**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 39357

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**C-reactive protein may be a prognostic factor for the whole gastroenteropancreatic neuroendocrine tumors group**

Komaç Ö *et al*. Prognostic factor for the GEP-NET

Ömer Komaç, Göksel Bengi, Özgül Sağol, Mesut Akarsu

**Ömer Komaç,** Department of Internal Medicine, Dokuz Eylul University Faculty of Medicine, Izmir 35000, Turkey

**Göksel Bengi, Mesut Akarsu,** Department of Gastroenterology, Dokuz Eylul University Faculty of Medicine, Izmir 35000, Turkey

**Özgül Sağol,** Department of Pathology, Dokuz Eylul University Faculty of Medicine, Izmir 35000, Turkey

**ORCID number:** Ömer Komaç ([0000-0002-5675-2952](http://orcid.org/0000-0002-5675-2952)); Göksel Bengi ([0000-0002-7859-4094](http://orcid.org/0000-0002-7859-4094)); Özgül Sağol ([0000-0001-9136-5635](http://orcid.org/0000-0001-9136-5635)); Mesut Akarsu (0000-0001-9217-948x).

**Author contributions:** Bengi G, Komaç Ö, Akarsu M and Sağol Ö contributed equally to this work, designed the research, drafted the manuscript and provided administrative and technical support.

**Institutional review board statement:** This study was approved by the Dokuz Eylul University Ethics Committee.

**Informed consent statement:** Informed consent was provided by all participants.

**Conflict-of-interest statement:** None.

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**Manuscript source:** Unsolicited manuscript

**Correspondence to: Göksel Bengi, MD, Assistant Professor,** Department of Gastroenterology, Dokuz Eylul University Faculty of Medicine, Inciralti, Izmir 35000, Turkey. drgokselbengi@hotmail.com

**Telephone:** +90-532-4626972

**Fax:** +90-232-4123799

**Received:** April 20, 2018

**Peer-review started:** April 21, 2018

**First decision:** May 29, 2018

**Revised:** August 24, 2018

**Accepted:** October 23, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To identify the independent prognostic markers for the patients in the whole gastroenteropancreatic neuroendocrine tumors (GEP-NETs) group.

***METHODS***

Ninety-three patients who were diagnosed with GEP-NET within the specified period were included in this study. The data were retrospectively analysed. The relationship between all independent variables with 5-year survival status and calculated follow-up period (months) was assessed. In addition, the relationship between the independent variables was investigated.

***RESULTS***

When we compared the 5 year survival rate, there was a statistically significant relationship between age at diagnosis, male gender, tumor size, tumor stage, liver and/or distant metastasis, tumor grade determined by Ki-67 level and mitotic count and the level of C-reactive protein (CRP) that is one of the biochemical data. The mean survival (overall survival, OS) of the study group was 102.5 ± 6.3 (SD) mo. The percentages of 1, 3 and 5-year survival were 90%, 72% and 61%, respectively. Of the 93 patients in the study, 63 had a Ki-67 and the mitotic count determined same grade. Ki-67 levels in 29 patients and mitotic count in only 1 patient were higher grade. Risk of death rising %4 by the every 1 increase in the age at diagnosis, for male sex 2.0 fold, G3 according to mitosis count 3.0 fold, G3 according to Ki-67 level 3.7 fold, tumor stage 3 or 4 cases 12.7 fold, 1 cm increase in tumor size 9%, liver metastasis 6.1 fold, by every 1 mg/dL increase in CRP level 1.5%. There was a significant difference between the pancreas and stomach NETs in favor of stomach tumors in terms of survival.

***CONCLUSION***

As a result, as well as the fact that tumor site, stage, grade and Ki-67 level affect survival was shown, additionally it was observed that one of the biochemical parameters, CRP affected the course of the progression (particularly if it is> 20 mg/dL). However the relationship of the surgical resection of the lesion with survival could not be shown. With the need for larger scale and prospective studies, it was suggested that CRP level might be a poor prognostic factor for the entire GEP-NET group.

**Key words:** Gastroenteropancreatic neuroendocrine tumors; C-reactive protein; Prognostic factor; Neuroendocrine tumors; Gastrointestinal system

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**Core tip:** Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) constitute a heterogeneous group of tumors with variable clinical presentations, different growth rates and unpredictable prognoses. In our study, we aimed to identify the independent prognostic markers for the patients in the whole GEP-NET group. As a result, it was observed that one of the biochemical parameters, C-reactive protein (CRP) affected the course of the progression in the worst way (particularly if it is > 20 mg/dL). With the need for larger scale and prospective studies, it was suggested that CRP level might be a poor prognostic factor for the entire GEP-NET group.

Komaç Ö, Bengi G, Sağol Ö, Akarsu M. C-reactive protein may be a prognostic factor for the whole gastroenteropancreatic neuroendocrine tumors group. *World J Gastrointest Oncol* 2018; In press

**INTRODUCTION**

Neuroendocrine tumors are a group of heterogeneous tumors that may develop in almost all localizations of the body with malignant transformation of various neuroendocrine cells that are rarely seen, however, whose frequency is gradually increasing. The ones developing in the gastrointestinal system (GIS) are the most commonly seen. This group of tumors can be defined by their different degrees of differentiation, slow growth rates, some of them causing clinical syndromes by excess secretion of hormones due to their being functionally active and their showing lower malignancy potential compared to most epithelial tumors[1]. In gastroenteropancreatic neuroendocrine tumors (GEP-NET) it is difficult to make a clear interpretation in respect of prognosis due to reasons such as differences in tumor types, diversity of the molecular mechanisms responsible for pathology, the uncertainties in the effective oncogenic pathways and scarcity of the large scale and prospective randomized studies. In general, the average time it takes for these tumors to be diagnosed lasts 5-7 years due their presenting vague symptoms and they may not be correctly managed. The 5-year survival varies between 15% and 95% based on factors such as the location of the primary tumor, changes in tumor biology, the extensity of the tumor at the moment of diagnosis, treatment options and the competence of the center where the treatment is being made about the subject[2,3]. Along with the broadening of treatment perspectives also, question marks about which approach will be applied to which patient have appeared. Therefore, determination of the prognostic factors that affect survival and achieving their standardization has importance in respect of early identification of the patients who have tumor that may have an aggressive course and their treatment to be planned accordingly.

