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A single-center experience

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AIM: *In this study, we aimed to review the demographic histopathological and clinical findings and long-term results of our GEP-NET cases, as well as to re-evaluate our cases according to the new classification systems.*
MATERIAL AND METHOD: *46 patients diagnosed as GEPNETs were presented. Immunohistochemical studies were performed in all cases. The cases were divided into 3 groups according to their embryogenic origin (Foregut, Midgut and Hindgut). All cases re-evaluated according to recent WHO (2019) and AJCC (2017) TNM calcification. Investigation was made to find differences between the embryonic origins and to find correlation between stage and grading systems with each other.*
RESULTS: *The most common localization was appendix (52.3%) The distribution of cases according to embryologic origin were as follows: foregut tumors 13 cases (27.7%), midgut tumors 27 cases (57.4%) and hindgut tumors in 6 cases (12.8%). The Ki-67 ratio was evaluated in all patients, with a mean of 6.34%±2.51 (range: 1-80). The Ki-67 ratio was less than 3% in 82.6% of patients. Mitotic count was less than 2 per/10 HPF in 76% of patients. According to WHO 2019 most of patients were Grade 1 Neuroendocrine Tumor (65.2%) and there were only 2 Neuroendocrine Carcinoma (NEC) cases. According to AJCC 2017 most cases were Stage 1 (52.1%) and only 4 cases were Stage 4. The grades and stages of our cases were statistically significantly correlated.*
Overall survival did not differ significantly with regard to embryologic origin (log-rank test, p=0.062). The median overall survival was 106±7.4 months. The 5-year cumulative survival rate was 84.1±5.6 years. Seven patients died during this time with a median time of 5 months (range: 1-31 months). In the Cox regression analysis, the percentage of Ki-67 was found to have a statistically significant effect on overall survival (p=0.000)
CONCLUSION: *Correlation was noticed between WHO 2019 and AJCC 2017 classification for grade and stage and controlled trials must be undertaken to develop a single diagnostic algorithm and to change the future management of such patients.*

KEY WORDS: Neuroendocrine Tumors, Gastroenteropancreatic neuroendocrine tumor

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are caused by malignant transformation of cells in the diffuse neuroendocrine system that regulates secretion and motility in the gut. GEP-NETs constitute 2% of all neoplasms [1].

GEP-NETs may be hormonal inactive or they may present with different clinical findings by releasing excessive hormones such as carcinoma syndrome, insilinoma, glucagoma, gastrinoma. Hormonal inactive GEPNETs may not cause any clinical findings and the diagnosis may be completely incidental.

Cell differentiation is the main prognostic marker of neuroendocrine neoplasms. These tumors have different degrees of differentiation as well as slow growth rates.

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Malignancy potentials are much lower than other epithelial gastrointestinal tumors. Well-differentiated lesions have a better prognosis than poorly differentiated lesions [2]. Survival probability of well-differentiated NETs is 35% for 5 years compared to 4% of poorly. Early diagnosis of well-differentiated tumors before metastases can improve survival markedly from 30 to 120 months. Early diagnosis and therapy with somatostatin alone or with other chemotherapeutic, surgical, and advanced technological procedures have significant impact [3].
The aim of this study was to determine the demographic, clinical and pathological characteristics of GEPNETs to discuss current diagnosis, treatment and long-term results of our gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients and to re-evaluate our cases according to the new classification systems.

Material and Methods

Patients

The study group comprised 46 patients (26 males, 20 female) with GEP-NET who were followed-up between 2009 and 2018. The clinical and pathologic characteristics of the patients were examined retrospectively. Demographic features, diagnostic methods, pathologic features, metastasis patterns, operation type, treatment modalities, and survival were recorded for each patient.

Histopathological Evaluation

All of the pathological preparations were investigated again to reclassify tumors according to the 2019 WHO classification[4].
All of our samples were determined by formalin and prepared by embedding in paraffin blocks after tissue follow-up. Tissue blocks were cut at 4 microns thick and stained with hematoxylin-eosin, then examined under a light microscope. Immunohistochemical studies performed in all cases. TNM staging was performed according to the American Joint Committee on Cancer (2017) classification [5].
For immunohistochemical study, tissue sections with a thickness of 3-4 microns were mounted on silanized slides. Chromogranin A, Synaptophysin, and Ki67 were used as anticorrosion panels. The streptavidin-biotin complex was used for the immunohistochemical technique. In assessing the mitotic index, the regions with the highest intensity of mitotic activity were selected. Mitosis was counted on the surface corresponding to 2 mm area or 10 large magnification (x400) area. Ki-67 antibody was used to evaluate the proliferation index of tumors (percentage of positive cells counted in the highest density regions).

