Defining prognostic parameters of well-differentiated gastric neuroendocrine tumors based on metastatic potential: a two-center experience

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Abstract

Background: **Gastric neuroendocrine tumors [gNETs] are heterogeneous tumors and we are still unable to predict the behavior of these tumors. We aim to define the prognostic parameters of well-differentiated gNETs based on metastatic potential and to evaluate the current classification systems.**

Patients and methods: **We retrospectively retrieved 44 well differentiated gNET cases who underwent radical surgery between 2000-2015 at two tertiary-care centers.**

Results: **Among the 44 well-differentiated gNET patients, 17 (38%) patients had metastatic disease to lymph nodes and/or distant sites, while 27 (62%) were confined to the stomach. Higher risk of metastasis was observed with increasing tumor size, grade, depth of invasion and with type-3 and solitary tumors. 30 (68%) patients had type-1 gNET and 14 (32%) had type-3 gNET. Majority of the type-1 cases (76,6%) were Grade 1 [G1] and type-3 cases (78,5%) were Grade 3 [G3]. Type-1 subgroup had no G3 tumor, and type-3 had no G1. Grade 2 [G2] tumors were more controversial, with metastatic and non-metastatic cases. G2 cases with a >10% Ki67 expression or type-3, had a worse prognosis. Although most of the type-1 gNETs had an indolent course, 6 of 30 (20%) patients had metastatic disease. Metastasizing type-1 gNETs were ≥10 mm in diameter or extended to/beyond the submucosa.**

Conclusion: **Regarding our results, tumor type, grade, size, focality and depth of invasion are the prognostic parameters for gNETs, based on metastatic potential. Besides these parameters, a two-tiered grading system with a 10% Ki-67 proliferation index cut-off value could be considered for right treatment choice.** (Acta gastroenterol. belg., **2022,** 85, **339-345**).

Keywords: gastric neuroendocrine tumors, grade, clinicopathologic classification; prognosis.

Introduction

Gastric neuroendocrine tumors [gNETs] are a heterogeneous group of tumors clinical and pathologically (1). Because of their heterogeneous biologic behavior, the prediction of prognosis is still difficult and determining the right treatment choice is a highly challenging issue for clinicians. Although gNETs are rare tumors, according to Surveillance, Epidemiology, and End Results [SEER] data, the number of patients has increased significantly in the last decade (2) and gNETs have become more significant.

Treatment modalities are mostly designed according to clinicopathologic classification in which gNETs are divided into three subtypes. The most common type is type-1 gNETs, they are associated with hypergastrinemia and autoimmune chronic atrophic gastritis. Type-2 gNETs are associated with multiple endocrine type 1 neoplasia [MEN1] and Zollinger-Ellison syndrome [ZES], while type-3 gNETs occur sporadically (3). Although this classification system mostly determines the biological behavior of gNETs, the determination of histomorphological features, mitotic index and Ki-67 proliferation index is mandatory.

The World Health Organization [WHO] established a grading system depending on these parameters. This grading system for gastroenteropancreatic neuroendocrine tumors was issued in 2000; revised in 2010 and 2017 (Table 1).

However, we are still unable to predict the behavior of all gNETs, despite different classifications. For instance, although most of type-1 gNETs are grade 1 according to the WHO classification system and exhibit an indolent course, a minority of them could metastasize and have a poor overall survival (4,5). The clinical approach to these tumors varies significantly among clinicians from an endoscopic follow-up to surgical resection, primarily depending on the clinicians' experience At this point, it is important to identify the right histopathological parameters to guide the clinicians.

In this study, we investigated the correlation between metastasis and various clinicopathological parameters, and interpreted the current classification and grading systems. We re-evaluated forty-four well-differentiated gNET patients who underwent surgical resection at two tertiary-care centers (Hacettepe University Hospital and Yuksek Ihtisas Education and Research Hospital) in Turkey, retrospectively.

