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Type 3 Gastric Neuroendocrine Neoplasm Clinical Features: A Multicenter Study in Korea

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Background: The aim of this study was to investigate clinicopathologic features of type 3 gastric neuroendocrine neoplasm (NEN) by treatment modality.

Methods: The Korean Society of Gastrointestinal Cancer conducted the Korean Gastroenteropancreatic Neuroendocrine Tumor Registry, a retrospective registry database of gastroenteropancreatic neuroendocrine tumors from 16 hospitals in Korea. The normal serum gastrin level range was defined as <100 pg/mL, and gastric NEN patients with normal gastrin level were selected for analysis.

Results: Among 358 patients with gastric NEN, 21 (5.9%) patients were classified with type 3 gastric NEN. The median age was 53 years (range 30-74). According to the WHO 2010 classification, 13 (61.9%) patients had grade 1, and 8 (38.1%) patients had grade 2 or 3. Endoscopic treatment was performed in 14 (66.7%) patients, and surgery was performed in 7 (33.3%) patients. The tumor size was smaller in the endoscopic treatment group than in the surgery group (0.6 cm vs 1.3 cm, p=0.006). After treatment, there was one recurrence in the surgery group.

Conclusion: In small size Type 3 gastric NEN, endoscopic treatment was associated with a good prognosis, compared to surgery. Thus, endoscopic treatment can be used an alternative modality in selected cases of type 3 gastric NEN.

Key Words: Stomach, Neuroendocrine neoplasm, Type 3, Endoscopic resection, Surgery

INTRODUCTION

Gastric neuroendocrine neoplasms (NENs) are a rare condition, however, the incidence has increased, due to widespread endoscopic surveillance.[1,2] Gastric NENs account for 6-8 percent of gastrointestinal NENs.[1,2] Evidence for gastric NEN pathogenesis and advances in clinical treatment have evolved as diagnostic and treatment approaches have been investigated and developed.

In 1993, Rindi et al. first classified gastric NENs into three types: type 1, arising on chronic atrophic gastritis in the context of pernicious anemia; type 2, multiple endocrine neoplasms (MEN-I)/gastrin-producing neoplasm in Zollinger-Ellison syndrome; type 3, no specific background disease.[3] Type 1 and 2 gastric NENs are related to hypergastrinemia and type 3 gastric NENs occur sporadically, irrespective of

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gastrin 3. Type 1 and 2 gastric NENs are considered to be benign and are associated with a good prognosis.[4,5] However, type 3 gastric NEN is aggressive and is associated with lower overall survival.[6,7] Endoscopic resection is an effective treatment for type 1 and 2 gastric NENs. However type 3 gastric NEN requires gastrectomy and lymph node dissection for curative treatment and good outcomes.[4,8]

Some studies have recently shown the efficacy of endoscopic resection in type 3 gastric NENs. A recent study reported that endoscopic resection could be considered for type 3 gastric NEN that presented with a less than 2 cm-sized confined submucosal layer.[9] However, there are only a limited number of studies that have compared endoscopic resection and surgery treatment results for type 3 gastric NEN. The aim of this study was to investigate the clinicopathologic features of type 3 gastric NEN according to treatment modality.

MATERIALS AND METHODS

The Korean Gastroenteropanreatic Neuroendocrine Tumor Registry was conducted by The Korean Society of Gastrointestinal Cancer from 2012. This registry was a retrospective database of gastroenteropancreatic neuroendocrine neoplasm collected from 16 tertiary hospitals in Korea. The registry database and standard analyzing protocols were approved by each institutional review board of all participating hospitals. Between January 2002 and December 2012, a total of 358 patients with gastric NENs were registered. Type 3 gastric NEN was defined as NEN with serum gastrin level less than 100 pg/mL and not associated with MEN-1 or Zollinger-Ellison syndrome.

Gastric NEN treatment was determined by the gastroenterologists in each hospital, considering tumor size, number of tumors, depth of tumor and lymph node involvement by computed tomography and endoscopic ultrasonography, with endoscopic resection or surgery. Endoscopic mucosal resection or endoscopic submucosal resection was performed in the endoscopic treatment group. Wedge resection, subtotal gastrectomy or total gastrectomy was performed in the surgery group.

Continuous variable data were presented as the median with ranges. To compare the two surgery and endoscopic treatment approaches, the Mann-Whitney U-test was used for continuous variables, and Fisher's exact test was used for categorical variables. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc. Chicago, IL, USA).

