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Study Protocol of the Japan NEN Registry: A Multicenter, Prospective Registry of Patientswith Pancreatic, Gastrointestinal, Pulmonary, Bronchial, and Thymic Neuroendocrine Neoplasm

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Abstract

Introduction: Both the diagnosis and the treatment of patients with neuroendocrine neoplasm (NEN) have recently improved globally. Since little data has been presented on the current situation of NEN treatment in Japan, Japan Neuroendocrine Tumor Society (JNETS) established the Japan NEN Registry study and constructed a registry of Japanese NEN patients with a primary site of the pancreas gastrointestinal tract, lungs, bronchi, and thymus in order to clarify the current status of NEN treatment in Japan.

Methods and analysis: The Japan NEN Registry study is a large, multi-institutional prospective cohort study designed by JNETS to clarify actual clinical practice and corresponding outcomes for patients with pathologically diagnosed NENs. At enrollment, demographic characteristics, baseline values and survival event information are reported in an electronic case report form via website. The primary endpoint is overall survival time starting from the date of diagnosis, while the secondary endpoint is progression-free survival starting from the first date of each treatment.

Ethics and dissemination: This study is being conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research.

The protocol of this cohort study was created in December 2014 and approved by the ethics review committee of Kyoto University Hospital (version 1.0 approval no. E2383, dated Jan 5, 2015). It was subsequently revised to collect treatment information and follow-up clinical outcomes in December 2018, and the ethics review committee of Kyoto University Hospital approved the protocol (Approval No. R1857-1, date April 19, 2019), and the individual institutional review boards of all participating facilities approved this study (TRIAL REGISTRATION: UMIN-CTR: UMIN000016380). The results of this study will be submitted to peer-reviewed international papers.

Trial registration: UMIN-CTR: UMIN000016380

Strengths and limitations of this study:

- This registration is proposed to provide real-time information on the status of NEN patients in Japan which has not been elucidated so far.
- We intend to prospectively collect information on treatments for these patients with corresponding outcomes.
- This study allows quantitative, descriptive, and comparative analyses, which will evaluate associations among risk factors, treatment, and outcomes for NEN in Japan.

Keywords:

Registry; Neuroendocrine neoplasm; Japan

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Abbreviations: AC: Atypical Carcinoid; CEA: Carcinoembryonic Antigen; CT: Computed Tomography; CYFRA: Cytokeratin 19 fragment; ECOG: Eastern Cooperative Oncology Group; ENETS: European Neuroendocrine Tumor Society; EUS: Endoscopic Ultrasound; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography; GH: Growth Hormone; GI-NEN: Gastrointestinal Neuroendocrine Neoplasm; IGF-1: Insulin-like Growth Factor 1; iPTH: intact Parathyroid Hormone; JNETS: Japan Neuroendocrine Tumor Society; LCNEC: Large:cell Neuroendocrine Carcinoma; MANEC: Mixed Adenoneuroendocrine Carcinoma; MRI: Magnetic Resonance Imaging; NEC: Neuroendocrine Carcinoma; NEN: Neuroendocrine Neoplasm; NET: Neuroendocrine Tumor; NSE: Neuron Specific Enolase; PanNEN: Pancreatic Neuroendocrine Neoplasm; PRL: Prolactin; ProGRP: Pro:Gastrin Releasing Peptide; PS: Performance Status; RFA: Radiofrequency Ablation; SASI: Selective Arterial Secretin Injection; SCLC: Small-Cell Lung Cancer; SEER: The Surveillance, Epidemiology and End Results; TACE: Trans-hepatic Arterial Chemoembolization; TAE: Trans-hepatic Arterial Embolization; TC: Typical Carcinoid; US: Ultrasound; VIP: Vasoactive Intestinal Peptide; WHO: World Health Organization

Introduction

Neuroendocrine neoplasm (NEN) is a type of tumor arising from neuroendocrine cells, which produces various kinds of hormones, some of which cause severe clinical symptoms. It has become clear that NEN can occur in any organ throughout the body due to the diffuse neuroendocrine system.

