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Research Article

Clinicopathological Features of Gastroenteropancreatic Neuroendocrine Tumors: A Retrospective Evaluation of 149 Cases

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Abstract

Objectives: Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are heterogeneous tumor groups, and they are rarely seen. Our study aims to analyze the clinicopathologic, demographic, and survival features of patients with GEP-NET.

Methods: The data of 149 patients was collected retrospectively. Clinicopathologic, demographic, and survival features of patients with GEP-NET were investigated. Survival analysis was performed by using the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed to determine independent prognostic predictors of overall survival (OS).

Results: Of 149 patients with GEP-NET, 65 patients (43.6%) were female and 84 patients (56.4%) were male. The most common, primary site of GEP-NET was stomach (40.3%). It was followed by pancreas (17.4%), small bowel/appendix (16.8%), colorectal (14%), and unknown primary (11.5%), respectively. The 3- and 5-year OS rate for the entire cohort were 69% and 60%, respectively. Median OS was not calculated, but the mean OS was 66.2 months. The factors significantly affecting the OS rate were age, grade, presence of metastasis at diagnosis, tumor diameter, and Ki-67 proliferation index in the univariate analysis. However, age was only meaningful in the multivariate analysis.

Conclusion: Patients with GEP-NET under 50 age who have smaller tumor diameter, lower tumor grade, Ki-67 proliferation index, and absence of metastasis at the diagnosis have more prolonged survival.

Keywords: Gastroenteropancreatic neuroendocrine tumor, overall survival, outcomes.

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Neuroendocrine tumors (NETs) may originate from neuroendocrine cells in different organs. An NET exhibits a more indolent clinical spectrum compared to the malign epithelial tumor. NETs may occur in many organs such as the stomach, pancreas, duodenum, colon, rectum, or parafollicular C cells of the thyroid gland. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare tumors. They exhibit different clinical, biological, and functional behaviors.[1] The most common, primary tumor sites of GEP-NETs are jejunum, ileum, and duodenum in studies performed.[2,

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[3] GEP-NETs may present different clinical features according to primary tumor localization. It separates into three groups, including hindgut, midgut, and foregut, depending on embryological derivation.[4] Histological differentiation, grading, and staging of tumor tissue determine the method of treatment and prognosis of GEP-NETs.[5] According to World Health Organization (WHO) 2010 classification, GEP-NETs are classified into three groups: low grade or grade I (G1)—well-differentiated tumors and/or Ki-67 index < 3%; intermediate grade or grade II (G2)—well-differentiated tumors and/or Ki-67 index 3%–20%, and high-grade or grade III (G3)—poorly differentiated tumors as neuroendocrine carcinomas with Ki-67 index > 20%.[6] Management of the disease requires a multidisciplinary approach. Curative treatment for these patients is surgery, but most of the patients are already advanced at the diagnosis of the disease. In this study, we aimed to define the clinicopathologic, demographic, and survival features of patients with GEP-NETs.

Methods

A total of 149 patients who were diagnosed with GEP-NETs between January 2010 and January 2019 were included in this study. All patients were fully informed and approved by the ethics committee of the Adana City Training and Research Hospital. Demographic and clinicopathological data of the patients, including age, gender, tumor location, embryological origin, Ki-67 proliferation index, distant metastasis, and survival time were recorded. Tumor grading was determined by the Ki-67 proliferation index according to WHO histopathological classification.[7] In all cases, immunohistochemistry for synaptophysin, chromogranin, and Ki-67 was performed in Adana City Training and Research Hospital Department of Pathology.

Results

One hundred and forty-nine patients were included in this study, where 65 patients (43.6%) were female and 84 patients (56.4%) were male. The median age of the patients was 57.0. The most common primary site was stomach (40.3%), followed by pancreas (17.4%), small bowel/appendix (16.8%), colorectal (14%), and unknown primary (11.5%), respectively. When GEP-NETs were classified depending on the embryological origin, GEP-NETs were derived from the foregut in 88 patients (66.6%), from the midgut in 23 patients (17.4%), and from the hindgut in 21 patients (16.0%). G1, G2, and G3 tumors were found in 92 (61.8%), 28 (18.8%), and 29 (19.4%) patients, respectively. Ki-67 index ≤ 2% was detected in 84 (60.8%) patients, between 3% and 20% in 33 (23.9%) patients, and >20% in 21 (15.3%) patients. However, the Ki-67 index was not detected in 11 (7.3%) of the patients. Distant metastasis was detected in the 53 patients (35.6%), and it was not detected in 96 patients (64.4%) at diagnosis. When the tumor diameter of the patients was examined, tumor diameters of 50 patients (47.6%) were <2 cm, for 20 patients (19.0%) were 2–4 cm, and for 35 patients (33.4%) were >4 cm. Characteristic features of the patients with GEP-NET were summarized in Table 1.

