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Thymomas: clinical-pathological correlations

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Aim. **Since World Health Organization (WHO) histologic typing of tumors of the thymus publication in 1999 only a few studies correlated this classification with the clinical features of the patients. We present the results of a retrospective analysis on patients, operated on for a thymoma, whose specimens were available, to compare the WHO thymoma histologic classification to the clinical behavior of the tumors.**

Methods. **The specimens of 69 patients, who underwent surgical treatment between 1983 and 1998, were analyzed, comparing the clinical features of the patients and the hystological typing of the neoplasm, according to the WHO classification. A survival analysis of clinical and pathological prognostic factors was carried out.**

Results. **The incidence of thymus-related syndrome was related to the histological subtype and increases progressively from A to B3, while in C subtype the incidence was nihl. With a mean follow-up of 108 months (range 54-239 months), we experienced 6 intrathoracic recurrencies, 3 of those were intrapleuric and 3 mediastinal. At the last follow-up, 52 patients were alive; 1 with disease. Five deaths were related to the tumor (2 mediastinal and 3 intrapleuric relapses). Actuarial five-year and ten-year survival was 95% and 88.9%. Because of the absence of deaths related to thymomas in most samples it was not possible to perform a comparison among different histological types and different clinical stages.**

Conclusion. **The WHO histologic classification seems to correlate with the incidence of thymus related syndromes and the clinical stage of Masaoka. Despite the higher incidence of recurrences in type B3 and C thymoma the WHO classification did not prove to be a prognostic factor.**

KEY WORDS: Thymoma - Masaoka staging - Surgery - WHO histological classification - Follow-up - Prognosis.

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Thymomas are neoplasms originating from the thymic epithelial cells, characterized by an extreme variability in histological appearance, as well as in clinical behavior.[1, 2] This wide heterogeneity is at the origin of controversy about the clinical-pathological correlation in thymomas, mostly based on the significance of histologic appearance in this tumor.[3]

In the past, several histologic classifications have been proposed, but none of those appeared fully reliable to predict the clinical course of the disease.[4-6] Most pathologists agreed that the histologic appearance had no prognostic relevance. Moreover, clinical features of the tumor (*i.e.* grade of invasiveness and presence of thymus-related syndrome) and the radicality of the surgical exeresis were universally considered as prognostic factors.[7-10]

In 1999, the World Health Organization (WHO) published a new histologic classification system, resulting from the work of an international committee; it combines the various former classifications and defines different subtypes with numbers and letters.[11]

This system is based on 2 criteria: first the shape of the neoplastic cells and then the proportion in lymphocytes. On this basis, there are 2 types of thymoma: in type A the epithelial cells appear spindle or oval, while in type B these cells are dendritic or plump. Tumors that combine these 2 morphologies are des-

ignated as type AB. Type B thymomas are further subdivided in B1, B2, B3 subtypes, according to the increasing ratio of atyphia in the neoplastic cells. Thymic carcinomas are classified as type C thymoma.

The validity of this classification as a prognostic tool is matter of discussion, even if the preliminary results are encouraging.[12-14]

We present the results of our retrospective analysis on 69 patients, who underwent surgical exeresis at the Division of Thoracic Surgery of the University of Pisa between 1983 and 1998, aiming to compare the WHO thymoma histologic classification to the clinical behavior of the tumors.

Materials and methods

The specimens of 69 patients, who underwent surgical treatment between 1983 and 1998, were analyzed, comparing the clinical features and the hystological typing of the neoplasm, according to the WHO classification. There were 34 males and 35 females, with a mean age of 56±13.9 years (range 25-83 years).

Pathology

The thymomas were fixed in formalin, embedded in paraffin and then stained with hematoxilin-eosin. The histologic evaluation was performed in at least 3 sections for each specimen. The immunohistochemical evaluation has been performed in at least 1 section for each specimen, using monoclonal antibodies against CD3 (1:50), CD5 (1:20), pan-cytokeratin (1:100) and CD20 (1:50). Semiquantitative analysis has been performed at the optical microscope with a field 10×.