In general, NEN is an uncommon disease. According to the Surveillance, Epidemiology and End Results (SEER) program in the United States, the number of patients has been increasing and the annual incidence was 5.25 per 100,000 population in 2004, approximately 5-times greater than 1.09 per 100,000 population reported in 1973 [1]. The reason for this increase has not yet been clarified, but the improvement of disease recognition and diagnostic techniques might be considered major reasons [2].

According to Ito et al., the annual incidence of pancreatic NEN (PanNEN) in Japan was estimated to be 1.01/100,000 population in 2005, and that of gastrointestinal NEN (GI-NEN) was 2.10/100,000 [3]. They conducted a second survey in 2010, and reported that each of PanNEN and GI-NEN incidences had increased [4]. Interestingly, the incidence of midgut NEN was lower in Japan compared to the data reported from the SEER database or other European registries [4]. Similar lower incidences of midgut NEN have been reported from other Asian countries [5,6]. Achieving a more precise analysis of NEN patients in Japan thus seems likely to contribute to a more comprehensive understanding of NEN, at least for Asian NEN patients.

Recently, a new classification method based on the growth kinetics of tumor cells (number of cell nuclear fission images and Ki67 index [%]) was proposed in the 2010 World Health Organization (WHO) classification [7] for PanNEN and GI-NEN. NEN has been classified as NET G1/G2 (Grade 1/Grade 2) and neuroendocrine carcinoma (NEC). Several articles have discussed whether the present cutoff value for Ki67 index is optimal [8-11]. We consider this to be an urgent problem concerning Asian NEN patients. In addition, although surgical treatment is the first choice for patients with resectable NEN, several arguments have remained regarding what type of operation is the best suitable for prolongation of patient survival and how the surgery should be performed for patients with distant metastases. More precise analysis with registry is necessary to solve these problems for gastroenteropancreatic NEN patients.

Pulmonary, bronchial, and thymic neuroendocrine tumors comprised of malignant carcinoma such as large-cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer (SCLC), and typical and atypical carcinoid. Those tumors form a pathologically and clinically heterogeneous group [12]. According to the SEER program in the United States, the total annual incidence of pulmonary and bronchial NEN since 2003 is 1.57/100,000 [13]. SCLC is the most common pulmonary and bronchial NEN, representing 15%–20% of invasive lung cancers, and LCNEC is said to make up 1.6%–3% of resectable lung cancers. Thymic NEN is a very rare cancer; with the incidence of 0.02/100,000 people annually in the SEER report [14]. According to the Japan Surgical Society statistics in a study of surgical cases in Japan, carcinoid was seen in 198 patients (0.6%), LCNEC in 492 patients (1.4%), and SCLC in 581 patients (1.7%) among 34,228 primary lung cancer patients in 2011 [15]. Thymic NEN was seen in only 41 patients (0.9% of 4,463 thymic tumors). Surgery is the mainstay of the treatment of Typical Carcinoid (TC) and Atypical Carcinoid (AC) based on the general principle of complete resection with preservation of as much normal lung tissue as possible [16]. LCNEC has conventionally been handled as a large-cell lung cancer with a pathology differing from that of small cell lung cancer. LCNEC is a challenging tumor, and its poor prognosis is also related to the difficulty of preoperative diagnosis.

Although treatment and diagnosis of NEN have changed globally in recent years, the situation of current clinical practice in Japan has not been clearly identified. To improve the outcome of NEN treatment in Japan, it is necessary to clarify pathology and prognosis of NEN as well as patient distribution.

Thus we established a registry system for NEN patients with the primary site of pancreas, gastrointestinal tract, lungs, bronchi, and thymus in Japan.

