Thymic Epithelial Tumors: Prognostic Significance and Relationship between Histology and the New TNM Staging System

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Abstract

Background This study aims to describe the relationship between the new tumor nodes metastasis (TNM) staging and World Health Organization (WHO) classification and to identify how these two variables relate to each other and whether they possess a prognostic value in predicting survival and recurrence of disease.

Methods Medical records of 54 patients who underwent surgery for thymic epithelial tumors between 1996 and 2015 were reviewed.

The histologic type of neoplasm was classified according to the criteria of WHO and staging was evaluated using the new TNM classification system.

Results A significant correlation between the TNM stages and the histological classification was found ($p < 0.001$). Complete resection is related to both TNM stage and histological grading ($p < 0.001$). Evaluation of the 5- and 10-year survival curves shows how these are significantly correlated only at the stage ($p = 0.03$ and $= 0.04$, respectively). The risk of death at 5 and 10 years for stages III to IV is six and three times higher than in stages I to II, respectively. Regarding the disease-free survival, there is significant correlation with both staging and histology ($p = 0.001$ and $= 0.02$, respectively).

Conclusions There is a significant correlation between the new TNM staging and the histological grade WHO. The ability to implement a complete resection, the overall and disease-free survival is closely related to the thymoma stage. Furthermore, both histotype and stage correlate with disease-free survival. In fact, the least aggressive stages, both WHO and TNM, have a free time out of disease superior to advanced stages.

Keywords
- thymoma
- surgery
- pathology
- mediastinal tumor
- prognosis

Introduction

Thymoma is the most common mediastinal neoplasm in adults accounting for 50% of all mediastinal neoplasms. However, it can be considered a rare disease with an incidence of 3/1,000,000 inhabitants per year.[1] It is well known for its heterogeneous oncology behavior, variability in histological appearance, and association with autoimmune diseases, the most common of them being myasthenia gravis (MG). A new staging for thymoma was proposed in 2014 and subsequently published in the eighth edition of the tumor nodes metastasis (TNM) classification of malignant

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tumors.[2,3] This study aims to describe the correlation between the new TNM staging and the World Health Organization (WHO) classification and to identify, through regression models, how these two variables relate to each other and whether they have a prognostic value in predicting survival and recurrence of disease.

Methods

Patients

The study was conducted in Ferrara University hospital, which is a tertiary center for thoracic surgery. All patients receiving surgery with curative intent for thymoma at our department between January 1995 and December 2016 were identified using the institution's database. A retrospective analysis of these patients' records was performed.

Therefore, patients with definitive histological diagnosis of thymic carcinoma, thymic carcinoid, thymic hyperplasia, thymolipoma, primary thymic lymphoma, or thymic cyst were excluded from the study. Patients who received nonsurgical treatments were also excluded. Preoperative assessment in a patient with a suspected thymoma includes routine blood tests, electrocardiography, pulmonary function tests and arterial blood gas analysis, computed tomography scan of the chest and upper abdomen, neurologic consultation in case of associated MG, and chest magnetic resonance imaging in selected cases. Comorbidities and postoperative complications were defined according Charlson Comorbidity Index score.[4] Ethical approval for this study was sought and obtained from the local ethic committee.

Histological and Clinical-Pathological Staging

The histologic type of neoplasm was classified according to WHO 1999 criteria, updated in 2004.[5,6] All samples were reclassified according to the most recent 2004 criteria. The tumor stage was determined according to the new TNM classification system.[2,3] Myasthenic patients were divided into five stages, depending on muscular involvement and symptom severity, following the guidelines of the Medical Scientific Advisory Board of the MGFA.[7]

Surgical Treatment

Surgery included resection of the thymoma, always associated with total thymectomy. Extended resections were performed in cases of gross involvement of surrounding organs including mediastinal pleura, lung, pericardium, and superior vena cava. Where radical resection (R0) was not possible because of the invasiveness of the tumor, the resection was defined incomplete (R1). Surgical approaches included median sternotomy, thoracotomy, clamshell incision, and video-assisted thoracoscopic surgery (VATS). The choice of technique was accomplished in relation to age, clinical condition of the patient, size, and invasiveness of the neoplasm found both preoperatively and surgically.

