

RESEARCH ARTICLE

Survival Analysis and Prognostic Factors for Neuroendocrine Tumors in Turkey

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Abstract

Background: This study aimed to determine the demographical distribution, survival and prognostic factors for neuroendocrine tumors monitored in our clinic. **Materials and Methods:** Data for 52 patients who were admitted to Cumhuriyet University Medical Faculty Training Research and Practice Hospital Oncology Center between 2006 and 2012 and were diagnosed and treated for neuroendocrine tumors were investigated. **Results:** Of the total, 30 (58%) were females and 22 (42%) were males. The localization of the disease was gastroenteropancreatic in 29 (56%) patients and other sites in 23 (44%). The most frequently involved organ in the gastroenteropancreatic system was the stomach (n=10, 19%) and the most frequently involved organ in other regions was the lungs (n=10, 19%). No correlation was found between immunohistochemical staining for proteins such as chromogranin A, synaptophysin, and NSE and the grade of the tumor. The patients were followed-up at a median of 24 months (1-90 months). The three-year overall survival rate was 71%: 100% in stage I, 88% in stage II, 80% in stage III, and 40% in stage IV. The three-year survival rate was 78% in tumors localized in the gastroenteropancreatic region, and 54% in tumors localized in other organs. In the univariate analysis, gender, age, performance status of the patients, grade, localization, surgical treatment, and neutrophil/lymphocyte ratio (≤ 5 versus > 5) affected the prognosis of the patients. **Conclusions:** Most of the tumors were localized in the gastroenteropancreatic region, and the three-year survival rate in tumors localized in this region was better than the tumors localized in other sites. Surgical treatment was a positive independent prognostic factor, whereas Grade 3 and a neutrophil/lymphocyte ratio of > 5 were negative independent prognostic factors.

Keywords: Neuroendocrine tumors - survival - prognostic factors - Turkey

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Introduction

Epithelial neuroendocrine tumors (NET) are a large group of cancer originating from the neuroendocrine cells and have different clinical presentations and different prognosis due to their endocrine secretions such as serotonin and histamine. Although NETs are found in many anatomical regions, they are frequently seen in the lungs and the gastroenteropancreatic system. According to surveillance, epidemiology, and end results data, the annual incidence of these tumors in United States was reported as 5.25/100,000 in 2004 (Yao et al., 2008).

The term carcinoid was first used by a pathologist, Siegfried Oberndorfer, in 1907 to denote that they are more benign than normal adenocarcinomas of the gastrointestinal tract. As there have been problems in the classification of NET until today, in order to eliminate confusion in the terminology of NET, the classification was revised (Rindi et al., 2010; WHO 2010). WHO classification can be seen in Table 1. To determine the grade of the tumor,

necrosis, labeling index, and the number of mitoses are used in lung and thymus NET, and the number of mitoses, Ki67 index, and labeling index are used in GEP-NET (gastroenteropancreatic neuroendocrine tumor) (Klimstra et al., 2010). Many immunohistochemical stainings are performed in differential diagnoses. chromogranin A and synaptophysin are two immunohistochemical stainings with high sensitivity and specificity, which are quite useful in the confirmation of the diagnosis of NET, and especially giant cell neuroendocrine carcinomas (Travis et al., 1998; Lloyd, 2003).

Surgical resection is generally a curative treatment in early stage tumors. However, in advanced stage tumors, it can be fatal due to uncontrolled hormone secretion or progression of the tumor. Clinically, carcinoid syndrome can cause flushing, diarrhea, and fibrosis in the intestine, mesentery, and right heart valves. Somatostatin analogues consisting of octreotide and lanreotide can be used in the symptomatic treatment of carcinoid syndrome. However, in time, everolimus, one of the new goal-directed agents,

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became an option in Grade 1-2 patients who developed resistance to somatostatin analogues (Yao et al., 2011); whereas in poorly differentiated tumors (Grade 3), chemotherapeutic agents such as cisplatin, etoposide, streptozotocin, dacarbazine can be effective in treatment (Grade 3).

This study aimed to determine the demographical distribution, survival analysis, and prognostic factors of the neuroendocrine tumors were monitored in our clinic.

Materials and Methods

The demographic, clinical, and histopathological data of the patients who were admitted to Cumhuriyet University Medical Faculty Training Research and Practice Hospital's Oncology Center between 2006 and 2012 and were diagnosed with and treated for neuroendocrine tumor, were obtained by examination of the patient files and hospital records.

