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Prognostic grading after complete resection for thymic malignancies

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Abstract. – OBJECTIVE: Despite the World Health Organization (WHO) and Masaoka classifications have been widely accepted as the main describers of prognosis determinants in thymic malignancies, so far, these have been considered independently from one another. We have reviewed our single-centre 40-year results after surgical treatment of thymic malignancies evaluating the inter-relationships between the clinical, surgical and pathological variables and investigating their prognostic impact in completely resected patients.

PATIENTS AND METHODS: A surgical series of 347 patients was reviewed and, of these, 305 with complete resection enrolled. Long-term and disease-free survival (LTS, DFS) analyses were performed. Kaplan-Meir curves for WHO histotypes and Masaoka-stages were inspected and matched with the log-rank test; the Cox regression analysis was adopted in a multivariable approach.

RESULTS: Considered independently, the WHO-histotypes did not differentiate clearly from one to another in terms of LTS and DFS; however, types A-AB-B1-B2 and B3-C clustered in 2, statistically different, malignancy groups (LTS, DFS: Cox-$p < 0.001$). Masaoka staging was confirmed to be a relevant prognostic determinant, even if no evident difference between stages I vs II and stages III vs IV emerged when the Masaoka-classification was factored in. Thus, when investigating 13 surgical and pathological factors of invasiveness, these showed a clustering in 2 groups according to the presence/absence of pathological proven infiltration in the peri-thymic structures (LTS, DFS: Cox-$p < 0.001$). By matching the WHO-malignancy clusters and infiltration clusters, 4 classes may be identified, which proved to have a distinct prognostic significance: (LTS-Cox: stage-I vs stage-II, $p = 0.003$; III: $p < 0.001$, IV: $p < 0.001$; DFS-Cox: stage-I vs stage-II, $p < 0.001$; III: $p < 0.001$; IV: $p < 0.001$).

CONCLUSIONS: When analyzing the long-term outcome of patients underwent complete resection for thymic malignancies, the combination between pathological and surgical variables showed accurate prognosis predictability.

Key Words:
Thymoma, Masaoka-classification, WHO-classification.

Introduction

Although widely accepted and commonly used, the current classification systems for thymomas are sometimes considered sub-optimal as proven by the absence of any official staging system proposed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). To provide a standard procedure enabling physicians and researchers to compare results, the International Committee of the World Health Organization (WHO) attempted to establish a Consensus on Histological Classification in 1999[1] and proposed a more complex system based on subtypes over the years[2]. Despite the current status of the histologic classification of thymomas has been largely adopted, there is some body of evidence that many questions remain unanswered. In particular, if we consider the histology of this tumour as the main prognostic predictor, we do not take into account the degree of invasiveness.

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On the other hand, the anatomical classification of Masaoka et al[3] subsequently revised by Koga et al[4] represents the most widely and pragmatically accepted staging system. However, this framework does not consider the histological degree of malignancy of the tumour and it is therefore somewhat biased at the practical level.

Furthermore, the oncological significances of the WHO histological classification and the Masaoka staging have usually been analyzed independently from each other[5-15]. The substantial narrowness of these two classifications in predicting the prognosis (one independently for the other) has recently prompted some Authors[16] for the search of a histological and anatomical subclassification of deeper detail and, consequently, of greater complexity[2,17]. This, coupled with the extreme rarity of thymomas[18], would make these classifications not reproducible and their validation practically impossible.

It is important to keep in mind that histology and invasiveness represent two distinct aspects of the same neoplasm. Therefore, the inter-relationship of the WHO-histology and the Masaoka classifications, along with the confounding effect of one over the other, should be considered in order to deal with these tumours appropriately.

The aim of the present study is to review our 40-yrs long-term case load in thymic malignancies treatment, evaluating the inter-relationships between the clinical, surgical and pathological variables and investigating the prognostic grading of completely resected patients.

Patients and Methods

Following relevant communication to the Institutional Review Board (IRB) on this retrospective observational study on anonymised data, we have reviewed the clinical data of a surgical series of 347 thymoma patients operated from 01/70 to 12/2010 in the Department of Thoracic Surgery of the Catholic University of the Sacred Heart, School of Medicine, Rome, Italy.