In general terms, it is thought that the C-reactive protein (CRP) is a non-specific inflammatory biomarker and CRP value which is the indicator of inflammation increase, seriously increases especially in hematopoetic and some solid malignancies and this situation plays an important role in disease pathogenesis and progression[4,5]. The prognostic importance of the CRP level especially in malignancies such as pancreatic and esophageal adenocarcinoma, soft tissue sarcoma, chronic lymphocytic leukemia has been shown with studies[6-8]. In this pioneer study we made, we aimed to identify the independent prognostic markers for the patients in the whole GEP-NET group.

**MATERIALS AND METHODS**

Ninety-three patients 18 years of age and over who have been diagnosed GEP-NET by surgical resection and/or non-surgical sampling in Dokuz Eylül University Hospital between the dates January 2002 and June 2012 were included in this study. The data of the patient at the moment of diagnosis were scanned retrospectively.

The independent variables were specified and recorded as gender, age, primary tumor location, tumor diameter, non-surgical sampling condition, surgical resection condition, liver metastasis condition, extrahepatic distant metastasis condition, tumor stage (according to AJCC 2010 criteria, TNM)[9], tumor grade determined according to mitotic count and Ki-67 level (WHO 2010 criteria, as grade 1-2-3)[10], hemoglobin (HGB) level (g/dL), anemia condition (WHO criteria M < 13, F < 12 g/dL), albumin (ALB) level (g/dL), hypoalbuminemia condition (WHO criteria, < 3.5 g/dL), lactate dehydrogenase (LDH) level (U/L), CRP level (mg/L), elevated CRP condition (< 5 mg/L, between 5-20 mg/L, > 20 mg/L), erythrocyte sedimentation rate (ESR) (mm/h), ESR elevation (Westergren method).

The sections were immunstained with Ki-67 antibody (Ventana; anti-Ki67 30-9). Ki-67 labeling index was calculated as the percentage of Ki-67 immunoreactive cells on a total of 2000 neoplastic cells counted in hotspot areas. The counts were performed manually on camera captured images. Mitotoic index was calculated as the number of mitotic figures in at least 50 HPFs in hot spot areas. The other diseases that may affect the patient data (like CRP) were screened over file and the data determined to be affected were not included in the study.

The dependent variables were designated as 1-3 and 5 year survival condition, the time (months) elapsed between the diagnosis date and the outcome date. In order to create the 5-year follow-up process, the patients who were diagnosed after the date June 15, 2012 were not included in the study. As the outcome date, the dates of death for the patients who died during this process and the date June 15, 2017 for the other patients was established.

Since the present sample diameters were smaller than 1 cm and small quantities of material can be obtained by these procedures, the patients who were diagnosed by endoscopic excisional biopsy, endoscopic incisional biopsy, fine-needle aspiration biopsy and full layer biopsy were named as the non-surgical sample group.

***Statistical analysis***

SPSS 22 program was used for statistical analysis. Descriptive statistics, figures and percentages for categorical variables, mean, SD values for numeric variables were presented. Crosstabs were created for categorical data, *χ*2 test was used in multiple and pairwise group comparisons. Kaplan-Meier method was used for survival analyses. Spearman’s rho correlation analysis was made between the independent variables. The factors affecting survival were determined and multivariate models were created. To determine the prognostic values of these, Cox proportional hazards test was made. ROC curve analysis was made with the numerical variables affecting survival. And consequently, sensitivity and specificity levels were determined and cut-off values were calculated[11,12]. In the single-variable analysis made by logrank test, age, gender, tumor diameter, multiple metastases, liver metastasis, CRP level, Ki-67 grade, mitosis grade, grade and clinical stage are meaningfully related with survival. Since the independent variables’ showing meaningful relationship among themselves will change the model direction, independent variables for the multivariate model have been tested among themselves. Age and gender distributed normally according to other independent variables have not shown significant relationship with multiple metastases, liver metastasis, Ki-67 grade, mitosis grade, grade, CRP level and none of the clinical stage variables. However, Ki-67 grade, mitosis grade, grade and clinical stage variables are significantly related among themselves. Liver metastasis is a part of multiple metastases and these 2 variables are also related with each other. A model that will be constructed to explain death that contains independent variables showing meaningful relationship with each other would be faulty. Therefore, Cox proportional hazards models have been constructed by adding each parameter (Ki-67 grade, mitotic index grade, grade, clinical stage, liver metastasis, CRP level, tumor diameter) individually on the age and gender variables. When the alpha level of significance is below 0.05, it has been accepted as significant. ROC curve analysis was made between death/alive status and CRP level. And consequently, sensitivity and specificity levels were determined and cut-off values were calculated for CRP. This study has been approved by Dokuz Eylül University School of Medicine's non-invasive clinical research ethics committee (22.06.2017/2017/17-48). Patient information has been kept confidential and the study was conducted according to the Helsinki declaration.

**RESULTS**

Considering the demographic data, the average age of the whole group at the moment of diagnosis was determined as 53.45 ± 13.46 standard deviation (SD). The youngest patient included in the study was 18 and the oldest was 83 years old. Negative meaningful relationship was determined between the age of the patients at the moment of diagnosis and 5-year survival (*P* = 0.019). Fifty-five percent of the patients were of female gender. Meaningful relationship in favor of female gender was detected between gender and 5-year survival (*P* = 0.014). The mean primary tumor diameter was 3.1 ± 3.45 (SD) (cm). Positive meaningful relationship was present between the tumor diameter and 5-year survival (*P* = 0.013). The relationship between the demographic data of the patients and numeric independent variables with 5-year survival is provided in Table 1.

