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Is There a Need for New Classifications to Predict Prognosis in Gastroenteropancreatic Neuroendocrine Carcinomas?

Gastroenteropankreatik Nöroendokrin Karsinomlarda Prognozu Tahmin Etmek için Yeni Sınıflandırmalara Gerek var mı?

Özgün Araştırma
Research Article

Emel Tekin, Arzu Avci, Nese Ekinci

ÖZ

Amaç: *Nöroendokrin neoplaziler (NEN) sıklıkla akciğer ve gastroenteropankreatik (GEP) sistem organlarında yerleşir. Nöroendokrin karsinom (NEK) oldukça yüksek malignite potansiyeline sahip olup GEP NEN lerin %5 ini oluşturur. Bu çalışmada Dünya Sağlık Örgütü (DSÖ) 2010 sınıflamasında derece 3 olarak tanımlanan Ki-67 proliferasyon indeksi %20 nin üzerinde olan olgularda prognozla ilişkilendirilerek yeni bir Ki-67 indeks değerinin belirlenmesi amaçlandı.*
Yöntem: *2008-2015 tarihleri arasında İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi Tıbbi Patoloji Bölümünde GEP NEK tanısı almış 34 olgunun demografik, klinikopatolojik özellikleri ve yaşam süreleri retrospektif olarak değerlendirildi.*
Bulgular: *Hastaların çoğu erkek cinsiyetinde (%76,5) olup, ortalama yaş 63,9 idi. Ki-67 ≤%65 olan olgularda ortalama yaşam süresi 15 ay iken, >%65 olanlarda 7 ay olarak saptandı (p=0.232).*
Sonuç: *Son zamanlarda yapılan çalışmalar NEK olarak tanımlanan yüksek dereceli NEN lerin heterojenite gösterdiğini ve bu tümörlerin biyolojik subgruplara ayrılabileceğini öngörmektedir. Araştırmacılar NEK lerin iki kategoriye ayrılmasını önermektedir: Ki-67 indeksi %20-55 ve >%55. Bizim çalışmamızda, hayatta kalma oranı açısından en anlamlı fark proliferasyon indeksi %65 değerinde gözlenmiştir ve bu farklılık literatürü destekler niteliktedir. Tek merkez çalışması ve hasta sayısının sınırlı olması nedeniyle bulgularımızın daha geniş serili çalışlmalarla desteklenmesi gereklidir.*

Anahtar kelimeler: *Nöroendokrin neoplazi, nöroendokrin karsinom, gastroenteropankreatik sistem, Ki-67 proliferasyon indeksi*

ABSTRACT

Objective: *Neuroendocrine neoplasms (NEN) are frequently located in the lung and gastroenteropancreatic (GEP) system organs. Neuroendocrine carcinoma (NEC) constitutes 5% of GEP NENs and has a very high malignancy potential. In this study, it is aimed to determine a new threshold value in addition to the 20% Ki-67 proliferation index that was specified as a threshold value for predicting survival in patients with grade (G) 3 tumors according to World Health Organization (WHO) 2010 classification.*
Method: *Demographic, clinicopathologic features and survival rates of 34 patients diagnosed with GEP NEC between 2008-2015 in İzmir Katip Celebi University Atatürk Training and Research Hospital Medical Pathology Clinic were evaluated retrospectively.*
Results: *Most of the 34 (76.5%) cases were male and the average age was 63.9 years. Median survival rates were 15, and 7 months in patients with Ki-67 indexes of ≤65% and >65%, respectively (p=0.232).*
Conclusion: *Recent studies have shown heterogeneity of high-grade NENs, identified as NEC and foreseen their subdivision into biological subgroups. The researchers suggest that the NECs should be divided into two categories as patients with Ki-67 indexes of 20-55% and >55%. In our study, the most significant difference in survival rates was observed when 65% was selected as threshold value for Ki-67 index which supports the results of other studies in the literature. Since the number of our cases is limited and it is a single-center study, the findings obtained needs to be further investigated in studies with greater number of case series.*

Keywords: *Neuroendocrine neoplasia, neuroendocrine carcinoma, gastroenteropancreatic system, Ki-67 proliferation index*

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INTRODUCTION

Neuroendocrine carcinoma (NEC) belongs to a rare subgroup of Neuroendocrine neoplasms (NENs) with high malignancy potential. Only 5% of the gastrointestinal (GI) NENs are in NEC morphology [(1)].