Material and methods

Gastric neuroendocrine tumors diagnoses and surgically resected between 2000 and 2015 were retrieved from the Pathology Department of Hacettepe University and Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey. Mixed adenoneuroendocrine tumors and poorly differentiated neuroendocrine carcinomas were

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Table 1. — **World Health Organization 2017 classification system for gastric neuroendocrine neoplasms compared to 2010 classification**

2010 WHO classification	**Grade**	**Mitotic count /10 HPFs**	**Ki-67 labeling index, %**
Neuroendocrine tumor (NET) Grade 1	Low	<2	< 3
Neuroendocrine tumor (NET) Grade 2	Intermediate	2-20	3-20
Neuroendocrine carcinoma (NEC) Grade 3	High	>20	> 20

2017 WHO classification	**Grade**	**Differentiation**	**Mitotic count /10 HPFs**	**Ki-67 labeling index, %**
Neuroendocrine tumor (NET) Grade 1	Low	Well differentiated	<2	<3
Neuroendocrine tumor (NET) Grade 2	Intermediate	Well differentiated	2-20	3-20
Neuroendocrine tumor (NET) Grade 3	High	Well differentiated	>20	>20
Neuroendocrine carcinoma, small cell type (SCNEC)	High	Poorly differentiated	>20	>20
Neuroendocrine carcinoma, large cell type (LCNEC)	High	Poorly differentiated	>20	>20

not considered. Between 2000-2015, 58 patients (41 patients from Hacettepe University and 17 patients from Yuksek Ihtisas Education and Research Hospital) were found. Fourteen of 58 patients, underwent an antrectomy or distal subtotal gastrectomy to decrease the gastrin levels to prevent the development of neuroendocrine tumors and were excluded from the analysis. The remaining forty-four patients who underwent surgery for removal of the primary tumor were evaluated in this study.

Clinicopathological findings of the patients were reviewed by two pathologists for the following parameters; the number of mitoses per 10 high-power fields [HPFs], Ki-67 proliferation index, tumor size, tumor location, tumor focality, depth of gastric wall invasion, and also T stage and regional lymph node/ distant metastases according to 8th Edition of the the American Joint Committee on Cancer [AJCC]'s TNM Classification. Immunohistochemical tests for chromogranin-A, synaptophysin, and Ki67 were performed in all cases. A diagnosis of the neuroendocrine tumor was confirmed with positivity for chromogranin and synaptophysin. Tumors were classified as type-1 gNET when histological evidence of atrophy or intestinal metaplasia or neuroendocrine cell hyperplasia in the gastric body was confirmed; otherwise they were classifed as type-3.

The grade was assigned based on the Ki67 index and the mitotic count. While assessing the Ki67 labeling index, the highest nuclear labeling (hot spot) area was identified and a digital photograph at high magnification was taken. The percentage of stained tumor cells per 500-2,000 neoplastic cells was analyzed from the captured images.

Grade 1 [G1] tumors were those with < 2 mitoses/10 HPFs and < 3% Ki67 index, Grade 2 [G2] tumors were those with 2–20 mitoses/10 HPFs or 3–20% Ki67 index and Grade 3 [G3] NETs were those with > 20 mitoses/10 HPFs or > 20% Ki67 index according to 2017 revised classification. While grading the tumors, if there was an incompatibility between the Ki-67 labeling index and mitotic count, the higher value was accepted for the classification.

All patients' demographic and clinical data were obtained from clinical records in the Hacettepe University and Yuksek Ihtisas Education and Research Hospital database.

All statistical analyses were performed by using The Statistical Package for the Social Sciences [SPSS] version 21.0 for Windows (IBM Corp.; Armonk, NY, USA). Chi-square test, Fisher's exact test, T-test, Mann Whitney U test and Kruskal Wallis test were employed to compare the groups. The receiver operating characteristic [ROC] curve was used to determine the best cut-off value of tumor diameter for metastatic cases. Two-sided p values of less than 0.05 were considered statistically significant.

