Original Article

Clinicopathologic Features of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) s: A Single-Center Experience

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Abstract
Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogenous group of neoplasms originating from the neuroendocrine system of the gastrointestinal tract and pancreas. There aren't many large well-designed studies investigating NETs in Turkey.
Aims: To define the clinicopathologic, demographic and survival features of patients with GEPNETs.
Study Design: Retrospective observational cohort study.
Methods: In this study, we reviewed hospital records of patients. The data was analyzed retrospectively and we investigated clinical, pathological and survival features and prognosis of patients with GEP-NETs (n=128) admitted to medical oncology department between 2003 and 2014. Survival curve estimation was performed using the Kaplan-Meier method. Univariate and multivariate Cox regression models were utilized to assess prognostic factors for survival.
Result: Among 128 patients with GEP-NETs, 61 (47.7%) were female and 67 (52.3%) were male. The most common site of tumor was stomach (36.7%). The most common stage at diagnosis was stage 4 (40.9%). The median follow-up period was 37 months. Three-years overall survival (OS) rate was 78% and 5-years OS rate was 69%. The factors that can significantly affect OS rate were clinical stage, grade, presence of metastasis at diagnosis and Ki-67 proliferation index; these factors were associated with 3 and 5-years OS rate. Moreover, grade (Hazard ratio (HR)=8.34, 95% CI: 2.16-32.22, p=0.01) and presence of metastasis at diagnosis (HR=3.18, 95% CI: 1.30-7.77, p=0.01) predicted OS independently in multivariate model, when adjusted for age and gender.
Conclusion: Higher grade and presence of metastasis at diagnosis were found to be negative independent prognostic indicators of survival in patients with GEP-NETs.
Key words: Gastroenteropancreatic neuroendocrine tumor, carcinoid tumour, neuroendocrine tumor

Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) are rare tumors with heterogeneous biological, functional and clinical behaviors [1]. Neuroendocrine cells may arise from various tissues of the body. Previous studies reported that jejunum/ileum and pancreas are the most common primary tumor locations of NET of the GEP system with changing percentages between 16-29% and 31-34% in various demographic case series [2-4]. There is a remarkable increase in the observed prevalence of GEP-NETs, due to increased awareness of disease and advanced diagnostic procedures.

The histological differentiation, grading and staging of tumor tissue define the mode of treatment and prognosis of GEP-NETs [5-6]. According to World Health Organization (WHO) 2010 classification, GEP-NETs are classified into 3 subgroups: well-differentiated tumors, separated into low-grade (G1) (mitotic count < 2/10 HPF and/or Ki-67 index <3%) and intermediate-grade (G2) (mitotic count 2-20/10 HPF and/or Ki-67 index 3-20%) categories and poorly differentiated tumors as high-grade (G3) neuroendocrine carcinomas (mitotic count > 20/10 HPF and/or Ki-67 index >20%) [7-8]. However recent studies reported high-grade (G3) tumors may have a heterogeneous biological behaviour in itself affecting both prognosis and response to treatment [9-10].

The aim of this study is to define the clinicopathologic, demographic and survival features of patients with GEPNETs diagnosed and treated in a tertiary reference oncology center for neuroendocrine tumors.

MATERIALS AND METHODS

In this retrospective and descriptive study, we reviewed the records of 128 patients who admitted to department of medical oncology, between 2003-2014 and diagnosed as GEP-NET. Ethical approval for this study was obtained from Ethics Committee with the number of 16969557-1201. Demographic and clinicopathological data such as patients age, gender, tumor location, embryological origin, presence of carcinoid syndrome, Ki-67 proliferation index, mitotic activity, presence of lymph node and distant metastasis, surgical and medical history of GEP-NET and long term survival rate were collected.

Tumor grading was determined with Ki-67 proliferation index and mitotic activity based on WHO histopathological classification published in 2010. Staging was done according to the seventh edition of the AJCC/UICC TNM classification.

Overall survival (OS) was defined as the time from diagnosis to death or last follow-up in living patients.

Statistical Analysis

The statistical analysis was performed using SPSS ver.16.5 (Statistical Package for social Sciences for Windows 16.5 Inc., Chicago, II, USA). All categorical variables were reported as frequencies and group percentages. Survival curve estimation was performed using the Kaplan-Meier method. Univariate and multivariate Cox regression analysis were used to assess factors that predict overall survival. Confidence interval (CI) was selected as 95% and p value of 0.05 was set for statistically significance.

