Factors Affecting Survival in Neuroendocrine Tumors: A 15-Year Single Center Experience

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Abstract

**Background:** Neuroendocrine tumors are a heterogeneous group of tumors that can originate from all of the neuroendocrine cells in the body, mostly from the gastrointestinal tract. In addition to early diagnosis, streaming patients into appropriate prognostic groups is an important component of treatment. In this study, we examined the factors that affect survival in patients we followed in our center between 2000-2016. **Methods:** The demographic data, clinical and pathological features of patients were obtained from their medical files. TNM staging and tumor grading were performed according to AJCC and WHO 2010 classification. SPSS 15.0 for Windows programme was used for statistical analysis. **Results:** 85 patients (32 male, 53 female) were included into the study. The median age of the patients was 55.7 (27-83) years. Eighty percent of the tumors were of gastroenteropancreatic system, most commonly stomach (27.1%) origin. Nineteen patients (22.4%) died during follow-up. In univariate analysis; age (p<0.001), stage (p=0.002), primary tumor localization (p=0.005), grade (p<0.001), Ki-67 value (p<0.001), number of metastases (p=0.001) and type of surgery (p<0.001) were found to be factors affecting survival. Age (p=0.024) and Ki67 (p <0.001) were the independent prognostic factors for survival in multivariate analysis. For the cut-off value of 6%, Ki-67 had a sensitivity of 83.3% and specificity of 71.4% for survival determination. **Conclusion:** Ki-67 ratio and age were the most important factors affecting survival in neuroendocrine tumors in our study. Ki-67 ratio has a high sensitivity and specificity for predicting survival, a cut-off value of 6% may be used to predict survival. **Keywords:** Age- grade- Ki-67- neuroendocrine tumor- survival

Introduction

Neuroendocrine tumors (NET) are a heterogeneous group of tumors that can originate from all of the neuroendocrine cells in the body, mostly from the lung and gastrointestinal tract including stomach, pancreas, small and large intestine, rectum. They can occur at any age, although it is often seen over 50 years. The incidence of NET is higher in men than in women. Even though they usually exhibit indolent clinical course, they may become very aggressive and rapidly become metastatic. Since most of NET are not functional, they often cause no signs and symptoms, which makes early diagnosis difficult and decreases survival by reducing the chance of curative treatment (Yao et al., 2008). In addition to early diagnosis, streaming patients into appropriate prognostic groups is an important component of treatment. However, the absence of frequently accepted classifications limits its benefit on survival (Bilimoria et al., 2007).

There is insufficient information about the incidence and frequency of many NET subgroups, including those with unknown primaries. In addition, long-term follow-up and survival-related data are limited in NET patients. The survival and the factors affecting it in patients with NET in many countries have not been identified. This suggests that further studies on prognostic parameters are needed (Oh et al., 2012).

In this study, we evaluated the prognostic significance of the clinicopathologic parameters routinely used in daily practise and the treatments administrated to the NET patients that we followed in our center between 2000 and 2016.

Materials and Methods

Patients who were diagnosed with pathologically verified NET and treated and followed up at our clinic between 2000 and 2016 were included in the study. The data concerning patients’ age, gender, complaint for hospital admission, smoking history, the presence

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of carcinoid syndrome, stage, location of the primary, the location and number of metastases, type of surgery and treatment applied were obtained from their medical files. Patients with incomplete data, missing data, or multiple primers were excluded from the study. A total of 85 patients (32 males and 53 females) were included in the study. The TNM staging of patients and grading (G) of the tumor were performed according to AJCC and 2010 WHO classification, respectively (Bosman, 2010); World Health Organization; International Agency for Research on Cancer. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: International Agency for Research on Cancer).

The study protocol was approved by the Corporate Ethics Committee and found to comply with ethical principles for epidemiological investigations.

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics were given as mean, standard deviation, minimum, maximum for numerical variables, number and percentage for categorical variables. The numerical variables in the independent two groups were analyzed by Student t test and Mann Whitney U test if normal distribution condition was provided and not met, respectively. The comparisons of ratios between groups were made with Chi Square Analysis. Monte Carlo simulation was applied when conditions were not met. The survival analyzes were performed with Kaplan Meier Analysis. Determinants for survival were examined by Cox Regression Analysis. In univariate analysis, forward stepwise model was used for values with p<0.100. The cut-off values were determined by using Roc Curve Analysis. The statistical significance level of alpha was accepted as p <0.05.

