RESEARCH ARTICLE

Neuroendocrine tumors in the Iran Cancer Institute: Predictive Factors of Patient Survival

Sanambar Sadighi[1]*, Ghodratollah Roshanaee[2], Saba Vahedi[1], Easa Jahanzad[3], Mohammad Ali Mohagheghi[4], Alireza Mousavi-Jarahi[5,6,7]

Abstract

   Background: Neuroendocrine tumors have widespread and different clinical presentations and prognoses. This study was conducted to assess their survival time and prognostic factors in Iran. **Materials and Methods:** In a retrospective cohort study, 189 patients diagnosed of having neuroendocrine carcinoma were chosen. The tumor and clinical characteristics of the patients were modeled with a Cox proportional hazard approach. Survival was assessed using Kaplan-Meyer curves. **Results:** Crude median survival time was 30 months. Women survived longer than men (the median survival time for women was 40 and for men was 24 months). Age (<60 *vs* >60 years old with hazard ratio (HR) of 2.43, 95% CI 1.3-4.5), primary pathology report (carcinoid vs. others with HR 5.85 cm, 95% CI 2.4-14.3), tumor size cm (for 5-10, HR of 3.1, 95% CI 1.6 and for >10 HR of 8.2, 95% with 95% CI 3.1-21.9), and chemotherapy with single drug (taking vs. not taking with a HR 2.2, 95% CI 1.1-4.8) had significant effects on overall survival of patients. **Conclusions:** Survival time in patients with neuroendocrine carcinomas is related to demographics, clinical characteristics, tumor histology, and subtype specific treatment.

Keywords: Neuroendocrine neoplasms - carcinoid tumors - survival - Cox proportional hazard model - chemotherapy

Introduction

   Neuroendocrine neoplasms (ICD OM rubrics of XX.XX) include heterogeneous families of tumors with complex and wide clinical behavior (Modlin et al., 2008). The incidence of neuroendocrine neoplasms in the United States is 2.5 to 5 cases per 100,000 persons per year (Modlin et al., 2003; Yao et al., 2008) The incidence of this tumor has not been evaluated in Iran. However, 8 neuroendocrine neoplasms cases per 100 cases of other cancers have been reported in a cancer center in Tehran (Sadighi et al., 2013).

   Neuroendocrine systems include organs with cells that have the capability of amine precursor uptake and decarboxylation. Neuroendocrine carcinomas have been found in a wide range of organs and viscera in humans and their most common site of origin is in gastrointestinal and lung systems (Al-Khafaji et al., 1999; Kulve et al., 1999).

   In lung, neuroendocrine tumors are divided into two categories: small cell and large cell (Harkema et al., 1992). Small cell carcinoma of the lung is highly malignant and has a poor prognosis (Junker et al., 2000). Patients with neuroendocrine carcinoma of gastrointestinal origin have also had metastases at the time of diagnosis. Stomach includes 33-55% of extrinsic pulmonary neuroendocrine

carcinomas and other common sites of disease in gastrointestinal are the esophagus, pancreas and colorectal areas (Kang et al.,2007; Brener et al., 2004).

   Survival of patients with neuroendocrine carcinoma and its influential factors are different, so that the median survival of untreated patients is usually 4-6 months (Lee et al., 2007). The National Cancer Registry of Spain has reported that 67% of these patients had metastatic disease with a 1.7 month median survival (Galanis et al., 1997). In Sorbye and colleagues study with 305 patients, the median survival was 11 months (Sorbye et al., 2013). In this study the physical performance, tumor origin, serum LDH and elevated platelet count have had a significant effect on survival. In Moertel and colleagues study on patients with gastrointestinal neuroendocrine carcinoma, median survival was 19 months (Moertel et al., 1990).