The performance status of the patients was evaluated by the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of the admission. While the staging of the disease was completed according to 2010 TNM staging, the grading of the disease was completed according to WHO (2010).

By using SPSS version 15.0 for analysis, frequency tests, and chi-square tests were carried out; for the comparison of median values between groups, the Mann-Whitney U-test was performed. The survival rates were calculated using the Kaplan-Meier analysis. Multivariate analysis (Cox regression analysis) was used for the evaluation of independent risk factors that had an effect on survival. The p values ≤ 0.05 were accepted as statistically significant.

Results

A total of 52 patients, 30 (58%) females and 22 (42%) males were included in the study. The median age of all patients was 56 years (7-84 years); the median age of females was 49 years (7-84 years) and the median age of males was 61 years (22-83 years). However, there was no statistically significant difference between females and males in terms of median age ($p=0.223$). The age of the patients at the time of diagnosis was found as below 65 in 32 (62%) patients, and 20 patients were 65 years and above (38%). For treatment of the patients, while surgery was performed in 36 (69%) patients, chemotherapy was administered to 23 (44%) patients and radiotherapy was administered to 8 (15%) patients; in 12 (23%) patients somatostatin analogue was used, in 15 (65%) patients cisplatin+etoposide was used, and in 8 (35%) patients other chemotherapy agents were used. The demographic

characteristics, stages, and treatment protocols are shown in Table 2.

While the localization of the disease was in the gastroenteropancreatic region in 29 (56%) patients and in other regions in 23 (44%) patients, the most frequently involved organ in the gastroenteropancreatic region was the stomach ($n=10$, 19%) and the most frequently involved organ in the other regions was the lungs ($n=10$, 19%). A neuroendocrine tumor was detected concurrently with the adenocarcinoma in one patient, which was primarily localized in the lungs, and in one patient in which it was primarily localized in the rectum. In the pathological characteristics of the patients, perineural invasion was found in 7 (20%) patients, and lymphovascular invasion was found in 12 (52%) patients. Grades 1 and 2 were detected in 30 (63%) patients, and Grade 3 was detected in 19 (37%) patients. The most frequently used immunohistochemical stains were chromogranin A, synaptophysin and neuron-specific enolase (NSE) stains. Thirty-six (92%) patients were positively stained with chromogranin A, 38 (95%) patients were positively stained with synaptophysin, and 21 (71%) patients were positively stained with NSE. Positive staining with both chromogranin A and synaptophysin was seen in 33 (87%) patients, positive staining with chromogranin A and NSE was observed in 13 patients (65%), positive staining with synaptophysin and NSE was seen in 13 (65%) patients, and positive staining with all three stains was seen in 12 (63%) patients. Combined staining characteristics were seen most frequently in chromogranin A and synaptophysin stains with a frequency of 87%. The localization, pathological, and staining characteristics of the disease are shown in

Table 2. The Demographic Characteristics, Stages, and Treatment Protocols

The demographic characteristics	No. of patients (%)
Sex (the median age)	Male (61 years) 22/52 (42)
	Female (49 years) 30/52 (58)
Age	<65 years 32/52 (62)
	≥ 65 years 20/52 (38)
Comorbidity	19/52 (37)
Family history	9/52 (17)
Performance status	ECOG0-1 30/52 (58)
	>ECOG1 22/52 (42)
Stage	I 15/52 (29)
	II 9/52 (17)
	III 9/52 (17)
	IV 19/52 (37)
Treatment	Surgery 36/52 (69)
	Somatostatin analogue 11/52 (21)
	Chemotherapy 23/52 (44)
	Cisplatin+Etoposide 15/23 (65)
	Other 8/23 (35)
	Radiotherapy 8/52 (15)

Table 1. WHO Classification was Revised in 2010 (Rindi et al., 2010)

Grade	Lung, thymus	GEP-NET*
Low (G1)	Carcinoid tumor	Neuroendocrine tumor grade 1
Intermediate (G2)	Atypical carcinoid tumor	Neuroendocrine tumor grade 2
High (G3)	1. Small cell carcinoma	1. Neuroendocrine carcinoma grade 3, small cell carcinoma
	2. Large cell neuroendocrine carcinoma	2. Neuroendocrine carcinoma grade 3, large cell neuroendocrine carcinoma

*GEP-NET: Gastroenteropancreatic Neuroendocrine Tumor

Table 3.