According to the latest 2010 classification of the World Health Organization (WHO), gastroenteropancreatic (GEP) NENs were divided into 3 groups as Grade 1,2, and 3 tumors. Grade 3 NEC is a tumor with >20 mitosis/10 HPF and / or Ki-67 index of >20% [(2)]. As a result of increasing number of recent studies performed, NECs have been shown be non-homogeneous entities and it has been predicted that they can be separated into biological subgroups [(3)].

Ki-67 proliferation index threshold values recommended for grading system in 2010 WHO are insufficient to predict the behavior of some tumors [(4-8)].

In this study, it is aimed to determine a new threshold value in addition to the Ki-67 proliferation index of 20% hat was specified as a threshold value for predicting survival in patients with G3 tumors according to WHO 2010 classification.

MATERIALS and METHODS

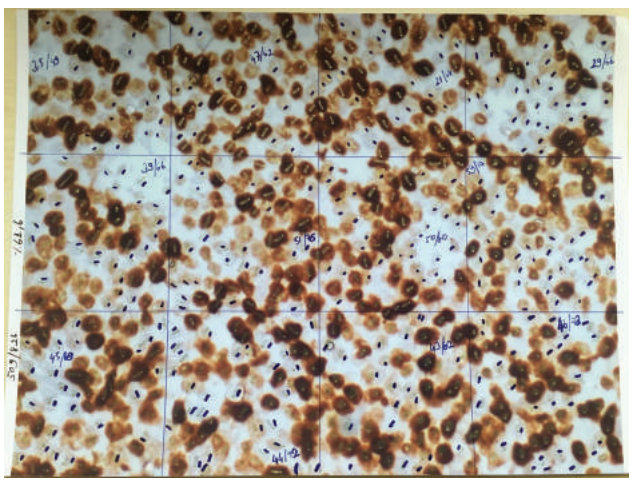
A total of 34 patients with diagnosis of GEP NEC between 2008-2015 in Izmir Katip Celebi University Atatürk Training and Research Hospital Medical Pathology Clinic were evaluated retrospectively; either endoscopic biopsy or surgical resection specimens were examined in the study. Approval for the study was obtained from the Ethics Committee of our hospital. Of these 34 patients, endoscopic biopsy specimens of 9,resection specimens of 21 patients and 4 tissue blocks sent for consultation were analyzed. Resection types used to obtain specimens were as follows; Whipple procedure (n:2), segmental colectomy (n:4), total gastrectomy (n:13), , and low anterior resection (n:2). The tissue blocks sent for our consultation were retrieved via gastric endoscopic biopsy (n:1), total gastrectomy (n:2), and segmental colectomy (n:1). Hematoxylin&eosin (HE) and immunohistochemically (IHC) stained slides were obtained from the archives and reevaluated by two pathologists. The details about the clinical assessment, prognosis and follow-up of the patients were obtained and evaluated retrospectively from the hospital database. The patients with neuroendocrine hyperplasia, neuroendocrine dysplasia, neuroendocrine tumor (NET) G1/G2 and mixed adenoneuroendocrine carcinoma (MANEC) were excluded from the study. The details about age, sex of the patients and localization of the tumors were obtained from pathology reports, endoscopic findings and reports of imaging methods.

Biopsy, and surgical resection materials diagnosed as NEC were reassessed under light microscope according to the parameters of histological pattern (solid-insular/trabecular-glandular), number of mitosis/10 high power fields (HPF) and Ki-67 proliferation index. The number of mitosis was determined for each case by two pathologists through microscopic examination of 10HPF.

