Differences in clinical features and outcomes between patients with thymoma and those with thymic carcinoma

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ABSTRACT

Background: Thymic epithelial tumors (TETs), which consist of thymoma and thymic carcinoma, are a rare cancer demonstrating specific morphological and clinical features. The clinical characteristics and outcomes of TETs have been gradually revealed with large-scale, retrospective data obtained with international cooperation.

Methods: The study was a retrospective review of 187 Japanese patients with TETs from 1976 to 2012 at our institution. The clinical features of TETs, including demographics, histology, staging, treatment interventions, and overall survival (OS), were investigated. Differences in survival were assessed using Kaplan-Meier method and uni- and multivariate Cox proportional hazards regression analyses.

Results: The 187 patients included 52 patients with stage I, 37 with stage II, 22 with stage III, and 76 with stage IVa/IVb tumors according to the Masaoka-Koga Staging System. On histology, 5 patients had type A, 33 had type AB, 19 had type B1, 39 had type B2, and 15 had type B3, while 68 patients had thymic carcinoma, including 12 with neuroendocrine carcinomas according to the 2004 WHO classification. Immunological complication was seen in 26 patients, only in the thymoma group (23.4%). Most of the symptomatic patients at presentation were
those who had myasthenia gravis or extension with thymic carcinoma. Secondary cancers were seen in 25 patients (13.3%). The overall 5- and 10-year survival rates were 85.4% and 33.8%, respectively, for thymoma and 71.5% and 2.3%, respectively, for thymic carcinoma. OS was significantly different between thymoma and thymic carcinoma in stage IVa. The stage and whether the tumor was thymoma or thymic carcinoma were significant determinants of survival on multivariate analysis.

**Conclusions:** The roles of treatment interventions for thymoma and thymic carcinoma should be investigated separately because of the differences in their clinical features and prognosis.


**1. Background**

Thymic epithelial tumors (TETs), comprising thymoma and thymic carcinoma, are rare cancers defined by the European Union, their annual incidence is approximately 0.15 cases in the United States[1] and 3.2 cases in Netherland[2] per 100,000 person-years. TETs are extremely heterogeneous, with an exceedingly broad spectrum of morphological appearances with immunological complications. Thymomas show bioactivity with organotypic features that lead to autoimmune manifestations, whereas thymic carcinomas do not show immunological activities; thus, patients with thymic carcinoma usually have symptoms associated with tumor extension or metastasis because of loss of organotypia or higher atypia.

The clinical characteristics and prognostic factors of patients with TETs remain poorly known because of their rarity[3]. Therefore, the International Thymic Malignancy Interest Group (ITMIG) has been organized, and consensus agreements are now available despite the low level of evidence in support of treatment modalities, with some single-arm phase II studies or a few retrospective studies based on small groups of treated patients with diverse backgrounds[4]; thus, the optimal therapeutic strategy remains controversial. In previous studies, treatments for thymoma and thymic carcinoma have been basically the same, but
recently it has been suggested that the two types of tumors should be considered separately[5]. In addition, ITMIG has proposed the use of the Masaoka-Koga staging system[6] and the 2004 World Health Organization (WHO) histological classification, and these have been accepted[7]. Thus, it is necessary to review and clarify these clinical entities based on the proposed criteria. Furthermore, the National Comprehensive Cancer Network has updated its guideline for the clinical management and treatment of TETs, despite its rarity[8].

The objective of the present study was to retrospectively clarify the clinical characteristics, prognosis, and prognostic factors of patients with thymoma and thymic carcinoma according to the 2004 World Health Organization (WHO) classification[7] in our institution over a 30-year period.

2. Methods

2.1. Database

This retrospective study was a review of patients diagnosed with TETs identified from the databases at Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (Tokyo, Japan) between January 1976 and December 2012. Codes were used from the International Classification of Diseases (9th edition).
This retrospective study was approved by the institutional ethics board.

2.2. Patients and histological evaluation

A retrospective review was performed to collect the demographic and treatment data of 187 consecutive Japanese patients diagnosed with TETs. The pathological review was performed by a thoracic pathologist (TH) according to the 2004 WHO classification and the Masaoka-Koga staging system[6]. The diagnosis of thymic carcinoma was referred by hematoxylin-eosin staining and immunohistochemistry using CD5 and/or CD117 (c-KIT) and/or p63 to exclude other malignant thoracic tumors, as well as supplemental testing for terminal deoxynucleotidyl transferase (TdT) to distinguish carcinomas from thymomas. Clinical factors were also examined. Data were collected in accordance with the International Thymic Malignancy Interest Group (ITMIG) Standard Definitions and Policies[4].

