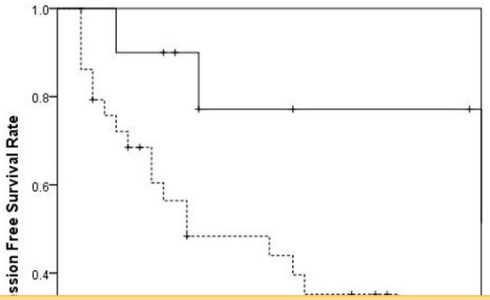
Clinical outcomes of everolimus in patients with advanced, nonfunctioning pancreatic neuroendocrine tumors: a multicenter study in Korea

Kyong Joo Lee[1] · Jae Hee Cho[2] · Sang Hyub Lee[3] · Si Young Song[4] · Kwang Hyuk Lee[5] · Seok Jeong[6] · Ji Kon Ryu[3] · Sang Myung Woo[7] · Seungmin Bang[4] · Jong Kyun Lee[5] · Tae Hoon Lee[8] · Woo Hyun Paik[3] · Yong Tae Kim[3] · Woo Jin Lee[7]

- Efficacy of everolimus for pNET
- 40 patients of metastatic or recurrent pNETs
- Median PFS was 20 months (2-38 mo)

Table 4. Treatment-related adverse event after everolimus

Toxicity	Grade	
	All grades	Grade 3 or 4
Stomatitis	19 (47.5%)	2 (5%)
Skin rash	13 (32.5%)	1 (2.5%)
Anemia	5 (12.5%)	1 (2.5%)
Diarrhea	4 (10%)	1 (2.5%)
Thrombocytopenia	3 (7.5%)	0
Pneumonitis	1 (2.5%)	0
Cough	1 (2.5%)	0
Hyperglycemia	1 (2.5%)	0



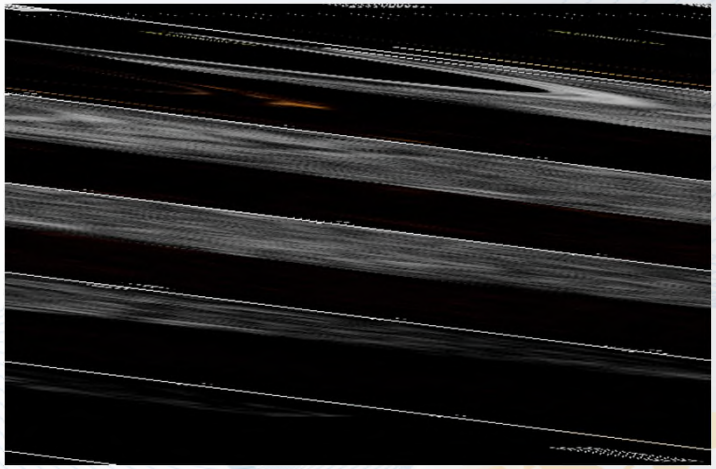
WHO grade act as the most important factor for everolimus response
Everolimus has similar therapeutic effects in Korean patients

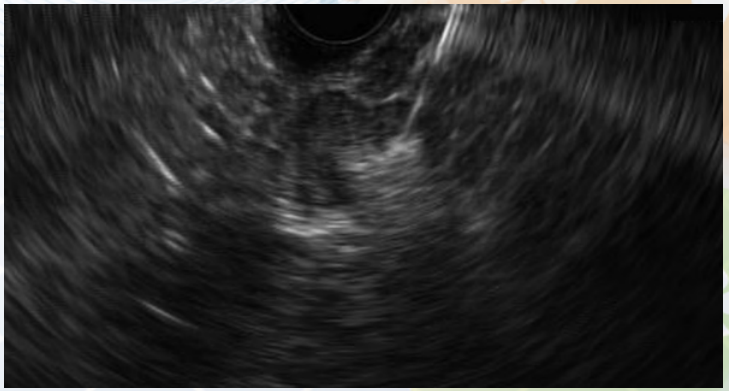
Lee KJ, Cho JH et al. Cancer Chemother Pharmacol. 2017