Only cases undergoing complete resection (CR-R0) were considered and this was decided so as to remove any possible confounding effect due to the presence of residual disease (micro or macro) after thymectomy.

The CR of the thymoma was performed using the extended trans-sternal thymectomy, as defined by Jaretzki and Wolff[19]. Tumour stage was determined according to the Masaoka-classification[3]. Moreover, we evaluated in details the degree of invasiveness, considering separately the following factors: (1) no capsule infiltration; (2) capsule infiltration; (3) capsule and fat infiltration; (4) pleura adherence; (5) pericardium adherence; (6) both pleura and pericardium adherence; (7) parenchyma adherence; (8) pleura infiltration; (9) pericardium infiltration; (10) parenchyma infiltration; (11) pleura/pericardium adherence with pleura/pericardium infiltration; (12) pleura and pericardium infiltration; (13) metastatic disease. The terms “adherent” or “adherence” were used to defined a tumor apparently involving a surrounding structure where, conversely, the infiltration was not confirmed at definitive pathological examination.

Before data analysis, all cases were reviewed by the same expert pathologist (L.L.) and staged according to the WHO classification[2]. To do this, paraffin-embedded tissue blocks were retrieved for all patients from the hospital tissue archive, and new sections were cut for histologic review.

The indications to administer adjuvant radiotherapy were not uniform because of the long time span considered, and because some of the patients received adjuvant treatment in other centres. However, the main indications to adjuvant therapy were: (1) the confirmed infiltration of the surrounding organs or (1) the pathologic evidence of thymic carcinoma. Radiotherapy was administered to the tumour bed plus a 1.5 cm margin to a total dose of 45-55 Gy, with 1.5-1.8 Gy fractionation. In not-resectable cases, cisplatin-based chemotherapy was administered using doxorubicin, cyclophosphamide, and prednisone or etoposide. All patients were followed-up for disease relapse/recurrence or mortality by matching data in the thoracic surgery, neurology and radiotherapy.

Statistical Analysis

A prognostic stratification combining and integrating pathological and surgical features was tested. The predictability of the Long-Term Survival (LTS, calculated from surgery to the last date of follow-up) and the Disease-Free Survival (DFS, calculated from surgery to the discovery of the first recurrence if any) according to this stratification was compared with that of the most commonly used Masaoka staging. A secondary analysis on the LTS and the DFS truncated at 5, 10, 20 and 30 years, and on the disease-specific mortality for the sub-group of

the deceased subjects, was also performed. Survival analyses were performed using the Kaplan-Meier method and survival curves were compared with the log-rank test. Cox models were fitted after checking for the proportionality of hazards with the Grambsch and Therneau's tests[20]. *Post-hoc* comparisons between different histotypes, Masaoka-Stages, and different levels of neoplastic local invasiveness were tested. The "goodness of fit" of the models fitting the Masaoka staging and our "integrated thymoma classification" was checked by comparing the Harrell's C-coefficient and the coincidence of the Nelson-Aalen cumulative hazard curve with the Cox-Snell residual curve. The limit for statistical significance was set at $p < 0.05$. All tests were two-sided. All analyses were performed in STATA/SE V10.0 software package.

Results

The study sample consisted of 305 subjects (only patients underwent CR-R0 were included in the analysis). Male/Female ratio was 1.03 (155/150), with a mean age of 49 ± 14 years (range 8-84 years). The main clinical, surgical and pathological findings are summarized in Table I. The median LTS time for the entire sample was 305 months, while the median DFS time was 256 months.

Masaoka-Classification, Neoplastic Local Invasiveness, and WHO-Histology

According to the Masaoka classification, 110 (42%) subjects were classified as stage I, 74 (28%) as stage II, 73 (28%) as stage III, and only 7 (3%) as stage IV; the remaining 38 patients

Table I. Main demographic, clinical, surgical and pathological characteristics of the study population.