While the mean HGB level of the patients was detected as 12.21 g/dL ± 1.99 (SD), the mean plasma ALB level was determined as 4.08 g/dL ± 0.53 (SD). While the mean LDH level of the patients was observed as 291.1 U/L ± 213.1 (SD), the smallest LDH value was 109 U/L and the highest 1659 U/L. The mean ESR was determined as 37.7 mm/h ± 25.9 (SD). No statistically meaningful difference was found between 5-year survival and HGB, ALB, LDH and ESR values of the patients (*P* = 0.54-0.07-0.11-0.09). The mean CRP level was determined as 22.5 mg/dL ± 33.8 (SD). Statistically significant relationship was present with 5-year survival (*P* = 0.02).

The mean survival time of the patient group was [overall survival (OS)] 102.5 ± 6.3 (SD) mo. And the 1, 3 and 5-year survival percentages were determined as 90%, 72% and 61%, respectively. There was no meaningful relationship between non-surgical sampling, surgical resection or both of the procedures performed (17 patients) with 5-year survival (*P* = 0.25, 0.62, 0.38). The same tumor grade was detected in 13 of these 17 patients, and in 4 patients, the resection material predicted a higher grade. Negative strong 5-year survival relationship was detected in the group with Liver metastasis and the group with extrahepatic distant organ metastasis (*P* < 0.001-*P* < 0.001). According to tumor stages, it was OS 132.8 ± 4.3 (SD) mo in the stage 1-2 group and OS 69.7 ± 8.5 (SD) mo in the stage 3-4 group. When mitotic count is taken as the basis for tumor grading, it was OS 111 ± 6.2 (SD) mo in G1 group and OS 35.1 ± 11.3 (SD) mo in G3 group. When Ki-67 level was taken as the basis, it was detected as OS 124.6 ± 6.1 (SD) mo in G1 group and OS 54.4 ± 12.7 (SD) mo in G3 group (*P* < 0.001). While in 5 of the 20 patients whose Ki-67 level was detected as G3, the Ki-67 was stated numerically in the report (30%, 37%, 45%, 80%, 90%), the Ki-67 value of 15 patients was stated categorically (> 20%). Consistency was achieved between the tumor grades determined according to mitotic count and Ki-67 level in 63 patients (68%), in 29 of the remaining 30 patients Ki-67 level and in 1 patient mitotic count predicted a higher grade.

OS was 92.9 ± 8.7 (SD) mo (*P* = 0.34) in anemic patients, OS 91 ± 15.7 (SD) mo (*P* = 0.60) in hypoalbuminemia patients, OS 93.5 ± 9.5 (SD) mo (*P* = 0.28) in the ones with elevated ESR found, OS 118.1 ± 8.2 (SD) mo in the ones with CRP level detected< 5 mg/L, OS 118.6 ± 12.2 (SD) mo in the ones with CRP level found between 5-20 mg/L, OS 72.3 ± 10.5 (SD) in the ones with CRP level > 20 mg/L (*P* = 0.009). The relationship between the categorical independent variables and survival times of the patients is given in Table 2.

The correlation of the independent variables with each other is given in Table 3. Statistically significant correlation at varying levels between tumor diameter, tumor stage, the tumor grades determined according to mitotic count and Ki-67 level was detected. Statistically significant correlation (*P* < 0.001) at a perfect level (99%) was present between the tumor grade calculated on the basis of Ki-67 level and the tumor grade stated in the report because mitotic count predicted a higher grade in only 1 of the 93 patients. Statistically significant correlation was present between the CRP level with the tumor diameter and tumor stage. A statistically significant correlation was not determined between the tumor grade calculated on the basis of Ki-67 level or mitotic count with CRP level. Five-year survival rate according to primary tumor locations is given in Table 4. The most frequent primary organ involvement was determined as stomach, pancreas and colon, respectively. Survival rates were determined as 79%, 48%, 54%, respectively. The survival difference relationship between Pancreatic and Stomach NETs are given in Table 5. Statistically significant difference in respect of survival was present between the two tumor groups (*P* = 0.016).

Relative levels of death risk increase in unit changes of the determined variables are given in Table 6. In the Cox proportional hazards model created with patients age, gender, tumor grade calculated according to mitosis number or Ki-67 level of the patients, tumor diameter, tumor stage and presence of Liver metastasis, each 1 year increase in age increases death risk relatively 4%, being a male 2.0 times as much compared to female, G3 tumor 3.0 times as much compared to G1 or G2 on the basis of mitosis number, G3 tumor 3.7 times as much compared to G1 or G2 on the basis of Ki-67 level, again 3.7 times as much compared to G1 or G2 in case that the grade stated in the report is G3, tumor stage being 3-4 12.7 times as much compared to its being 1-2, each 1 cm increase in tumor diameter 9 % relatively, presence of liver metastasis 6.1 times

To determine the patients died in the 5-year patient follow-up, when the cut off value of the CRP value was taken as 3.85 mg/L, its sensitivity was determined as 80%, specificity 45%, when taken as 5 mg/L which is the universal “cut off” value of CRP, sensitivity as 76%, specificity 47%, when the ”cut off” value was taken as 20 mg/L, its sensitivity was determined as 56% and specificity as 79%. Also, it was seen that the CRP level being over 20 mg/L increased the death risk relatively 3.2 times as much (95%CI: 14.5-7.1). In Figure 1, there were 0.7 units that remained under the curve.