Median follow-up time was 24.1 months, and 1-, 3-, and 5-year OS rates were 87%, 69%, and 60%, respectively. From the total of 149 patients, 47 patients died. As median OS had not been reached for the patients, mean OS was calculated, and it was 66.2 months in our study. Univariate analysis was performed by age subgroup, gender, primary tumor site, embryological origin, tumor grading, Ki-67 pro-

Tablo 1. Demographic, clinicaland survival features of the patients

	Total (n=149)	%	Exitus (n=42)	$P_{log\ rank}$ for OS
Sex				
Female	65	43.6	17	0.367
Male	84	56.4	25	
Age				
<50	51	34.2	3	<0.001
≥50	98	65.8	39	
Primary tumor site				
Colorectal	21	14	8	0.005
Pancreas	26	17.4	10	
Small bowel/appendix	25	16.8	3	
Stomach	60	40.3	12	
Primary unknown	17	11.5	9	
Embryological origin[a]				
Foregut	88	66.6	22	0.135
Midgut	23	17.4	3	
Hindgut	21	16.0	8	
Tumor grading				
I	92	61.8	8	<0.001
II	28	18.8	13	
III	29	19.4	21	
Ki-67 proliferation index[b]				
≤2%	84	60.8	10	<0.001
3-20 %	33	23.9	9	
>20 %	21	15.3	23	
Distant metastasis				
Absent	96	64.4	11	<0.001
Present	53	35.6	31	
Tumor diameter[c]				
<2 cm	50	47.6	9	0.001
2-4 cm	20	19.0	5	
>4 cm	35	33.4	16	

[a]Avaliable in 132 patients; [b]Avaliable in 138 patients; [c]Avaliable in 105 patients.

liferation index, tumor diameter, and presence of metastasis at diagnosis to identify prognostic factors for survival. Age subgroup (p=0.001), tumor grading (p<0.001), Ki-67 proliferation index (p<0.001), tumor diameter (0.001), and presence of metastasis (p<0.001) were found to be significantly related to OS. Multivariate analyses were performed to parameters that were significantly found in the univariate analysis. In multivariate analysis, only age subgroup was detected as a meaningful variable for predicting OS (HR = 8.1, 95% CI = 1.0 – 65.0, p=0.04). Univariate and multivariate analyses of factors for predicting OS are summarized in Table 2 and survival curves are shown in Figure 1.

Statistical Analysis

The Chi-squared or Fisher's exact tests were performed to analyze the association between the clinicopathological parameters. The Kaplan–Meier curves and the log-rank test were used to analyze the association between patient-related clinical parameters and survival time. OS was defined as death occurring after being diagnosed with GEP-NETs. If the patients were still alive at the last clinical evaluation, their data were censored. Univariate analyses of the clinicopathological factors were performed using a Cox proportional hazards model to obtain the hazard ratios (HRs) and 95% confidence interval (CI) values. All analyses were performed using the SPSS software (version 18). P<0.05 was considered to be statistically significant.