Statistical Analysis

For categorical variables, absolute and percentage frequencies are reported, while for numeric variables average and standard deviation are reported. The graphic description was made using bar graphs and pie charts. The comparison between groups was performed using *t*-test for numeric variables, while for categorical variables Pearson chi-square test or, in case of low number, the exact Fisher's exact test was adopted. Overall survival (OS) and disease-free survival (DFS) defined as freedom from recurrence in case of complete resection (R0) or as time-to-progression in case of incomplete recurrence (R1–R2) were calculated from the day of surgery. For survival analysis, time was calculated in months, from the date of thymectomy until the date of death for reasons related to thymic neoplasia or other causes. The disease-free follow-up, expressed in months, was evaluated over the 10 years after surgery. Survival analysis was undertaken using the Kaplan–Meier method. The comparison between groups was evaluated using the Cox regression model by reporting its hazard ratio (HR) and *p* value.

Results

Clinical

►**Table 1** illustrates the patients' characteristics. Our cohort included 54 patients, 27 women, and 27 men with a mean age at the time of surgery was 60.8 years (range, 23–84 years). Twenty patients (37.04%) presented with MG and their mean age was 59 years (range, 30 and 83 years). Thirty-five patients (64.8%) had the following onset symptoms: two (5.7%) patients with pneumonia, three (8.6%) with retrosternal pain, six (17.1%) with cough, one with dyspnea (2.9%), one with mediastinal syndrome (2.9%), two with pleural effusion (5.7%), and twenty patients (57.1%) with myasthenic symptoms. The mean Charlson Comorbidity Index was of 4.7, ranging between 2 and 13.

Table 1 Clinical characteristics of patients

	Number	%
Male/female	27/27	50/50%
Average age (range)	60.8 (23–84)	–
Myasthenic	20	37%
Onset symptoms		
Asymptomatic	19	35.2%
Symptomatic	35	64.8%
Myasthenia	20	57.1%
Cough	6	17.1%
Retrosternal pain	3	8.6%
Pneumonia	2	5.7%
Pleural effusion	2	5.7%
Dyspnea	1	2.9%
Mediastinal syndrome	1	2.9%
Charlson Comorbidity Index average (range)	4.7 (2–13)	–

Surgical Approach

Twenty-two (40.7%) thymectomies were performed using thoracoscopic approach and 32 (59.3%) cases underwent open procedures with the following surgical approaches: 5 clamshells (9.3%), 10 thoracotomies (18.5%), and 17 median sternotomies (31.5%), including 2 VATS (3.7%) thymectomies were converted to thoracotomy.

Complete resection (R0) was achieved in 43 (79.63%) patients; the remaining 11 cases (20.37%) underwent partial resection (R1).

Mean operative time was 210 minutes for open procedures and 150 minutes for minimally invasive approaches.

Mean hospital stay was 3 days in case of the mini-invasive procedures, and 9 days for open approaches ($p = 0.027$). It has to be noted that one patient had a 68-day hospital stay without whom the average hospitalization would have been 7 days. In 16 cases, intensive care unit (ICU) stay was required. Twelve of these (75%) received open surgeries. Almost half of myasthenic patients (45.0%, 9/20) required ICU stay.

Correlation between Histology and TNM

On the basis of WHO histological classification, 9 patients (16.7%) were detected with type A thymoma, 14 (25.9%) with type AB, 15 (27.8%) with type B1, 10 (18, 5%) with type B2, and 6 (11.1%) with type B3. Regarding the new TNM staging 37 (68.4%) patients were found at stage I, 1 (1.9%) at stage II, 9 (16.7%) at stage IIIA, 3 (5.6%) at stage IIIB, 4 (7.4%) at stage IVA, and zero patients at stage IVB.