**DISCUSSION**

It has been shown that despite the general assumption that GEP-NETs are quite rare, benign, slow growing tumors, they are much more prevalent than thought and the course is bad in some patients. Due to the nonspecific nature of the symptoms and findings, these are generally misinterpreted and the diagnosis is delayed. Consequently, in the commonly seen GEP-NET groups, metastases are seen in about 65% of the newly diagnosed cases[13]. Although anatomic imaging is useful for correct diagnosis, lack of sensitive and specific plasma or genetic markers that can be used for screening early lesions or micrometastasis poses a major obstacle at the diagnosis and treatment process. Therefore, the increase of the number and reliability of the available prognostic and diagnostic factors has importance in respect of the correct management of the patient and the disease[14].

In GEP-NET group, the 5-year survival varies between 15% and 95% based on factors such as the location of the primary tumor, changes in tumor biology, the extensity of the tumor at the moment of diagnosis, treatment options and the competence of the center where the treatment is being made about the subject[2,3]. The 5-year survival rate in our study which has a heterogeneous tumor group was determined at a level similar to literature with 61%.

In a meta-analysis made by Jensen *et al*[15], the age increase at the moment of diagnosis, being of male gender, presence of liver metastasis and tumor diameter increase have been indicated as bad prognostic factors**.** Similar results were determined in our study also. These parameters may express bad prognosis in all tumor groups, however, it is not yet known why male gender increases the death risk for the GEP-NET group, 56% of the patients in the stage 4 group being males in our study may be the reason of this situation. As also stated in a meta-analysis made by Yao *et al*[2], tumor grade increase, decrease in tumor differentiation and presence of distant metastasis were determined in our study also as bad prognostic factors. However, it is known that this situation is not unique to NETs.

In a study made on GEP-NETs, it has been indicated that as the grade of the tumor increases, the risk for metastasis development increases and the tumor differentiation decreases as expected[16]. In our study also, similarly, significance at positive directional and moderate correlation level was present between the tumor stage and grade (*P* < 0.001 rho = 0.53). It was seen that between stage 3-4 and G3 tumors, particularly, the correlation rate rose to 97%. This situation suggests that the parameters that define tumor grade are a good indicator for the proliferative process and prognosis also.

In a study where the effect of tumor grade in metastatic GEP-NETs on prognosis was evaluated[16], 5-year survival had been determined as 87% in G1 tumors, 38% in G2 tumors, and 0% in G3 tumors, in our study, 5-year survival in the metastatic patient group was determined as 66% in G1 tumors, 25% in G2 tumors and 8% in G3 tumors. This situation can be evaluated as the stage and grade has an impact on survival independent of each other also.

It is known that the organ where the most frequent metastasis is seen in the GEP-NET group is the Liver. In a study made regarding GEP-NETs, the Liver metastasis rate in the stage 4 patient group had been given as 89%[16], in our study, it was determined as 100%. This situation can be explained by the invasive GEP-NET cells reaching the liver, first over the portal venous system.

In a study made, the opinion that the Ki-67 level detected in advanced stage pancreatic NETs (PNET) is the most important prognostic factor had been expressed, and it had been stated on the other hand that presence of Liver metastasis independent of Ki-67 level was also an important survival determinant[17]. In our study when the whole GEP-NET group was evaluated, similarly to this study, in tumors that were G3 group according to Ki-67 level, 3.6 times as much increase in death risk was determined compared to the G1-G2 tumor group and in presence of Liver metastasis also the death risk increase was determined as 6.1 times as much. This situation shows that Ki-67 level and presence of Liver metastatis has prognostic importance for the whole GEP-NET group. In a study made with well-differentiated GEP-NETs however[15], contrary to this opinion, results suggesting that Ki-67 level reflects proliferative activity, however does not affect survival have been found.

As well as studies that indicate mitotic count in GEP-NET group has a prognostic importance close to Ki-67 level also[18,19], there are studies that indicate that Ki-67 level is a stronger prognostic factor[20]. In a study made with GEP-NET cases within this context, when the cases that concordance cannot be achieved between these two parameters, it has been seen that Ki-67 level determined the high grade in 87% of the cases and this situation was observed correlated with survival. In our study also, similarly, Ki-67 level predicted a higher grade in 29 patients. Among the causes of this situation, mitotic count being affected from conditions such as tissue fixation and sample thickness, indistinguishability of the apoptotic cells precisely during the count and the possibility of counting only little part of the cells in proliferative phase by this method can be shown. In the same study[21], it has been detected that 65% of the cases where concordance could not be achieved between Ki-67 and mitotic count in respect of tumor grade were nonsurgical sampling material, the reason for this was shown as the relative smallness of the sample size and possibility of sample collection from the tumor tissue with low metabolic rate erroneously. In another study, when cytologic and histologic metarials of 27 GEP-NET patients were evaluated, the same tumor grades have been determined[22]. In our study also nonsurgical sampling material was present in 16 of the 30 cases that concordance could not be attained, no meaningful difference appeared in this respect.

In a study made by Sorbye *et al*[23], when they divided the G3 NETs in two groups by using a cut-off value of 55% for Ki-67 level, 4 mo of meaningful statistical difference has been determined in survival and response to treatment. In another similar study, it was said that independent of the stage of the disease, as Ki-67 level increases, survival without progression decreases[20]. In our study, while Ki-67 value in 5 of the 20 patients determined as G3 according to Ki-67 level was numerically indicated (30%, 37%, 45%, 80%, 90%), Ki-67 value of 15 patients were categorically (> 20%) indicated. The 5-year survival of these five patients turned out to be 0%, however, since the numeric Ki-67 levels of the other patients were not available, a statistics could not be made between Ki-67 level increase and survival.

In a study made, it is remarked that for NETs tumor grade is a progression marker of higher priority compared to stage[20], however, in our study although the confidence interval was wide, it was determined that the tumor stage being 3 or 4 increases death risk 12.7 times as much, and the grade being 3 increases that 3.6 times as much, therefore, we think that tumor stage has as much prognostic importance as tumor grade.

