Prognostic value of the 2017 World Health Organization Classification System for gastric neuroendocrine tumors: A single-center experience

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ABSTRACT

Background/Aims: Gastric neuroendocrine tumors (G-NETs) are rare tumors, but their incidence is gradually increasing. Despite the existence of many classification systems, determining prognosis and planning treatment in patients with G-NETs remains a clinical challenge. In this study, the prognostic value of the World Health Organization (WHO) 2017 grading system and the effect of surgery on survival in low grade neuroendocrine tumors were investigated.

Materials and Methods: G-NETs who were diagnosed between January 2000 and May 2017 were included in the study. Patients' demographic characteristics, treatment details, and survival data were obtained from medical charts. Pathological samples were re-classified according to the WHO 2017 grading system.

Results: Of the total 94 evaluated patients, 50 (53.2%) were classified with G1 NETs, 37(39.4%) with G2 NETs, 4(4.2%) with well-differentiated G3 NETs, and the remaining 3 patients with poorly differentiated G3 neuroendocrine carcinoma (NEC). The median follow-up time was 83.2 months. There was a statistically significant difference in 5-year progression free survival (PFS) between G1 tumors (100%) and G2 tumors (76%) ($p<0.001$). However, there was no statistically significant deference in 5-year overall survival rate (OS) for G1 (97%) and G2 (82%) tumors ($p=0.141$). When G2 and G1 NETs were compared according to their surgical approach, radical surgery was more frequently performed in patients with G2 tumors ($p<0.001$). However, radical surgery did not improve PFS in G1 and G2 NETs.

Conclusion: The WHO 2017 NET classification system may have low prognostic value for determining the prognosis of patients with G1 and G2 tumors. Radical surgery for G1 and G2 NETs did not improve PFS in our study.

Keywords: Gastric neuroendocrine tumors, WHO 2017 neuroendocrine tumor classification, prognosis, grade

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that originate from the multipotent stem cells of the neuroendocrine cell system. Theoretically, they can develop from and in any organ in the body (1, 2). Due to the rarity of gastric NETs (G-NETs), there are inadequate research works to determine the prognosis of this disease (3). Therefore, the purpose of this research is to evaluate the prognostic value of the World Health Organization (WHO) 2017 classification and the effects of radical surgery on survival in Grade 1 (G1) and Grade 2 (G2) NETs, which were investigated in our retrospective descriptive case series study. NETs vary from being benign to high-grade malignant and in their clinicopathological characteristics (4-6). G-NETs are mostly asymptomatic, and very few of them secrete hormones and amines to cause carcinoid syndrome (4). For this reason, an early diagnosis of non-functional NETs is usually not possible. NETs are diagnosed at a later stage due to the symptoms of primary and metastatic lesions, or incidentally in asymptomatic patients who undergo evaluation for unrelated conditions (2, 7). G-NETs are very rare tumors diagnosed in 1-2/1,000,000 individuals per year, further accounting for less than 10% of gastrointestinal NETs (8). However, there is a growing incidence of G-NETs in recent years due to an advanced experience in pathological diagnosis, physician awareness, and increased endoscopic surveillance (9, 10). The primary and most effective treatment

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of G-NETs at this moment is surgical resection. However, due to an increased incidence of G-NETs and their variable response to treatment, G-NETs have become a challenging issue for clinicians. In neuroendocrine tumors, an accurate determination of prognostic groups affects the treatment choice. Because of the rare and heterogeneous clinicopathologic features of the disease, the consensus about a standard classification is yet to be achieved. A new and comprehensive classification is needed due to NETs' pathological differences and the unpredictability of prognosis. In this manner, the European Neuroendocrine Tumor Society updated the consensus guidelines for gastroduodenal neoplasms (11), and the WHO issued a new classification in 2017 (Table 1). According to the WHO classification system, G-NETs are classified based on differentiation and proliferation, which are determined according to the mitotic activity and Ki-67 immunostaining. Additionally, mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) are defined as a new classification category. MiNENs combine neuroendocrine and non-neuroendocrine components, usually an adenocarcinoma, but may also include others, such as squamous cell carcinoma or acinar cell carcinoma. Furthermore, to qualify as a MiNEN, each component should comprise at least 30% of the tumor cell population (12).

Table 1. World Health Organization Classification 2017 for neuroendocrine neoplasms.