The relationship between the WHO histological type and the new TNM staging is shown in ►**Fig. 1**.

There is an association between staging system and histology ($p = 0.003$), but it is challenging to define recurring groups because for some TNM stages the sample size is too small. TNM stages are divided into two groups: early stages (stage E) made by stages I and II, and advanced stages (stage A) determined by stages IIIA, IIIB, and IV. Stage E consisted of 38 cases (70.4%) and stage A of 16 cases (29.6%). The correlation between early and advanced stages and histological subtypes is shown in ►**Table 2**.

Table 2 Correlation between TNM stages and WHO types

	A	AB	B1	B2	B3
Stages E (I, II)	7	12	13	6	0
Stages A (IIIA, IIIB, IV)	2	2	2	4	6

Abbreviations: TNM, tumor nodes metastasis; WHO, World Health Organization.

Histological subtypes were also subdivided in two groups: Group 1 made by A, AB, B1 and group 2 consisting in types B2 and B3. Group 1 included 38 patients (70.4%) and group 2 16 patients (29.6%).

►**Table 3** shows a significant correlation between histological subtypes and TNM stages with a 78% of global agreement ($p < 0.001$).

Correlation between Masaoka and the 8th Edition of TNM Staging System

►**Table 4** shows the correlation between Masaoka and the new TNM staging system: Masaoka stage II cases only were redistributed in TNM stage I for 8 (80%), stage II (10%), and stage IIIA (10%).

Regression Analysis

►**Table 5** shows the results of the regression model considering TNM staging as the outcome variable: Stage E showed a higher proportion of myasthenic patients ($p = 0.07$) and complete resection (R0) surgeries ($p < 0.001$). The 10-year recurrence rate was 5.6% for stage E and 60% for stage A ($p < 0.001$). The 5-year survival was 94.7% for stage E and 62.6% for stage A as shown in ►**Fig. 2** ($p = 0.002$). The 10-year survival rate was 81.58% for stage E and 62.58% for stage A as shown in ►**Fig. 3** ($p = 0.001$).

►**Table 6** demonstrates the results of the regression model considering WHO histology as the outcome variable: a complete resection (R0) was achieved 94.74% of patients in group 1 and 43.75% in group 2 ($p < 0.001$). In addition, the

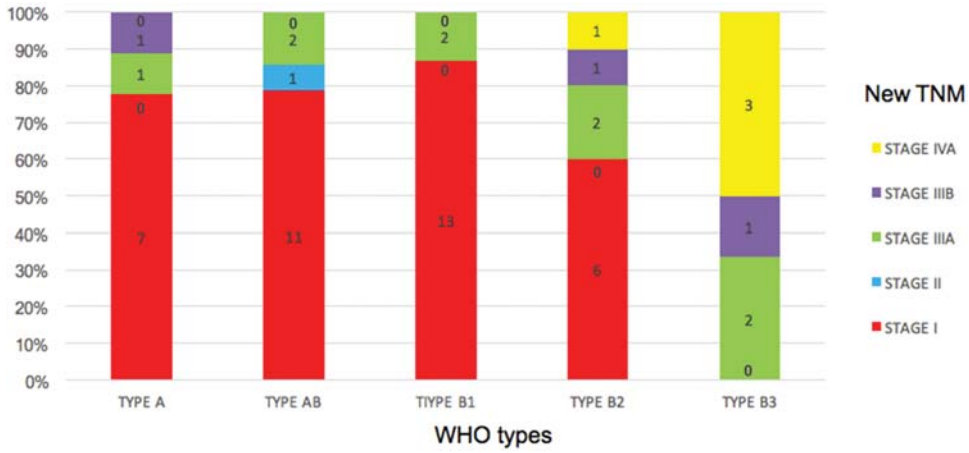

Fig. 1 Histogram representing the relationship between tumor nodes metastasis (TNM) stages and World Health Organization (WHO) types.