RESULTS

Patients Demographic and Clinicopathologic Characteristics

One hundred and twenty-eight patients diagnosed with GEP-NET were included in this study. Among 128 Turkish patients with GEP-NETs, 67 (52.3%) were men and 61 (47.7%) were women. The median age was 51.5 (range 17-81). Five (3.9%) of the patients had carcinoid syndrome and 3 (2.3%) patients detected as having MEN-1 syndrome. The most common sites were stomach (47/128, 36.7%) and pancreas (39/128, 30.5%) followed by small bowel/appendix (20/128, 15.6%), colon-rectum (9/128, 7%) and metastatic NETs of unknown primary (6/128, 4,7%). Other sites included ampulla of vater (5/128, 3.9%), liver (1/128, 0.8%) and gall bladder (1/128, 0.8%). Among 47 patients of gastric NETs, type 1, 2 and 3 gastric NET distribution were as follows, 27 as type 1, one case as type 2 and 19 cases as type 3. Gastric NET type 1 was detected more in women (19 women, 8 men) while type 3 was detected more in men (13 men, 6 women).

Ki-67 index ≤2% were detected in 40 (31.3%) patients, between 3% and 20% in 25 (19.5%) patients, and >20% in 14 (10.9%) patients. It was not defined in 38.3% of the patients. Thirty-three (25.8%) patients had mitotic rate of <2/10, and 20 (15.6%) had mitotic rate of 2 to 20/10 and 2 (1.6%) had mitotic rate of >20/10. Grade of 17 tumors could not be classified but for the rest, over half of the tumors (56.8%) were grade 1, 28.8 % were grade 2 and 11.7% were grade 3 and 2,7% of the tumors were evaluated as MANEC according to WHO 2010 classification.

Among 115 patients whose stages could be classified based on TNM staging, sixteen (13.9%) patients presented with stage 0, 18 (15.7%) patients with stage 1, 15 (13%) patients with stage 2 and 19 (16.5%) with stage 3, 47 (40.9%) patients with stage 4. In overall group, 47 (36.7%) patients had distant metastasis at diagnosis. The most common metastatic organ was liver, 45 patients had liver metastasis, 3 patients had liver and bone metastasis, 2 patients had liver and ovarian metastasis, 1 patient had lung and 1 had brain metastasis. The characteristics of study population with GEP-NETs are listed in Table 1.

Therapeutic interventions

Overall, 70.3% of the patients (n=90) underwent surgery with curative intent. Endoscopic radical surgery including endoscopic mucosa resection (EMR) and endoscopic submucosal dissection (ESD) were also performed in 11 cases with gastric NETs. Fourteen patients underwent metastasectomy for liver metastases. Locoregional therapies such as transarterial chemoembolization (TACE), radiofrequency ablation and transarterial radioembolization (TARE) were carried out in 11, 6 and 12 cases, respectively. A total of 69 patients received some type of systemic treatment including chemotherapy and biological therapy during the course of their disease. Forty-four patients received somatostatin analogues and half of them (22 patients) were treated as first-line treatment. The most common first-line chemotherapy combinations included platinum-etoposide (24 patients) and streptozocin-based chemotherapy (11 patients). Seven patients received everolimus and 1 patient received sunitinib. Eleven patients received capecitabine-temozolomide regimen as second-line or subsequent therapy.

Survival and prognostic factors

After a median follow-up of 37 months, 3-year OS rate was 78% and 5-year OS rate was 69%. Cancer-related deaths (specifically due to GEPNETs) occurred in 33 (25.8%) patients. While median OS has not yet been reached for all cohort, it was 50.9 months (95% CI, 21.5-80.3) for metastatic group. Univariate analysis was performed based on age, gender, primary tumor site, embryological origin, histopathological grading, stage, ki-67 proliferation index and presence of metastasis at diagnosis to identify prognostic factors for survival. Stage ($p=0.001$), grade ($p<0.001$), presence of metastasis at diagnosis ($p<0.001$) and Ki-67 proliferation index ($p=0.01$)

were found to be significantly related to OS. Clinical stage 3/4, higher grade, metastatic presentation and higher Ki-67 proliferation index were significant poor prognostic factors. On the other hand, age, gender, primary tumor site and embryological origin were not found to be related to survival rates in univariate analysis. The significant prognostic factors for OS in univariate analysis were subjected to multivariate analysis, adjusted for age and gender. Grade (Hazard ratio (HR)=8.34, 95% CI: 2.16-32.22, p=0.01) and presence of metastasis at diagnosis (HR=3.18, 95% CI: 1.30-7.77, p=0.01) predicted OS independently. Higher grade and metastatic presentation were identified as independent predictors of poor survival. There was no difference in 3 and 5-year OS rate between pancreatic NETs and non-pancreatic NETs (p=0.316). Univariate and multivariate analyses of factors for predicting OS are shown in Table 2 and survival curves are displayed in Figure 1.

