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Tumor Recurrence and Survival in Patients Treated for Thymomas and Thymic Squamous Cell Carcinomas: A Retrospective Analysis

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ABSTRACT

Purpose
Thymic epithelial tumors (TET) are rare epithelial neoplasms of the thymus with considerable histologic heterogeneity. This retrospective study focused on the correlation of WHO-defined TET histotypes with survival and tumor recurrence in a large cohort of patients receiving different modes of treatment.

Patients and Methods
Two hundred twenty-eight patients were followed for up to 21 years (median, 60 months; range, 1 to 252 months) after primary surgery. Forty-two patients received adjuvant radiotherapy (mean dose, 53 Gy), and 33 patients recieved adjuvant chemotherapy.

Results
Seventy-six (88%) of 86 patients with WHO type A, AB, and B1 thymomas were treated by surgery alone, with three tumor relapses after 3 to 10 years (median, 3.4 years). Twelve of 67 patients with WHO type B2 and B3 thymomas in Masaoka stages I and II were treated by adjuvant radiotherapy without evidence of tumor recurrence after 1 to 12 years (median, 4 years). Among 75 patients with B2 and B3 thymomas with incomplete resection or a tumor stage III or higher, the recurrence rate was 34% (n = 23) after 0.5 to 17 years (median, 5 years) in patients receiving adjuvant radiochemotherapy, compared to 78% (seven of nine patients) in patients without adjuvant radiochemotherapy. Incomplete tumor resection was associated with a high recurrence rate (65%) and a poor prognosis ($P < .01$).

Conclusion
The long-term outcome of TET patients is related to tumor stage, WHO histotype, completeness of surgical removal, and type of treatment. Prospective trials are warranted to formally address the efficacy of adjuvant therapy in the treatment of localized and advanced malignant TETs.

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INTRODUCTION

Since introduction of the current WHO classification in 1999,[1] thymic epithelial tumors (TET) are subdivided into three major categories, termed A, B, and C (thymic carcinomas). Type B thymomas are further subdivided into the subcategories B1, B2, and B3. Moreover, thymomas with histologic features of both type A and B tumors are termed AB (mixed). The majority of type C tumors are thymic squamous cell carcinomas (TSCCs), while other histologic differentiations, such as adenocarcinomas, clear-cell carcinomas, and so on are uncommon. Frequently, organotypical thymomas first come to clinical attention through paraneoplastic autoimmune phenomena, among which myasthenia gravis (MG) is by far the most common.[2]

Controversies about thymoma classification had prevented detailed comparison of international studies in the past.[3-6] Since introduction of the WHO classfication, several retrospective studies demonstrated that the classification can predict clinical tumor behavior and patient outcome.[7-9] Moreover, these studies suggested that not only

Table 1. Duration of Clinical Follow-Up in the Different Histologic Thymoma Subtypes

Tumor Type	No. of Cases (N = 228)	Duration of FU (months)	Median FU (months)
Noncombined tumors			
A	21	6-132	30
AB	48	9-252	48
B1	13	12-192	120
B2	58	3-240	60
B3	28	4-204	62
TSCC	11	1-117	36
Combined tumors			
B1 + B2	4	21-58	34
B2 + B3	43	4-252	65
B3 + TSCC	2	84-108	84

Abbreviations: FU, follow-up; TSCC, thymic squamous cell carcinoma.

tumor stage, but also the histologic subtype, as defined by the WHO classification, may be an independent prognostic parameter. In the present retrospective study, we set out to generate a more comprehensive characterization of clinical and prognostic features of the different WHO thymoma subtypes. Particular attention was paid to thymomas with histologic features of more than one WHO subtype (combined thymomas[10]), which have been poorly characterized thus far. Moreover, it was the aim of this study to identify and better define risk groups among TET patients in order to provide a rationale for future prospective, randomized clinical treatment trials.

PATIENTS AND METHODS

Patients, TET Classification, and Definition of Combined TETs and Staging

Patient data were based on histology, as well as information contained in hospital charts, including physical examination and the result of ancillary techniques such as chest x-rays, sequential biopsies, and laboratory tests using a questionnaire that was developed for this study and approved by the local ethics committee. The questionnaire was used by the clinical co-authors and was sent to the physician in charge of the patient. Follow-up data were obtained after informed consent of the patient or, if deceased, of his or her relatives. From a total cohort of 545 TETs, which were evaluated with regard to histologic subtype, age, and sex, 228 cases could be followed for their clinical course after TET removal over a maximum period of 21 years (median, 60 months; range, 1 to 252). The remaining patients were lost to follow-up. There were no statistical differences regarding the duration of follow-up between the different histological subgroups (Table 1). TETs were classified according to WHO criteria as: type A (medullary, spindle cell), type AB (mixed), and type B (cortical), with subtypes B1, B2, and B3.[1] Given the great heterogeneity of tumors summarized under the category of type C thymomas, we decided to include only TSCCs in this category. Thymomas with areas unequivocally corresponding to more than one histologic subtype (eg, substantial type B1 areas in a thymoma otherwise corresponding to type B2) in more than 10% of the sampled tissue were termed combined thymomas.[10] Of note, type AB thymomas, although mixed in type, are exempted from this category by WHO definition.