The study was performed in agreement with the clinical standards laid down in the 1975 Declaration of Helsinki and its revision in 2004 and was approved by the Research Ethics Committee of Hacettepe University.

Results

A total of forty-four well differentiated gNET cases were included in the study. This entire cohort comprises 18 (41%) males and 26 (59%) females, with a male-to-female ratio of 0.69. The mean age at initial diagnosis was 55,5 years (range 27-94). According to the WHO 2017 grading system, 23 (52,3%) gNETs were classified as G1, 10 (22,7%) as G2 and 11 (25%) as G3. According to the clinicopathological classification, 30 (68%) patients had type-1 gNET and 14 (32%) had type-3 gNET. There was no type-2 gNET in our study cohort. Distal subtotal gastrectomy was performed for 14 (31,8%) patients, a total gastrectomy for 29 (65,9%), and a proximal gastrectomy for 1 (2,3%) patient. The tumor size ranged

Table 2. — **Clinicopathological characteristics of the patients with gNETs (*n*=44)**

Variables	
Age, year (median)	27-94 (55,5)
Gender (n) Female Male	 26 (59%) 18 (41%)
Tumor size (mm)*	0,8-130 (33,1)
Tumor location (n)* Cardia-corpus (upper 2/3) Antrum (lower 1/3)	 37 (84,1%) 7 (15,9%)
Tumor focality (n) Solitary Multifocal	 23 (52,3%) 21 (47,7%)
Tumor grade (n) Grade 1 Grade 2 Grade 3	 23 (52,3%) 10 (22,7%) 11 (25%)
Tumor type (n) Type-1 Type-2 Type-3	 30 (68%) 0 14 (32%)
Surgical procedure (n) Distal subtotal gastrectomy Total gastrectomy Proximal gastrectomy	 14 (31,8%) 29 (65,9%) 1 (2,3%)
Depth of invasion (n) Intramucosal Submucosa Muscularis propria Subserosa Serosa	 6 (13,5%) 18 (41%) 2 (4,5%) 14 (32%) 4 (9%)
Other mucosal disorders (n) KAG+IM Neuroendocrine cell hyperplasia None	 14 (32%) 24 (54,5%) 6 (13,5%)
T status (n) T0 T1 T2 T3 T4	 1 (2,3%) 19 (43,2%) 6 (13,5%) 14 (32%) 4 (9%)
Lymph node metastases (n) N0 N1 Nx	 28 (63,6%) 15 (34,1%) 1 (2,3%)
Distant metastasis (n) M0 M1	 36 (81,8%) 8 (18,2%)

n: number of patients, N0: no lymph node metastasis, N1: metastatic to lymph nodes, Nx: unknown lymph node metastasis, M0: no distant metastasis , M1: metastatic to distant sites *For multifocal tumors, size and location of the tumor were given based on the largest tumor mass.

from 0.8 mm to 120 mm, with a mean of 33,1 mm. The tumor was located in the upper 2/3 of the stomach (corpus, fundus, cardia) in 37 (84,1%) patients. The tumor occurred as a solitary mass in 23 (52,3%) patients and multifocally in 21 (47,7%) patients. Seven patients had metastatic disease, 5 of whom had also positive regional lymph nodes, 10 patients only had locoregional disease. The clinicopathological characteristics were summarized in Table 2.

We have divided well-differentiated gNETs into two groups as metastatic (lymph nodes and/or distant sites) and non-metastatic. A comparison between these two groups was made to determine the risk factors for metastases. Regarding our results, the risk of metastasis has increased, with the increasing tumor grade, depth of invasion and T stage of the tumor significantly. Besides, the risk of metastases were higher in type-3 and solitary tumors. A significant correlation was not found with tumor location, patient age and gender. The clinicopathological characteristics of metastatic and non-metastatic gNETs and two-sided p values were summarized in table 3. Of 31,5 mm was found to be the best discriminator for risk on locoregional or metastatic disease with 82,4% sensitivity and 14,8% specificity (area under the curve [AUC]:0.858).

