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# Incidence and clinical characteristics of gastroenteropancreatic neuroendocrine tumor in Korea: a single-center experience

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**Background/Aims:** Neuroendocrine tumors (NETs) may originate from heterogeneous neuroendocrine cells. The incidence is increasing worldwide, and World Health Organization (WHO) updated its classification in 2010. We investigated clinical characteristics of gastroenteropancreatic NETs in a single center.

**Methods:** Clinicopathologic characteristics of patients with pathologically confirmed gastroenteropancreatic NET in Seoul St. Mary Hospital from March 2009 to August 2011 were retrospectively analyzed. The grade and stage were determined according to WHO 2010 classification and TNM Staging System for Neuroendocrine Tumors (7th ed., 2010) of American Joint Committee on Cancer.

**Results:** One hundred and twenty-five patients (median age, 50; male, 61.3%) were analyzed. Among 100,000 patients who visited the hospital, incidence was 24.1. Only two patients (1.6%) had a functional NET. The rectum (n = 99, 79.8%) was most common primary site and found in early stage. The prevalence by stages was 84.7% stage I, 8.9% stage IV, 4.8% stage II, and 1.6% stage III. The pathology grading was 74.5% grade 1, 12.7% grade 2, and 12.7% grade 3. Tumor stage correlated positively with pathologic grade (Spearman's rank correlation coefficient, 0.644).

**Conclusions:** Wide range of clinicopathological features of Korean gastroenteropancreatic NETs were demonstrated using WHO 2010 classification. Rectal NET was most frequent and found in early stage.

**Keywords:** Neuroendocrine tumors; Gastro-enteropancreatic neuroendocrine tumor; Epidemiology; Incidence; Survival

## INTRODUCTION

Neuroendocrine tumors (NETs) may originate from heterogeneous neuroendocrine cells in various organs. Most NETs are more indolent than other epithelial malignancies, although they can be aggressive and resistant to therapy. NETs can occur in the gastrointestinal tract, pancreas, lung, parathyroid gland, adrenal gland, pituitary gland, or parafollicular C cells of the thyroid gland. The distribution of NETs differed according to ethnicity in the Analysis of the Surveillance, Epidemiology, and End Results (SEER) registry of the USA. In this registry, most common sites were the lung in Caucasians and the rectum in African American and Asian/Pacific Islander populations.

The annual incidence of NETs was 5.25/100,000 in



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the SEER registry in 2004, which represents a 4-fold increase compared with the incidence in 1973 [1,2]. The rate of increase was greater in the cancer registry of Norway [3]. In Asians, the incidence has been reported as 2.2/100,000, and the percentage of NETs with a gastroenteropancreatic origin was 58.2% in the rectum, 11.4% in the pancreas, 9.5% in the stomach, 5.6% in the duodenum, 5.6% in the jejunum/ileum, 7.0% in the colon, and 2.8% in the appendix [1]. In data from Japan collected using a nationwide stratified random sampling method, the prevalence and annual incidence rates of pancreatic NETs were 2.23/100,000 and 1.01/100,000, respectively. For gastrointestinal NETs, the prevalence and the annual incidence rates were 3.45/100,000 and 2.10/100,000, respectively. Gastrointestinal NETs comprised 30.4% of foregut, 9.6% of midgut, and 60.0% of hindgut NETs [4].

The characteristics of NETs, such as the cell of origin, bioactive products, and markers of proliferative activity have been studied for several decades [5-10]. The diagnosis and treatment guidelines for NETs in the World Health Organization (WHO) and European Neuroendocrine Tumor Society (ENETS) classifications have become more sophisticated during this time [11,12]. The WHO classification has served as a basis for establishing the criteria for practical management, as reflected in the guidelines of many scientific societies [13-17]. However, few studies have reported on the application of the most recent WHO 2010 classification. In this study, we surveyed the incidence and clinical features of gastroenteropancreatic NETs according to the new WHO classification in single tertiary center in Korea.