Tumor stage was determined following the modified Masaoka classification:[11] I, encapsuled tumor; II, infiltration of mediastinal fat; III, infiltration of neighboring organs; IVa, pleural or pericardial dissemination; IVb, lymphatic or hematogenous metastases.

Statistical Analyses

Associations between categorical variables were determined by using the Yates corrected χ^2 test. Prognostic factors were analyzed by the Kaplan-Meier method, and comparisons between curves were made using the log-rank test. To investigate the relative importance of various factors for postoperative survival (age, sex, stage, histology, resections status, presence of myasthenia gravis, adjuvant therapy, tumor recurrences), the Cox proportional hazards model was applied. The best model was selected by backwards elimination of nonsignificant factors. To test for association between predictors, Fisher's exact test was used.

$P < .05$ was assumed significant unless otherwise stated. SPSS 9.0 (SPSS Inc, Chicago, IL) was applied for all statistical analysis.

RESULTS

Epidemiologic and Histopathologic Findings

The epidemiologic findings are summarized in Tables 2 and 3. Among a total of 179 TETs without combined features, the most frequent histologic subtypes were B2 (25%), followed by AB (21%), and B3 (12%) thymomas. The least frequent tumor entities were type A (9%) and B1 (6%). The average age at diagnosis for all thymoma subgroups was 55 to 65 years, with the exception of patients with type A thymomas, who were significantly older at presentation (average age, 67 years; $P < .001$). There was a moderate female sex predilection for type AB and B1 thymomas (male:female = 1:2), while type A, B2, and B3 tumors were encountered in males and females at similar frequencies. By contrast, TSCCs were more frequent in males than in females.

In addition to these 179 cases, there were 49 thymomas exhibiting combined features, mostly combinations of WHO type B2 and B3 thymomas (43 of 49 cases). Age and sex distribution of these combined, type (B2+B3) thymomas were similar to those of conventional type B2 tumors.

Clinical Findings

Correlation between WHO histologic subtype and tumor stage. The vast majority (> 90%) of type A, AB, and B1 thymomas were detected in Masaoka stages I and II. By contrast, type B2, B3 thymomas, and TSCC were detected in advanced stages III and IV at significantly higher frequencies (50% at presentation; $P < .01$; Tables 4 and 5).

Tumor size was not correlated with these differences, since type A and AB thymomas on average were even larger than type B thymomas (median diameter, 7 cm; range, 2 to 22 cm versus median, 6 cm; range, 0.8 to 30 cm; Mann-Whitney-U test, $P < .01$, data not shown).

Table 2. Epidemiologic Features of All Thymoma Cases Listed in the Würzburg Thymoma Registry

Tumor Type	No. of Patients (N = 545)	%	Male (n = 246)	Female (n = 299)	Sex Ratio (m:f)*	Age at Diagnosis (years)	
						Range	Median
Noncombined							
A	41	7.5	20	21	0.95	35-88	69
AB	142	26.0	52	90	0.58	18-89	63
B1	31	5.7	10	21	0.48	14-83	54
B2	102	18.7	46	56	0.82	15-83	55
B3	54	9.9	28	26	1.1	29-87	63
TSCC	68	12.5	43	25	1.7	12-82	59
Combined							
B1 + B2	11	2.0	6	5	1.2	37-71	52
B2 + B3	87	16.0	36	51	0.7	14-82	57
B3 + C	7	1.3	5	2	2.5	46-78	52
B2 + MNT	1	0.2	0	1	—	—	71
B2 + TSCC	1	0.2	0	1	—	—	49

Abbreviations: TSCC, thymic squamous all carcinoma; MNT, micronodular thymoma.
*Sex ratio (m:f) of the total population was 0.83.

Association of Histologic Thymoma Subtypes With MG

Among 228 patients in whom laboratory testing for autoimmune disorders had been performed, 120 (52.6%) had MG. MG was particularly frequent in type B1 thymomas and combined thymomas with a B1 component (70% and 75%, respectively; Table 6). MG was significantly more frequent in type B1, B2, and B3 thymomas (noncombined and combined) than in type A and AB thymomas (Yates corrected χ^2, $P < .01$). Presence of MG did not show statistical correlation with survival on a multivariate analysis.