When the data was analyzed, type-3 tumors were more common in men (71,4%) and in elderly patients (median age 64,5). Tumor size was significantly larger in type-3 tumors (median tumor diameter of 62,5 mm), leading to higher T stages as well. Lymph node metastases and distant metastases were significantly higher in type-3 patients. The majority of the type-1 cases were G1 (76,6%) and type-3 were G3 (78,5%). Type-1 subgroup had no G3 tumor, and type-3 had no G1. The data was summarized in Table 4.

Six of 30 (20%) type-1 gNET patients had locoregional spread to lymph nodes and 1 of them also had liver metastases. Four of them had G1, and two had G2 tumors. Three tumors were solitary, 3 were multifocal. Three of them invaded the submucosa, 2 the subserosa and 1 the serosa. Diameter of the tumors was 37,3 mm (9, 10, 15, 35, 35, 120 mm respectively). The mean diameter of non-metastatic type-1 gNETs was 10,02 mm (range 0,8-45 mm).

Seven of 30 type-1 gNETs, and 3 of 14 type-3 gNETs had G2 tumors. To understand the metastatic potential of G2 gNETs, we have detailed and summarized the histopathological features in table 5. Five G2 gNETs were metastatic to lymph nodes and/or distant sites and 5 were confined to the stomach. The mean diameter of non-metastatic G2 gNETs' was 15 mm (5, 10, 15, 20, and 45 mm), while for the metastatic ones it was 50 mm (10, 40, 50, 70, and 120 mm). Mean value for Ki-67 proliferation index was 5,2 (range of 3%-10%) for non-metastatic G2 gNETs and 11 (range of 4%-16%) for metastatic G2 gNETS. Case 2 and 8 are shown in figure 1.

Discussion

Gastric neuroendocrine tumors are a heterogeneous group of tumors derived from diffuse neuroendocrine cells (1). gNETs' frequency among all gastroenteropancreatic neuroendocrine tumors is in the range of 5-14.6% (6), and the overall incidence of gNETs has increased

Table 3. — **Clinicopathologic characteristics of metastatic and non-metastatic gNETs**

Variables	Metastatic tumors (n=17)	Non-metastatic tumors (n=27)	p value
Age, mean, years, (range)	60,35 (43-72)	54,3 (27-94)	NS (p=0,230 t-test)
Size, mean, mm (range)	56,1 (9-130)	18,7 (0,8-110)	
Gender (n) Female Male	 7 (41%) 10 (59%)	 19 (70%) 8 (30%)	NS (p=0,055 chi-square test)
Tumor grade (n) Grade 1 Grade 2 Grade 3	 4 (23,5%) 5 (29,4%) 8 (47,1%)	 19 (70,4%) 5 (18,5%) 3 (11,1%)	P=0,005 (Fisher's exact test)
Tumor type Type-1 Type-3	 6 (35,2%) 11 (64,7%)	 24 (88,8%) 3 (11,1%)	P<0,001 (chi-square test)
Depth of invasion (n) Intramucosal Submucosa Muscularis propria Subserosa Serosa	 0 3 (17,6%) 0 11 (64,7%) 3 (17,6%)	 6 (22,2%) 15 (55,6%) 2 (7,4%) 3 (11,1%) 1 (3,7%)	P=0,000 (Fisher's exact test)
Tumor focality (n) Solitary Multifocal	 16 (94,1%) 1 (5,9%)	 13 (48,1%) 14 (51,9%)	P=0,005 (chi-square test)
T status (n) T1-T2 T3-T4	 3 (17,6%) 14 (82,4%)	 23 (85,2%) 4 (14,8%)	P=0,000 (chi-square test)
Tumor location (n) Cardia Fundus Korpus Antrum	 3 (17,6%) 3 (17,6%) 8 (47,1%) 3 (17,6%)	 5 (18,5%) 3 (11,1%) 15 (55,6%) 4 (14,8%)	NS (p=0,936 Fisher's exact test)

