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Original Article

Thymic epithelial tumors: a clinicopathologic study of 249 cases from a single institution

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Abstract: The WHO histological classification for thymic epithelial tumors of 2004 edition is widely used, but its prognostic value is still controversial. In the present study we collected 249 Chinese patients with thymic epithelial tumors from West China Hospital of Sichuan University since 1999-2009 to assess the prognosis relating to tumor stages, histological classifications, MG and adjuvant therapy. There were 18 cases of type A (7.2%), 97 of type AB (39.0%), 22 of type B1 (8.8%), 63 of type B2 (25.3%), 16 of type B3 (6.5%) thymomas and 33 of thymic carcinomas (13.3%). According to the Massaoka staging, there were 107 patients in stage I (43%), 73 patients in stage II (29.3%), 50 patients in stage III (20.1%) and 19 in stage IV (7.6%). 101 patients (40.6%) complicated with MG, the incidence of MG was highest in type B3 thymomas, then in B2, none of thymic carcinomas complicated with MG. Cox regression analysis showed the Masaoka stage was the most important prognostic factor. Besides of staging, WHO histological classification was also an independent prognostic factor. The age, gender, MG and adjuvant therapy have no significant influence to the prognosis of the patients.

Keywords: Thymic epithelial tumors, WHO classification, Masaoka stage, MG, prognostic value

Introduction

Thymic epithelial tumors (TETs) include thymomas and thymic carcinomas. TETs are the most frequent tumors of the anterior part of the mediastinum; some of them are associated with autoimmune diseases. The most important morphologic feature of TETs is epithelial tumor cells always mix with lymphocytes. The histologic classification of TETs is difficult and highly controversial due to the heterogeneity of neoplastic epithelial cells. In 2004, the world health organization (WHO) classification of thymic tumors divided TETs into six types: A, AB, B1, B2, B3 and thymic carcinoma [1]. Masaoka staging system was used for thymic tumors since 1981 [2]. It is widely accepted that stage is the most important prognostic factor in TETs, but the role of histologic classification as an independent prognostic factor has been controversial. In this current retrospective study, we collected and analyzed 249 cases of TETs from the West China Hospital of Sichuan University, during 1999 and 2009. It is one of the most extensive series of thymic epithelial tumors treated in a single institution. Our purpose is to discuss the morphologic features and clinicopathologic correlations of them and assess the prognostic significance of WHO classification.

Materials and methods

Subjects

Two hundred and forty-nine surgically treated cases of thymic epithelial tumors were collected from the Department of Pathology, West China Hospital of Sichuan University between 1999 and 2009. The specimens were fixed with 10% formalin and embedded in paraffin, serial 4-6 μm sections were prepared, and then stained using hematoxylin and eosin (H&E). All of them were reviewed by two pathologists and reclassified according to the 2004 WHO classification system; some difficult cases were viewed with the famous German thymus pathologist Dr. Müller-Hermlink using a multiheaded microscope. The discrepancies were resolved by joint discussion. The clinical data including age, sex, symptoms, locations of the tumors and the follow up data of some patients was obtained. The stages were determined accord-

Table 1. Frequency of MG associated with the histological classification of TETs

WHO type	MG+ (%)	MG-	Total
A	8 (44.4)	10	18
AB	25 (25.8)	72	97
B1	10 (45.5)	12	22
B2	45 (71.4)	18	63
B3	13 (81.3)	3	16
Thymic ca	0 (0)	33	33
Total	101	148	249

WHO, world health organization; MG, myasthenia gravis; Thymic ca, Thymic carcinoma.

ing to the Masaoka system. The morphologic features, the relationship between histologic classification and tumor stage were analyzed, the prognosis relating to tumor stage, histological classification, myasthenia gravis (MG) and adjuvant therapy were evaluated.

Statistical analysis

SPSS 17.0 software was applied for statistical analysis. The χ^2 test and Fisher exact test were used for enumeration data. Prognostic factors were analyzed by using the Kaplan-Meier method and log rank test were used for comparisons between curves. Cox regression analysis was used to investigate the effect of multiple predictors (age, sex, location, stage, histology, presence of MG, adjuvant therapy) on survival.

