

The Clinicopathological Characteristics of Gastrointestinal Neuroendocrine Tumors; An Analysis of 65 Cases

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Background : This study was designed to investigate gastrointestinal neuroendocrine tumors with an emphasis on their clinicopathological characteristics. **Methods :** Sixty-five cases were reviewed and classified as typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SmCC). We performed immunohistochemistry to characterize the expression of the immunoreactivity for synaptophysin, chromogranin, gastrin, somatostatin, thyroid transcription factor-1, p53 and Ki-67. **Results :** Most commonly, the tumors were located in the rectum (54%), followed by the stomach (23%) and colon (9%). Histologically, the tumors were classified as 49 TCs, 4 ACs, 6 LCNECs and 6 SmCCs. Most tumors were stained positive for synaptophysin and/or chromogranin. Four LCNECs and one SmCC were p53-positive. The carcinoids revealed a low level (<5%) of reactivity for Ki-67, while $\geq 30\%$ of the cells showed reactivity for Ki-67 in the majority of LCNECs and SmCCs. Six patients with metastatic carcinoids were older than those patients without metastasis (64 vs 48 years, respectively, $p=0.004$). Furthermore, the size of tumors was larger for the patients with metastatic carcinoids than for the patients with nonmetastatic carcinoids (2.3 vs 0.5 cm, respectively, $p=0.005$). **Conclusion :** Old age, large tumor size and muscle invasion are associated with high grade neuroendocrine tumor and lymph node metastasis for those patients with carcinoids.

Key Words : Gastrointestinal tract; Carcinoid tumor; Small cell carcinoma; Neuroendocrine carcinoma; p53; Ki-67

Neuroendocrine cells are distributed throughout the body. They form either small organs (*i.e.* anterior pituitary), distinct cell clusters within other tissues (*i.e.* pancreatic islets), or a network of cells that's dispersed in the thymus, thyroid, lung and gastrointestinal tract.¹ Although the gastrointestinal tract has the largest population of neuroendocrine cells, neuroendocrine tumors of the gastrointestinal tract are relatively rare.

Neuroendocrine tumors encompass various tumors that range from low grade to high grade. They are classified into typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SmCC) in the lung. At extrapulmonary sites that include the gastrointestinal tract, the diagnostic criteria and terminology for neuroendocrine tumors show slight variations, even though it has been proposed to classify them according to their pulmonary counterparts in the uterine cervix.²

According to the WHO classification of neuroendocrine tumors of the gastroenteropancreatic system in 2000, these tumors are

divided into well-differentiated neuroendocrine tumors that show either benign behavior or uncertain malignant potential, well-differentiated neuroendocrine carcinomas that are characterized by low-grade malignancy, and poor differentiated (usually small cell) neuroendocrine carcinomas of high-grade malignancy.³ The classifications are then subdivided on the basis of the localization and biology of the tumors. This classification is difficult to apply to gastrointestinal neuroendocrine tumors due to the system's complexity. Furthermore, LCNEC is not clearly defined, despite the fact that gastrointestinal neuroendocrine tumors are obviously derived from the neuroendocrine cell system. In this study, we categorized gastrointestinal neuroendocrine tumors based on the classification of neuroendocrine tumors of the lung in order to simplify the diagnostic criteria.

Immunohistochemical staining for synaptophysin and chromogranin was done to evaluate how useful these markers are for making the diagnosis of gastrointestinal neuroendocrine tumors. The expressions of p53 and Ki-67 were studied to evaluate their

usefulness as biologic markers. In addition, the immunoreactivity for gastrin and somatostatin was evaluated to investigate whether or not the gastrointestinal tumors were functioning. Finally, we also performed immunostaining for thyroid transcription factor-1 (TTF-1), which is a marker that's commonly expressed in pulmonary high grade neuroendocrine carcinomas.

MATERIALS AND METHODS

Patients

Cases were selected if the tumor cells showed the histological features of neuroendocrine cells, as was confirmed by their immunoreactivity for synaptophysin, chromogranin A, and/or neuron specific enolase. Sixty-five cases of neuroendocrine tumors

of the gastrointestinal tract were initially retrieved from the Pathology File of Korea University Medical Center, and these cases were diagnosed from August 1996 to August 2005. Information on the location and size of the tumor, the type of procedure and the date of the initial diagnosis was obtained from the surgical pathology reports. Clinicopathological data, including gender, age at the time of diagnosis, initial symptoms and the lymph node or distant metastases were obtained from the patients' medical charts and the electronic hospital records. The tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system.⁴

