



March 22nd, 2018

KGC 2018 in Kaorea

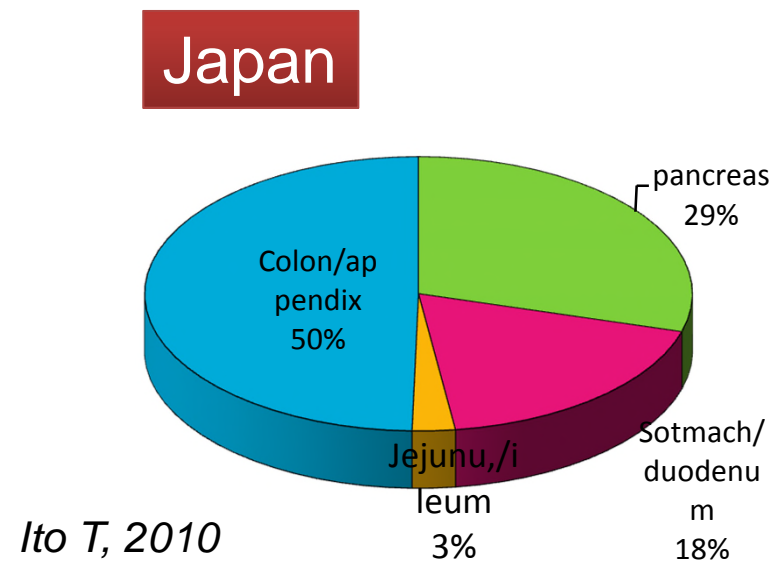
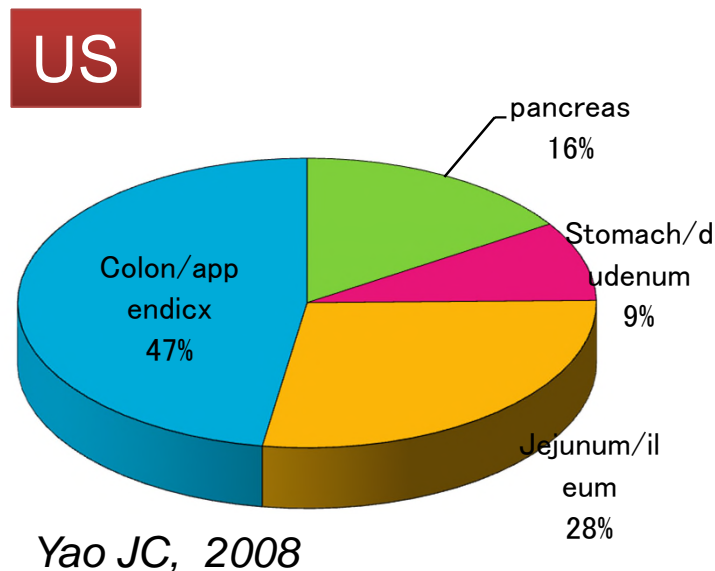
Sharing the experience of GEP-NETs based on JNETS multicenter study of the diagnosis and management of GEP-NETs in Japan

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Why we established JNETS?

- Japan Neuroendocrine tumor society (JNETS) has been established in 2012.
- There are several differences in clinical phenotype of NET tumors in between patients in Japan and in western countries.



Why we established JNETS?

- ✓ To understand the present situation of NET treatment in Japan, nation-wide gastroenterologists, endocrinologists, surgeons, radiologists and pathologists have established Japan NeuroEndocrine Tumor Society (JNETS) in 2012.
- ✓ One of the activities of this society include establishment of the registry system for NET patients toward the revision of the guideline.

