Prognostic and clinical relevance of the World Health Organization schema for the classification of thymic epithelial tumors : a clinicopathologic study of 108 patients and literature review

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Study objectives: Controversy has ensued about the prognostic relevance of the new World Health Organization (WHO) schema for the classification of thymoma. In this study, we present the clinical and histologic features of 108 thymomas and evaluate the usefulness of this histologic schema in view of the prognosis.

Design: Retrospective, clinicopathologic analysis of our experience and a review of recent literature.

Setting: Department of Thoracic and Cardiovascular Surgery of a university hospital.

Methods: A series of 108 thymomas were reviewed and classified by the new WHO schema. The clinical characteristics and the survival outcome were investigated in reference to the WHO subtypes. The Cox proportional hazards model was applied to determine the factors affecting the tumor-related survival. Recent literature on the prognostic relevance of the WHO schema was reviewed.

Results: There were 7 type A tumors, 25 type AB tumors, 12 type B1 tumors, 32 type B2 tumors, 20 type B3 tumors, and 12 type C tumors. The histologic subtype closely correlated with the Masaoka stage ($p = 0.00$). The tumor-related survivals at 5 years and 10 years were 88.0% and 77.9%, respectively. Stage III and IV tumors had a significantly worse prognosis than stage I or II tumors ($p < 0.05$). Type B3 tumors had an intermediate prognostic ranking in comparison with the carcinomas and with the other groups. On multivariate analysis, the WHO subtype (A-B2 vs B3 vs C) could predict the tumor-related survival, but the Masaoka stage was the most important prognostic factor affecting the postoperative survival ($p = 0.026$).

Conclusion: The Masaoka stage is the most important determinant of survival in surgically resected cases of thymoma. To clarify the prognostic relevance and clinical usefulness of the WHO schema, consistent parameters reflecting the surgical outcome and development of the diagnostic tools that could improve the interobserver agreement within type B are needed.

Most thymomas are composed of a mixture of neoplastic epithelial cells and nonneoplastic lymphocytes, with the proportion among them varying widely from case to case and in different lobules of the same tumor. Unlike most other epithelial tumors, in which the separation of benign from malignant and the grading of the malignancy are established with relative ease, thymomas pose difficulties in segregating along these lines because of their great variability in the cytologic and structural patterns. As a result, the

classification of thymoma for many years has remained a subject of controversy.

Bernatz et al (1) classified thymoma into four categories based on the lymphocyte/epithelial cell ratio and the shape of the epithelial cells: predominantly spindle cell, predominantly lymphocytic, mixed, and predominantly epithelial cell. No significant correlation was noted between this histologic typing and the clinical outcome, and the only important prognostic factor was the invasiveness. (2,3) In 1989, Kirchner and Muller-Hermelink (4) proposed a functional classification of thymomas based on the morphologic resemblance of the tumor with various compartments of the normal thymus, and five types of organotypic thymic epithelial tumors were proposed: medullary, mixed, predominantly cortical, cortical, and well-differentiated thymic carcinoma. Some studies (5,6) showed that this classification was useful in prediction of the prognosis, whereas doubt was cast on its clinical relevance. (7,8) In 1999, the World Health Organization (WHO) histologic typing of tumors of the thymus was published. (9) In this scheme, thymomas are evaluated on the combined basis of the morphologic appearance of the neoplastic epithelial cells (spindle, oval, and so forth) and the relative number of these cells vis-a-vis the nonneoplastic lymphocytes. The prognostic relevance of this classification has been discussed in several studies, (10-14) but it still remains to be conclusively determined. Some reports (10-12) place emphasis on the clinical relevance of the WHO schema, whereas other reports (13,14) display skepticism about its clinical validity.

In this study, we retrospectively reviewed surgically resected thymomas classified on the basis of the new WHO schema and evaluated its clinical usefulness. Through the review of recent literature, we would like to suggest some prerequisites necessary for the future study in respect of the prognostic and clinical relevance of the WHO schema.

MATERIALS AND METHODS

Patients and Surgical Strategy

One hundred twenty-six consecutive patients with thymoma were treated at our institute during the period from January 1992 to June 2002. Eighteen patients were excluded from the study: 6 patients who were initially treated elsewhere, 4 patients who received preoperative chemotherapy or radiotherapy, 7 patients in whom open biopsy alone was performed, and 1 patient who died of sepsis after operation. Therefore, a total of 108 cases of thymoma were considered for review.