Histopathology

The tumors were subdivided into four categories as TC, AC, LCNEC and SmCC according to the classification of pulmonary

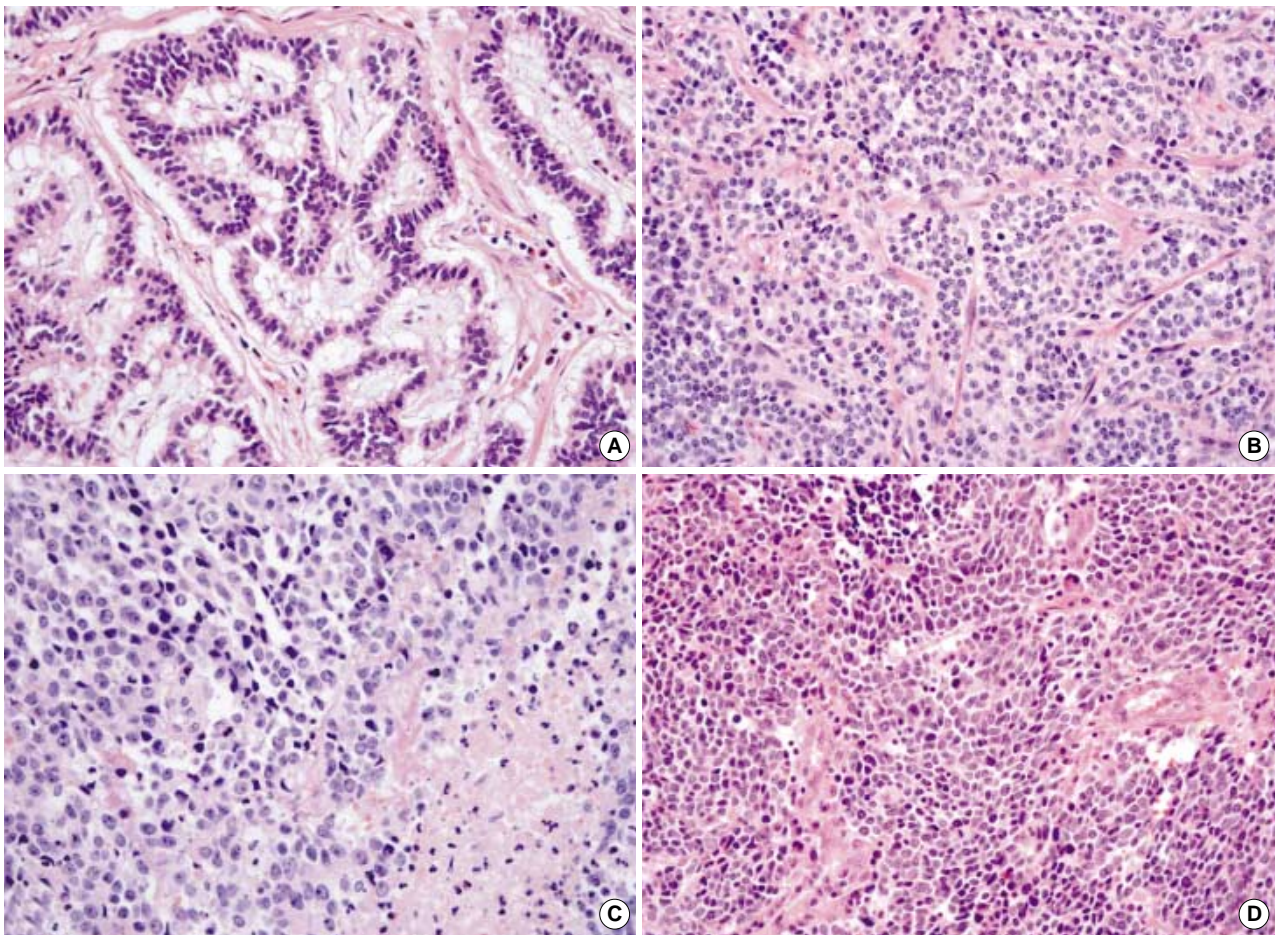


Fig. 1. Gastrointestinal neuroendocrine carcinomas. (A) Typical carcinoid of the rectum growing in trabecular pattern. (B) Atypical carcinoid of the stomach growing organoid nesting arrangement. Mitoses are infrequently seen. (C) Large cell neuroendocrine carcinoma in the colon. Necrosis is present and mitoses are numerous. Tumor cells are generally large, with moderate to abundant cytoplasm. Nucleoli are frequent and prominent. (D) Small cell carcinoma in the stomach. Tumor cells are densely packed, small, with scant cytoplasm, finely granular nuclear chromatin and absence of nucleoli.