All patients were treated with surgery, radiotherapy, chemotherapy, and/or best supportive care. Staging using the Masaoka-Koga staging system was determined by computed tomography, magnetic resonance imaging, positron emission tomography, or bone scanning. Histology was also classified according to the 2004 WHO classification. Clinical factors including age, sex, histological subtypes, staging,
immunological complications, secondary malignancies, first-line treatment modality, and survival were also examined. The medical records and laboratory data for each patient were retrieved for analysis and assessment of treatments for TETs. Patients were treated with curative-intent or palliative-intent surgery, radiotherapy, chemotherapy, or a combination of these modalities.

2.3 Statistical analysis

Descriptive statistics were used to summarize the patients’ baseline characteristics. Survival time was defined as the period from the date of initiation of first-line treatment (surgery, radiotherapy, chemotherapy, or best supportive care) to the date of death from any cause or last follow-up using the Kaplan-Meier method. Patients lost to follow-up were censored at the time of the last contact. These endpoints reflected clinical practice due to the retrospective nature of the data. The Kaplan-Meier method was used to estimate overall survival and 5-year and 10-year survival rates to examine the prognoses of thymoma and thymic carcinoma patients. Since the ITMIG Standard Definitions and Policies recommended that the 5-year survival rate in thymic carcinomas and the 10-year survival rate in thymomas be examined, this was done. The correlation between the 2004 WHO
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classification and Masaoka-Koga Stage was evaluated using a nonparametric measure of statistical dependence between the two variables.

The log-rank test was used to identify prognostic factors for survival on the uni- and multivariate analyses. Candidate variables analyzed included age (<70 vs. ≥70 years), gender (male vs. female), staging, immunological complications, secondary malignancies, histological subtypes according to WHO classification 2004. Significance on univariate analysis and multivariate Cox proportional hazard model were defined as \( p < 0.05 \). All statistical analyses were performed using JMP9 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics of thymoma and thymic carcinoma

Of the 187 patients, 119 patients (67 males, 52 females) had thymomas, and 68 patients (38 males, 30 females) had thymic carcinomas. Their median age was 58 years with thymoma and 63 years with thymic carcinoma. On histology, 5 patients had type A, 19 had type B1, 39 had type B2, 15 had type B3, and 33 had type AB, while the 68 patients with thymic carcinoma included 12 with neuroendocrine carcinomas according to the 2004 WHO classification. Histologic examination
revealed 8 subtypes of thymic carcinoma and 3 uncommon subtypes: 42 patients had squamous cell carcinoma (63.6%), 10 patients (13.4%) had neuroendocrine carcinoma (3 patients had small cell carcinoma, 2 patients had large cell neuroendocrine carcinoma, and 5 patients had carcinoid), 4 patients had mucoepidermoid carcinoma (6.1%), and 1 patient had lymphepithelioma-like carcinoma. Eight patients had either other histological types or were missing data. Paraneoplastic syndrome was seen in 26 patients, only in the thymoma group (23.4%). No patients in the thymic carcinoma group had autoimmune-related manifestations. Most of the symptomatic patients at presentation were those who had myasthenia gravis or thymic carcinoma. Secondary malignancies were seen in 25 patients (13.3%). At diagnosis, 52 thymoma patients (43.7%) had stage I, 31 (26.1%) had stage II, 12 (10.1%) had stage III, and 24 (20.1%) had stage IVa/IVb according to the Masaoka-Koga Staging System, whereas 6 thymic carcinoma patients (8.8%) had stage II disease, 10 (14.7%) had stage III disease, 16 (23.5%) had stage IVa disease, and 36 had stage IVb disease (52.2%). A variety of immunological paraneoplastic complications were observed in 13 thymoma cases (10.9%).

The patients’ characteristics are summarized in Table 1. The median follow-up at
the time of analysis for all 187 patients was 43.9 months (range: 0.3-404.8 months).

3.2. Treatment modalities and strategies for thymoma and thymic carcinoma

First-line treatment of thymoma was 93.7% for curative-intent (91.6% of patients with thymoma was surgery, 5.9% of them was radiotherapy) whereas that of thymic carcinoma was 62.7% (44.8% of patients with thymic carcinoma was surgery, 19.1% of them was radiotherapy).