Subjects' characteristics	N (%)	Surgical characteristics	N (%)
Age		Date of surgery	
(Range)	8; 84	(Range)	1970; 2011
(Mean ± SD)	49 ± 14	< 1990	98 (32%)
< 30	26 (9%)	1991-2000	103 (34%)
30-39	50 (16%)	> 2000	104 (34%)
40-49	77 (25%)	Pericardium resection	
50-59	69 (23%)	No	205 (67%)
60-69	54 (18%)	Yes	65 (21%)
> 70	21 (7%)	Pericardium infiltration	
Gender		No	208 (68%)
Female	150 (49%)	Yes	33 (11%)
Male	155 (51%)	Adherent	31 (10%)
Myasthenia		Pleural resection	
No	49 (16%)	No	157 (52%)
Yes	256 (84%)	Yes	107 (35%)
Type of adjuvant therapy		Pleural infiltration	
None	165 (54%)	No	161 (53%)
Radiotherapy	121 (40%)	Yes	58 (19%)
Chemotherapy	4 (1%)	Adherent	46 (15%)
Radio-chemotherapy	11 (4%)	Parenchymal resection	
Masaoka-classification		No	225 (74%)
Stage-I	110 (42%)	Yes	45 (15%)
Stage-II	74 (28%)	Parenchymal infiltration	
Stage-III	73 (28%)	No	230 (75%)
Stage-IV	7 (3%)	Yes	23 (8%)
WHO-classification		Adherent	19 (6%)
A	13 (4%)	Infiltration capsula-fat	
AB	31 (10%)	No	129 (42%)
B1	41 (13%)	Capsula only	32 (10%)
B2	165 (54%)	Capsula and fat	100 (33%)
B3	38 (12%)	Vasal infiltration	
C	12 (4%)	No	248 (81%)
		Yes	14 (5%)
		Phrenic nerve infiltration	
		No	249 (81%)
		Yes	13 (5%)

could not be accurately classified due to some missing information. LTS and DFS did not differ between stage I and stage II (HR_{LTS} = 0.970.47; 2.00], n.s.; HR_{DFS} = 1.460.49; 4.37], n.s.), while a difference could be observed for stage III and stage IV (see Table II and Figure 1). *Post-hoc* pairwise comparisons showed statistically significant differences of LTS and DFS between stages II, III and IV, with HR's ranging from 2.45 to 14.43 (data not shown). Given the prognostic performance of the Masaoka classification, which failed to discriminate stages I vs II, and stages III vs IV, we evaluate the prognostic impact of other13 parameters concerning tumour invasiveness. At the light of the results on LTS and DFS from the Cox regression analysis (Table II), tumours with a pathologically proven infiltration of the pleura, pericardium and/or parenchyma were labelled as "invasive tumours" (including thymomas with vascular and phrenic nerve invasion). All other tumours, including those were such local infiltration was subsequently not confirmed at definitive pathology ("adherent" tumours) were labelled "non-invasive tumors". Finally, metastatic thymomas were considered as a separate class. This three-group classification according with these 13 parameters was shaped according to the pathological background and by comparing, with a *post-hoc* analysis, the items with a degree of local invasiveness that was dubious. Statistically significant differences were observed when comparing: "pleura infiltration" vs. "pleura adherence" (HR_{LTS}: 3.721.05; 13.21], p = 0.042; HR_{DFS}: 5.911.08; 32.36], p = 0.040); "pleura/pericardium adherence and infiltration" vs. "pleura adherence" (HR_{DFS}: 8.741.45; 52.62], p = 0.018). Invasive thymomas showed significantly worse LTS and DFS when compared to

Table II. Hazards for overall mortality and recurrence by Masaoka classification and neoplastic local invasiveness. Results from the Cox-Regression-Analysis.