neuroendocrine tumors.⁵ TC is characterized by round to oval cells with a moderate nucleus-to-cytoplasm ratio, finely granular nuclear chromatin and less than two mitoses/10 high power field (HPF) (Fig. 1A). The AC tumor cells are similar to those of TC, but they demonstrate 2-10 mitoses/10 HPF or they often show punctuate necrosis (Fig. 1B). LCNEC is characterized by cells with more cytoplasm, prominent nucleoli and a coarser chromatin pattern (Fig. 1C). SmCC resembles its pulmonary homonyms, having scant cytoplasm, finely granular nuclear chromatin, absent or faint nucleoli, and nuclear molding (Fig. 1D). Necrosis is frequent, but mitoses are $\geq 11/10$ HPF for both LCNEC and SmCC.

Tissue microarray construction

A representative formalin-fixed, paraffin-embedded block con-

taining tumor was selected for each of the 54 available cases. The arrays were constructed with using the 1 mm punch on the Beecher arrayer (Beecher Instruments, Wisconsin, USA). The cases were reviewed on the conventional hematoxylin and eosin-stained slides, and the areas of interest were marked out on each slide. With using a marker pen, the corresponding region was circled on the 'donor' paraffin block. The samples were then arrayed on to a 'recipient' blank block. A total of 39 samples were available for the array.

Immunohistochemistry

Sections ($4 \mu\text{m}$) were cut from a tissue microarray block and also from 15 other representative blocks that were not available for the construction of tissue microarray. For the immunohistochemistry, the sections were deparaffinized and rehydrated. The