Discussion

In this study, the clinicopathological features of the 149 patients with GEP-NETs were collected and demonstrated. GEP-NETs are heterogeneous tumors that may originate anywhere in the gastrointestinal tract. It is separated into two groups, depending on localization of the tumors: pancreatic NET and gastrointestinal NET.[8] The most common localizations of these tumors are small bowel and appendix, as shown in studies.[9] The most common tumor site was small bowel in the US Surveillance Epidemiology and End Results (SEER) analysis.[10] Stomach, pancreas, and rectum were the most common in a study performed by Fang et al.[11] In our research, the most common tumor localization was the stomach. In the light of these studies, tumor localization may change from center to center.[12]

Patients characteristically present with GEP-NETs at age 50–60.[13] The mean age of patients covered in this study was 57.0. According to the SEER database, 53% of patients with NETs present with localized disease, 20% have locoregional disease, and 27% have distant metastases at the time of diagnosis.[14] Metastatic disease was found in 24.8% of patients in the study performed by Zhang et al.[15] In another study done by Fang et al., the metastatic disease rate was 21.8% at the time of diagnosis.[11] In our study, 35.6% of patients had distant metastasis, whereas 64.4% of patients had localized disease.

Most of the patients were male in a study performed by Uppin et al.[16] In a study conducted by Sedef et al., 56% of patients were male and 44% were female.[17] Moreover, Dogan et al. reported the occurrence of GEP-NET in 53% females and 47% males.[18] Our study included 56.4% males and 43.6% females. There was no significant difference in tumor localization on the basis of gender.

Our study could not calculate the median OS, but we obtained the mean OS as 66.2 months. The 5-year survival rate was 60% in our study; 72.8% in the study by Fang et al., and 50% in SEER registries from the United States.[3] In different studies performed in Europe, the 5-year survival rate was found between 75% and 79%.[2, 5,19] Our results showed that the patients who had a G1 tumor, low Ki-67 proliferation index, absence of metastasis, smaller tumor, and age less than 50 years had more prolonged survival. Age subgroup, tumor grading, Ki-67 proliferation index, distant metastasis status, and tumor diameter were the statistically significant parameters for prognostic factors in the univariate analysis that was performed in our study. But

Tablo 2. Univariate and multivariate analyses of factors for predicting overall survival

	Univariate		Multivariate	
	Hazard ratio	**p**	**Hazard ratio**	**p**
Age subgroup	7.6 (2.3-24.7)	0.001	8.1 (1.0-65.0)	0.04
Gender	0.75 (0.4-1.3)	0.368	-	-
Primary tumor site	0.96 (0.74-1.2)	0.75	-	-
Embryological origin	1.1 (0.7-1.7)	0.54	-	-
Tumor grading	3.9 (2.6-5.7)	<0.001	2.2 (0.6-8.1)	0.22
Ki-67 proliferation index	3.8 (2.6-5.7)	<0.001	1.3 (0.4-4.6)	0.60
Distant metastasis	0.1 (0.06-0.26)	<0.001	2.1 (0.8-5.3)	0.11
Tumor diameter	2.0 (1.3-3.0)	0.001	1.1 (0.7-1.9)	0.53