	Overall mortality (N = 305)			Disease recurrence (N = 305)		
	D/N	HR [95% CI]	*p* value	R/N	HR [95% CI]	*p* value
Masaoka-classification						
Stage-I	23/110	1	7/110	1		
Stage-II	11/74	0.97 [0.47; 2.00]	0.932	6/74	1.46 [0.49; 4.37]	0.496
Stage-III	24/73	2.37 [1.33; 4.22]	0.003	25/73	8.46 [3.64; 19.66]	< 0.001
Stage-IV	3/7	8.60 [2.47; 29.91]	0.001	3/7	21.10 [5.29; 84.16]	< 0.001
Neoplastic local invasiveness						
Non-invasive tumors						
No capsule infiltration	22/103	1	7/103	1		
Capsule infiltration	1/20	0.31 [0.04; 2.34]	0.258	0/20	0 [0;]	1.000
Fat infiltration	1/17	0.67 [.09; 5.01]	0.693	1/17	1.41 [0.17; 11.54]	0.751
Pleura adherence	4/29	0.87 [0.30; 2.54]	0.799	2/29	1.15 [0.24; 5.54]	0.865
Pericardium adherence	2/11	2.53 [0.58; 10.92]	0.215	1/11	2.90 [0.35; 23.72]	0.321
Pleura and pericardium adherence adherence	1/13	0.61 [0.08; 4.56]	0.630	3/13	5.20 [1.34; 20.23]	0.017
Invasive tumors						
Parenchyma adherence	2/6	2.27 [0.53; 9.75]	0.269	2/6	8.27 [1.70; 40.27]	0.009
Pleura infiltration	6/12	3.23 [1.30; 8.02]	0.011	4/12	6.78 [1.96; 23.43]	0.002
Pericardium infiltration	1/3	1.14 [0.15; 8.59]	0.900	1/3	5.00 [0.61; 40.74]	0.133
Parenchyma infiltration	5/9	4.01 [1.50; 10.75]	0.006	5/9	12.92 [4.05; 41.17]	< 0.001
Pleura/pericardium adherence and pleura/pericardium infiltration	3/7	3.58 [1.06; 12.07]	0.039	3/7	10.02 [2.58; 38.87]	0.001
Pleura and pericardium infiltration	9/24	2.37 [1.09; 5.17]	0.029	9/24	8.32 [3.09; 22.42]	< 0.001
Metastatic tumors						
One or more metastases	3/7	8.84 [2.52; 30.98]	0.001	3/7	20.60 [5.15; 82.42]	< 0.001
Non-invasive tumors	31/193	1		14/193	1	
Invasive tumors	26/61	2.99 [1.77; 5.05]	< 0.001	24/61	7.05 [3.64; 13.67]	< 0.001
Metastatic tumors	3/7	9.50 [2.80; 32.25]	< 0.001	3/7	16.70 [4.67; 59.73]	< 0.001

Acronyms: D: number of deceased subjects; R: number of subjects with recurrence; N: total number of subjects; HR: hazard ratio; CI: confidence interval.

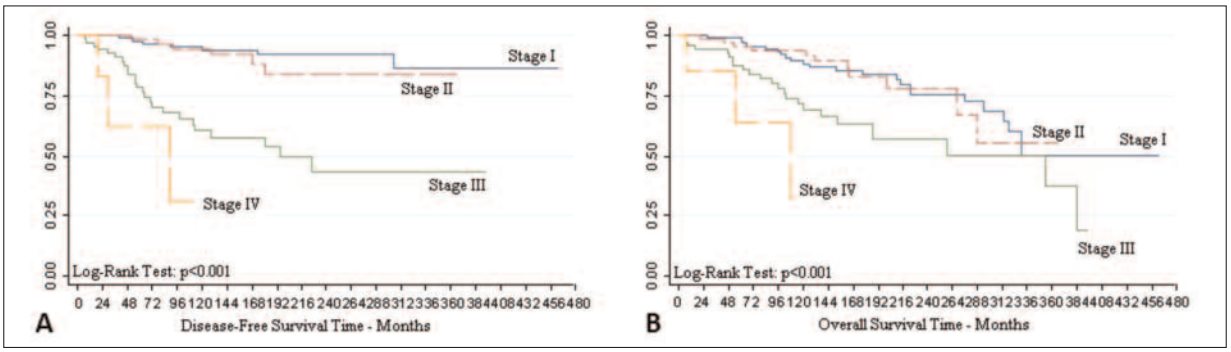

Figure 1. Overall *(A)* and disease-free *(B)* survival Kaplan-Meier curves by Masaoka classification.