With the exception of type A thymomas, tumors were significantly smaller when associated with clinical MG (MG+) than in the absence of MG ($P < .001$, Mann-Whitney-U-test), probably as a result of the fact that patients with MG came to clinical attention earlier. However, the observation that some MG+ thymomas measured up to 18 cm (median diameter, 5.0 cm) leads us to suggest that thymomas may grow over long periods before autoimmune manifestations occur. Neither the histologic tumor subtype nor tumor size were significantly correlated with antiacetylcholine-receptor autoantibody titers in the patient's serum (type A thymomas: median, 23 nmol/L; range, 1.6 to 32 nmol/L; type AB thymomas: median, 5.9 nmol/L; range, 1 to 67 nmol/L; type B1 thymomas: median, 12.7 nmol/L; range, 6 to 70 nmol/L; type B2 thymomas: median, 13 nmol/L; range, 2 to 170 nmol/L; type B3 thymomas: median, 10 nmol/L; range, 1.7 to 50 nmol/L).

Table 3. Epidemiologic Features of the Thymoma Cases Included in the Follow-Up Study

Tumor Type	No. of Patients (N = 228)	%*	Male (n = 98)	Female (n = 130)	Sex Ratio (m:f)†	Age at Diagnosis	
						Range	Median
Noncombined							
A	21	9.2	11	10	1.1	35-88	69
AB	48	21.1	16	32	0.5	18-78	62
B1	13	5.7	4	9	0.4	41-66	53
B2	58	25.4	23	35	0.7	29-83	57
B3	28	12.3	16	12	1.3	29-76	59
C	11	4.8	8	3	2.7	34-73	57
Combined							
B1 + B2	4	1.8	3	1	—	38-67	56
B2 + B3	43	18.9	15	28	0.5	27-75	57
B3 + TSCC	2	0.9	2	0	—	48-56	—

Abbreviation: TSCC, thymic squamous cell carcinoma.
*64.4% of the cases were submitted from authors' institutions; 42% of the cases came from the Würzburg center; 22% from the institutions of the co-authors.
†Sex ratio (m:f) of the total population was 0.75.

Table 4. Distribution of Masaoka Tumor Stage in the Noncombined Thymoma Subtypes

	Thymoma Subtype											
	A (n = 21)		AB (n = 48)		B1 (n = 13)		B2 (n = 58)		B3 (n = 28)		TSCC (n = 11)	
Stage	No. of Specimens	%	No. of Specimens	%	No. of Specimens	%	No. of Specimens	%	No. of Specimens	%	No. of Specimens	%
I	14	67	29	60	3	23	5	9	0	0	0	0
II	4	19	17	35	10	77	25	43	14	50	4	37
III	2	10	2	5	0	0	22	38	10	36	5	45
IVa	0	0	0	0	0	0	4	7	4	16	1	10
IVb	1	5	0	0	0	0	2	4	0	0	1	10

Abbreviation: TSCC, thymic squamous cell carcinoma.

Primary Tumor Resection Status and Frequency of Local Recurrences

In agreement with the distribution of tumor stage, the completeness of tumor removal varied significantly among the different thymoma subtypes. Thus, complete tumor resection (R0) was achieved in virtually all type A and AB thymomas (type A, 92%; type AB, 96%), and in the vast majority of type B1 thymomas (89%). Adjuvant therapy (aT) was infrequently applied in these groups (10 of 76 cases; Tables 7 and 8). By contrast, R0 resection in type B2, B3 thymomas, and TSCC was achieved in only 70%, 60%, and 31% of cases, respectively. Fifty-nine percent of patients with type B2, B3 thymomas, or TSCC received aT (Tables 7 and 8). Combined thymomas that included type B1 and B2 areas were too infrequent to give conclusive information, but seemed to behave like noncombined B1 thymomas in that tumor relapses, even in an incompletely resected (R1) tumor, were not observed. Combined thymomas with B2 and B3 areas behaved like noncombined B2 and B3 thymomas and complete tumor resection was achieved in only 44% of these cases. Sixty-three percent of patients with combined B2 and B3 thymomas received aT (Tables 7 and 8).