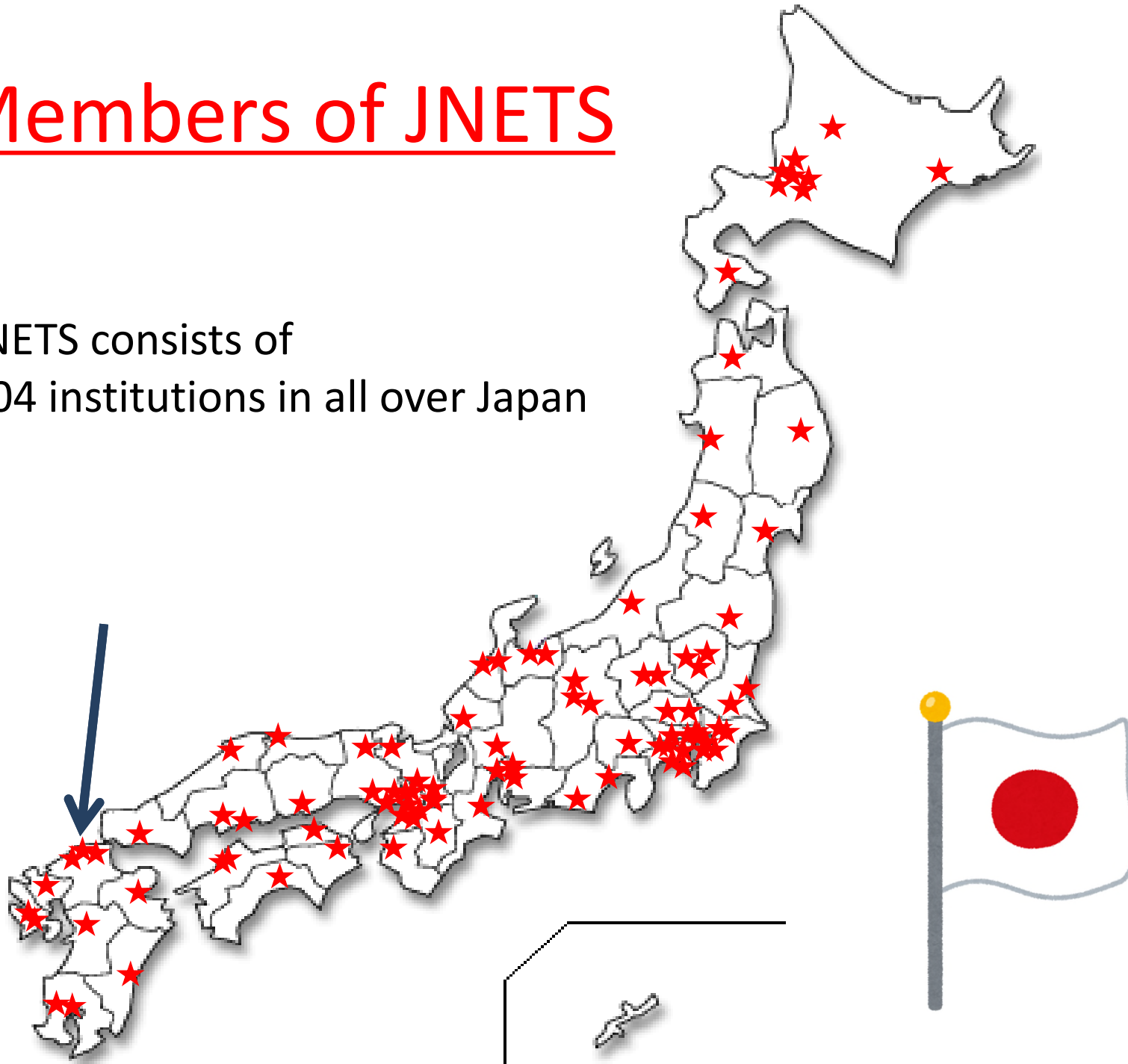


Purposes of Japan Neuroendocrine Tumor Soc

1. Prevaling new treatments and knowledge to the institutions at the annual conference.
2. Establishing a guideline of medical care for NET patients in Japan.
3. Establishing a registry system for NET patients and analyzing NET properties to create clinical evidences.

Members of JNETS

JNETS consists of
304 institutions in all over Japan



NET Registry System (TRINET1332)