The grading was performed based on cell proliferation rates (mitotic activity and Ki-67 index) according to the WHO 2010 GEP NEN pathological classification. Overall survival was defined as the time elapsed from diagnosis to death. The information about patients' survival status (dead/alive) was obtained from the Central Population Registry Administration System, which was accessed through software program of Probel Hospital Information Management System.

Evaluation of IHC markers: Analyzes for primary antibodies of synaptophysin (Leica, 27G12, NCL-L-SYNAP-299), chromogranin A (Leica, 5H7, NCL-CHROM-430) and Ki-67 protein (Leica, K2, PA0230) performed for each case were evaluated.

In our study "hot spot" staining areas in Ki-67 stained slides were identified under microscope and then these areas were photographed at 40X magnification and transferred to digital medium [9]. Photographs in digital format were printed on A4 size glossy photo paper and 12 equal squares were drawn on the paper with a pencil. Within each square, all tumor cells and positively stained Ki-67 cells were counted using pencils with different colors. In all images, 500-2000 cells were counted by this method and the percentage of stained areas with Ki-67 was determined (Figure 1). When determining the Ki-67 index, all stained cells irrespective of their staining intensities were counted, with paying attention to whether the stained cells were neuroendocrine cells (differentiating between lymphocytes, epithelial cells) or not. In cases of incompatibility between the number of mitosis and Ki-67 proliferation index, the highest grade was taken into consideration.



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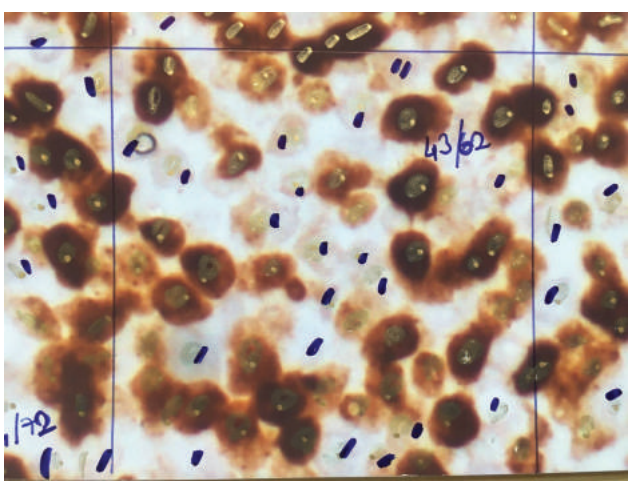

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Figure 1. Calculation method for Ki-67 proliferation index.

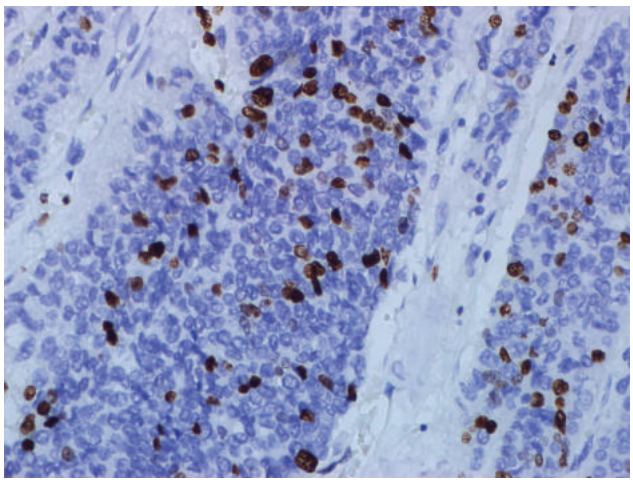
Statistical Method

All analyses were performed using the SPSS 17.0 statistical package program. The fitness of numerical variables to normal distribution was tested with the Shapiro-Wilk Test. Categorical variables were described using frequency and percentage and numerical variables with mean and standard deviation or median and minimum-maximum values. Kaplan-Meier method was used for survival analysis. The median survival rate of the different groups were compared using log-rank test. The study was conducted at 95% confidence level ($p<0.05$ was accepted as the level of statistical significance).