Our goals in the surgical resection of thymoma have included a complete removal of all the thymic tissue, exploration of both pleural cavities to determine if satellite lesions are present, and confirmation that no secondary neoplasms exist. We preferred a median sternotomy because complete surgical exploration of the chest could be conducted. The posterolateral thoracotomy was occasionally done for the thymoma involving lungs, pleura, or both. Extended thymectomy was defined as the resection of the entire thymus and mediastinal fat tissue between the both phrenic nerves; thymomectomy was defined as the resection of thymoma leaving residual thymic tissue; and debulking was defined as removal of the tumor as much as possible, usually at least more than two thirds of the tumor.

Pathology and Staging

At least five sections were examined for histologic typing of the tumor in every patient, and additional sections were examined if the R1 resection was suspected. Hematoxylin-eosin-stained sections were available for reevaluation of the histologic diagnosis in 108 patients with thymoma. Histologic typing of thymoma was done according to the new WHO schema, as follows (11): type A thymomas are composed mainly of the epithelial cells, ie, lymphocytes are rare throughout all the sections. The epithelial cells in most cases are spindle or oval shaped, without nuclear atypia. Type AB thymomas exhibit tumor loci with features of Type A thymoma in addition to the lymphocyte-rich areas. The segregation between the two components is usually sharp. Type B1 thymomas are lymphocyte predominant tumors that resemble the normal functional thymus in the view that it combines large expanses with the appearance practically indistinguishable from that of the normal thymic cortex, with areas resembling thymic medulla. Type B2 thymomas are characterized by pale and polygonal neoplastic epithelial cells scattered individually or in small clusters among immature lymphocytes. Perivascular spaces are common and the tumor cells exhibit palisading around the spaces. Type B3 thymomas are composed predominantly of epithelial cells with admixture of minor components of immature lymphocytes. Tumor cells have a clear or eosinophilic cytoplasm, well-defined cytoplasmic margins, and exhibit mild atypia. Foci of squamous metaplasia and perivascular spaces are common. Type C thymomas exhibit clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs.

To facilitate the survival analysis, we assigned each thymoma to one of the WHO subtypes (A, AB, B1, B2, B3, C). However, three cases were combinations of type B2 and B3 thymomas. We classified these "B2 plus B3 thymomas" to B3 thymomas when there was any area in which the diagnostic histology of B3 could be recognized.

The classification system of Masaoka et al (15) was adopted as the staging system. The stage was determined by review of the surgical records and pathologic reports. Tumors classified as stage II, III, or IV were considered invasive.

Statistical Analysis

The statistical difference of the average value was examined with the Student t test. To compare the categorical variables, the [chi square] or Fisher exact test were performed. The survival rate was calculated by the Kaplan-Meier method, and the statistical difference in survival was determined with the log-rank test. Deaths that were related to the thymoma were considered as events. Deaths resulting from the deterioration of myasthenia gravis (MG) were considered thymoma related. All the deaths that were not related to the tumor were considered as censored observations. To identify the prognostic factors, the multivariate analysis, using the Cox proportional hazards regression model, was performed. The following variables were considered as possible prognostic candidate factors: age, sex, presence of MG, tumor size, completeness of the resection, Masaoka

stage, and the WHO histologic type. These analyses were performed with statistical software (version 11.0; SPSS; Chicago, IL).

RESULTS

Clinical Features

There were 63 male patients (58.3%) and 45 female patients (41.7%), with a mean age of 46.5 [+ or -] 13.8 years ([+ or -] SD) [range, 20 to 83 years]. Fifty-one patients (47.2%) were in stage I, 35 patients (32.4%) were in stage II, 13 patients (12.0%) were in stage III, and 9 patients (8.3%) were in stage IV. MG was associated in 44 patients (40.7%). The treatment profiles of these 108 patients are summarized in Table 1. Our strategies in the adjuvant therapy were as follows: no adjuvant therapy in stage I thymomas, radiotherapy in the invasive or incompletely resected thymomas, and chemotherapy (with or without radiotherapy) in the well-differentiated thymic carcinomas or thymic carcinomas regardless of the stage. The postoperative adjuvant therapy was done in 47 patients (43.5%). Forty-six patients received radiotherapy (mean dose, 5,140 [+ or -] 685 cGy; range, 4,500 to 6,300 cGy). Seventeen patients received postoperative chemotherapy: cyclophosphamide, doxorubicin, vincristine, and cisplatin in 14 patients; 5-fluorouracil, etoposide, and cisplatin in 2 patients; and ifosfamide, etoposide, and cisplatin in 1 patient.

