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Treatment, prognostic markers, and survival in thymic neuroendocrine tumors

A single center experience of 41 patients

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Abstract

Neuroendocrine tumors of the thymus (NETTs) are rare but aggressive, and lead to poor overall survival. This retrospective study was designed to analyze factors that correlate with the prognosis of patients with NETTs.

From 1999 to 2015, 41 ongoing patients with NETTs were enrolled in this study. The clinical data and outcome were compiled. Overall survival (OS) rate was analyzed using the Kaplan–Meier method in univariate analysis and the Cox-model was used in multivariate analysis.

Of the 41 NETTs patients analyzed (31 male and 10 female), 12 were typical carcinoma, 14 were atypical carcinoma, 14 were small-cell carcinoma and, 1 was large-cell carcinoma. The median follow-up time was 29 months (range, 9.0–69.0). In total, 25 patients died of cancer-related disease by the last follow-up. The 3- and 5-year survival rates for all patients were 42.7% and 23.4%, respectively. Among the prognostic factors analyzed by multivariate analysis, low tumor grade, complete resection, and a negative chromogranin A (CgA) expression were positively correlated with survival.

The surgical treatment of NETTs, CgA negative, and low grade of NETTs were associated with a statistically significant better prognosis. However, large, multicenter studies are required to fully validate these prognostic factors.

Abbreviations: CgA = chromogranin A, CK = creatine kinase, CT = computed tomography, H&E = hematoxylin and eosin, NETTs = neuroendocrine tumors of the thymus, SAS = Statistical Analysis System, SEER = Surveillance, Epidemiology and End Results, WHO = World Health Organization.

Keywords: chromogranin A, neuroendocrine tumor, prognosis, thymus, treatment

1. Introduction

Neuroendocrine tumors of the thymus (NETTs) are rare malignancies, accounting for approximately 2% to 5% of thymic carcinomas.[1,2] Several hundred cases have been reported since the first identification in 1972.[3] NETTs occur more often in men, and peak in incidence at age 60.[2,4] Unlike most thymic tumors, NETTs exhibit more locally advanced characteristics and have a higher rate of metastasis than thymic carcinomas.[5,6] Patients typically present with a mass in the mediastinum and symptoms including cough, dyspnea, chest pain to superior vena cava syndrome.[7] Up to 25% of patients present with multiple endocrine neoplasia type I symptoms.[2,8]

The Masaoka-Koga stage classification system is commonly used for NETTs staging.[9] According to the 2015 World Health Organization (WHO) criteria, the descriptive term "grade" is used instead of the differentiation. NETTs are categorized as low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or high-grade (large-cell neuroendocrine carcinoma, small-cell carcinoma) tumors.[10] To date, no study has used the new criteria to determine the clinical outcomes of patients who underwent multimodality therapy.

The NETTs are aggressive tumors with poor overall survival and most of the previously published studies are retrospective studies with small sample sizes.[2,3,7] In this retrospective study, we evaluate the factors that affect the prognosis of patients with NETTs.

2. Materials and methods

This retrospective analysis was approved by the Institutional Review Board of the Chinese People's Liberation Army General Hospital. All involved data were from the hospital medical database and used exclusively for academic research. The data involving human participants were analyzed anonymously.

2.1. Patient selection and exclusion

Patients were eligible for this study if they were pathologically confirmed as having a thymic neuroendocrine tumor. Patients with a history of other known tumors were excluded.

2.2. Histologic definition for neuroendocrine tumor of thymic

We retrospectively reviewed all the hematoxylin and eosin (H&E)-stained slides. According to the 4th WHO criteria of

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NETTs, typical and atypical carcinoids are defined as low-grade and intermediate-grade neuroendocrine carcinomas, which show a relative low mitotic rate and less, or no, areas of necrosis. Large-cell carcinomas and small-cell carcinomas are classified as high-grade neuroendocrine carcinoma, which show a higher mitotic rate and extensive areas of necrosis.