RESULTS

The mean age of the patients was 63.9±13.5 years. 26 (76.5%) patients were male and 8 (23.5%) were female. Material types including consultation blocks were endoscopic biopsy specimens for 10 (29.4%) and radical resection materials for 24 (70.6%) patients. Tumor localizations were as follows; esophagus (n:2; 5.9%), stomach (n:17; 50%), duodenum (n:5; 14.7%), pancreas (n:2; 5.9%), colon (n:6; 17.6%) and rectum (n:2; 5.9%). The median follow-up period was 8 (0-78) months. At the last assessment 5 (14.7%) patients were alive and 29 (85.3%) patients were dead.

Histologic pattern was glandular-trabecular in 7 (20.6%) and insular-solid in 27 (79.4%) patients (Figure 3). The median counts of mitotic cells was 56.5 (5-185)/10HPF. Mean Ki-67 index was 65.5±20.8% (21.8%-98.2%) (Figure 2). Synaptophysin expression was negative in 1 (2.9%), 1+ in 11 (32.4%), 2+ in 13 (38.2%) and 3+ in 9 (26.5%) patients. Chromogranin A expression was negative in 16 (47.1%), 1+ in 9 (26.5%), 2+ in 5 (14.7%) and 3+ in 4 (11.8%) patients (Figure 4).



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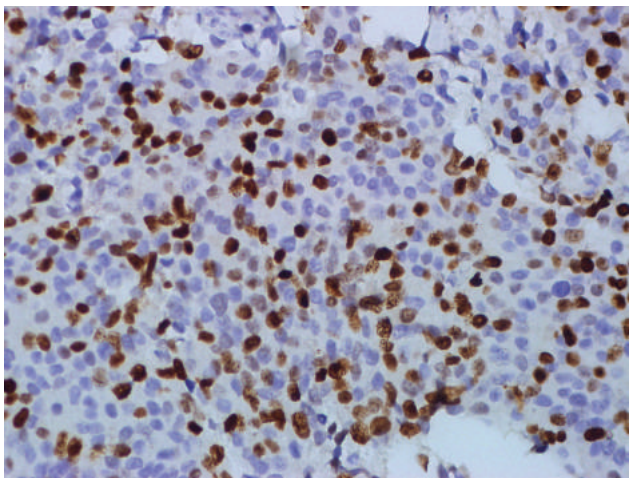

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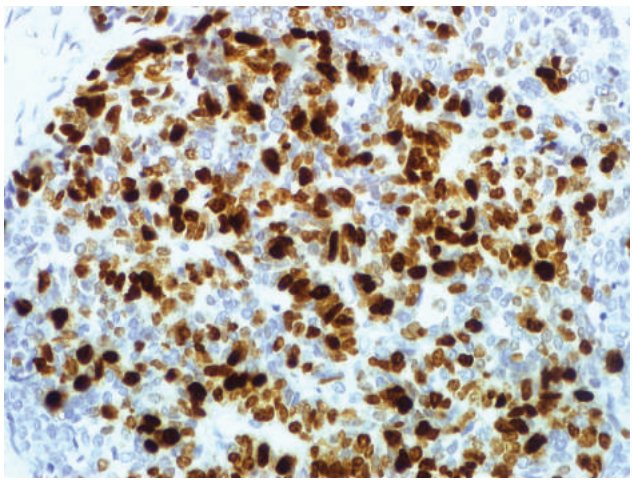

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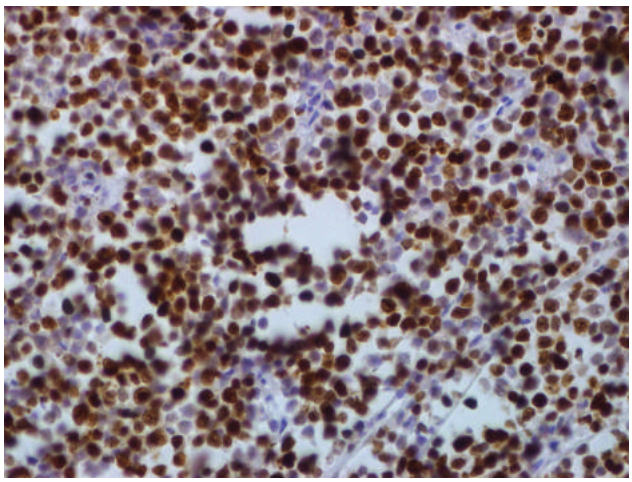