Results

Histologic classification

In 249 thymic epithelial tumors there were 18 cases of type A (7.2%), 97 of type AB (39.0%), 22 of type B1 (8.8%), 63 of type B2 (25.3%), 16 of type B3 (6.5%) thymomas and 33 of thymic carcinomas (13.3%). The thymic carcinomas included 21 cases of squamous cell carcinoma, 6 cases of neuroendocrine carcinoma, 4 cases of lymphoepithelioma-like carcinoma, 1 of adenocarcinoma and 1 of sarcoidcarcinoma. The thymomas with mixed histological types were not included in this study.

Clinical data

Totally 134 male and 115 female patients were included, M:F was 1.17:1, ages ranged from 9 to 78 years (median=49). Of these patients, there were 216 cases of thymoma and 33 cases of thymic carcinoma. The ages of thymoma patients ranged from 12-78 years (median= 48.5), M:F was 1.1:1. The ages of thymic carcinoma patients were from 9-70 years (median=7), M:F was 1.75:1. The follow up data were obtained for 126 patients, the time of follow-up was from 1 to 152 months (median=65).

All the tumors were located in mediastinum. There were 235 cases (94.4%) in anterior mediastinum in which 143 cases were in anterosuperior mediastinum. 11 cases were located in medium mediastinum including 2 of type A, 8 of type AB thymoma and 1 of thymic squamous carcinoma. The exact locations in mediastinum of the other 3 cases were unclear.

Most patients were complained of cough, chest pain and dyspnea. 101 (40.6%) patients (8 of type A, 25 of type AB, 10 of type B1, 45 of type B2, 13 of type B3) were complicated with myasthenia gravis. 6 (2.4%) cases (5 of type AB and 1 of type B1) combined with pure red cell aplastic anemia. Each 1 of type A thymoma patient was complicated with hypothyroidism or pemphigus vulgaris respectively. Each 1 of type AB was complicated with nephritic syndrome, atrial fibrillation, stomach carcinoma or breast carcinoma respectively. Some patients were asymptomatic and the thymic tumors were detected by routine physical examination. For most cases, myasthenia gravis subsided or disappeared after surgery, but there were 2 patients turned up to myasthenia crisis when the tumors were removed. For a type B1 and a B3 thymoma patient, myasthenia gravis appeared even after surgery. The incidence of MG was highest in B3, and then was B2 and B1, none of the thymic carcinomas combined with MG (**Table 1**). The incidence rate of MG in thymomas and thymic carcinomas had significant difference ($P < 0.005$), also the incidence of MG in type B3 had significant difference with which of type A, AB and B1 ($P < 0.05$).

Pathological features

Grossly, the tumors were round, oval or irregular shaped. The largest tumor dimension ranged from 1.0 to 20 cm (mean 7.6 cm), the consistence varied from fishlike to firm, and most with moderate consistence. 44 cases (18.9%) had cystic change which dimension ranged from 0.1 cm - 5 cm. The fluid in the cyst was clear, turbid or like bean dregs. The cut surfaces of thymomas were lobulated or tubercular, cystic change presented in 41 cases while the cut surfaces of

Table 2. Histological classification and Masaoka staging of 249 cases of TETs

Histological Classification	Masaoka staging				
	I (%)	II (%)	II (%)	IV (%)	Total
A	14 (77.8)	4 (22.2)	0 (0)	0 (0)	18
AB	71 (73.2)	17 (17.5)	9 (9.3)	0 (0)	97
B1	12 (54.5)	7 (31.8)	3 (13.6)	0 (0)	22
B2	9 (14.3)	37 (58.7)	14 (22.2)	3 (4.8)	63
B3	1 (6.3)	6 (37.5)	6 (37.5)	3 (18.7)	16
Thymic ca	0 (0)	2 (6.1)	18 (54.5)	13 (39.4)	33
Total (%)	107 (43)	73 (29.3)	50 (20.1)	19 (7.6)	249

Thymic ca: Thymic carcinoma.

