Study Protocol of the Japan NEN Registry: A Multicenter, Prospective Registry of Patients with 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 institutional individual 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 Chemomobilization; 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 classify 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 primary site of pancreas, gastrointestinal tract, lungs, bronchi and thymus.
Clinical findings

Demographics

Data collection

Pathological findings

Treatment and surveillance

Statistical analysis

Patient and public involvement

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 this registry. When pathologically proven, patients are registered with informed consent.
<table>
<thead>
<tr>
<th>Categories</th>
<th>Variables</th>
</tr>
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<tbody>
<tr>
<td>Variables</td>
<td>birth date, participant’s initials, gender</td>
</tr>
<tr>
<td></td>
<td>date of informed consent</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>date of initial diagnosis, date of study registration, diagnosed at a prior hospital or not</td>
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<td></td>
<td>ECOG PS, smoking status</td>
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<td></td>
<td>Functional or nonfunctional NEN</td>
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<tr>
<td></td>
<td>(if applicable) type of functional NEN (insulinoma, gastrinoma, glucagonoma, VIPoma, or others)</td>
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<td></td>
<td>Hereditary or sporadic NEN</td>
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<td></td>
<td>(if applicable) type of hereditary NEN</td>
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<td></td>
<td>prevalence of endocrine symptoms</td>
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<td></td>
<td>primary/metastatic lesion</td>
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<td></td>
<td>organ site(s), size of tumor, depth of invasion, number of primary lesions (within 3, 4 or more)</td>
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<td></td>
<td>clinical TNM stage</td>
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<tr>
<td></td>
<td>clinical TNM stage (ENETS and/or UICC/AJCC)</td>
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<td></td>
<td>abnormal laboratory data (tumor markers and hormones)</td>
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<tr>
<td></td>
<td>chromogranin A, NSE, histamine, insulin, gastrin, glucagon, VIP, iPTH, calcium, PRL, GH, IGF-1, catecholamine</td>
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<td></td>
<td>modalities by which NEN was suspected or diagnosed</td>
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<td></td>
<td>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</td>
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<tr>
<td></td>
<td>additional baseline data*</td>
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<td></td>
<td>endoscopic findings, immunostaining of biopsy samples, somatostatin receptor scintigraphy and six tumor markers (NSE, ProGRP, carcinoembryonic antigen [CEA], CA19-9, DUPAN2, CYFRA)</td>
</tr>
<tr>
<td>Pathological findings</td>
<td>date of pathological diagnosis</td>
</tr>
<tr>
<td></td>
<td>methods of sample obtained</td>
</tr>
<tr>
<td></td>
<td>surgical resection, endoscopic resection, or biopsy</td>
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<tr>
<td></td>
<td>WHO classification</td>
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<tr>
<td></td>
<td>grade of differentiation, Ki67 index, mitotic index, vascular invasion</td>
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<td></td>
<td>stainability of hormone markers</td>
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<tr>
<td></td>
<td>chromogranin A, synaptophysin, CD56, NSE</td>
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<tr>
<td></td>
<td>pathological TNM stage</td>
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<td></td>
<td>pathological TNM stage (ENETS and/or UICC/AJCC)</td>
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</table>
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 being collected from 2019.

### Table 1: Collected by the Japan NEN Registry study.

<table>
<thead>
<tr>
<th>Treatment and surveillance*</th>
<th>surgical resection, or endoscopic resection</th>
<th>macroscopic characteristics, surgical method (including endoscopic resection), date of resection, radicality</th>
</tr>
</thead>
<tbody>
<tr>
<td>resection of liver metastasis (if applicable)</td>
<td>macroscopic characteristics, surgical method, date of resection, radicality</td>
<td></td>
</tr>
<tr>
<td>adjuvant therapy</td>
<td>hormone therapy, targeted therapy, chemotheraphy, other drugs, best overall response</td>
<td></td>
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<tr>
<td>systemic therapy</td>
<td>locoregional therapy</td>
<td></td>
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<tr>
<td>outcome surveillance</td>
<td>survival, disease progression, recurrence</td>
<td></td>
</tr>
</tbody>
</table>

* Information on treatment and surveillance is being collected from 2019.

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.

### 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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References