   In a study on patients with colorectal neuroendocrine carcinoma as the primary origin, median survival was 10 months and survival rates at 1, 2 and 3 years were 46%, 26% and 13%, respectively (Bernick et al., 2004). In 53 neuroendocrine carcinoma patients with gallbladder origin, median survival after chemotherapy was 8 months, and one and two-year survival rates were 28% and 0%, respectively (Fujii et al., 2001). In patients with metastatic colorectal neuroendocrine carcinoma, 5-year survival rate

[1]*Department of Internal Medicine, [3]Department of Pathology [4]Department of Surgical Oncology, Cancer Research Center, Tehran University of Medical Sciences, [5]Department of Social Medicine, Shahid Beheshti University of Medical Sciences, Tehran, [2]Biostatistics Department, Hamadan University of Medical Sciences, Hamedan, [7]Medical School, Sabzevar University of Medical Sciences and Health Services, Sabzevar, Iran [6]Health Science Center, Simon Frazer Center, British Colombia, Canada *For correspondence: ssadighi@tums.ac.ir

was 6 months (Garcia et al., 2010). In a study on 178 cases with neuroendocrine tumors of gastroenteropancreatic (GIP) tract, physical functional status, degree of tumor differentiation, distant metastasis and tumor type showed significant association to survival of the patients (Wang et al., 2012). As there are no reports on survival and prognostic factors related to neuroendocrine tumors in Iran, this study aimed to determine the survival time and prognostic factors among patients referred to Cancer Institute in Tehran from 2004 to 2010.

Materials and Methods

In a retrospective cohort study, 189 patients with different neuroendocrine tumors who had referred to our specialty cancer treatment center (the Cancer Institute, Tehran University of Medical Sciences) were evaluated. The survival time of patients was followed up by periodic visits and phone calls to their families. Survival time was defined from the time of diagnosis in our center until death of the patient or end of the study.

In this study the effect of different factors, such as sex, age, tumor location, disease stage, treatment type, primary pathologic diagnosis, grade of tumor, origin of disease, lymph node involvement, metastasis to other organs, necrosis, tumor metastasis, metastases location were evaluated. The Kaplan-Meier was used to evaluate the survival function and the Cox proportional hazards model was used to evaluate the prognostic values of factors related to the survival of the patients. All the analyses was performed using SPSS software version 16. Any p-value of less than 0.05 was considered as statistically significant for comparisons.

Results

A total of 189 patients (100 men and 89 women) with neuroendocrine carcinoma in different anatomical locations of the body were studied. The mean and median age of the subjects was 49.6±16.8 and 51 years old, respectively. 112 (52.3%) patients died before the end of study with a mean survival time of 47.8±3.7 months and median survival time of 30 months.

Women survived longer than men (the median survival time was 40 for women and 24 months for men); 1, 3 and 5 year survival rates were 0.75%, 0.45% and 0.33%, respectively. The one, three, and five year survival rates for men were 0.68%, 0.40%, and 0.26%, respectively. These figures for women were 0.75, 0.52 and 0.42. Figure
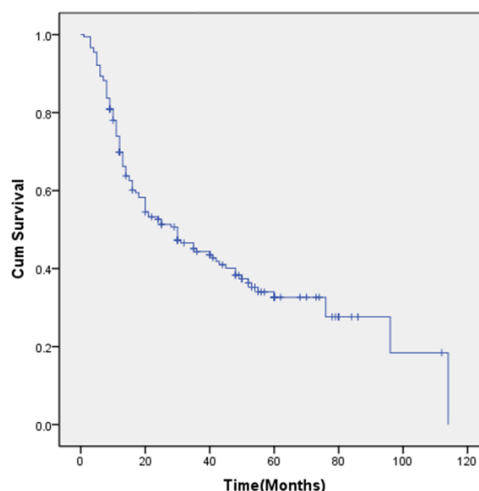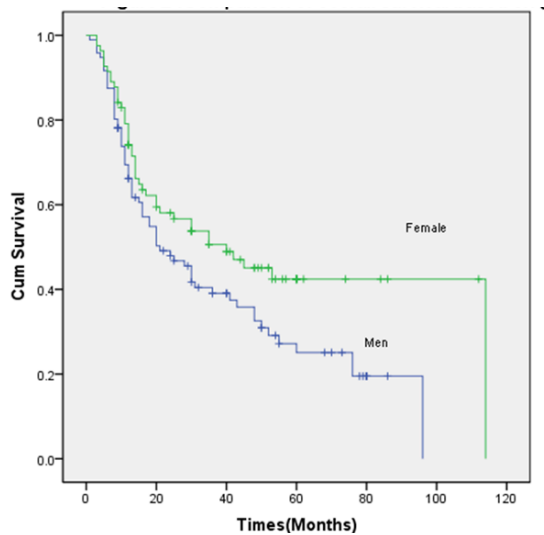