Tumor relapses were rare in completely removed type A, AB, and B1 thymomas (2% to 11%), and in stage I and II type B2 and B3 thymomas with R0 resection (Tables 9, 10, and 11). Relapses were observed 7 to 204 months after primary surgery (median, 75 months). Tumor recurrences in type A, AB, and B1 thymomas occurred between 30 and 114 months after primary surgery and all were treated by surgery alone. All of the patients survived the tumor relapse for up to 13 years of follow-up. In more advanced (stage III) type B2 and B3 thymomas, tumor relapses occurred in 36% and 40% of cases, respectively (Tables 9, 10, and 11). Incomplete tumor removal (R1 and R2) was a strong independent predictor of recurrence in combined and noncombined type B2 and B3 thymomas (40% and 72%, respectively; Table 11).

Table 5. Distribution of Masaoka Tumor Stage in the Combined Thymoma Subtype

	Combined Thymomas					
	B1 + B2 (n = 4)		B2 + B3 (n = 43)		B3 + TSCC (n = 2)	
Stage	No. of Specimens	%	No. of Specimens	%	No. of Specimens	%
I	2	50	1	2	0	0
II	2	50	18	42	0	0
III	0	0	12	28	2	33
IVa	0	0	8	19	0	0
IVb	0	0	4	9	0	0

Abbreviation: TSCC, thymic squamous cell carcinoma.

Correlation of Clinical Features and Tumor Variables With Survival

Patient variables such as age, sex, presence of MG, or tumor size did not show a statistical correlation with survival on a multivariate analysis.

Association of Masaoka stage with survival. Tumor stage was one of the most important factor predicting survival in TET patients. There were no tumor-related deaths

Table 6. Frequency of MG in Different Histologic Thymoma Subtypes

Tumor Type	No. of Patients (N = 228)	MG+ (n = 120)	MG− (n = 108)	Percentage of MG+ Cases*
Noncombined				
A	21	6	15	29
AB	48	20	28	42
B1	13	9	4	70
B2	58	34	24	59
B3	28	18	10	65
TSCC	11	0	11	0
Combined				
B1 + B2	4	3	1	75
B2 + B3	43	29	14	67
B3 + TSCC	2	1	1	50

Abbreviations: MG, myasthenia gravis; TSCC, thymic squamous cell carcinoma.
*53% of the total population was MG+.

Table 7. Treatment Modalities in Noncombined Thymomas

Treatment	Thymoma Subtype (No. of patients)					
	A	AB	B1	B2	B3	TSCC
Surgery alone	17	44	15	21	7	1
Surgery + RT	1	4	2	14	7	3
Surgery + CT	1	1	0	1	4	0
Surgery + RCT	1	0	0	4	4	5

Abbreviations: TSCC, thymic squamous cell carcinomas; RT, radiotherapy; CT, chemotherapy; RCT, radio-chemotherapy.

(TRD) in patients with Masaoka stage I tumors, while the 10-year survival probability in stage IV tumors was 47% ($P < .0001$). However, while the survival rate among patients with Masaoka stage III and IV tumors was very similar during the first five years after resection (88% in stage III *v* 85% in stage IV tumors), the rate of lethal outcome in stage III reached a plateau line after that time (10-year survival rate, 83%), while lethality of stage IV tumors dropped further (Fig 1A). Moreover, although the prognosis of patients with Masaoka stage II tumors at initial presentation was generally excellent, there were some tumor-related deaths in patients with stage II tumors more than 10 years after surgery.

Correlation of WHO tumor histotype with survival. Histologic tumor subtype, as defined by the WHO classification, was a powerful prognostic parameter ($P < .001$; Fig 1B). There were no tumor-related deaths in patients with type A, AB, and B1 thymomas, while lethality of type B2, B3 thymomas, and TSCC was 9%, 19%, and 17%, respectively (Table 12). There were no statistically significant differences between B2 and B3 thymomas and TSCC regarding survival. The only group of combined thymomas with enough data to provide meaningful information were tumors with combinations of type B2 and B3 features. Lethality in this tumor group was not statistically different from respective noncombined TET (B2, B3 thymomas, or TSCC; Table 13).

Association of tumor resection status with survival. Incomplete tumor resection (R1 and R2) was an adverse prognostic factor with significant influence on survival ($P < .05$; Fig 2A), the difference becoming most evident more than 10 years after resection (5-year survival rate: 92% in R0 resected tumors *v* 83% in R1+R2 resected tumors; 10-year survival rate: 78% in R0 resected tumors *v* 47% in R1+R2 resected tumors; 20-year survival rate: 67% in R0 resected tumors *v* 34% in R1+R2 resected tumors).