Results

A total of 85 patients, 32 (37.6%) male and 53 (62.4%) female, were included in the study. The median age was 55.7 (27-83) years. Eighty percent of the tumors were of gastroenteropancreatic system, most commonly stomach (27.1%) origin.

According to WHO classification, well differentiated NET (G1), moderately differentiated NET (G2) and neuroendocrine carcinoma (NEC)(G3) were detected in 53 (62.1%), 6 (7.1%), 26 (30.8%) patients, respectively. According to the AJCC / UICC staging, 31 (36.5%) patients had stage 1; 6 (7.1%) patients had stage 2; 11 (12.9%) patients had stage 3; 37 (43.5%) patients had stage 4 disease. Of the 59 (69.4%) patients, 54 (63.5%) and 5 (5.9%) underwent curative and palliative surgery, respectively. The lymph node metastasis was detected in 18 (30.5%) patients. At the time of diagnosis, 44.8% of patients had distant metastases (Table 1).

The somatostatin analogs to 25 (36.8%) patients, metastatic first-line cytotoxic chemotherapy (CT) to 36 (44.1%) patients, and second line CT to 6 (7.4%) patients were given as systemic treatment. 3 (3.5%) patients received everolimus. Two patients (2.3%) received peptide receptor radionuclide therapy (PRRT) (Table 1).

It was observed that the tumor grades varied with the localization of the tumors. Statistically significant

| Table 1. Demographic Data, Applied Treatments and Response Rates |
|---------------------------------------------------------------|
| Mean±SD | Min-Max |
|---|---|
| Age | 55.7±14.4 | 27-83 |
| Ki-67 ratio (%) | 15.4±23.1 | Jan-95 |
| Mitosis number | 3.8±9.6 | 0-50 |
| Number of metastases | 0.87±1.12 | 0-3 |
| Gender | Male | 32 | 37.6 |
| | Female | 53 | 62.4 |
| Smoking | 30 | 35.3 |
| Symptom | Abdominal pain | 54 | 63.5 |
| | GIS hemorage | 8 | 9.4 |
| | Weight loss | 5 | 5.9 |
| | Symptomatic | 5 | 5.9 |
| | Hot flushes | 3 | 3.5 |
| | Back pain | 2 | 2.4 |
| | Shortness of breath | 3 | 3.5 |
| | Swallowing difficulty | 2 | 2.4 |
| | Jaundice | 1 | 1.2 |
| | Palpable mass | 1 | 1.2 |
| | Diarrhea | 1 | 1.2 |
| Carcinoid Syndrome | 7 | 8.2 |
| Grade | G1 | 53 | 62.1 |
| | G2 | 6 | 7.1 |
| | G3 | 26 | 30.8 |
| Stage | I | 31 | 36.5 |
| | II | 6 | 7.1 |
| | III | 11 | 12.9 |
| | IV | 37 | 43.5 |
| Primary Localization | Stomach | 23 | 27.1 |
| | Pancreas | 18 | 21.2 |
| | Small bowel | 10 | 11.8 |
| | Appendix | 10 | 11.8 |
| | Unknown primary | 9 | 10.6 |
| | Lung | 8 | 9.4 |
| | Colorectal | 7 | 8.2 |
| Metastases | None | 47 | 55.3 |
| | Liver | 34 | 40 |
| | Lung | 2 | 2.4 |
| | Bone | 2 | 2.4 |
| Lymph Node Metastases | No | 41 | 69.5 |
| | Yes | 18 | 30.5 |
| Surgery Type | None | 26 | 30.6 |
| | Curative | 54 | 63.5 |
| | Palliative | 5 | 5.9 |
| Octreotide | 25 | 36.8 |
| Octreotide response | PR | 10 | 14.7 |
| | SD | 13 | 19.1 |
| | PD | 2 | 2.9 |
| Everolimus | 3 | 4.4 |
| Everolimus response | PR | 1 | 1.5 |
| | SD | 2 | 2.9 |
Factors Affecting Survival in Neuroendocrine Tumors

Differences were found in tumor grades of patients with primary lung (p=0.001), stomach (p=0.0001), and pancreas (p=0.022) compared to the others. G2 ratio of patients with primary lung, G3 ratio of patients with primary stomach and G1 ratio of patients with primary pancreas were significantly higher than the other primaries (Table 3).