Figure 1. Probability of Survival of Patients with Neuroendocrine Carcinoma

Table 1. Characteristics of Patients with the Diagnosis of Neuroendocrine Carcinomas and Tumors Referred to Our Cancer Treatment Center

	Level	N (%)	Median Survival months	Lag log - rank statistics	P value
Sex	Man	100 (52.9)	24	3.9	0.049
	Woman	89 (47.1)	40		
Diagnosis age	Under 60 years old	137 (72.5)	48	27.1	0.001
	60 years old	52 (27.5)	13		
Tumor grade	Differentiated	68 (36.6)	96	71.6	0.001
	Low differentiation	53 (30.1)	30		
	Moderately differentiated	27 (15.3)	15		
	Without distinction	28 (15.9)	11		
Tumor necrosis	Yes	113 (37.6)	14	36	0.001
	No	68 (62.4)	76		
Chemotherapy	Yes	130 (71.4)	20	12.2	0.001
	No	52 (28.6)	32		
Metastasis	No	73 (40.8)	76	16/3	0.001
	Yes	106 (59.2)	16		
Lymph node metastasis	Yes	378 (80.3)	17	10.3	0.001
	No	93 (19.7)	53		
Surgery type	R0	75 (39.7)	76	54/32.4	0.001
	R1	18 (9.5)	41		
	R2	16 (8.5)	12		
	Biopsy only	80 (42.3)	14		
Tumor size (cm)	<5	68 (43.3)	76	32.8	0.001
	10-May	73 (46.5)	18		
	>10	16 (10.2)	9		
First diagnosis	Carcinoid	51 (27.4)	114	52	0.001
	Adenocarcinoma	40 (21.5)	13		
	Round cell tumor	35 (18.8)	13		
	Undifferentiated carcinoma	32 (17.2)	13		
	Neuroectodermal	23 (12.4)	-		
	Other tumors	8 (2.7)	12		

Figure 2. Probability of Survival Based on Sex of Patients (p=0.039)

Table 2. Factors Affecting Survival Using the Cox Model in Our Study

Risk factors	Sub types	Confidence interval
Sex	Man	1
	Woman	0.74 (0.42-1.29)
Diagnosis age	60>	1
	60 = <	2.43 (1.33-4.48)
Tumor grade	No	1
	Yes	1.59 (0.79-3.5)
	Differentiated	1
Tumor necrosis	Moderately differentiated	1.13 (0.44-2.96)
	Low differentiation	1.12 (0.46-3.6)
	Without distinction	1.43 (0.54-3.8)
Chemotherapy	Yes	1
	No	2.22 (1.04-4.76)
Metastasis	No	1
	Yes	(0.7-2.21) 1.24
Lymph node metastasis	No	1
	Yes	2.57 (1.24-5.3)
Surgery type	R0	1
	R1	2.16(0.78-6)
	R2	2.23 (0.89-6.1)
	Biopsy only	1.21 (0.6-2.4)
Tumor size (cm)	< 5	1
	10-May	3.1(1.59-6.1)
	> 10	8.2(3.1-21.9)
Primary diagnosis	Carcinoid	1
	Others	5.85 (2.4-14.3)

1 shows the Kaplan-Meier overall survival function among all subjects and comparison of survival based on gender is shown in Figure 2. The measured characteristics of the tumors showed that the primary origin of the tumor was gastrointestinal tract in 52 patients (27.5%), chest in 33 patients (17.5%), abdomen in 32 patients (16.9%), head and neck in 25 patients (13.2%), pelvis in 16 patients (8.5%). In 32 patients (16.9%) the origin was unknown (Table 1).

The results of the multivariate analysis (the Cox proportional model) showed that age (<60 *vs* >60 years old with hazard ration (HR) of 2.43, 95% CI 1.3-4.5), primary pathology report (carcinoid *vs* others with HR 5.85m, 95% CI 2.4-14.3), tumor size (for 5-10, HR of 3.1, 95% CI 1.6 and for >10 HR of 8.2,95% with 95% CI 3.1-21.9), and chemotherapy with single drug (taking vs. not taking with HR 2.2, 95% CI 1.1-4.8) had significant effect on the survival of patients (Table 2).