The types of treatment modalities are also summarized in Table 1.

3.3. Clinical outcomes of thymoma and thymic carcinoma by stage and histological classification.

3.3.1 Stage

The median OS for thymoma was 235.2 months (95% CI, 137.3-not reached), whereas that of thymic carcinoma was 32.4 months (95% CI, 23.7-52.2) (p < 0.0001) in all stages of Masaoka-Koga Stage. Survival of thymoma for Stages I, II, III, IVa, and IVb was not reached, not reached, 171.83, 110.09, and 83.81 months, respectively. The 5-year and 10-year survival rates were 85.4% and 71.5%, respectively.
Differences in thymoma and thymic carcinoma respectively. On the other hand, survival of thymic carcinoma for Stages II, III, IVa, and IVb was 78.9, 56.4, 27.3, and 21.7 months, respectively. The 5-year and 10-year survival rates were 33.8% and 2.3%, respectively. (Figure 1)

3.3.2 Histological classification

The 5-year and 10-year survival rates were 100% and censored in type A, 96.3% and 73.8% in type AB, 90.9% and 68.2 in type B1, 79.8% and 67.3% in type B2, and 61.6% and 61.5% in type B3, respectively. On the other hand, the median OS for thymic carcinoma was 36.4 months (95% CI, 23.7-52.2) in all stages. The 5-year and 10-year survival rates were 36.3% and 6.2%, respectively. The median OS for high-grade histology was 24.7 months, while that for low-grade histology was 36.8 months. In neuroendocrine carcinoma, the median survival was 43.9 months. The median survival of the 6 well-differentiated neuroendocrine carcinoma patients was 36.4 months [95%CI 7.5-92.0], with a 5-year survival rate of 20.0%, and that of the 5 poorly-differentiated neuroendocrine carcinoma patients was 43.9 months [95% CI 5.6-127.4], with a 5-year survival rate of 20.0%.

3.3.3 Correlation between the 2004 WHO classification and Masaoka-Koga


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**Stage**

The distribution of the WHO classification and Masaoka-Koga stage of these 187 patients is shown in Table 2. The proportions of advanced stages (Masaoka-Koga stages III, IVa, and IVb) increased gradually from Type A thymoma to thymic carcinoma. There was a significant correlation between the WHO classification and Masaoka-Koga stage (Spearman's rank correlation coefficient=0.69, \( p < 0.0001 \)).

**3.4. Prognostic factors affecting survival by uni- and multivariate analysis**

In univariate analysis, age and entire of Masaoka-Koga stages were significantly different in survival in thymoma. However, no difference was seen in thymic carcinoma. Early stages (I and II in Masaoka-Koga stage) and advanced stages (IVa and IVb) of both thymoma and thymic carcinoma were significantly difference in survival in multivariate analysis (Table 3).

**4. Discussion**

The present retrospective analysis examined the clinical outcomes of 187 patients with TETs. This study of an unselected population resulted in similar clinical characteristics and outcomes to those of previously reported, large,
Based on the Müller-Hermelink classification[9], the World Health Organization (WHO) classification for thymomas was firstly proposed in 1999[10]. In the 2004 WHO classification, thymic carcinoma was classified separately from thymoma, and thymic neuroendocrine carcinoma was also moved to this category[7]. The histologic grades of the WHO classification are associated with oncological characteristics and prognosis. Types A and AB have a better prognosis, while the higher histological subtypes from types B1, B2, and B3 to carcinoma have a worse prognosis in retrospective studies[11-13]. In contrary, other studies were not correlated between survival and WHO classification. These limitation were regarded as reproducibility of diagnosis of TETs[14-16]. Additionally, it seems us to be associated with immunological complication and secondary malignancies although our study was not associated with prognosis. Types A and AB thymoma have a low association with myasthenia gravis, whereas type B1 and type B2 are more likely to be associated with myasthenia gravis. Up to 45%, the patients with thymoma demonstrate myasthenia gravis[17, 18]. In thymic carcinoma, 13 subtypes are classified in WHO classification. 60%-70% of all thymic carcinoma are subtypes of squamous cell carcinoma and lymphoepithelioma-like carcinoma.
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Recent biomarker investigations explored c-KIT is a characteristic of thymic carcinoma[19]. Clinically, thymomas and thymic carcinomas present different recurrent sites, as thymomas mainly involve pleural dissemination opposed to distant metastasis in thymic carcinoma[20]. As for the WHO classification, there are still some limitation, in that distinguishing even thymoma and thymic carcinoma subtypes remains difficult. Concerning Staging systems, Masaoka-Koga staging systems are widely accepted in both thymoma and thymic carcinoma. It means, the analysis of prognostic factor in thymoma and thymic carcinoma has too much problems with mismatch diagnosis, confounding of clinical entities, or intermingled management.