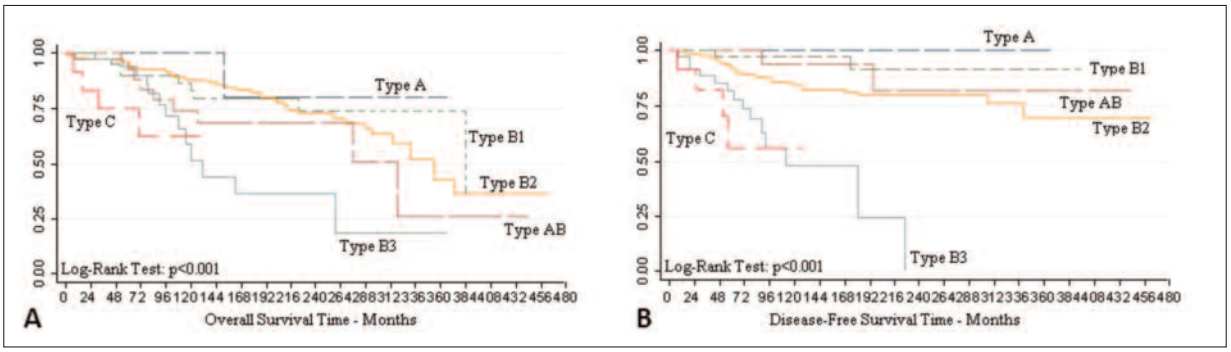

Figure 2. Overall *(A)* and disease-free *(B)* survival Kaplan-Meier curves by WHO – Histology classification.

those non-invasive (HR_{LTS}: 2.991.77; 5.05], $p < 0.001$; HR_{DFS}: 7.053.64; 13.67], $p < 0.001$), with a stronger effect in metastatic diseases (HR_{LTS}: 9.50 [2.80; 32.25], $p < 0.001$; HR_{DFS}: 16.70 [4.67; 59.73], $p < 0.001$). Survival analysis based on the WHO-histology classification revealed as type A, AB, B1 and B2 had a similar and better LTS and DFS when compared to type B3 and C (see Table III and Figure 2). Statistically significant differences in the LTS and DFS were found from a *post-hoc* analysis, where B3 and C types were compared to type A, B1, B2, with HRs ranging between 3.06 to 18.59. Based on these findings (Table III), histotypes A, AB, B1 and B2

Table III. Hazards for overall mortality and recurrence by WHO classification and tumor malignancy. Results from the Cox-Regression-Analysis.

		Overall mortality (N=305)			Disease recurrence (N=305)		
		D/N	HR [95% CI]	*p* value	R/N	HR [95% CI]	*p* value
WHO-classification							
Low-malignancy	A	1/13	1		0/13	1	
	AB	9/31	4.14 [0.52; 32.79]	0.178	2/31		
	B1	9/41	2.24 [0.28; 17.70]	0.446	2/41	0.90 [0.13; 6.38]	0.914
	B2	39/165	2.54 [0.35; 18.51]	0.358	27/165	3.22 [0.76; 13.55]	0.111
High-malignancy	B3	13/38	7.77 [1.01; 59.56]	0.048	14/38	14.68 [3.31; 65.12]	< 0.001
	C	4/12	13.23 [1.46; 119.76]	0.022	4/12	16.68 [3.02; 92.00]	0.001
Low-malignancy		58/250	1		31/250	1	
High-malignancy		17/50	3.32 [1.89; 5.82]	< 0.001	18/50	6.18 [3.34; 11.44]	< 0.001