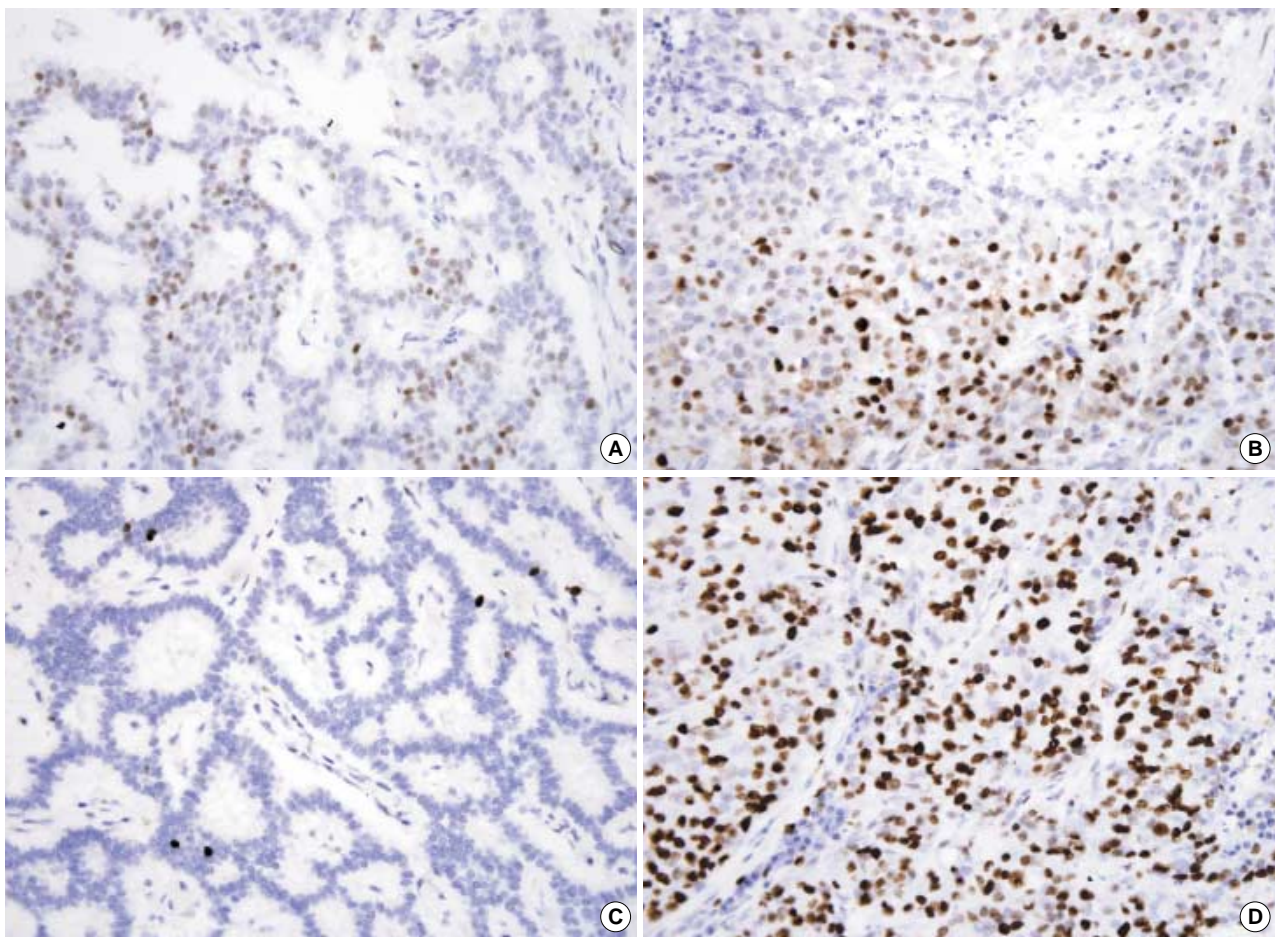


Fig. 2. Immunohistochemical study on typical carcinoid and large cell neuroendocrine carcinoma. (A) Typical carcinoid of the rectum showing a moderate degree of positivity for p53 in about 40% of the tumor cells overall. (B) Large cell neuroendocrine carcinoma of the stomach showing a marked degree of positivity for p53 in most of the tumor cells. (C) Typical carcinoid of the rectum showing a few scattered tumor cells that are positive for Ki-67 staining. (D) Large cell neuroendocrine carcinoma of the stomach showing a strong positivity for Ki-67 in most of the tumor cells.

slides were placed in 10 mM of citrate buffer (pH 6.0), and they were heated in a microwave for 5 min for three times. They were then incubated with each antibody for 30 min at room temperature. After incubation with secondary antibodies (Dako, EnVision kit, Denmark) for 30 min at room temperature, antigen visualization was achieved by applying diaminobenzidine chromogen (Dako, ChemMate, Denmark) in hydrogen peroxide solution. The sections were counterstained with Mayer's hematoxylin.

Table 1 shows the characteristics of the antibodies we used. The p53 and Ki-67 staining was evaluated by counting the number of positive tumor cells per 1,000 tumor cells. Immunostaining for p53 (Fig. 2A, B) was considered positive when the tumor cells revealed diffusely strong nuclei. On the other hand, all the tumor cells that stained positive for Ki-67 (Fig. 2C, D) were counted for the evaluation, regardless of the intensity of staining. Positivity was defined as any tumor cell that was stained by gastrin antibody (cytoplasmic staining, Fig. 3), somatostatin antibody (cytoplasmic staining, Fig. 4), TTF-1 (nuclear staining), chromogranin (cytoplasmic staining) and synaptophysin (cytoplasmic staining).

Table 1. Characteristics of the antibodies

Antibody	Type	Source	Dilution
Synaptophysin	Polyclonal rabbit	Zymed, USA	1:100
Chromogranin	Monoclonal mouse	Dako, Denmark	1:100
Gastrin	Polyclonal rabbit	Lab Vision, USA	1:200
Somatostatin	Polyclonal rabbit	Lab Vision, USA	1:200
TTF-1	Monoclonal mouse	Dako, Denmark	1:100
p53	Monoclonal mouse	Novocastra, UK	1:50
Ki-67	Monoclonal mouse	Dako, Denmark	1:400

TTF-1, thyroid transcription factor-1.

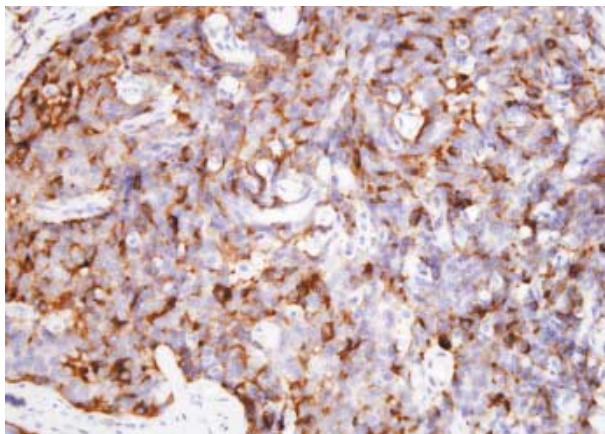


Fig. 3. Typical carcinoid of the duodenum showing cytoplasmic staining for gastrin.