Material and Methods

Study design

The Japan NEN Registry study is a large multi-institutional prospective cohort study to clarify the actual tumor distribution and clinicopathological status of NEN patients in Japan (Figure 1). Recruitment for the NEN Registry study began in January 2015 and is planned to continue until November 2024.

The Japan NEN Registry study is funded by the Japan Neuroendocrine Tumor Society (JNETS). The protocol of this cohort study was created in December 2014 and approved by the ethics review committee of Kyoto University Hospital (version 1.0 approval no. E2383, dated Jan 5, 2015). The protocol was subsequently revised to collect treatment information and follow-up clinical outcomes in December 2018, and the ethics review committee of Kyoto University Hospital approved the revised protocol (approval no. R1857, dated February 19, 2019). The individual institutional review boards of all participating facilities approved this study. Data collection of follow-up is planned to start from January 2015 and continue until November 2024.

Study group and participants

Members of the JNETS (hospitals or institutional departments) are participating in this registry and enrolling patients.

Essential inclusion criteria of patients are as follows:

1) Patients histologically or pathologically diagnosed with NEN of the

pancreas, gastrointestinal tract, lung, bronchi or thymus after 1 January 2012 and continued follow-up after the date of ethics review committee approval from each hospital or institute;

2) For PanNEN and GI-NEN, patients pathologically diagnosed with NET G1/G2, NEC or mixed adenoendocrine carcinoma (MANEC) according to the 2010 WHO criteria;

3) For pulmonary and bronchial NETs, patients pathologically diagnosed with TC, AC, or LCNEC according to the 2004 WHO criteria;

4) For thymic NEN, all participants confirmed histologically or pathologically; and

5) Confirmation of written informed consent from the participant (or if age of the patient is under 20, consent from a substitute person (an individual considered to be able to express the intention and interests of the patient, such as parental authority or legal representative of the patient)). All of the requirements listed avobe must be met for inclusion in the study.

Exclusion criteria are as follows:

1) Patients diagnosed with SCLC;

2) Patients already registered to this study at another hospital or institution; or

3) Patients assessed as inappropriate for this research due to the other reasons. If any of the above conditions applies, the individual will be excluded.

Data collection

Whole collected clinical data were listed in Table 1.

Demographics

Participant's birth date, initials (to avoid duplicate registrations of the same participants at different institutes), gender, and date of informed consent are obtained as baseline information.

Clinical findings

Basic clinical information (date of initial diagnosis, date of study registration, diagnosed at a prior hospital or not, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, functional or non-functional NEN, type of functional NEN (if applicable), hereditary or sporadic NEN, type of hereditary NEN (if applicable), prevalence of endocrine symptoms caused by excess hormone release, primary/metastatic lesions (organ site[s], size of tumor, depth of invasion, number of primary lesion [within 3, 4 or more]), clinical TNM stage (European Neuroendocrine Tumor Society or Union for International Cancer Control [UICC] and/or American Joint Committee on Cancer [AJCC]), laboratory data (tumor markers and hormones; chromogranin A, neuron-specific enolase (NSE), histamine, insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), intact parathyroid hormone (iPTH), calcium, prolactin (PRL), growth hormone (GH), insulin-like growth factor 1 (IGF-1), catecholamine), and imaging or endoscopic modalities by which NEN was suspected or diagnosed) is obtained as baseline characteristics.

In addition to these characteristics, additional baseline data on endoscopic findings, immunostaining of biopsy samples, somatostatin receptor scintigraphy and six tumor markers (NSE, progastrin-releasing peptide (ProGRP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, DUPAN2, CYFRA) is also being collected from 2019 in accordance with the revised protocol.

Pathological findings

As information about pathological findings, the following data are obtained: 1) date of pathological diagnosis; 2) the method by which histological or pathological samples were obtained; 3) WHO classification (grade of differentiation, Ki67 index, mitotic index, vascular invasion); 4) stainability of hormone markers; and 5) pathological TNM stage. Pathological findings are evaluated by local pathologists at each institution. Pathological TNM stage is assessed using the European Neuroendocrine Tumor Society (ENETS) and the UICC TNM Classification of Malignant Tumors (6th edition) [17].