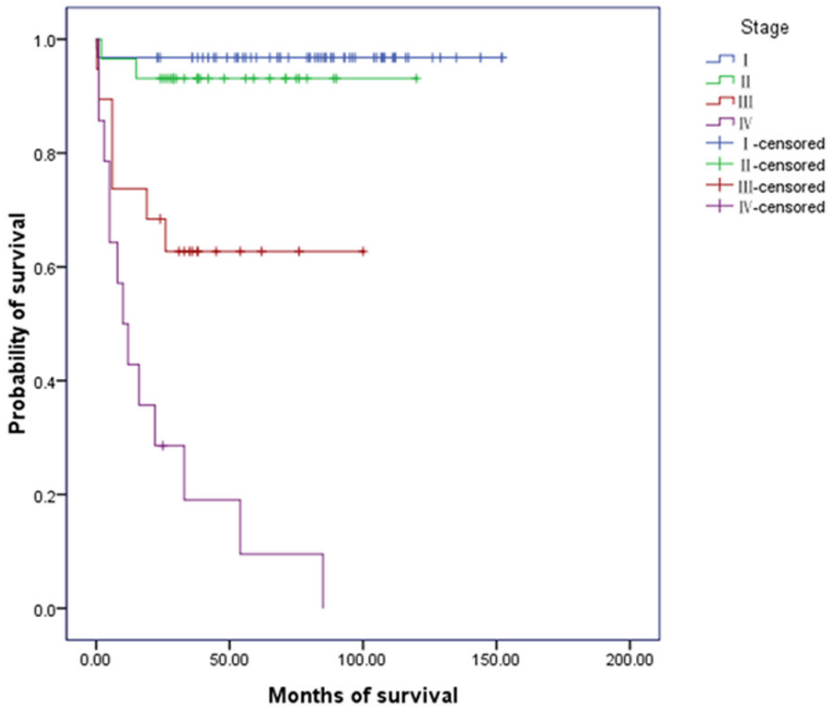

Figure 1. Survival curves of TETs according to the stages.

all the thymic carcinoms were not lobulated, cystic change presented only in 3 cases.

Type A thymomas were composed mainly of spindle or oval epithelial cells, lymphocytes we re scanty. The epithelial cells interweaved; they could be arranged in storiform (2 cases), gland like structures (3 cases) or rosette-like structures (2 cases). The tumor cells lacked of nuclear atypia except one case, in that case, the epithelial cells presented focal obvious nuclear atypia with frequent mitosis. Type AB thymomas exhibited the features of type A thymoma in addition to lymphocyte-rich B areas. The segregation of the two patterns was sharp or indistinguishably admixed. There were 3 cases which had obvious nuclear atypia also presented with tumor giant cells in type A-like area.

The tumor cells in type B1 thymomas were small, oval shaped and scattered with very little atypia. Perivascular spaces were found in 4 cases without palisading of the epithelial neoplastic cells. The tumor cells in type B2 thymomas were larger and much more than those of type B1. These polygonal cells scattered individually or aggregated in small clusters among immature lymphocytes with obvious atypia. Perivascular spaces were found in 38 cases with palisading of the tumor cells. Type B3 thymomas were composed predominantly of epithelial neoplastic cells admixed with a minor component of lymphocytes. The tumor cells were round or polygonal shape with mild to moderate atypia. In 7 cases, the tumors cells were large with prominent nucleoli resembling those of type B2, tumor giant cells were found in 4 of these 7 cases accompanied with active mitosis. Perivascular spaces were found in 12 cases with palisading of the tumor cells. Foci of squamous metaplasia presented in 8 cases.