DISCUSSION

GEP-NETs are a group of heterogeneous neoplasm, that originate from diffuse endocrine system of gastrointestinal tract and may occur in different anatomic localizations. It is reasonable to classify these tumors into 2 categories as pancreatic NETs (PNETs) and gastrointestinal NETs because these two groups have different genetic and molecular characteristics [11-12]. These tumors may have different clinical presentations due to release of endocrine secretions such as serotonin or histamine. Some PNETs are functional tumors that produce hormones, causing to clinical syndromes. It is critical to manage these symptoms associated with hormone excess for both quality of life and survival [13]. Although these tumors have been considered to be rare neoplasms, many studies show the incidence has increased significantly in recent years mostly because of improvements in diagnostic procedures [3].

Previous studies showed that small bowel and appendix were the most common localizations for NETs [14-16]. However, in our study the most common tumor site was stomach (36.7%), followed by pancreas (30.5%), small bowel/appendix (15.6%) and colon-rectum (7.0%). US Surveillance, Epidemiology and End Results (SEER) national cancer registry between 1973-1997 were analyzed and 11.427 patients were diagnosed as carcinoid tumors. Of the 11.427 cases included, the most common site was small bowel (44.7%) followed by rectum (19.6%), appendix (16,7%), colon (10.6%) and stomach (7.2%) [16]. In 2012, Wang et al. published their retrospective analysis of 178 patients in a single-institution in South China and the most common site was pancreas (34.8%) followed by rectum (20.2%) and stomach (14.0%) [17]. In a recent study, Yalcin et al. reported real world data on diagnosis and treatment management in over 1000 patients with GEP-NETs from 15 countries and in their study the most common primaries included pancreas (43%) and stomach (17%) [18]. It is very clear that GEP-NET site location frequency analysis can change from center to center. The most reasonable explanation for these inconsistencies may be ethnicity and racial disparities, geographic region where the center locates but another fact is the experience of the center.

According to the retrospective analysis of 71 patients who were followed up by Dogan et al. at Ankara University Medical School between 1997 and 2008, 53% of patients were women and 47% were men while in study of Maggard et al. 56% were women and 44% were men [16,19]. In our study, 47.7% of the patients were female and 52.3% were male. No statistically significant difference was found in tumor localization according to sex, but among gastric NET subtypes, gastric NET type 1 was detected more in women (19 women, 8 men) while type 3 was detected more in men (13 men, 6 women). This may be explained by the fact that type 1 gastric carcinoids usually develop in patients with chronic atrophic gastritis which is an autoimmune disease, and most autoimmune diseases are far more prevalent among women than men which has been proven in many studies [20-21].

In SEER database, the mean age of all GEP-NET population was 61.4. While patients with appendix tumors were the youngest (54.4), patients with small bowel tumors were found as the oldest (65.1) [16]. In our study, mean age was 50.45 years and there was no statistically significant difference between groups in terms of age at the time of diagnosis (p=0.429). The ten-year gap between the median diagnostic ages of NETs in two studies is determined mainly by general younger population of our community. In general, for most malignancies, the median age of diagnosis is younger compared to world cancer statistics. In addition, our patient group was selected from patients who were followed between 2003-2014 years and the development of technology and diagnosis methods in the last 20 years may be another reason to be diagnosed at an earlier age.