Treatment and surveillance

Information on treatment and surveillance has been collected since 2019 according to the revised protocol. The following data are collected:

1) Surgical resection/endoscopic resection (macroscopic characteristics, surgical method (including endoscopic resection), date of resection, radicality);

2) Resection of liver metastasis (if applicable; macroscopic characteristics, surgical method, date of resection, radicality);

3) Adjuvant therapy;

4) Systemic therapy (hormone therapy, targeted therapy, chemotherapy, other drugs, best overall response);

5) Locoregional therapy (trans-hepatic arterial chemoembolization (TACE), trans-hepatic arterial embolization (TAE), radiofrequency ablation (RFA)); and

6) Outcome surveillance (overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS)).

Statistical analysis

OS will be analyzed using the Kaplan-Meier method, and the prognostic impact of baseline individual data on survival will be analyzed using Cox proportional-hazards modeling. Subgroup analyses will also be performed according to demographics, clinical findings, and pathological findings. All statistical analyses will be performed at the Translational Research Center for Medical Innovation (TRI), Foundation for Biomedical Research and Innovation at Kobe (FBRI).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research

Discussion

In this Japan NEN registry, we designed to collect real-time numbers and clinicopathological data for pancreatic, gastrointestinal, pulmonary, bronchial, and thymic NENs. Ito et al. estimated the incidence of newly diagnosed GI-NENs to be 2.01/100,000 population, indicating that approximately 24,000 new NEN patients arise each year in Japan. The Japan NEN registry has so far registered 300-400 patients per year, suggesting that roughly around 1%–2% of patients in whole country are going to be collected by this registry.