And in a study made with well-differentiated GEP-NETs; while lymph node positivity was detected in 44% of the ileal NETs smaller than 1 cm, lymph node metastasis was not determined in any of the appendix NETs again smaller than 1 cm, within this context it was indicated that tumor dimensions provide information about the clinical course, however, the location of the tumor is also important[24]. In the study we have made, lymph node metastasis was present in only 6% of the 34 cases with tumor diameter 1 cm and less. As the reason for this situation, the heterogeneity of our study group and 22 patients having early stage stomach NET detected coincidentally by endoscopic method can be shown[25].

It is indicated that in GEP-NETs the only curative method is surgical resection[14], however, in our study no meaningful relationship was determined between neither nonsurgical sampling nor presence of surgical resection and survival (*P* = 0.25, 0.62). As a reason for that; the groups that underwent nonsurgical sampling and surgical resection among the patients in our study being heterogeneous within themselves may be shown. For example; while nonsurgical sampling procedure was applied only for diagnostic purposes in the advanced stage inoperable patient group, it has been a curative method in early-stage stomach tumors. Presence of surgeries made for palliative or diagnostic purposes also in the group that underwent resection might have ruined the survival relationship expected to be seen.

In a compilation[11], while the location primary NETs are most prevalently found was indicated as GIS (about 60% of all cases), bronchopulmonary system takes the 2nd place (27%), it is said that within the GIS the most frequently seen region is the small intestine (34%), this is followed by rectum (23%), colon (19%), stomach (7.7%), pancreas (7.5%) and appendix (6.6%), respectively. In our study, the frequency was determined as stomach (31.2%), pancreas (26.7%), colon (14%) and ileum (7.5%). As the reason of this difference between literature and our study, our probable inability in detecting some of the GEP-NETs we had planned to include in the study, the incidental stomach NET detection in one of us being frequent, our being a reference center in respect of pancreas fine needle aspiration sampling by EUS, and the difficulties in sampling the Ileal NET group by imaging with endoscopic method may be shown as examples.

In a compilation that Grin *et al*[26] have written about GEP-NETs, it has been asserted that endoscopic excisional biopsy is generally sufficient for stomach tumors smaller than 1 cm, these show very rare malignant progression. They have indicated that the risk of malignant progression for the same group tumors increases in relation with the tumor diameter and grade increase. In our study, while the 5-year survival of the stomach NET patients with tumor diameter less than 1 cm was 90%, it realized as 40% in the patient group over 1 cm (*P* = 0.01).

When the survival relationship between the Pancreatic and Stomach NETs was evaluated, statistically significant difference in favour of Stomach NETs was determined between the two tumor groups in respect of survival (*P* = 0.016). This situation had been similarly indicated in another study also[27]. As the reason for this situation; determination of the nonfunctional PNETs at a more advanced stage, their progressing worse due their being almost poorly differentiated and the increase in the number of incidentally detected early stage stomach NET because of the incease in the frequency of endoscopic imaging may be shown.

In a recent study made by Freis *et al*[28] with 100 GEP-NEC patients, elevated lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) levels were indicated to be related with survival, relationship between blood hemoglobin (HGB) and albumin (ALB) levels and survival has not been determined, erythrocyte sedimentation rate (ESR) was not evaluated in the study. In our study no relationship was determined between LDH, ALB, HGB and ESR levels and survival (*P* = 0.11, 0.07, 0.28, 0.09, respectively).

CRP is an acute phase protein and is produced in the liver. Acute phase response is stimulated by IL-6 released from macrophage and T cells. Any condition of acute or chronic inflammation may cause CRP increase by activating IL-6. These conditions include infections, autoimmune diseases and malignancies. As a result, CRP is sensitive but nonspecific marker[29]. For this reason, the CRP level of the 21 patients in whom CRP elevation developed due to non-tumor related causes were not taken into account in our study. In our study, negative significant relationsip was present between the CRP level increase and survival for the whole GEP-NET group (*P* = 0.009). The mean survival was determined as 118.1 mo in the patient group with CRP level < 5 mg/L, 118.6 mo in the group with level 5-20 mg/L and 72.3 mo in the group with level > 20 mg/L. It was seen that each increase of CRP value by 1 mg/L increased the death risk relatively at the rate of 1.5%. It was observed that when CRP level is greater than 20 mg/L, death risk relatively increased 3.2 times as much and when this value is taken as cut off, its sensitivity is 56% and specificity is 79% for occurrence of death. According to these results, CRP level, especially when it is above 20 mg/L, can be qualified as bad prognostic factor for the GEP-NET group. This situation was shown for the first time for the entirety of the GEP-NET group. Wiese *et al*[30], in a study made with PNET group, have determined that there is relationship between CRP level at the moment of diagnosis and survival, it has been indicated that high CRP values may be an independent prognostic factor for the PNET group. Moreover, correlation between Ki-67 level which is another prognostic factor and CRP level not having been detected in our study reinforces the opinion that CRP value is an independent prognostic factor for the whole GEP-NET group.

As the limitations of our study; its having been made retrospectively, the treatment methods other than tumor resection not having been taken into evaluation, the functionality status of tumors not having been evaluated, inability of determining some patients at the process of case collection since difficulty may be experienced in specifying the GEP-NET group according to the current ICD-10 diagnostic coding (for example; if malignant neoplasm of stomach diagnostic code is assigned to a patient who has stomach NET, the patient may be evaluated as adenocarcinoma of stomach), inability of making the statistics planned to be made according to tumor location because the number of some sub-groups were low and inability of making additional analyses since Ki-67 level was not precisely stated in the pathological data especially before the year 2010 may be shown.