In 2003, Modlin et al. published their series of 13715 carcinoid tumors. They reported the distant metastasis rate (DMR) of GEP-NET as 25.7% between 1973-1991 years and 15.5% between 1992-1999 years [14]. In study of Wang et al. DMR was found to be 23% at diagnosis and 28.1% in follow-up period [17]. In our patient cohort, de-novo metastatic patients were representing 36.7% of all cases. In terms of primary site, 46.2% of pancreatic NETs, 25.5% of gastric NETs and 41.2% of small bowel NETs were metastatic at diagnosis. The hypothesis of late diagnosis of pancreatic NETs is the nature of disease as asymptomatic presentation. Gastric NETs that were metastatic at diagnosis were type 3, which known as already aggressive neuroendocrine tumors although histological parameters show intermediate proliferative indices. There may be several reasons related to higher de-novo metastatic rate in this study: Only 5 of 128 patients (3.9%) had carcinoid syndrome, so patients admitted to hospital in late stages with asymptomatic disease and lack of awareness. Secondly, our clinic is the referral oncology center for NETs, while metastatic patients are directed to our center, patients with early stages of

disease are usually taken care of locally. In our study group most common metastatic organ for GEP-NETs was liver, other metastatic sites were bone, ovarian, lung and brain.

As surgery is the only potentially curative treatment option for GEP-NETs, it should be considered both in early stages and resectable metastatic disease [22]. In our patient cohort, 70.3% of the patients underwent surgery with curative intent. In 111 patients, 56.8% were grade 1, 28.8% grade 2 and 11.7% grade 3. Wang et al. reported the rate of curative intent surgery as 75.9% and 51.5% of these patients were evaluated as grade 1, 18.3% grade 2 and 30.2% grade 3 [17]. Additionally, Foltyn et al., evaluated the prognostic role of Ki-67 proliferation index in 2012. Among 61 patients, 62.3% were grade 1, 19.7% grade 2 and 18% grade 3 [23].

In our cohort, median follow-up time was 37 months, and OS rates at 3 and 5-years were found as 78% and 69%, respectively. In univariate analysis, small intestine-appendix and colorectal NETs were demonstrated to be having the best prognosis; both 3-year and 5-year OS rates were 90% and 89% respectively. While 3-year OS rate was found as 69% and 5-year OS rate was 49% for pancreatic NETs, it was 81% and 74% respectively for gastric NETs. There was no difference in both 3 and 5-year OS rates between these 4 groups based on tumor site of origin (p=0.275). Pancreatic and gastric NETs were diagnosed in late stages and their grades were higher, hence OS rates of these two were least favorable for site of origins.

In series of Modlin et al. with 13715 carcinoid tumors between 1992 and 1999, 5-year OS rate was 67.2% for all carcinoids; according to the localization of the tumor, the best results were obtained in rectal NETs with a rate of 87.5%, followed by appendix and small intestine with 76.3% and 76.1%, respectively. For gastric NETs, 5-year OS rate was 75.1% and the worst results were obtained in colon NETs with 69.5%. In this study, factors affecting OS were determined as tumor stage and presence of metastasis [14]. Foltyn et al. concluded that Ki-67 proliferation index is an important and necessary parameter in determining the prognosis of GEP-NETs [23]. In study of Van Gompel et al. published in 2004, it was found that the most important factors affecting OS were embryological origin and symptomatic presentation, whereas size of the primary tumor and presence of liver metastasis did not predict survival [15]. Wang et al. showed that 3-year and 5-year OS rates were found as 66.7% and 54.5%, respectively. In their study, it was concluded that the most important factors associated with OS were grade, functional status and presence of distant metastasis [17]. In study of Yucel et al. with 52 cases, published in 2013, 3-year OS rate was found as 71%. In the subgroup analysis, OS rate was 100% in stage 1, 88% in stage 2, 80% in stage 3 and 40% in stage 4. In Yucel's study; gender, age, performance status, grade, tumor localization, surgical treatment and neutrophil / lymphocyte ratio (≤ 5 or > 5) were found to affect prognosis, however only three of them became independent prognostic factors: surgical treatment (HR=0.003, 95% CI: 0.006-0.159, p<0.001), tumor of grade 3 (HR=11.8, 95% CI: 1.9-72.8, p=0.007) and a neutrophil/lymphocyte ratio of >5 (HR=4.4, 95% CI: 1.2-15.7, p=0.022) [24]. On the other hand, in study of Esin et al. with 72 patients of well differentiated NETs, 5-year OS rate was 77.5% and there found to be no relation between grade and Ki-67 proliferative index and OS rates [25]. In another study, Yildiz et al.provided retrospective data of 86 patients with GEP-NETs and they reported the factors that were correlated significantly with survival as the number of lymph nodes, multifocality, metastases, and stage; however no independent variable could be determined in multivariate analysis [26].

