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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan

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Abstract
Background There have been few epidemiological studies on gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Japan.
Methods We examined the epidemiology of GEP-NETs [pancreatic endocrine tumors (PETs) and gastrointestinal neuroendocrine tumors (GI-NETs)] in Japan in 2005 using a nationwide stratified random sampling method.
Results A total of 2,845 individuals received treatment for PETs. Prevalence was estimated as 2.23/100,000 with an annual onset incidence of 1.01/100,000. Non-functioning tumor (NF)-PET constituted 47.4%, followed by insulinoma (38.2%) and gastrinoma (7.9%). Distant metastases were reported in 21% patients with NF-PETs and occurred more frequently as tumor size increased (>2 cm). Multiple endocrine neoplasia type 1 (MEN-1) was detected in 10% of

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PETs but only in 6.1% of NF-PETs. NF-PETs were detected incidentally by physical examination in 24% patients. In 2005, an estimated 4,406 patients received treatment for GI-NETs. Prevalence was estimated as 3.45/100,000, with an annual onset incidence of 2.10/100,000. The locations of GI-NETs varied: foregut, 30.4%; midgut, 9.6%; and hindgut, 60.0%. Distant metastases were observed in 6%. Lymph node metastases occurred more frequently as tumor size increased (>1 cm). The frequency of MEN-1 complications was 1%. Physical examination revealed GI-NETs in 44% patients. The frequency of symptomatic GI-NETs was 3.4%. Interestingly, 77.1% of patients with foregut GI-NETs had type A gastritis.

Conclusion Our results show there are large differences in GEP-NETs between Japan and Western nations, primarily due to differences in the presence of MEN-1 in NF-PETs and the location, symptomatic status, and prevalence of malignancy in GI-NETs.

Keywords Neuroendocrine tumor · Endocrine pancreatic tumor · Gastrointestinal neuroendocrine tumors · Nationwide survey · Epidemiology

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which derive from the neuroendocrine cell system and have widely divergent clinical presentations, are relatively infrequent, constituting approximately 2% of all neoplasms; they are typically indolent, slow-growing tumors [1, 2]. In Western nations, pancreatic endocrine tumors (PETs) occur in approximately 1 per 100,000 population and represent 1–2% of all pancreatic neoplasms [3–5]. Gastrointestinal neuroendocrine tumors (GI-NETs) occur in approximately 1.95–2.5 per 100,000 population, with carcinoid syndrome most frequently associated with midgut GI-NETs tumors [6–10]. However, the US Surveillance Epidemiology and End Results (SEER) program recently suggested that the incidence and prevalence of NETs has increased substantially over the past three decades, which may partly reflect the increased number of diagnoses of benign and incidentally identified lesions due to the increased availability of advanced endoscopic and radiological imaging [11]. On the other hand, there have been few epidemiological studies on NETs in Japan [12, 13], and thus, no comprehensive research exists on which Japanese investigators can base their discussions on the diagnosis and treatment of this disease among Japanese patients. Furthermore, a substantial amount of information, including the difference in incidence compared to that in Western nations, remains unknown. Therefore, the Neuroendocrine Tumor Workshop Japan (NET Work Japan) conducted a preliminary investigation to understand the status quo of NETs in Japan which focused on the incidence of PETs and GI-NETs over a 3-year period from 2002 to 2004 [14]. On the basis of the results of this preliminary survey, we conducted a nationwide survey to examine the epidemiology of GEP-NETs in Japan using a stratified random sampling method to select departments of medical facilities in which patients with GEP-NETs were treated in 2005. This paper is the latest report on the status of GEP-NETs in Japan.

Methods

We conducted a nationwide survey to examine the epidemiology of GEP-NETs in Japan. The subjects were patients with GEP-NETs (including PETs and GI-NETs) who received treatment from January 1 to December 31, 2005. We obtained the list of all hospitals, including the name and address of and the number of beds and the departments in each hospital, from the Ministry of Health, Labor, and Welfare in Japan. The departments of gastroenterology, gastroenterological surgery, endocrinology, and the metabolic medicine departments in each hospital were listed, and the method of stratified random sampling was used to select departments for the survey [15]. The sampling rates were 5, 10, 20, 40, 80, 100 and 100% for the strata of general hospitals with less than 100 beds, 100–199 beds, 200–299 beds, 300–399 beds, 400–499 beds, 500 or more beds and university hospitals, respectively. To increase the efficiency of this survey, we added some relevant departments where many patients with GEP-NETs were expected to be treated. They were considered a special stratum, and were all selected. The study consisted of two surveys, each using a different questionnaire. In the first survey, a simple questionnaire was used to inquire about the number of patients with GEP-NETs who visited those departments and were treated in 2005. This questionnaire was directly mailed to the heads of 5,773 randomly selected departments with the

