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Research Article

General Characteristics and Prognostic Factors on Survival in Neuroendocrine Tumor Patients Diagnosed with Carcinoid Syndrome: Erciyes Multidisiplinary Neuroendocrine Tumor (NET) Group Experience

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Abstract

Objectives: Carcinoid syndrome is one of the functional neuroendocrin tumor symptom. It is a very rare disease and a little known about this syndrome. We aimed a study that evaluating general characteristics and prognostic factors on survival in NET patients diagnosed with carcinoid syndrome.

Methods: All patients diagnosed with neuroendocrine tumor were retrospectively reviewed in our institution. The patients diagnosed carsinoid syndrome were included in this study. General characteristics were recorded. Prognostic factors on survival were analysed with Cox regression. Kaplan Meier method was used for overall survival.

Results: Among 450 patients diagnosed neuroendocrine tumor in our hospital, 29 of them (6.4%) were presented with carcinoid syndrome. The univariate analysis revealed that age, high tumor grade and ki67 score were correlated with poor overall survival and the multivariate analyses revealed that older age were correlated with poor overall survival. The median OS were 61 months in all grades and 64 months for grade 1 tumors, 45 (13-76) months for grade 2 tumors, 5 months for grade 3 tumors and there were statistically significant difference (p=0.007).

Conclusion: Age, grade, ki67 score are important prognostic factor. Age is an independent prognostic factor that affecting survival in carcinoid syndrome patients.

Keywords: Carcinoid syndrome, overall survival, predictive factors

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Neuroendocrine tumors are heterogenous malignancies that arise from the neuroendocrin system.[1] Although they are rare tumors, their incidence and prevalence have been increasing last few years[2] Neuroendocrin tumors mostly non functional so they are diagnosed incidentally[3] but functional tumors are diagnosed with some clinical

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symptoms related with secreted bioactive amins. Carcinoid syndrome is one of the functional neuroendocrin tumor symptom and it is recognized with flushing, diarrhea, abdominal pain, wheezing, heart disease.[4]

Carcinoid syndrome affects approximately 20% of NET patients.[5] This syndrome often occurs when the tumor metastasize to liver and vasoactive amins like histamine, serotonine arise to systemic circulation[4] Carcinoid syndrome mostly occur in patients diagnosed NET derived from midgut but it may be seen in other NET such as lung, pancreas. [6] In localized neuroendocrin tumors derived from midgut, sufficient metabolisition of serotonin results in rare carcinoid syndrome symptoms.[6] The presence of carsinoid syndrome symptoms' influence on survival isn't well known. It is thought that the presence of carcinoid syndrome is not directly associated with prognosis. The worse prognosis of carcinoid syndrome is related with tumor burden.[7]

We conducted a study that evaluating general characteristics and prognostic factors on survival in neuroendocrin tumor patients that diagnosed with carcinoid syndrome.

Methods

All neuroendocrine tumor patients were discussed in our neuroendocrine tumor council since 2004. All patients diagnosed with neuroendocrin tumor in this council were retrospectively reviewed. Data collected from the hospital's patient records included patient characteristics, primary tumor location, staging, grade, ki67 levels, metastatic sites, tumor marker (Chromogranin A, NSE, 5-hydroxyindoleacetic asid), number of metastatic sites, treatments, date of death. Carcinoid syndrome was described with pathognomic clinical symptoms include flushing, diarrhea, abdominal pain, palpitation, right valvular heart disease. Flushing alone or right valvular heart disease alone were accepted carcinoid syndrome in diagnosed with neuroendocrine tumor patients. If there are no these symtoms we accepted carcinoid syndrome when there are two of three symptoms among diarrhea, abdominal pain, palpitation in diagnosed with neuroendocrine tumor patients.

Grade were defined as Grade1, 2 and 3 according to WHO classification system.[8] Reference interval of CgA (Chromogranin A) level was 1-100 ng/mL, NSE (neurone specific enolase) level was 15-17 ng/mL, 5 HIAA (hydroxyindolacetic acid) level was 2-10 mg/day.