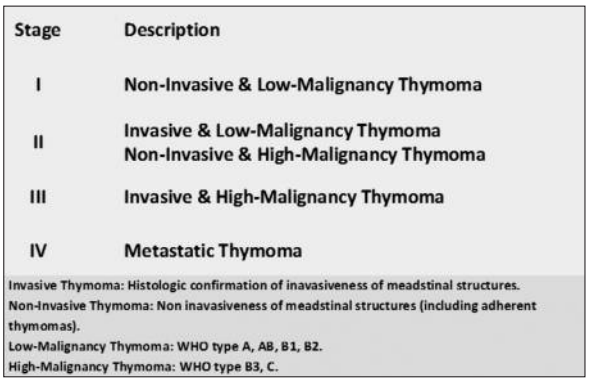

Figure 3. Graphical description of the "Integrated" thymoma classification.

clustered into one group of tumours characterized by low malignancy, while histotypes B3 and C formed one cluster of high malignancy, the latter showing a much worse prognosis than the former (HR_{LTS} = 3.32 [1.89; 5.82], $p < 0.001$; HR_{DFS} = 6.18 [3.34; 11.44], $p < 0.001$).

"Integrated" Prognostic Classification

Considering both tumour invasiveness (non-invasive/invasive) and malignancy (low/high-malignancy), a post-surgical 4-class prognostic grading ("integrated classification") was defined as it follows (see also graphical description in Figure 3):

Class I: non-invasive and low-malignancy tumours;
Class II: non-invasive and high-malignancy tumours or invasive and low-malignancy tumours;
Class III: invasive and high-malignancy tumours;
Class IV: all metastatic tumours

The cross-matched distribution of the study subjects by the characteristics of thymomas and classes of this classification is reported in Table IV. LTS and DFS trends are shown in Figure 4. From the Cox regression analysis (Table V) significant differences emerged in LTS and DFS starting from Class-II (Stage-II: HR_{LTS}: 2.47 [1.37; 4.47], $p = 0.003$; HR_{DFS}: 7.12 [3.32; 15.27], $p < 0.001$). None of these HRs changed when the presence of neurological para-neoplastic syndrome was included in the regression models. The distribution of subjects according to the Masaoka classification and the "integrated classification" (with a class-migration effect) is reported in Table V.

Table IV. Cross-matched distribution of the study subjects by tumor invasiveness, tumor malignancy and by "Integrated" thymoma classification.

Tumor malignancy →	Invasiveness ↓	Integrated classification							
		Class I		Class II		Class III		Class IV	
		Low	High	Low	High	Low	High	Low	High
Non-invasive	No capsule infiltration	99 (57%)	0	0	3 (5%)	0	0	0	0
	Capsule infiltration	19 (11%)	0	0	1 (2%)	0	0	0	0
	Fat infiltration	13 (8%)	0	0	4 (7%)	0	0	0	0
	Pleura adherence	26 (15%)	0	0	3 (5%)	0	0	0	0
	Pericardium adherence	6 (3%)	0	0	4 (7%)	0	0	0	0
	Pleura and pericardium	10 (6%)	0	0	2 (4%)	0	0	0	0
Invasive	Parenchyma adherence	0	0	4 (7%)	0	0	2 (9%)	0	0
	Pleura infiltration	0	0	7 (13%)	0	0	5 (24%)	0	0
	Pericardium infiltration	0	0	2 (4%)	0	0	1 (5%)	0	0
	Parenchyma infiltration	0	0	6 (11%)	0	0	3 (14%)	0	0
	Pleura/pericardium adherence and pleura/ pericardium infiltration	0	0	3 (5%)	0	0	4 (19%)	0	0
	Pleura and pericardium infiltration	0	0	17 (30%)	0	0	6 (29%)	0	0
Metastatic tumors	≥ 1 metastases	0	0	0	0	0	0	2 (29%)	5 (71%)