The Masaoka-Koga stage and tumor diameter were recorded along with other variables. The demographic data were extracted from the medical records from the Chinese People's Liberation Army General Hospital. For patients that underwent surgery, the maximum diameter of the tumor was measured in the tumor itself. For patients that did not undergo surgery, the maximum diameter of the tumor was measured on the chest computed tomography (CT) images; the family cancer history was defined as first-degree relatives of people with tumor history. We also used the Masaoka staging system, WHO staging system, and other variables that potentially influenced survival, such as immunohistochemical results and neuroendocrine markers.

2.3. Statistical analysis

Continuous variables were presented as mean and range. Follow-up status was obtained from institutional records. Duration of survival was calculated from the date of diagnosis to the date of death or the last follow-up. The patients still alive till the last follow-up or lost follow-up was considered as the censored data. Statistical analysis of survival was performed using the Kaplan–-Meier and univariable log rank tests. The multivariate analysis by using Cox-model to determine the prognostic factors. All data analyses are performed by Statistical Analysis System (SAS) version 9.4 (SAS Institute, Inc., Cary, NC). A *P*-value less than .05 was considered statistically significant.

Table 1

Demographic character of patients.

	Number of patients*
Gender	
Male/female	31 (75.6%)/10 (24.4%)
Age, y	
Mean ± SD, range	50.8 ± 10.4 (33–79)
Symptom	
Yes/no	28 (68.3%)/13 (31.7%)
Smoking status	
Never	27 (65.9%)
Former	11 (26.8%)
Current/ever	3 (7.3%)
Family cancer history	
Yes/no	8 (19.5%)/33 (80.5%)
Treatment	
Surgery	8 (19.5%)
Surgery + adjuvant treatment	13 (31.7%)
Chemotherapy	7 (17.1%)
Chemoradiotherapy	13 (31.7%)
Surgery approach	
No surgery	20 (48.8%)
Incomplete/complete resection	5 (12.2%)/16 (39.0%)
Overall survival, mo	
Mean (median, range)	31.4 (26, 9.0–69.0)
Live status	
Dead	25 (61.0%)
Alive with cancer/without cancer	8 (19.5%)/8 (19.5%)

Former smoker = quit smoking more 6 months at the lung cancer diagnosis date.
SD = standard deviation.
* Unless otherwise indicated, data are the number of patients and data in parentheses are percentages.

3. Results

3.1. Patient characteristics

We identified 41 continuous patients who met the eligibility criteria for this study from June 1999 to October 2015. A list of patient characteristics is reported in Table 1. Of the 41 patients, 31 (75.6%) were men and the mean age was 50.8 ± 10.4 years (range, 33–79 years). The pathologic confirmation of 19 patients (46.3%) was obtained by percutaneous fine needle aspiration and the remaining 22 patients (53.7%) were diagnosed by surgical resection.

3.2. Tumor characteristics

Among all the tumors, 12 (29.3%) were typical carcinoma, 14 (34.1%) were atypical carcinoma, 14 (34.1%) were small cell, and 1 (2.4%) was large cell. Patients were staged and classified according to the 4th WHO tumor staging system and Masaoka-Koga staging system. The tumor markers include Ki67 (%), chromogranin A (CgA), creatine kinase (CK), and synaptophysin. The clinical characteristics of the tumors are shown in Table 2.

3.3. Follow-up, survival, and prognostic factors

The median follow-up time was 29 months (range, 9.0–69.0). At the last follow-up, 25 patients (61.0%) died because of cancer-related disease, 8 patients (19.5%) were still alive but with cancer, and 8 patients (19.5%) were alive and free of cancer. The mean length of survival for all patients was 31.9 months, and the 3- and 5-year survival was 42.7% and 23.4%, respectively. Among all factors evaluated, the tumor grade, family history, treatment method, surgery method, and CgA status showed significant correlation with survival in univariate analysis. The following factors did not show a significant correlation with survival: gender, WHO stage, Masaoka-Koga stage, smoking status, Ki67 (%), CK, synaptophysin, or blood carbohydrate antigen.