Statistical

Median, min, max and frequencies were defined. The Kaplan–Meier method and log-rank test were used to analyze survival. Cox regression method was used to identify poor prognostic factors on overall survival. OS was defined as the time from diagnosis to death or last evaluation. A

Table 1. General characteristis of patients diagnosed with carsinoid syndrome

Characteristics (n=29 patients)	n	%
Age years, min.–max.	52 (16-79)	
Symptoms		
Abdominal pain	14	48
Diarrhea	15	52
Flushing	20	69
Palpitation	14	48
Gender		
Male	13	45
Female	16	55
Primary site		
Small bowel	8	28
Colon	1	3
Stomach	5	15
Apendix	1	3
Pancreas	8	28
Lung	2	7
Unknown primary	4	14
Stage		
Metastatic	23	79
Nonmetastatic	6	21
Grade		
Grade 1	18	62
Grade 2	6	21
Grade 3	5	17
Surgery		
Yes	12	41
Curative	5	17
Palliative	7	24
No	17	59
CgA levels		
High	12	41
Not high	5	18
Unknown	12	41
NSE levels		
High	14	48
Not high	11	38
Unknown	4	14
5-OHIAA levels		
High	12	41
Not high	7	24
Unknown	10	35
Metastatic site		
Liver	20	69
Lung	7	24
Bone	8	28
Lymph node	12	48
Others	4	14
Number of metastatic site		
1	13	56
2 and upper	10	44
Somatostatin analogous		
Yes	19	65
No	10	35
Chemotherapy		
Cisplatin-etoposide	16	55
5FU+Streptozosine	8	28
Capecitabine +Temozolamide	5	17
PRRT		
Yes	4	14
No	25	86
Cardiac involvement		
Yes	7	24
No	4	14
Unknown	18	62

CgA: Chromogranin a; NSE: Neuron specific enolase; HIAA: hydroxyindolacetic acid; PRRT: Peptide receptor radionuclide therapy.

Table 2. Univariate and multivariate cox regression analyses for overall survival in patients diagnosed carcinoid syndrome

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Male vs female	1.37 (0.488–3.865)	0.548		
Age	1.04 (1.003–1.080)	0.036	1.050 (1.006–1.096)	0.026
Grade (1,2,3)	2.68 (1.232–5.871)	0.013	1.953 (0.646–5.905)	0.236
Ki67 score	1.028 (1.003–1.053)	0.030	1.021 (0.978– 1.067)	0.341
Metastatic vs not	31.155 (0.192–5067.362)	0.186		
Metastatic site				
1 vs ≥2	0.953 (0.343–2.647)	0.926		
Liver metastasis				
No vs yes	3.466 (0.780–15.402)	0.102		
CgA level				
High vs not	1.457 (0.300–7.069)	0.640		
NSE level				
High vs not	2.619 (0.883–7.764)	0.083		
5OHİAA				
High vs not	0.760 (0.239–2.416)	0.642		
Cardiac involvement				
Yes vs no	0.613 (0.136–2.771)	0.525		

HR: Hazard ratio; CI: Confidence interval; NSE: Neuron specific enolase; CgA: Chromogranin a; HIAA: hydroxyindolacetic acid.

p value <0.05 was regarded statistically significant. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

Results

General Characteristics of Patients

Among 450 patients diagnosed neuroendocrine tumor in our hospital, 29 of them (6.4%) were presented with carcinoid syndrome. The median age were 52 (16-79) years old among carcinoid syndrome patients. Thirteen of them were male (45%) and 16 of them (55%) female. The most common primary site were small bowel and pancreas with 8 patients (28%) each one. Eighteen of them (62%) were grade 1, 6 of them (21%) were grade 2, 5 of them (17%) were grade 3. Other characteristics were summerized in Table 1.

Univariate and Multivariate Analysis

The univariate analysis revealed that age (95% CI 1.04, p=0.036), high tumor grade (95% CI 2.68, p=0.013) and ki67 score (95% CI 1.028, p=0.030) were correlated with poor overall survival (Table 2). We evaluated prognostic factors such as age, grade and ki67 levels with multivariate analysis. The multivariate analyses revealed that older age were correlated with poor overall survival, with a hazard ratio of 1.050 (1.006-1.096) (p=0.026) (Table 2).