Table 8. Treatment Modalities in Combined Thymomas

Treatment	Combination (No. of patients)		
	B1 + B2	B2 + B3	B3 + TSCC
Surgery alone	3	13	0
Surgery + RT	1	10	0
Surgery + CT	0	5	0
Surgery + RCT	0	5	2

Abbreviations: TSCC, thymic squamous cell carcinoma; RT, radiotherapy; CT, chemotherapy; RCT, radio-chemotherapy.

Table 9. Frequency of Tumor Relapses in Noncombined and Combined Thymomas

Tumor Type	No. of Patients (N = 184)	Recurrences (N = 41)	
		No. of Patients	%
Noncombined			
A	18	2	11
AB	48	1	2
B1	12	1	8
B2	35	8	22
B3	25	11	44
TSCC	7	3	43
Combined			
B1 + B2	3	0	0
B2 + B3	34	13	38
B3 + TSCC	2	2	100

Abbreviation: TSCC, thymic squamous all carcinoma.

Association of tumor recurrences with survival. Tumor recurrence was associated with a high risk for tumor-related deaths and was thus the most important single denominator related to long-term survival on multivariate analysis ($P < .01$; Fig 2B). Tumor recurrence occurred as late as 17 years (204 months) after primary surgery (median interval between primary surgery and relapse, 51 months; range 7 to 204 months).

Effects of adjuvant therapy on tumor recurrence and survival. Data on the effect of aT were often incomplete and thus not suited for statistical analysis. Moreover, in contrast to the regimes for adjuvant radiotherapy, which appeared largely similar (n = 42; mean total dose, 53 ± 9 Gy), there was a marked variation in the applied specific chemotherapeutic regimens, which included: cisplatin, adriamycin, cyclophosphamide/ifosfamide;[12] cyclophosphamide, doxorubicine, vincristine, prednisolone; cyclophosphamide, vincristine, adriamycin, prednisolone, procarbazine, bleomycin;

Table 10. Frequency of Tumor Relapses in Thymomas With Complete Surgical Removal at Primary Diagnosis

Relapses*	Thymoma Subtype (No. of patients)				
	A	AB	B1	B2	B3
Stage I tumors	0/12	1/29	0/3	0/5	0/1
Stage II tumors	0/3	0/17	1/9	0/12	1/19
Stage III tumors	1/2	0/2	0/0	3/8	2/10

*Combined B1 + B2 thymomas were included among the B1 category; combined B2 + B3 and B3 + C thymomas were included among the B3 category.

Table 11. Frequency of Tumor Relapses With Incomplete Surgical Removal at Primary Diagnosis

Relapses*	Thymoma Subtype (No. of patients)				
	A	AB	B1	B2	B3
Stage I tumors	0/0	0/0	0/0	0/0	0/0
Stage II tumors	0/0	0/0	0/1	1/3	2/5
Stage III tumors	0/0	0/0	0/0	1/3	4/5
Stage IV tumors	1/1	0/0	0/0	2/4	12/15

*Combined B1 + B2 thymomas were included among the B1 category; combined B2 + B3 and B3 + C thymomas were included among the B3 category.

Table 12. Frequency of Tumor-Related Deaths in Noncombined Thymomas

Tumor Type	No. of Patients (N = 189)	TRD (n = 12)		Masaoka Stage in Patients With TRD		
		No. of Patients	%	II	III	IV
A	22	0	0	—	—	—
AB	57	0	0	—	—	—
B1	14	0	0	—	—	—
B2	58	5	8.6	1	2	2
B3	26	5	19.2	—	2	3
TSCC	12	2	16.7	—	—	2

Abbreviations: TRD, tumor-related death; TSCC, thymic squamous cell carcinoma.

adriamycin, cyclophosphamid, vincristine/etoposide; etoposide, ifosfamide, cisplatin, epirubicine; Taxol; and high-dose polychemotherapies with autologous stem-cell transplantation. The heterogeneity of these treatments precludes formal analysis. As a group, adjuvant chemotherapy apparently had no influence on the outcome of patients with type A, AB, and B1 thymomas as well as on that of patients with R0 resected type B2 or B3 tumors in stage II, since there were only three tumor recurrences and no tumor-associated deaths in these groups (no recurrences among 11 type B2 and B3 thymomas treated with adjuvant radiotherapy *v* one tumor recurrence among 16 type B2 and B3 thymomas without further treatment; Tables 9 to 13). Among 14 patients with R0 resected type B2, B3 thymoma or TSCC in Masaoka stage III, five patients had been treated by adjuvant radiotherapy. There was no tumor recurrence in this group compared to 33% (three of nine cases) tumor relapses in R0 resected stage III tumors without aT.