Statistical Analysis

All calculations were operated in IBM SPSS Statistics 24.0. Comparison of categorical variables was performed using the Pearson chi-square test as appropriate. Continuous variables are presented as mean values ± standard error unless otherwise indicated, and were compared using t-tests. Spearman's test was used for correlation. Kaplan–Meier test and multivariate Cox regression analyses were used for survival time analyses. A p-value <0.05 was considered significant.

Ethic

Forty-six GEPNETs diagnosed at Gazi Yasargil Education and Research Hospital for 10 years (2009-2018) were presented after obtaining approval from the Ethics Committee of Hospital (University of Health Science Gazi Yasargil Research and Training Hospital, Clinical Research Ethics Committee, number 183, date 14.02.2018). All studies involving the "human" component were carried out in accordance with the Helsinki Declaration 2008 principles. Patients' consents were taken.

Results

Demographic Characteristics

Of the 46 patients included in the study, 20 were female (43.5%) and 26 (56.5%) were male. The age range was between 11-81 years with the mean of 38.83 years.

Clinical Features

All the cases were non-functional and abdominal pain was the most common symptom. In addition, dyspeptic symptoms were present in 25% of the patients. Bloating, constipation, rectal bleeding, weight loss, and low back pain were noticed at lower frequencies. None of the cases presented with carcinoid syndrome or symptoms related to hormonal secretion. All were sporadic cases of GEP-NET.

Table I - *Diagnostic and therapeutic procedures.*

	Procedures	n. 46
Surgery	Total gastrectomy	3
	Small bowel resection	2
	Appendectomy	24
	Distal gastrectomy	2
Endoscopy	Gastric polypectomy or EMR	5
	Colorectal polypectomy or EMR	6
Biopsy	Endoscopic biopsy from stomach	2
	Tru-cut biopsy from liver	2

All cases were examined by abdominal ultrasonography. Computed tomography was performed in 27 patients, endoscopy in 13 patients, magnetic resonance imaging in 8 patients, and positron emulsion tomography (PET-CT) in 7 patients.
Endoscopy was performed in 13 patients. 11 patients were diagnosed and treated with endoscopic polypectomy or endoscopic mucosal resection. Two of the 13 patients had liver metastasis of the stomach tumor and were diagnosed by gastric biopsy. In 2 patients diagnosed with liver true-cut biopsy, the main tumor was in the small intestine and pancreas. The remaining 24 patients had appendectomy, 3 had total gastrectomy, 2 had small bowel resection, and 2 had distal pancreatectomy (Table I).

Histopathologic Characteristics

According to the WHO 2019 classification of grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatobiliary organs, 30 cases were Grade 1, 10 Grade 2, 4 Grade 3, and 2 cases Neuroendocrine Carcinoma (NEC) (Table II).
According to American Cancer 2017 Common Classification staging criteria for neuroendocrine neoplasms, the cases were most on Stage 1 (52.1%). Nodal disease was present in 2 patients and metastasis in 4 patients (Table III). Two of 4 metastatic patients had a stomach tumor, 1 had a tumor in the small intestine, 1 had a pancreatic tumor.
The distribution of cases according to embryologic origin were as follows: foregut tumors 13 cases (27.7%), midgut tumors 27 cases (57.4%) and hindgut tumors in 6 cases (12.8%). The most common location was the appendix (n: 24) with a rate of 52.1% followed by the stomach with a rate of 21.7% (Table IV).
Comparing the Stage and Grading systems of the patients, 74.1% of Stage 1 patients were Grade 1 NET (Table V). According to the Spearman's correlation test, the Grades and Stages of our cases were statistically significantly correlated.
The Ki-67 ratio was evaluated in all patients, with a mean of 6.34%±2.51 (range: 1-80). The Ki-67 ratio was less than 3% in 82.6% of patients. The mean Ki-67 of the 7 patients who died was 46%. Mitotic count was less than 2 per/10 HPF in 76% of patients

Table II - *Histopathological features according to WHO 2019 classification.*

Terminology WHO 2019	**n. 46**
NET, G1	30
NET, G2	10
NET, G3	4
NEC, small cell type (SCNEC)	1
NEC, large cell type (LCNEC)	1
MINEN	0
Differentiation	
Well differentiated	40
Poorly differentiated	6
Well or poorly differentiated	0
Grade	
Low	32
Intermediate	8
High	6
Mitotic Count (per/10HPF)	
<2	35
2 to 20	8
20>	3
Ki 67 Index	
< 3	38
3 to 20	5
20>	3