When the relationship between the staining characteristics and the grade of tumor is considered, no correlation was found between chromogranin A, synaptophysin, and NSE. The correlation between staining characteristics and grade of tumor is shown in Table 4.

The patients were followed up at a median of 24 months (1-90). Recurrence was seen in only 1 (2%) patient and was seen after 62 months. While there was metastasis in 19 (37%) patients during the diagnosis, metastasis developed in 4 (8%) patients at a median of 26 months (12-74 month) during the follow-up, and there was metastasis in a total of 23 (44%) patients. The liver was the most frequently involved metastatic organ (n=16, 70%). The other metastatic organs were the brain (n=3, 13%), lungs (n=2, 9%), and bone (n=2, 9%), respectively.

The three-year overall survival rate was 71%. The three-year overall survival rate according to the stages was determined as 100% in Stage I, 88% in Stage II, 80% in Stage III, and 40% in Stage IV. In the univariate analysis, gender (p=0.002), age (p=0.003), performance status of the patients (p<0.001), grade (p<0.001), localization (p=0.038), surgical treatment (p<0.001), and neutrophil/lymphocyte ratio (≤ 5 versus > 5 , p=0.003) affected the prognosis of the patients. In the multivariate analysis, surgical treatment (HR: 0.003, 95% confidence interval:

Table 3. The Localization, Pathological, and Staining Characteristics of the Disease

		No. of patients (%)
Localization	Gastroenteropancreatic	29/52 (56)
	Stomach	10/52 (19)
	Appendix	7/52 (13)
	Colorectal	5/52 (10)
	Small intestine	4/52 (8)
	Pancreas	3/52 (6)
	Other	23/52 (44)
	Lung	10/52 (19)
	Breast	7/52 (13)
	Unknown primary	5/52 (10)
	Prostate	1/52 (2)
Pathology	Lymphovascular invasion (+)	12/23 (52)
	Perineural invasion (+)	7/20 (35)
	Grade 1,2	33/52 (63)
	3	19/52 (37)
Staining	Cromogranin A (+)	36/39 (92)
	Synaptophysin (+)	38/40 (95)
	NSE* (+)	21/30 (71)
	Crom**+Synap [#]	33/38 (87)
	Crom+NSE	13/20 (65)
	Synap+NSE	13/20 (65)
Crom+synap+NSE	12/19 (63)	

*NSE: Neuron-specific enolase, **Crom: Cromogranin A; [#]Synap: Synaptophysin

Table 4. The Correlation between Staining Characteristics and Grade of Tumor

Staining characteristics		Grade 1, 2 n (%)	Grade 3 n (%)	p value
Cromogranin A	Negative	-	3 (100)	0.066
	Positive	23 (63)	13 (37)	
Synaptophysin	Negative	1 (50)	1 (50)	0.659
	Positive	23 (61)	15 (39)	
NSE*	Negative	3 (43)	4 (57)	0.633
	Positive	8 (53)	15 (40)	

*NSE: Neuron-specific enolase

Table 5. The Prognostic Factors of Patients

		Univariate analysis		
		No. of patients	3-year overall survival	p value
Sex	Male	22	23	0.002
	Female	30	88	
Age	<65 years	32	84	0.003
	≥ 65 years	20	41	
Comorbidity	No	32	77	0.237
	Yes	19	50	
Performance status	ECOG 0-1	30	95	<0.001
	>ECOG1	22	36	
Grade	1,2	33	83	<0.001
	3	19	22	
Localization	Gastroenteropancreatic	28	78	0.038
	Other	23	54	
Surgery	No	16	15	<0.001
	Yes	36	89	
Neutrophil/lymphocyte ratio	≤ 5	31	86	0.003
	> 5	21	38	

		Multivariate analysis		
		p value	HR	95% Confidence interval
Surgical treatment		<0.001	0.03	0.006-0.159
Grade 3		0.007	11.8	1.9-72.8
Neutrophil/lymphocyte >5		0.022	4.4	1.2-15.7

0.006-0.159, p<0.001), Grade 3 (HR:11.8, 95% confidence interval: 1.9-72.8, p=0.007), and a neutrophil/lymphocyte ratio of > 5 (HR: 4.4, 95% confidence interval:1.2-15.7, p=0.022) became independent prognostic factors. The prognostic characteristics of patients are shown in Table 5.