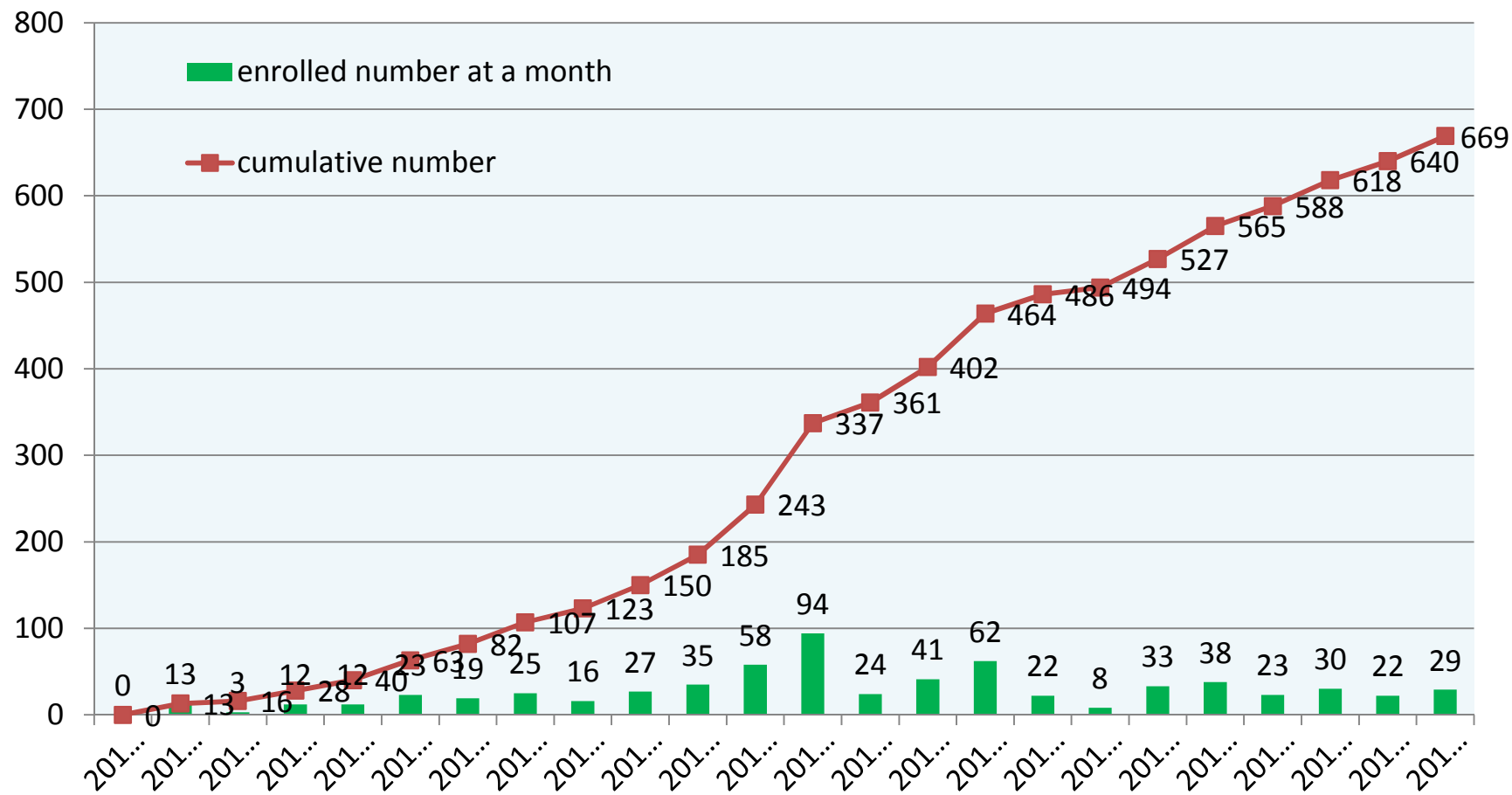
- ✓ **Patients** : Patients with histologically proved neuroendocrine tumor located in pancreas, digestive tract, lung, bronchus or thymus.
- ✓ **Source of funds** : Japan NeuroEndocrine Tumor Society (JNETS)
- ✓ **Data center** : Translational Research Informatics Center
1-5-4 Minatomjima-minamimahchi, Chuo-ku, Kobe, Hyogo, Japan

- ✓ **Representative** : Shinji Uemoto (Chief Director of JNETS)
- ✓ **Participants** : Institutions joining in JNETS
- ✓ **Study period** : 2015/1/1 ~ 2024/11/30 (planning to extend)
 - ※ Patients diagnosed as NET from 2012 can be registered.
 - ※ We have started analyzing data to resolve clinical questions.