Table III - *AJCC 2017 Classification staging*

TNM (AJCC 2017)	
T	Tx
	T1
	T2
	T3
	T4
N	N0
	N1
M	M0
	M1a
	M1b
	M1c
Stage (AJCC 2017)	
Stage	1
	2
	3
	4

Table IV - *The stages of the tumors and the embryologic origins*

	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**	**n. 46**
Forgut					
Stomach	6	1	1	2*	10
Pancreas	0	2	0	1**	3
Midgut					
Small Bowel	0	1	1	1***	3
Appendix	15	9	0	0	24
Hindgut					
Left colon	1	0	0	0	1
Rectum	4	1	0	0	5
Totally	26	14	2	4	46

*liver metastasis, ** liver+lung metastasis, *** peritoneum metastasis

Immunohistochemical Characteristics

Preparations were evaluated with chromogranin, synaptophysin, neuron specific enolase (NSE) and CD56. Chromogranin was positive in 24 out of 30 cases and synaptophysin in 18 out of 26 cases. NSE was done in 24 cases and 18 were positive whereas CD56 was done in 10 cases of which 8 were positive (Table VI).

Follow Up And Survival

The median duration of follow-up at the center was 55.5 months (between 1-125). In the Kaplan-Meier analysis overall survival did not differ significantly with regard to embryologic origin (log-rank test, p=0.062). The median overall survival was 106±7.4 months and it did not differ according to sex (p=0.98). The 1-year cumulative survival rate was 87±5 years and the 5-year cumulative survival rate was 84.1±5.6 years. Seven patients died during this time with a median time of 5 months (between 1-31 months). In the Cox regression analysis, the percentage of Ki-67 was found to have a statistically significant effect on overall survival (p=000).

Discussion

The incidence and prevalence of GEP-NET have increased due to the increased availability of advanced endoscopic and radiological imaging. In Desari et al study of the 64/971 cases of NETs [6], retrospective, population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results (SEER) program, the age-adjusted incidence rate increased 6.4-fold from 1973 (1.09 per 100/000) to 2012 (6.98 per 100/000) with the highest in patients 65 years or older 8-fold rise to 1.75 25.3 per 100/000 persons. This increase occurred across all sites, stages, and grades. In the SEER 18 registry grouping (2000-2012), the incidence rates were 3.56 per 100 000 in gastroenteropancreatic sites. Maggard *et al.* and Modlin *et al.* observed that the average age for NETs at diagnosis were 60.9 and 61.4 years respectively [7,8]. Contrary to the literature, the mean age in our series was 38.83 year.

There are multiple classification criteria for neuroendocrine tumors. Neuroendocrine tumors can be classified according to anatomical locations, biological activity and tumor histology. Neuroendocrine tumors were divided into three groups according to the embryonic origin. The ones located in the lung, bronchus, liver, gallbladder, pancreas, stomach and duodenum are fore gut; jejunum, ileum, appendix and the right two-thirds of the transverse colon are midgut; the left one-third of the transverse colon to the upper anal canal are hindgut origin [16,17]. There are articles that give different opinions about where GEPNETs are located most frequently [18]. 26.08% of our cases were located in foregut, 60.08% in midgut and 13.04% in hindgut. In our cases, appendicitis was the most common site (52.3%). This may be due to the presence of carcinoma tumor foci incidentally in appendectomy specimens.

In the last decade, attempts to unify the available classification systems have been made. The 2010 World Health Organization (WHO) classification of NETs based on the Ki67 proliferative index and mitotic count has provided clinically relevant and prognostically useful criteria; however, it has not been adopted worldwide and has been applied only in a few studies [9].

Finally, in 2019, the WHO grading system changed the definition of grade 3 NETs/NECs and the treatment strategies with new concepts of grade 3 NET/NEC [10]. The TNM scoring systems developed by the American Joint Committee on Cancer / Union for International Cancer Control (AJCC/UICC) in 2009 was changed in 2017. For this reason, the comparison of data from different centers becomes difficult or impossible. In our study, we re-evaluated the grade and stage of our patients according to WHO 2019 and AJCC 2017 classification. According to the pathology preparations that we reevaluated considering the new classification system; G1-NET was detected in 30 patients, G2-NET in 10 patients, G3-NET in 4 patients, small cell type NEC (SCNEC) in 1 patient, and large cell type NEC (LCNEC) in 1 patient in our series. Mixed neuroendocrine non-neuroendocrine neoplasms (MINEN) was not detected. On the other hand, in our series the most common Stage was Stage 1. We found a statistically significant relationship in the two-way correlation of both classification