Statistical analysis

For the intervariable assessment, the Mann-Whitney U test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for the dichotomized variables. Differences were considered significant for p values <0.05. All statistical analyses were performed by using the software SPSS 12.0.1 for Windows (SPSS Incorporation, Illinois, USA).

RESULTS

Demographic characteristics of the patients and tumors

The demographic characteristics of the subjects are shown in Table 2. The mean age of the patients was 50.5 years (range: 20-77 years) and there were no significant differences according to

Table 2. Distribution of demographic characteristics of patients and tumors (n=65)

	TC (n=49)	AC (n=4)	LCNEC (n=6)	SmCC (n=6)
Age (years)	48.4 (20-69)	61.5 (47-70)	53.5 (43-67)	57.3 (38-77)
Women	19 (38.8%)	4 (100%)	3 (50.0%)	1 (16.7%)
Site				
Stomach	4 (8.2%)	2 (50%)	5 (83.3%)	4 (66.7%)
Duodenum	5 (10.2%)	0	0	0
Ileum	1 (2.0%)	0	0	0
Appendix	2 (4.1%)	0	0	0
Colon	4 (8.2%)	0	1 (16.7%)	1 (16.7%)
Rectum	32 (65.3%)	2 (50%)	0	1 (16.7%)
Anal canal	1 (2.0%)	0	0	0

TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine tumor; SmCC, small cell carcinoma.

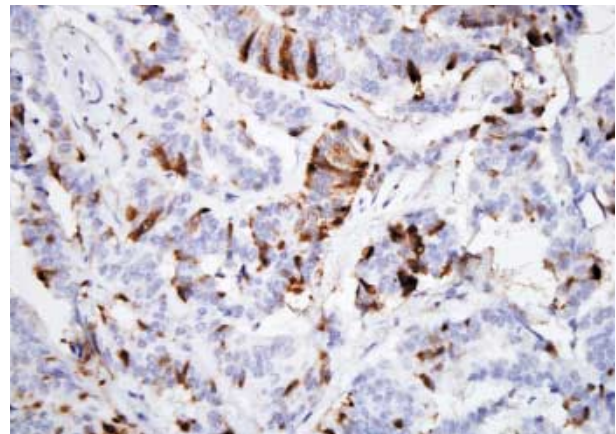


Fig. 4. Typical carcinoid of the rectum showing cytoplasmic staining for somatostatin.

the histological categories of the tumors. The tumors were located as follows: 15 in the stomach, 5 in the duodenum, 1 in the ileum, 2 in the appendix, 6 in the colon (1 in the descending colon and 5 in the sigmoid colon), 35 in rectum and 1 in the anal canal. The tumors were categorized into the following four groups: 49 TCs, 4 ACs, 6 LCNECs and 6 SmCCs. Five out of 6 LCNECs and 4 of 6 SmCCs were detected in the stomach. All the tumors found in duodenum, ileum, appendix and anal canal were TCs.

Clinical symptoms and signs

Thirty-five patients presented one or more gastrointestinal signs and/or symptoms (Table 3). The most common clinical manifestation was abdominal pain and/or discomfort (29%). Right lower quadrant pain was the sole manifestation of two patients with appendiceal carcinoid. Indigestion, constipation and anal bleeding were other frequent symptoms. Nausea and/or vomiting were present in the patients with gastric neuroendocrine tumors, while hematochezia and tenesmus were manifested by the patients with rectal neuroendocrine tumors. Cuta-

Table 3. Frequency of symptoms in gastrointestinal neuroendocrine tumors by organ site (n=65)

	Stomach (n=15)	Duodenum (n=5)	Ileum (n=1)	Appendix (n=2)	Colon (n=6)	Rectum (n=35)	Anal canal (n=1)
Pain/discomfort	5	1	1	2	4	6	0
Indigestion	0	0	1	0	1	3	0
Constipation	0	0	0	0	1	4	0
Anal bleeding	0	0	0	0	1	3	1
Nausea/vomiting	4	0	0	0	0	0	0
Hematochezia	0	0	0	0	0	4	0
Tenesmus	0	0	0	0	0	3	0
Diarrhea	1	0	0	0	0	1	0

Table 4. Distribution of clinicopathologic characteristics (n=65)