## METHODS

The patient cohort from Seoul St. Mary Hospital from March 2009 to August 2011 was obtained. Pathology reports were searched to identify patients diagnosed with a carcinoid tumor, NET, small cell carcinoma of the gastrointestinal tract, or functional pancreatic endocrine tumors such as insulinoma, gastrinoma, glucagonoma, VIPoma, and so on. One hundred and twenty-five cases were found. One case of poorly differentiated gallbladder carcinoma with neuroendocrine features was excluded because it did not meet the criteria of mixed adenoneuroendocrine carcinoma in the WHO 2010 classification.

The following clinicopathological characteristics of all patients were collected from medical records: gender, age, symptoms, primary location, tumor stage, tumor size, functional status of the tumor, date of the initial diagnosis, treatment modality, and date of death or the last follow-up. The tumor grade was determined according to the WHO 2010 classification and the Union for International Cancer Control (UICC) TNM Staging System for Neuroendocrine Tumors (7th ed., 2010) of the American Joint Committee on Cancer.

## RESULTS

The number of patients with a pathology diagnosis was 124. Among the 100,000 patients who visited the hospital, the incidence was 24.1. The characteristics of the patients and tumors are presented in Table 1. The median age was 50 years (range, 27 to 79), and males comprised 61.3% of the population. Only two patients (1.6%) had a functional NET: one was an ectopic adrenocorticotropic hormone (ACTH)-secreting tumor (pancreatic NET, serum ACTH level 863.93 pg/mL) and the other a carcinoid

**Table 1. Clinical features of the patients**

| Variable | Value |
|---|---|
| Male sex | 78 (61.3) |
| Age, yr | 50 (27–79) |
| Functional tumor | 2 (1.6) |
| Presence of MEN I | 0 |
| Accompanying symptoms | |
| No symptom | 91 (73.4) |
| Abdominal pain | 11 (8.9) |
| Bowel habit change | 4 (3.2) |
| Weight loss | 4 (3.2) |
| Diarrhea | 3 (2.4) |
| Hematochezia | 3 (2.4) |
| Jaundice | 2 (1.6) |
| Abdominal mass | 2 (1.6) |
| Edema | 2 (1.6) |
| Tenesmus | 1 (0.8) |
| Dyspepsia | 1 (0.8) |

Values are presented as number (%) or median (range).
MEN, multiple endocrine neoplasia type 1.

syndrome (rectal NET with hepatic metastasis, serum chromogranin level 105.79 ng/mL), and there were no cases of multiple endocrine neoplasia type 1. Most of the patients (n = 91, 73.4%) were asymptomatic and had been diagnosed at a routine health examination. The symptoms were not specific and included abdominal pain, change in bowel habits, and weight loss.

The distribution of primary sites is listed according to location in Table 2. The rectum (n = 99, 79.8%) was the most common primary site. Other primary sites were the duodenum (n = 7, 5.6%), pancreas (n = 6, 4.8%), stomach (n = 4, 2.4%), colon (n = 3, 2.4%), liver (n = 2, 1.6%), gall bladder (n = 2, 1.6%), and appendix (n = 1, 0.8%).

The stage and histological characteristics are shown in Table 3. The most common stage was stage I (84.7%), followed by stage IV (8.9%), stage II (4.8%), and stage III (1.6%). The liver (n = 10) was the most common metastatic site. Other metastatic sites were bone (n = 2), brain (n = 1), and pelvic cavity (n = 1). The most common histological grade was G1 (74.5%), followed by G2 (13.7%) and G3 (11.8%). The primary tumor size was larger in tumors in the pancreas and liver compared with tumors in other sites. Pancreatic and hepatobiliary NETs appeared to be diagnosed at a higher and more aggressive pathological stage in than were other gastrointestinal NETs, although the number of cases was small. Colorectal NETs were diagnosed at an earlier stage compared with duodenal and gastric NETs. The median primary tumor size was significantly smaller for G1 and G2 tumors than for G3 tumors (5.7 ± 4.0 mm vs. 53.3 ± 43.8 mm, $p < 0.01$). Tumor stage correlated positively with histological grade (Spearman's rank correlation efficient, 0.644; $p < 0.01$).