Complete tumor resection, low-grade tumor status, and negative CgA were identified as significant correlative factors to increase survival by multivariate Cox-model analysis (Table 3). The survival curves of complete resection, tumor grade and CgA are shown in Figs. 1 to 3, respectively.

4. Discussion

NETT is a rare tumor, with approximately 500 cases reported worldwide in recent decades,[7,11,12] the majority of which are case reports[13,14] and small group analyses.[15,16] In the Surveillance, Epidemiology and End Results (SEER) registry analysis, the incidence of NETTs was approximately 0.18 per 1 million each year from 2000 to 2006. The reported incidence rate had risen compared with the period from 1979 to 1999;[2,15] however, this is may be because of improved diagnostic techniques.

Among the retrospective studies, the 2 largest studies included 205 and 254 patients each.[11,12] The 5-year survival rate varied among studies from approximately 20% to 68%. Possible

Table 2

Demographic characters of all tumors.

	Number of patients*
Cell type	
Small cell	14 (34.1%)
Large cell	1 (2.44%)
Atypical carcinoma	14 (34.1%)
Typical carcinoma	12 (29.3%)
Tumor grade	
Low-grade	12 (29.3%)
Intermediate-grade	14 (34.1%)
High-grade	15 (36.6%)
Tumor size, cm	
Mean ± SD, range	7.6 ± 3.3 (2–15)
WHO stage	
I/II/III/IV	6 (14.6%)/6 (14.6%)/7 (17.1%)/22 (53.7%)
Masaoka-Koga stage	
I/II/III/IV	10 (24.4%)/8 (17.1%)/4 (9.8%)/19 (46.3%)
Ki 67	
Missing	16
<10%/≥10%	9 (36.0%)/16 (64.0%)
Blood cancer antigen	
Missing	11
Positive/negative	16 (53.3%)/14 (46.7%)
Chromogranin A	
Missing	11
Positive/negative	9 (30.0%)/21 (70.0%)
Creatine kinase	
Missing	10
Positive/negative	25 (80.6%)/6 (19.4%)
Neuron-specific enolase	
Missing	27
Positive/negative	6 (42.9%)/8 (57.1%)
Synaptophysin	
Missing	4
Positive/negative	31 (83.8%)/6 (16.2%)
Thyroid transcription factor-1	
Missing	20
Positive/negative	8 (38.1%)/13 (61.9%)

SD = standard deviation.

* Unless otherwise indicated, data are the number of patients and data in parentheses are percentages.

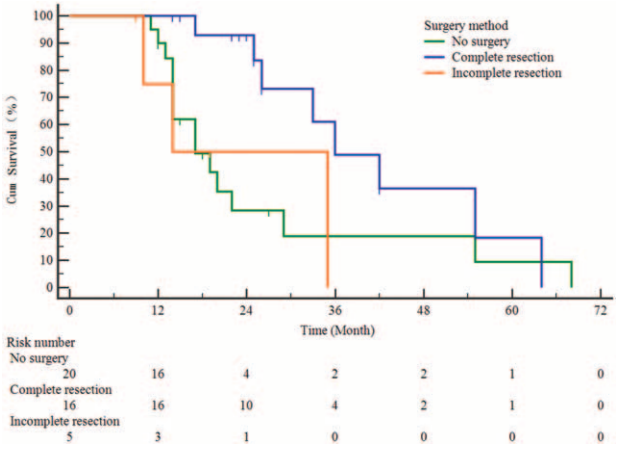

Figure 1. Kaplan–Meier estimate of overall survival in patients with different surgery approach (blue, complete resection, n = 16; orange, incomplete resection, n = 5; green: no surgery, n = 20, *P* = .006).

reasons for the varied outcome may be a difference in the percentage of thymus small-cell cancer cases, different treatment methods and different inclusion criteria for each study. In the present study, the 5-year survival rate was 23.4%. This was lower than the rate in other studies because of the large percentage of patients having thymic small-cell cancer and the number of patients who did not undergo surgery.