Throughout our study, significant relationship was determined between diagnosis age, gender, tumor size, tumor stage, tumor grade specified individually according to mitotic count and Kİ-67, presence of Liver metastasis and extrahepatic distant metastasis with survival as indicated in the literature also. Nevertheless, it was shown, especially in the relationship between stomach and pancreas NETs, that the tumor location can also affect survival. Differently from some studies present in literature, it was concluded in our study that tumor stage also is a parameter at least as important as tumor grade. Again, differently from the articles that show Ki-67 level similar with the prognostic effect of mitotic count, the Ki-67 level having determined the tumor grade by itself in almost our whole patient group, its increasing death risk more compared to mitotic count and the margin of error being larger during mitotic count from a technical aspect, suggests that Ki-67 level is a more important grading parameter and a more efficient prognostic factor.

In conclusion, in literature; small scale studies that include patients according to the involved sites, presence of metastasis, the stage or grade condition are present, however, studies that approach the GEP-NET group holistically are only a few. Since it is known that all GEP-NETs can metastasize independent of the tumor grade and stage, specifying the follow-up parameters that can be used for the whole of this disease group and the factors that affect clinical course, and determining the confidence level of the available parameters has importance. It was seen in our study that CRP level which is one of the biochemical parameters evaluated for whether it can be a prognostic factor for the GEP-NET group or not, has affected the disease course in a bad way especially when it is > 20 mg/dL. We think that CRP level is an independent bad prognostic factor for the whole GEP-NET group. In case that this situation is shown by prospective and controlled studies to be made, the patients thought to progress aggressively according to the CRP level at the moment of diagnosis can be determined in advance and the treatment option can be planned accordingly and CRP level can be used as a follow-up parameter.

**ARTICLE HIGHLIGHTS**

***Research background***

Neuroendocrine tumors are the tumors that develop as a result of the malignant transformation of neuroendocrine cells that may be seen in all localizations of the body whose frequency is gradually increasing. They are most commonly seen in the gastrointestinal system (GIS). They may cause various clinical syndromes, their malignancy potentials show differentiation. In general, they progress less malignant compared to epithelial tumors. The 5-year survival varies between 15% and 95% based on factors such as the location of the primary tumor, changes in tumor biology, the extensity of the tumor at the moment of diagnosis and the treatment options. In general terms, determination of the C-reactive protein (CRP) level which is a marker of inflammation at a seriously high rate especially in poor prognostic hematopoietic and some solid malignancies, suggests that it may have prognostic significance. In several studies made, it is indicated that the CRP level has prognostic importance in malignancies such as pancreatic adenocarcinoma, soft tissue sarcoma and chronic lymphocytic leukemia.

***Research motivation***

In gastroenteropancreatic neuroendocrine tumors (GEP-NET), it is difficult to make a clear interpretation in respect of prognosis due to reasons such as differences in tumor types, diversity of the molecular mechanisms responsible for pathology, scarcity of the large scale and prospective randomized studies and the possibility of development of various clinical syndromes. In general, the average time it takes for these tumors to be diagnosed lasts 5-7 years due their presenting vague symptoms and they might not be correctly managed. Therefore, determination of the prognostic factors that affect survival and achieving standardization of these has importance in respect of early identification of the patients who have tumor that may have an aggressive course and their treatment to be planned accordingly.

***Research objectives***

To specify the survival status and time of the patients in the study; to evaluate the relationship between the location of the tumor, its extensity, size, pathological characteristics, sampling method and certain laboratory data of the patients and survival; to specify the prognostic importance of the variables found meaningful.

***Research methods***

Ninety-three patients 18 years of age and over who have been diagnosed GEP-NET by surgical resection and/or non-surgical sampling in Dokuz Eylül University Hospital between the dates January 2002 and June 2012 were included in this study. The data of the patient at the moment of diagnosis were scanned retrospectively. The independent variables were specified and recorded as a group of demographical, radiological, surgical, pathological and specific laboratory data. The dependent variables were designated as 1-3 and 5 year survival condition, the time (months) elapsed between the diagnosis date and the outcome date. In order to create the 5-year follow-up process, the patients who were diagnosed after the date June 15, 2012 were not included in the study. As the outcome date, the dates of death for the patients who died during this process and the date June 15, 2017 for the other patients was established. Since the present sample diameters were smaller than 1 cm and small quantities of material can be obtained by these procedures, the patients who were diagnosed by endoscopic excisional biopsy, endoscopic incisional biopsy, fine-needle aspiration biopsy and full layer biopsy were named as the non-surgical sample group.

***Research results***

Negative meaningful relationship was determined between the age of the patients at the moment of diagnosis and 5-year survival (*P* = 0.019). Fifty-five percent of the patients were of female gender. Meaningful relationship in favor of female gender was detected between gender and 5-year survival (*P* = 0.014). The mean primary tumor diameter was 3.1 ± 3.45 (SD) (cm). Positive meaningful relationship was present between the tumor diameter and 5-year survival (*P* = 0.013). The mean CRP level was determined as 22.5 mg/dL ± 33.8 (SD). Statistically significant relationship was present with 5-year survival (*P* = 0.02). The mean survival time of the patient group was (overall survival, OS) 102.5 ± 6.3 (SD) mo. And the 1, 3, and 5-year survival percentages were determined as 90%, 72% and 61%, respectively. Negative strong survival relationship was detected in the group with Liver metastasis and the group with extrahepatic distant organ metastasis (*P* < 0.001-*P* < 0.001). When mitotic count is taken as the basis for tumor grading, it was OS 111 ± 6.2 (SD) mo in the G1 group and OS 35.1 ± 11.3 (SD) mo in the G3 group. When Ki-67 level was taken as the basis, it was detected as OS 124.6 ± 6.1 (SD) mo in the G1 group and OS 54.4 ± 12.7 (SD) mo in the G3 group (*P* < 0.001). OS was 118.1 ± 8.2 (SD) mo in the ones with CRP level detected < 5 mg/L, OS 118.6 ± 12.2 (SD) mo in the ones with CRP level found between 5-20 mg/L, OS 72.3 ± 10.5 (SD) in the ones with CRP level > 20 mg/L (*P* = 0.009). When pancreas and stomach NETs were compared in respect of survival, the survival time of Pancreas NETs were found lower as statistically significant (*P* = 0.016). To determine the patients died in the 5-year patient follow-up, when the cut off value of the CRP value was taken as 3.85 mg/L, its sensitivity was determined as 80%, specificity 45%, when taken as 5 mg/L which is the universal “cut off” value of CRP, sensitivity as 76%, specificity 47%, when the ”cut off” value was taken as 20 mg/L, its sensitivity was determined as 56% and specificity as 79%. Also, it was seen that in the CRP levels each 1 mg/dL increases death risk relatively %1,5 and being over 20 mg/L increased the death risk relatively 3.2 times as much (95%CI: 14.5-7.1).