Table 3 Relationship between the two WHO groups and the two TNM stages

	Early stages (TNM stages I–II)	Advanced stages (TNM stages III–IV)	*p*-Value
Group 1 (WHO types A, AB, B1)	32	6	<0.001
Group 1 (WHO types B2, B3)	6	10	<0.001

Abbreviations: TNM, tumor nodes metastasis; WHO, World Health Organization.

Table 4 Correlation between TNM and Masaoka stages

	Stage I	Stage II	Stage IIIA	Stage IIIB	Stage IV
Masaoka I	29	0	0	0	0
Masaoka IIA	7	0	1	0	0
Masaoka IIB	1	1	0	0	0
Masaoka III	0	0	8	3	0
Masaoka IVA	0	0	0	0	4

Abbreviation: TNM, tumor nodes metastasis.

recurrence was found in 10.53% of cases of group 1 and 46.67% of group 2 ($p = 0.003$).

The survival at 5 and 10 years was 92.11 and 76.32%, respectively, for group 1; while in group 2 it was 68.75% at 5 years and 50% at 10 years ($p = 0.03$ and 0.057, respectively) (►**Table 6**; ►**Figs. 2** and **3**).

Survival Analysis

Overall 5- and 10-year survival was 85.2 and at 75.9%, respectively. When stratified by stage and histology, a significant 5-year OS difference was observed in stage E and A patients ($p = 0.015$) but in histological subgroups (►**Fig. 2**), the probability of death at 5 years for stage A patients was approximately seven times higher than for stage E patients (HR = 7.62). This value was corrected with possible confounding factors. For all the corrections made in this study (age, gender, MG, radicality, Charlson Comorbidity Index), only the Charlson Comorbidity Index was found related to survival and recurrence, so it was the only factor taken into account to adjust the results. We found that stage only was a 5-year OS strong independent prognostic factor (p value corrected = 0.034) and the HR resulted to be 6.44.

►**Fig. 3** illustrated 10-year survival analysis: a significant correlation with stage only ($p = 0.002$) was found. The adjusted 10-year OS analysis showed that stage is a strong independent prognostic factor ($p = 0.044$). Stage A patients have a 10-year death probability which is three times higher than stage E patients (HR = 3.15).

►**Fig. 4** shows survival analysis using DFS as a measure of outcome: a significant relationship with both histology ($p = 0.005$) and stage (<0.001) was identified. After the correction of the results, the relationship remained significant. Group 2 had a risk of recurrence 10 years, which was five times higher than group 1 (HR = 4.89 and $p = 0.021$). Stage A is likely to have recurrence 15 times higher than stage E (HR = 15.18 and $p = 0.001$).

Discussion

In 2014, a new staging for thymoma was proposed, which was subsequently published in 2016 in the eighth edition of the TNM classification of malignant tumors.[2,3] There are no studies in literature analyzing the correlation between the new staging system with other variables such as the WHO histotypes and MG. The main objective of this study was to evaluate the correlation between the new TNM staging system and histological WHO classification. Another goal of this study was to analyze how these two elements interrelate one another in terms of clinical presentation and the long-term outcome. Different studies have been published to

Table 5 Relationship between TNM stage and other variables

	Stage E	Stage A	*p*-Value
Average age (±SD)	61.6 (±12.47)	58.9 (±15.5)	0.50
Sex M/F	18/20 (47.37/52.63%)	9/7 (56.25/43.75%)	0.55
Myasthenic	17 (85%)	3 (15%)	0.07
Charlson Comorbidity Index average (±SD)	4.2 (±1.4)	5.9 (±3)	0.03
Surgery VATS/open	18/20 (47.37/53.63%)	4/12 (25/75%)	0.002
R0/R1	38/0 (100/0%)	11/5 (68.75/31.25%)	<0.001
Recurrence yes/no	2/36(5.26/94.74)	9/6 (60/40%)	<0.001
Death at 5 years yes/no	2/36 (5.26/94.74%)	6/10 (37.5/62.58%)	0.002
Death at 10 years yes/no	7/31 (18.42/81.58%)	6/10 (37.5/62.58%)	0.001

Abbreviations: SD, standard deviation; TNM, tumor nodes metastasis; VATS, video-assisted thoracoscopic surgery.
Note: Regression model considering TNM staging as the outcome variable.