Discussion

In this study, neuroendocrine carcinomas of different anatomical locations were studied. The primary source of tumor was gastrointestinal in 52 patients, chest in 33 patients, abdomen in 32 patients, head and neck in 25 patients and pelvic cavity in 16 patients. The primary origin of the tumor was unknown in 32 patients. Our results are in accordance with a similar conducted research in Turkey in which gastrointestinal and lung have been reported as major sites of neuroendocrine tumors (Yocel, et al 2013). In a study by Sorbye and colleagues the primary tumor site was pancreas and colon in 64 patients (Sorbye et al., 2013). In another study, many of these tumors were seen at the esophagus and colon (Brener et al., 2004). In Wang and colleagues report, 55% of these tumors had originated from the pancreas and rectum (Wang et al., 2012).

In this study, the estimated median survival was 30 months and three and five years survival rates were 45% and 33%, respectively. Although a Chinese report of lung neuroendocrine tumors showed median survival of 48 months, the 5-year-survival rate was 39.6% that is very close to our report (Zeng et al., 2013). These results are significantly better than Sorbye and colleagues (with a median survival of 11 months with 9.5% survival rate for three years).

High survival rate in the present study could be because of its patients' low median age (51 years old) compared to a median age of 61 years old in Sorbye and colleagues. However, some studies have estimated a 5-year survival which is much higher than this study (Durante et al., 2009; Demirci et al., 2014).

In our study, the sex ratio (male to female) was 53% to 47%. The effect on survival was significant in univariate test but not significant in the presence of the other survival variables. In studies which this ratio was 50 to 50, no significant effect was observed on survival, except Garcia-Carbonero and colleagues who found gender as a significant prognostic factor (Garcia et al., 2010).

In this study, approximately 73% of the patients were more than 60 years old and age had an effect on survival. So persons with age <60 years old had 35 months more survival than patients with age >60 years old. Risk of death in patients >60 years old had a 2.5-fold increase in Garcia-Carbonero and colleagues (Garcia et al., 2010). 53% of patients were younger than 60 years old and age had a significant effect on their survival. However, in Wang and colleagues age had no effect on survival (Wang et al., 2012). This difference is probably because of difference in the follow-up period of their study. The median follow-up period in this study was approximately 5 times more than the other mentioned reports.

In different studies from Asian Pacific region surgery was a positive independent prognostic factor of patients' survival (19, 20). Still surgical resection was generally a curative treatment in early stage tumor. Although 59% of our patients had metastatic disease at first diagnosis, 58% of all patients underwent radical surgery. So it is not surprising that surgery was a prognostic factor in univariate but not multivariate analysis.

Sanambar Sadighi et al

In our study, patients who did not receive chemotherapy were 2.22 times more at risk of death than patients receiving chemotherapy. This effect was mainly related to single agent chemotherapy while combination chemotherapy was associated with a shorter lifespan. Sorbye and colleagues results were similar in treatment of neuroendocrine tumors (Sorbye et al., 2013). There is another study using combination of docetaxol and cisplatin in the treatment of metastatic neuroendocrine tumors of unknown origin regardless of differentiation of tumors (Demirci et al., 2014). However, only 3.4% of tumors were reported as well differentiated and toxicity was high.

In this study the risk of death was 2.57 times increased in patients who had metastasis, in line with earlier studies. Tumor size was the other effective factor on survival rate. By increasing tumor size, the risk of death was increased. In a study by Medrano-Guzmán and colleagues (2011), univariable analysis showed that tumor size was effective on survival. However, this variable had no effect in the presence of other variables.

The primary diagnosis of patients had effect on survival. So if patients were diagnosed with carcinoid tumor, had six times less risk of death than cases with other primary pathology reports. If first diagnosis of neuroendocrine tumor is done according to pathology, better differentiation of tumor cells can be seen. Patients can have better outcome than others with diagnosis based on supplementary studies. Our result is similar to another study from China which reported 13.1% typical carcinoid tumor with 75% 5-year-survival that is much more than small cell carcinomas (Wu et al., 2014).