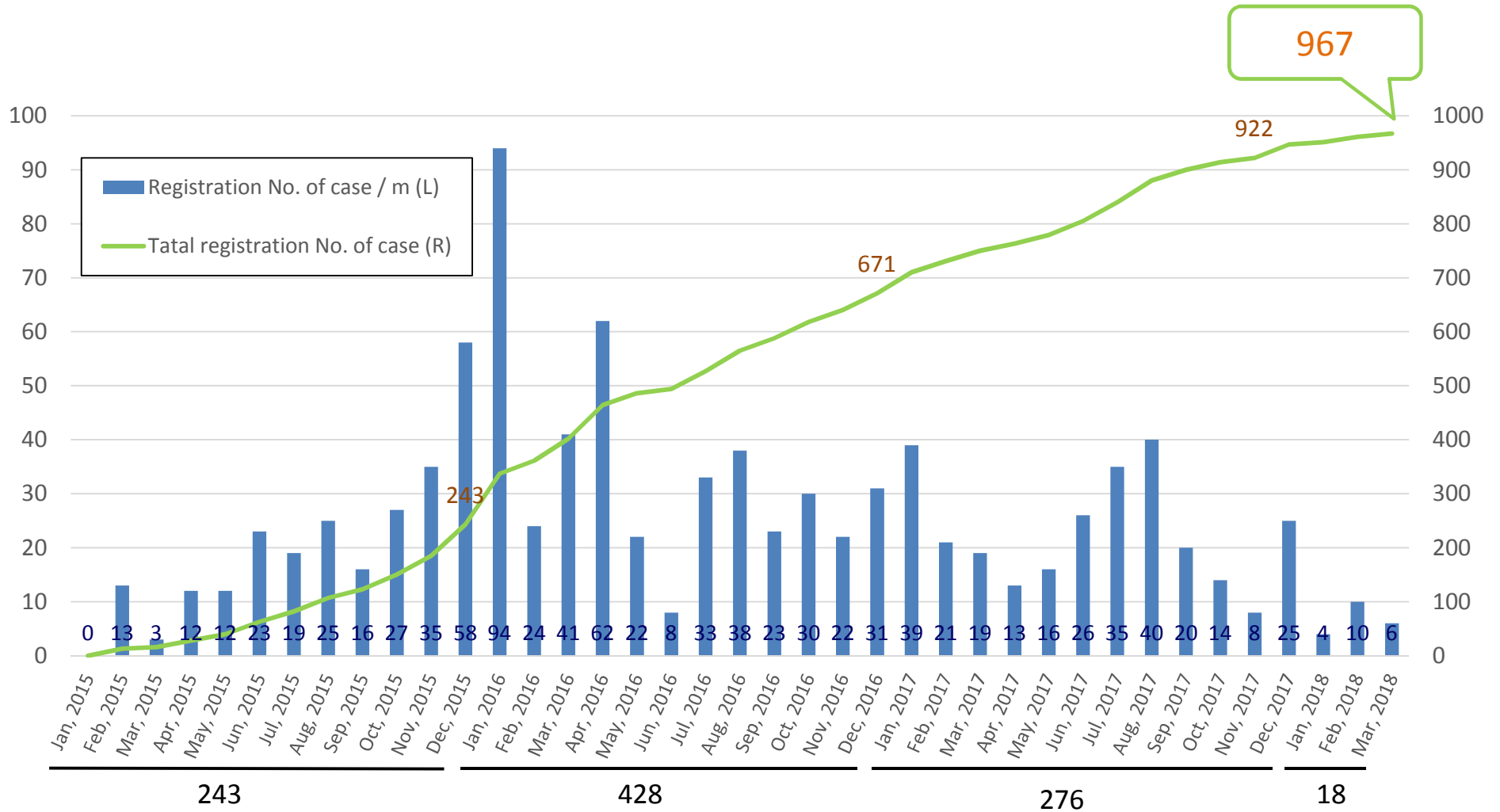
Selection criteria

1. Histologically proved neuroendocrine tumors located in pancreas, digestive tract, lung, bronchus or thymus diagnosed after January 1st,2012.
2. Follow-up/treated patients at the hospital approved by institutional review board (IRB).
3. The enrollment should be consented by the patient. (opt-in)