Overall Survival

The median OS were 61 (33.37-88.62) months in all grades. The median OS were 64 months for grade 1 tumors, 45 (13-76) months for grade 2 tumors, 5 months for grade 3 tumors and there were statistically significant difference (p=0.007). 5 years overall survival were 64% for grade 1, 42% for grade 2 (Fig. 1).

The median OS were 45 (28-61) months for metastatic disease. In nonmetastatic group the median OS were not reached (p=0.029) (Fig. 1).

The median OS were 64 (38-89) months for patients whose CgA levels were high and 45 months for patients whose CgA levels were not high. There were no statistically significant difference (p=0.63) (Fig. 1).

The median OS were 30 (6-53) months for patients whose NSE levels were high and 61 (37-84) months for patients whose NSE levels were not high. Although the median OS were longer in NSE not high group compared wit high group, this difference didn't reach statistically significance. (p=0.06) (Fig. 1).

The median OS were 64 (3-124) months for patients whose 5-HIAA levels were high and 47 (41-52) months for patients whose 5-HIAA levels were not high. There were no statistically significant difference (p=0.63) (Fig. 1).

The median OS were 61 (16-105) months for patients who

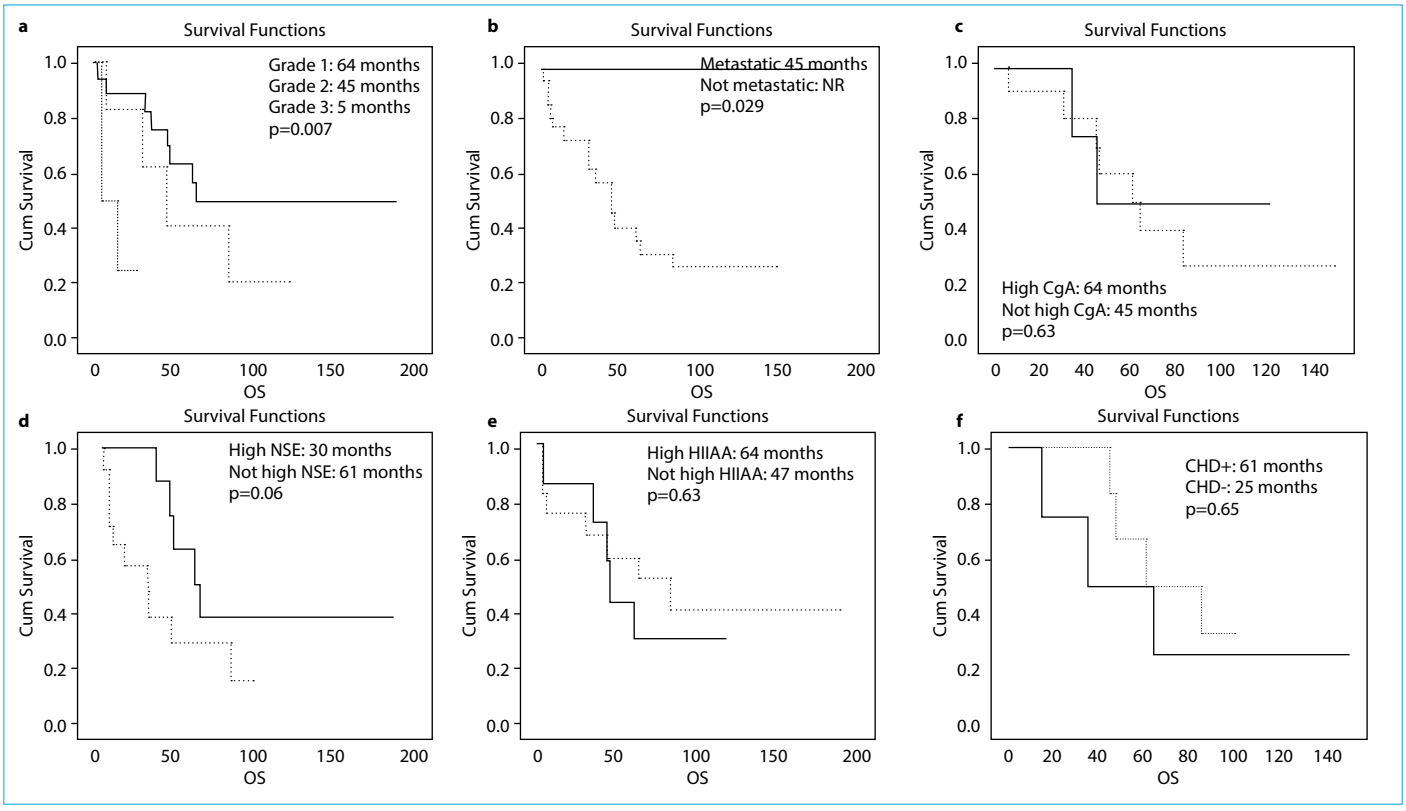

Figure 1. Overall survival according to grade, metastasis status, NSE, CgA, Carcinoid heart disease. **(a)** OS according to grade. **(b)** OS according to metastasis status. **(c)** OS according to CgA level. **(d)** OS according to NSE. **(e)** OS according to HIAA. **(f)** OS according to Carcinoid heart disease (CHD).

had carcinoid heart disease and 24.5 (0-83.02) months for patients who had no carcinoid heart disease. There were no statistically significant difference (p=0.52) (Fig. 1).

Discussion

It is thought that presentation with carcinoid syndrome was a negative prognostic factor in neuroendocrine tumors.[9] In this study we demonstrated that general characteristics of carcinoid syndrome patients and the factors that affect overall survival in these patients.