Endoscopic ablation Tx for pNET

EUS-ethanol ablation for solid tumor (n=20)

- **SPT (n=9)**
- **PNET (n=11)**
  - **Functioning (n=1)**
  - **Non-functioning (n=10)**

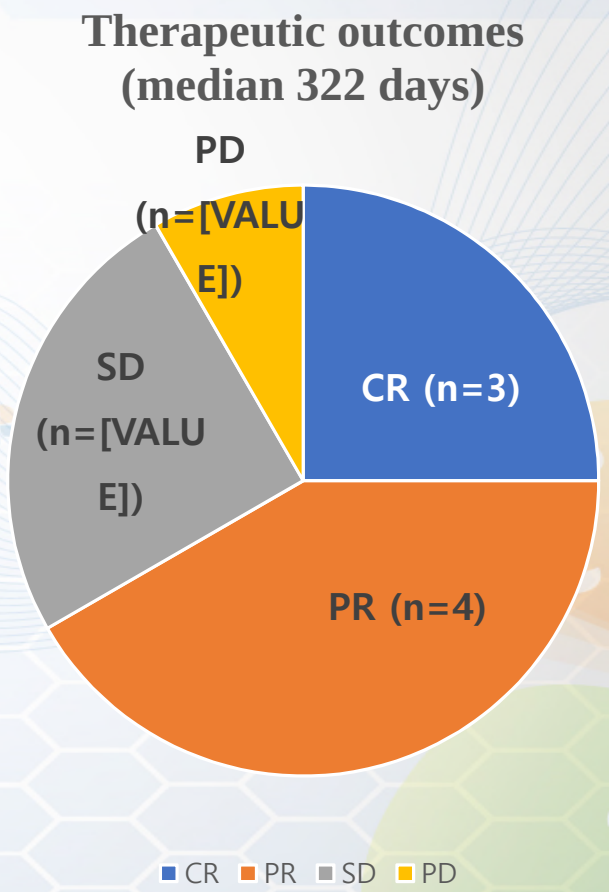




Paik WH, Kim YT et al. (abstract)

Therapeutic outcomes

EUS guided ethanol ablation fo pNET		N = 11
Sex	Male Female	5 6
Site	Head Body/tail	6 5
Size (median, mm)	Initial Post-ablation size (median 192 days)	12 (8-21) 10 (0-14)
EtOH dose	(mean±SD, ml)	1.05 ± 0.86
Adverse events	Acute pancreatitis (necrotizing panreatitis) Abdominal pain	2 (1) 5
FU duration (median, day)		322 (126-552)
Surgical resection after ablation		0



Paik WH, Kim YT et al. (abstract)

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- Korean retrospective GEP-NEN registry

➢Korean multicenter study
- Epidemiology and clinical manifestation according to different sites
- Therapeutic outcomes and novel therapeutic approach in Korea

