Primary neuroendocrine tumors of the thymus: Clinical review of 22 cases

ZHENGBO SONG¹ ² and YIPING ZHANG¹ ²

¹Department of Chemotherapy, Zhejiang Cancer Hospital;
²Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology, Hangzhou, Zhejiang 310022, P.R. China

Received December 20, 2013; Accepted July 18, 2014
DOI: 10.3892/ol.2014.2490

Abstract. Primary neuroendocrine tumors of the thymus are rare mediastinum tumors, which present a distinct type of tumor, which exhibit morphological and biological neuroendocrine features including the production of numerous biogenic amines. The aim of the present study was to evaluate factors influencing long-term survival in patients with primary neuroendocrine tumors of the thymus. A total of 22 patients exhibiting primary thymic neuroendocrine tumors, who were treated at the Zhejiang Cancer Hospital (Hangzhou, China), between 1995 and 2012 were reviewed. Survival curves were plotted using the Kaplan-Meier method and the Cox proportional hazards model was used for multivariate analysis. The overall five-year survival rate was 45.5% and the median survival time was 59 months in all of the patients. Histological grade (P<0.001), Masaoka-Koga stage (P=0.003) and surgical resection status (P=0.004) were identified to be associated with patient survival time. Furthermore, multivariate analysis identified that the histological grade was an independent prognostic factor, which was applicable to all patients (P=0.009). Therefore, the histological grade and Masaoka-Koga stage, as well as surgical resection status present three prognostic factors in patients exhibiting primary thymic neuroendocrine tumors.

Introduction

Neuroendocrine tumors of the thymus are rare, with an annual incidence of 0.01/100,000 in the USA (1). The histogenesis of neuroendocrine tumors varies and the tumor may arise from ectopic tissues in the mediastinum or present within the thymus (2). Thus, the histopathological classification, prognosis and treatment of primary neuroendocrine carcinomas of the thymus remain controversial.

According to the World Health Organization (WHO) (2), neuroendocrine tumors are included in the thymic carcinoma group and classified as two histopathological types; well-differentiated neuroendocrine carcinomas (typical and atypical carcinoid) and poorly differentiated neuroendocrine carcinomas (small cell carcinoma and large cell neuroendocrine carcinoma). The well-differentiated neuroendocrine carcinomas show a low grade of biological aggressiveness, while poorly differentiated neuroendocrine carcinomas are considered to be high-grade neuroendocrine tumors. As there have only been a small number of patients with neuroendocrine tumors of the thymus reported in the literature (3-7), a consensus has not been reached concerning the prognostic factors of primary neuroendocrine tumors of the thymus.

The aim of the present study was to evaluate the factors influencing long-term survival in 22 patients with primary neuroendocrine tumors of the thymus and to explore the role of various prognostic factors.

Patients and methods

Patient eligibility. The records of 22 patients exhibiting primary neuroendocrine tumors of the thymus, who were treated at the Zhejiang Cancer Hospital (Hangzhou, China), between 1995 and 2012, were reviewed. The 22 patients included 14 males and eight females, with a median age of 49.5 years. The histological type was determined according to the 2004 WHO classification (2) and the staging was performed for all patients according to the Masaoka-Koga system (8). Recurrence or metastases were identified using chest computed tomography (CT), as well as ultrasound and/or CT of the abdomen. The study was approved by the ethics committee of Zhejiang Cancer Hospital (Hangzhou, China).

Patient treatment. A total of ten patients underwent surgical resection following first diagnosis. A total of 9 patients received chemotherapy, 8 patients received radiation therapy, 3 patients received chemotherapy and radiotherapy and two patients received no further treatment. The detailed treatment of the 22 patients is shown in Table I.