Well Differentiated NETs	Ki-67 index	Mitotic index
Neuroendocrine tumor (NET) G1	< 3 %	< 2/10 HPF
Neuroendocrine tumor (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumor (NET) G3	>20 %	>20/10 HPF
Poorly Differentiated NETs		
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasms (MINENs/MENENs)		

HPF: High power field, 0.2 mm^2.
Table 1 was adjusted from World Health Organization (WHO) 2017 Neuroendocrine Tumour Grading System.

MATERIALS AND METHODS

This study included the patients diagnosed with GNETs between January 2000 and May 2017 at the Hacettepe Cancer Institute. Pathological examinations confirmed the diagnosis of all the patients. Additionally, this study included patient characteristics such as demographic details, medical history, clinical features, imaging findings, treatment details, and survival outcomes. However, patients with other co-existing neoplasms, severe chronic disease and mixed neuroendocrine tumors that were defined as MiNENs and patients who did not accept follow-ups were excluded from the study. Iron deficiency anemia and vitamin B12 deficiency could be observed as the first symptom; therefore, we examined vitamin B12 and iron values of patients. All patients had been treated with endoscopic resection, subtotal/total gastrectomy, antrectomy, and an endoscopic follow-up. Subtotal/total gastrectomy and antrectomy were defined as radical surgery. All the patients were pathologically diagnosed with primary G-NETs by expert pathologists at our institution. Pathologic diagnosis was based on the typical morphological characteristics of tumor tissue and the expression of neuroendocrine markers, such as chromogranin A (CgA), synaptophysin (Syn), and cluster of differentiation (CD)56. The Ki-67 index, an indicator of cell proliferation, was calculated based on at least 500 cells in an area of higher nuclear labeling ("hot spots"). Mitoses in 50 high-power fields (HPF, 0.2 mm^2) in the areas of higher density were expressed per 10 HPF (2.0 mm^2) (13).

According to the WHO 2017 grading system, G-NETs were classified into three groups: well-differentiated neuroendocrine neoplasms (NENs), poorly differentiated NENs, and MiNENs. According to the Ki-67 proliferation index and mitotic rate, G-NETs were classified into three grades: G1, Ki-67 index <3%, mitotic rate <2/10 HPF; G2, Ki-67 index 3-20%, mitotic rate 2-20/10 HPF; and grade 3 (G3), Ki-67 index >20%, mitotic rate >20/10 HPF (Table 1). When there was any inconsistency between the Ki-67 index and mitotic rate while grading the tumors, then the higher value was accepted for the classification. The Hacettepe University Ethics Committee approved the conduct of this study.

Statistical analysis

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). The Mann–Whitney U test, chi-square test, and Student's t-test were employed for the comparisons between the groups. Tumors with missing values were omitted from the analyses. Two-sided p values of less than 0.05 were considered as statistically significant. Progression-free survival (PFS) was defined as the time interval from the time of diagnosis to the first disease recurrence, onset of certain symptoms, or death from any cause if disease did

not reoccur. Overall survival (OS) was defined as the time interval from diagnosis to death from any cause. Survival rates were estimated by using Kaplan–Meier analysis and compared by using the log-rank test.

RESULTS

Among the 94 patients evaluated according to the WHO 2017 classification (14), 50 (53.2%) patients were classified with G1 NETs, 37 (39.4%) with G2 NETs, 4 (4.2%) with well-differentiated G3 NETs, and the remaining 3 (3.2%) patients were classified with poorly differentiated G3 neuroendocrine carcinoma (NEC). One of the patients with poorly differentiated NEC had large cell tumor histology. The median follow-up duration of the study was 83.2 months (range: 1-201 months). Table 2 summarizes the patients' demographic and clinical characteristics. The median patient age was 53 years (range: 19-82). The gender ratio was balanced. The tumor sizes ranged from 2 mm to 90 mm, with a median of 9 mm. The tumors were mostly located in the corpus of the stomach and strongly positive for neuroendocrine markers, such as CgA (97.8%), Syn (97.4%), and CD56 (100%). In total, 74 (79%) patients showed symptoms during diagnosis. The most common symptoms upon initial presentation were abdominal pain/discomfort (55, 59%) and acid reflux or heartburn (22, 23%), followed by dysphagia (16, 17%), nausea and vomiting (10, 11%), and bleeding (6, 6%). The occurrence of vitamin B12 deficiency or iron deficiency as first symptoms had no considerable effect on PFS and OS in the patients diagnosed with GNETs. Somatostatin receptor imaging was performed only for well-differentiated somatostatin receptor positive tumors, and a high expression of somatostatin receptors was detected in only 25% of patients. On the basis of a blood test, elevation in lactate dehydrogenase levels was detected in three patients (3.2%), who had undifferentiated G3 NEC. Table 3 summarizes the determined invasion depth, progression, local recurrence, and metastasis ratios.