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abovementioned sampling rate. Returned questionnaires providing information on 951 patients (368 patients with PETs and 583 with GI-NETs) were received from 621 departments. Next, the second questionnaire was forwarded to these 951 patients, and it was completed and returned by 344 patients (152 with PETs, 192 with GI-NETs), a response rate of 36.2%. It requested detailed clinical information on the individual patients treated, including etiology, symptoms and procedures for diagnosing GEP-NETs, as well as complications, treatments and prognosis. Patients with PETs were classified according to clinical symptoms and analyzed from the viewpoint of the number of patients in each disease category, frequency of malignancy, association with multiple endocrine neoplasia type 1 (MEN-1), and prevalence of resection. GI-NETs were classified according to the anatomical location in the gut and analyzed with regard to the number and frequency of symptomatic patients, metastases, and resection. The diagnosis of GEP-NETs was left to the judgment of each institution. With regard to PETs, patients with clinical symptoms and elevated plasma hormone levels were diagnosed as having a functioning PET. On the other hand, patients without clinical symptoms and with no elevation of plasma hormone levels were diagnosed as having a non-functioning tumor (NF-PET), regardless of whether the hormone production was evaluated by immunohistochemical or mRNA detection in the tumor cells.

The estimation was based on the assumption that the mean number of patients among the departments that responded to the survey was equal to that among the departments that did not respond. The total number of patients was then corrected using the proportions of duplicate cases and inappropriate cases. The population of Japan in 2005 reported by the Japanese government was used to estimate the prevalence rate of GEP-NETs. The guidelines of the Nationwide Epidemiological Survey Manual [15], issued by the Research Committee on the Epidemiological of Intractable Diseases, Ministry of Health, Labour and Welfare, was used to estimate the crude incidence rate, and the prevalence rate was multiplied by the proportion of patients who were newly diagnosed with GEP-NETs in 2005.

Results

Epidemiology of PETs in Japan in 2005

On the basis of data derived from the first survey, the total number of patients treated for PETs in the year 2005 was estimated as 2,845 [95% confidence interval (CI) 2,455–3,507], and the overall prevalence was 2.23 per 100,000 population (95% CI 1.93–2.76). The total number of patients treated for functioning tumors was estimated as 1,627 (95% CI 1,404–2,005.6), and the overall prevalence was 1.27 per 100,000 population (95% CI 1.10–1.57). The total number of patients treated for insulinoma was estimated as 1,067 (95% CI 921–1,315), and the overall prevalence was 0.84 (95% CI 0.73–1.04). The total number of gastrinoma patients was estimated as 280 (95% CI 242–345), and the overall prevalence was 0.22 (95% CI 0.19–0.27). On the other hand, the total number of NF-PET patients was estimated as 1,218 (95% CI 1,053–1,453), and the overall prevalence was 0.95 (95% CI 0.82–1.17) (Table 1).

Table 1 Epidemiology of pancreatic endocrine tumors (PET) in Japan in 2005

Total number of patients treated for PETs	
Functioning tumors	1,627
Non-functioning tumors	1,218
Total number of PETs	2,845
Overall prevalence of PETs (per 100,000 population)	
Functioning tumors	1.27
Non-functioning tumors	0.95
Total number of PETs	2.23
Incidence rate of PETs (per 100,000 population)	
Functioning tumors	0.50
Non-functioning tumors	0.51
Total number of PETs	1.01

Furthermore, on the basis of the data obtained in the second survey, the incidence rate of PETs in 2005 was estimated as 1.01 per 100,000 population (95% CI 0.88–1.25). The incidence rate of functioning tumor was 0.50 (95% CI 0.44–0.62) and that of NF-PET was 0.51 (95% CI 0.43–0.64).

Distribution of PETs in Japan in 2005

The distribution of PETs in Japan in 2005 is shown in Table 2. Functioning tumors comprised 49.3% of PETs (95% CI 41.4–57.3). On the other hand, NF-PET showed the highest frequency, constituting 47.4% (95% CI 39.4–55.3). The next most frequent PETs were insulinoma (38.2%) and gastrinoma (7.9%). Glucagonoma, somatostatinoma, and VIPoma revealed low frequencies of 2.6, 0.7, and 0%, respectively.