NS: not significant

Table 4. — **Comparison of Type-1 and Type-3 gNETs**

	Type-1 (n=30)	Type-3 (n=14)	P value
Gender (n) Female Male	 22 (73,3%) 8 (26,6%)	 4 (28,5%) 10 (71,4%)	p=0,005 (chi-square test)
Median Age (yrs)	53 (38-94)	64,5 (43-80)	p=0,044 (Mann Whitney U test)
Median tumor size (mm)	8,5 (0,8-120)	62,5 (40-130)	p<0,001 (Mann Whitney U test)
Tumor grade (n) Grade 1 Grade 2 Grade 3	 23 (76,6%) 7 (23,3%) 0	 0 3 (21,4%) 11 (78,5%)	p<0,001 (chi-square test)*
T stage (n) T1-T2 T3-T4	 26 (86,6%) 4 (13,3%)	 0 14 (100%)	p<0,001 (chi-square test)
Tumor focality (n) Solitary Multifocal	 10 (33,3%) 20 (66,6%)	 13 (92,8%) 1 (7,1%)	P<0,001 (chi-square test)
Lymph node metastases (n) N0 N1 Nx	 23 (76,6%) 6 (20%) 1 (3,3%)	 5 (35,7%) 9 (64,2%)	p=0,007 (Fisher's exact test)
Distant metastases (n) M0 M1	 29 (96,6%) 1 (3,3%)	 9 (64,2%) 5 (35,7%)	p=0,002 (Fisher's exact test)

*it was categorized "Grade 1+Grade 2" as one group and "Grade 3" as an other group.

Table 5. — **Histopathological features of Grade 2 gNETs**

	Tumor diameter (mm)	Tumor type	Mitotic count/10 HPFs	Ki67 labeling index, %	Depth of invasion	Lymph node metastasis	Distant metastasis
Case 1	5	Type-1	6	5	Submucosa	No	No
Case 2	10	Type-1	4	5	Submucosa	No	No
Case 3	15	Type-1	2	3	Muscularis propria	No	No
Case 4	20	Type-1	2	3	Submucosa	No	No
Case 5	45	Type-1	10	10	Subserosa	No	No
Case 6	10	Type-1	2	4	Submucosa	Yes	No
Case 7	40	Type-3	4	8	Subserosa	Yes	Yes
Case 8	50	Type-3	17	16	Subserosa	Yes	Yes
Case 9	70	Type-3	5	15	Subserosa	Yes	No
Case 10	120	Type-1	15	12	Subserosa	Yes	No