Thymic carcinomas were similar with the same histological types of extrathymic carcinomas with a small number of mature lymphocytes and plasma cells. They had not organotypical features of thymic differentiation. There were 8 cases of keratinizing squamous carcinomas, 13 cases of nonkeratinizing carcinomas, 6 ca-

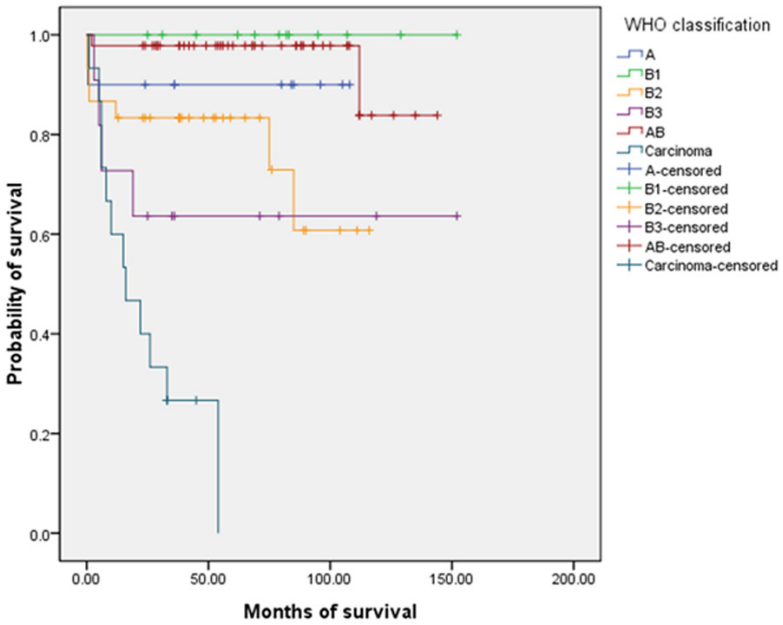

Figure 2. Survival curves of TETs according to the histologic classification.

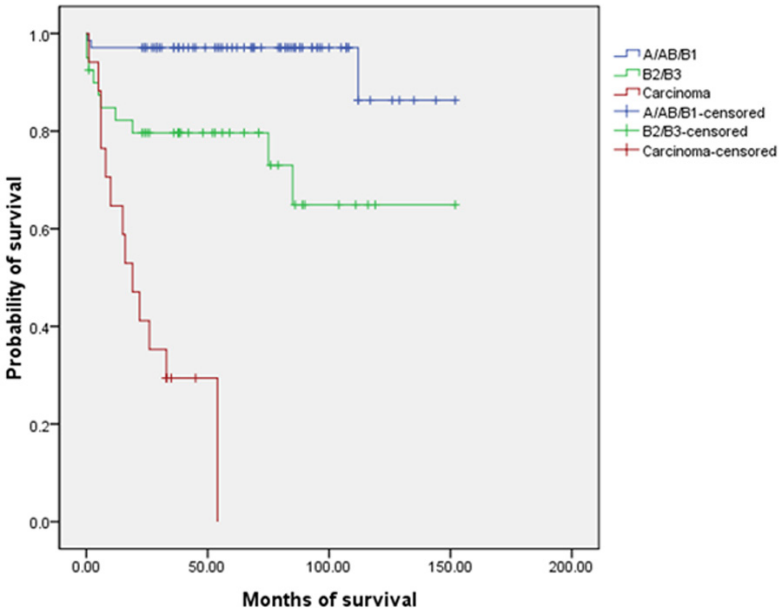

Figure 3. Survival curves of type A/AB/B1, B2/B3 thymomas and thymic carcinomas.

ses of neuroendocrine carcinomas, 4 cases of lymphoepithelioma-like carcinomas, 1 of sarcomatoid carcinoma and 1 of adenocarcinoma.

