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Best prognostic factor of neuroendocrine tumors: Grade or Stage? A multidisciplinary single-center study

UPPER GI

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ABSTRACT

Background/Aims: Currently, there is no definite consensus about the prognostic factors of neuroendocrine tumors (NETs). We evaluate epidemiology, survival and especially prognostic factors in NETs.

Materials and Methods: Patients who had a NET and were diagnosed between 2000 and 2014 at a tertiary care center were included. Demographic data, tumor characteristics and survival rates were evaluated, retrospectively.

Results: Two-hundred and thirty-three patients (123 male, 110 female; median age, 55 years [16–92 years]) took part in the study. Primary NET sites were the lung (n=56), stomach (n=50), pancreas (n=39), colorectal (n=21), small intestine (n=19), and appendix (n=19). According to the NET classification by the WHO in 2010, 60% (n=140) of patients were grade-1, 15% (n=35) were grade-2, and 25% (n=58) were grade-3. According to TNM staging, 88 patients (37.8%) were stage I, 30 patients (12.8%) were stage II, 22 patients (9.5%) were stage III, and 93 patients (39.9%) were stage IV. Univariate analysis revealed significant associations between gender, age, grade, lymph node metastasis, distant metastasis, stage, and the number of organs impacted by metastases and overall survival. However, with multivariate analysis only age greater than 55 years, advancing grade, and inoperable tumors were significantly associated with shortened survival. Five-year survival was 81% in grade-1, 34% in grade-2, and 9% in grade-3 NETs.

Conclusion: This study is the most comprehensive study in Turkey that has evaluated NETs using a multidisciplinary approach. Also, we suggest that age, operability and especially grade rather than stage are the most important prognostic factors in NETs.

Keywords: Neuroendocrine tumor, grade, stage, Ki-67 index, prognostic factors

Original Article

INTRODUCTION

Neuroendocrine tumors (NETs) are rare tumors that account for approximately 1%–2% of all neoplasms (1). Using data gathered between 1973 and 2004 from an epidemiological database in the United States, The Surveillance Epidemiology and End Results (SEER) study reports the incidence of NETs as 5.25 per 100.000 persons (2). The incidence and prevalence of these tumors have been increasing in recent decades (3).

The observed changes in the incidence and prevalence of NET may be partly due to the rising number of asymptomatic NET cases that are incidentally identified because of the increased availability of modern endoscopic and radiological imaging techniques (4,5). Current data suggest that PET with [^{68}Ga-DOTA]-D-Phe(1)-Tyr(3)-octreotide effectively identifies metastatic NETs (4) and that endoscopic ultrasound is one of the important diagnostic methods both during the evalua-

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tion of NETs or NET suspicion and for the decision of operability (5). Most trials have broadly agreed that NET tumors primarily arise from the gastrointestinal tract and pancreas (65%) and the bronchopulmonary system (25%), while 10% of NETs originate from other sites, including the urogenital system, head and neck, thymus, breast, and skin (5-7).

Both previous and current World Health Organization (WHO) classifications make distinction between well-differentiated and poorly differentiated neoplasms. All well-differentiated neoplasms, whether benign or metastatic, are now called neuroendocrine tumors *(NETs)* and graded as grade 1 (G1) (Ki-67 ≤2% or ≤2 mitoses/10 BBA) or grade 2 (G2) (Ki-67: 3%–20% or 3–20 mitoses/10 BBA). In comparison, poorly differentiated neoplasms are called neuroendocrine carcinomas and graded as grade 3 (G3) (Ki-67 >20% or >20 mitosis/10 BBA). The term "carcinoid" is now synonymous with G1 well-differentiated neuroendocrine tumors (8). After the WHO 2010 classification of neuroendocrine tumors by grade, histopathologic features were found to be more important than tumor-nodes-metastasis (TNM) staging in prognosis. It was revealed in a recent study that overall survival (OS) is longer in patients with grade 1 NETs than for grade 2, for which in turn OS is longer compared to grade 3 NETs (9).