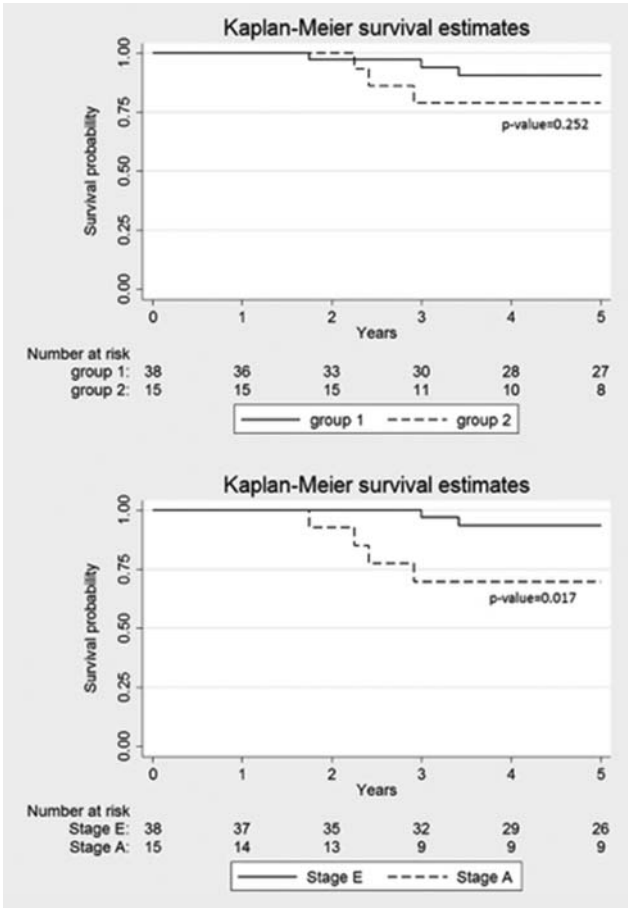

Fig. 2 Five-year adjusted survival curves.