Association of WHO histological subtypes with stage

The clinical stages were assessed according to Masaoka staging system. There were 107 patients in stage I (43%), 73 patients in stage II (29.3%), 50 patients in stage III (20.1%) and 19 in stage IV (7.6%). Their associations with the histological subtypes were shown in **Table 2**. The majority of type A thymomas (77.8%) were in Stage I, 22.2% were in stage II; none was in stage III and IV. There were 73.2% type AB thymomas in stage I, 17.5% were in stage II, 9.3% in stage III and none was in stage IV. Most type B1 thymomas were in stage I (54.5%) and stage II (31.8%), but some cases were in stageIII (13.6%), and none in stage IV. Type B2 and B3 thymomas were more invasive and more cases were in either stage III or stage IV. Most of thymic carcinomas (93.9%) were in stage III and stage IV, only 2 were in stage II and none was in stage I. The stages of type A/AB/B1 and B2/B3 thymomas ($P < 0.005$), type B2/B3 thymomas and thymic carcinomas ($P < 0.005$) had significant differences.

Associations of clinical stages with survival

Follow-up information was available for 126 cases, the time of follow up was 1-152 months, and the median follow up time was 65 months. There were 24 patients died from thymic epithelial tumors, meanwhile each a patient died due to gastric carcinoma, pneumonia or septic shock. The 5 year and 10 year overall survival rates of patients in stage I, II and III were 97%, 93% and 86%, respectively, whereas the 5 year overall survival rate of patients in stage IV was only 31%. The survival curves according to the clinical stages were shown in **Figure 1**, the survival curves of Masaoka I and III (P=0.000), I and IV (P=0.000), II and III (P=0.003), II and IV (P=0.000), III and IV (P=0.005) had significant differences.

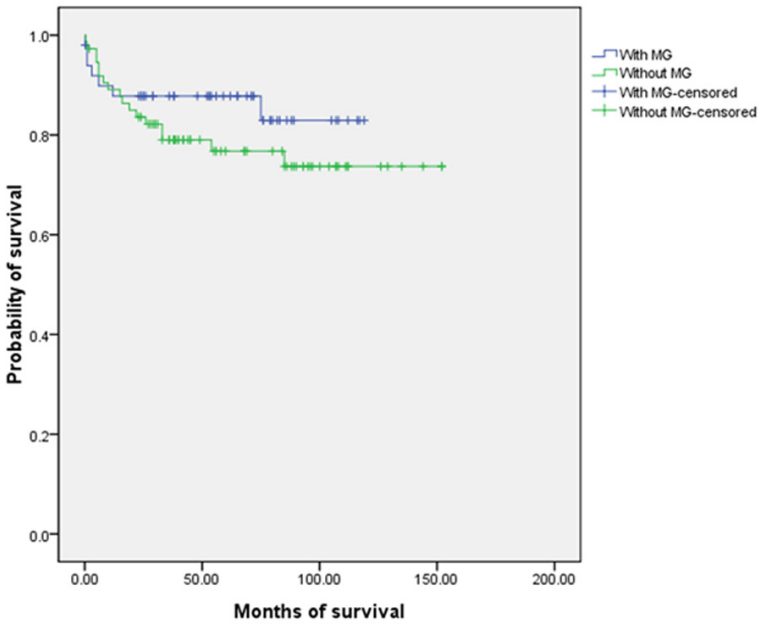

Figure 4. Survival curves of TETs with or without MG.

Associations of histological classification with survival

The 5 year and 10 year overall survival rates of patients with type A thymomas were 94%, only one patient died of infection after surgery; For the patients with type AB thymomas, the 5 year and 10 year overall survival rates were 99% and 93%, respectively, there were two patients died during the follow-up period, one was due to gastric carcinoma, another was pneumonia; For the patients suffered type B1, none of them died at the end of follow up. There were 8 patients with type B2 thymomas died of thymic tumor, the 5 year and 10 year overall survival rates were 92% and 81%, respectively; For the patients suffered type B3 thymomas and thymic carcinomas, The 5 year overall survival rate were 81% and 55%, respectively. The survival curves according to the histological classification were shown in **Figures 2**, **3**. The prognosis of type A, AB and B1 thymomas were much better than that of type B2, B3 thymomas and thymic carcinomas. The survival curves of type A, AB and B1 thymomas had significant difference with that of type B2, B3 thymomas and thymic carcinomas. (log rank test: *P*=0.000).

