Original Article

Clinical Usefulness of the WHO Histological Classification of Thymoma

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Purpose: Rosai et al. published the World Health Organization (WHO) classification of thymic epithelial tumors in 1999, and its clinical usefulness seems to be established. It is our purpose to find the clinically relevant diagnostic points in the WHO Histological Classification of Thymoma.
Methods: Thymomas surgically removed from 100 consecutive patients at Juntendo University Hospital between October 1983 and February 2002 were classified according to the WHO histological classification. We assessed overall survival and recurrence-free rate calculated for each tumor type in the WHO classification compared with those of tumors classified by the Masaoka system.
Results: The thymic epithelial tumors in this series comprised 10 type A, 15 type AB, 18 type B1, 21 type B2, 33 type B3, and 3 type C tumors according to the WHO classification. Based on the Masaoka system, the disease was stage I in 53 patients, stage II in 30, stage III in 15, and stage IV in 2. The 15-year recurrence-free rate was 100% for type A, AB and B1, while the rates for types B2 and B3 were 66.7% and 54.5%, respectively. The 10-year recurrence-free rate was 66.7% for type C. The 15-year recurrence-free rate of the 64 patients with type A, AB, B1, and B2 thymomas was significantly higher from that of the 33 patients with type B3 thymoma (p=0.0026).
Conclusion: When using the WHO classification, it is critical to distinguish type B3 thymoma from other tumor types. (Ann Thorac Cardiovasc Surg 2005; 11: 367–73)

Key words: B3 thymoma, World Health Organization classification, prognosis

Introduction

Thymic epithelial tumors are the most frequent tumors of the anterosuperior mediastinum. Numerous histological classifications of thymic epithelial tumors have been proposed. Rosai et al.[1)] published the World Health Organization (WHO) histological classification of thymic epithelial cell tumors in 1999, and the association of this classification with clinical features seems to be established.[2-5)] A clinical staging system for thymoma was reported by Masaoka et al.[6)] in 1981, and this system has been evaluated in many reports.[7-17)] To find a clinically important point in the WHO classification, we assessed overall survival and recurrence-free rate calculated for each tumor type in the WHO classification compared with those of tumors classified by the Masaoka system.

Methods

This study included 100 consecutive patients who underwent surgical resection of epithelial tumors of the thymus between October 1983 and February 2002 at our department in Juntendo University Hospital. There were 59 men and 41 women who ranged from 19 to 78 years old, with a mean age of 51.1 years. The median follow up was 84.7 months.

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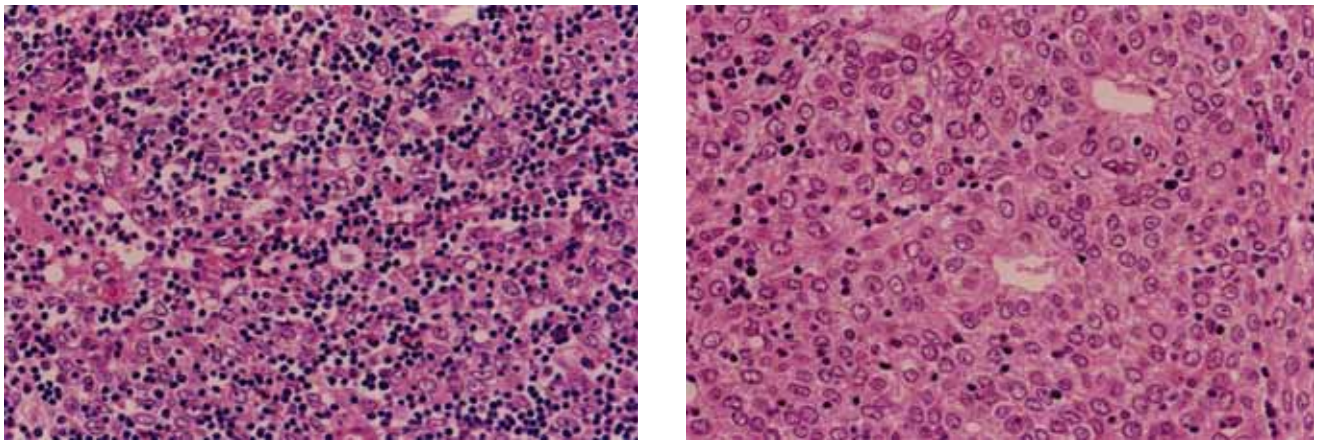