Clinical features and diagnosis of PETs in Japan in 2005

Age and gender

With regard to the age of onset, 45.4% patients developed PETs in their 50s–70s (Fig. 1), while the peak age of onset

Table 2 Distribution of pancreatic endocrine tumors (2005)

Functioning tumors (%)	
Insulinoma	38.2
Gastrinoma	7.9
Glucagonoma	2.6
Somatostatinoma	0.7
VIPoma	0
Non-functioning tumors	47.4
No reply	3.3
Total	100

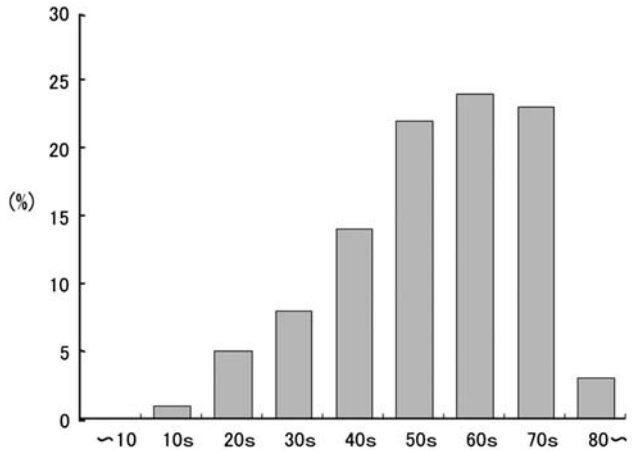

Fig. 1 The age distribution of onset of pancreatic endocrine tumors

was in the 60s (24.3%). The mean age at onset was 57.6 years (men 56.4; female 57.7). Males and females constituted 36.8 and 62%, respectively, of all patients. In 4.6% of responses, the sex was not specified. These results indicated that more females have PET than males in Japan (male:female 1:1.6) (Table 3).

Tumor location, size, number, and metastasis

With regard to tumor location, 38.2% of all PET patients had the lesion in the pancreatic head (95% CI 30.4–45.9), 31.6% in the pancreatic body (95% CI 24.2–39.0), and 32.9% in the pancreatic tail (95% CI 25.4–40.4). No significant difference in frequency was found between different tumor locations. The location was unknown in 3.9% patients, and no response regarding tumor location was given in 4.6% of cases. No significant correlation was detected between disease and tumor location.

The mean tumor size was 3.03 cm (Fig. 2). Tumors that were 1 cm or larger but smaller than 2 cm were found in the highest number of patients (38%), followed by tumors that were 2 cm or larger but smaller than 3 cm (15%). Tumors that were 3 cm or larger were found in 33% of patients. Interestingly, tabulation by disease showed that

Table 3 Clinical features of patients with pancreatic endocrine tumors (2005)

Mean age at onset	57.6 years (M 56.4, F 57.7)
M:F	1:1.6
Frequency of malignancy	21%
Mean tumor size	3.03 cm
Mean number of tumors	1.4
Diagnostic opportunity	
Symptomatic	60%
Health examination	24%
Mean duration of symptoms	21.7 months
Association with smoking status	None
Association with alcohol use	None
Presence of MEN-1	10%
Frequency of surgery	84%
Case-fatality rate	9.0%

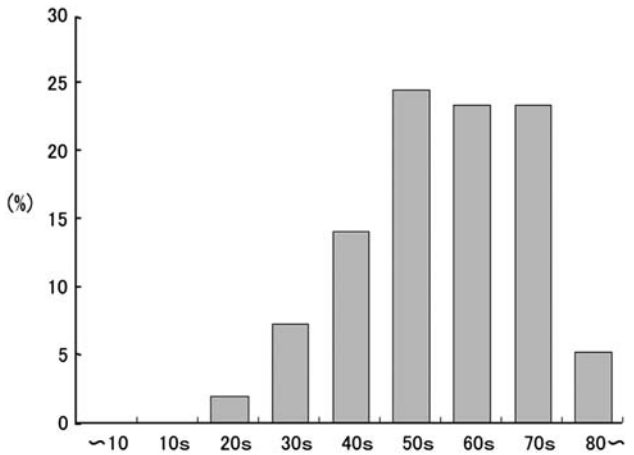

Fig. 2 The age distribution of onset of gastrointestinal neuroendocrine tumors

the tumors were 2 cm or larger in approximately 70% of NF-PET patients. Meanwhile, the tumors were smaller than 2 cm in approximately 70% of insulinoma patients. Tumors in insulinoma patients were small at the time of diagnosis. The disease could be diagnosed even when the tumors were small, probably because insulinoma is a symptomatic disorder.

The mean number of tumors per patient was 1.37. A single tumor was found in 82% of patients. A single tumor was observed in 76, 75, and 89% of patients with insulinomas, gastrinomas, and NF-PETs, respectively.