***Research conclusion***

CRP is an acute phase protein and is produced in the liver. Acute phase response is stimulated by IL-6 released from macrophage and T cells. Any condition of acute or chronic inflammation may cause CRP increase by activating IL-6. These conditions include infections, autoimmune diseases and malignancies. As a result, CRP is sensitive but nonspecific marker. For this reason, the CRP level of the 21 patients in whom CRP elevation developed due to non-tumor related causes were not taken into account in our study. According to the results, CRP level, especially when it is above 20 mg/L, can be qualified as bad prognostic factor for the GEP-NET group. This situation was shown for the first time for the entirety of the GEP-NET group. Moreover, correlation between Ki-67 level which is another prognostic factor and CRP level not having been detected in our study reinforces the opinion that CRP value is an independent prognostic factor for the whole GEP-NET group.

***Research prospectives***

In literature, small scale studies that include patients by assigning different subgroups for GEP-NETs are present, however, studies that approach the GEP-NET group holistically are only a few. Since it is known that all GEP-NETs can metastasize, specifying the follow-up parameters that can be used and the factors that affect clinical course has importance. It was seen in our study that CRP level which is one of the biochemical parameters affected the disease course in a bad way for the GEP- NET group, especially when it is > 20 mg/dL. We think that CRP level is an independent bad prognostic factor for the whole GEP-NET group. In case that this situation is shown by prospective and controlled studies to be made, the patients thought to progress aggressively can be determined in advance according to the CRP level at the moment of diagnosis and the treatment option can be planned accordingly and CRP level can be used as a follow-up parameter.

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**P-Reviewer:** Sharma V, Zhang Z, Tomizawa M **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Oncology

**Country of origin:** Turkey

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Relationship of demographic data and numeric independent variables with 5-year survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Patient group** ***n* = 93** | **5-yr survival****Yes ( alive )*****n* = 57** | **5-yr survival****No ( dead )*****n* = 36** | ***P* value** |
| **Age (yr)** |  Mean: 53.45 SD: 13.46 | Mean: 50.9SD: 12.2 | Mean: 57.4SD: 13.6 | **0.02** |
| **Gender (F/M)** |  F 54.8%  M 45.2%  | F 64.9% M 35.1%  | F 38.9% M 61.1%  | **0.01** |
| **Tumor diameter (cm)** |  Mean: 3.1 SD:3.45 | Mean: 2.39SD: 3.56 | Mean: 4.20SD: 3.03 | **0.01** |
| **Hgb level (g/dL)*****n* = 89** | Mean: 12.21SD: 1.99 | Mean: 12.31SD: 1.86 | Mean: 12.05SD: 2.22 | **0.54** |
| **Albumin level (g/dL) *n* = 87** | Mean: 4.08SD: 0.53 | Mean: 4.16SD: 0.56 | Mean: 3.94SD: 0.44 | **0.07** |
| **LDH level (U/L)*****n* = 83** | Mean: 291.1SD: 213.1 | Mean: 255.6SD: 95.11 | Mean: 347.5SD: 316.5 | **0.11** |
| **CRP level (mg/L)*****n* = 72** | Mean: 22.5SD: 33.8 | Mean: 14.63SD: 25.48 | Mean: 37.31SD: 42.25 | **0.02** |
| **ESR (mm/h)*****n* = 63** | Mean: 37.7SD: 25.9 | Mean: 33.905SD: 24.3329 | Mean: 45.429SD: 27.8039 | **0.09** |

F: Female; M: Male; Hgb: Hemoglobine; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ESR: Erytrocyte sedimantation rate; SD: Standart deviate.