By contrast, the frequency of tumor recurrences in high-risk patients with type B2 or B3 thymomas and TSCC with R1 or R2 tumor resection appeared to be lower in patients recieving aT than in patients without it (34% recurrences in the aT+ group *v* 78% in the aT− group; $P = .12$). However, this trend did not translate into a significant difference in TRDs (three [14%] of 22 cases in the aT+

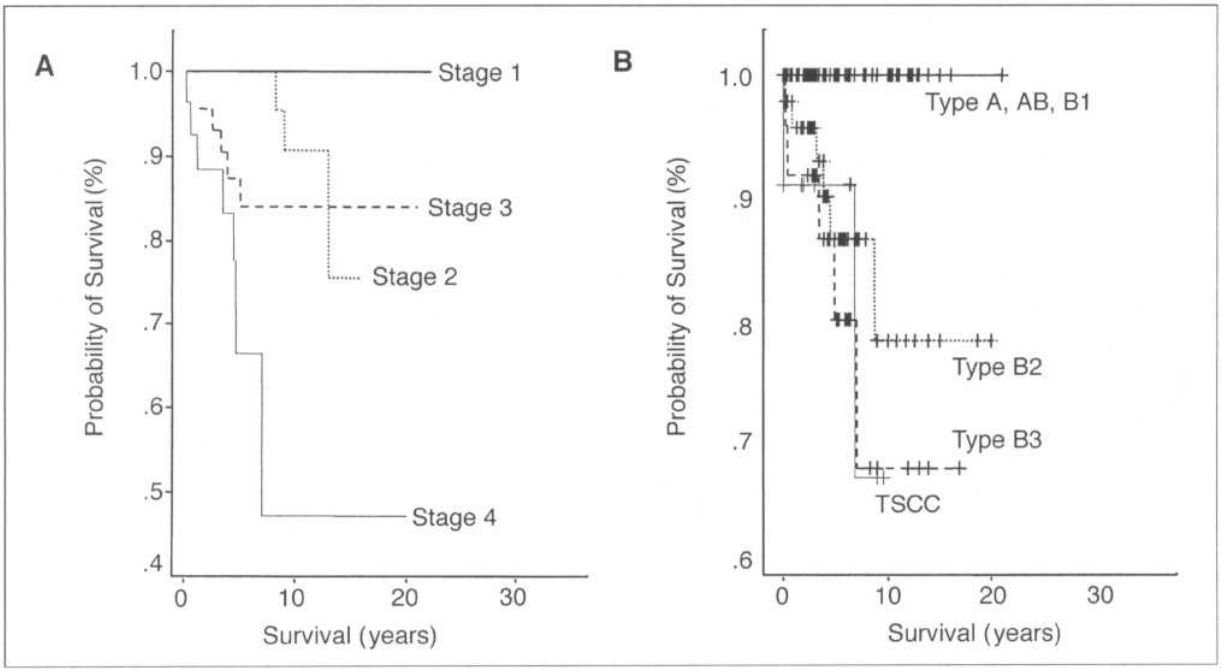

Fig 1. Correlation between Masaoka tumor stage (A) and histological thymoma subtype (B) with survival. TSCC, thymic squamous cell carcinoma.

Table 13. Frequency of Tumor-Related Deaths in Combined Thymomas

Tumor type	No. of Patients (N = 53)	TRD (n = 6)		Masaoka Stage in Patients With TRD		
		No. of Patients	%	II	III	IV
B1 + B2	4	0		—	—	—
B2 + B3	45	6	13.3	2	2	2
B3 + TSCC	4	0		—	—	—

Abbreviations: TRD, tumor-related death; TSCC, thymic squamous cell carcinoma.

group *v* three [38%] of eight TRD in the aT− group; $P = .73$). R1 + R2 resected stage III tumors treated only by adjuvant radiotherapy showed a high frequency of local failures (three of six cases).

DISCUSSION

The current WHO classification of thymic epithelial neoplasms[1] is based on morphological features, such as the presence of an immature lymphoid component and on the degree of cytologic atypia. This study confirms the notion[13] that the WHO classification of TET in fact reflects the biologic nature of the different histologic tumor subtypes. A common problem for clinicians is the information that the tumor contains more than one histologic WHO thymoma subtype (combined thymoma[10]), raising uncertainity about the therapeutic management. In this series, 21% of cases showed combinations of type B1, B2, B3, and TSCC features in various proportions, with combinations of type B2 and B3 being by far the most common. Our retrospective data indicate that combined thymomas (here defined as unequivocal features of more than one WHO subtype in > 10% of the sampled tissue) share similar epidemiologic and clinical features with their noncombined counterparts with the most aggressive component of the tumor generally deciding over the clinical behavior.