Discussion

NETs are a heterogeneous group of tumors that can be seen in different anatomical localizations and can cause different clinical presentations due to endocrine secretions such as serotonin and histamine. Although they are rarely seen tumors, in recent years, many community based studies reported that their rate of incidence has gradually increased (Maggard et al., 2004, Yao et al., 2008).

NETs are seen in all age groups. In a community based study that was conducted by Maggard et al. (2004) in 11,427 patients with carcinoid tumors, they found that the mean age was 61 years and 54% of the patients were female (Maggard et al., 2004). Doğan et al. (2012) reported that 53% of 71 patients who were followed-up with the diagnosis of NET at Ankara University between 1997 and 2008 were female and the median age of the patients was 52 years (18-85 years) (Doğan et al., 2012). In the current study, the median age of the patients was 56 years and 58% were female; similar to the other studies, the rate of female incidence was greater than in the males.

In the study of Maggard et al. (2004) while these tumors were found in the gastroenteropancreatic region in 55%, in this region they were most frequently found in the small intestines at a rate of 45% (Maggard et al., 2004). Following the small intestine, they reported the rate of incidence as: rectum 20%, appendix 17%, colon 11%, and stomach 7% in decreasing frequency. In the current study, prevalence in the gastroenteropancreatic

region was 55%; however, unlike the study of Maggard et al., it was seen most frequently in the stomach. In 2010 Yıldız et al. (2010) published the data (86 patients who had GEP-NET) of Cerrahpaşa Hospital. In their study, the most frequently seen region was the stomach (Yıldız et al., 2010). Özyalvaçlı et al. (2012) reported that the most frequently seen localization was the appendix with a ratio of 37% in 41 patients who had GEP-NET (Özyalvaçlı et al., 2012). Doğan et al. (2012) reported the localization of the tumor in 71 patients with NET as: lungs 22%, stomach 21%, pancreas 13%, other regions 44%. The current study also reported tumors most frequently in the lungs at a rate of 19% and in the stomach at a rate of 19%. The second most common organ outside the gastroenteropancreatic region was the breasts. Although primary breast NET (2-5%) is rarely seen in the literature, different from this study, primary gastric NET was found at a rate of 14% (Tavassoli and Devilee, 2003; Hauso et al., 2008; Yao et al., 2013).

Stains such as chromogranin A, synaptophysin, and NSE are among the examples of immunohistochemical stains that are used in the differential diagnosis of patients with NET (Zjačić-Rotkvić and Berković, 2010; Stojšić et al., 2011; Massironi et al., 2012). There are studies defending that there is a correlation between the staining characteristics of the tumor and the grade of the tumor. According to these studies, chromogranin A positive staining is seen mostly in well differentiated NETs, whereas NSE positive staining is seen in poorly differentiated NETs (Shayanfar and Shahzadi, 2009; Korse et al., 2012). Furthermore, the plasma levels of chromogranin A are used in disease follow-up and are thought to have role in prognosis (Kulke et al., 2011; Chou et al., 2012; Jensen et al., 2013). In the current study, synaptophysin was positively stained at a rate of 95%, chromogranin A was positively stained at a rate of 92%, and NSE was positively stained at a rate of 70%. The most common combined positive staining was seen with chromogranin A and synaptophysin. In the current study, no correlation was found between the immunohistochemical stains such as chromogranin A, synaptophysin, and NSE and the grade of the tumor; however, we believe that this result is related to the low number of patients.

Approximately 50% of the patients with NET have regional and distant metastasis at the time of diagnosis (Maggard et al., 2004; Hauso et al., 2008; Doğan et al., 2012). Yao et al. reported the stage of the disease in 35,618 patients who were diagnosed as NET between 1973 and 2004 as: stage was not reported in 20% of the patients, localized disease in 40% of the patients, regional disease in 19% of the patients, and metastatic disease in 21% of the patients (Yao et al., 2008). Doğan et al. reported that the disease was in the advanced stage in 49% of the patients and 11% were Stage III, and 38% were Stage IV (Doğan et al., 2012). Similar to the current study, 46% of the patients were at the local stage, 17% were in Stage III, and 37% were in Stage IV.

The metastasis in patients with NET was to the lymph nodes at the beginning, then metastasis to distant organs such as liver and bone occurred (Metz and Jensen, 2008).