Histologic Features: Relationship With Masaoka Stage and Completeness of Resection

The clinical features of each histologic subtype are summarized in Table 2. There was no significant difference in the tumor size between each subtype of thymoma. MG was most frequent in type B thymomas with respect of other types ($p = 0.00$) and tended to be more frequent in type B2 or B3 thymomas. A significant correlation between the histologic subtype and Masaoka stage was noted ($p = 0.00$), and the proportions of advanced-stage tumors gradually increased from type A to type C. The proportion of invasive tumors and complete resection was investigated according to the WHO schema, as shown in Table 3. The frequency of the invasive tumors and the rate of incomplete resection were higher in types B3 and C than other histologic subtypes ($p < 0.01$).

Survival

Median follow-up time for all 108 patients was 40.5 mouths (range, 2.0 to 122.0 months), and a follow-up survey was successfully completed for all patients. During the follow-up period, 20 deaths occurred. Fourteen patients (70%) died of tumor-related causes, and the remaining 6 patients died of other causes (cardiovascular diseases [n = 3], traffic accident [n = 1], delayed mediastinitis [n = 1], and primary lung cancer [n = 1]). The overall survival rates at 5 years and 10 years were 80.2% and 71.1%, respectively. Tumor-related survival rates at 5 years and 10 years were 88.0% and 77.9%, respectively. The survival curves according to Masaoka stage are shown in Figure 1. The 5-year and 10-year survival rates were 100% and 95% in stage I, 91.4% and 81.3% in stage II, and 73.9% and 46.2% in stage III, respectively. In patients with stage IV disease, the median survival time was 29.0 months. Although the number of patients was small in stage IV disease, there was an obvious difference in survival between stage III and IV disease ($p = 0.008$). The survival rate in stage II disease was lower than that in stage I disease, but no significant difference was noted ($p = 0.12$). The survival curves according to the WHO

schema are shown in Figure 2. The survival rate gradually decreased from types A or B1 to type C, with the exception of type AB. There were two tumor-related deaths in patients with type AB thymomas: one patient who underwent a complete resection for stage II disease and another patient who underwent a complete resection for stage I disease died of tumor recurrence at 73 months and 84 months, respectively. Type B3 thymomas had an intermediate prognostic ranking in comparison with type C and with the other types. When we simplified the histologic subtypes to three subgroups (type A-B2/B3/C), a more distinct survival pattern could be outlined. The difference in survival was statistically significant between the subgroups, as shown in Figure 2 (right).

[FIGURES 1-2 OMITTED]

The difference in survival between complete and incomplete resection was significant ($p = 0.00$), as shown in Figure 3. However, there was no difference in survival between the extended thymectomy ($n = 75$) and thymomectomy ($n = 29$) [$p = 0.18$, data not shown]. Of 88 patients with the complete resection, 8 patients (9.1%) had tumor recurrence (median time to recurrence, 52.0 months). The initial sites of recurrence were local in two patients, pleura in three patients, and lungs in three patients.

[FIGURE 3 OMITTED]

Multivariate Analysis

In the univariate analysis, completeness of the resection ($p = 0.000$), Masaoka stage ($p = 0.000$), and WHO histologic type (A-B2/B3/C) [$p = 0.000$] were risk factors for tumor-related deaths. The multivariate analysis was performed with application of the backward elimination method, as shown in Table 4. The Masaoka stage was the most significant risk factor with respect to tumor-related survival ($p = 0.026$). In terms of the WHO schema, types B3 and C had an increased risk for death, but these values were below the level of statistical significance ($p = 0.088$). Because the WHO histologic type significantly correlated with the Masaoka staging system, a separate Cox regression analysis was performed that incorporated only the WHO histologic type along with the other covariates. In this analysis, completeness of the resection had a modest impact on the survival ($p = 0.063$), and the WHO histologic type was an important determinant of the tumor-related survival ($p = 0.001$).