To date, there have been only a few studies in Turkey on the epidemiology of NETs (10,11). None of which were comprehensive enough to quantify prevalence and incidence of NETs, therefore these rates remain unclear in Turkey. The objective of this study is to determine the population screening of these tumors in a center from Turkey based on patient characteristics, tumor characteristics, treatment, and survival during the period of 2000 to 2014. We also evaluate the factors affecting survival with NETs.

MATERIALS AND METHODS

Between January 2000 and January 2014, two hundred thirty three patients with NET who were treated in a tertiary care center in collaboration with the departments of oncology-endocrinology-gastroenterology-surgery-pathology-radiology and nuclear medicine were enrolled in the study. All patients were evaluated every two weeks in the above mentioned center using a multidisciplinary approach. Ethics committee approval and informed consent were received (ethics committee approval number: 2014/332) for this retrospective study. Patients were followed-up for at least 1 year. Typical and atypical carcinoid tumors and large cell neuroendocrine carcinomas were included among the bronchopulmonary NETs. Functional NETs, such as insulinoma or glucagonoma, except for NETs with carcinoid syndrome, were excluded from the study. Participants lived in 10 cities in the center regions of Turkey. The patients were evaluated retrospectively for demographical, carcinoid syndrome and other symptoms, diagnostic methods (CT, octreotide scintigraphy, Ga-68 PET-CT), primary tumor site, lymph node metastasis, distant organ metastasis, metastatic organ counts, TNM staging, annual incidence rates, tumor characteristics, grade at diagnosis (according to the Ki-67 index or mitoses/10BBA), treatment modalities (surgery, chemotherapy, somatostatine analogues, everolimus, sunitinib and peptide receptor radionuclide therapy), operation type (curative, palliative or none) and overall survival.

Patients with pathological examination results supported by the World Health Organization (WHO) 2010 classification were recruited to the study as grade 1 NET, grade 2 NET, and grade 3 NET. Pathological examination of the cases that were diagnosed before 2010, were re-evaluated according to the WHO 2010 criteria by a single pathologist.

Survival rates were calculated by the Life Table, Kaplan Meier and Cox Regression methods. Overall survival was defined as the interval between the beginning of treatment and the date of death or last known alive.

RESULTS

Patients characteristics

A total of 233 patients were enrolled. Among these patients, 123 patients (52.8%) were male and 110 patients (47.2%) were female. When we consider age at diagnosis, the peak years was the sixth decade and the median age was 57 years (range, 16–84 years) and 53 years (16–92 years) in males and females, respectively, and the median age was 55 years in all patients. The most common site was lung in parallel with the literature. We could not find the origin in 19 patients (8.1%) with NET. Interestingly, 10 NET cases who were previously diagnosed with liver metastasis and with unknown primary then scanned with Ga-68 PET CT, which showed that their primary origin was the pancreas. The number of primary tumor sites are shown in Table 1.

Incidence rates

There were 55 diagnoses (23.5%) during the first seven year period between January 2000 and January 2007, however there

Table 1. Primary tumor sites of neuroendocrine tumors between 2000 and 2014 in our center

Primary tumor site	Number of patients	%
Lung	56	24.0
Stomach	50	21.4
Pancreas	39	16.7
Colorectal	21	9.0
Small intestine	19	8.1
Appendix	17	7.3
Unkown primary	19	8.1
Others	12	5.1

Other primary sites: 3 bladder, 2 breast, 2 cervix uteri, 1 ovarian, 1 renal, 1 larynx, 1 nasopharenx, 1 gall bladder

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were 178 diagnoses (76.5%) during the second seven year period between January 2007 and January 2014. Moreover, approximately half of the patients (49.3%) were diagnosed in the last three years. The incidence of NETs is increasing all over the world as well as in Turkey (Figure 1).