Associations of MG with survival

There were 50 patients complicated with MG in the 126 cases which had follow up information. Among this group, 7 patients died of thymic tumors. The 5 year overall survival rate were 88%. For the other 76 cases without MG, 19 patients died and 16 were due to thymic tumors. The 5 year overall survival rate were 77%. The survival curves with or without MG were shown in **Figure 4**. There was no difference between thymoma patients with and without MG on survival analysis (log rank test: *P*= 0.298).

Adjuvant therapy and survival

19 patients received radiotherapy after removal of the tumor while 20 patients received chemotherapy after surgery. Only 10 patients had both radiotherapy and chemotherapy. Among these patients, 19 cases had follow up data including 1 case of type AB, 1 of B1, 5 of B2, 3 of B3 thymomas and 9 of thymic carcinomas. Totally 11 patients died of tumor including 2 cases of type B2, 3 of B3 thymomas and 6 of thymic carcinomas. If we compared the overall survival rates of the patients with or without adjuvant therapy, we found the 5 year and 10 year overall survival rates were higher in the group without adjuvant therapy (*P*= 0.002).

Multivariate analysis of survival

The clinical stage and histological classification had significant influence to the survival rate of the patients with thymic epithelial tumors on single factor analysis. Cox regression analysis showed that the Masaoka stage was the most important prognostic factor in the patients with thymic epithelial tumors (*P*=0.000) while the ages, sex, with or without MG had no prognostic value on multivariate analysis of survival. WHO histological classification also had significant influence to the survival rate on Cox regression analysis if the clinical stage were excluded (*P*=0.014).

Discussion

Thymic epithelial tumors are account for 20% of the tumors in mediastinum, they are the most frequent tumors of the anterior mediastinum, especially in the anterosuperior part of

mediastinum, a small number of TETs were found in the neck, lung and pleural [3]. In our study, 235 cases (94.4%) were in the anterior mediastinum which more than 60% were in the anterosuperior part of mediastinum.

The most common type of thymoma in our study was type AB (39%), the next was type B2 (25.3%), B1 (8.8%), A (7.2%) and B3 (6.4%). The distribution of the subtypes was consistent with that reported in the literatures except the relative low proportion of type B3 [4, 5]. There were 7 cases of combined thymoma (B3 combined with B2) which the B3 component were more than 30% were not included in the study. For some view, if the component of B3 in the mixed thymomas exceeded 30%, it should be taken as type B3 thymoma. So the type B3 thymomas would be more than type A and B1 if these 7 cases were included in the study. Usually, the type A thymomas were taken as benign tumor, but the biological behavior of them was questioned recently. In a study of Moran [6], 41 cases of type A thymoma showed different degree of invasive growth pattern, in another report, Pulmonary metastasis was identified from an encapsulated cervical ectopic type A thymoma [7]. In this study, there were 4 cases of type A thymoma in stage II in which one case showed obvious atypia with 1-4 mitosis 10/HPF and focal necrosis. Rosai et al [8] reported 13 cases type A thymoma which had nuclear atypia, active mitosis or focal necrosis, they suggested type A thymoma should be divided into A1, A2, A3 according to the degree of atypia, analogous to the subtypes currently used for type B thymomas.

Among the 101 (40.6%) patients with MG, 2 patients presented MG after total removal of thymomas. It had been reported previously that the onset of MG after total thymectomy happened in 1.5-28% of cases without MG [9-11], the reason was not clear. Some scholars believed that thymomas could produce large numbers of mature T-cells which could be released into the peripheral blood. The T lymphocytes could survive in the periphery blood for many years even after thymectomy and they would stimulate autoantibody production leading to subsequent autoimmune diseases [12, 13]. The incidence of myasthenia gravis in thymoma patients was related to the subtypes. In our study, it was highest in type B3, followed by B2, B1, A and AB. Okumura concluded type A and AB thymomas were less frequently accompanied with MG than type B. Among type B thymomas, they found that type B2 was most frequently associated with MG, followed by type B1 [14]. In Chen's study, type B2 and B3 were shown to be most frequently complicated with MG [4]. Besides myasthenia gravis, there were 6 cases (2.4%, 5 of AB and 1 of B1) complicated with pure red cell aplastic anemia. Rosenow et al [15] thought spindle cell thymomas were more likely to be associated with pure red cell aplastic anemia, however, in another report, none of the thymoma with pure red cell aplastic anemia was spindle cell type [16]. Due to the low incidence, the relationship between pure red cell aplastic anemia and the histological type of thymoma was still unclear.