Distant metastasis was observed in 21% of all PET patients (95% CI 4.6–27.5), in 32.3% of NF-PET and 25% of gastrinoma patients, but only in 5.4% of insulinoma patients.

Multivariate analysis was performed with disease as the variable in order to ascertain whether there were any

correlations between location, size, number of tumors, and distant metastasis. A significant correlation was observed only in NF-PET between tumor size (2 cm or larger) and distant metastasis ($p = 0.01$).

Symptoms, diagnostic opportunity, smoking, and drinking

Symptomatic PET was found in 43% (95% CI 35.5–51.3). Sixty percent of patients with symptoms were diagnosed at their hospital visit (95% CI 52.1–67.7). Meanwhile, the disease was accidentally diagnosed in 24% (95% CI 17.5–31.2) of patients with no symptoms when they visited the hospital for a health checkup. The most frequent initial symptoms were hypoglycemia-derived signs (48.5%), followed by upper abdominal pain and back pain (17.8% each), diarrhea (6.9%), gastric/duodenal ulcer (6.0%), jaundice (3.0%), and rash (2.0%) (Table 4). The mean duration from the initial onset of symptoms until the diagnosis of disease was 21.7 months in the patients with symptoms. The most frequent duration range was 3 to <6 months (14%). Meanwhile, five or more years elapsed before diagnosis in 8% of patients.

Next, we reviewed the possible relationship between the onset of the PET and smoking/drinking and examined the correlations. Twenty-two percent (95% CI 15.7–29.0) were smokers, consuming 23.8 cigarettes a day for 25.4 years on average. A total of 42% (95% CI 33.6–49.3) drank alcohol. Five percent were heavy drinkers and 37% were occasional drinkers. However, no significant correlation was observed between development of PETs and smoking ($p = 0.31$) or drinking ($p = 0.26$).

Presence of multiple endocrine neoplasia type-1

Ten percent (95% CI 5.1–14.6) of PET patients concurrently had MEN-1. The highest percentage of concurrent MEN-1 was found in patients with gastrinoma (25%), followed by patients with insulinoma (14%). The percentage of NF-PET patients with MEN-1 was 6.1%. In the present study, concurrent MEN-1 was not found in any neuroendocrine tumor disease other than PET. Multivariate analysis showed no significant correlations between concurrent MEN-1 and age, sex, or tumor size.

Frequency of surgery and case fatality rate

Surgery was performed in 84% of PET patients. 90% in insulinoma, 83% in NF-PET, and 67% in gastrinoma. The resection rate was low in gastrinoma patients with a high malignancy rate. Mortality of PET patients was 9% (95% CI 4.6–13.8) in 2005, while the mortality of NF-PET patients was higher (14%).

Epidemiology of GI-NETs in Japan in 2005

On the basis of the first survey, the total number of patients treated for GI-NETs in the year 2005 was estimated as 4,406 (95% CI 3,321–5,420). The total numbers of patients treated for foregut, midgut, and hindgut tumors in this group were 1,338 (95% CI 1,009–1,646), 423 (95% CI 319–520), and 2,645 (95% CI 1,994–3,254), respectively. The overall prevalence of GI-NETs was 3.45 per 100,000 population (95% CI 1.93–4.24). The overall prevalences of foregut, midgut, and hindgut tumors were 1.05 (95% CI 0.59–1.29), 0.33 (95% CI 0.18–0.41), and 2.07 (95% CI 1.56–2.55), respectively (Table 5).

On the basis of the second survey, the incidence rate of PETs in 2005 was estimated as 2.10 per 100,000 population (95% CI 1.56–2.54). The incidence rates of foregut, midgut, and hindgut tumors in this group were 0.64 (95% CI 0.48–0.77), 0.20 (95% CI 0.15–0.24), and 1.26 (95% CI 0.94–1.52), respectively.

Table 4 Symptoms of patients with pancreatic endocrine tumors (2005)

Hypoglycemia-derived signs (%)	48.5
Upper abdominal pain/back pain (%)	17.8
Diarrhea (%)	6.9
Gastric/duodenal ulcer (%)	6.0
Jaundice (%)	3.0
Rash (%)	2.0
Others (%)	15.8

Table 5 Epidemiology of gastrointestinal neuroendocrine tumor (GI-NET) in Japan in 2005

Total number of patients treated for GIC	
Foregut	1,338
Midgut	423
Hindgut	2,645
Total number of GI-NETs	4,406
Overall prevalence of GICs (per 100,000 population)	
Foregut	1.05
Midgut	0.33
Hindgut	2.07
Total number of GI-NETs	3.45
Incidence rate of GICs (per 100,000 population)	
Foregut	0.64
Midgut	0.20
Hindgut	1.26
Total number of GI-NETs	2.10