Ninety rectal NET lesions were endoscopically resected, including endoscopic mucosal resection (EMR) in 64 patients and endoscopic submucosal dissection in 26 patients. Seven patients received surgical treatment after endoscopic resection because of a positive resection margin in five patients, and suspicion of adenocarcinoid tumor in one patient. One patient received a hepatectomy because of delayed diagnosis of metastasis after EMR. Finally, 14 patients with a rectal NET received surgery, which included eight transanal resections, five low anterior resections, and one hepatic wedge resection. Among the five cases of margin-positive rectal NETs, there was no remaining NET found in the surgically removed tissue. There was no recurrence after endoscopic resections during the follow-up (mean, 54 months). Other modalities of treatment were chemotherapy for two patients (one as adjuvant chemotherapy and one after recurrence), and one each of transarterial embolization, radiotherapy, and somatostatin antagonist. Three patients with hepatic metastasis died at 9, 16, and 40 months after their initial diagnosis.

**Table 2. Primary site of neuroendocrine tumors**

| Site | No. (%) |
|---|---|
| Rectum | 99 (79.8) |
| Duodenum | 7 (5.6) |
| Pancreas | 6 (4.8) |
| Stomach | 4 (3.2) |
| Colon | 3 (2.4) |
| Liver | 2 (1.6) |
| Gall bladder | 2 (1.6) |
| Appendix | 1 (0.8) |

Among the seven patients with a duodenal NET, four patients received laparoscopic wedge resection, and two patients received endoscopic resection. There was no tumor recurrence in these patients during the follow-up (median, 51 months). One patient with a duodenal NET was managed supportively because of hepatic metastasis, and this patient died 1 month after the initial diagnosis.

Among the six patients with a pancreatic NET, four received surgery, which included a pylorus-preserving pancreatoduodenectomy, a laparoscopic distal pancreatectomy, debulking surgery with gastrojejunostomy, and a distal pancreatectomy with left nephrectomy. Postoperative radiotherapy and adjuvant systemic chemotherapy were given to two patients with a pancreas tail lesion. There was no recurrence for during the 52- and 55-month follow-ups in these patients. Two patients received supportive care after surgery, and two received systemic chemotherapy without surgery with a median survival of 9 months.

Among the four patients with a gastric NET, three patients received endoscopic resection, and there was no tumor recurrence in these patients during the follow-up (median, 51 months). One patient received a total gastrectomy and systemic chemotherapy because of an incomplete resection for direct pancreatic invasion, and this patient died 15 months after the initial diagnosis.


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**Table 3. Histopathologic characteristics and stage**