DISCUSSION

In this study, the histologic subtype based on the WHO classification could be determined in all the 108 patients. Among the histologic subtypes, the most frequent histologic subtype was type B2 (29.6%), followed by type AB (23.1%). In our series, type A was more unusual (seven cases, 6.5%) than those in the other studies, (12,14,16,17) which reported the proportion of type A to be 13.8 to 22.0%. Although a larger proportion of the type A thymoma in other studies might result from a failure to detect lymphocyte-rich areas due to low number of blocks, we thought that it was mainly due to the selection bias because our series was not population based but addressed clinical cases. MG was associated mainly with type B thymomas rather than other types ($p = 0.00$), and tended to be more frequent in type B2 or B3 thymomas. A similar

distribution of MG was reported in other series. (10-13)

We observed that the histologic subtype closely correlated with the Masaoka staging system. The proportion of the advanced-stage tumors gradually increased, and the percentage of the invasive tumors among type B3 and C thymomas was 90.0% and 91.7%, respectively. As we expected, the proportion of the complete resection was lower in the patients with type B3 and C thymomas, as shown in Table 3.

In terms of prognosis, tumor-related survival correlated with Masaoka stage, as shown in Figure 1. The difference in survival between stages II and III ($p = 0.04$) and between stages III and IV ($p = 0.008$) was statistically significant. No significant difference in survival was found between stage I and II disease ($p = 0.12$). Similar results have been observed in other studies, (5,6,10,12) and the presence of the capsular invasion--we think--has little prognostic value.

In regard to the WHO schema, the prognosis was good in the patients with type A or B1 thymomas, with no tumor-related deaths. In comparison with the carcinoma group, the other subtypes showed similar prognosis for survival. Among them, type B3 thymomas showed an intermediate prognostic ranking. Type B3 thymoma represents a particular group that remains controversial in the literature. Several investigators (10,12) have reported a worse prognosis of their type B3 thymoma cases compared to the type B2 thymomas, whereas the other reports (11,13,14) contain no significant difference in survival between type B2 and B3 thymomas. The difference in the prognostic value of B3 histology is thought to arise from the following: first, there might be a significant interobserver variability in the histologic typing of thymomas. Dawson et al (18) assessed the ability of three histopathologists to classify thymomas as cortical, medullary, or mixed pattern of tumors. They reported that the interobserver and intraobserver agreements were only moderate ([kappa] = 0.48 and [kappa] = 0.59., respectively). Rieker et al (14) also used the K statistics for the interobserver agreement within various histologic subtypes, classified according to the WHO schema. In the complete WHO classification (types A/AB/B1/B2/B3/C), the interobserver agreement was good ([kappa] = 0.87); however, the interobserver agreement within the "bioactive'" group (B1, B2, B3) was only moderate ([kappa] = 0.49). The problem is the determination of the cutoff points between the different categories adjacent to each other, especially between the bioactive groups with type B3 histology. Second, the WHO classification does not clearly define how to deal with the mixed thymomas involving type B3, and previous reports (19,20) dealt with such forms of mixed thymomas in different ways. In studies concerning the prognostic relevance of the WHO schema, Chen et al (11) counted "B3" when the B3-like areas made up > 30% of the total area, whereas Nagakawa et al (12) counted B3 when there were any areas with B3 histology. Finally, the proportion of the invasive tumors and the complete resection was different between the studies, as listed in Table 5. For example, in the study of Chen et al, (11) the proportion of the invasive tumors was similar between type B2 and type B3 thymomas, and there was no significant survival difference between these two types. In contrast, Okumura et al (10) observed difference in survival between type B2 and type B3, and the proportion of the invasive tumors was higher in the type B3 thymomas in their report. Considering that the tumor invasiveness is the most important prognostic factor for the postoperative survival,

(2,3,18) the proportion of the invasive tumors and the complete resection could affect the prognostic value of type B3 histology.

In our series, type B3 thymomas showed intermediate prognostic ranking, and these results made us consider this histologic type as an intermediate group between type A-B2 and type C. Simplification and bringing them into three groups (A-B2/B3/C) presented a more distinct pattern of survival, and it gave the prognostic factor for survival on the univariate analysis. This simplified classification has been also highlighted by the high interobserver agreement ([kappa] = 0.95) as Rieker et al (14) reported. We thought that the simplified classification into three subgroups might be useful in the future research and/or therapeutic planning for the thymic epithelial tumors.

