Modified Masaoka Stage and Size Are Independent Prognostic Predictors in Thymoma and Modified Masaoka Stage Is Superior to Histopathologic Classifications

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Introduction: The prognostic value of histopathologic classifications of thymoma is debated. Problematic reproducibility might cause this controversy. We studied the prognostic significance of three histopathologic classifications of thymomas after three thoracic pathologists agreed upon thymoma subtype and invasion. We also compared the outcome to established prognostic parameters.

Methods: Patients, surgically treated for thymic epithelial neoplasm at Mayo Clinic (1942–2008), were staged according to the modified Masaoka staging and the recently proposed staging by Moran. Three thoracic pathologists independently classified all cases according to the World Health Organization, Bernatz, and proposed Suster and Moran classification. Only thymoma that all three pathologists diagnosed as the same histopathologic subtype and extent of invasion were included in outcome analysis.

Results: In 214 (proposed Suster and Moran classification), 145 (World Health Organization classification), and 120 cases (Bernatz classification), reviewers agreed upon subtype of thymoma and invasion and follow-up was available. Median follow-up time was 7.5–7.7 years (range between classifications). All histopathologic classifications were associated with overall survival (OS) and disease-free survival ($p \leq 0.0001$ to $p = 0.048$); only Bernatz classification was independent of modified Masaoka staging associated with OS ($p = 0.04$). Modified Masaoka stage predicted outcome independent of all histopathologic classifications and resection status and strongly correlated with the proposed Moran stage (correlation coefficient, 0.95). Thymoma size and age were prognostic parameters for OS independent of any histopathologic classification.

Conclusions: Histopathologic classifications of thymomas are associated with prognosis but are in general not independent predictors of outcome. Modified Masaoka stage and proposed Moran staging are independent prognostic parameters for thymoma and superior to histopathologic classifications.

Modified Masaoka staging and complete resection consistently have been shown to predict prognosis in thymoma.[1–5] Recently, Moran et al.[6] also proposed a staging system for thymoma and showed correlation with outcome. Although currently the World Health Organization (WHO) classification is used for the morphologic classification of thymomas, several histological classifications have been proposed and used in the past; however, their prognostic significance and ability to guide further treatment have been controversial.

Evidence suggests that histopathologic reproducibility of thymomas might be problematic with only moderate to substantial interobserver agreement for the WHO classification with reported κ values of 0.45–0.65[7–9]; only one study achieved good agreement using a weighted κ ($\kappa = 0.87$).[10] Moreover, in an analysis of 456 patients, we recently demonstrated that the interobserver variability in the classification of the histologic type using the current WHO classification,[11] the classification by Bernatz[12] and the previously proposed classification by Suster and Moran (S&M)[13] affects the prognostic value of the histologic classification.[9] In addition, Zucali et al.[7] showed that problematic reproducibility of the morphologic classification of thymomas has some effect on patient management. Furthermore, although thymomas are considered malignant, patients usually have a favorable prognosis. Therefore, long-term follow-up is essential for outcome studies. Moreover, studies have been limited by a relative low incidence of thymomas. These difficulties might explain, at least in part, the variable prognostic results for histologic classifications. To exclude the effect of interobserver variability, in this study, we focused only on cases in which three thoracic pathologists independently agreed upon histologic type and invasion. Thus, this represents an idealized cohort which is perhaps not directly applicable to routine clinical care, but provides a mean to assess the innate predictive capacity of several histologic classifications and staging systems. We studied the prognostic value of clinical features and histopathologic

classifications including the current WHO classification, the classification by Bernatz, and the proposed S&M classification in thymomas that were independently classified as the same subtype by three thoracic pathologists. We also compared the prognostic value of clinicopathologic staging systems such as modified Masaoka stage and the staging system that was recently proposed by Moran and clinical parameter to identify important prognostic features of thymomas.

PATIENTS AND METHODS

Patients

All cases from patients who underwent surgery for thymic epithelial neoplasm at Mayo Clinic between 1942 and 2008 were collected (these patients are part of a previously reported patient population).[9] In our database, we only included patients until 2008 to allow for a reasonable follow-up time. Medical records were studied including the surgical reports. Tumor size was measured at time of gross examination of the specimen. Tumor size was used in complete and incomplete resection specimens but not biopsies. Based on microscopic assessment of invasion and extent of tumor as described in the surgical report, patients were staged according to the modified Masaoka staging and the recently proposed staging by Moran et al. as previously summarized.[9]

The Institutional Review Board of Mayo Clinic Rochester approved the study (IRB# 08-003478).