| Characteristic | Rectum (n = 99) | Duodenum (n = 7) | Pancreas (n = 6) | Stomach (n = 4) | Colon (n = 3) | Liver (n = 2) | Gall bladder (n = 2) | Appendix (n = 1) |
|---|---|---|---|---|---|---|---|---|
| Tumor size, mm | 5.0 (1–21) | 8 (6–38) | 59 (13–160) | 5 (5–35) | 3 (3–6) | 85 (70–100) | 32 (30–34) | 1 |
| Metastasis | | | | | | | | |
| Lymph node | 3 (3.0) | 1 (14.3) | 4 (66.7) | 0 | 0 | | 2 (100) | 0 |
| Liver | 3 (3.0) | 1 (14.3) | 3 (50.5) | 0 | 0 | 2 (100) | 1 (50) | 0 |
| Stage | | | | | | | | |
| I (n = 105) | 93 (93.9) | 4 (57.1) | 1 (16.7) | 3 (75.0) | 3 (100) | 0 | 0 | 1 (100) |
| II (n = 6) | 1 (1.0) | 2 (28.6) | 2 (33.3) | 0 | 0 | 0 | 1 (50) | 0 |
| III (n = 2) | 2 (2.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IV (n = 11) | 3 (3.0) | 1 (14.3) | 3 (50.0) | 1 (25.0) | 0 | 2 (100) | 1 (50) | 0 |
| Histologic grade[a] | | | | | | | | |
| G1 (n = 76) | 63 (81.8) | 5 (71.4) | 1 (16.7) | 3 (75.0) | 3 (100) | 0 | 0 | 1 (100) |
| G2 (n = 13) | 12 (15.6) | 1 (14.3) | 0 | 0 | 0 | 0 | 0 | 0 |
| G3 (n = 13) | 2 (2.6) | 1 (14.3) | 5 (83.3) | 1 (25.0) | 0 | 2 (100) | 2 (100) | 0 |

Values are presented as median (range) or number (%).
[a]Available in 77 of rectal neuroendocrine tumors.

Among the three patients with a colonic NET, all patients received endoscopic resection. One patient received right hemicolectomy due to elevated Ki-67 (5% to 7%) and a positive resection margin. One patient received anterior resection because of a positive resection margin. There was no remaining NET found in the surgically removed tissue. There was no tumor recurrence in colonic NET patients during the follow-up (median, 57 months).

One patient with a hepatic NET received surgery and adjuvant systemic chemotherapy because of a remnant tumor, and this patient survived for 4 months. The other patient with a hepatic NET was managed supportively because brain metastasis, and this patient survived for 2 months. Two cases of gallbladder NETs which had been suspected cholecystitis were diagnosed as NETs pathologically after surgery. One patient received an additional curative hepatectomy and adjuvant systemic chemotherapy, and tumor recurrence was found in the pelvis 46 months later. The tumor was excised, and this patient was given second-line chemotherapy. The other patient received systemic chemotherapy because of multiple hepatic metastases and survived for 10 months.

## DISCUSSION

This study demonstrated wide range of clinicopathological features of Korean gastroenteropancreatic NETs using WHO 2010 classification with long-term follow-up in single tertiary hospital. Rectal NETs were the most frequent type of gastroenteropancreatic NET and were found at early stage at the time of diagnosis in this study. Hepatobiliary NETs were diagnosed at later stages and showed worse prognosis than other gastroenteropancreatic NETs. This study showed that tumor grade and stage according to WHO 2010 classification and TNM Staging System for Neuroendocrine Tumors (7th ed., 2010) of American Joint Committee on Cancer were correlated positively. Most studies of gastroenteropancreatic NETs have involved patients in Western countries, and there are a few Japanese and Korean reports of gastroenteropancreatic NETs [4,18,19]. However, little has been published on the epidemiology of NETs since the release of the WHO 2010 classification. This study may provide useful information for the further characterization of gastroenteropancreatic NETs in Korean populations.

It is recommended that NETs should be classified using the WHO 2010 classification [11]. The previous WHO 2000 classification had not achieved widespread

acceptance in diagnostic practice in the USA for several reasons: (1) the embedding of stage-related information within the grading system, (2) the complicated clinicopathological classification schemes, and (3) the category "uncertain behavior," which has met with resistance from both clinicians and pathologists [2]. The ENETS has recently proposed two complementary classification tools: a grading classification and a site-specific staging system [12,20]. The prognostic validity of the UICC TNM system as proposed by the ENETS has been established [2,21-23], but similar validation studies are needed for the recently introduced WHO 2010 and UICC TNM (7th edition) classification and staging schemes. In this study, tumor grade correlated significantly and positively with stage.