Follow-up. Patients were followed up every three to six months for the first five years, and once per year thereafter. Each patient's medical history, details of physical examinations and thoracic
Table I. Characteristics of 22 patients.

| Case | Gender/age, years | Histology | Masaoka-Koga stage | Surgery | Treatment | At diagnosis | During disease | OS, months |
|------|------------------|-----------|--------------------|---------|-----------|--------------|---------------|------------|
| 1    | M/70             | AC        | I                  | Yes     | No        | No           | No            | 154+      |
| 2    | M/50             | SCC       | IV                 | No      | Chemo     | Supraclavicular LN | Lung | 11.2      |
| 3    | F/39             | LCNEC     | III                | Yes     | Radiotherapy | No           | Lung, bone   | 17.6      |
| 4    | M/50             | AC        | IV                 | No      | Chemo     | No           | Bone          | 27.5      |
| 5    | F/49             | TC        | II                 | Yes     | Radiotherapy | No           | No            | 126+      |
| 6    | F/40             | AC        | II                 | Yes     | Radiotherapy | No           | No            | 141+      |
| 7    | M/38             | AC        | II                 | Yes     | Radiotherapy + Chemo | No           | No            | 75+       |
| 8    | F/51             | AC        | II                 | Yes     | Radiotherapy + Chemo | No           | No            | 61+       |
| 9    | F/52             | AC        | II                 | Yes     | Radiotherapy | No           | No            | 53+       |
| 10   | M/29             | AC        | II                 | Yes     | Radiotherapy | No           | No            | 28+       |
| 11   | M/29             | AC        | I                  | Yes     | No        | No           | No            | 39+       |
| 12   | M/51             | SCC       | III                | No      | Radiotherapy + Chemo | No           | Liver, lung   | 27        |
| 13   | M/24             | TC        | II                 | Yes     | Radiotherapy | No           | Liver, bone   | 59        |
| 14   | M/57             | AC        | III                | No      | Radiotherapy | No           | No            | 67+       |
| 15   | M/61             | LCNEC     | IV                 | No      | Chemo     | Lung         | Bone          | 11+       |
| 16   | F/48             | SCC       | IV                 | No      | Chemo     | Supraclavicular LN | Lung | 11        |
| 17   | F/43             | LCNEC     | III                | No      | Radiotherapy | No           | Bone, lung    | 32        |
| 18   | M/59             | SCC       | IV                 | No      | Chemo     | Liver        | Supraclavicular LN | 6        |
| 19   | M/55             | LCNEC     | IV                 | No      | Chemo     | Lung         | Bone          | 11        |
| 20   | M/55             | SCC       | IV                 | No      | Chemo     | Bone         | Lung          | 15        |
| 21   | M/49             | AC        | IV                 | No      | Chemo     | Lung         | Liver         | 38        |
| 22   | F/47             | TC        | IV                 | No      | Chemo     | Lung         | LN            | 115+      |

M, male; F, female; AC, atypical carcinoid; LCNEC, large cell neuroendocrine carcinoma; SCC, small cell carcinoma; TC, typical carcinoid; Chemo, chemotherapy; LN, lymph node; OS, overall survival.
CT scans were recorded. The last follow-up was on Jan 30, 2013, with a median follow-up period for all patients of 109 months (range, 15-185 months).

**Statistical analysis.** Survival curves were calculated (using the Kaplan-Meier method) commencing from the date of the confirmed pathology to the date of mortality or the last follow-up. The log-rank test was used to compare overall survival (OS) time between different factors, including gender, age, tumor stage and surgery status. Multivariate analysis was performed using the Cox proportional hazards model and statistical analysis was performed using the SPSS version 15 software (SPSS, Inc., Chicago, IL, USA). Confidence intervals were calculated at the 95% level and P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Clinical characteristics.** The clinical characteristics of the 22 patients are listed in Table I. The 22 patients enrolled in the present study included 14 males and eight females, with a median age of 49.5 years. In total, 10 of the 22 individuals underwent surgery. The pathological stage was I and II in nine patients, and III and IV in 13 patients. According to the WHO criteria (2), based on the histopathological differentiation, all 22 cases were divided into two types; well-differentiated (n=13) and poorly differentiated (n=9) neuroendocrine carcinomas.