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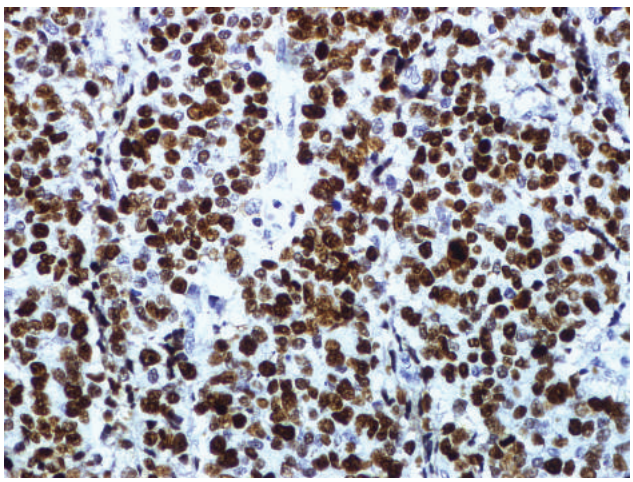

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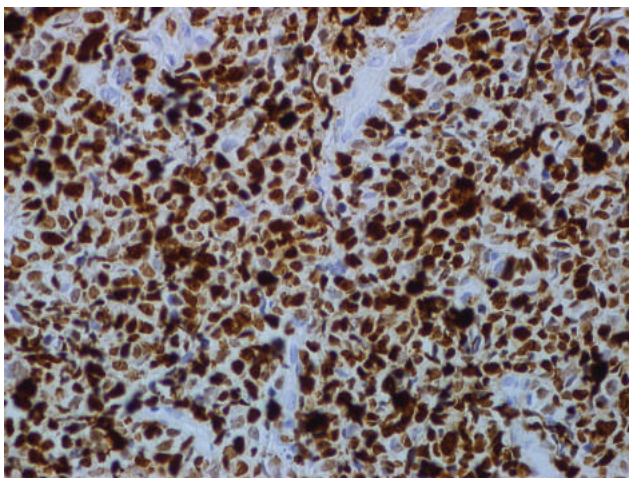

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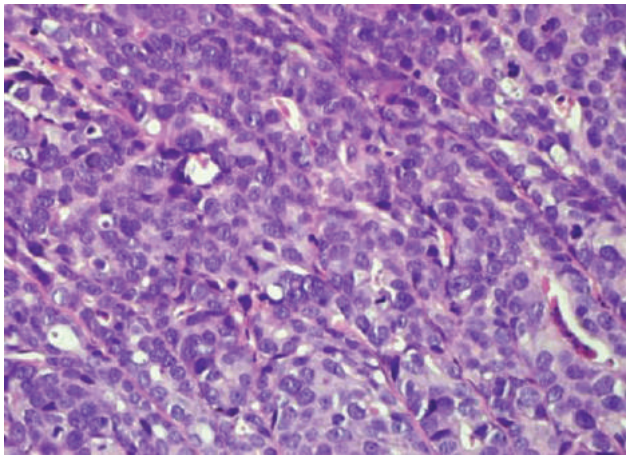
Figure 2. Case examples that reflect different Ki-67 indexes: 21.8% (A), 44.7% (B), 61% (C), 76.8% (D), 82.6% (E), 91.1% (F).