There were some differences in the study populations or statistical methods between the recent reports concerning the WHO schema (Table 5). We think that there should be some degree of consensus on the research methods. First, we suggest that the tumor-related survival rather than the overall survival should be used for the evaluation of the survival outcome. As it might be expected, with the patients having neoplastic diseases with a prolonged course, other modes of death are responsible for a significant number of mortalities. For example, the tumor-related death was only 32% in the study of Wilkins et a1 (21) and 35% in the study of Regnard et al. (22) Tumor-related death should be regarded as an "event" in the survival analysis. Second, type C thymomas should be regarded as a different category of the disease. Type C tumors obviously had a much more aggressive nature, and a poorer prognosis, and they comprised several histologic entities with different prognosis. (9) Therefore, it is desirable that future clinical studies should be performed separately for type C thymomas and for the other types of thymomas. Finally, there should be consensus on the method to deal with the mixed thymomas involving type B3, as we mentioned above.

CONCLUSION

In the present study, the Masaoka stage is the most important determinant of survival in the thymoma patients. A prognostic value of the WHO histologic classification was noted when the schema was simplified and to bring the entity into three subgroups (A-B2/B3/C). To clarify the prognostic relevance and clinical usefulness of the WHO schema, certain prerequisites or consensus are necessary in the future studies.

Table 1--The Treatment Profiles of 108 Patients Treatment Patients, No. (%)Operation performed Extended thymectomy 75 (69.4) Thymomectomy 29 (26.9) Debulking 4 (3.7)Completeness of resection Complete 88 (81.5) Incomplete 20 (18.5)Adjuvant therapy None 61 (56.5) Radiotherapy 30 (27.8) Radiotherapy plus chemotherapy 16 (14.8) Chemotherapy 1 (0.9)Table 2--Clinical Features of Different ThymomaSubtypes Classified According to WHO Schema * Patients, MG,Type No. Age, yr No. (%)A 7 58.6 [+ or -] 15.9 0 (0.0)AB 25 44.0 [+ or -] 14.7 7 (28.7)B1 12 49.2 [+ or -] 13.1 6 (50.0)B2 32 40.0 [+ or -] 10.1 18 (56.3)B3 20 48.7 [+ or -] 12.5 13