Epidemiologic findings, such as distribution of age and sex, were similar among all histologic thymoma subtypes and were therefore not of prognostic value. The association with paraneoplastic MG was high among combined and noncombined type B thymomas and low among A and AB tumors. MG+ thymomas were significantly smaller than MG− thymomas, possibly as a result of the fact that they came to clinical attention earlier. However, MG was not a prognostically relevant parameter on statistical analysis. In

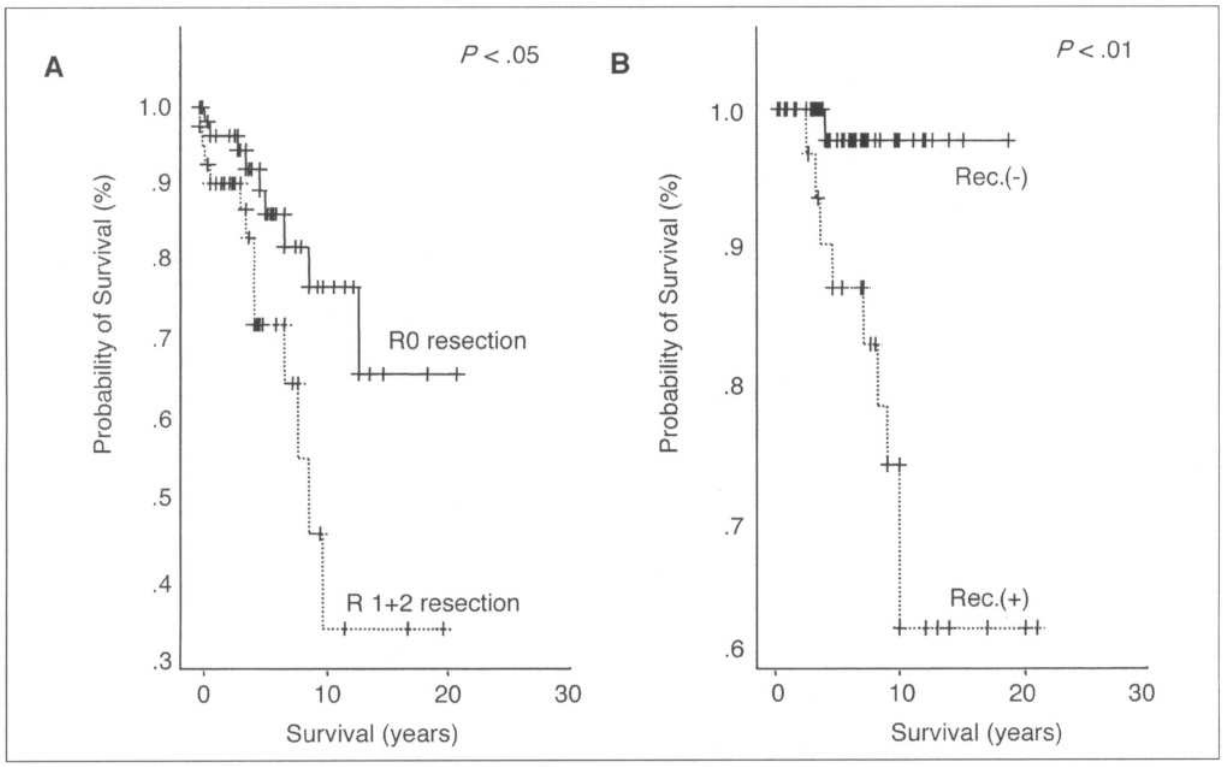

Fig 2. Correlation between (A) resection status and (B) tumor recurrence with survival. R0, complete tumor resection; R1, incomplete tumor resection by histology; R2, incomplete tumor resection by macroscopy. Rec, recurrence.

Table 14. Proposal of a Stage-Adopted Thymoma Therapy Regimen Tentative for Testing (percentages indicate the expected frequency within a given histologic tumor subgroup)

	Masaoka Stage II		Masaoka Stage III		
Tumor Type	R0	R1 + R2	R0	R1 + R2	Masaoka Stage IV
A, AB, B1*	no aT	ws/aT ?	aT ?	ws/aT ?	aRCT
Expected frequency, %	95	< 5	< 5	< 5	< 5
B2, B3, TSCC†	aRT ?	aRT/RCT ?	aRT/RCT ?	aRCT	aRCT
Expected frequency, %	33	8	19	12	20

NOTE. Question marks represent tentative treatment options.
Abbreviations: R0, complete tumor resection; R1 + R2, incomplete tumor resection; a, adjuvant therapy; ws, wait and see; aRCT, adjuvant radiochemotherapy; TSCC, thymic squamous cell carcinoma; aRT, adjuvant radiotherapy; RCT, radio-chemotherapy.
*"Low-risk" thymomas, including combined B1 + B2 thymomas (expected frequency, 38% of all thymoma cases).
†"High-risk" thymomas, including combined B2 + B3 and B3 + TSCC thymomas (expected frequency, 62% of all thymoma cases).

confirmation of earlier reports, independent prognostic factors in this large retrospective analysis were Masaoka tumor stage,[7,9,13] the histologic thymoma subtype, resection status[2,14,15] (complete *v* incomplete), and tumor recurrences.[16] Consequently, all of these parameters will have to be taken into account for adaequate therapeutic decisions.