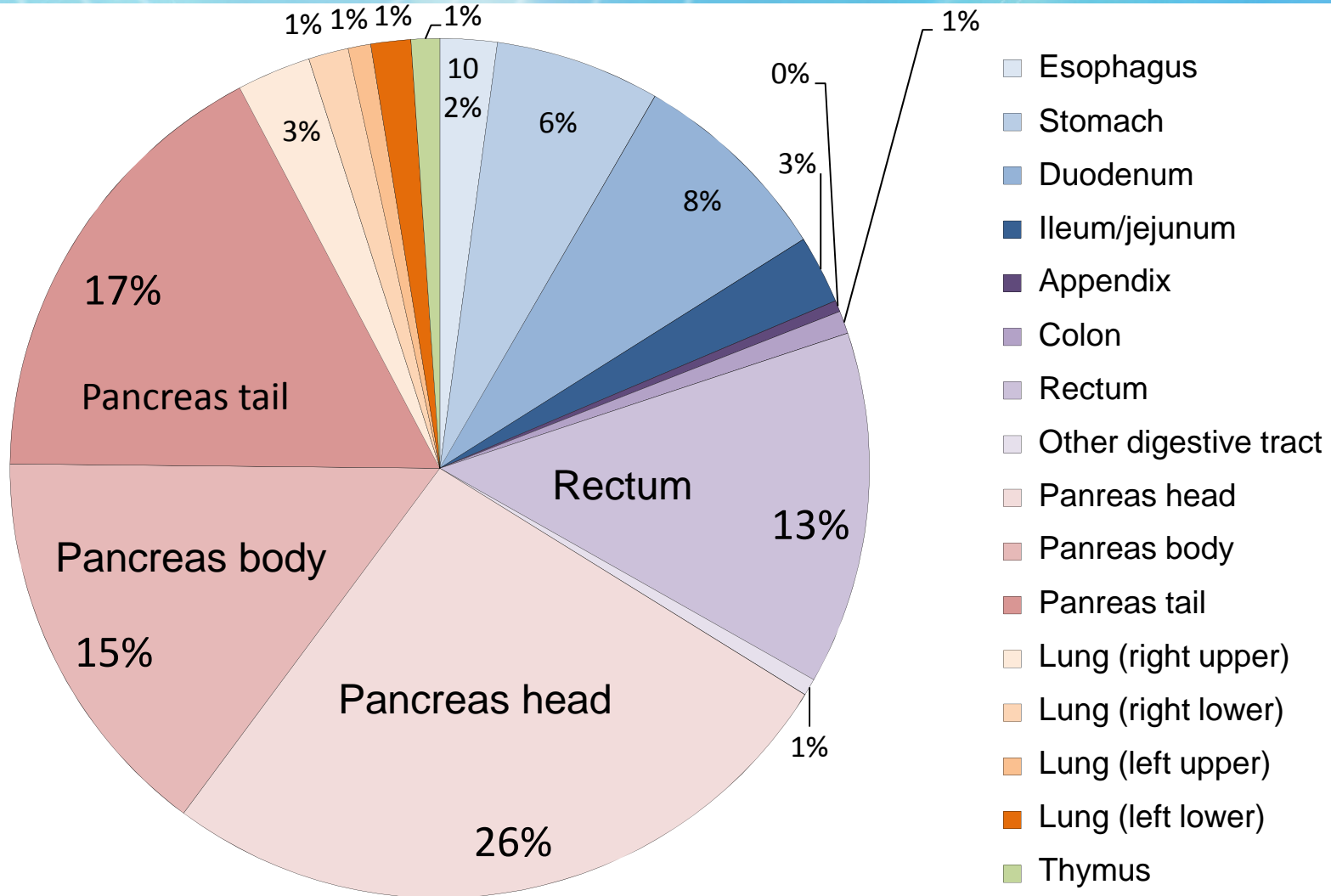
Increasing enrollment in the registry



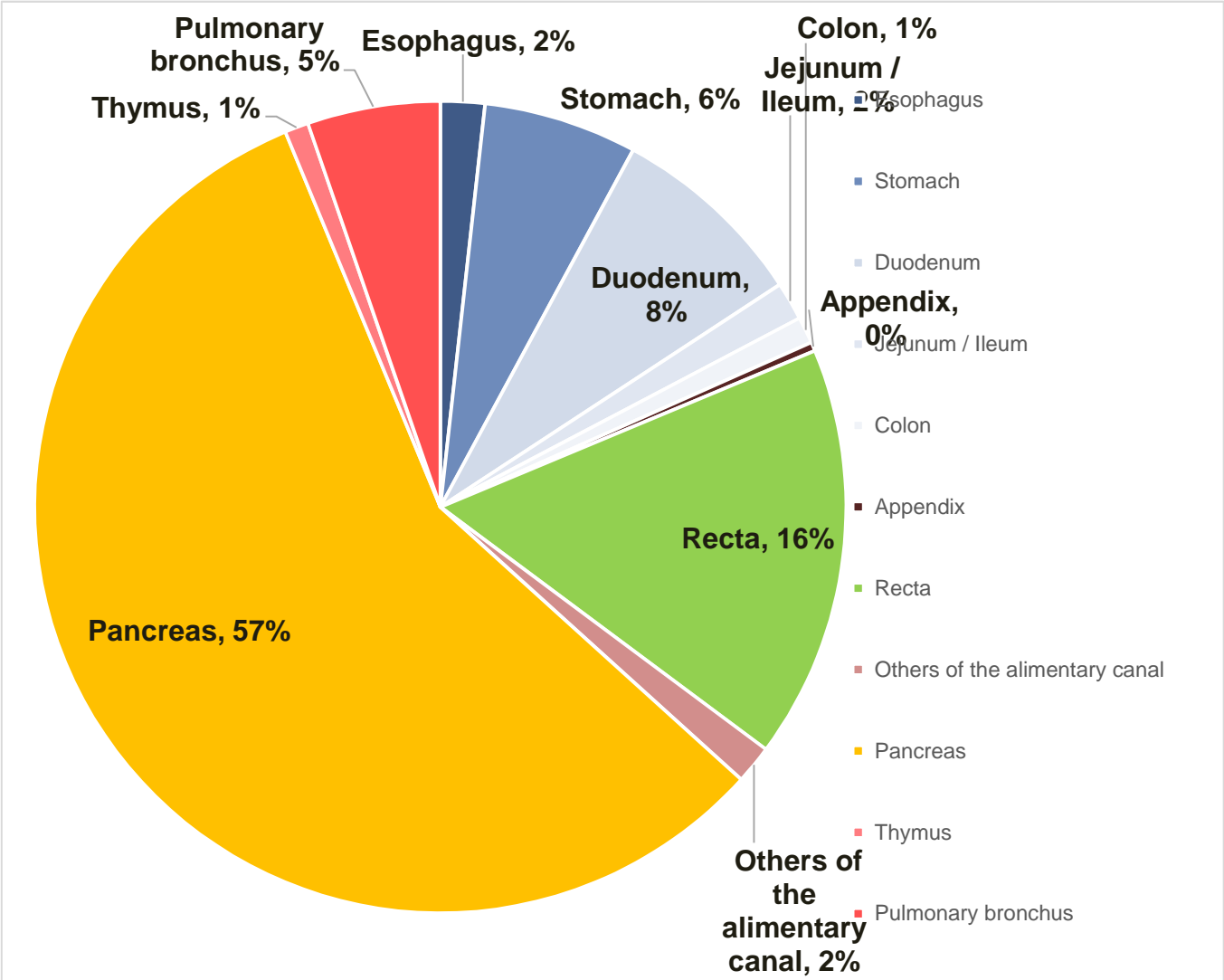
Increasing enrollment in the registry



Primary tumor location of the NET patients in this registry

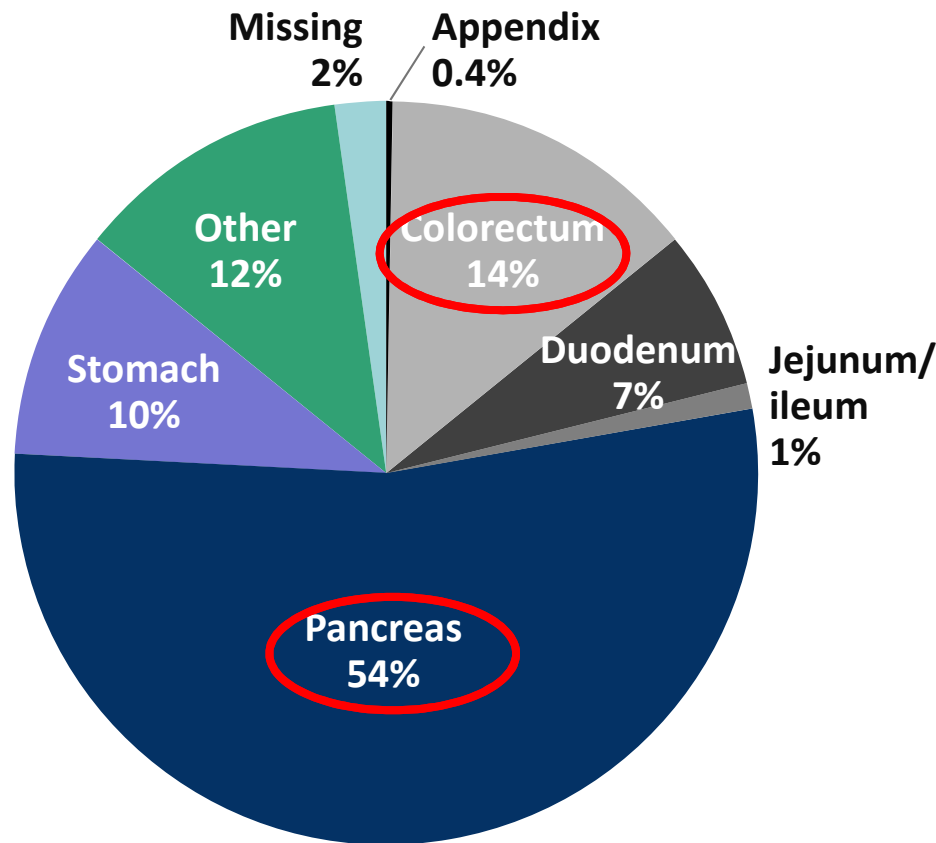


Primary tumor location of the NET patients in this registry





Pancreas: The most common primary site in Asian patients

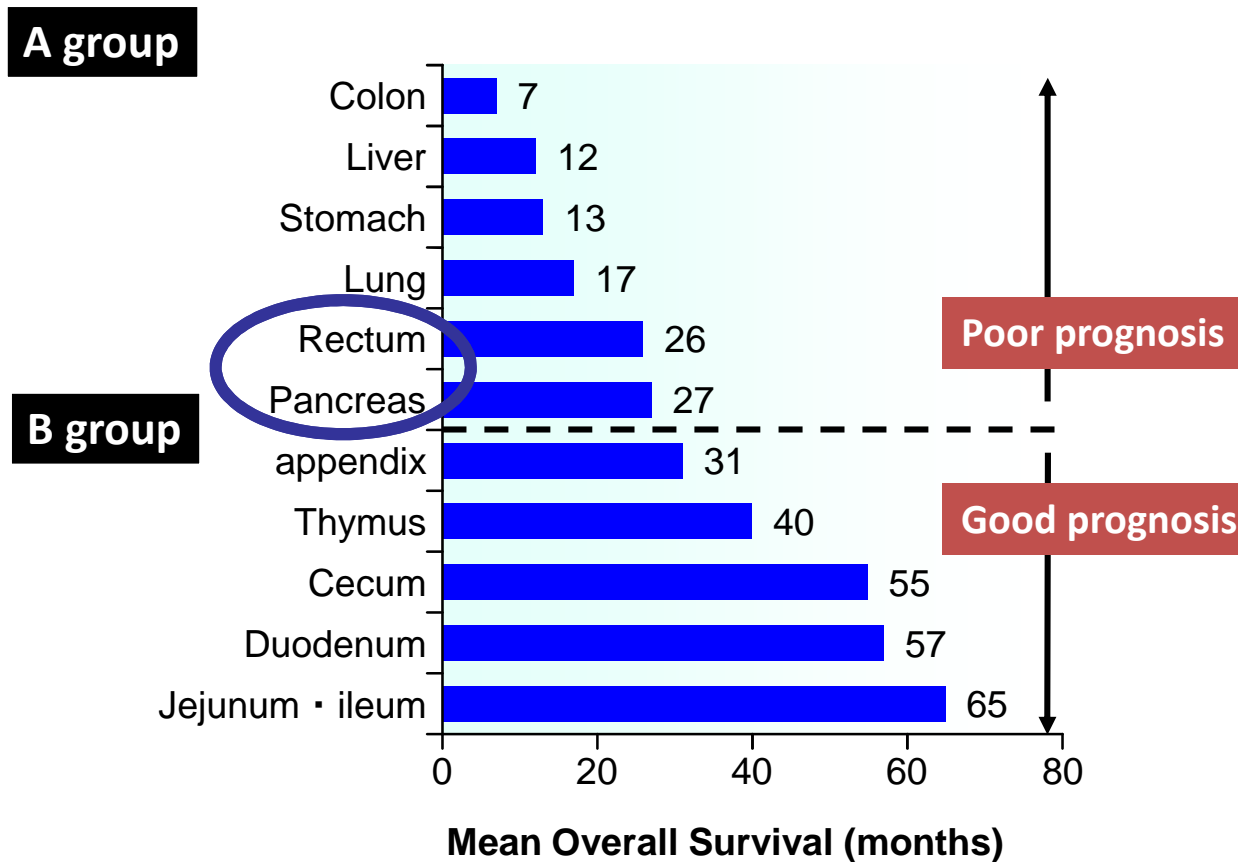


- Data from the EGM GEP NET registry show that the pancreas is the most common primary tumour location in Asian patients, and next is rectum.
- Differences have been observed in the clinical presentation and management of patients who are Asian compared with those who are non-Asian

Prognosis of NET G1/G2 in different primary location

– SEER (US) 、 1988-2004 –

Prognosis with distant metastases



Study design of PROP-UP study

PROP-UP study

Retrospective and prospective observational study on the prognosis of patients with unresectable GEP-NENs or recurrent GEP-NENs after curative resection

PROP-UP 1 study

Retrospective multicenter study to estimate cut-off Ki-67 index between G1 and G2