Two different pathologists (F.B. and G.F.), without any informations about the patient's clinical features and prognosis, performed histologic diagnosis. Specimens which showed cyto-architectural features, reliable to 2 different histologic types, have been classified as the more malignant.

Clinical study

Clinical findings and survival data were recorded for each patient. The data analyzed included: sex, age, association with thymus-related syndrome, local invasiveness and/or metastasis (according to Masaoka clinical staging), neoadjuvant and adjuvant therapies, site of relapse and disease-free survival.

Patients with Masaoka stage I thymomas underwent surgery, patients with stage IIA, IIB and III thymomas underwent surgery and postoperative radiotherapy (whenever the conditions of the patient allowed it) and patients with stage IVA underwent surgery plus pleural and systemic chemotherapy or chemo-radiotherapy. After 1998, advanced stage thymomas with clinical or radiological signs of spreading to the surrounding organs or to the pleura (stage III and IVA of Masaoka) were enrolled in a protocol of neoadjuvant chemotherapy, surgery and postoperative radiotherapy.

In our series, 11 patients underwent neoadjuvant therapy and 48 adjuvant therapy: among these latter, 33 received radiotherapy, 1 chemotherapy, 5 endopleural plus systemic chemotherapy and 5 chemoradiotherapy. The neoadjuvant and adjuvant chemotherapy scheduling was PEVP16 (Cis-Platin i.v. 75 mg/sqm, day 1; Epidoxorubicin i.v. 100 mg/sqm, day 1; Etoposide i.v. 120 mg/sqm, days 1, 3, 5). The radiotherapy was administered using opposite anterior and posterior parallel fields at doses of 4 500 cGy for complete resections or 6 000 cGy for incomplete resections, delivered in 5 or 6 weeks respectively with 5 fractions per week.

Statistical analysis

The statistical analysis has been performed by the Stat-Soft software. Results are expressed as mean± standard deviation. Survival was evaluated from the date of surgical treatment until death or the last follow-up [June 30th, 2003]. Patients who died due to cause(s) other than thymoma without evidence of disease were censored at death. Survival curves were estimated by the Kaplan-Meyer's product-limit method and were compared by using the long-rank test. The χ^2 test was used for comparison between proportions, whereas Fisher's exact test was used when the cell frequencies were small. The P-values reported for this test were for two-sided tests.

In this study, a P-value less than 0.05 was considered significant in all comparisons.

Results

Patient's characteristics are listed in Table I.

The incidence of thymus-related syndrome is significantly (P=0.01) related to the histological subtype

TABLE I.—*Patients's characteristics.*

Patients's characteristics	N
Sex (M *vs* F)	34 *vs* 35
Age (mean±SD)	56±13.9
Staging of Masaoka	
I	13 (18.8%)
IIa	5 (7.2%)
IIb	35 (50.7%)
III	10 (14.5%)
IVa	6 (8.7%)
Thymus-related syndrome	
Overall	37 (53.6%)
Myasthenia gravis	33 (47.8%)
Hypogammaglobulinemia	3 (4.3%)
Red cells aplasia	1 (1.4%)
Histotype	
A	5 (7.2%)
AB	7 (10.1%)
B1	18 (26.1%)
B2	18 (26.1%)
B3	17 (24.6%)
C	4 (5.8%)
Neo-adjuvant chemotherapy	
Yes *vs* No	11 *vs* 58
Adjuvant therapies	
CT	1
Endopleural+systemic CT	5
RT	33
CT+RT	5

CT: chemotherapy. RT: radiotherapy.

and increases progressively from A to B3, while in C subtype the incidence was nihl (Figure 1). According to the histologic classification, we observed: 5 type A thymomas (7.2%), 7 type AB (10.1%), 18 type B1 (26.1%), 18 type B2 (26.1%), 17 type B3 (24.6%), 4 type C (5.8%). According to the Masaoka staging, in the examined group, 13 patients had a stage I thymoma (18.8%), 5 stage IIa (7.2%), 35 stage IIb (50.7%), 10 stage III (14.5%), 6 stage IVa (8.7%).