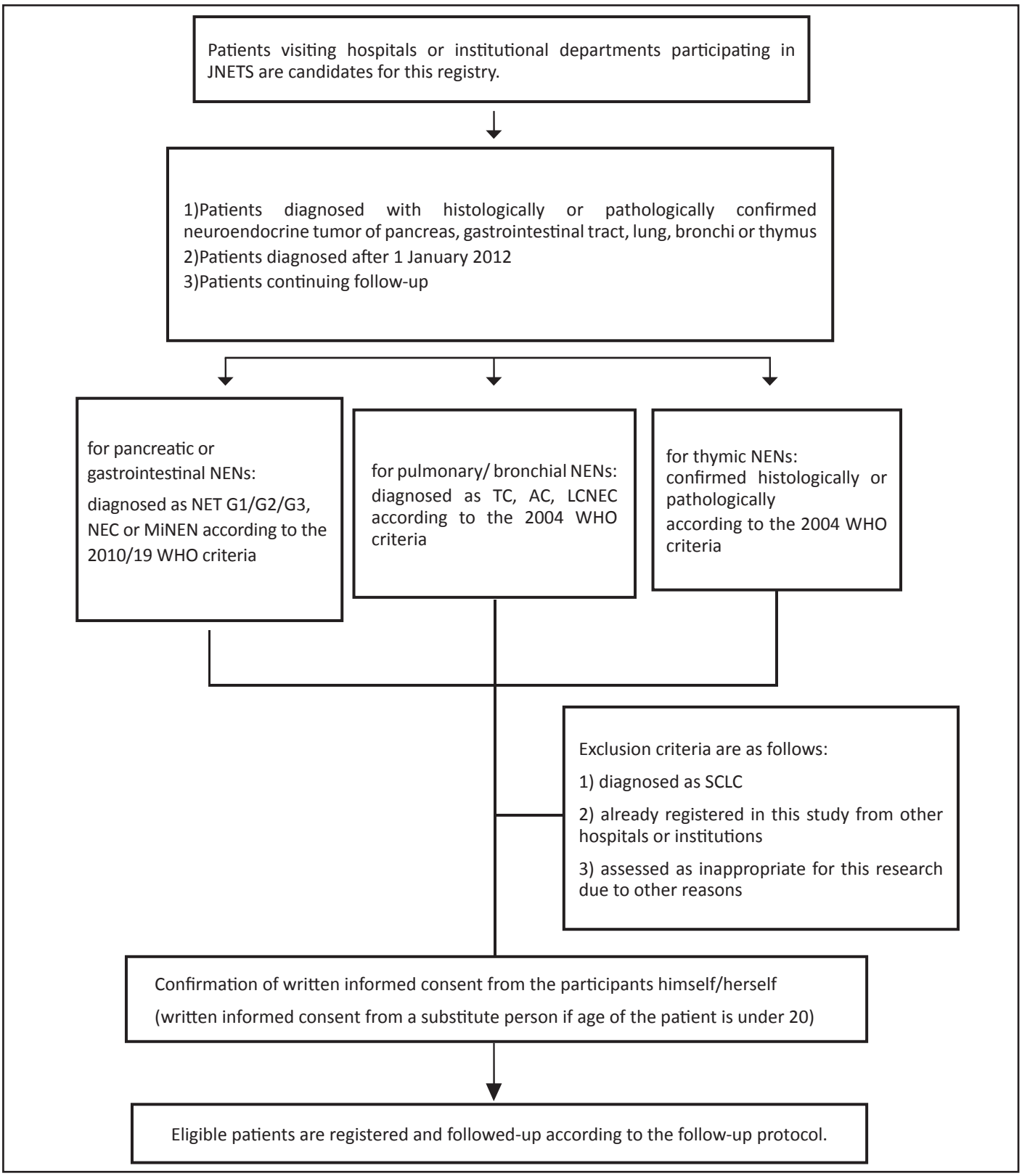

Figure 1: Study design of the Japan NEN Registry study. In brief, patients of neuroendocrine tumors of pancreas, gastrointestinal tract, lung, bronchi or thymus visiting the hospitals participating in JNETS are candidates for the registry. When pathologically proven, patients are registered with informed consent.

	Categories	Variables
Variables	birth date, participant's initials, gender	
	date of informed consent	
Clinical findings	date of initial diagnosis, date of study registration, diagnosed at a prior hospital or not	
	ECOG PS, smoking status	
	Functional or nonfunctional NEN	Functional or nonfunctional NEN (if applicable) type of functional NEN (insulinoma, gastrinoma, glucagonoma, VIPoma, or others)
	Hereditary or sporadic NEN	hereditary or sporadic NEN (if applicable) type of hereditary NEN
	prevalence of endocrine symptoms	
	primary/metastatic lesion	organ site(s), size of tumor, depth of invasion, number of primary lesions (within 3, 4 or more)
	clinical TNM stage	clinical TNM stage (ENETS and/or UICC/AJCC)
	abnormal laboratory data (tumor markers and hormones)	chromogranin A, NSE, histamine, insulin, gastrin, glucagon, VIP, iPTH, calcium, PRL, GH, IGF-1, catecholamine
	modalities by which NEN was suspected or diagnosed	CT, MRI, US, endoscopy, Endoscopic Ultrasound (EUS), somatostatin receptor imaging, Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET), Selective Arterial Secretin Injection (SASI) test, endoscopic findings, immunostaining of biopsy samples
	additional baseline data*	endoscopic findings, immunostaining of biopsy samples, somatostatin receptor scintigraphy and six tumor markers (NSE, ProGRP, carcinoembryonic antigen [CEA], CA19-9, DUPAN2, CYFRA)
Pathological findings	date of pathological diagnosis	
	methods of sample obtained	surgical resection, endoscopic resection, or biopsy
	WHO classification	grade of differentiation, Ki67 index, mitotic index, vascular invasion
	stainability of hormone markers	chromogranin A, synaptophysin, CD56, NSE
	pathological TNM stage	pathological TNM stage (ENETS and/or UICC/AJCC)