**Table 2 Relationship beween categorical independent variables and survival times**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Mean survival (mo)** | **Standard deviation****(± mo)** | **1-yr survival****%**  | **3-yr survival****%** | **5-yr survival****%** | ***P* value** |
| **All patients**  | *N* = 93 | 102.5 | 6.3 | 90 | 72 | 61 |  |
| **Non-surgical (non-invasive) sampling**  | Yes (*n =* 56)No (*n =* 37) |  101.9 | 7.3 | 91 | 75 | 66 | **0.25** |
| 93.2 | 10.3 | 89 | 67 | 54 |
| **Surgical resection**  | Yes (*n =* 54)No (*n =* 39) | 99.6 | 8.4 | 89 | 70 | 59 | **0.62** |
| 97 | 8.5 | 92 | 74 | 64 |
| **Liver metastasis** | Present (*n =* 38)Absent (*n =* 55) | 61.3 | 9.5 | 81 | 47 | 29 | **< 0.001** |
| 122.6 | 5.5 | 96 | 89 | 83 |
| **Extrahepatic metastasis** | Present (*n =* 23)Absent (*n =* 70) | 32 | 5.8 | 78 | 30 | 08 | **< 0.001** |
| 124 | 6 | 94 | 85 | 78 |
| **Stage** | 1 (*n =* 35)2 (*n =* 7) | 132.8 | 4.3 | 100 | 94 | 91 | **< 0.001** |
| 100 | 100 | 100 |
| 3 (*n =* 13)4 (*n =* 38) | 69.7 | 8.5 | 84 | 70 | 54 |
| 81 | 47 | 29 |
| **Grade mitotic count** | 1 (*n =* 62)2 (*n =* 21)3 (*n =* 10) | 111 | 6.2 | 97 | 84 | 72 | **< 0.001** |
| 87.1 | 14.4 | 81 | 57 | 52 |
| 35.1 | 11.3 | 70 | 30 | 10 |
| **Grade Ki-67 level** | 1 (*n =* 43)2 (*n =* 30)3 (*n =* 20) | 124.6 | 6.1 | 97 | 90 | 86 | **< 0.001** |
| 83.9 | 9.9 | 90 | 66 | 50 |
| 54.4 | 12.7 | 75 | 40 | 25 |
| **Anemia condition** | Present (*n =* 42)Absent (*n =* 47) | 92.9 | 8.7 | 90 | 71 | 57 | **0.34** |
| 110 | 8.6 | 90 | 76 | 68 |
| **Hypoalbuminemia** | Present (*n =* 10)Absent (*n =* 77) | 91 | 15.7 | 100 | 70 | 60 | **0.60** |
| 105.4 | 6.8 | 89 | 75 | 63 |
| **ESR elevation** | Present (*n =* 30)Absent (*n =* 33) | 93.5 | 9.5 | 93 | 76 | 60 | **0.28** |
| 117.7 | 9.2 | 93 | 81 | 72 |
| **CRP elevation****(mg/L)** | < 5 (*n =* 28)5-20 (*n =* 20)> 20 (*n =* 24) | 118.1 | 8.2 | 100 | 85 | 78 | **0.009** |
| 118.6 | 12.2 | 90 | 80 | 75 |
| 72.3 | 10.5 | 83 | 66 | 41 |

CRP: C-reactive protein; ESR: Erytrocyte sedimantation rate.

**Table 3 Correlation analysis table prepared with tumor properties and C-reactive protein level**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Correlation coefficients (r)** | **Tumor diameter (cm)** | **Tumor stage** | **Tumor grade (mitotic index)** | **Tumor grade****(ki-67 level)** | **Tumor grade****(determined)** | **CRP (mh/L)** |
| **Tumor diameter (cm)** | \_\_\_ |  |  |  |  |  |
| **Tumor stage** | **0.76b** | \_\_\_ |  |  |  |  |
| **Tumor grade****(mitotic count)** | **0.37b** | **0.39b** | \_\_\_ |  |  |  |
| **Tumor grade****(ki-67 level )** | **0.59b** | **0.55b** | **0.75b** | \_\_\_ |  |  |
| **Tumor grade****(determined)** | **0.57b** | **0.53b** | **0.78b** | **0.99b** | \_\_\_ |  |
| **CRP(mg/L)** | **0.25a** | **0.26a** | 0.22 | 0.17 | 0.17 | \_\_\_ |

a*P* < 0.05; b*P* < 0.001. CRP: C-reactive protein.

**Table 4 Five-year survival rate according to primary tumor location**

|  |  |  |  |
| --- | --- | --- | --- |
| **Tumor location** ***n =* 93** | ***N*** | **%** | **Survivors at the end of 5 yr (%)** |
| **Appendix** | 3 | 3.2 | 100 |
| **Duodenum** | 2 | 2.2 | 100 |
| **Ileum** | 7 | 7.5 | 43 |
| **Liver** | 2 | 2.2 | 50 |
| **Colon** | 13 | 14 | 54 |
| **Stomach** | 29 | 31.2 | 79 |
| **Esophagus** | 1 | 1.1 | 0 |
| **Pancreas** | 25 | 26.9 | 48 |
| **Periampullary** | 7 | 7.5 | 43 |
| **Rectum** | 4 | 4.3 | 75 |

**Table 5 Survival difference relationship between pancreatic and stomach neuroendocrine tumors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Tumor location** ***n =* 54** | **5 -year survival****Yes*****n =*  35** | **5-year survival****No*****n =*  19** | ***P* value** |
| **Stomach****Pancreas** |  53.7% 46.3% | 65.7% 34.3% | 31.5%68.5%  | **0.016** |

**Table 6 Relative death risk increase in unit changes of determined variables**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Significance level (*P*)** | **Relative increase in death risk according to unit change (times more)** |  **95%CI** |
| **Lower limit** | **Upper limit** |
| **Age (yr)** | 0.041 | 1.04 | 1.007 | 1.066 |
| **Gender (M/F)** | 0.015 | 2.0 | 1.028 | 3.976 |
| **Tumor diameter (cm)** | 0.02 | 1.09 | 1.014 | 1.169 |
| **Tumor grade****(Ki-67) (3/1-2)** | < 0.001 | 3.6 | 1.873 | 7.206 |
| **Tumor grade****(mitosis) (3 / 1-2)** | 0.006 | 3.0 | 2.823 | 13.362 |
| **Determined tumor grade (3/1-2)** | < 0.001 | 3.6 | 1.873 | 7.206 |
| **Tumor stage****(3-4/1-2)** | < 0.001 | 12.7 | 3.869 | 41.708 |
| **CRP level (mg/L )** | 0.005 | 1.01 | 1.022 | 1.253 |
| **Liver metastasis (P/A)** |  < 0.001 |  6.1 |  2.823 |  13.362 |

F: Female; M: Male; CRP: C-reactive protein; ESR: Erytrocyte sedimantation rate; P: Present; A: Absent.



**Figure 1 ROC curve of the relationship between C-reactive protein level and death/alive status.** CRP: C-reactive protein.