In our study carcinoid syndrome frequency were 6.4% of all neuroendocrine tumor patients in our hospital. Halperin et al.[5] reported 19% incidence of carcinoid syndrome and in a review it varied 3% to 21%.[3] Carcinoid syndrome diagnosis is difficult because of it's subjective nature and lack of accurate biochemical marker. For these reasons carcinoid syndrome prevalence differs in literature. Carcinoid syndrome prevalance is less common than the past. Because early diagnose of neuroendocrine tumors are more common due to advances in imaging and endoscopic technics. In our study the most common symptom was flushing in 20 (69%) patients followed diarrhea (52%) and abdominal pain (48%). In a report flushing were 91.4% and diarrhea were 61.2%.[1]

Small bowel and pancreas were the most common primary sites with 28%. Similarly to our study the most common primary site in carcinoid syndrome were small bowel with 32% in a report[5] and 40.3% in another one.[1] Small bowel is an expected most common site for carcinoid syndrome because it derives from midgut. It is known that midgut neuroendocrine tumors were secreting serotonin more than foregut or hindgut tumors.[10]

Although carcinoid syndrome was seen mostly in metastatic carcinoids it could be seen in non metastatic disease. Ovarian and bronchial carcinoids could cause carcinoid syndrome without liver metastasis but carcinoid syndrome of gastrointestinal neuroendocrine tumors without liver metastasis were unexpected event.[11] Seventy nine of the patients in our study were initially metastatic but 29% of them were nonmetastatic. Ten percentage of metastatic group didn't have liver metastasis. One possible reason for this is the unappreciated occult liver metastasis. Other possible reason could be that serotonin secreted from tumors enters into circulation via lymph nodes and last possible reason were that liver doesn't inhibite serotonin.[12] But these hypothesis were not proven. Previously the frequency of carcinoid syndrome with no metastatic disease were reported with incidence of 11.9

and 37.2%.[5,1] There were a significant overall survival difference between metastatic and nonmetastatic disease in our study. There were no event seen in nonmetastatic patients. Although we have found that the metastas status was an independent prognostic factor on overall survival in univariate analyses this didn't revealed in multivariate analyses.