(65.0)C 12 55.6 [+ or -] 12.9 0 (0.0)Total 108 46.5 [+ or -] 13.8 44 (40.7) Masaoka Stage, No.Type Size, cm I II III IVA 7.9 [+ or -] 3.5 4 3AB 6.1 [+ or -] 1.8 18 6 1B1 4.9 [+ or -] 2.6 8 4B2 6.2 [+ or -] 2.9 18 9 5B3 6.2 [+ or -] 3.0 2 12 3 3C 6.9 [+ or -] 3.1 1 1 4 6Total 6.2 [+ or -] 2.8 51 35 13 9* Data are presented as mean [+ or -] SD unless otherwise indicated.Table 3--Invasiveness and Completeness of ResectionAccording to WHO Schema * Variables A AB B1Patients 7 25 12Invasiveness ([dagger]) 3 (42.9) 7 (28.0) 4 (33.3)Complete resection 7 (100) 22 (88.0) 12 (100) ([double dagger]) Variables B2 B3 CPatients 32 20 12Invasiveness ([dagger]) 14 (43.8) 18 (90.0) 11 (91.7)Complete resection 29 (90.6) 11 (55.0) 7 (58.3) ([double dagger])* Data are presented as No. or No. (%).([dagger]) Percentage of the invasive tumors in eachsubtype of thymomas.([double dagger]) Percentage of complete resection amongthe each subtype of thymomas.Table 4--Multivariate Analysis of the Risk Factor forTumor-Related Deaths Hazard 95% Confidence Variables Ratio Interval p ValueModel 1 * Masaoka stage 0.026 I 1 Reference II 0.54 0.17-1.69 III 1.64 0.61-4.39 IV 7.74 1.88-31.93 WHO subtype 0.088 A-B2 1 Reference B3 1.43 0.57-3.55 C 2.09 0.85-5.12Model 2 ([dagger]) WHO subtype 0.001 A-B2 1 Reference B3 1.18 0.49-2.83 C 3.89 1.72-8.79 Resection 0.063 Complete 1 Reference Incomplete 3.08 0.94-10.12* All prognostic candidate factors included.([dagger]) Masaoka stage excluded.Table 5--Review of Literature on Prognostic Relevance of the WHOHistologic Typing of Thymomas Source A ABOkumura et al (10) (n = 273) No. (%) * 18 (6.6) 77 (28.2) Invasive, No. (%) ([dagger]) 2 (11.1) 32 (41.6) CR, No. (%) ([double dagger]) 18 (100) 76 (98.7)Chen et al (11) (n = 200) No. (%) 8 (4.0) 68 (34.0) Invasive, No. (%) 4 (50.0) 7 (10.0) CR, No. (%) Not reportedChalabrcysse et al (13) (n = 90) No. (%) 9 (10.0) 16 (17.8) Invasive, No. (%) 3 (33.3) 2 (12.5) CR, No. (%) 7 (77.8) 16 (100)Rieker et al (14) (n = 218) No. (%) 43 (19.7) 20 (9.2) Invasive, No. (%) 18 (41.9) 8 (40.0) CR, No. (%) Not reported (overall: 91/218 = 77.1%)Nakagawa et al (12) (n = 130) No. (%) 18 (13.8) 56 (43.1) Invasive, No. (%) 9 (50.0) 28 (50.0) CR, No. (%) Not reported (overall: 124/130 = 95.4%) Source B1 B2Okumura et al (10) (n = 273) No. (%) * 55 (20.1) 97 (35.5) Invasive, No. (%) ([dagger]) 26 (47.3) 67 (69.1) CR, No. (%) ([double dagger]) 52 (94.5) 88 (90.7)Chen et al (11) (n = 200) No. (%) 17 (8.5) 39 (19.5) Invasive, No. (%) 7 (42.0) 28 (72.0) CR, No. (%) Not reportedChalabrcysse et al (13) (n = 90) No. (%) 11 (12.2) 22 (24.4) Invasive, No. (%) 3 (27.3) 12 (54.5) CR, No. (%) 10 (90.9) 18 (81.8)Rieker et al (14) (n = 218) No. (%) 24 (11.1) 82 (37.6) Invasive, No. (%) 11 (45.8) 43 (52.4) CR, No. (%) Not reported (overall: 91/218 = 77.1%)Nakagawa et al (12) (n = 130) No. (%) 15 (11.5) 29 (22.3)

Invasive, No. (%) 13 (86.7) 27 (93.1) CR, No. (%) Not reported (overall: 124/130 = 95.4%) Source B3 COkumura et al (10) (n = 273) No. (%) * 26 (9.5) (-) Invasive, No. (%) ([dagger]) 22 (84.6) (-) CR, No. (%) ([double dagger]) 24 (92.3) (-)Chen et al (11) (n = 200) No. (%) 27 (13.5) 36 (18.0) Invasive, No. (%) 20 (74.0) 33 (92.0) CR, No. (%) Not reportedChalabrcysse et al (13) (n = 90) No. (%) 15 (16.7) 17 (18.9) Invasive, No. (%) 14 (93.3) 16 (94.1) CR, No. (%) 8 (53.3) 1 (5.9)Rieker et al (14) (n = 218) No. (%) 10 (4.6) 39 (17.9) Invasive, No. (%) 9 (90.0) 35 (89.7) CR, No. (%) Not reported (overall: 91/218 = 77.1%)Nakagawa et al (12) (n = 130) No. (%) 12 (9.2) (-) Invasive, No. (%) 12 (100) (-) CR, No. (%) Not reported (overall: 124/130 = 95.4%) Source CommentsOkumura et al (10) (n = 273) No. (%) * Survival analysis: tumor-related survival Invasive, No. (%) ([dagger]) Tumor-related deaths: 25 of 66 deaths (37.9%) CR, No. (%) ([double dagger]) Mixed type: not statedChen et al (11) (n = 200) No. (%) Survival analysis: overall survival Invasive, No. (%) Tumor-related deaths: not reported CR, No. (%) Mixed type: B2 + B3 [right arrow] B3 if B3 area > 30%Chalabrcysse et al (13) (n = 90) No. (%) Survival analysis: overall survival Invasive, No. (%) Tumor-related deaths: 20 of 36 deaths (55.6%) CR, No. (%) Mixed type: not statedRieker et al (14) (n = 218) No. (%) Survival analysis: tumor-related survival Invasive, No. (%) Tumor-related deaths: 37 of 70 deaths (52.9%) CR, No. (%) [kappa] ratio within B1-3: 0.49Nakagawa et al (12) (n = 130) No. (%) Survival analysis: tumor-related survival Invasive, No. (%) Tumor-related deaths: 17 of 33 deaths (51.5%) CR, No. (%) Mixed type: B2 + B3 [right arrow] B3 if any B3 area exist* Percentage of each histologic type.([dagger]) Percentage of invasive tumors among each subtype.([double dagger]) Percentage of complete resections (CRs)among each subtype.