The prognostic factors reported in the previous study included the completeness of resection, tumor size, Ki67 expression, tumor differentiation, and Masaoka-Koga staging.[11,12,17] However, many factors can be debated. The WHO reclassified NETTs in 2015 and abandoned classification by differentiation.[10] The new system reclassifies the atypical and typical carcinoid as low-grade and medium-grade NETTs, respectively, while the large-cell and small-cell NETTs are now defined as high-grade NETTs. In the present study, we use the new classification system for NETTs. To our knowledge, this is the first study to use the new classification to evaluate predictors of prognosis.

In this study, poor prognostic factors include a high grade of NETTs, incomplete resection, and CgA positive status. We also

Table 3

Variables affecting survival in patients with neuroendocrine tumors of thymus.

		Univariate analysis		Multivariate analysis	
Variable	**5-y survival % (95% CI)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Tumor grade			.02		.02
Low-grade	35.6% (0.0%, 74.6%)	Reference		Reference	
Intermediate-grade	22.5% (0.0%, 49.9%)	1.84 (0.59, 5.74)		2.58 (0.57, 11.67)	
High-grade	6.7% (0.0%, 19.3%)	3.95 (1.40, 11.16)		5.49 (1.40, 21.58)	
Family cancer history			.01		.27
Yes	23.6% (6.4%, 40.9%)	3.68 (1.27, 10.62)		2.19 (0.57, 8.34)	
No	0.0% (0.0%, 0.0%)	Reference		Reference	
Surgery method			.006		.04
No surgery	9.0% (0.0%, 24.5%)	3.67 (1.39, 9.69)		4.65 (1.17, 18.46)	
Complete resection	43.1% (12.3%, 73.8%)	Reference		Reference	
Incomplete resection	0.0% (0.0%, 0.0%)	5.86 (1.58, 21.77)		5.38 (0.92, 31.53)	
Chromogranin A			.03		.04
Negative	16.9% (0.0%, 36.8%)	Reference		Reference	
Positive	0.0% (0.0%, 0.0%)	2.95 (1.05, 8.30)		2.39 (0.68, 8.45)	

CI = confidence interval, HR = hazard ratio.

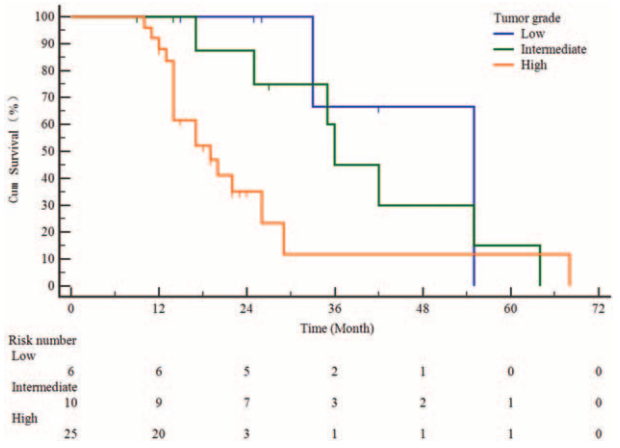

Figure 2. Kaplan–Meier estimate of overall survival in patients with different tumor grade (blue, low grade, n=12; green, intermediate-grade, n=14; orange: high grade, n=15, *P*=.02).

perform the multivariate analyses, since it was more rigorous than univariate analysis, which valid the tumor grade, surgery method, and CgA as the prognostic factors. The positive family cancer history was no longer a prognostic factor in the multivariate analyses. The CgA functions in the storage of peptide hormones and catecholamines in neuroendocrine cells.[18] CgA levels are also positively correlated with tumor size and extension in midgut carcinoid tumors.[19,20] In addition, it is also an independent predictor of poor prognosis and decreased survival in gastroenteropancreatic neuroendocrine tumors.[21,22] This is the first report of CgA as a poor predictive factor for NETT. However, given that CgA was not tested in 11 cases (26.8%), a potential selection bias exists in the study.