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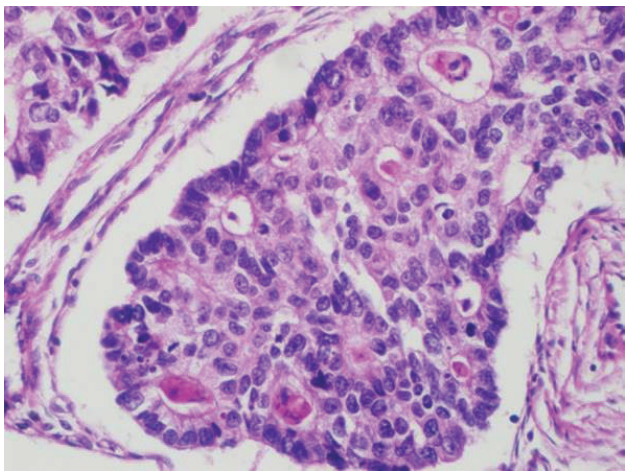

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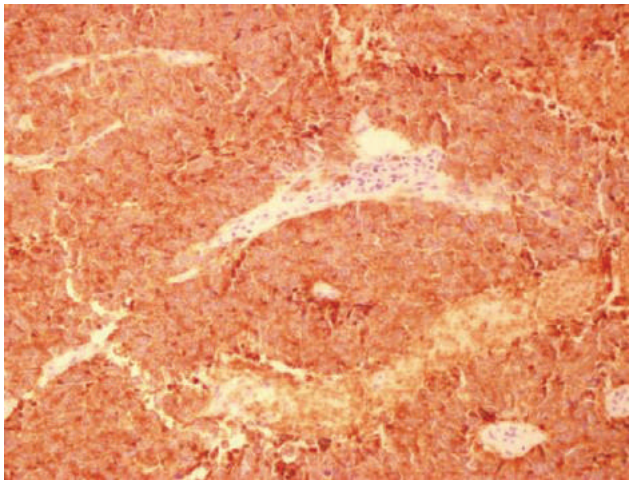
Figure 3. NECs with different histologic patterns, H&E.



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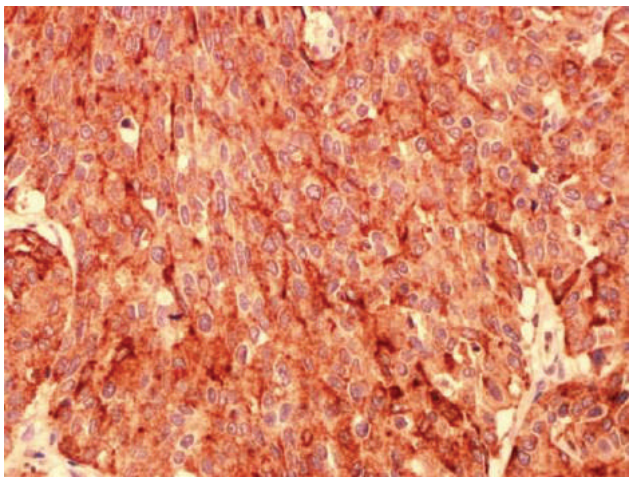

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Figure 4. Examples of sinaptophysin and chromogranin A staining.

Among different threshold values of mitosis, 20 mitosis/10HPF had the utmost predictive value in survival analysis. Median survival rates were 18, and 8 months in patients with ≤20, and >20 mitosis/10HPF, respectively (p=0.435).

Results of survival analyses performed with different threshold values of Ki-67 indexes are summarized in Table 1. Among different threshold values of Ki-67 indexes, Ki-67 index of 65% had the utmost predictive value in survival analysis. Median survival rates were 15, and 7 months in patients with Ki-67 indexes of ≤65% and >65%, respectively (p=0.232).

Median survival times were 16, and 5 months in patients aged <70, and ≥70 years (p=0.004 respectively). While they were 8 months in male and 13 months in female patients, (p=0.193); 13 months in

Table 1. Survival analysis of different threshold values for Ki-67 indexes.