Lymph node metastasis were detected in 16 (17.2%) cases. Of these patients, ten (28%) were diagnosed with G2 tumor, three patients (75%) with G3 well-differentiated NET, and remaining three patients (100%) with poorly differentiated NEC. None of the patients with G1 NETs had lymph node metastasis at the time of diagnosis. During the follow-up, only one patient with G1 NET (2%) had local recurrence, and the patient is still living with the disease after more than ten years. Other patients with G1 NETs did not show any progression or metastasis during the 126-month follow-up. On the contrary, in patients with G2 tumors, progression was observed in 9 (24%) of the 37 patients. A total of ten patients had metastasis: seven (19%) were G2, two (50%) were G3, and one (33%) was NEC. According to WHO, the three- and five-year PFS rates for patients with G1 and G2 tumors were 100%, 100%, 80%, and 76%, respectively (Figure 1)

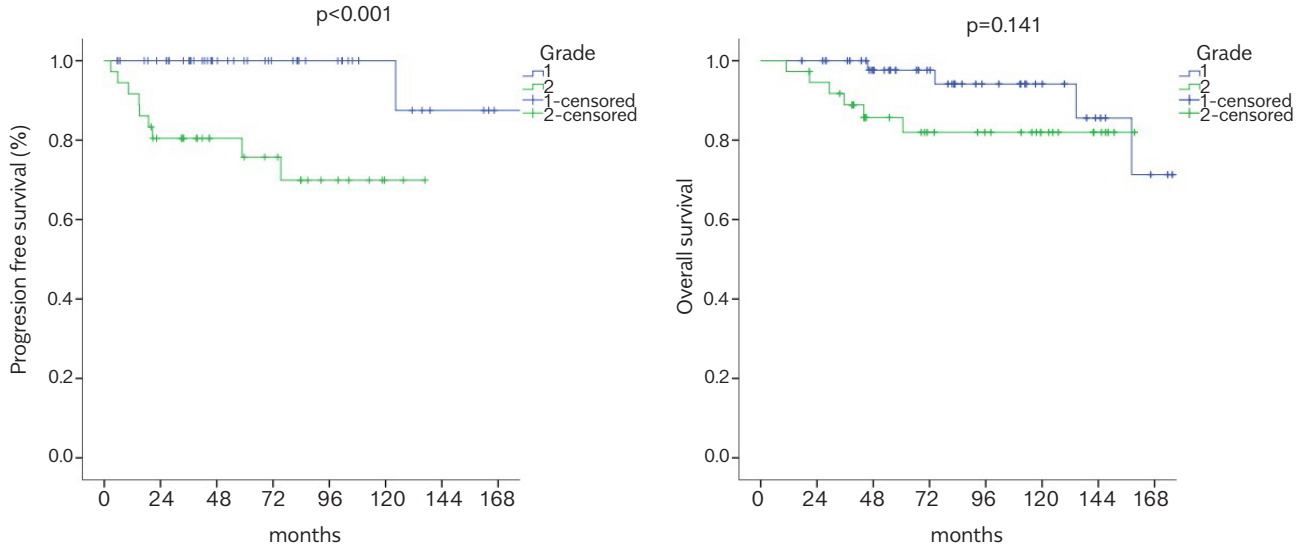

Figure 1. Progression-free survival and overall survival of Grade 1 and Grade 2 GNETs.

Table 2. Demographic and clinical characteristics of the patients with G-NENs (n=94).