PROP-UP 2 study

Prospective multicenter study to verify the results of PROP-UP 1

Study protocol for Prospective Observational Study 1 on the Prognosis of Patients with Unresectable Advanced Gastrointestinal and Pancreatic Neuroendocrine Tumors (PROP-UP 1 study) in Japan



- No previous observational studies on the prognosis of advanced gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [pancreatic neuroendocrine neoplasms (PNENs) and gastrointestinal neuroendocrine neoplasms (GI-NENs)] exist in Japan.
- Against this background, the present study aimed to clarify the actual status of advanced digestive system originated NEN in Japan by surveying the prognosis of NEN patients diagnosed with curative unresectable disease or recurrent disease following curative resection.

Methods and analysis of PROP-UP1



- We planned a retrospective and prospective observational study on the prognosis of patients with advanced GEP-NENs (PROP-UP 1 and 2).
- PROP-UP 1 is a retrospective multicenter study. PROP-UP 2 is a prospective study to verify the results of PROP-UP 1. This PROP-UP 1 included individuals diagnosed with unresectable or recurrent after curative resection GEP-NENs.
- ***The primary endpoint of this study was set as the overall survival starting from the day of diagnosis as curatively unresectable or recurrence after curative resection, while the secondary endpoint was the progression-free survival starting from the day of diagnosis as curatively unresectable or recurrence after curative resection.***

Schedule for observation, testing and reporting

Item	At diagnosis of unresectable/recurrent disease	At registration	At time of scheduled reporting					
			2016	2017	2018	2019	2021	2021
Patient background characteristics	○							
Anamnesis/complications	○							
Disease information	○							
Histopathological diagnosis	○							
Overall condition	○	○	○	○	○	○	○	○
Information at onset (only for cases of recurrence after curative resection)	○							
Treatment information for NET		○	○	○	○	○	○	○
Outcome			○	○	○	○	○	○
Exacerbation of NET		○	○	○	○	○	○	○

*It is assumed that the observation period of this study will be extended to December 31, 2020.