Since many studies have reported various parameters as prognostic factors for OS in patients with GEP-NETs; we performed our statistical analysis based on all abovementioned demographic, clinical and pathological determinants. As a consequence of univariate analysis,

the most important factors affecting OS significantly were found as clinical stage, grade, presence of distant metastasis at diagnosis and Ki-67 proliferation index. Among all, higher grade (HR=8.34, 95% CI: 2.16-32.22, p=0.01) and metastatic presentation (HR=3.18, 95% CI: 1.30-7.77, p=0.01) were independently predictive of poor survival in multivariate model.

Our study has some limitations. First of all, relatively low number of sample size especially in the categories of variables may seem to negatively affect the statistical analyses. However, a post-hoc power analysis revealed a power >0.9 in most of the survival analyses, indicating that the number of subjects in current study was adequate for the statistical analyses utilized. Secondly, this study introduces inherent biases of all retrospective designs. Thirdly, the majority of the patient group was advanced stage NET as making our cohort heterogeneous however our survival analyses were successful compared to the best data reported so far. Lastly, tumor grading was determined based on previous WHO histopathological classification published in 2010.

CONCLUSION

This is a retrospective study of 128 GEP-NET patients who are diagnosed and/or treated in a reference cancer clinic across the country. In this study, we have shown that higher grade and presence of metastasis at diagnosis are two negative independent indicators for survival in patients with GEP-NETs. Owing to the rarity of this tumor type and lack of necessary awareness among clinicians for NETs, further demographic NET registries are needed to understand the biology and course of disease.

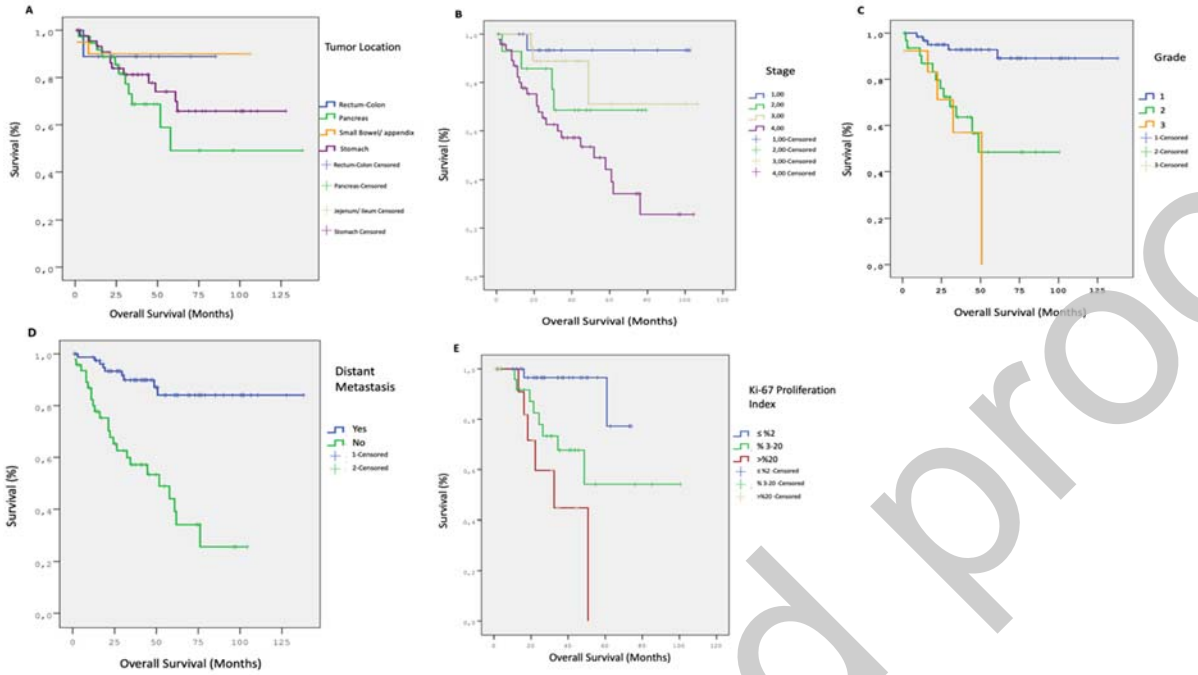

Figure 1 – Overall survival (A) Overall survival by tumor location (B) Overall survival by stage (C) Overall survival by histological grading (D) Overall survival by presence of distant metastasis (E) Overall survival by Ki-67 proliferation index

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