A B

Fig. 1.
A: Type B2 thymoma: tumor cells are smaller than in the type B3 tumor, with more immature lymphocytes. The cells have distinct nucleoli. (Hematoxylin and eosin stain, ×100)
B: Type B3 thymoma: polygonal cells with scanty lymphocytic infiltrates. The borders between the cells are clearly defined with occasional variation of cell size and irregularity of the nuclear margins. (Hematoxylin and eosin stain, ×100)

For pathological examination, sections obtained from the surgical specimens were fixed in formaldehyde, stained with hematoxylin-eosin, and examined by one of the authors (a pathologist: T. U.). The tumors were classified according to the WHO histological classification of thymoma.[1] This classification divides all thymomas into two types depending on whether the tumor cells are spindle/oval-shaped or polygonal (dendritic or plump/epithelioid). Thymomas composed of the former type of cells are designated as type A, whereas tumors composed of the latter type of cells are classified as type B. In addition, tumors composed of both types of cells are designated as type AB. Type B tumors are further divided into the B1, B2 (Fig. 1A), and B3 (Fig. 1B) subtypes depending on the extent of lymphocyte infiltration and the shape of the tumor cells. Carcinoma of the thymus is designated as type C.

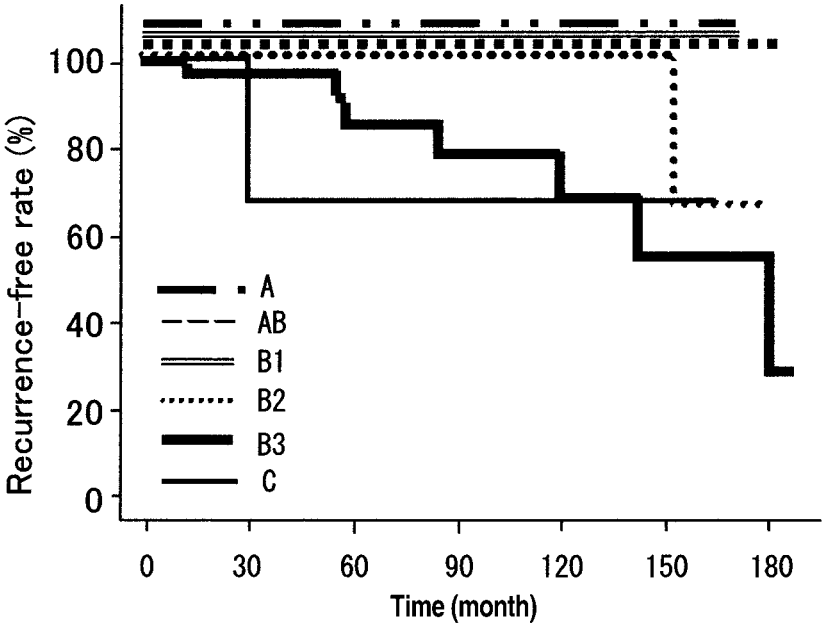
The thymomas were also classified by the Masaoka staging system.[6] Clinical stages were defined: Stage I—macroscopically encapsulated and microscopically no capsular invasion; Stage II—1. macroscopic invasion into surrounding fatty tissue of mediastinal pleura, or 2. microscopic invasion into capsule; Stage III—macroscopic invasion into neighboring organ; Stage IVa—pleural or pericardial dissemination; Stage IVb—lymphogenous or hematogenous metastasis.