Distribution of GI-NETs in Japan in 2005

The distribution of GI-NETs in Japan in 2005 is shown in Table 6. In this group, 30.4% (95% CI 25.2–38.4) of the patients' tumors were located in the foregut. The frequency of a midgut location was only 9.6% (95% CI 5.3–13.5). Most GI-NETs were located in the hindgut, at a rate of 60.0% (95% CI 50.8–64.8). In terms of the anatomical site, the rectum had the highest occurrence rate (55.7%) (95% CI 48.7–62.8), followed by the duodenum (16.7%) (95% CI 11.4–21.9), and the stomach (15.1%) (95% CI 10.0–20.2). Meanwhile, the occurrence of GI-NETs was very low in the colon (2.1%) (95% CI 0.1–4.1), jejunum (1.6%) (95% CI −0.2 to 3.3), and ileum (0.6%) (95% CI −0.2 to 3.3).

Clinical features and diagnosis of GI-NETs in Japan in 2005

Age and gender

With regard to the age of onset, 70.9% of patients developed GI-NETs in their 50s–70s; the peak age was in the 50s (23.9%) (Fig. 3). Mean age at onset was 59.8 years (men 61.3; female 57.3). In this group, 64.0 and 32.3% of patients were males and females, respectively. No responses regarding sex were given in 3.6% of cases. In Japan, PETs occurred more frequently in males than in females (2.1) (Table 7).

Table 6 Distribution of gastrointestinal neuroendocrine tumors (2005)

Foregut (esophagus/stomach/duodenum) (%)	30.4
Midgut (jejunum/ileum/vermiform appendix) (%)	9.6
Hindgut (large intestine/colon) (%)	60.0
Total (%)	100

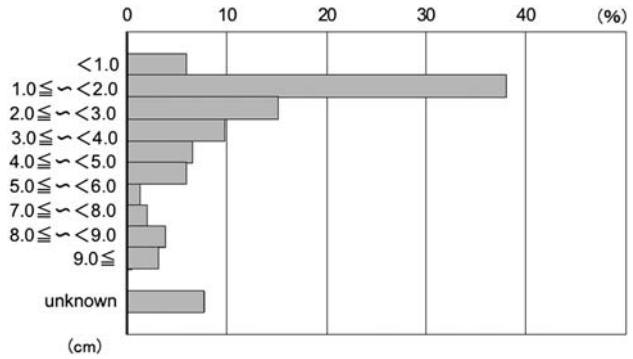

Fig. 3 The size distribution of pancreatic endocrine tumors

Tumor size, number, and metastasis

The mean tumor size was 1.34 cm. Tumors that were 0.5 cm or larger but below 1 cm were the most frequent (34%), followed by tumors that were 1 cm or greater but below 1.5 cm (27%) (Fig. 4). Tumors that were 2 cm or larger were found in 14% of cases.

The average number of tumors per patient was 2.12. A single tumor was found in 87% patients. With regard to the depth of invasion into the wall of the digestive tract, the submucosal layer (sm) accounted for the greatest proportion (51%) (95% CI 44.0–58.1), followed by the mucosal layer (m) (12%) (95% CI 7.4–16.6), the proper muscle (pm) (6%) (95% CI 2.8–9.7), and the serous membrane(s) (7%) (95% CI 3.6–11.0). Lymph node metastasis was observed in 9% (95% CI 5.3–13.5) of GI-NET patients. The incidence of distant metastasis by site was high in the ileum (66.7%) and jejunum (33%), but low in the rectum

Table 7 Clinical features of patients with gastrointestinal neuroendocrine tumors (2005)

Mean age at onset	59.8 years (M 61.3, F 57.3)
M/F	2:1
LN metastasis	4%
Metastasis to other organs	6%
Mean tumor size	1.34 cm
Mean number of tumors	2.1
Diagnostic opportunity	
Symptomatic	31%
Health examination	44%
Mean duration of symptoms	4.7 months
Association with smoking status	None
Association with alcohol use	None
Presence of carcinoid syndrome	3.4%
Presence of MEN-1	1.0%
Presence of type A gastritis	4.0%
Frequency of surgery	89%
Case-fatality rate	4.0%

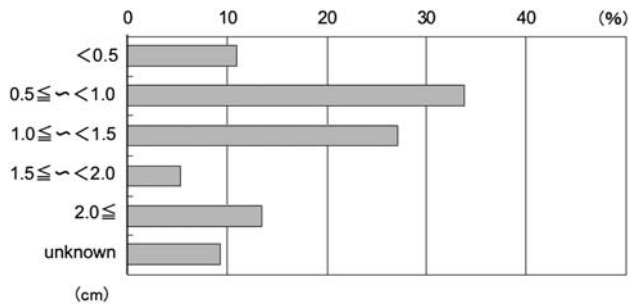

Fig. 4 The size distribution of gastrointestinal neuroendocrine tumors

(6%) and colon (0%). Multivariate analysis was performed to identify correlations between the site of lesion, tumor size, number of tumors, lymph node metastasis, and distant metastasis. A significant correlation ($p = 0.01$) was found only between the tumor size (≥1 cm) and lymph node metastasis ($p = 0.01$).