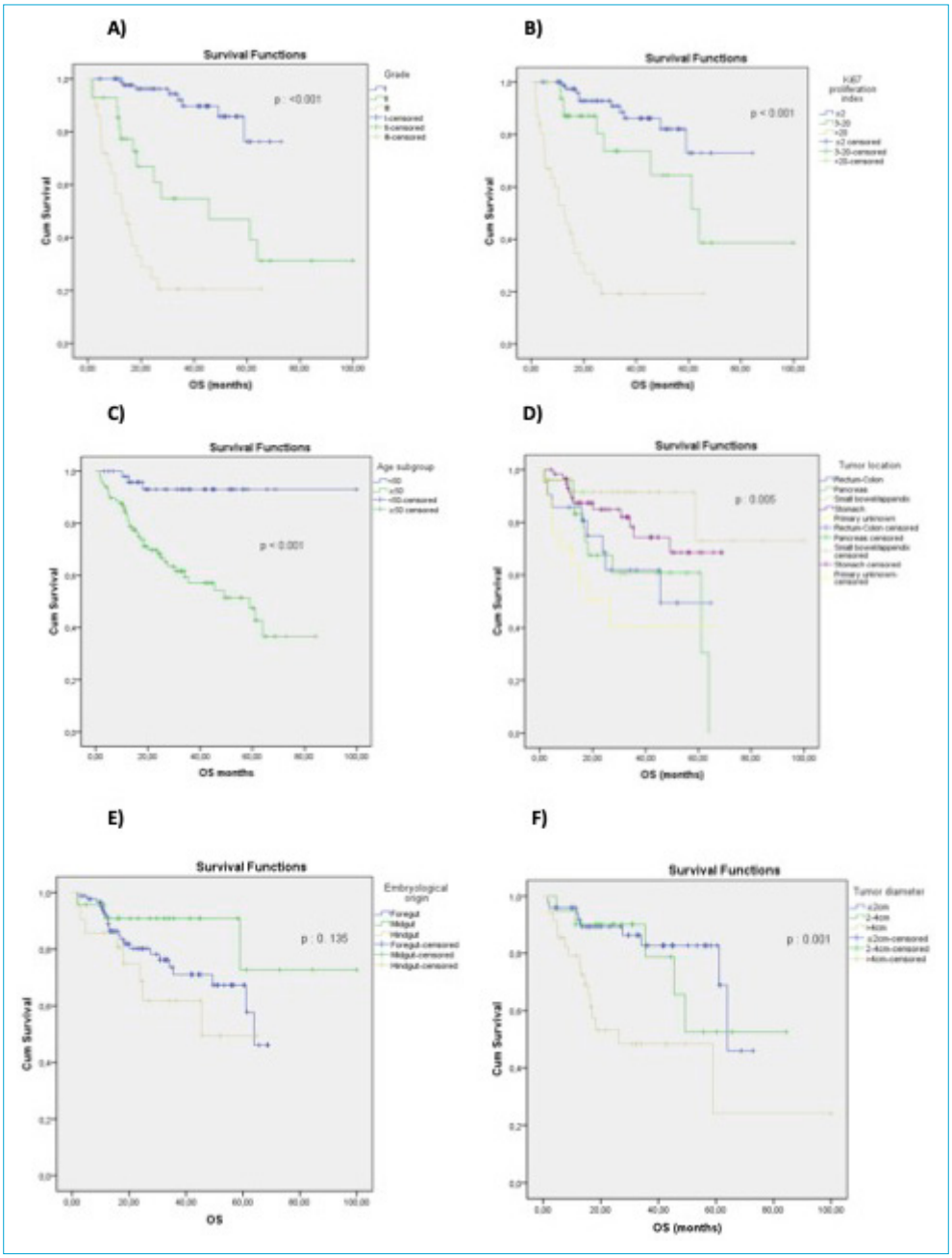

Figure 1. Overall survival **(a)**, overall survival by grade **(b)**, overall survival by Ki-67 proliferation index **(c)**, overall survival by age subgroup **(d)**, overall survival by tumor diameter **(e)**, overall survival by embiyological origin **(f)**, overall survival by tumor diameter

Abbreviation: GEP NET; gastroenteropancreatic neuroendocrine tumor.

gender was not detected as a prognostic factor. That gender was not a predictive factor was shown in different studies that were published in the literature. Age subgroup was detected meaningful only in the multivariate analysis.[5,20] Tumor stage and presence of metastasis were among the factors affecting the OS in the study of Modlin et al.[9] The presence of metastasis, grade, and age have been among the factors that affect the OS in a study by Fang et al.[11] Another study performed by Yildiz et al. included 86 patients with GEP-NET; the significantly related factors to OS were the number of lymph nodes, multifocality, metastases, and stage, however, no independent variable was detected in multivariate analysis.[21] In another study that included 128 patients, performed by Telli et al., grade and metastatic presentation were the independent predictors for survival in multivariate analysis.[22]

Our study has some limitations. First, our study was retrospective. Second, the number of patients was lower in the current study than that is multicenter studies and extensive epidemiological studies in the literature. Third, tumor grading was determined according to WHO histopathological classification that was published in 2010.

Conclusion

In conclusion, this is a retrospective study that included 149 patients with the diagnosis of GEP-NET. We found an independent, statistically significant association between survival rate and age. Gastric NETs were the most frequent type of GEP-NETs in this study. Nevertheless, large-scale, multicenter, and prospective studies are warranted for these patient populations in the future.

Disclosures

Ethics Committee Approval: This study started after obtaining ethics approval from the T. C. The Ministry of Health, Health Sciences University Adana Numune Training and Research Hospital Scientific Research Evaluation Commission. (Date of Approval: 23.09.2020; Decision Number: 1079; Number: SBÜANEAH. EK. 2020/1079).

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