To find a clinically important point in the WHO classification, we assessed overall survival and recurrence-free rate calculated for each tumor type in the WHO classification compared with those of tumors classified by the Masaoka system. The overall survival rate and the disease-free rate at the maximum follow up period were calculated by the Kaplan-Meier method. Only death of the tumor was calculated for statistical analysis of the overall survival rate. Statistical analysis was performed by the log-rank test and $p<0.05$ was considered statistically significant. Statview version 5.0 (for PC) was used for all analyses.

Results

The thymic epithelial tumors in this series comprised 10 type A, 15 type AB, 18 type B1, 21 type B2, 33 type B3, and 3 type C tumors according to the WHO classification. Based on the Masaoka system, the disease was stage I in 53 patients, stage II in 30, stage III in 15, and stage IV in 2.

There was postoperative recurrence of thymoma in 9 patients, including one survivor. The mode of recurrence was pleural dissemination in 7 patients, mediastinal lymph node involvement in one, and metastasis to the liver and bone in one. None of the type A, AB, or B1 thymomas showed recurrence. The 15-year recurrence-free rates for type A and B1 thymomas were 100%, whereas the rate decreased to 66.7% and 54.5% for types B2 and B3, respectively (Fig. 2). The recurrence-free rate of the 64 patients with type A, AB, B1, and B2 thymomas was sig-



No. of patients at risk

Type A	10	9	7	5	3	2	0
Type AB	15	13	8	6	5	2	2
Type B1	18	13	9	7	2	2	0
Type B2	21	15	9	7	6	5	1
Type B3	33	25	21	13	11	6	3
Type C	3	3	2	1	1	1	0

Fig. 2. Recurrence-free curves according to the World Health Organization histologic classification system.

nificantly higher from that of the 33 patients with type B3 tumor (p=0.0026) (Fig. 3).

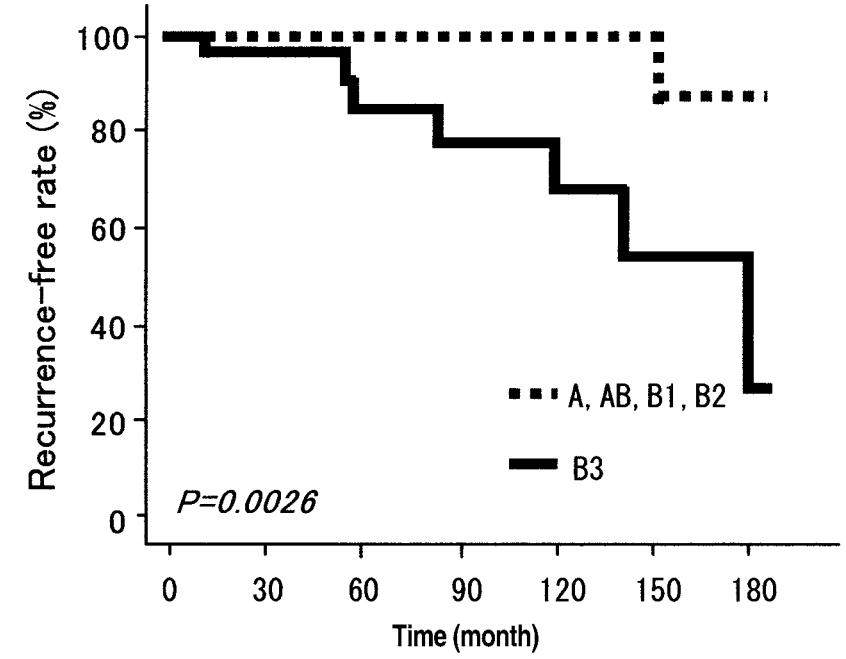
According to the Masaoka staging system, the recurrence-free rate was 100% (53/53) in stage I, 86.7% (26/30) in stage II, 73.3% (11/15) in stage III, and 50.0% (1/2) in stage IV. Thus, the recurrence-free rate showed a decrease as the disease advanced. The 15-year recurrence-free rates for stage I and II disease were 100% and 74.6%, respectively. The 10-year recurrence-free rate for stage II disease tended to be higher than that with stage III (p=0.0510). The 5-year recurrence-free rate for stage II disease was higher than that with stage IV disease (p=0.0138) (Fig. 4).