Symptoms, diagnostic opportunity, presence of MEN-1, smoking, and drinking

Symptomatic GI-NETs were observed in 3.4% of patients (95% CI 1.4–5.3). GI-NETs were diagnosed at the time of hospital visit in patients presenting with symptoms (31%) (95% CI 24.2–37.3). In as many as 44% (95% CI 37.2–51.3), GI-NETs were accidentally found at health examinations when patients visited the hospital without symptoms. The most frequent initial symptom was abdominal pain (27.1%), followed by fecal occult blood/bloody stool (24.3%), and constipation (10.0%) (Table 8). Diarrhea (4.3%) and flushing (1.4%) were low in frequency. In symptomatic cases, an average of 4.7 months elapsed from the development of initial symptoms until detection. The frequency of concurrent MEN-1 was low (1.0% of GI-NET patients) (95% CI 0.5–1.4). Next, we examined the relationship between the onset of GI-NETs and smoking/drinking. Twenty-six percent (95% CI 19.4–31.7) were smokers, consuming 20.8 cigarettes a day for 29.0 years, on average. A total of 39% (95% CI 33.6–49.3) were drinkers (8% were heavy drinkers and 31% were occasional drinkers). However, significant correlations were not observed between the onset of GI-NETs and smoking ($p = 0.31$) or drinking ($p = 0.34$).

Presence of type A gastritis

Because type A gastritis is thought to be involved in the development of gastric GI-NETs, we examined the coexistence of type A gastritis in this study. Type A gastritis coexisted in 4.2% (95% CI 1.3–7.0) of GI-NET patients, and the foregut was the site of the lesion in all cases. Type A gastritis coexisted in 77.1% of patients with foregut lesions. The frequency of concurrent type A gastritis was particularly high in patients with gastric GI-NETs (87.1%). Analysis of the correlation between the existence of type A gastritis and foregut lesions showed a significant correlation ($p < 0.001$).

Table 8 Symptoms of patients with gastrointestinal neuroendocrine tumors (2005)

Abdominal pain/back pain (%)	27.1
Fecal occult blood/bloody stool (%)	24.3
Constipation (%)	10.0
Nausea (%)	8.6
Diarrhea (%)	4.3
Appetite loss (%)	4.3
Ileus (%)	2.9
Anemia (%)	2.9
Flushing (%)	1.4
Others (%)	18.4

Frequency of resection and case fatality rate

Among all of the GI-NETs, 89.1% were resected by surgery or endoscopic resection. Mortality of GI-NET patients was 4.2% (95% CI 1.3–7.0) in 2005. Mortalities according to the site of lesion were 4.9, 0, and 3.6% in the foregut, midgut, and hindgut, respectively.

Discussion

NETs are thought to be rare tumors characterized by their capacity for hormone production; they often follow an indolent course [16]. Recent data have shown a significant increase in the diagnosed incidence of NETs over the past decades [17, 18]. However, the epidemiological data regarding NETs in Japan remain unclear. Therefore, only limited research exists to serve as a basis for discussion among Japanese investigators with regard to the diagnosis and treatment of this disease. We believe that a detailed, nationwide survey of the epidemiology, diagnosis, and treatment of NETs in Japan should provide information that can be used to begin to establish the importance of GEP-NETs in Japan and to enable better planning for future directions in research into and management of GEP-NETs. In the present study, we elucidate for the first time the epidemiology of GEP-NETs in Japan by analyzing the replies to questionnaires sent to medical institutions all over Japan.