	TC (n=49)	AC (n=4)	LCNEC (n=6)	SmCC (n=6)
Size (cm)	0.7 (0.2-3.0)	1.9 (0.7-3.5)	7.1 (3.0-10.0)	7.3 (1.5-12.5)
Muscle invasion	6 (12.2%)	2 (50.0%)	6 (100%)	5 (83.3%)
Metastasis	4 (8.2%)	2 (50.0%)	5 (83.3%)	5 (83.3%)
LN	4 (8.2%)	2 (50.0%)	5 (83.3%)	4 (66.7%)
Distant	1 (2.0%)	1 (25.0%)	1 (16.7%)	1 (16.7%)
Stage				
I	43 (87.7%)	2 (50.0%)	0	1 (16.7%)
II	3 (6.1%)	0	0	2 (33.3%)
III	2 (4.1%)	1 (25.0%)	5 (83.3%)	2 (33.3%)
IV	1 (2.0%)	1 (25.0%)	1 (16.7%)	1 (16.7%)

TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SmCC, small cell carcinoma.

neous flushing, which is known as a hallmark feature of the carcinoid syndrome, was present in one patient with the atypical carcinoid of the stomach.

Clinicopathological characteristics

Table 4 shows the clinicopathologic features of the gastrointestinal neuroendocrine tumors according to the histological type. The mean tumor sizes of the TC, AC, LCNEC and SmCC were 0.7 cm (range: 0.2-3.0), 1.9 cm (0.7-3.5), 7.1 cm (3.0-10.0) and 7.3 cm (1.5-12.5), respectively. Comparing the high grade neuroendocrine carcinomas (LCNEC and SmCC) with the carcinoids (both the typical and atypical carcinoids), the mean tumor size of the high grade neuroendocrine carcinomas (7.2 ± 3.3 cm, mean ± standard deviation) was significantly larger than that of the carcinoids (0.8 ± 0.7 cm, p<0.001). In addition, muscular invasion was more frequently observed for the high grade neuroendocrine carcinomas (92%) than for the carcinoids (15%, p<0.001). Most patients with TCs were at an early stage with

Table 5. Frequency of positive immunoreactivity according to histological type of neuroendocrine tumors (n=54)

	TC (n=41)	AC (n=4)	LCNEC (n=5)	SmCC (n=4)
Synaptophysin	40 (75.9%)	4 (100%)	5 (100%)	3 (75.0%)
Chromogranin	19 (46.3%)	2 (50.0%)	1 (20.0%)	2 (50.0%)
Gastrin	3 (7.3%)	0	0	0
Somatostatin	11 (26.8%)	1 (25.0%)	0	0
p53 (≥ 10%)	0	0	4 (80.0%)	1 (25.0%)
TTF-1	0	0	0	0
Ki-67				
<5%	41 (100%)	4 (100%)	1 (20.0%)	0
5-30%	0	0	0	0
30-60%	0	0	1 (20.0%)	2 (20.0%)
≥60%	0	0	3 (60.0%)	2 (20.0%)

TC, typical carcinoid; AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SmCC, small cell carcinoma; TTF-1, thyroid transcription factor-1.

Table 6. Comparison between typical or atypical carcinoids according to lymph node metastasis (n=53)

	Lymph node metastasis		p-value
	Absent (n=47)	Present (n=6)	
Age (years)	47.6 (20-65)	63.5 (51-70)	0.004
Women	19 (40.4%)	4 (66.7%)	NS
Size (cm)	0.6 (0.2-1.2)	2.3 (1.2-3.5)	0.005
Muscular invasion	3 (6.4%)	5 (83.3%)	<0.001
Immunohistochemistry	n=41	n=4	
Gastrin	3 (7.3%)	0	NS
Somatostatin	11 (26.8%)	1 (25.0%)	NS

NS, not significant.

stage I in 43 (88%) patients, while most LCNECs were advanced at the time of diagnosis with stage III in five patients (83%) and stage IV in one (17%). Metastatic disease was identified at the time of diagnosis in 4 TCs (8%) patients, 2 ACs (50%) patients, 5 LCNECs (83%) patients and 5 SmCCs (83%) patients. A second malignancy was found in five patients. Adenocarcinoma was identified in one rectal SmCC patient and one rectal TC patient. One patient with rectal TC had gastric marginal zone B-cell lymphoma, another patient with gastric LCNEC had multiple myeloma, and the last patient with duodenal TC had hypopharyngeal carcinoma.

Immunohistochemistry

The results of the immunohistochemistry are shown in Table 5. A total of 54 cases were available for analysis. Immunohistochemically, 96% of the tumors showed a positive reaction for synaptophysin and 44% of the tumors showed a positive reaction for chromogranin A.