The Masaoka staging of the thymomas correlates (P=0.02) with the WHO histological classification with more advanced stages in the B2, B3 and C subtypes.

With a mean follow-up of 108 months (range 54-239 months), we experienced 6 intrathoracic recurrencies, 3 of those were intrapleuric and 3 mediastinal. At the last follow-up, 52 patients were alive; 1 with disease. Five deaths were related to the tumor (2 mediastinal and 3 intrapleuric relapses). Twelve patients died for causes not related to the originary thymoma. As regards the staging and the histological classification of the 5 patients who died for a recurrence, 2 were at stage III, 2 at stage IIb and 1 at stage IVa; 3 were type B3 and 2 type C. The patient who is living with a mediastinal relapse had a stage III type B2 thymoma.

Actuarial five-year and ten-year survival was 95% and 88.9% (Figure 2).

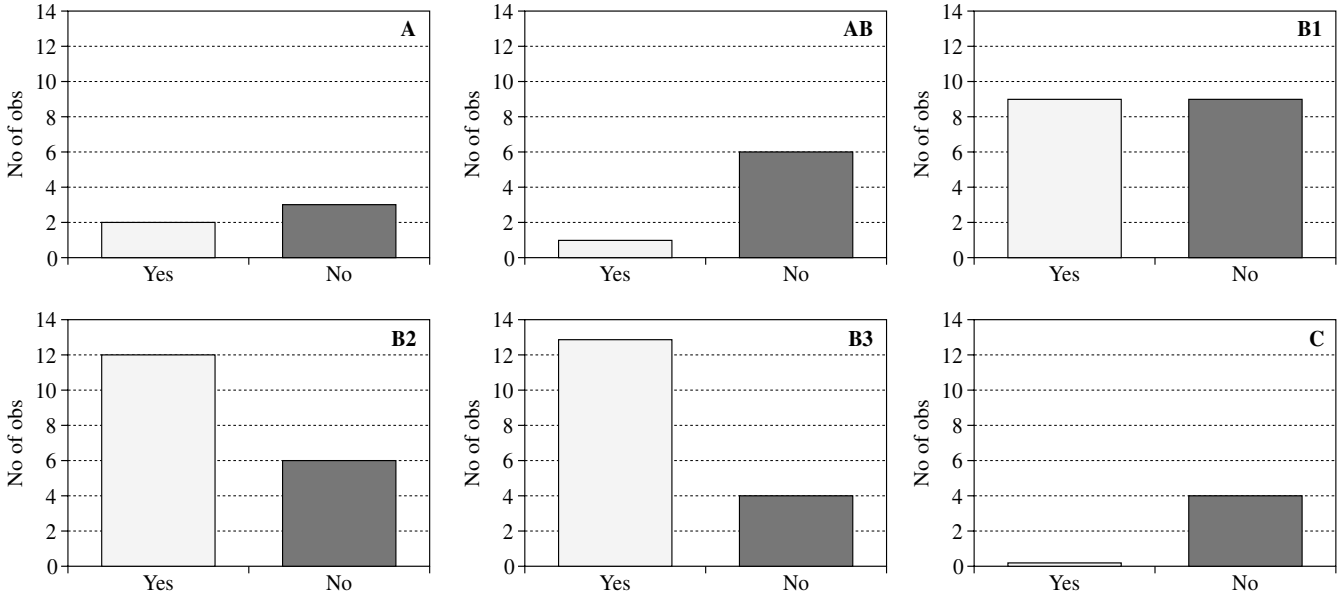

Figure 1.—Correlation between thymus-related syndromes and histological classification (P=0.01).