Variables	G1 NET	G2 NET	G3 NET	G3 NEC	p	All G-NEN
Age, year (range)	52 (28-82)	47 (19-45)	63 (53-80)	63 (46-73)	NS	51 (19-82)
Gender						
Male n(%)	21 (42%)	17 (46%)	2 (50%)	2 (67%)	NS	43 (46%)
Female n(%)	29 (58%)	20 (53%)	2 (50%)	1 (33%)		51 (54%)
Tumor size, mm (range)	8 (2-30)	7 (2-18)	47 (30-80)	63 (46-73)	<0.001	15 (2-90)
Immunohistochemical features						
Cg A (+) n (%)	47 (100%)	37 (100%)	3 (75%)	2 (67%)	0.005	89 (97.8%)
Syn (+)	36 (100%)	35 (100%)	2 (67%)	1 (50%)	0.003	74 (97.4%)
CD56 (+)	3 (100%)	4 (100%)	2 (100%)	1 (100%)	NS	10 (100%)
Tumor Location, n (%)						
Cardia (upper 1/3)	10 (20%)	9 (24%)	3 (75%)	0 (0%)	NS	52 (55%)
Corpus (middle 1/3)	27 (54%)	21 (56%)	1 (25%)	3 (100%)		22 (23%)
Antrum (lower 1/3)	13 (26%)	7 (19%)	0 (0%)	0 (0%)		20 (22%)
Iron deficiency anemia						
No	30 (60%)	22 (60%)	3 (75%)	2 (67%)	NS	57 (60%)
Yes	19 (39%)	15 (40%)	1 (25%)	1 (33%)		36 (39%)
Missing	1 (1%)	0 (0%)	0 (0%)	0 (0%)		1(1%)
Vitamin B12 deficiency						
No	45 (92%)	35 (94%)	4(100%)	2(67%)	NS	86 (91%)
Yes	3 (6%)	2 (4%)	0 (0%)	1 (33%)		6 (7%)
Missing	1 (2%)	1 (2%)	0 (0%)	0 (0%)		2 (2%)
Somatostatin receptor imaging						
Expression (+)	1 (8%)	6 (33%)	1 (100%)	0 (0%)	NS	8 (25%)
Expression (-)	12 (92%)	12 (67%)	0 (0%)	0 (0%)		24 (75%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
LDH						
>ULN	0 (0%)	0 (0%)	1 (25%)	2 (67%)	<0.001	3 (3%)
≤ULN	49 (98%)	37 (100%)	3 (75%)	1 (33%)		90 (96%)
Missing	1 (2%)	0 (0%)	0 (0%)	0 (0%)		1 (1%)
H. pylori infection (+)						
No	34 (67%)	32 (84%)	3 (100%)	2 (100%)	NS	71 (76%)
Yes	15 (29%)	5 (13%)	0 (0%)	0 (0%)		20 (21%)
Missing	2 (4%)	1 (3%)	0 (0%)	0 (0%)		3 (3%)

G-NEN: gastric neuroendocrine neoplasm; G1 NET: neuroendocrine tumor grade 1; G2 NET: neuroendocrine tumor grade 2; G3 NET: neuroendocrine tumor grade 3; G3 NEC: neuroendocrine carcinoma grade 3; Cg A: Chromogranin A; Syn: Synaptophysin; LDH: Lactate Dehydrogenase; ULN: upper limit of normal; H. pylori: *Helicobacter pylori*; NS: non-significant.

Table 3. Patient characteristics and treatments according to grade.

	All G-NEN	G1 NET	G2 NET	G3 NET	G3 NEC	p
Depth of invasion, n (%)						
Mucosa/Submucosa	76 (84%)	49 (100%)	26 (72%)	1 (33%)	0 (0%)	<0.001
Muscularis propria/Serosa	14 (16%)	0(0%)	10 (28%)	2 (67%)	2 (100%)	
Lymph node metastasis, n (%)						
No	77 (83%)	49 (100%)	27 (73%)	1 (25%)	0(0%)	<0.001
Yes	16 (17%)	0 (0%)	10 (27%)	3 (75%)	3 (100%)	
Recurrence, n (%)						
Local	4 (27%)	1(100%)	3 (33%)	0 (0%)	0 (0%)	<0.05
Metastasis	11 (73%)	0 (0%)	6 (67%)	2 (100%)	3 (100%)	
Treatments						
Follow-up	44 (47%)	32 (64%)	12 (32%)	0 (0%)	0 (0%)	<0.001
Subtotal/TotalGastrectomy	42 (45%)	15 (30%)	23 (62%)	2 (50%)	2 (67%)	
Antrectomy	5 (5%)	3 (6%)	2 (6%)	0 (0%)	0 (0%)	
Chemotherapy	3 (3%)	0 (0%)	0 (0%)	2 (50%)	1 (33%)	

G-NEN: gastric neuroendocrine neoplasm; G1 NET: neuroendocrine tumor grade 1; G2 NET: neuroendocrine tumor grade 2; G3 NET: neuroendocrine tumor grade 3; G3 NEC: neuroendocrine carcinoma grade 3.