**Survival analyses.** Table II shows the results of the univariate analyses of the clinicopathological factors evaluated in the present study. At present, a total of 11 patients have survived, however, 11 patients succumbed to the disease prior to the final follow up date. The median survival time for all patients was 59 months, and the five-year OS rate was 45.5%, with ten patients surviving longer than five years. Patients with
Primary neuroendocrine tumors of the thymus are rare, with ~400 cases reported in the literature to date; the majority of which are case reports (3-7, 9-11). The median age at diagnosis has been relatively young in the majority of studies, ranging between 40 and 60 years. A male predominance has also been observed in the literature, which is consistent with the findings of the current report.

In a series of 15 patients reported by Fukai et al (5), the five-year survival rate was 33%, and of the 14 cases reported by de Montpreville et al (3) the five-year survival rate was 31%. The overall five-year survival rate in the present study was 45.5% (Table II), which is consistent with that reported in earlier studies (3,5). However, the median OS was shorter than that of previous reports (1,12,13), which may be due to more than half of the patients reported in the present study not undergoing surgery.

As the diagnosis of primary neuroendocrine tumors of the thymus is rare, only a small number of retrospective studies are available. Therefore, a standard therapeutic strategy has not yet been defined. Surgery remains the standard method for the treatment of thymic tumors compared with non-surgical options according to the Surveillance, Epidemiology, and End Results database analysis (1). In the present study, the results are considered to be meaningful.

In conclusion, thymic neuroendocrine tumors are associated with a poor prognosis. However, further study is required to fully validate the prognostic factors and determine a standard treatment for thymic neuroendocrine tumors.

References

1. Gaur P, Leary C and Yao JC: Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg 251: 1117-1121, 2010.
2. Travis WD, Brambilla E, Müller-Hermelink HK, et al (eds): WHO Classification of Tumours. Pathology & Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press, Lyon, pp145-147, 2004.
3. de Montpreville VT, Macchiarini P and Dulmet E: Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of fourteen cases. J Thorac Cardiovasc Surg 111: 208-211, 1999.
4. Cardillo G, Treggiari S, Paul MA, et al: Primary neuroendocrine tumours of the thymus: a clinicopathologic and prognostic study in 19 patients. Eur J Cardiothorac Surg 37: 814-818, 2010.
5. Fukai I, Masaoka A, Fujii Y, et al: Thymic neuroendocrine tumor (thymic carcinoid): a clinicopathologic study in 15 patients. Ann Thorac Surg 67: 208-211, 1999.
6. Moran CA and Suster S: Thymic neuroendocrine carcinomas with combined features ranging from well-differentiated (carcinoid) to small cell carcinoma. A clinicopathologic and immunohistochemical study of 11 cases. Am J Clin Pathol 113: 345-350, 2000.
7. Moran CA and Suster S: Neuroendocrine carcinomas (carcinoid tumor) of the thymus: a clinicopathologic analysis of 80 cases. Am J Clin Pathol 114: 100-110, 2000.
8. Koga K, Matsumo Y, Noguchi M, et al: A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 44: 359-367, 1994.
9. Wang DY, Chang DB, Kuo SH, et al: Carcinoid tumours of the thymus. Thorax 49: 357-360, 1994.
10. Brambilla E and Lantuejoul S: Thoracic neuroendocrine tumors. Ann Pathol 25: 529-544, 2005 (In French).
11. Gal AA, Kornstein MJ, Cohen C, et al: Neuroendocrine tumors of the thymus: a clinicopathological and prognostic study. Ann Thorac Surg 72: 1179-1182, 2001.
12. Moran CA: Primary neuroendocrine carcinomas of the mediastinum: review of current criteria for histopathologic diagnosis and classification. Semin Diagn Pathol 22: 223-229, 2005.
13. Cardillo G, Rea F, Lucchi M, et al: Primary neuroendocrine tumors of the thymus: a multicenter experience of 35 patients. Ann Thorac Surg 94: 241-246, 2012.