Histopathologic Classification

All cases were reviewed by three thoracic pathologists (ACR, ESY, MCA), who were blinded to outcome and independently classified thymomas according to the current WHO classification, the Bernatz classification and the proposed S&M classification as previously summarized.[9]

If more than one subtype was present, the predominant subtype was used for analysis. Any case that was thought to be thymic carcinoma by one or more reviewers was excluded from the study.

Invasion was categorized according to the current WHO classification as recently summarized.[9]

Only thymomas that were diagnosed as the same histologic subtype and same extent of invasion by all three reviewers were included in outcome analysis.

Statistical Analysis

The Pearson correlation coefficient was calculated to measure the association between modified Masaoka and proposed Moran staging (considering them continuously).

Two types of survival analyses were conducted: Overall survival (OS) and disease-free survival (DFS). Survival curves were estimated using the Kaplan–Meier method and were compared across categorical predictors using log-rank tests. The 5-year survival estimates were calculated using the Kaplan–Meier method. Univariate associations among patient characteristics, histopathologic classifications, and staging with outcome (OS and DFS) were assessed with Cox proportional hazards regression models. Multivariable Cox proportional hazards regression was used to estimate the overall effects of each staging type and

histopathologic classification, adjusted for additional characteristics (age, weight loss at presentation, thymoma size, resection status, and modified Masaoka stage). Hazard ratios and 95% confidence intervals (CI) were reported. Harrell's c-index was used as a measure of the predictive accuracy for each model.[14] The c-index can range from 0 to 1, and larger values indicate better predictability from the model; a value of 0.5 indicates that the model does no better than chance alone.

All analyses were performed using SAS version 9 (Cary, NC). All p values reported are unadjusted for multiple testing so the reader may interpret at his or her own discretion. Overall p values less than 0.05 were considered statistically significant. Furthermore, pairwise comparisons (i.e., comparing between WHO subtypes) were regarded as statistically significant if the p value was less than 0.05 divided by the number of possible comparisons (Bonferroni).

RESULTS

All three reviewers agreed upon a diagnosis of thymoma in 413 cases (of 456). Figure 1 presents numbers of reviewed thymomas, histopathologic agreement, available follow-up, and statistically analyzed cases. A median of three slides per tumor (range, 1–32) was available for review, correspondent to a median of 0.5 slides per cm tumor. The clinical characteristics of the patients are summarized in Table 1. Follow-up was available in 376 patients. The overall 5-year DFS estimate was 91.7% (95% CI: 88.6%–94.9%); the OS estimate was 75.8% (95% CI: 71.2%–80.4%). The median survival estimate could not be calculated as the median was never reached (too few events).

Table 2 summarizes the outcome of patients with thymoma by morphologic classification. The median follow-up time and 5-year DFS and OS estimates are similar between the histopathologic classifications.

WHO, Bernatz, and Proposed Suster & Moran Classifications Are of Prognostic Significance for Thymoma but Only Bernatz Classification Is Independent of Modified Masaoka Stage

In univariate analysis, all three studied histopathologic classifications are significantly associated with OS and DFS (Table 3). Kaplan–Meier curves for OS are illustrated
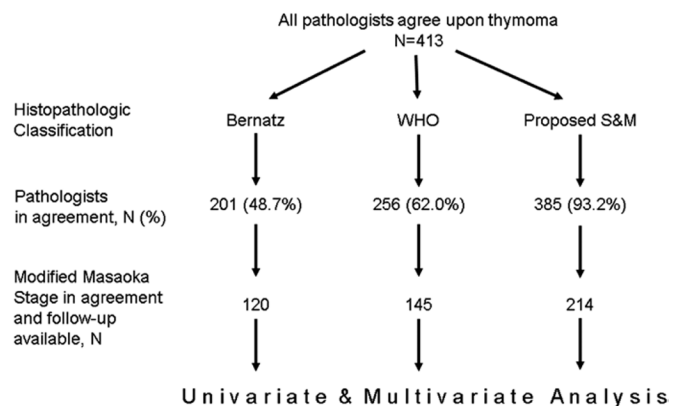

FIGURE 1. Numbers of reviewed thymomas, morphologic agreement, available follow-up, and statistically analyzed cases.