Treatment and surveillance*	surgical resection, or endoscopic resection	macroscopic characteristics, surgical method (including endoscopic resection), date of resection, radicality
	resection of liver metastasis (if applicable)	macroscopic characteristics, surgical method, date of resection, radicality
	adjuvant therapy	
	systemic therapy	hormone therapy, targeted therapy, chemotherapy, other drugs, best overall response
	locoregional therapy	TACE, TAE, RFA
	outcome surveillance	survival, disease progression, recurrence
* Information on treatment and surveillance is being collected from 2019.		

Table 1: Collected by the Japan NEN Registry study.

There are two types of studies to analyze Japanese NEN patients. One is a population-based study, in which we can collect a higher total number of patients, although the data accumulated may be less detailed. The other is a registry-based study, in which we may be able to collect a smaller number of patients with more detailed data. The former type has advantage of being able to compare incidence by year and to investigate the trend, while the latter allows more specific analysis. This study is intended to be the latter registry-based study. In many nationwide population-based studies for cancer patients including NEN, Ki67 index has not been examined for NEN patients, despite being critical for assessment of NEN malignancy. The SEER database is one of the biggest databases for malignancies, but unfortunately it does not include Ki67 index for NEN cases. To date, few nationwide registries around the world have included Ki67 index of NEN patients. The Spanish R-GETNE registry gathered 2,813 patients and analyzed survival according to several factors, including Ki67 index [18]. A report from Chile compared the survival rate with similar factors, but the initial cohort was comprised only 166 patients [19]. Both of these investigations were from non-Asian countries. Because racial and regional discrepancies have been assumed to affect prevalence and incidence of NEN, those data are not directly applicable to patients from Asian countries such as Japan. A registry study has been reported from Taiwan, but it also lacks the data for Ki67 index. Although our current registry covers around 1%-2% of patients in Japan, the registry is collecting specific detailed factors that are certain to provide important insight.

The categories of information that we are collecting in the current registry have thus been decided based on not only the WHO classification of NEN but also other baseline characteristics related with OS and PFS. To adapt to changes in classifications including WHO, we are collecting raw data for Ki67 index, differentiation, lympho-vascular invasion and others, resulting in our ability to readily apply the new 2019 WHO classifications to our registry. Moreover, we are collecting factors relating to hereditary diseases which have not been fully described in former registries. We are also collecting treatment options and intending to clarify the relationship between the mode of treatment and patient prognosis. Although the main purpose of this registry is to elucidate the current status of NEN patients and their survival in Japan, we additionally prepare to collect data that may provide useful clues for resolving several important clinical problems such as SSTR assessment in NEC, the relationship between macroscopic findings of NEN and patient survival, and the clinical state of patients with non-symptomatic NEN in whom tumor cells are stained positively for hormones including glucagon, VIP or somatostatin.

Strength of this registry is that all the registered patients are pathologically diagnosed with NENs. Patients with distant metastasis are often diagnosed from CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) alone. This, in turn, could lead to misdiagnosis of other type of malignancies. Our registry involves a prospective cohort, and pathological diagnosis of NEN is indispensable for registration.

Conclusion

In summary, this registration is conducted to provide real time information on the status of NEN patients in Japan. In addition, we are prospectively collecting information on treatments for these patients and corresponding outcomes. This will allow quantitative, descriptive, and comparative analyses, which will evaluate associations between risk factors, treatments, and outcomes in Japanese patients with NEN.

Declarations

Funding

This registry is funded by the Japan Neuroendocrine Tumor Society (JNETS).

Authors' contributions

MT, IT, KI, KS US, MF, and MI conceived and designed the study, and were responsible for the final decision to submit for publication. All authors were involved in the development, review, and approval of the manuscript. All authors read and approved the final manuscript.

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