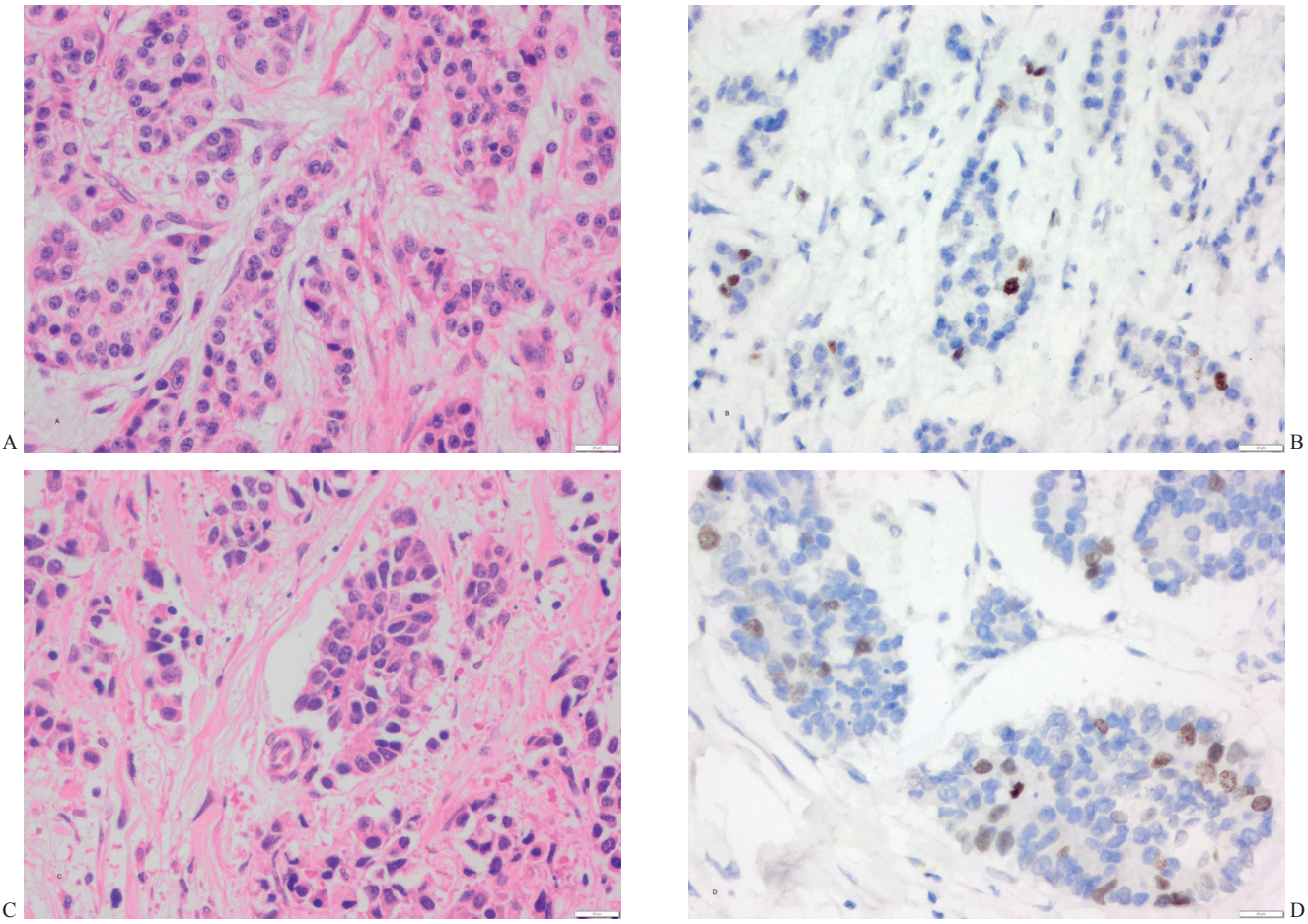

Figure 1. — A. Case 2, a non-metastatic G2 gNET with 4 mitoses/10 HPF (H&Ex400) B. Ki-67 proliferation index is 5% (Ki-67 immunohistochemistryx400). C. Case 8, a metastatic G2 gNET to lymph nodes and liver with 17 mitoses/10 HPF (H&Ex400) D. Ki-67 proliferation index is 16% (Ki-67 immunohistochemistryX400).

significantly (6-10 times) in the last 50 years (6,7,8,9). When we retrieved gNETs in our institution, we noted that 54,2% of gNETs were diagnosed in the last one-third of the study period. Improved diagnostic techniques, increased frequency of endoscopic and radiological imaging, improved awareness of pathologists and clinicians have increased the incidence of gNETs. Also widespread use of proton pump inhibitors may have increased the incidence (10). The increasing incidence of gNETs has made these tumors more significant.

Because of their heterogeneous biological behavior and associated treatments, prognosis for patients with gNETs remain unclear. To date, the most common predictive systems for gNETs are the AJCC and European Neuroendocrine Tumour Society [ENETS] staging system, which are based on the depth of tumor invasion, the number of metastatic lymph nodes, and the presence/absence of distant metastases.