The maximum tumor diameter is also regarded as an independent prognostic factor in many studies.[7,11,12,15,17] However, in our study, the tumor diameter was not correlated with survival. This difference may be explained by selection bias. Most patients were undergoing surgery resection in previous studies, and the tumor diameter was measured in the actual tumor samples. In our study, 20 out of 41 patients (48.78%) did not undergo surgery, so the maximum tumor diameter was measured from chest CT images, which may not represent an accurate tumor diameter. In addition, most surgery cases were at a relatively early stage of disease, while the most unresectable cases were at a later stage. It is possible that tumor size may play a more important role in early-stage than in late-stage tumors.

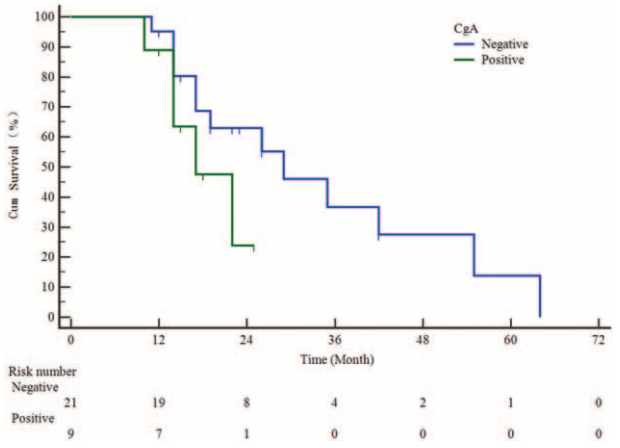

Figure 3. Kaplan–Meier estimate of overall survival in patients with different CgA status (blue, CgA positive, n=9; green, CgA negative, n=21, *P*=.03).

As previously reported, we identified that the prognosis for completely resected patients was better than the prognosis for other patients.[7,11,12] Compete resection often involves resection of the tumor along with removal of the pericardium, pleura, or great vessels. A large resection increases surgical risk. However, it may be beneficial, since a radical surgical excision offers the best chance of prolonged survival and is the only known curative therapy. Resection is recommended for NETTs in most previous studies and in the present study.

Previous studies analyzing the effectiveness of chemotherapy and radiotherapy have shown mixed results.[11,12,16,23] In this study, we did not identify chemotherapy or radiotherapy as positive prognostic factors. However, this may because of the limited number of cases and the retrospective design of this study. Expression of Ki67, which was recognized as a marker of progression in neuroendocrine tumors, was reported to correlate with the prognosis in prior studies.[15,24] A higher expression level of Ki67 correlated with a worse prognosis for the patients with a 10% threshold reported for a poor prognosis. In our study, Ki67 expression failed to correlate with the prognosis. This may be because of the potential bias of our study, in which Ki67 expression level was only available in 25 out of 41 patients (60.98%). Our study also highlights the poor predictive character of the Masaoka-Koga staging system, which was opposed of some previous studies.[11,15]

In addition to the retrospective design, other limitations of this study include the data coming from a single institution and the small sample size. However, we believe the results are valid for the small patient population used in this study.

In conclusion, the surgical treatment of NETTs, even requires extended resection to achieve a radical resection makes positive effective to prolong the survival. Expression of CgA and high grade of NETTs were associated with a statistically significantly poorer prognosis in NETTs. However, large multicenter studies are required to fully validate the prognostic factors and to revise the NETTs staging system.

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