During follow-up, 19 (22.4%) patients died. 5-, 10-, and 15-year survival rates of all patients were 75.2%, 67.8%, and 60.3%, respectively; while median survival time was not reached. According to gradings, 5-,10- and 15-year survival rates were found as 95%, 95%, and 95% for G1; 91.1%, 67.5%, and 67.5% for G2; 19.1%, 19.1%, and 19.1% for G3; respectively; According to stages, 5-,10- and 15-year survival rates were found as 97.1%, 93.3%, and 93.3% for stage I+II; 88.3%, 74.1%, and 55.0% for stage III; 57.4%, 38.3%, and 38.3% for stage IV; respectively (Table 2).

Age (p=0.007), Ki-67 ratio (p=0.001), number of

Table 1. Continued

| Mean±SD | Min-Max |
|---------|---------|
| 1. line CT | 36 44.1 |
| 1.line CT response | CR 6 8.8 |
| PR 17 17.6 |
| SD 7 10.3 |
| PD 5 7.4 |
| 2. line CT | 6 7.4 |
| 2.line CT response | PR 4 5.9 |
| SD 2 1.5 |
| 3. line CT | 3 4.4 |
| 3.line CT response | SD 2 2.9 |
| PD 1 1.5 |
| PRRT | 2 2.9 |

Table 2. Primary Tumor Localizations According to Grades

| Primary Localization | G1(n=53) | G2(n=6) | G3(n=26) | p |
|----------------------|----------|--------|----------|---|
| Lung                 | n 5 % 9.4 | 3 % 50 | 0 % 0 | 0 % 0 | 0.001 |
| Stomach              | 7 % 13.2 | 0 % 0 | 16 % 61 | 6 | 0.001 |
| Pancreas             | 16 % 30.2 | 1 % 16 | 7 % 1 | 3 | 0.022 |
| Small bowel          | 7 % 13.2 | 2 % 33 | 1 % 4 | 15 | 0.627 |
| Colorectal           | 3 % 5.7 | 0 % 0 | 4 % 15 | 3 | 0.164 |
| Appendix             | 10 % 18.9 | 0 % 0 | 0 % 0 | 0.164 |
| Unknown              | 5 % 9.4 | 0 % 0 | 4 % 15 | 3 | 1 |
| Overall Survival (Years) | G1(%) | G2(%) | G3(%) | Total(%) |
| 5                    | 95 | 91.1 | 67.5 | 19.1 | 75.2 |
| 10                   | 95 | 67.5 | 67.5 | 19.1 | 67.8 |
| 15                   | 95 | 67.5 | 67.5 | 19.1 | 60.3 |
| Stage (Years)        | I+II (n=37) | III (n=11) | IV (n=37) | p |
| 5                    | 97 | 88.3 | 57.4 | 0.001 |
| 10                   | 93.3 | 74.1 | 38.3 | 0.001 |
| 15                   | 93.3 | 0.55 | 38.3 | 0.001 |

G1, well differentiated; G2, moderately differentiated; G3, neuroendocrine carcinoma
mitosis (p=0.031), number of metastases (p=0.016), the ratio of gastric localization of the primary tumor (p=0.001), presence of distant metastases (p=0.028), presence of lymph node metastases (p=0.049) and CT utilization rates (p=0.001) were statistically significantly higher in patients with exitus compared with those alive. In addition, the rates of G3 (p=0.001) and stage IV disease (0.016) were significantly higher, whereas curative surgery rate was significantly lower (p=0.007) in patients who died (Table 3).

In univariate analysis; age (p<0.001), stage (p=0.002), primary tumor localization (p=0.005), grade (p <0.001), Ki-67 ratio (p<0.001), the number of metastasis (p=0.001) and the type of surgery (p <0.001) were found to be the factors affecting survival (Table 4). When factors affecting the OS were evaluated, age (p=0.024) and Ki-67 ratio (p<0.001) were found to be the most significant factors according to Forward Stepwise analysis based on model consisted of variables of which p values were determined as <0.100 in univariate analysis (age, smoking, primary tumor localization, grade, stage, metastasis, type of surgery, Ki-67 ratio) (Table 5).