Table V - *Correlation the AJCC Stage and WHO 2019 Grading systems*

		Garde 1 Net	Grade 2 Net	Grade 3 Net	Sc Net	Lc Nec
StageTNM	1	20	5	1	0	0
	2	8	4	2	0	0
	3	0	1	1	0	0
	4	2	2	0	1	1
Total	30	10	4	1	1	

Spearman's correlation test was applied (p:0. 037)

Table VI - *Immunohistochemically features*

	+/n	-/n
Chromogranin	24/30	6/30
Synaptophysin	18/26	8/26
NSE	18/24	6/24
CD56	8/10	2/10

+/n: Number of patients stained positive / total number of patients stained
-/n: Number of patients stained negative / total number of patients stained

systems. In other words, most of our patients were Grade 1 NET, and the same patients were frequently on Stage I simultaneously.

Neuroendocrine tumors can be sporadically and with MEN, Von Hippel Lindau, neurofibromatosis type 1 and tuberous sclerosis [11]. GEP-NETs are tumors that can coexist with other cancers of the breast, ovary, endometrium, and esophagus [12]. All of the patients included in our study were sporadic and no other malignancy was detected.

Pathologist experienced in NETs should determine visual examination of the tumor and the selective use of stains, such as Ki-67, CgA, synaptophysin, and others for proper classification [13]. In our series, chromogranin was positive in 24 out of 30 cases and synaptophysin in 18 out of 26 cases. According to Joseph *et al.* and Simpson *et al.* NSE is diffusely expressed in the cytoplasm of all the GEPNETs [14,15]. In our study, NSE was done in 24 cases and was positive in 18 of the cases.

Ki-67 is an excellent marker of cell proliferation. Ki-67 is expected to correlate with mitosis and necrosis since it represents tumor proliferation. Therefore, Low Ki-67 expression is a predictor of good prognosis due to its representation of slow tumor growth and high Ki-67 expression is a predictor of poor prognosis due to its representation of rapid tumor growth [16]. The mean of Ki 67 ratio of our cases were 6.34% ± 2.51 while the Ki 67 rate of 7 patients who died during the follow-up period was significantly higher (mean: 46%).

Biochemical markers are nonspecific in NETs. Dry flushing is symptom for pheochromocytoma and carcinomas. Diarrhea occur due to hormones or biogenic amines. Peptic ulcer, hypoglycemia, and bronchoconstriction associated with different tumors could be noticed in NETs [17]. Neuroendocrine cells produce granin family of proteins and peptides, especially chromogranin A (CgA) which is the most useful tumor biomarker in the diagnosis and management of GEP-NETs [18].

Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, single-photon emission CT (SPECT), and SPECT/CT have been used in the evaluation of patients with neuroendocrine tumors (NET). For detection of undetermined primary tumours PET/CT is superior. Octreopeptide and MIBG imaging have roles in eligibility for therapy with either Y-90 or Lu-177 labeled DOTA octreopeptides or I-131 MIBG [19]. In our study, all patients were evaluated first by ultrasonography. The second most common imaging was CT. We preferred MRI in the evaluation of rectal GEPNETs and in the evaluation of liver metastases. PET-CT was performed to 7 patients. Of all 4 metastatic patients, 2 had metastatic mass in the liver, and PET-CT was performed to find the primary origin, and the origin was found to be pancreas and small intestine.

The main treatment of GEPNETs is the surgical removal of the tumor and regional lymph nodes. On the other hand, small, single, non-invasive, and endosonographically determined GEPNETs of the stomach, duodenum, and rectum can be removed endoscopically [20-22]. Surgical intentions for NETs could be curative or palliative primary tumor and its regional lymph nodes resection; cytoreductive regional or distant metastatic resection; palliative resection of disease of bleeding, obstruction, or perforation without cytoreductive intent; and resection of multiple endocrine neoplasia syndromes associated lesions [21,23]. Of the 46 patients in our series, 24 underwent appendectomy, 3 underwent total gastrectomy, 2 underwent small bowel resection, and 2 underwent distal pancreatectomy. Eleven patients (6 colorectal and 5 gastric) underwent endoscopic polypectomy or endoscopic mucosal resection. The most common operation in our series was appendectomy. Appendectomy would be enough in tumor with tip location, less than 1 cm, without mesoappendix invasion, and lymphovascular invasion, and low mitotic index. Pathologic examination of the specimen should be done carefully. With tumors located at the base with lymphovascular or mesoappendiceal invasion or high mitotic index, right hemicolectomy and lymph node resection should be surgical options [21,23-24]. In none of our cases, the necessity of right hemi colectomy was found.