In conclusion, if first diagnosis of neuroendocrine tumor is done according to pathology, patients can have better outcome than others with diagnosis based on molecular or immunohistochemistry studies. Survival with having neuroendocrine carcinomas is not only related to primary characteristics of patients and tumors, but also to choosing the best treatment available for subtype and stage of the disease.

Acknowledgements

References

Al-khafaji B, Noffsinger A, Miller M, et al (1999). Immunohistologic analysis of GI and pulmonary carcinoid tumors. *Hum Pathol*, **29**, 992.

Bernick P, Klimstra S, Shia Jea (2004). Neuroendocrine carcinomas of the colon and rectum. *Dis Colon Rectum*, **47**, 163-9.

Brenner B, Shah M, Gonen M (2004). Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. *Br J Cancer*, **90**, 1720-6.

Demirci U, Coskun U, Karaca H, et al (2014). Docetaxel and cisplatin in first line treatment of patients with unknown primary cancer: a multicenter study of the Anatolian Society of Medical Oncology. *Asian Pac J Cancer Prev*, **15**, 1581-4.

Durante C, Boukheris H, Dromain C, et al (2009). Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr Relat Cancer*, **16**, 585-97.

Fujii H, Aotake T, Horiuchi T et al (2001). Small cell carcinoma of the gallbladder: a case 45 report and review of 53 cases in the literature. *Hepatogastroenterology*, **48**, 1588-93.

Galanis E, Frytak S, Lloyd R (1997). Extrapulmonary small cell carcinoma. *Cancer*, **79**, 1729-36.

Garcia-Carbonero R, Capdevila J, Crespo-Herrero G (2010). Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the national cancer registry of Spain (RGETNE). *Ann Oncol*, **21**, 1794-803.

Harkema J, Jones S, Naydan D, Wilson D (1992). An atypical neuroendocrine carcinoma in the lung of a beagle dog. *Vet Pathol*, **29**, 175-9.

Junker K, Wiethege T, Muller K (2000). Pathology of small-cell lung cancer. *J cancer Res clin oncol*, **7**, 361-8.

Kang H, O'Connell J, Leonardi M (2007). Rare tumors of the colon and rectum: a national review. *Int J Colorectal Dis*, **22**, 183-9.

Kulve M, Mayer R (1999). Carcinoid tumors. *N Engl J Med*, **340**, 858-68.

Lee S, Lee J, Ryu M (2007). Extrapulmonary small cell carcinoma: single center experience with 61 patients. *Acta Oncol*, **46**, 846-51.

Medrano-Guzman R, Lopez-Garcia SC, Torres-Vargas S, Gonzalez-Rodriguez D, Alvarado-Cabrero I (2011). Resectability of primary gastroenteropancreatic neuroendocrine tumor as a prognostic factor for survival. *Cirugia y Cirujanos*, **79**, 459-564.

Modlin I, Lye K, Kidd M (2003). A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*, **97**, 934-59.

Modlin I, Oberg K, Chung D, et al (2008). Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*, **9**, 61-72.

Moertel C, Kvols L, O'Connell M (1991). Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin: evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer*, **68**, 227-32.

Sadighi S, Jahanzad I, Ghadirian L, et al (2013). Assessing the prevalence and characteristics of neuroendocrine tumors in patients attending Tehran Imam Khomeiny referral hospital. *J Mazand Univ Med Sci*, **23**, 232-6.

Sorbye H, Welin S, Langer SW, et al (2013). Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. *Ann Oncol*, **24**, 152-60.

Wang Y-h, Lin Y, Xue L, et al (2012). Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995-2012) in South China. *BMC Endocr Disord*, **12**, 30-9.

Wu B, Hu Y, Sun J, et al (2014). Analysis on the characteristics and prognosis of pulmonary neuroendocrine tumors. *Asian Pac J Cancer Prev*, **15**, 2205-10.

Yao J, Hassan M, Phan A, et al (2008). One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*, **26**, 3063-72.

Yocel B, Babakan NAKanan T, Ayeren A (2013). Survival analysis and prognostic factors for neuroendocrine tumors in Turkey. *Asian Pac J Cancer Prev*, **14**, 6687-92.

Zeng YJ, Liv L, We H, et al (2013). Clinicopathologic features and prognosis of GIP neuroendocrine tumors:Analysis from a single institution. *Asian Pac J Cancer Prev*, **14**, 5775-81.