Ki-67 indexes (%)	Median Survival (months)	CI 95%	Log-rank p
≤45	5	0-15.3	0.992
>45	8	4.2-11.8	
≤50	5	0-10.8	0.667
>50	10	2.8-17.2	
≤55	5	0-12.2	0,962
>55	8	0,8-15.2	
≤60	5	0-12.2	0,962
>60	8	0.8-15.2	
≤65	15	1.9-28.1	0.232
>65	7	4.1-9.9	
≤70	13	2.3-23.7	0.338
>70	8	0-16.7	
≤75	13	4-22.1	0.282
>75	6	-	
≤80	8	0-17.5	0.660
>80	8	2.2-13.8	

patients with gastric tumors and 5 months for patients with tumors of other localizations, (p=0.548). When all patients were evaluated, the overall median survival rate was 15 months. Univariate analyses were performed when evaluating the survival rates.

DISCUSSION

NENs have wide spectrum of morphologic types from well differentiated to poorly differentiated tumors [10]. Most commonly (35-55%) they are localized in the lung and followed by GEP system organs [11]. According to the latest 2010 classification of the WHO, GEP NENs are divided into 3 groups as follows: G1 NET <2 mitosis/10 HPF and Ki-67 index≤: 2%, G2 NET 2-20 mitosis/10 HPF and/or Ki-67 index: 3-20%, G3 NEC >20 mitosis/10HPF and/or Ki-67 index: >20% [2].

NECs belong to a rare subgroup of NENs with high malignancy potential and can develop in any organ in the body. Only 5% of the GI NENs have a Ki-67 index of 20%. Tumors are mostly detected in esophagus, stomach, pancreas and large bowels [1,11]. Primary localization can not be detected in up to 30% of the tumors [12].

These tumors are generally positively stained for synaptophysin, a marker of neuroendocrine differentiation, and weakly positive for chromogranin A. Chromogranin A positivity indicates a more mature tumor and the presence of expressions of both markers is an indication of good prognosis [13,14]. Recent studies have shown that poorly differentiated NENs are not homogeneous and may be divided into biological subgroups [3]. There is a need to define precise criteria at the morphological and molecular level. For example, the genetic mutation pathways of well-differentiated pancreatic NETs differing from those of pancreatic NECs suggest that different pathways are responsible for the process of tumorigenesis [15].

Male gender predominance (60%) and seventh decade as the average age of diagnosis are reported for these tumors in many multicenter studies. In our study, male predominance (76.5%) was observed and the disease was predominantly found in older patients (63.9±13.5 years) in accordance with the literature. Variable incidence rates for organ-based NECs have been reported in the literature (e.g. 7% for pancreas and 40% for colon) [16,17]. In our study, GEP NECs were most frequently located in stomach (50%), followed by colon (17,6%), duodenum (14.7%), esophagus, pancreas and rectum (5.9%).

In the study of Sorbye et al., [4] significantly longer survival rates were observed in patients with Ki-67 indexes of <55% relative to those with Ki-67 indexes of ≥55%. Although clinical observation in terms of prognosis and response to chemotherapy have demonstrated that NECs with Ki-67 indexes of >55%, responded better to platinum-based chemotherapy, their median survival rates were demonstrated to be 4 months shorter than the NEN patients with Ki-67 indexes ranging between 20 and 55%. In the light of this information, the researchers suggested that NECs should be divided into two categories as those with Ki-67 indexes of 20-55% and >55%. In the study of Heetfeld et al., [5] contrary to multiple survival analysis, in univariate survival analysis, Ki-67 indexes of >55% was found to be associated with poor prognosis. In the study of Xie et al., [18] a decrease in survival rate was demonstrated with increasing values of Ki-67, while no such relationship could be shown between increased number of mitosis and survival rates. When the cases were divided into two groups according to the number of mitoses based on the threshold value of 36/10HPF, the number of mitosis was found to be independent prognostic factor according to Cox regression analysis (p=0.031). According to this study, tumor size, lymph node status, Ki-67 proliferative index, number of mitoses and postoperative adjuvant chemotherapy were found to be independent prognostic factors for gastric NECs. In the study of La Rosa et al.,