In functional GEPNETs, the clinic changes according to localization of the tumor and secreted hormones. Symptoms such as hypoglycemia due to hormonal effects, diarrhea, palpitations, tachycardia, anxiety, sweating, flushing are seen. Functional-nonfunctional distinction in GEPNETs has no prognostic significance. Since these tumors have very slow growth characteristics, diagnosis may be delayed in non-functional cases. For this reason, most of the patients may have metastasis at admission. Metastases usually occur in the liver [25-27]. In a series of 13.715 cases by Modlin et al., the metastasis rate was 25.7% between 1973 and 1991, whereas it decreased to 15.5% between 1992 and 1999 [28]. In our series, 4 patients (8.6%) had metastases. Two of these patients had liver, one had peritoneum and the other had liver and lung metastases.

GEPNETS with liver metastasis could be operated curative or palliative. Cytoreductive ablative therapies with surgical resection improve survival and quality of life compared to non-operated patients (70%–90% vs 50% at 5 years) in selected series [21,23,29].

Conclusion

GEP-NETs are increasing day by day especially in specific rectum, small intestine, and stomach with advances in diagnosis. However, the treatment has not changed dramatically. Most surgeons and physicians have limited medical education regarding GEP-NETs, less experience in dealing with these tumors. Detailed physical examination should be done for suspected NETs. Controlled

trials must be undertaken to develop a single diagnostic algorithm. New staging systems will be needed in order to determine the true frequency of these tumors and guide predictably effective targeted therapy.
In our study, we re-evaluated the grade and stage of our patients according to WHO 2019 and AJCC 2017 classification and we demonstrated the there was a correlation between these systems.

Riassunto

Obiettivo: In questo studio, abbiamo mirato a rivelare i risultati istopatologici e clinici demografici e i risultati a lungo termine dei nostri casi GEP-NET, nonché a rivalutare i nostri casi in base ai nuovi sistemi di classificazione.
Materiale e Metodo: Sono stati presentati 46 pazienti con diagnosi di GEPNET. Sono stati condotti studi immunoistochimici in tutti i casi. I casi sono stati divisi in 3 gruppi in base alla loro origine embriogenica (Foregut, Midgut e Hindgut). Tutti i casi sono stati rivalutati secondo la recente calcificazione TNM WHO (2019) e AJCC (2017). È stata condotta un'indagine per trovare differenze tra le origini embrionali e per trovare una correlazione tra i sistemi di stadio e di classificazione tra loro.
Risultati: La localizzazione più comune è stata l'appendice (52,3%). La distribuzione dei casi in base all'origine embriologica è stata la seguente: tumori foregut 13 casi (27,7%), tumori midgut 27 casi (57,4%) e tumori posteriori in 6 casi (12,8%). Il rapporto Ki-67 è stato valutato in tutti i pazienti, con una media del 6,34% ± 2,51 (intervallo: 1-80). Il rapporto Ki-67 era inferiore al 3% nell'82,6% dei pazienti. La conta mitotica era inferiore a 2 per / 10 HPF nel 76% dei pazienti. Secondo l'OMS 2019 la maggior parte dei pazienti erano tumori neuroendocrini di grado 1 (65,2%) e c'erano solo 2 casi di carcinoma neuroendocrino (NEC). Secondo l'AJCC 2017, la maggior parte dei casi era Fase 1 (52,1%) e solo 4 casi erano Fase 4. I gradi e le fasi dei nostri casi erano statisticamente significativamente correlati.
La sopravvivenza globale non differiva in modo significativo per quanto riguarda l'origine embriologica (log-rank test, p = 0,062). La sopravvivenza globale mediana è stata di 106 ± 7,4 mesi. Il tasso di sopravvivenza cumulativo a 5 anni era di 84,1 ± 5,6 anni. Sette pazienti sono morti durante questo periodo con un tempo mediano di 5 mesi (intervallo: 1-31 mesi). Nell'analisi di regressione di Cox, la percentuale di Ki-67 ha avuto un effetto statisticamente significativo sulla sopravvivenza globale (p = 0.000)
Conclusione: È stata notata una correlazione tra WHO 2019 e la classificazione AJCC 2017 per il grado e lo stadio e devono essere intrapresi studi controllati per sviluppare un singolo algoritmo diagnostico e cambiare la gestione futura di tali pazienti.

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