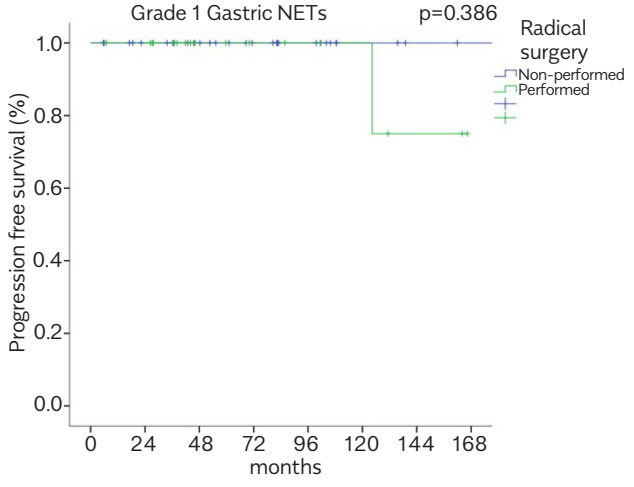

Figure 2. The effect of radical surgery on progression-free survival in Grade 1 GNETs.

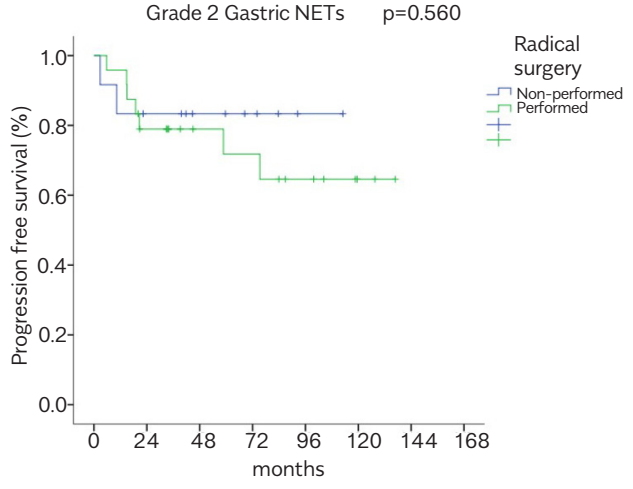

Figure 3. The effect of radical surgery on progression-free survival in Grade 2 GNETs.

(p<0.001). However, no significant difference was found between the three- and five-year OS rates of patients with G1 and G2 tumors: 100%, 97%, 89%, and 82%, respectively (Figure 1) (p=0.141). When patients with G2 and G1 tumors were compared according to their surgical approach, radical surgery (total/subtotal gastrectomy and antrectomy) was more frequently performed in the patients with G2 tumors: 68% (25/37) and 36% (18/50)

(p<0.001), respectively. However, there were no differences in PFS between 18 patients with G1 tumors who underwent surgery and 32 patients who did not undergo surgery (Figure 2) (p=0.386). Similarly, there were no statistically significant differences in the PFS rates between 25 patients who underwent surgery and 12 patients with G2 tumors who did not undergo surgery (Figure 3) (p=0.560).

DISCUSSION

There is an increasing incidence of G-NETs with variable prognoses, and the identification of predictive risk recurrence and prognosis for these patients remains a clinical challenge despite the changes in the WHO 2017 NET classification system. Our study showed that the WHO 2017 NET classification may be inadequate in determining the specific prognosis of patients with G1 and G2 tumors. Although patients with G1 and G2 NETs had different PFS rates in our study, their OS rates were similar. Additionally, there was no considerable difference in PFS between patients with G1 and G2 tumors who underwent radical surgery. Furthermore, our study might be the first study in the literature to show that radical surgery does not provide any additional benefit in terms of PFS or OS in patients with G1 and G2 tumors. Thus far, it has been reported that surgery is the primary curative treatment option for G-NETs (15-20). A recent study detected the existence of lymphatic and distant metastasis was detected independent risk factor in neuroendocrine tumors; however, this study did not show the contribution of primary surgery (21). Additionally, Schreckenbach et al. (22) showed that hepatic resection in liver metastatic neuroendocrine tumors does not improve OS. However**,** Kim et al. (23) reported that G1 and G2 NETs without lymphovascular, perineural, or submucosal invasion and tumor size less than 1 cm could be treated with endoscopic or minimally invasive surgery.