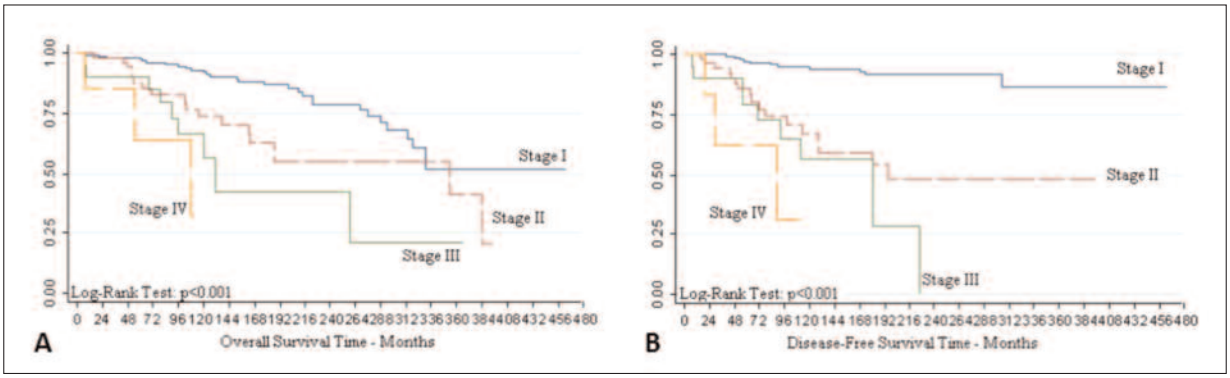

Figure 4. Overall *(A)* and disease-free *(B)* survival Kaplan-Meier curves by the "integrated" thymoma classification.

Diagnostic Assessment

The "goodness of fit" of the Cox models for the LTS and the DFS, regressing the Masaoka classification and the "integrated classification" separately, seemed comparable according to the coincidence of the Nelson-Aalen cumulative hazard curves with the Cox-Snell residual curves (figures not shown). However, the Harrell's C-coefficient, that measures the proportion of pairs of subjects in which the predictions obtained from the fitted model are concordant with the observed proportions, suggested that the model fitting the "integrated classification" was preferable (Masaoka-staging: Harrell's C_{LTS} = 0.6445, Harrell's C_{DFS} = 0.7644; "integrated classification": Harrell's C_{LTS} = 0.6791, Harrell's C_{DFS} = 0.7617). As data show, the concordance is always higher in the model fitting the "integrated classification".

Additional Analyses

Myasthenia Gravis (MG)

The Cox-regression analysis estimated statistically significant HRs for both LTS and DFS (Non-MG vs MG - HR_{LTS}: 3.54[1.76; 7.14], $p < 0.001$; HR_{DFS}: 3.04 [1.43; 6.47], $p = 0.004$).

Although MG had a strong impact on patients' outcome, when a multivariable Cox-re-

Table V. Hazards for overall mortality and recurrence by WHO classification and tumor malignancy. Results from the Cox-Regression-Analysis.

	Overall mortality (N = 305)			Disease recurrence (N = 305)		
	D/N	HR [95% CI]	*p* value	R/N	HR [95% CI]	*p* value
Integrated classification						
Class I	29/173		1	11/173		1
Class II	18/56	2.47 [1.37; 4.47]	0.003	17/56	7.12 [3.32; 15.27]	< 0.001
Class III	9/21	4.18 [1.96; 8.90]	< 0.001	9/21	11.47 [4.67; 28.16]	< 0.001
Class IV	3/7	10.37 [3.02; 35.56]	< 0.001	3/7	21.76 [5.85; 80.87]	< 0.001

Distribution of subjects according to the Masaoka-classification and by the "integrated thymoma classification"

		Integrated classification			
		Class I	Class-II	Class-III	Class IV
Masaoka classification	Stage I	103	55	15	0
	Stage II	4	13	38	0
	Stage III	0	5	16	0
	Stage IV	0	0	0	7

gression analysis, including major prognostic predictors was performed, its impact lost statistical significance and, therefore, it was not considered in the formulation of the "integrated classification".

Truncated LTS and DFS Analysis

The Masaoka classification and the "integrated classification" were compared with respect to LTS and DFS after follow-up time was truncated at 5, 10, 20 and 30 years from surgery, and HRs estimated at each time-point. The results of this analysis (data not showed) confirmed the pattern showed by non-truncated data, with a substantial non-distinction of Stage I and II in the Masaoka classification and a significant distinction already at 5 yr in the "integrated" thymoma classification (HR: 4.26 [0.44; 40.97], n.s. for Masaoka; HR: 6.33 [1.58; 25.32], $p = 0.009$ for "integrated classification").