In this study, the total number of patients treated for PETs in the year 2005 was estimated as 2,845, the overall prevalence of PETs was 2.23 per 100,000 population, and the incidence rate of PETs in 2005 was estimated as 1.01 per 100,000 population. Recently, Yao et al. [17] reported that the incidence rate of PETs in the United States between 2002 and 2004 was estimated to be 0.32 per 100,000 population per year using the SEER 9 registry data. An ethnic survey showed that the incidence rate of PET per 100,000 population was 0.32 in Caucasian Americans, 0.36 in African Americans, 0.25 in Asian Americans, and 0.20 in Indian/Alaskan/Pacific Island natives [17]. Since the incidence rate of PET in Asian Americans in the study by Yao et al. was only approximately 70% of the levels in White or African Americans, this result indicated that the incidence rate in Asian

Americans might be lower. However, the data on Asian Americans cannot simply be applied to the Japanese people too because of differences in climate, environment, and diet. Our study data suggest that the incidence of new-onset PET in 2005 was approximately 1.01 per 100,000 population in Japan, which was approximately three times the annual incidence of new-onset PET in the United States (0.32 per unit population) [17] and approximately four times that of Asian Americans. The possible reasons for the higher number of pre-existing and new PET patients in Japan may be the improvement in diagnostic tools used during health examinations, including routine abdominal ultrasonography and easy access to advanced imaging technology (CT, MR, etc.) [14]. Such speculation is supported by the fact that as many as 24% of our study subjects were found to have PET accidentally during routine health examinations, although they did not have any symptoms. Furthermore, according to Yao et al. [17], more males than females had PETs (1.4:1); however, our survey results in Japan were different: females were found to be more frequently affected than males (1:1.6).

On the other hand, the total number of patients treated for GI-NETs in the year 2005 in Japan was estimated as 4,406, the overall prevalence of GI-NETs was 3.45 per 100,000 population, and the incidence rate of GI-NETs in 2005 was estimated as 2.10 per 100,000 population. The annual incidence of new-onset GI-NETs (2002–2004) in the United States was 2.53 per 100,000 population [17], which was similar to the incidence rate of 2.10 in Japan. However, there were marked differences in the distribution of GI-NETs in our present study and previous reports in Western countries. The distribution of GI-NET lesions in new patients in the United States is reported to be 19.4% in the foregut, 38.7% in the midgut, and 41.9% in the hindgut. Similarly, 30–60% of GI-NETs were reported to be midgut GI-NETs in European countries [6, 19, 20]. In contrast, in our study of the Japanese population, 30.4% were in the foregut, 9.6% in the midgut, and 60.0% in the hindgut. Interestingly, the data for Asian Americans alone (21.2% in the foregut, 8.2% in the midgut and 70.6% in the hindgut) [17] were similar to the present Japanese data, where the incidence in the midgut was small and the incidence in the hindgut was high. We theorize that the difference in GI-NET incidence location between Japanese and those in Western nations may be due to racial or ethnic differences, although there is no scientific evidence to confirm this hypothesis. In addition, one of the reasons for the elevation of hindgut GI-NET frequency in Japan may be that periodical health examinations that include colonoscopy are common in Japan, so small GI-NET tumors are easily detected [14]. More males had GI-NETs than females in the United States (1.2:1) [17], and the present study also showed that the number of male GI-NET patients was larger than the number of females in Japan (2:1).

Patients with NETs belonging to the MEN-1 syndrome present deletions on chromosome 11q13 [2]. The rates of association with MEN-1 in functional PETs were not different between Japan and Western nations [2, 6]. However, the association of MEN-1 in NF-PETs was observed in only 6.1% of cases in Japan. Furthermore, the presence of MEN-1 in GI-NETs in this study was only 1.0%, whereas approximately 30% of NF-PETs were reported to be associated with MEN-1 in Western nations [2]. The difference in the frequency of MEN-1 in NF-PETs and GI-NETs between Japan and Western nations may be due to racial differences.

Insulinoma is reported to be malignant in 5–15% of cases, whereas the other PETs are malignant in 50–90% of cases, with metastases usually developing in the regional lymph nodes initially, in the liver later, and subsequently at distant sites [21]. Furthermore, a recent analysis of prognostic factors in NF-PET revealed that poor differentiation, nodal metastases, liver metastases, Ki-67 >5% and weight loss were significantly associated with mortality [22]. Our study in Japan also showed that only 5.4% of insulinoma patients had distant metastases, whereas as many as 32.3% of NF-PET and 25% of gastrinoma patients had distant metastases. These results were not considerably different from the overseas results. In contrast, symptomatic GI-NETs and distant metastases were observed in only 3.4 and 6%, respectively, of GI-NET cases. Furthermore, distant metastasis of colon GI-NETs was not observed. In Western nations, it has been reported that approximately 10–60% of GI-NET cases are symptomatic and malignant GI-NETs [6, 23, 24]. Thus, comparatively large differences between Japan and Western nations can be noted. An interesting report on 2,459 cases of colon GI-NET in the United States has recently been published [25]. In this report, lymph node metastases were observed in 48% and distant metastases were present in 24%. Furthermore, a multivariate analysis revealed that differences in age, size, depth of invasion, lymph node involvement, distant metastasis, and location were significant. The ratio of hazard to overall survival significantly increased, particularly in patients with the following characteristics: 65 years or older, Caucasian, tumor size $\geq$1 cm, and depth of invasion into or beyond the muscularis propria. In our study, we observed a significant relationship only between size (>1 cm) and lymph node metastases in all GI-NET cases based on multivariate analysis. Furthermore, we observed a significant relationship only between size (>2 cm) and distant metastasis in all NF-NET cases based on multivariate analysis. This finding suggests that, even in NF-PET patients, distant metastasis may occur more frequently when the tumor is 2 cm or larger. Although the