As the metastatic potential is an indicator of prognosis, we compared several clinicopathologic parameters of metastatic and non-metastatic patients. Tumor type, tumor size, depth of invasion, tumor focality, and tumor grade were found to be significant risk factors for metastasis. The risk for metastases was higher in type-3 and solitary tumors and further related to tumor size, grade and depth of invasion.

In our cohort, type-3 gNETs occurred solitary, were greater in size and more invasive in growth in comparison with type-1 gNETs, and had a worse prognosis with significantly higher metastatic potential (11,12). This is in agreement with existing literature.

There was a male predominance (71,4%) and most type-3 tumors were seen in elderly patients (median age of 64,5), again in agreement with other studies, also showing a worse clinical outcome (13,14).

Although type-1 gNETs mostly have an indolent course, we know that they occasionally can metastasize, and it is important to predict these cases. Among 30 type-1 gNET cases 6 were metastatic to lymph nodes and/or distant sites. The prevalence of metastasis for type-1 gNETs has been reported as 3-5% in various studies (15,16). The rate was higher in our study, 20% in our type-1 gNET cases, cause we included patients who underwent radical surgery.

In literature, tumor size ≥ 10 mm and invasion of the muscularis propria were reported to be associated with a higher risk of lymph node metastases for patients with type-1 gNETs (4,17-20). In our cohort, none of the intramucosal tumors had a metastatic disease. Tumor size was ≥10 mm for 5/6 metastatic cases (83,3%) and all invaded the submucosa, subserosa or even serosa. Statistical analysis was not feasible for our study, but when we look closer to the 6 metastatic type-1 cases, 4 cases were G1 and 2 were G2.

Our data showed that tumor grade is correlated with tumor type and prognosis in gNETs. In our cohort, 23,3% of type-1 gNETs were G2, while the others were G1; and 21,4% of type-3 gNETs were grade 2, while the remaining were G3.

The World Health Organization grading uses a wide range of 2-20 mitotic count and 3-20% Ki67 proliferation index for grade 2 gNETs. In our study, Ki-67 proliferation index was in the range of 3-10% for seven cases and 11-20% for three cases. The latter cases have metastasized. Hauck et al. reported that patients with tumors with a Ki67 of 3-9% showed a better response to treatment and significantly longer survival as compared to patients with tumors with a Ki-67 of 10–20% (21). We only have a limited number of cases, but in our cohort clearly the grade 2 cases with a Ki67% >10% and the type-3 subgroup had a worse prognosis and more aggressive behavior.

Because of the heterogeneous biological behavior, determining the right treatment choice is a highly challenging issue for clinicians. Treatment schemes are mainly based on clinicopathological classification. According to the ENETS consensus guidelines for type-1 tumors, surveillance or local resection is recommended if the tumor is <10 mm in size. Surgical resection is recommended for patients if the tumor extends beyond the submucosa (22). Antrectomy could be a potential option for recurrent or multifocal (>5-6 foci) type-1 gNETs (23) because it reduces gastrin levels by removing gastrin secreting G cells, which cause neuroendocrine cell hyperplasia and tumors, thereby ensuring the regression of these lesions (24,25).

In agreement with existing literature, we recommend:

1. an endoscopic ultrasound and ^{68}Ga-DOTATATE PET/CT examination (26) for type-1 gNETs if the tumor size is ≥10 mm and/or invades the submucosa. An endoscopic follow-up or local endoscopic resection should be utilized, if the tumor size is <10 mm and/or the tumor is intramucosal. Antrectomy could be an appropriate option for multifocal tumors. Surgical treatment should be considered for type-3 gNETs.
2. a two-tiered grading system as low and high grade, using the threshold 10% for Ki-67 labelling, rather than the current three-tiered system. In this system, a more aggressive treatment with surgery could be considered for high grade tumors.

Our study had several limitations. It was a retrospective study with a limited number of patients and a lack of clinical information about patients. Further studies in more extensive series are needed to evaluate the WHO 2017 neuroendocrine tumor classification system's prognostic value and to define more appropriately the prognostic parameters.

Conflict of interest: none.

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