Carcinoid syndrome and the other symptoms

The carcinoid syndrome rate was found to be 11.1%. Small intestine and pancreatic originated NETs were the most common sites concurrent with carcinoid syndrome with 26.3% and 23.1%, respectively. Also, 18 of the 26 patients with carcinoid syndrome (69.2%) were metastatic, and all of them had liver metastasis. The most common symptom was abdominal pain, which was present in 75 patients (32.2%). Interestingly, 47 patients (20.1%) were diagnosed incidentally. Other frequent symptoms were dyspeptic complaints (15.1%), weakness (9.4%) and weight loss (8.2%).

Metastases

We found that 88 patients (37.8%) were stage I, 30 patients (12.8%) were stage II, 22 patients (9.5%) were stage III and 93 patients (39.9%) were stage IV at diagnosis, according to TNM staging. The most common metastatic organ was the liver with 75.2% among all metastatic NETs. The pancreas, lung and small intestine were the most common primary sites in the metastatic patients with 61.5%, 33.9%, and 26.3%, respectively. The metastasis rates were 24%, 19%, and 11.7% in patients with gastric, colorectal and appendix NET, respectively.

Tumor characteristics

One hundred and forty patients (60%) were grade 1 NET, 35 patients (15%) were grade 2 NET and 58 patients (25%) were grade 3 NET. Among the grade 1 NET patients, the most common origin was the appendix, among the grade 2 NET patients, the most common origin was the lung and among the grade 3 NET patients the most common origin was unknown origin. The tumor characteristics are summarized in Table 2.

Treatment

Surgery

Overall, 163 patients (70%) had surgical resection for treatment. Fifty-six percent of patients underwent curative surgical resection, and 14% of patients underwent palliative surgical resection.

Somatostatin analogue and targeted therapy

Forty-six patients (19.7%) were treated with only somatostatin analogue, 11 patients (4.7%) were treated with somatostatin analogue plus everolimus combination and 2 patients were treated with sunitinib.

Chemotherapy

Cytotoxic chemotherapy was administered to 59 patients who were mostly grade 2 and 3. Forty-one patients received platin based chemotherapy, 12 patients received 5-flourourasil based chemotherapy and 6 patients received capesitabin plus temozolamid combination in the first line chemotherapy. Thirty-one patients with grade 3 neuroendoendocrine carcinom were not given chemotherapy because of the performance status.

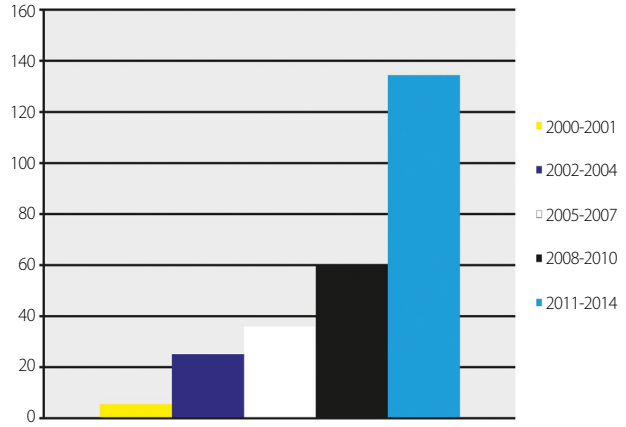

Figure 1. Number of NET patients by year in the center of Turkey

Table 2. WHO 2010 classification of neuroendocrine tumors by grade regarding primary tumor sites

Primary tumor site	Grade 1	Grade 2	Grade 3
Lung	22 (39%)	12 (22%)	22 (39%)
Stomach	38 (76%)	4 (8%)	8 (16%)
Pancreas	24 (62%)	8 (20%)	7 (18%)
Colorectal	16 (76%)	3 (14%)	2 (10%)
Small Intestine	15 (78%)	2 (11%)	2 (11%)
Appendix	16 (94%)	1 (6%)	0
Unknown Primary	6 (32%)	4 (21%)	9 (47%)
Others	3 (25%)	1 (8%)	8 (67%)
Total	140	35	58

WHO: World Health Organization

Peptide receptor radionuclide therapy (PRRT)

Ten patients (4.3%) were treated with PRRT, namely Lutetium (LU-77) DOTA-NOC and/or Yttrium (Y-90) DOTA-NOC treatment.