The proportion of grade 1 tumors in carcinoid syndrome were 62%, of grade 2 were 21% and of grade 3 were 17% in our study. Similarly our study, in a study they reported that carcinoid syndrome presented with more likely grade 1 followed grade 2 and 3.[5]

In our study the median overall survival was 61 months in all grades. Overall survival were differed significantly according to grade. And we found high tumor grade and ki67 levels were associated with poor prognosis in univariate analyses. Halperin et al.[5] demonstrated that carcinoid syndrome were associated with poor overall survival. Similarly our study they found 60 months overall survival for all grades. In this study they found low grade and metastatic stage were significantly associated with carcinoid syndrome presantation.

The median age was 52 years old in our study and we have found the age was only one independent prognostic factor in multivariate analyses for overall survival. In a report the median age of study population was 62 and they found similar to our study that the age was poor prognostic factor in neuroendocrin tumor patients.[13]

Some biomarkers such as CgA, NSE, 5HIAA may be used for diagnosis and follow up in neuroendocrin tumors. Impact of these markers' high levels on carcinoid syndrome patients' prognosis are not well known. We saved available biomarker levels and we compared the patients whose biomarker levels were high with not high according to overall survival. The median overall survival in patients with high CgA group were longer than not high group. But this was not statistically significant. Reversly in a study they found high CgA levels were shorter overall survival than others.[14] In this study they compared CgA levels in neuroendocrine carcinomas that unknown carcinoid syndrome and they included patients diagnosed gastroenteropancreatic neuroendocrine tumor. We included all grades and all primary sites in our study. This was the another difference from this study. In a report they demonstrated that in well differantiated neuroendocrine tumors CgA levels are predictive for shorter overall survival.[15] In another study they showed CgA accuracy were 76% for well differentiated NETs and 50% for poorly differentiated NEC.[16] In our study 17 percentage of patients were grade 3 and this could be reason for low accuracy of CgA.

We demonstrated that NSE and 5-HIAA are not prognostic markers for carcinoid syndrome.

NSE is a low sensitive marker for neuroendocrine tumor except for small cell cancer.[17] Previously similar to our study they reported that NSE, CgA, 5HIAA are not associated with survival.[18] In our study the patients that had high levels of 5HIAA didn't have significantly different OS compared with not high group. In a study they reported that the patients had high 5HIAA levels were associated with shorter overall survival compared with patients who had not high levels in neuroendocrin tumor.[13] In a study NSE determined a predictor marker of more aggresive disease.[19] In our study the patients have high levels of NSE were poor overall survival but this was not statistically significant. If the amount of our study population were not small, the difference could be significant.

In our study 24% of the patients had cardiac involvement. In previous studies frequency of carcinoid heart disease were reported varied from 1.4 to 60%.[1,20,21] Although carcinoid heart disease is an important cause of morbidite and mortality, in our study carcinoid heart disease were not associated with poor overall survival.

Our study had some limitations. Firstly it was a retrospective study. Carcinoid syndrome diagnoses were made by clinical symptoms. Clinical symptoms could be subjective. We include biomarkers if they were available. Information of some biomarker levels were lack. Some patients didn't have echocardiogram so we couldn't determine status of cardiac involvement of all patients. Our study population were small.

In conclusion carcinoid syndrome is a rare clinical syndrome. Age, grade, ki67 score is an important prognostic factor. Age is an independent prognostic factor that affecting survival in carcinoid syndrome patients.

Disclosures

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 29.01.2020, number: 2020/73).

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Conflict of Interest: The authors declare that there is no conflict of interest.

Authorship Contributions: Concept – E.D., M.I., F.B.; Design – E.D., H.D., G.C.S.; Supervision – H.D., U.A.; Materials – E.D., F.O., S.G., A.Y., E.S.; Data collection and/or processing – E.D., H.D., M.I., M.O., F.B.; Analysis and/or interpretation – E.D., H.D., M.I., E.S., Ş.G., F.O., A.Y., M.O., U.A., G.C.S., F.B.; Literature search – E.D., H.D., M.O., U.A., F.B.; Writing – E.D., H.D., M.I., M.O., F.B.; Critical review – E.D., H.D., M.I., E.S., Ş.G., F.O., A.Y., M.O., U.A., G.C.S., F.B.

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