Only death due to the tumor was calculated for statistical analysis of the overall survival rate. Among the 100 patients, there were 19 deaths. To investigate pure association between the thymic tumor and prognosis, 14 patients were excluded for statistical analysis of the overall survival rate: 5 died of myasthenia gravis, 1 died of pure red cell aplasia, 3 died of other cancers, 1 died of cerebral infarction, and 4 died of unknown causes. Five patients died of recurrent thymoma: 4 (12.1%) of 33 patients with B3 thymoma and 1 (33.3%) of 3 patients with C thymoma (Fig. 5).

When classified according to the Masaoka system, death occurred in 0 (0%) of the 46 stage I patients, 2 (8.0%) of the 25 stage II patients, 2 (15.4%) of the 15 stage III patients, and 1 (50.0%) of the two stage IV patients. The death rate increased as the stage advanced. There were significant differences in the 5-year survival rate between stages III and IV and between stages II and IV (p=0.0108 and p=0.0016, respectively) (Fig. 6).

Discussion

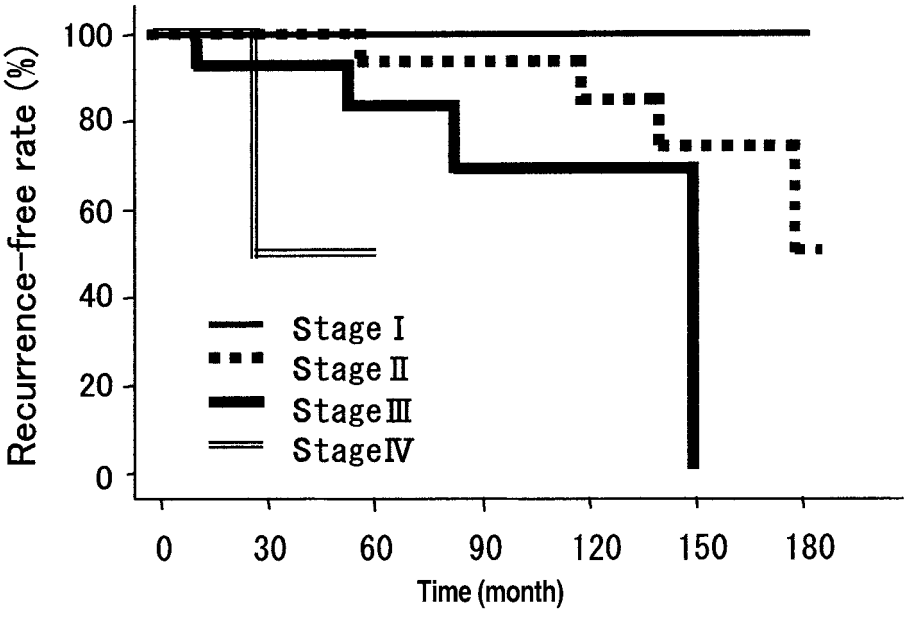
The prognosis of thymic epithelial cell tumors has varied widely in the reports published to date. The stage according to the Masaoka system is generally regarded as one of the most important prognostic factors. This system is a clinical staging method for thymoma and its value has been established by a number of studies.[7-17] Okumura et al.[12] reported that the 20-year survival rates of patients