Survival

The median duration of follow-up was 32 months (min-max: 1–168 months). Ninety-three patients (39.9%) had died during follow-up. Among the exitus patients, 23 patients were grade 1, 20 patients were grade 2 and 50 patients were grade 3. For all NETs, the 1-year survival rate was 75%, 3-year survival rate was 63% and 5-year survival rate was 53%.

The association between survival and several factors, including age, sex, primary tumor site, carcinoid syndrome, grade (WHO staging), presence of lymph nodes and distant organ metastasis, number of metastasis sites and TNM

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Table 3. Multivariate analyses with the Cox-regression method for survival

	Odds	95% CI for exp (B)	p
Age			
>55 years	1		
≤55 years	2.64	1.61–4.34	p<0.001
Surgical Treatment			
None	1		
Palliative	1.18	0.66–2.11	p=0.696
Curative	3.83	2.10–6.99	p<0.001
Grade			
Grade 3	1		
Grade 2	3.21	1.85–5.58	p<0.001
Grade 1	9.47	4.96–18.06	p<0.001

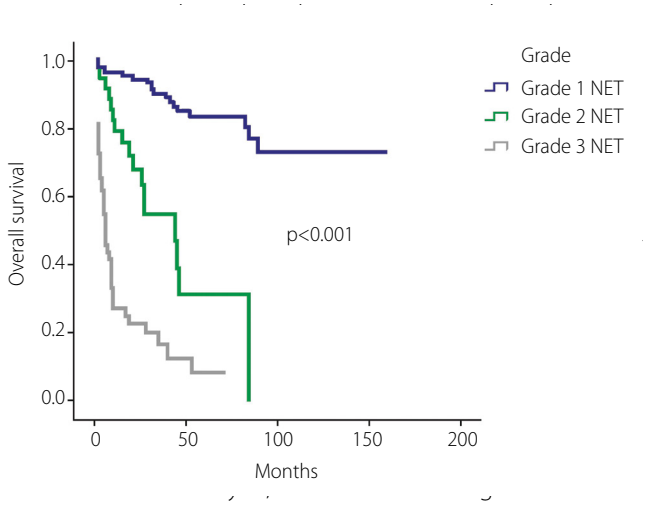

Figure 2. Comparison of the survival analyses in grade 1, grade 2, and grade 3 NETs

only age, surgical treatment and grade. Factors, including age over 55 years old, advancing grade and treatment of tumor without surgery, shorten the median survival time in NETs (Table 3).

One year survival was 96% in grade 1, 77% in grade 2, and 23% in grade 3 NET. Three-year survival was 89% in grade 1, 48% in grade 2, and 14% in grade 3 NET. Five-year survival was 81% in grade 1, 34% in grade 2, and 9% in grade 3 NET. The median survival was 6 months in grade 3 patients (95% CI: 4.35–7.65 months), 44 months in grade 2 patients (95% CI: 23.88–64.12 months), and in grade 1 patients the median survival could not be reached (p<0.001) (Figure 2).

The five-year survival rates were 78%, 47%, and 0% for typical carcinoid tumors, atypical carcinoid tumors, and neuroendocrine carcinomas in lung, respectively. Additionally, in gastroenteropancreatic (GEP) NETs, the 5-year survival rates were 82%, 28%, and 10% for grade 1, grade 2 and grade 3 NETs, respectively.