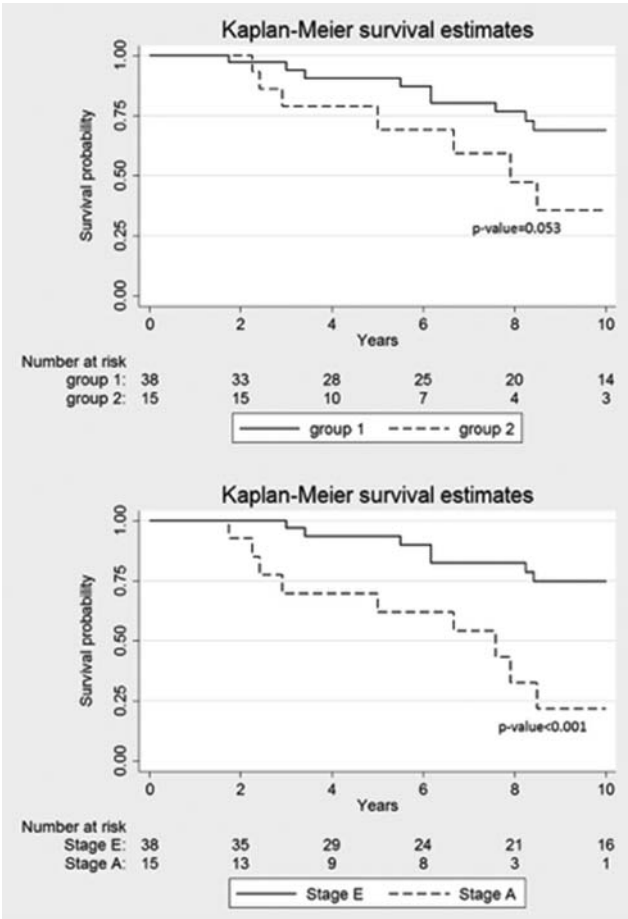

Fig. 3 Ten-year adjusted survival curves.

Table 6 Relationship between WHO groups and other variables

	Group 1	Group 2	*p*-Value
Average age (±SD	59.7 (±13.9)	63.6 (±12.1)	0.03
Sex M/F	21/17 (55.26/44.74%)	6/10 (37.5/62.5%)	0.23
Myasthenic	15 (75%)	5 (25%)	0.57
Charlson Comorbidity Index average (±SD)	4.1 (±1.5)	6.1 (± 2.7)	0.005
Surgery VATS/open	17/21 (44.74/55.26%)	5/11 (31.25/68.75%)	–
R0/R1	36/2 (94.74/5.26%)	7/9 (43.75/56.25%)	<0.001
Recurrence yes/no	4/34 (10.53/89.47%)	7/8 (46.67/53.33%)	0.003
Death at 5 years yes/no	3/35 (7.89/92.11%)	5/11 (31.25/68.75%)	0.03
Death at 10 years yes/no	9/29 (23.68/76.32%)	8/8 (50/50%)	0.057

Abbreviations: SD, standard deviation; VATS, video-assisted thoracoscopic surgery; WHO, World Health Organization.
Note: Regression model considering WHO histology as the outcome variable.

evaluate the prognostic role of WHO classification with conflicting results.[8–10] Although most authors showed trend toward a survival decrement proceeding from A to B3 histotypes, there is still no clear evidence of the histologic subgroups impact on outcome.[11,12] The results indicate that there is a significant correlation between the new TNM staging and the histological grade WHO: stages I and II are more frequently associated with histologic groups A, AB, and B1, as well as stages III and IV are more associated with groups B2 and B3. It can also be seen how the percentage of stages III and IV is much higher in B2 than A, AB, and B1, reaching 100% in B3. We can, therefore, define that histologic degrees B2 and B3 are closely associated with stages III and IV of the new TNM staging.

These results may have important clinical repercussions: in the case of preoperative diagnosis of thymoma type B2 and B3, neoadjuvant treatments may increase the full resection rate, according to Lucchi and Gregory.[13,14] In addition, patients with