No. of patients at risk

Type A,AB,B1,B2	64	50	33	25	16	11	3
Type B3	33	25	21	13	11	6	3

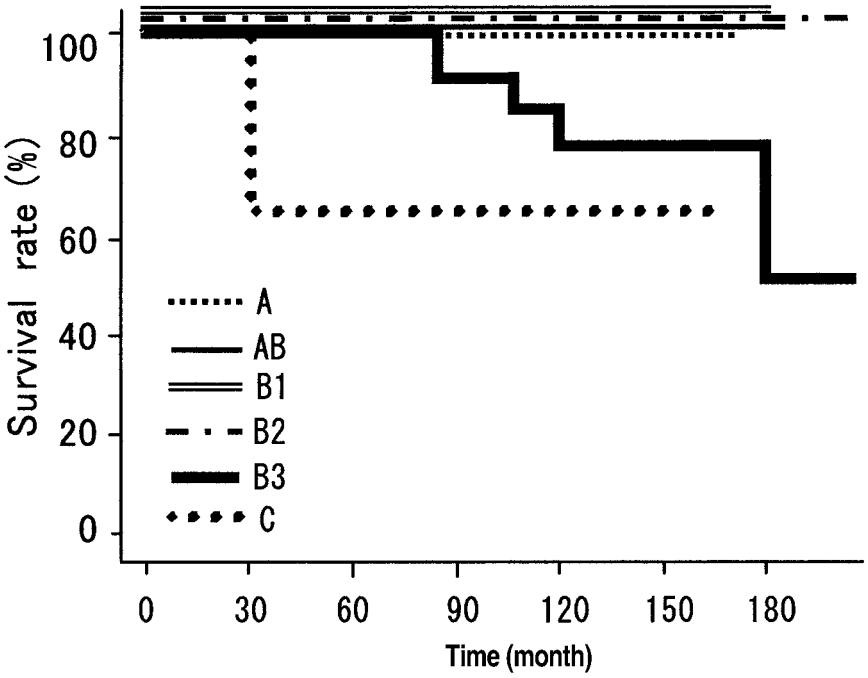
Fig. 3. Recurrence-free rates for a combination of type A, AB, B1, and B2 versus type B3.



No. of patients at risk

Stage I	53	37	25	19	12	8	2
Stage II	30	25	19	11	10	6	3
Stage III	15	13	11	6	3	1	0
Stage IV	2	2	2	0	0	0	0

Fig. 4. Recurrence-free curves according to the Masaoka staging system.



No. of patients at risk

Type A	10	9	7	5	3	2	0
Type AB	15	13	8	6	5	2	2
Type B1	18	13	9	7	2	2	0
Type B2	21	15	9	6	6	5	2
Type B3	33	26	23	14	11	6	3
Type C	3	3	2	1	1	1	0

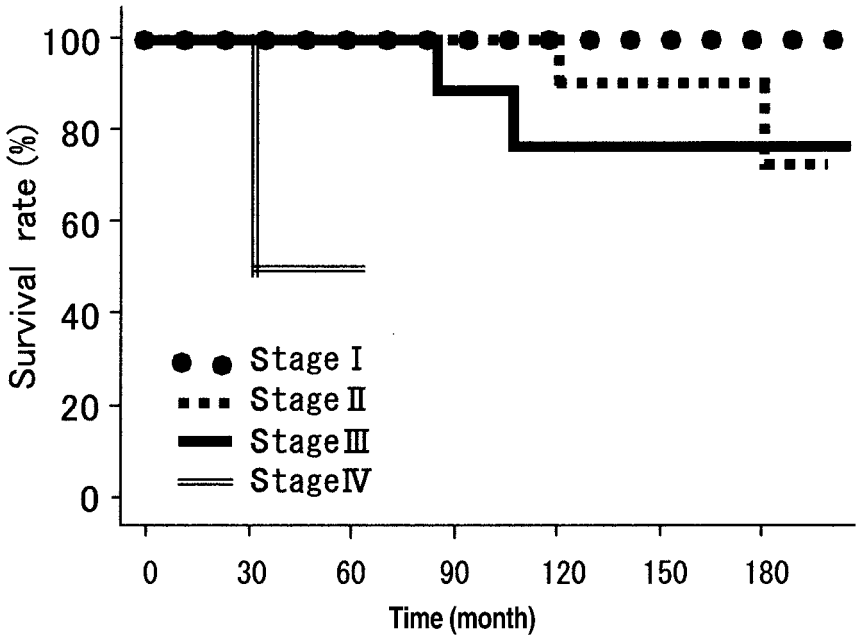
Fig. 5. Overall survival curves according to the World Health Organization histologic classification system.

with Masaoka stage I, II, III, IVa, and IVb thymoma were 90%, 90%, 56%, 15%, and 0%, respectively. Stage I thymoma is considered to be curable by completely surgical resection, while stage II or more advanced disease should be treated by resection plus adjuvant therapy.