relationship between MEN-1 and distant metastasis could not be examined in NF-PET patients in our study, this relationship was examined in a recent European paper [26]: MEN-1 patients with NF-PETs of 2 cm or less did not have shorter life expectancies than those who did not have any pancreaticoduodenal tumors. This report suggests that surgery may not be beneficial for MEN-1 patients with NF-PETs of 2 cm or less.

In the present study, we examined the effect of smoking and alcohol consumption on NETs; however, no significant correlation with NETs was detected. Recently, the independent effects of multiple risk factors associated with NETs were reported [27]. In that report, similar to our results, smoking and alcohol consumption were not associated with NETs. Interestingly, the report noted that a family history of cancer was a significant risk factor for all GEP-NETs, and that a long-term history of diabetes mellitus was a significant risk factor for gastric NETs, particularly in women. Therefore, in future research it will be important to focus on diabetes as a risk factor for the development of gastric NETs, especially among women with a positive family history of cancer.

Chronic hypergastrinemia is associated with enterochromaffin-like (ECL) cell hyperplasia, which may progress to gastric GI-NET. In type A gastritis, which is characterized by hypergastrinemia caused by negative feedback due to reduced gastric acid secretion, atrophic gastritis may be intensively observed in the gastric body, and GI-NETs have been shown to frequently develop in this condition [28]. Rindi et al. [29] classified gastric GI-NETs into three types: type 1 is associated with type A gastritis and hypergastrinemia; type 2 is associated with MEN-1 with Zollinger–Ellison syndrome and hypergastrinemia, and type 3 is a gastric GI-NET with no specific association. In our present study, type A gastritis coexisted in 4.2% of GI-NET patients, and the site of the lesion was the foregut in all of these patients with type A gastritis. Gastric GI-NET coexisted in 77.1% of patients with foregut lesions. Interestingly, concurrent type A gastritis was especially frequent among gastric GI-NET patients (87.1%).

Recently, prognostic factors of NETs were examined and have come to be well understood [10, 20, 30, 31]. Panzuto et al. [30] showed that the overall 5-year survival rate of NETs was 77.5%, and that pancreatic site, poor degree of tumor cell differentiation, and distant extrahepatic metastases are the major negative prognostic factors. Furthermore, a recent study by Pape et al. [20] showed that overall, the 5- and 10-year survival rates were 78 and 63%, respectively, and that time to progression after initial diagnosis was significantly shorter in pancreatic as compared with ileal NET. Furthermore, in this report, survival analysis revealed a significantly better clinical outcome for primary tumors smaller than 25 mm, absence of metastasis, absence of any clinical symptoms, positive immunohistochemical staining for chromogranin A and a lower Ki-67 index [20]. In the present study, we could not examine the long-term outcome in Japan. Therefore, we should consider risk stratification in the future management of NETs.

The biochemical diagnosis of NETs is based on hormone and amine release. Chromogranin A, which is used as a primary marker in Western nations, has been reported to increase in the plasma in 50–80% of patients with NETs, and has been shown to correlate with tumor size [19, 32]. However, chromogranin A is not generally used in Japan. Similarly, somatostatin receptor scintigraphy, which is used for the diagnostic imaging of PET location in Western nations [32–35], is not commonly used in Japan because it is not covered by health insurance. Since the introduction of chromogranin A as a diagnostic marker is desirable in Japan, NET Work Japan is currently collecting chromogranin A data in Japanese GEP-NET patients in order to obtain coverage by government health insurance.

These latest findings on GEP-NET were obtained through a nationwide field and epidemiological survey in Japan. Future studies should include more precise analysis such as central review of histopathological slides to confirm the diagnosis, but notable differences between Japan and Western nations were observed in the frequency of GI-NETs by site, frequency of symptomatic GEP-NETs, rate of distant metastasis, and coexistence of MEN-1 in NF-PET patients. Although no evidence was available concerning the basis of these differences, ethnicity is likely to be a factor.

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