[19] 30 mitoses/HPF was found to be the most effective threshold value in the prediction of survival. Milione et al., [6] and also Sorbye et al. associated Ki-67 threshold value of 55% with survival. According to univariate analysis; poorly differentiated morphology, >30 mitosis/10HPF and Ki-67 index of ≥55%, mismatch repair protein defect, CD117 expression, angioinvasion, mid-hindgut origin and stage IV were correlated with poor prognosis. In univariate analysis, poorly differentiated morphology, Ki-67 index of ≥55%, mismatch repair protein defect, mid-hindgut origin and stage IV were identified as independent negative prognostic markers. In multivariate analysis, well-differentiated morphology and Ki-67 indexes ranging between 20-55% were found to be independent prognostic markers for GEP NENs, while threshold value of 55% for Ki-67 index was detected as independent prognostic marker for tumors with poorly differentiated morphology [4]. Recent publications have shown the need to distinguish poorly differentiated G3 NETs from well differentiated G3 NETs according to morphological differentiation and Ki-67 proliferation indexes in cases with G3 [7,8]. In the light of the findings revealed in the study of Milione et al., [6] three different prognostic categories were identified when Ki-67 indexes and tumor morphology were used in combination as follows; type A GEP NEC (well-differentiated morphology and Ki-67 index of 20-55%); type B GEP NEC (poorly-differentiated morphology and Ki-67 index of ≥55%); type C GEP NEC (poorly-differentiated morphology and Ki-67 index of ≥55%). Accordingly, dramatic differences were found among these categories as for median survival rates; type A NECs 43.6 months; type B NECs 24.5 months and type C NECs 5.3 months (p<0.0001). Researchers found prognostic role of mitotic counts statistically less significant than Ki-67 proliferation index. Boo et al. [20] found that high Ki-67 proliferation index (>60%) correlated with tumor recurrence and histological differentiation. The results of the studies of various authors are summarized in Table 2.

Table 2. Ki-67 and survival results of the study of different authors.

	Ki-67 indexes and morphology Status	Median Survival (Months)
Sorby et al. [4]	Ki-67< 55% Ki-67 ≥ 55%	14 (10.7-17.3) 10 (8.4-11.6)
Heetfeld et al. [5]	NET G3 (median Ki-67 30%) NEC (median Ki-67 80%) Ki-67 index: ≤55% vs >50%	98.7 17 P<0.001
Xie et al. [18]	Ki-67 index: <70% vs ≥70% İncreased Ki-67 index	P=0.002 Decreased survival (p<0.001)
Milione et al. [6]	Well-differentiated morphology and Ki-67 index: 20-55%	43.6
	Poorly-differentiated morphology and Ki-67 index: 20-55%	24.5
	Poorly-differentiated morphology and Ki-67 index: ≥55%	5.3 (p<0.001)

In our study, information about medical treatment was not included in the survival analyses. According to the results of our study, median survival times were 15, and 7 months in patients with Ki-67 indexes of ≤65% and >65%, respectively (p=0.232). Some recent studies have shown that the Ki-67 proliferation index of the GEP NEC group is experiencing a breaking point in survival and response to treatment at a threshold level of 55% for Ki-67 proliferation index. The researchers suggest subgrouping these tumors into two or three categories that include type of differentiation [4,6].

When the data available in the literature and the results of our study are evaluated in combination, new arrangements seem to be needed to be made in the near future in GEP NEN grading and staging guidelines that take patient follow-up information and developing molecular information into account. In previous studies, the necessity of forming prognostic subgroups that evaluate proliferation index with morphological features, while receiving feedbacks on response to the therapy and survival rates, was emphasized [4,6]. Most of our findings were not statistically significant in univariate survival analysis because our study was single centered with limited

number of cases. However, some of our findings were in parallel with data available in the literature that support some of the hypotheses. This issue needs to be investigated further with larger scale series.

Ethics Committee Approval: Approval was obtained from İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (16.11.2016-289).

Conflict of Interest: The authors declare that they have no conflict of interest.

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