- Conclusion & future direction

International GEP-NET network

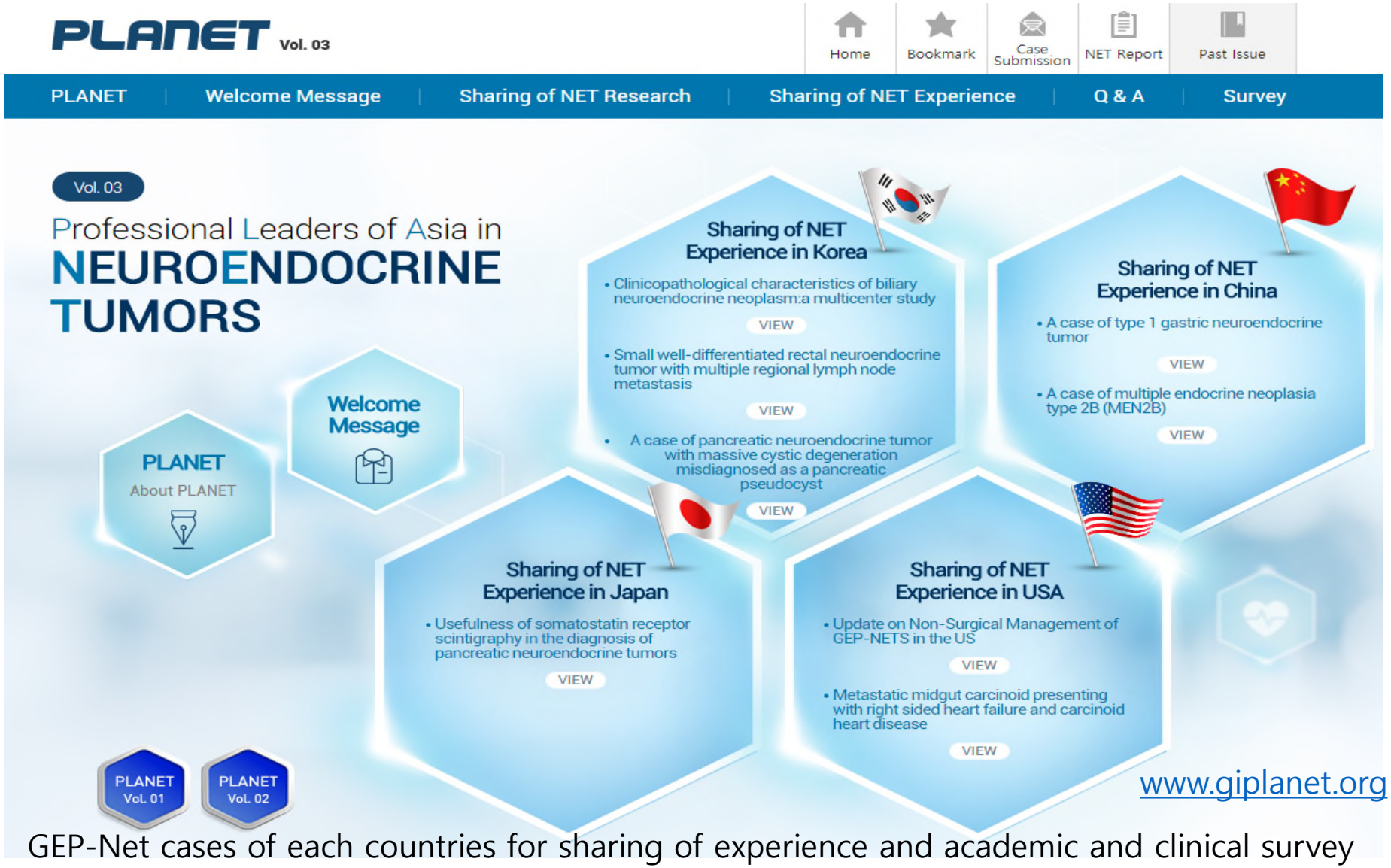
대한소화기암학회

➢NEGO symposium

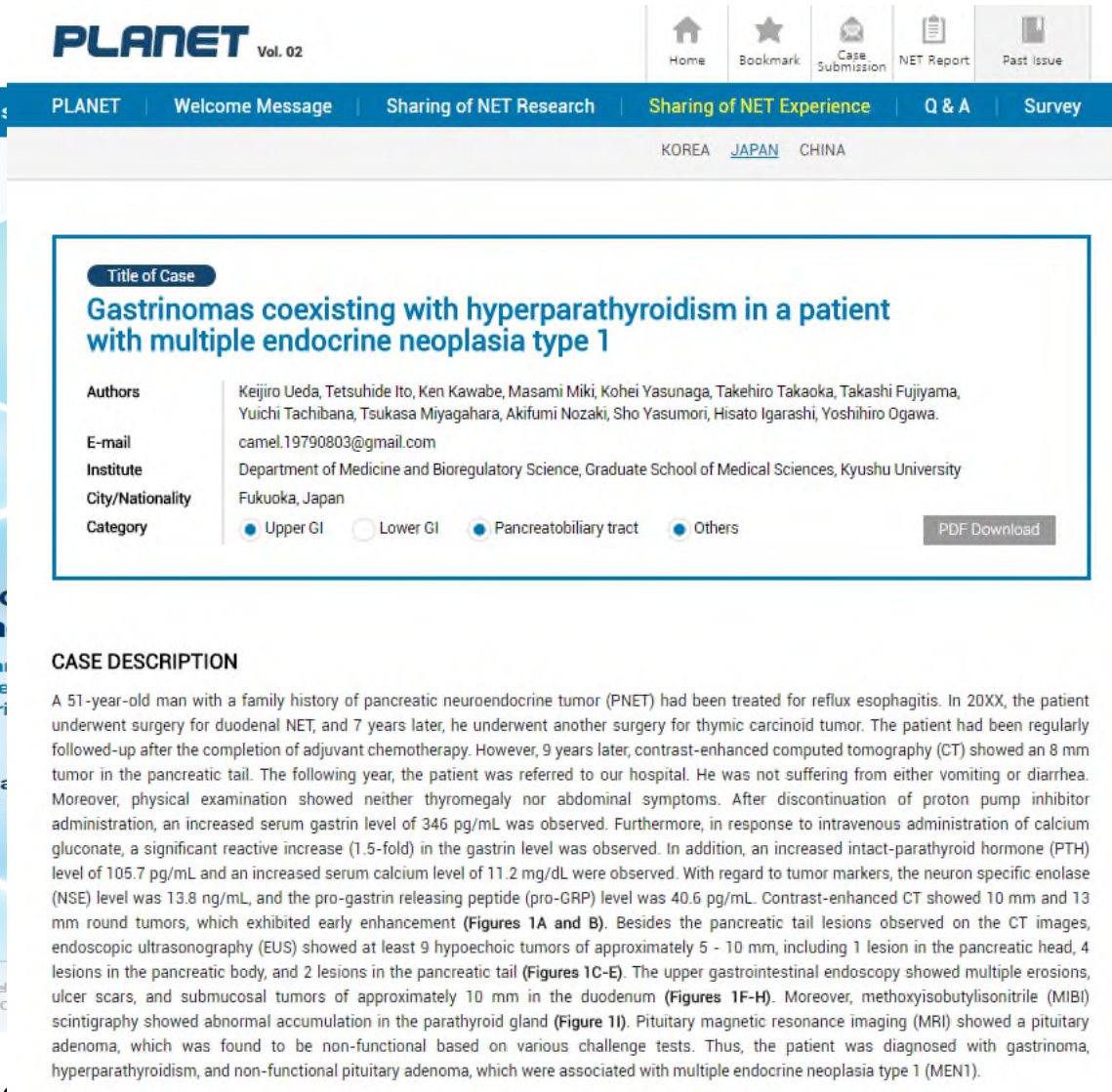
- 2014, 2015, 2016(IASGO presymposium)
- International expert consensus meeting
- Sharing the GEP-NET experience from clinical research in Asian Pacific region

➢NET case reports

- International e-news letter
- Case reports: sharing the experience of GEP-NET



GEP-Net cases of each countries for sharing of experience and academic and clinical survey



GEP-Net cases of each countries for sharing of experience and academic and clinical survey

Conclusion

- Clinical course of GEP-NET is highly variable according to site of origin.
- Multidisciplinary team approach, evolving clinical/basic research are essential for overcoming GEP-NET.
- For the accurate diagnosis and proper treatment of rare disease of GEP-NET, disease network by international communication are needed in Asian pacific countries.
- This symposium will be valuable foundation for the next steps of international cooperation and collaboration.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Gastroenteropancreatic Neuroendocrine Tumor (NET)
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