The TCs (Fig. 2A) and ACs presented p53-positive cells that were less than 10% of the total tumor cells, while four LCNECs (80%, Fig. 2B) and one SmCC (25%) presented more than 10% p53-positive tumor cells. With regard to the immunoreactivity for Ki-67, the immunoreactive cells never exceeded 5% in the TCs (Fig. 2C) and ACs, whereas more than 30% Ki-67 positive cells were observed in four LCNECs (80%, Fig. 2D) and all the SmCCs.

Only three TCs (7%) of the duodenum revealed immunoreactivity for gastrin (Fig. 3). Somatostatin was detected in 11 TCs (27%, Fig. 4) and one AC (25%). None of the LCNEC and SmCC stained for gastrin or somatostatin. Immunostaining for TTF-1 was negative in all the cases we examined.

Characteristics associated with metastasis in TC and AC

Six cases of TCs and ACs showed lymph node metastasis at the time of diagnosis, and 2 of them demonstrated distant metastasis. Table 6 demonstrates a comparison between the carcinoids with lymph node metastasis and those without metastasis. The patients with lymph node metastasis were more likely to be older (64 years) than those patients without metastasis (48 years, $p=0.004$). The tumor size was larger for the tumors with metastasis (2.3 cm) than it was for tumors without metastasis (0.6 cm, $p=0.005$). Muscle invasion of tumors was more frequently observed in the tumors with metastasis (83%) than in those tumors without metastasis (6%, $p<0.001$). The other parameters were

of no statistical significance.

DISCUSSION

TCs were most common among the 65 neuroendocrine tumors of the gastrointestinal tract that were diagnosed at Korea University Medical Center during the recent 10 years. They occurred in the rectum, stomach, colon, duodenum, appendix, ileum and anal canal in this descending order. ACs were identified only in the stomach and rectum.

The reported anatomic distribution of primary carcinoid tumors within the gastrointestinal tract varies depending on the sources of data. Epidemiologic studies performed in North America found that gastrointestinal carcinoid tumors arose more frequently in the appendix and small intestine than in the rectum or stomach.⁶ Godwin⁷ also reported that carcinoid tumors were most commonly found in the appendix. Modlin *et al.*⁸ reported the Surveillance, Epidemiology and End Results (SEER) database from an analysis of 13,715 carcinoid tumors, and they demonstrated that the small intestine was the most common site (42%), followed by the rectum (27%) and stomach (9%). However, a Japanese study⁹ and a Korean study¹⁰ reported that carcinoid tumors most commonly occurred in the rectum, followed by the jejunioileum and stomach. The relatively high frequency of carcinoid tumors in the rectum and stomach may be partly explained by the high prevalence of nontumorous gastrointestinal diseases as well as the widespread use of endoscopic examinations in Korea and Japan.

Gastrointestinal neuroendocrine tumors may or may not produce clinical manifestations. When symptoms do occur, they are due either to local tumor mass effects, the effects of tumor-engendered fibrosis or the effects of secreted bioactive products from the neoplasms, and especially those from the carcinoid tumors. The symptom caused by local tumor effects includes vague abdominal pain (invasion, intussusception, fibrous adhesions and hypermotility), and was the most common symptom found in this study. In the review of gastrointestinal carcinoids by Modlin *et al.*,⁶ they demonstrated that pain/discomfort was present throughout the gastrointestinal tract. Systemic symptoms such as anorexia and weight loss were rare in our study, and the most persisting symptoms were site-specific. The clinical presentation in our study was dominated by the advanced stage at the time of diagnosis regardless of the histological type (data not shown). However, one patient with LNEC of stage IV in our study did not manifest disease-related symptoms. Van

Gompel *et al.*¹¹ have found that the presence of symptoms at presentation affected the prognosis, while another study failed to correlate symptoms with survival.¹²

Several previous studies on carcinoid tumors showed that metastasis was less likely to be observed when the tumor size was <1 cm.¹³⁻¹⁶ Invasion of the muscularis propria or the deeper layers was also a risk factor for metastasis, and the depth of invasion was closely related to the tumor size. In our current study, most TCs (82%) were ≤ 1 cm in size and metastasis did not occur at the time of diagnosis for carcinoids ≤ 1 cm in size. Endoscopic tumor removal of gastric or rectal carcinoids has recently been cautiously tried when the carcinoids were rarely associated with metastasis or recurrence, based on the number and the size of tumor, the depth of invasion and the absence of depression or ulceration in the tumor.^{6,16,17} Thirty patients with TC or AC ≤ 1.2 cm in size were treated by polypectomy or endoscopic mucosal resection in our study. Local recurrence was not detected for these tumors during the follow-up period.