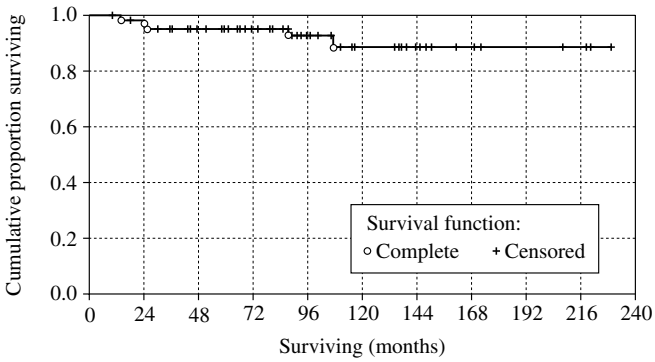

Figure 2.—Actuarial five-year and ten-year survival curves of patients resected for thymoma (n=69).

Because of the absence of thymoma related deaths in most samples it was not possible to perform a comparison among different histological types and different clinical stages.

Discussion

In this study, we analyzed retrospectively 69 patients operated on for thymoma, aiming to compare the clinical behavior of the tumor and the incidence of thymus-related syndromes to the histological types, according to the new WHO classification system.[11]

As a whole, 53.6% of patients had a thymus-related syndrome, in particular 47.8% had associated myasthenia gravis. This incidence, higher than that reported in most others series, might be due to patient's referral pattern.[2, 7, 9]

Analyzing the incidence of thymus-related syndrome in the different histological sub-types, we observed a significant higher progressive incidence from B1 to B3, a lower incidence in A and AB than in B types and nihl in C.

These data do not differ from those reported in literature and suggest that the WHO classification may reflect the immunological behavior of thymoma.[13] Moreover, this observation is congruent with those of one previous study, showing that the epithelial cells of thymoma lose their function progressively from B1 to B3, epithelial cells of type A thymoma are less functional compared to the B-type and type AB has an intermediate situation.[12] Type C thymoma seems to be immunologically non-functioning.

As regards the oncological significance of WHO classification, it was assumed that thymoma's cells are more aggressive from type A to type B3, being type C seems a different type of tumor, characterized, on the clinical side, by a much more aggressive nature. However, in our study, because of the absence of uncensored cases in most samples, it was not possible to perform the survival curves among different histological types. Despite the higher incidence of recurrences in type B3 and C thymoma the WHO classification did not prove to be a prognostic factor and that may be due to the small patients population, on the contrary, there are some recent reports highlighting the new WHO thymoma classification as an independent prognostic factor, only partially reflecting the correlation between the WHO histological classification system and the Masaoka staging system.[13, 14]

Though surgery remains the mainstay in the treatment of thymoma, the best strategy to be adopted in the more advanced forms is still under discussion.[15-19] The integration of surgery, radiotherapy and chemotherapy in the neoadjuvant and/or adjuvant setting, based on experience with other neoplasms, may be useful in improving the results of the therapy of this relatively rare disease.[20, 21]

In our series, 48 patients received adjuvant therapies and 11 underwent neo-adjuvant therapy. The choice of how to integrate surgery with radiotherapy and/or chemotherapy in the neoadjuvant and/or adjuvant setting was based on the clinical stage of the disease and on the patient's general condition. As previously published we reserved neoadjuvant chemotherapy to most stage III and IVa thymomas aiming to improve the radicality of the surgical exeresis and, consequently, the prognosis.[20, 21]

We did not experience mortality or major morbidity confirming that surgery for patients with thymoma is safe even in myasthenic patients. The quick recovery from the operation is a direct consequence of the improved medical management of the myasthenic symptoms.[22] Furthermore no patient died at the follow-up because of myasthenia gravis.

Conclusions

Our study suggests that the WHO histologic classification, which correlates with the incidence of thymus related syndromes and the clinical stage of Masaoka, may reflect the immunologic and clinical behavior of

thymomas. Despite the higher incidence of recurrences in type B3 and C thymoma, we were not able to prove that the WHO classification is a prognostic factor.

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