RESULTS

From the total of 358 patients with gastric NEN, 21 patients had type 3 NEN (Table 1). The median age was 53 years (range 30-74). Nine patients (43%) were male and twelve patients (57%) were female. Eight patients (38%) had abdominal pain or discomfort and thirteen patients (62%) were asymptomatic. The median gastrin level was 45.1 pg/mL (range 0.05-98). The tumor was mostly located within the organ body (85.7%). The median tumor size was 0.95 cm, based on endoscopy results (range 0.2-6.0).

Fourteen patients received endoscopic treatment including endoscopic mucosal resection (n=4) and endoscopic submucosal resection (n=10). Seven patients underwent surgery (Fig. 1). The age, gender, serum gastrin level and tumor location were not different between the two groups (Table 2). Tumor size was smaller in the endoscopic treatment group

Table 1. Baseline characteristics

Parameter	Values (median)
n	21
Age, years	53 (range 30-74)
Gender (male: female)	9:12
Gastrin (pg/mL)	45.1 (range 0.05-98.0)
Tumor location	
Antrum	1 (4.8%)
Body	18 (85.7%)
Fundus	3 (9.5%)
Tumor size	
Endoscopy (cm)	0.95 (range 0.2-6.0)
Pathology (cm)	0.8 (range 0.3-8.0)
WHO 2010	
G1	13 (61.9%)
G2	7 (33.4%)
G3	1 (4.7%)
Treatment	
Endoscopic resection	14 (66.7%)
Surgery	7 (33.3%)
Gastrectomy	4
Wedge resection	3
Stage	
T1	11 (52.4%)
T2	10 (47.6%)
Follow-up time (months)	27 (range 6-115)

WHO, World Health Organization;

Table 2. Clinicopathologic findings based on treatment modality

Parameter (median)	Treatment		p
	Endoscopy	Surgery	
n	14	7	
Age (yrs)	53 (range 30-69)	54 (range 35-74)	0.390
Gender (male: female)	4:10	5:2	0.687
Gastrin (pg/mL)	49.8 (range 0.05-98.0)	40.8 (range 4.5-77.7)	0.941
Tumor location			0.407
Antrum	0	1 (14.3%)	
Body	12 (85.7%)	6 (85.7%)	
Fundus	2 (14.3%)	0	
Tumor size (Before resection)	0.8 (range 0.2-1.5)	1.75 (range 1.5-6.0)	0.001
Tumor size (After resection)	0.6 (range 0.3-1.6)	1.3 (range 0.8-8.0)	0.006
WHO 2010			0.333
G1 & G2	14 (100%)	6 (85.7%)	
G3	0	1 (14.3%	
T Stage			0.001
T1	11 (78.6%)	0	
T2	3 (21.4%)	7 (100%)	
N stage			-
N0	-	4 (57.1%)	
N1	-	3 (42.9%)	

*Mann-Whitney U-test was used for continuous variables, Fisher's exact test was used for categorical variables.
WHO, World Health Organization;

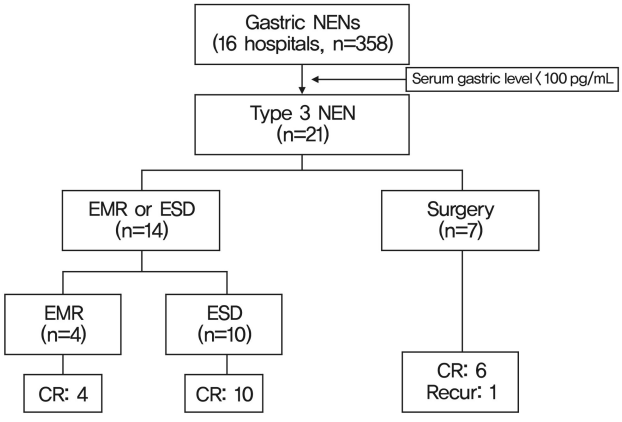

Fig. 1. Flow chart.

than in the surgery group (0.6 cm vs. 1.3 cm, p=0.006). WHO 2010 grade was not significantly different between the groups. However, there were more T2 disease diagnoses in the surgery group compared to the endoscopic treatment group (p=0.001). During follow-up, there was no recurrence in the endoscopic treatment group but there was one recurrence in the surgery group (p=0.333). The patient with recurrence was initially diagnosed as G3 disease stage, according to WHO 2010 guidelines and experienced recurrence 7 months after subtotal gastrectomy (Table 3).