The WHO 2017 G-NET classification did not offer much innovation in terms of G1 and G2 tumors; only the Ki-67 index ≤2% was changed to <3% for G1 NETs. These changes in the WHO 2017 classification might not be enough to resolve the inadequacy of determining the prognosis of patients with G1 or G2 NETs. Previously, Kim et al. showed that there was no difference in OS between patients with G1 and G2 tumors, and the WHO 2010 classification was inadequate to determine prognosis (3, 23, 24).

Improved pathological experience, increased endoscopic follow-up, physician awareness, widespread use of gastric acid inhibitors, and changes in lifestyle may also have effect on the growing incidence of G-NETs (7, 8, 23, 25, 26). For this reason, the lack of a fully accepted classification for G1 and G2 NETs has posed considerable clinical challenges.

Like Kim et al. (24), we showed in our study that G2 tumors recurred more than G1 tumors, but no survival differences were detected in patients with G1 and G2 tumors (24). Our study also showed that radical surgery was performed for G2 tumors for a greater number of times than for G1 tumors; however, radical surgery did not provide additional survival benefits. Therefore, more conservative approaches should be considered to reduce morbidity caused by radical surgery in patients with G2 tumors. Similarly, conservative approaches have been used in other NETs. Although surgical resection is still the main treatment approach in patients with pancreatic NETs, a recent study showed that in asymptomatic, small (less than 2 cm), incidentally discovered, non-functional pancreatic NETs follow-up could be an acceptable alternative (27).

In literature, treatment options for patients who had recurrent disease after radical resection are yet to be clarified. If possible, then re-surgery could be an appropriate option for patients with recurrent disease after radical surgery (28). However, considering the long PFS of low-grade neuroendocrine tumors, follow-up, and in case of progression, performing radical surgery may be a suitable option. Unfortunately, there is no evidence to support this strategy.

As mentioned before, the primary and main treatment for limited stage G3 tumors is surgery. After surgery, depending on tumor grade and differentiation, adjuvant chemotherapy may be administered to prevent metastasis and recurrence. Current guidelines for poorly differentiated G3 tumors recommend cisplatin/carboplatin and etoposide as the first-line treatment. The most significant changes in the WHO 2017 classification were made in terms of G3 tumors. Keeping their Ki-67 and mitotic indices independent, G3 tumors are divided into well- or poorly differentiated tumors. Until 2017, studies have shown that G3 tumors identified according to the WHO 2010 classification vary in survival outcomes. Patients with well-differentiated G3 neuroendocrine tumors with a high proliferation index also had various responses to platinum-based chemotherapy (29-32).

Somatostatin analogs provide hormonal symptom control and an anti-tumoral effect in NETs with a Ki-67 index less than 10% (29, 33-35). Somatostatin receptor

imaging is functional imaging used in the determination of tumor stage, as well as the suitability of systemic somatostatin-based therapies for advanced-stage NETs (36, 37). Lutetium-177- and Yttrium-90-labeled targeted radiotherapy and somatostatin analogs are employed as the primary systemic treatment agents (26). Although the use of somatostatin analogs in metastatic NETs has been reported to improve PFS, their OS benefits are yet to be demonstrated (38).

Our study had several limitations. This was a retrospective study with a limited number of patients with G3 tumors, along with a lack of information about the administration of somatostatin analogs in patients. Therefore, this study could not evaluate the effect of somatostatin analogs on G-NETs. The study did not have any data on gastric NET types and effect on the prognosis.

In conclusion, the WHO 2017 classification may have a low prognostic value to determine the prognosis of patients with G1 and G2 tumors. Despite having a higher recurrence risk than G1 tumors, radical surgery did not provide any additional survival benefits with G2 tumors. Therefore, conservative treatment approaches may be an alternative for patients with G1 and G2 tumors. Finally, future long-term studies that include larger and well-balanced patient populations are needed to evaluate the prognostic value of the WHO 2017 NET classification system.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hacettepe University (11 October 2016, GO 16/580-26).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – Y.K., O.K., E.E., C.S., S.Y.; Design – Y.K., S.L., V.S., S.Y., S.K.; Supervision – Y.K., E.E., S.Y., S.K.; Resource – Y.K.; Materials – E.E., C.S., O.K., S.K.; Data Collection and/or Processing – Y.K., S.K., S.Y.; Analysis and/or Interpretation – Y.K., S.L., V.S.; Literature Search - Y.K., S.Y.; Writing – Y.K.; Critical Reviews – Y.K., O.K., E.S., S.Y.

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