In detail, while the vast majority of type A, AB, and B1 thymomas behave in a benign fashion, single cases (five out of 82 in this series) may be encountered in more advanced stages and may require adjuvant treatment. By contrast, type B2 and B3 thymomas and TSCC have to be considered malignant tumors with a potential to metastasize. Our data confirm the clinical relevance to distinguish type B2 from B3 tumors, since type B3 tumors were somewhat more aggressive, with a significantly higher frequency of tumor relapses, as noted previously.[5,13,17] However, there was no significant difference with respect to survival between these two types.

In line with findings in other thymoma series,[7,18-20] aT as performed in some advanced TET in stages III and IV appeared to be effective in inducing long-lasting complete or partial remissions, although patient numbers were too small to allow for statistical analysis. Retrospective analysis of the applied chemotherapeutic regimens revealed a great spectrum of different protocols and further illustrated the need for stage-adopted, standardized clinical trials in the adjuvant therapy of thymomas. However, in line with other reports,[16,21,22] it was also apparent from our data that relapses or tumor progression of advanced type B2 and B3 thymomas and TSCC occurred despite intensive combined radiochemotherapy. Tumor recurrence had a highly significant adverse prognostic effect in type B thymomas and TSCC, but not in type A, AB, and B1 thymomas. Of note, a delay of up to 17 years between primary surgery and tumor recurrence was observed in this study. There were no data on the effect of neoadjuvant treatment in our cohort.[23]

In line with previous observations and concepts regarding stage-adopted aT,[7,24] we propose the following rationale for the adjuvant therapeutic management of thymomas, based on the clinicopathologic findings of this study (Table 14): thymomas of the subtypes A, AB, and B1 in Masaoka stages I and II with R0 tumor resection may not require adjuvant therapy. Rare cases of more advanced, R1 and R2 resected or recurrent tumors should be treated by surgery[25] and may require adjuvant therapy. By contrast, a previous study by Chen et al[7] showed that the prognosis of type B2 and B3 thymomas differs from that of type A, AB, and B1 thymomas, even in stage II tumors. We observed a single recurrence among 16 R0 resected type B2, B3, and TSCCs without further adjuvant treatment (6.3%). Adjuvant radiotherapy for completely resected stage II thymomas of the high-risk categories B2, B3, and TSCC has been advocated by many authors.[24,26] While some studies have found beneficial effects,[26-28] two very recent studies dealing with this problem did not find significant differences between treated and untreated patients,[29,30] although the follow-up periods of the latter studies were rather short and, of note, both relapses observed in these studies were high-risk (type B) thymomas. Obviously, more prospective data are required to evaluate the benefit of adjuvant radiotherapy in patients with R0 resected stage II type B2 and B3 thymomas and TSCCs.

Given the adverse prognostic impact of tumor recurrences on survival and the high rate of tumor recurrences in type B2 and B3 thymomas and TSCC in stage III+ as well as R1 and R2 resected tumors of one of these subtypes, aT should be considered in these situations. We did not observe tumor relapses in the five patients with R0 resected stage III type B2 and B3 thymomas and TSCC receiving postoperative irradiation. However, earlier reports suggested that in patients with pleural invasion, mediastinal irradiation alone might be insufficient to avoid pleural-based relapse, even after complete resection.[26]

By contrast, any incompletely (R1 or R2) resected tumor carries a high-risk for local recurrence when treated by adjuvant radiotherapy alone. A recent study reported encouraging results of multimodality treatments in patients with stage III thymomas.[31]

In conclusion, the present study and other published retrospective data on the clinical prognosis of the different histologic TET subtypes provide a preliminary basis to help in therapeutic decision making. Because existing strategies in the treatment of advanced aggressive TET are still unsatisfactory, our study may also aid in the formulation of the hypotheses needed to develop prospective and randomized phase II clinical trials adjusted to tumor histotype and Masaoka stage. Given the low incidence of TET, these trials will require an international multicenter design.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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