Table 3. Treatment outcomes

Parameter	Treatment		p
	Endoscopy (n=14)	Surgery (n=7)	
Complete remission	14 (100%)	6 (85.7%)	0.333
Recurrence	0	1 (14.3%)	
Mortality	0	1 (14.3%)	

*Fisher's exact test was used

DISCUSSION

The incidence of gastric NENs is increasing due to the advent of screening endoscopy. Gastric NENs are usually diagnosed at an early stage and incidentally.[10] Surgery is an acceptable treatment in patients with gastric NENs.[11,12] However, the treatment paradigm has changed as tumor behavior and treatment modalities are being investigated since gastric NENs were classified into 3 types.

The three types of gastric NEN have distinct endoscopic and histologic findings. Type 1 gastric NENs are often found

in the fundus and are mostly polypoid (78%), small (5-8 mm) and multicentric.[13,14] Histologically, most type 1 gastric NENs are G1 tumors with low Ki67 that are limited to the mucosa or submucosa.[13,15] Type 2 gastric NENs are usually less than 1 cm and multicentric.[16] Histologically, type 2 NENs are usually well-differentiated (G1 or G2). However, type 2 NENs are more frequently identified in metastases to abdominal lymph nodes and liver, compared with type 1 NENs 3. In comparison with type 1 and 2 gastric NENs, type 3 gastric NENs present as large (>2 cm) solitary lesions that grow from the normal gastric mucosa.[9] G3 (neuroendocrine carcinoma) is more common in type 3 gastric NENs. In addition, deep wall invasion is common and 60-75% of cases present with metastases.[3,17] Therefore, type 3 gastric NENs have an aggressive behavior and are associated with the poorest prognoses.

Type 1 and 2 gastric NENs that are within the submucosal layer are commonly treated by endoscopy.[18] In contrast, the standard treatment for type 3 gastric NENs is partial gastrectomy or total gastrectomy with local lymph node dissection.[19,20] Additional systemic chemotherapy is needed if the surgical result is not satisfactory or if surgery is not feasible.[21] Because partial gastrectomy and total gastrectomy are relatively invasive procedures, the risk of postoperative adverse events and the quality of life are a serious concern.[22,23] A recent study reported that gastric neuroendocrine tumor G1 types that have not yet advanced can be treated with endoscopic or laparoscopic surgery.[24] Another study reported that endoscopic treatment could be considered in cases where the tumor was less than 2 cm and confined to the submucosal layer and type 3 gastric NEN could be treated when there was no evidence of lymphovascular invasion.[9] Fifty patients with type 3 gastric NEN were treated with endoscopic mucosal resection (n=41) or endoscopic submucosal dissection (n=9) and during the follow-up period, there was no evidence of recurrence.[9]

In this study, we compared the treatment results in type 3 gastric NEN, based on treatment modality. To our knowledge, this is the first investigation to compare the treatment modality for type 3 gastric NENs. We used the Korean Gastroenteropancreatic Neuroendocrine Tumor Study in the Korean Society of Gastrointestinal Cancer and identified 21 patients with type 3 gastric NENs that were retrospectively enrolled from 16 tertiary hospitals. Fourteen patients received endoscopic treatment and seven patients underwent surgery. The treatment modality was decided after estimating the tumor size by endoscopy. If the tumor size was small and confined to the submucosal layer, endoscopic treatment was initially applied. The surgery group had larger tumor sizes and more lymph node metastases. There was one case with recurrence in the surgery group, in which the patient was diagnosed with stage G3 and lymph node metastasis. A recent study reported that there were no cases of lymphovascular, perineural invasion or lymph node metastasis among G1 or 2 patients with less than 1 cm-sized lesions.[25] Our study found similar results. Therefore, careful selection of patients is very important for accurately assigning treatment modality.

There were some limitations to this study. First, the study was retrospective and the number of enrolled patients were small, even though 16 tertiary hospitals participated. Many patients with gastric NEN did not evaluate the level of gastrin. Therefore, the number of type 3 gastric NEN might have been underestimated. Second, although G3 are known to be common in type 3 gastric NENs, there was only one case with G3 in this study. This might have introduced a selection bias. Third, the progression free survival and overall survival were not evaluated. Because there was only on incidence of recurrence in the surgery group, the survival could not be analyzed. However, this study assessed a relatively large numbers of type 3 gastric NENs and compared the treatment results. Therefore, the results of this study can provide guidance for assessment and treatment modality in type 3 gastric NENs.

In conclusion, endoscopic treatment showed similar treatment results when compared to surgery on small size (less than 1 cm) tumors that were confined to the submucosal layer in patients with type 3 gastric NENs. Additional research is needed and large and randomized controlled studies are needed to further assess the applications of the results of this study.

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Compliance with Ethical Standards

Disclosure Conflict of interest relevant to this article was not reported.

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