REFERENCES

(1) Bernatz PE, Harrison EG, Clagett OT. Thymoma: a clinico-pathologic study. J Thorac Cardiovasc Surg 1961; 42:424-444

(2) Lewis JE, Wick MR, Scheithauer BW, et al. Thymoma: a clinicopathologic review. Cancer 1987; 60:2727-2743

(3) Wick MR. Assessing the prognosis of thymomas. Ann Thorac Surg 1990; 50:521-522

(4) Kirchner T, Muller-Hermelink HK. New approaches to the diagnosis of thymic epithelial tumors. Prog Surg Pathol 1989; 10:167-189

(5) Pescarmona E, Rendima EA, Venuta F. Analysis of prognostic factors and clinicopathological staging of thymomas. Ann Thorac Surg 1990; 50:534-538

(6) Lardinois D, Rechsteiner R. Prognostic relevance of Masaoka and Muller-Hermelink classification in patients with thymic tumors. Ann Thorac Surg 2000; 69:1550-1555

(7) Kornstein MJ, Curran WJ Jr, Turrisi AT 3rd, et al. Cortical versus medullary thymomas: a useful morphologic distinction? Hum Pathol 1988;19:1335-1339
(8) Pan CC, Wu HP, Yang CF, et al. The clinicopathological correlation of epithelial subtyping in thymoma: a study of 112 consecutive cases. Hum Pathol 1994; 25:893-899
(9) Rosai J, Sobin LH. Histological typing of tumors of the thymus. In: World Health Organization international histological classification of tumors, 2nd ed. New York, NY: Springer-Verlag, 1999
(10) Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 2002; 94:624-632
(11) Chen G, Marx A, Wen-Hu C, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. Cancer 2002; 95:420-429
(12) Nakagawa K, Asamura H, Matsuno Y, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. J Thorac Cardiovasc Surg 2003; 126:1134 -1140
(13) Chalabreysse L, Roy P, Cordier JF, et al. Correlation of the WHO schema for the classification of thymic epithelial neoplasms with prognosis: a retrospective study of 90 tumors. Am J Surg Pathol 2002; 26:1605-1611
(14) Rieker RJ, Hoegel J, Morresi-Hauf A, et al. Histologic classification of thymic epithelial tumors: comparison of established classification schemes. Int J Cancer 2002; 98:900-906
(15) Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981; 48:2485-2492
(16) Engel P, Marx A, Muller-Hermelink HK. Thymic tumors in Denmark: a retrospective study of 213 cases from 1970-1993. Pathol Res Pract 1999; 195:565-570
(17) Kuo TT, Lo SK. Thymoma: a study of the pathologic classification of 71 cases with evaluation of the Muller-Hermelink system. Hum Pathol 1993; 24:766-771
(18) Dawson A, Ibrahim NB, Gibbs AR. Observer variation in the histopathological classification of thymoma: correlation with prognosis. J Clin Pathol 1994; 47:519-523
(19) Kirchner T, Schalke B, Buchwald J, et al. Well-differentiated thymic carcinoma: an organotypical low-grade carcinoma with relationship to cortical thymoma. Am J Surg Pathol 1992; 16:1153-1169
(20) Quintanilla-Martinez L, Wilkins EW Jr, Choi N, et al. Thymoma: histologic subclassification is an independent prognostic factor. Cancer 1994; 74:606-617
(21) Wilkins KB, Sheikh E, Green R, et al. Clinical and pathologic predictors of survival in patients with thymoma. Ann Surg 1999; 230:562-574
(22) Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996; 112:376-384
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