For the high grade neuroendocrine carcinomas, including the LCNEC and SmCC, most of the tumors were ≥ 3 cm in diameter and they had invaded the muscle proper or the deeper layers, while one SmCC was 1.5 cm in size and it had invaded the submucosa. According to the data from Rindi *et al.*,^{13,14} the overall mean size of the poorly differentiated gastric neuroendocrine carcinomas was 4.2 cm. Although the overall size of the gastrointestinal small cell carcinoma was not described, Brenner *et al.*¹⁸ suggested that the tumor size >5 cm was one of the prognostic factors for the patients with tumor confined to a localized anatomic region. When considering the tumor size and the highly aggressive features of high grade neuroendocrine tumors, local excision cannot be a treatment of choice. Unfortunately, there has been only limited data reported so far on the modalities to treat high grade gastrointestinal neuroendocrine carcinomas.

Regardless of the histological type, most neuroendocrine tumors showed immunoreactivity to either synaptophysin or chromogranin A. The expression of gastrin was identified only in a TC of duodenum (83.3%). Gastrin production has been known to be clinically significant for the patients with Zollinger-Ellison syndrome.¹⁹ In this study, however, none of the patients with gastrin production had peptic ulcer. This finding is consistent with the previous studies demonstrating that hormone production did not correlate with the clinical features.^{20,21} The expression of somatostatin by gastrointestinal carcinoid tumors has been variably reported in the previous studies,²²⁻²⁴ some of which have described somatostatin producing tumors of the duodenum as being clinically significant.

According to Burke *et al.*,^{21,22} somatostatin cell tumors of the duodenum were often malignant even though they showed a bland histological appearance, yet we didn't observe this finding in the current study.

Recent advances in molecular biology have provided new tools to determine the metastatic potential of human malignancies. Both mutation in the p53 gene and the abnormal expression of p53 protein are among the most common molecular abnormalities that have been detected in human malignancies. However, the overexpression of p53 has been uncommonly identified in gastrointestinal carcinoids.^{15,25} In the present study, none of the carcinoids revealed immunoreactivity for p53. A higher rate of overexpression of p53 was identified (80% in LCNEC and 25% in SmCC) in the high grade neuroendocrine carcinomas rather than in the TCs and ACs. This level of reactivity of the high grade neuroendocrine carcinoma was greater than that reported by Nassar *et al.*,²⁶ but it was less than that reported by Brenner *et al.*¹⁸ and by Brambilla *et al.*²⁷ for the neuroendocrine carcinomas of the lung. The cellular proliferation marker Ki-67 has been suggested as one of the potential indicators of malignant behavior in neuroendocrine tumors.^{28,29} Several studies have supported the validity of the Ki-67 proliferation index as a prognostic indicator for gastrointestinal carcinoids.^{14,29} In addition, high labeling of Ki-67 has also been reported in high grade gastrointestinal neuroendocrine carcinomas.^{18,26} In the current study, all the carcinoids showed a Ki-67 labeling index $<5\%$, while the mean Ki-67 labeling index was 59.6% in the LCNEC (ranging from 3.3% to 92.2%) and 56.0% in the SmCC (ranging from 37.8% to 76.2%). Therefore, the Ki-67 labeling index may assist in diagnosing high grade neuroendocrine carcinomas.

The presence of metastases has been known to be associated with the reduced 5-year survival of patients with carcinoids.^{8,30} Therefore, it is valuable to investigate the differences between carcinoids with metastasis and those without metastasis so as to predict the outcome of disease. In the current study, the patients with metastatic carcinoids were older than those patients with localized carcinoids, and the tumor size was more likely to be larger for the carcinoids with metastasis than for those without metastasis. These findings were similar to the results of a previous study by Jung *et al.*¹⁰ In addition, muscle invasion was more frequent for the metastatic carcinoids than for the localized carcinoids in the current study; however, immunohistochemical study did not demonstrate any significant differences. Therefore, the influence of the age of patients and the histological characteristics of tumors on the biologic behavior of TC and AC should be examined in further studies.

This study summarized the clinicopathologic characteristics of gastrointestinal neuroendocrine tumors according to the histological type as classified by their pulmonary counterparts. TC was a most frequent gastrointestinal neuroendocrine tumor, and the rectum was the most common site. For the TCs and ACs, the tumor size was smaller, metastasis was less frequent and the TNM stage was lower than that of the LCNECs and SmCCs. Immunoreactivity for p53 and Ki-67 was greater in the high grade neuroendocrine carcinoma than that in the carcinoids. An old age, large tumor size and invasion beyond the muscle layer were associated with high grade neuroendocrine tumor and lymph node metastasis for the carcinoid tumors.

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