The case registration period was 2 years, from January 1, 2014 through December 31, 2015. The observation end-date will be December 31, 2018 (3 years from the end of case registration). Data will be recorded at the time of image-diagnosis of curative-unresectable disease or recurrence after curative resection. Following registration, annual data will be collected once each year, on December 31, until the observation end-date

Outcome

Primary Endpoint

- Overall survival from diagnosis to the date of last follow-up or death.

Secondary Endpoint

- Progression free survival from diagnosis to the date of progression or death.

Main stratified analysis

- To assess a cut-off value of Ki-67 index between G1 and G2.

The primary endpoint of this study was set as the overall survival (OS) starting from the day of diagnosis as curatively unresectable or recurrence after curative resection, while the secondary endpoint was the PFS starting from the day of diagnosis as curatively unresectable or recurrence after curative resection. As an important stratification item, the Ki-67 index (%) will be stratified according to the WHO Classification (G1: $\leq 2\%$; G2: 3 to 20%; NEC: $>20\%$). Stratification will then be performed using 2%, 5%, 10% or any other arbitrary value as cutoff values for G1/G2, respectively, and analysis will be performed to determine the cutoff value most appropriate for predicting prognosis of NET patients.

PROP-UP Study | 登録時のデータ 発表内容の概要④

2016年11月25日時点

Clinical features of patients with GEP-NEN

1 / 3

Total number of PNEN (N=111)	no.(%)	Total number of GI-NEN (N=64)	no.(%)
Sex		Sex	
Male	56(50)	Male	35(55)
Female	55(50)	Female	29(45)
Age - yr median (range)	61(27-79)	Age - yr median (range)	67(32-80)
Primary site		Primary site	
Pancreatic head	54(49)	Foregut (esophagus/stomach/duodenum)	37(58)
Pancreatic body	17(15)	Midgut (jejunum/ileum/vermiform appendix)	5(8)
Pancreatic tail	39(35)	Hindgut (colon/rectum)	22(34)
Multiple lesions in pancreas	1(1)		
Grade(WHO 2010)		Grade(WHO 2010)	
Grade1	14(12)	Grade1	9(14)
Grade2	58(52)	Grade2	17(27)
NEC	34(31)	NEC	32(50)
MANEC	2(2)	MANEC	6(9)
No reply	3(3)		

PROP-UP Study | 登録時のデータ 発表内容の概要⑤

2016年11月25日時点

Clinical features of patients with GEP-NEN

2 / 3

Total number of PNEN (N=111)	no.(%)	Total number of GI-NEN (N=64)	no.(%)
Histologic status of NEC Well-differentiated Poorly-differentiated No reply	7(20) 25(74) 2(6)	Histologic status of NEC Well-differentiated Poorly-differentiated	4(13) 28(87)
Recurrent or Unresectable Recurrence after curative resection Unresectable No-reply	22(20) 89(80)	Recurrent or Unresectable Recurrence after curative resection Unresectable	18(28) 46(72)
Distribution of PNEN Non-functioning tumors Functioning tumors Gastrinoma Glucagonoma VIPoma ACTH producing tumor	99(89) 12(11) 6(5) 2(2) 1(1) 3(3)	Distribution of GI-NEN Non-functioning tumors Functioning tumors Gastrinoma Cartinoid syndrome	58(91) 6(9) 4(6) 2(3)

JNETS Registry System and PRP-UP study ; Conclusions



- JNETS registry is the first registration system for NET in Japan.
- JNETS registry study should greatly contribute to understanding the medical care of the NET patients and to establishing the evidence-based guideline in Japan.
- PROP-UP study is the first observational study to clarify the actual status of advanced (curative unresectable disease or recurrent disease following curative resection) digestive system originated NEN in Japan.

Japanese guideline for GEP-NETs.

Contents (58 CQs)



- Diagnosis (12 CQs)
- Histology (7 CQs)
- Surgical treatment (19 CQs)
- Medical management (14 CQs)
- GEP-NETs associated with MEN1 (6 CQs)

The first edition Published on April in 2015 by JNETS

Take Home Message

Strategy of medical treatment in Asia

Regarding the selection criteria for therapeutic agents, emphasis is placed on the balance between the primary site and Ki-67 / tumor volume.

Molecular-
• 1st line
(The result from RADIANT4
• 1st line
• Consider the side effects in

- we can not apply overseas guidelines, especially Europe and US to Asia as it is!
- Due to disease specificity, Asian original guideline revision is necessary.

is important