The incidence of NETs in this single-center study was 24.1/100,000, which is much higher than the population-based rate. This high incidence suggests that physicians, including endoscopists and radiologists, should be aware of the disease entity, its increasing incidence, and its even higher incidence in tertiary referral hospitals. Although the gastroenteropancreatic NET is a relatively rare tumor in Korea, a remarkable increase of the incidence of gastroenteropancreatic NETs was also reported [19].

In the SEER registry, the epidemiological data showed a difference between Asian Americans and other populations. Rectal NETs occurred at a markedly high frequency among Asian/Pacific Islander and American Indian/Alaskan native patients, and jejunal/ileal NETs were common in white and African American patients [1]. However, the data cannot be applied simply to the Korean people because of differences in climate, environment, and diet. In our study, the distribution of the primary tumor sites, as shown in Table 2, indicated a higher percentage of rectal NETs than that in the SEER database and in a Japanese nationwide survey [1,4]. About half of gastroenteropancreatic NETs were located in rectum and rectal NETs was most common gastroenteropancreatic NETs in Korean reports [18,19,24]. Most of the patients were symptom free and were diagnosed with a NET during routine health examination. Only two functional NETs were found in our patient cohort, giving an incidence of 1.7%, which is far lower than the 30% reported in other studies [25-27]. Together with a previous Japanese study [4], our data suggest that there is a difference in the prevalence of functional NETs between Western and Asian countries. This might be explained by differences in hormones or other characteristics between populations. In addition, the widespread use of endoscopy for cancer screening likely contributed to the higher percentage diagnosed in a routine health examination and nonfunctional NETs found at an early stage. The incidence of gastroenteropancreatic NETs has been on the rise, particularly in the rectum

Hepatobiliary NENs was reported as an independent predictor for poor outcome in previous Korean studies [18,19]. Although our study included small cases of hepatobiliary NETs, these NETs were diagnosed at later stages and showed worse prognosis than gastrointestinal NETs. Among gastrointestinal NETs, rectal NETs had an earlier stage than gastric/duodenal NETs. The percentages of stage II to IV of rectal NETs and gastric/duodenal NETs were 6.7% and 36.4%, respectively. The overall rate of nodal or distant metastasis was lower than in other studies [28-30]. The higher rates of rectal NETs and asymptomatic NETs, and lower rate of metastasis could be explained by the easy access to endoscopic examination in the Korean medical system. The risk of lymph node metastasis was reported to be low in rectal NETs with sizes smaller than 10 mm [31]. These lesions can be treated by regional treatments including endoscopic resection. Endoscopic resection was a major treatment modality for rectal NETs in this study and other Korean reports [18,31]. Nonspecific symptoms of hepatobiliary and pancreatic NETs may elude early diagnosis. The early diagnosis of NETs at those organs can be a future topic of study.

Our study had the following limitations. There might be limited information of included patients such as omission of histologic grade data in some rectal NETs due to retrospective study. Number of patients other than rectal NETs was small. Considering low incident rate of gastroenteropancreatic NETs, large scaled multicenter study is required to investigate nature of gastroenteropancreatic NETs in Korea.

In conclusion, this study demonstrates a wide range of clinicopathological features of gastroenteropancreatic NETs in Koreans. The new WHO 2010 classification was applied in the characterization of recently diagnosed NETs in a single tertiary center. Rectal NETs were the most frequent type of gastroenteropancreatic NET


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and were found at early stage at the time of diagnosis. Our findings may provide information for the diagnosis and treatment of patients with gastroenteropancreatic NETs.

## KEY MESSAGE

1. Rectal neuroendocrine tumors (NETs) were the most frequent type of gastroenteropancreatic NET and were found at early stage at the time of diagnosis in Korea.
2. Hepatobiliary NETs were diagnosed at later stages and showed worse prognosis than other gastroenteropancreatic NETs.
3. Tumor grade and stage according to World Health Organization 2010 classification and TNM Staging System for Neuroendocrine Tumors (7th ed., 2010) of American Joint Committee on Cancer were correlated positively.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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