In addition to the Masaoka stage, the extent of tumor resection (complete or incomplete),[10,15,16] tumor size,[15] presence or absence of complications,[18] and histological type[7,9,17] have all been reported as prognostic factors. With respect to histological type, the classification of Muller-Hermelink and Marino[19] has been reported as a useful prognostic factor. The WHO classification of thymoma was based on this histological classification and was published in 1999 to serve as the worldwide standard.[1] Although the WHO histological classification has been published recently, some studies have assessed it and the clinical value of this method seems to be established.[2-5] Accordingly, we assessed this classification in a retrospective study of consecutive 100 thymomas surgically resected at our department in Juntendo University Hospital. To find clinically important points in the WHO classification, we evaluated association between each WHO tumor type and the prognoses, compared with the Masaoka staging system.

According to the WHO classification, the recurrence rates for type B3 and C thymoma were high, being 24.2% and 33.3%, respectively. The 15-year recurrence-free rates for type A, AB, and B1 tumor were all 100%, whereas the rates for type B2 and B3 tumor were only 66.7% and 54.5%, respectively. For type C disease, the 10-year recurrence-free rate was 66.7%. When the 64 patients with type A to B2 thymoma were combined, their recurrence rate was significantly lower than that of the 33 patients with type B3 disease. Because there was one recurrent case of 21 B2 thymoma, B2 thymoma is thought to have low grade malignant potentiality. However, there was no patient who died of the tumor because of indolent tumor growth. Therefore, adjuvant therapy for B2 thymoma may not be necessary.

According to Okumura et al.,[2] the 20-year survival



No. of patients at risk							
Stage I	53	37	24	19	12	8	2
Stage II	30	25	20	13	12	9	5
Stage III	15	15	13	8	4	1	1
Stage IV	2	2	1	0	0	0	0

Fig. 6. Overall survival curves according to the Masaoka staging system.

rates after surgical resection of type A, AB, B1, B2, and B3 thymoma were 100%, 87%, 91%, 59%, and 36%, respectively. They also found no significant differences of the recurrence-free death rate between patients with each combination of type A, type AB, and type B1 tumor. Conversely, there were significant differences between patients with type AB and type B3 tumor (p=0.004), patients with type B1 and type B3 tumor (p=0.001), and patients with type B2 and type B3 tumor (p=0.04). Patients with type A tumor tended to show better survival compared with patients who had type B3 tumor (p=0.07), and patients with type B1 tumor also showed better survival compared with those who had type B2 tumor (p=0.06). Chen et al.[3] reported that the prognoses of type B2, B3, and C thymoma were worse than those of type A, AB, and B1 thymoma. In the present study, the recurrence-free rate of the type A, AB, B1, and B2 thymomas was significantly higher from that of the type B3 thymoma (p=0.0026).

The 15-year recurrence-free rates were 100% and 74.6% for Masaoka stage I and II thymoma, respectively. For stage II or more advanced tumors, the usefulness of adjuvant therapy has been suggested.[15,20] Our patients with stage II or more advanced thymoma received postoperative adjuvant radiation therapy, but the value of such therapy remains unclear. Regarding the association between WHO type and Masaoka stage, the ratio of invasive tumor increased as Masaoka stage advanced and the WHO classification shifted from A to C tumor. In conclusion, distinction of type B3 thymoma from type A, AB, B1, and B2 thymoma is clinically relevant because of the poor prognostic behavior of the B3 thymoma.

Conclusion

When using the WHO classification, it is critical to distinguish type B3 thymoma from other tumor types.

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