DISCUSSION

Neuroendocrine tumors are relatively rare, although their incidence is gradually increasing in Europe and the United States (US), partly because of the increased diagnosis related to the use of advanced imaging techniques. In the US, a two- to three-fold increase has been reported in the incidence of NETs (2). The diagnosis of NETs has increased over the last 5 years in Turkey. In our study, the frequency of NETs was nearly identical between 2000 and 2010 and between 2011 and 2014 based on the number of first diagnoses.

In recent studies, it has been reported that NET incidence is higher in men than in women (12,13). Nadler et al. (14) reported a mean age of incidence of 57 years. In our study, age/sex characteristics of patients were similar to those of previously published epidemiological studies (13-15).

Fifty-five years was the threshold age value for prognosis, and survival was found to be shorter in patients older than 55 years. In the registry study of 455 patients by Caldarella et al. (13), the threshold value for age was reported as 65 years, which means that patients older than 65 years had a shorter survival time after diagnosis. In another registry study, the SEER study authored by Yao et al. (2), 35,825 patients were separated into 3 groups by age (<30 years, 31–60 years, >60 years). Yao et al. (2) showed that survival time is shorter according to age, particular for those aged over 60 years (p<0.001). Further studies are needed to determine a cut-off value for the association between age and survival.

Clinical trials have reported that the lung is the most common site for NETs, with gastric NET incidence increasing and appendical NET decreasing in recent years (16). For our patients, the most common primary site was the lung and the least common site was the appendix. Our results show that the stomach is the second most common site. In a study performed in the Netherlands, 12% of the total number of NETs was reported as being of unknown origin (17), whereas this rate was 7.1% in another study (8). Similarly, the proportion of NETs of unknown origin in our study was 8.1%. With the development of imaging methods, such as Galium 68 PET-CT and endoscopic ultrasound, the rate of NETs with an unknown primary site has been reduced.

Pancreatic NETs were more frequently diagnosed with distant metastases than other NETs (13). According to the US SEER study (2), in a series of 35,825 cases between 1973 and 2004, distant metastases were present in 64% of PNETs, compared to 21% of colorectal, and 19% of small intestine NETs. In our study, distant metastases were more common in pancreatic NETs (61.5%), followed by lung and small intestine NETs, and this finding is similar to what has been reported in the literature. Generally, the most common primary site of metastatic NETs is the pancreas and the most common metastatic site for pancreatic NETs is the liver. Therefore, we can speculate that

unknown primary NETs with large liver metastases would generally originate in the pancreas. During scanning, pancreatic lesions may be obscured by visible liver metastases. Unlike other malignancies, very large NETs with widespread metastases may be present while the primary tumor is small. In our study, we reveal with Ga-68 PET-CT that 10 patients who were initially diagnosed with liver metastases with an unknown primary have cancer with the pancreas being the primary site. Therefore, first scanning the pancreas with multislice CT/MRI or Ga-68 PET CT to determine the primary origin may be appropriate in NETs with an unknown primary site.

Carcinoid syndrome occurs in only 10% of all patients with carcinoid tumors (18) and it is most often associated with midgut tumors (19). In their study, Soga et al. (20) reported a carcinoid syndrome rate of 7.7% in 11,842 patients. In another study, the frequency of carcinoid syndrome in 3379 patients with gastroenteropancreatic (GEP) NETs was 3.2% (21). Our rate was 11.2% for carcinoid syndrome, which is somewhat higher compared with previous studies. A carcinoid tumor is often only considered after the onset of carcinoid syndrome, which typically does not occur until the tumor metastasizes to the lungs or liver (22). Among our cases, carcinoid syndrome most often originated in NETs arising from the midgut and those with liver metastasis, as described in the literature.

For NETs, surgery is the primary therapy for local disease. Consistent with other studies, our study demonstrates improved survival rates with curative surgery (23-25). A multidisiplinary approach, including surgery, somatostatin analogues, chemotherapy, targeted therapy, and peptide receptor radionuclide therapy (PRRT), should be considered, and treatment should be individualized for patients with NETs.