Disease-Specific LTS

When comparing Masaoka and the "integrated classification" for thymoma-specific mortality, the HRs for Stage I vs II were 3.55 [0.36; 18.17] $p = 0.351$ for Masaoka and 3.14 [0.84; 11.80], $p = 0.089$ for Class I vs II of "integrated classification"; for StageI vs III these were 8.41[1.83; 38.59], $p = 0.006$ for Masaoka and 9.73 [2.49; 37.94], $p = 0.001$ for the "integrated classification"; for Stage I vs IV:33.16 [4.24; 259.33], $p = 0.001$ for Masaoka and 22.86 [3.67; 142.23], $p = 0.001$ for the "integrated classification".

Discussion

Many classifications have been described for thymoma[2,21,22]. Actually only two classifications reached a general consensus: the WHO histological system[1,2] and the anatomical Masaoka-Koga staging[3,4].

Recently, the WHO classification was not confirmed to have *per se* an accurate prognostic predictability. In particular, recent findings have demonstrated the same genetic background pattern and outcome in type A-AB, B1-B2 and B3-C thymomas[23], thus providing some of the rationale of recent recommendations for a histological re-classification.

Similarly, the prognostic role Masaoka classification has been almost reconsidered on the light of the results of more recent surgical series[7,24] and a meta-analysis focused on its predictive power/accuracy[25]; in details, the Masaoka staging is weak in shaping a proper (sharper) stage differentiation, in particular between stages I and II (Cox Regression: $p = 0.932$). On the other hand, the WHO-Histotypes A, AB, B1 and B2 did not differ greatly, while the distinction between types A-AB-B1-B2 and types B3-C was statistically significant (Cox-Regression: $p < 0.001$).

Our analysis, conducted on one of the largest monocentric series reported so far in the English literature (to the best of our knowledge), have evaluated an "integrated" post-surgical prognostic grading that takes into account the WHO-histology and the degree of severity of the invasiveness in CR-R0 thymoma patients. The integration of all aspects defined by both systems seems to allow a better discrimination between classes, if compared to that achievable with the Masaoka and WHO-classifications taken separately.

The level of predictive accuracy of such prognostic grading, and a sharper distinction among stage I and II, this benchmarked on overall mortality (Cox-Regression: $p = 0.003$) and risk of recurrence (Cox-Regression: $p < 0.001$), provide a strong indication for a deeper investigation about the role of adjuvant therapy in Masaoka stage-II thymomas. Future research should be conducted in order to investigate: (1) the prognostic differences of these two groups; (2) the proposition of a distinction in stage IIA and IIB; (3) the indications for adjuvant therapy in each of these two sub-stages.

Our report has the usual limitations of retrospective mono-centric studies on large clinical series: the long duration of patients inclusion and, despite adopting a method as accurate as possible, a certain degree of incompleteness of data. Albeit the awareness of the biases resulting from this, our policy adopted in the planning of this analysis has been to best preserve the reliability of the collected data, defining as "missing data" those ambiguous or not certain information. Finally, as reported above, only completely resected thymoma patients were included in the present analysis. Accordingly, the aim of this study is to better define (in a large long-term mono-centric clinical setting) the prognosis of thymoma patients after complete resection adopting a new approach, consisting in the integration of clinical and surgical variables with pathological ones.

Conclusions

Thymoma prognosis is a multifactorial entity: histology, degree of invasiveness severity, and their inter-dependence might all have a role in predicting the clinical behavior of these tumours and, thus, the clinical outcome, in spite of the best therapy provided. According with our results, we may assume that a new approach based on the integration of both the WHO histology and the degree of invasiveness severity should be taking into account when formulating the forthcoming thymoma classifications.

Indeed, although an accurate validation on large series of patients is mandatory, such "integrated classification" seems to have a promising accurate predictive power with regards to prognosis in completely resected thymoma patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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