It is widely accepted that the clinical stage is the most valuable independent prognostic factor for thymoma. In our study, the prognosis of the patients in stage I and II was much better than that of stage III and IV (P=0.000). In the multivariate analyses, the Masaoka stage was also the most important prognostic marker (P=0.000). Other features such as histologic type, age, sex had been evaluated in thymomas to predict clinical outcome. Most pathologists thought type A, AB and B1 were associated with less aggressive clinical behavior than type B2, B3 and thymic carcinomas. But there was still some controversy. Chalabreysse et al thought type A and AB had more potential to invasive than type B [17]. In a study of Rieker et al, the prognosis of the patients suffered type AB and B1 were much better than that of type A and B2 [18]. We found the prognosis of the patients with type A,AB and B1 were much better than that of type B2, B3, and thymic carcinomas, The survival curves of type A, AB and B1 thymomas had significant difference with that of type B2, B3 thymomas and thymic carcinomas, we concluded the WHO histological classification had independent prognostic value.

It was reported that the prognosis of thymoma was related with MG. Wilkins found the patients associated with MG had worse prognosis [19]. However, Park had contrary result; he revealed the patients with MG had better prognosis due to early diagnosis and treatment in time [20]. Chen showed although MG had prognostic significance among patients with type B2 or B3 thymomas on univariate analysis, there was no difference in survival between thymoma patients with and without MG on multivariate

analysis [4]. Our study showed the prognosis had no significant difference between patients with and without MG either on univariate analysis or multivariate analysis.

There were still some controversial about the use of adjuvant therapy. Some doctors thought the patients should receive chemotherapy or radiotherapy, especially those suffered type B2, B3 thymomas or thymic carcinomas due to the high local recurrence rates after totally removal of the tumors [21]. It was reported that local radiotherapy could improve the overall survival rates of the patients with type B2, B3 thymomas or thymic carcinomas, but not type A, B1, or AB [22]. However, some researchers suggested radiotherapy couldn't improve the survival rates of TETs [19, 23]. Chemotherapy was usually recommended not to be used alone. In our study, most of the patients (79%) received adjuvant therapies were belong to Masaoka III or IV, the 5 year and 10 year overall survival rates were higher in the group without adjuvant therapy (P=0.002). There should be some bias to compare the survival rate in different Masaoka stage tumors. In a retrospective study of Wilkins, they found the overall survival rates of the patients in Masaoka II-IV were lower than that of Masaoka I despite the status of adjuvant therapy. Evaluating the effect of adjuvant therapy might be influenced by the histological classification and clinical staging in the retrospective study of TETs.

Multivariate analysis showed Masaoka stage had the most important value to the survival (P=0.000). Considering the histological classification highly related to the clinical stage, the stage was excluded when we analyzed the value of histological classification on multivariate analysis. We concluded WHO histological classification also had significant influence to the survival if the stage was excluded (P=0.014). The result was the same with Okumura [24]. When he performed the multivariate analysis of the survival of thymic epithelial tumors, he also took the correlation between histological classification and clinical stage into consideration, each was subjected to multivariate analysis with age, sex, myasthenia gravis, and so on in one report.

In conclusion, we believed that Masaoka stage was the most important prognostic factor. WHO histologic classification was also an independent prognostic factor which could reflect the oncologic behavior of thymoma. Type B2 and B3 tumors had aggressive behavior compared with type A, AB, and B1 tumors. The WHO histologic classification could help the clinical practice about assessment and treatment of patients with TETs.

Disclosure of conflict of interest

None.

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