There was a statistically significant difference in survival rates in the Ki-67 ratio groups (p<0.001). Patients with a Ki-67 ratio of >20% had a statistically significant lower survival rate than those with ≤2% (p<0.001) and 3-20% (p=0.002). On the other hand, no significant difference in survival rates was detected between patients with Ki-67 value of ≤2% and 3-20% (p=0.094) (Figure 1). The median survival was 27±13.2 (95% CI:1.0-52.5)

### Table 3. Comparison of Characteristics of Patients with and without Exitus

| Last status | Exitus | Alive | p   |
|-------------|--------|-------|-----|
| Age | 63.4±12.2 | 52.9±14.3 | 0.007 |
| Ki-67 ratio (%) | 37.3±31.3 | 9.1±15.6 | 0.001 |
| Mitosis number | 18.3±22.9 | 1.5±1.5 | 0.031 |
| Metastases number | 1.39±1.24 | 0.68±1.02 | 0.016 |
| Gender | | | 0.891 |
| Female | 12 | 63.2 | 41 | 62.1 |
| Male | 7 | 36.8 | 25 | 37.9 |
| Carcinoid Syndrome | | | 0.341 |
| Lung | 0 | 0 | 7 | 10.6 |
| Stomach | 12 | 63.2 | 12 | 18.2 |
| Pancreas | 2 | 10.5 | 16 | 24.2 |
| Small bowel | 1 | 5.3 | 9 | 13.6 |
| Colorectal | 2 | 10.5 | 5 | 7.6 |
| Appendix | 1 | 5.3 | 9 | 13.6 |
| Known | 1 | 5.3 | 7 | 10.6 |
| Grade | | | <0.001 |
| G1 | 4 | 21.1 | 49 | 74.4 |
| G2 | 1 | 5.3 | 5 | 7.7 |
| G3 | 14 | 73.7 | 12 | 17.9 |
| Stage | | | 0.016 |
| I | 1 | 5.3 | 30 | 45.5 |
| II | 1 | 5.3 | 5 | 7.6 |
| III | 3 | 15.8 | 8 | 12.1 |
| IV | 14 | 73.7 | 23 | 34.8 |
| Metastases | 14 | 73.7 | 24 | 36.3 |
| Lymph Node Metastases | 5 | 66.7 | 13 | 28 |
| Cerrahi Tipi | | | 0.049 |
| None | 11 | 57.9 | 15 | 22.7 |
| Curative | 5 | 26.3 | 49 | 74.2 |
| Palliative | 3 | 15.8 | 2 | 3 |
| Octreotid | 6 | 33.3 | 19 | 38 |
| Everolimus | 2 | 11.1 | 1 | 2 |
| 1.line CT | 16 | 84.2 | 20 | 30.3 |
| 2.line CT | 2 | 13.3 | 4 | 20 |
| 3.line CT | 1 | 5.6 | 2 | 4 |

G1, well differentiated; G2, moderately differentiated; G3, neuroendocrine carcinoma; CT, chemotherapy

3600 Asian Pacific Journal of Cancer Prevention, Vol 19
months in the Ki67 >20% group, whereas median survival was not achieved in the other groups.

According to the ROC analysis for the determination of mortality, the sensitivity and specificity of the Ki-67 ratio were found to be 83.3% and 71.4% for the cut-off value of >6% (AUC:0.813 (%95 CI: 0.664-0.963) (Figure 2). The cumulative survival rate of patients with a Ki67 ratio of ≥6% was found to be statistically significantly lower than those with a Ki67 ratio of <6% (p<0.001) (Figure 1). The median survival was not reached in the group with a Ki67 ratio of <6% whereas it was 86±41.9 (95% CI:3.8-168.1) months in the group with a Ki67 ratio of ≥6%.