The present results also indicated a variety of clinical behaviors in thymoma and thymic carcinoma. The reason for no correlation of survival with WHO classification among thymomas may be affected with the small number of patients, immunological complication, or not enough events due to the long survival. In the thymoma group, the prognosis was mostly the same as previously reported, whereas in thymic carcinoma, even thymic squamous cell carcinoma, both indolent and aggressive clinical behaviors were found. In the thymic neuroendocrine tumors (or carcinoma) (TNETs), the present small cohort of
well-differentiated and poorly differentiated TNETs showed a similar clinical behavior[21]. In the present study, no patients of TNETS had the multiple endocrine neoplastic syndrome. The prognosis was poor as in the previously reported cases of TNETs[22]. The clinical entities of TNETs are being gradually made known. The European Society of Medical Oncology has already published a guideline for TNETs[23].

The key limitation of the present study was the small numbers of patients in each stage of thymoma or thymic carcinoma, resulting in absence of data compared to randomized trials. However, this is a common limitation in such studies of small numbers of patients with rare cancers. Second, this study was unable to follow up the patients, especially completely resected young patients having early stages or thymoma without immunological complications. Thus, there were more censored patients in the thymoma cohort.

Large-scale databases are being established in Japan, the United States, and Europe as the first step to conquering TETs. This approach for this rare cancer appears to be a role model for rare diseases. These database are based on the surgical cases, thus, it will not implicate the clinical entities of TETs. Therefore, the single institutional databases, as this, seemed to be still meaningful because of the
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consistency of treatment and pathological evaluation, which leads to a higher reliability for diagnosis of TETs. Nevertheless unified, multi-institutional, databases centered on the ITMIG are needed. Studies utilizing such databases will clarify the clinical entities and evolve treatment strategies, even though TETs are rare. However, these databases also cannot help escape from biased and limited data, concerning the reliability of diagnosis or treatment, due to the rarity.

Now, it is expected that prospective clinical trials will be increasing further, but there are still problems in that the fundamental diagnosis of TETs, especially thymic carcinomas, is difficult, as Wekslers has already pointed out[24]. In fact, in the WJTOG 4207L trial[25], 25% of patients diagnosed as thymic carcinoma in the local hospitals found to be improperly diagnosed when centrally reviewed. Thus, the results of such studies must be interpreted with care. Some cases of contamination with small sample size phase II studies will result in lack of power to find statistical hypothesis. Therefore, this will hope to note the guidelines not to be affected on the mismatch results. Investigators who plan clinical trials of thymic epithelial malignancies should incorporate central review by reliable pathologists who have experience with thymic epithelial malignancies. The importance of central review in the clinical trial for rare cancer was demonstrated in the multi-institutional
clinical trial of imatinib for c-Kit or platelet-derived growth factor receptor (PDGFR) positive sarcoma. In this trial, the concordance rate between the trial sites and central review with immunohistochemostrical staining was 63.3%[26]. Also, the guideline for gastrointestinal stromal tumor (GIST) recommends the prudent diagnosis in c-Kit negative GIST, which requires consulting a specialist of GIST, who has experience in additional antibody staining or c-Kit or PDGFR gene analysis[27, 28].

In summary, a detailed population-based series that highlighted the many challenges clinicians face when treating thymic malignancies, where evidence-based therapy information is limited, was presented. Also, the advantages of a single-institutional database, especially rare cancers, such as this study were pointed out, as well as the disadvantages. Although advances in surgical techniques, radiation planning, systemic therapy, and supportive care have been used in the care of patients with thymic malignancies, more research and collaborative efforts are needed to produce evidence-based guidelines. International database projects and multidisciplinary meetings supported by the ITMIG will undoubtedly help fulfill this need.
Competing interests

The authors have declared no conflicts of interest.

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References


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Figure 1

Survival Time (months)

Probabilities

thymic carcinoma

thymoma
Figure 2

(a) WHO classification

(b) Thymic epithelial tumors

(c) Thymoma

(d) Thymic carcinoma
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Additional file 1: Tables_ECC2013.docx, 50K
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