Today, choosing medical treatment options for NETs according to the WHO 2010 grade classification is seen as the appropriate approach (26). Treatment choices in this study were also made according to current therapy options for the treatment period. According to the WHO 2010 classification, NETs are grouped with respect to the Ki-67 index as NET grade 1, NET grade 2, and NET grade 3. Nadler et al. (14) reported the proportion of grade 1 NETs as 50%, grade 2 NETs as 36%, and grade 3 NETs as 14%. Another large study reported the proportions of patients with grade 1, grade 2, or grade 3 NETs as 59.7%, 31.2%, and 7%, respectively (27). According to the literature, the range of NETs by grade (from most frequent to rarest) is grade 1, 2, and 3. In our study, the most frequent grade was grade 1, which is similar to that reported in the literature. However, grade 3 NETs were more frequent than grade 2 in our population.

Survival is strongly associated with histological grade. According to the WHO 2000 classification, Yao et al. (2) found that the median survival duration in patients with G1 and G2 NETs was 124 and 64 months, respectively. Patients with G3 and G4 tumors had identical survival curves, and the median survival duration in these patients was 10 months. According to the WHO 2010 classification, Korse et al. (9) reported the 5-year OS of 24,759 NET patients diagnosed between 2001 and 2010 for grade 1 NETs, grade 2 NETs, and grade 3 NETs to be 80%, 63%, and 7%, respectively. In our study, the 5-year OS with grade 1 and grade 3 NETs (81% and 9%) was similar to that shown in the literature, however the 5-year survival with grade 2 NETs (34%) was shorter. Median survival was 6 months for grade 3 and 44 months for grade 2, however the median survival could not be reached in grade 1 NETs in our study. In Spain, it was reported that the 5-year OS with lung NETs is variable by the type of malignancy; OS was 0% for large cell neuroendocrine carcinomas, and 77% for lung carcinoids (3). Also, the 5-year OS with GEP NETs was 76% between 1994 and 2004, which is very similar to the 75% reported by the National Cancer Registry of Spain (27). In our study, the 5-year OS was 0% with large cell neuroendocrine carcinomas of the lung, 78% with lung typical carcinoids, 47% with atypical carcinoids, 85% with grade 1 GEP NETs, 33% with grade 2 GEP NETs, and 15% with grade 3 GEP NETs. To our knowledge, no sufficient clinical trials distinguishing grade 1, grade 2 and grade 3 NETs based on survival exist in the literature thus far.

This study has several limitations including its retrospective design, long-term of 14 years, number of patients who were lost to follow, changes in diagnostic methods, surgical techniques and treatment options during these 14 years. For example, the octreotide LAR dose was increased from 20 mg to 30 mg after the PROMID study in 2011, everolimus was added to octreotid LAR after the RADIANT study in 2011, chemotherapy regimens have varied by years (28), and PRRT was administered after 2012 in our center. Therefore, the overall survival rates may not reflect the correct current survival of NET patients. In addition, some biopsy specimens for re-evaluation were insufficient for re-evaluation before 2010 due to the number of patients who were lost to follow-up.

In conclusion, the importance of this study is that it is the widest study in Turkey to evaluate NETs by a multidisciplinary team. This study shows the incidence and prevalence trends for NETs in Turkey. New diagnostic methods, such as multislice CT/MRI and Ga-68 PET CT, may allow the identification of the pancreas as a primary site for NETs in patients with liver metastases. "Surgical treatment" may be considered as a positive independent prognostic factor, while "advancing grade" and "greater than age 55" are negative independent prognostic factors for NETs. Furthermore, this study indicates that grade might be more important than stage for the prognosis of NETs, unlike other malignancies. However, further observations from large studies are needed to detect changes in the prognosis of NETs.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University (2014/332).

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

Peer-review: Externally peer-reviewed.

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