Discussion

The naming and classification of NET have been changed several times, making it difficult to collect epidemiological information and compare studies published in the literature. The actual incidence of NETs is not known due to the lack of sufficient multicentric and epidemiological studies. This may explain the difference in incidence of NET between gender, race, country and continent (Hauko et al., 2008).

Over the last decade, attempts have been made to develop existing classification systems. There is limited data on long-term follow-up and survival in patients with NET. Because of infrequency and the differences in the diagnosis of NET, it is difficult to identify high risk factors. There are only a few studies that define prognostic factors, thus, factors affecting survival of patients with NET is lacking in many countries (Faggiano et al., 2012).

The median age of the patients at our study was 55.7 years, similar to other studies (Niederle et al., 2010; Araujo et al., 2013; Lewkowicz et al., 2013; Nikou et al., 2016). Five percent of the cases were asymptomatic. The incidence of carcinoid syndrome was 8.2%. Similar to other studies, the most common symptom was abdominal pain (Araujo et al., 2013; Lewkowicz et al., 2015). The most common disease grade seen in our study was G1. The most common localizations of the G1 disease were of the rectum and appendix in other studies, whereas it was of pancreas and appendix in our study (Niederle et al., 2010; Lewkowicz et al., 2015).

The pancreas and lung were the most common primary localizations in the study by Nikou et al., (2016). In another study, the most common primary localizations were alined as rectum, duodenum, pancreas and stomach while the most frequent stage, grade and metastatic site were stage 1, grade 1 and the liver, respectively (Lim et al., 2017). In our study, unlike other studies, the most common localizations were stomach, pancreas and small bowel (Garcia-Carbonero et al., 2010; Niederle et al., 2010; Lim et al., 2011; Lewkowicz et al., 2015). The most common distant metastasis site was liver.

Grade and Ki-67 ratio are required for pathologic classification and have prognostic significance. The Ki67 ratio was found to be <2% in most of the studies (Garcia-Carbonero et al., 2010; Niederle et al., 2010; Lim et al., 2011; Araujo et al., 2013; Lewkowicz et al., 2015; Nikou et al., 2016; Lim et al., 2017). Likewise, in our study, the Ki67 rate was found to be ≤2% in 63.1%, 3-20% in 7.1%, and >20% in 25% of patients.

The only curative treatment method in NET is the surgical resection. Surgery should be considered in patients with early stage, locoregional and resectable metastatic disease (Bilimoria et al., 2007). In our study, curative surgery was applied to 63.5% of patients and metastatic disease (Bilimoria et al., 2007). In our study, curative surgery was applied to 63.5% of patients and metastatic disease (Bilimoria et al., 2007). In our study, curative surgery was applied to 63.5% of patients and metastatic disease (Bilimoria et al., 2007).

Table 5. Survival Determining Factors in Multivariate Analysis

| Variables       | p     | HR      | %95 CI  |
|-----------------|-------|---------|---------|
| Age (Years)     | 0.024 | 1.067   | 1.009   | 1.128   |
| Ki67 %          | <0.001| 1.048   | 1.024   | 1.073   |

Figure 2. Receiver Operating Characteristic Curve Analyses for the Determination of Mortality, the Sensitivity and Specificity of the Ki-67 Ratio were Found as 83.3% and 71.4% for the cut-off value of >6% (AUC:0.813 (%95 CI: 0.664-0.963).
Abdullah Sakin et al

Asian Pacific Journal of Cancer Prevention, Vol 19, 2655-64.

primary tumor, presence of distant metastases, presence of mitosis, number of metastases, gastric localization of the in this group.

high tumor burden may explain the lower survival rates use of CT in the treatment of symptomatic patients with ratios of tumors in gastric localization. Furthermore, the gastric localization may be due to higher values of Ki-67 be the most significant factors. The lower survival rates in to be factors affecting survival in univariate analysis. In

metastases at the time of diagnosis, number of metastases, presence of lymph node metastasis and CT use were found to be factors affecting survival in univariate analysis. In

of lymph node metastases, G3 and stage IV disease and CT utilization rates were statistically significant higher in patients with exitus compared with those alive. The Ki-67 ratio and age were determined as the most important factors affecting survival. Ki-67 ratio has high sensitivity and specificity in predicting survival. We think that the Ki-67 ratio of ≥6% might be used to estimate survival.

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

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