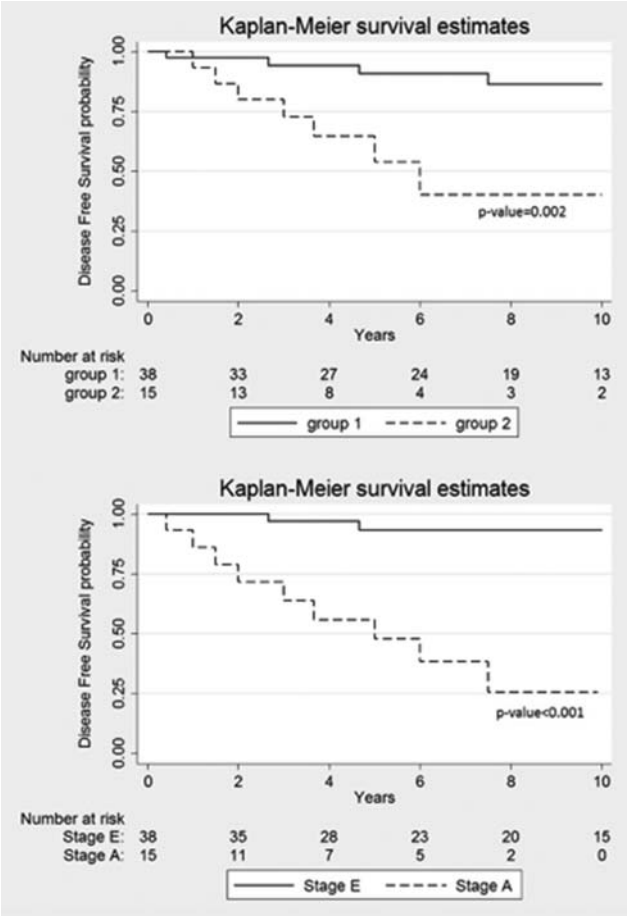

Fig. 4 Disease-free adjusted survival curves.

definitive diagnosis of type B2 or B3 thymoma, even in the case of complete resection, may be eligible for adjuvant treatments. In fact, the clinical practice guidelines of the European Society for Medical Oncology suggest considering both stage and histology in the evaluation of postoperative radiotherapy treatment.[15] Further prospective studies are required to confirm this preliminary data in the future.

Margaritora et al[16] found a significant survival advantage in thymoma patients with MG both in terms of OS and DFS; however, they pointed out no correlation between stage and MG. In our study, MG is a positive predictive factor of survival ($p = 0.07$): it is more frequent in stages I and II thymomas (17 cases), and rare in stages III and IV (only 3 cases). This association was also reported by other authors[17,18] and in our opinion could be explained by the stricter and prompt radiological examination performed on every myasthenic patients to exclude thymic disease.[19]

In literature, it is widely documented that the possibility of performing a complete resection is one of the most important prognostic factors influencing survival.[20,21] Not surprisingly, in our study the impact of the extent of surgical resection on outcome was confirmed: this was achieved in 100% of cases at early stages and in 69% of invasive stages, as reported by Detterbeck et al.[2] Furthermore, the possibility of performing a complete resection is statistically different between the two histological groups with a possibility to achieve a 95% radical resection in groups A, AB, and B1 and 44% in the B2 and B3 groups.

Our study also shows how stage and histological grading are an important prognostic factor for DFS. There is a significant difference between early stages and invasive stages, as well as between groups A, AB, B1, and groups B2 and B3. In stages III and IV, the 10-year recurrence rate was 60% and patients affected by B2 and B3 thymomas have a five times higher risk of recurrence than patients with A, AB, and B1 histotypes. We also highlighted that patients with invasive stages have risk of relapse at 10 years 15 times higher than early stages. The eighth edition thymic stage classification provides different advantages: it focuses on invasion of adjacent structures and therefore it reflects the ability to resect thymic malignancies and survival.[22] The association between histology and outcome could have important clinical consequences: it could justify stricter follow-up programs for patients with histopathologic diagnosis B2 or B3.

Several studies reported the role of open and thoracoscopic approach in terms of survival.[23] In the present study, comparing the data concerning the possible surgical approaches (open and mini-invasive), for stage and grading, it was found that the open approach has been used in the majority of cases. The percentages of use of this technique increase with increasing TNM stage (53% in early stages and 75% in advanced stages). However, it is important to point out that the mini-invasive approach significantly reduces the average time of the intervention (150 minutes) compared with the open technique (210 minutes) and also dramatically reduces the average stay time (3 vs 9 days).

Limitations

This investigation represents a single institution's experience, the cohort of patients was assessed retrospectively, and we acknowledge that there is inherent bias associated with this approach.

Conclusion

Our study shows that there is a correlation between the two WHO groups and the two TNM groups. MG is more frequently associated with early stage tumors. The ability to implement a full resection, the rate of recurrence, and survival are closely related to the thymoma stage. It also shows how both histotype and stage correlate with DFS. In fact, the least aggressive stages, both WHO and TNM, have a disease-free time superior to advanced stages.

Conflict of Interest
None.

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