ORIGINAL ARTICLE

Assessment of the ITMIG Statement on the WHO Histological Classification and of the Eighth TNM Staging of Thymic Epithelial Tumors of a Series of 188 Thymic Epithelial Tumors

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Received 17 September 2016; revised 18 June 2017; accepted 29 June 2017
Available online - 7 July 2017

ABSTRACT

Introduction: Thymic epithelial tumors (TETs) are rare intrathoracic malignancies that are categorized histologically according to the WHO classification, which was recently updated in 2015 on the basis of a consensus statement of the International Thymic Malignancy Interest Group (ITMIG); at the same time, the standard Masaoka-Koga staging system is scheduled to be replaced by the eighth edition of the TNM staging classification by the American Joint Committee on Cancer/Union for International Cancer Control consortium. Our objectives were to analyze the feasibility of assessing ITMIG consensus major and minor morphological and immunohistochemical criteria and the eighth edition of the TNM staging classification in a routine practice setting.

Methods: This is a single-center study conducted at the Louis-Pradel Hospital of Lyon University, one of the largest centers for TETs in France. Overall, a large surgical series of 188 TETs diagnosed in 181 patients between 2000 and 2014 at our center were analyzed.

Results: There were 89 men (49%) and 92 women (51%); 57 patients (31%) presented with myasthenia gravis at time of diagnosis. According to the WHO classification, there were nine type A thymomas (5%), 67 type AB thymomas (36%), 19 type B1 thymomas (10%), 46 type B2 thymomas (24%), 27 type B3 thymomas (14%), and 20 thymic carcinomas (11%). ITMIG consensus major criteria were identified in 100% of type A, AB, B1, and B2 thymomas. After restaging according to the eighth edition of the TNM staging classification, there were 127 stage I (84%), three stage II (2%), 17 stage IIIa (11%), no stage IIIb, two stage IVa (1%), and three stage IVb (2%) thymomas. Significant correlation between histological type and stage at diagnosis was maintained after restaging according the TNM classification.

Conclusion: Comprehensive analysis of our well-characterized surgical series of 188 TETs indicates the feasibility and the diagnostic value of the ITMIG consensus statement on WHO histological classification and highlights the major switch in staging when the eighth edition of the TNM staging classification is applied.

Keywords: Thymoma; Thymic carcinoma; Staging; Classification; Histopathology

Introduction

Thymic epithelial tumors (TETs) are rare intrathoracic malignancies that are categorized histologically according to the WHO classification,[1] which was recently updated in 2015 on the basis of a consensus statement of the

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Drs. Meurgey and Girard contributed equally to this work.

Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2017.06.072

International Thymic Malignancy Interest Group (ITMIG) published in 2014.[2,3] The classification distinguishes thymomas from thymic carcinomas (TCs); thymomas are further subdivided into different types (A, AB, B1, B2, and B3) based on the morphological features of epithelial tumor cells (polygonal or spindle cells), the relative proportion of the nontumoral lymphocytic component (decreasing from type B1 to B3), and resemblance to normal thymic architecture.[1–3] TCs are similar to their extrathymic counterpart, and the most frequent subtype is squamous cell carcinoma. Although the interobserver reproducibility of the WHO classification has been questioned over time,[4–6] the ITMIG consensus statement proposes major and minor morphological and immunohistochemical (IHC) criteria to better individualize each TET entity; these criteria were defined on the basis of a series of 58 prototypic and difficult-to-classify TETs.[2]

TETs are routinely staged according to the Masaoka-Koga staging system, which is a strong predictor of overall survival (OS).[7–10] Masaoka-Koga staging is a surgical pathology system that is assessable only after surgical resection. A unique feature of TETs is that the WHO classification is correlated with stage at diagnosis, what may explain its reported prognostic value.[1,11,12] The International Association for the Study of Lung Cancer Staging Prognostic Factors Committee, together with ITMIG, recently proposed a TNM-based staging system for thymic malignancies that is based on OS analyses of a retrospective international database of more than 10,000 cases[13]; the proposal was adopted in the eighth TNM staging classification by the American Joint Committee on Cancer/Union for International Cancer Control consortium.[14] In this staging system, all Masaoka stage I and II and some Masaoka stage III TETs are merged with stage I tumors on the basis of their similar prognosis; TNM stage II is defined by pericardium invasion; and TNM stage III tumors are further subdivided into two groups (T3 and T4), aiming at providing more help in formalizing resectability, a major driver of the treatment strategy in advanced TETs.[9,13,14]

Here we took advantage of a surgical series of 188 TETs to (1) analyze the feasibility of assessing ITMIG consensus major and minor morphological and IHC criteria in a routine practice setting and the diagnostic performance of those criteria for TETs histological subtyping and (2) assess the feasibility and relevance of the eighth edition of the TNM staging classification with regard to the Masaoka-Koga staging system.

Material and Methods

Study Design

This study was conducted at the Louis-Pradel Hospital, Hospices Civils de Lyon, a national expert center for the management of TETs that is recognized by the French National Cancer Institute through the appointment in 2012 of RYTHMIC (network for thymic malignancies) network as part of its rare cancer program.

The study consisted of pathological review of 188 TETs, which were diagnosed in 181 patients between January 2000 and December 2014 at our center, to assess histological diagnosis according to the WHO classification,[1,3] ITMIG consensus major and minor criteria,[2] and stage according to Masaoka-Koga[8] and the eighth edition of the TNM staging classification.[14] IHC stainings from the initial assessment and additional stainings were performed as per ITMIG consensus.[2] Review of clinical files was conducted to retrieve patients' characteristics, including preoperative imaging, operative reports, and follow-up.

Pathological Review

Consecutive cases with a diagnosis of TET were selected from the prospective registry of the Pathological Department of Pathology of Louis-Pradel Hospital. From a total of 229 cases, material was available for 195 cases, including 167 cases with nonmixed histological features, and 21 cases with mixed histological features but predominant subtype; seven cases with mixed TET were excluded to avoid complex analysis of histological criteria. Among the 188 cases that were included, 143 cases were from patients operated on in our center, and 45 were cases sent from outside the center for expertise. For patients who underwent surgical or percutaneous biopsy before resection of the tumor, only surgical specimens were reviewed. Pathological review was conducted by two thoracic pathologists, a senior pathologist (L. C.) and a junior pathologist (A. M.), by consensus. Paraffin blocks with formalin-fixed or alcohol, formalin, and acetic acid–fixated tissue and hematoxylin-eosin-saffron slides were available for all cases.

Review of ITMIG Consensus Major and Minor Morphological Criteria

ITMIG consensus major and minor morphological and IHC criteria were defined as per Marx et al.[2] (Supplementary Table 1).

Major criteria were defined as *consistently present* or *consistently absent*; minor criteria were characterized as *typical*, *common*, or *rare*. For type A thymomas, we also searched for an atypical variant showing increased mitotic activity (four or more mitosis per 10 high power fields) and coagulative tumor necrosis. For type A and AB thymomas, the component of immature terminal deoxynucleotidyl transferase (TdT)-positive T cells was quantified in three grades, as per ITMIG consensus.[2]