Although primary localization of the liver is very rare in NETs, the metastasis of GEP-NETs is especially in the liver to a great extent (Mougey and Adler, 2007). In the current study, the ratio of the patients that the primary localization was unknown but who were diagnosed with liver metastasis was 10%. Additionally, 70% of the metastases were seen in liver.

In community based studies, the five-year overall survival rate for all patients was 50-70% (Maggard et al., 2004; Hauso et al., 2008), whereas the five-year survival rate in GEP-NETs was reported at a rate of 45-60% (Lepage et al., 2007; Yao et al., 2008; Lepage et al., 2010). In 71 patients with NET, Doğan et al. reported the median survival as 66 months, and median disease-free survival as 30 months (Doğan et al., 2012). In an article published in 2011 by Stoyianni et al., they reported the median survival results (1253 patients) of 21 studies with GEP-NET as 10.8-37 months (Stoyianni et al., 2011). While the three-year overall survival rate of our patients was 71%, the three-year survival rate in GEP-NETs was 78%; this rate was 54% in tumors out of GEP-NETs and this result was found statistically in favor of GEP-NETs.

The most accurate criteria for malignancy in NETs were adjacent organ invasion and metastasis. Of these criteria, diameter, lymphovascular and perineural invasion, mitotic index, and Ki67 index were found to be the most important prognostic parameters (Klöppel et al., 2007; Yıldız and Serdengeçti, 2012). In the current study, different from these parameters, the importance of gender, age, comorbidity, performance status, grade of the tumor, localization (gastroenteropancreatic versus other organs), surgical treatment, and neutrophil/lymphocyte ratio were investigated. As a result, it was detected that other parameters except comorbidity had prognostic importance. It was seen that prognosis was statistically better in female patients, in patients younger than 65, in patients who had ECOG performance of 0 and 1, in Grade 1 and 2 patients, in GEP-NETs, in patients undergoing surgery, in patients who had a neutrophil/lymphocyte ratio lower than 5. In community based study of Maggard et al., they stated that gender and ethnicity are correlated with survival and they reported that the male gender had high risk of mortality (Maggard et al., 2004). In 35,618 patients with NET, Yao et al. determined the predictive factors for prognosis as histopathology, histological grade, primary tumor site, gender, age, and race. The investigators demonstrated that the prognosis in tumors that are seen in combination with adenocarcinoma are more poorly affect in the male gender, in the elderly (aged above 60), advanced grade and stage, and in tumors localized in the liver (Yao et al., 2008).

As a result of the development and growth of the tumor, chronic inflammatory process develops by the increase in inflammatory cells in the stromal tissue and blood vessels that are found between the tumor and the normal tissue. In the normal tissue, immune response by T-lymphocytes develops against the tumor. Thus, in patients with cancer, the presence of T-lymphocyte cells is important for demonstration of the immune response against the tumor (Ropponen et al., 1997; Shimada et al., 2010). In recent years, the small number of lymphocytes is thought to

be associated with poor prognosis and the correlation of the neutrophil/lymphocyte ratio with prognosis are investigated in many cancers such as colorectal, ovarian, and lung cancers. In these investigations, the neutrophil/lymphocyte ratio was generally stratified according to 5 (≤ 5 versus >5) and it was shown that in patients with a neutrophil/lymphocyte ratio greater than 5, the prognosis is affected more poor (Walsh et al., 2005; Sarraf et al., 2009; Chua et al., 2011). This is similar to the current study, which investigated the correlation between neutrophil/lymphocyte ratio (≤ 5 versus >5) and survival. While the three-year overall survival was 38% in patients with a neutrophil/lymphocyte ratio of >5 , it was 86% in patients with a neutrophil/lymphocyte ratio of ≤ 5 . It was found that at the same time, the neutrophil/lymphocyte ratio, in combination with surgical treatment and grade, are independent prognostic factors.

In conclusion, most of the tumors were localized in gastroenteropancreatic region, and the three-year survival rate in tumors localized in this region were found to be better than the tumors localized outside the gastroenteropancreatic region. No correlation was found between chromogranin A, synaptophysin, and NSE staining and the grade of the tumor. Female gender, young age, low grade, good status of performance, and surgical treatment were determined as positive factors affecting the prognosis. Surgical treatment became the positive independent prognostic factor, whereas Grade 3 and a neutrophil/lymphocyte ratio of >5 became negative independent prognostic factors.

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