Editorial

# Editorial on "assessment of the ITMIG statement on the WHO histological classification and of the 8th TNM staging of thymic epithelial tumors, of a series of 188 thymic epithelial tumors"

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Thymic epithelial neoplasms are malignant tumors arising from the thymus that account for 0.2–1.5% of all malignancies but are the most common non-lymphomatous primary neoplasms of the anterior mediastinum (1,2). Because of the rarity of these tumors, which include thymoma, thymic carcinoma, and thymic neuroendocrine neoplasms, much less information regarding optimal detection, staging, and treatment is known when compared to more common thoracic neoplasms such as lung cancer. However, increased interest in the mediastinum, the anatomic region of the thorax located between both lungs, and disease processes that may be found there, particularly thymic epithelial neoplasms, has recently led to greater international collaboration and ultimately resulted in the formation of the International Thymic Malignancy Interest Group (ITMIG). This multidisciplinary organization provides an infrastructure for studying these lesions and, with the formation of an international thymic malignancy database, it is hoped that large-scale multi-institutional studies will continue to advance the scientific knowledge of these tumors (3). Since its inception, ITMIG has crafted and published numerous standards and policy papers, guidelines, and recommendations aimed at addressing specific topics, knowledge gaps, and limitations of existing guidelines, two of the most significant of which include the histologic classification of and the staging system used for thymic epithelial neoplasms.

In September 2014, ITMIG held its fifth annual meeting in Antwerp, Belgium, at which time several proposals were made, including a consensus statement regarding the histologic classification of and a detailed tumor-node-metastasis (TNM) classification and stage grouping for use with thymic epithelial tumors (4). These guidelines were published in a supplement to the *Journal of Thoracic Oncology* and distributed to ITMIG members at the annual meeting. The ITMIG consensus statement on histologic classification was published in 2014 and informed the updated World Health Organization (WHO) classification that was published in 2015 (5,6). In this classification system, thymomas are differentiated from thymic carcinomas, and the former are subdivided into several types (A, AB, B1, B2, and B3) based on features such as epithelial tumor cell morphology (polygonal or spindle cells), proportion of non-tumoral lymphocytic component, and similarity to the architecture of normal thymus (5,6). Previous versions of the WHO classification for thymic epithelial tumors have been criticized and the interobserver reproducibility of the criteria has been questioned (7-9). In order to better individualize each specific thymic epithelial tumor entity, the ITMIG consensus statement introduced major and minor morphological and immunohistochemical criteria defined based on a series of 58 prototypic and difficult-to-classify thymic neoplasms (5).

At least 15 different stage classification systems have been proposed and used in the clinical setting for the management of thymic epithelial tumors. The Masaoka

and Masaoka-Koga staging systems have been most commonly employed, the latter of which has been previously recommended for use by ITMIG. However, these systems were derived from relatively small data sets; for instance, the Masaoka system was crafted from data on 91 patients and the Koga modification was developed from data on only 76 patients (10-12). In many instances, various institutions have interpreted these staging systems and employed them in clinical practice differently, thus limiting effective communication and collaboration in the multidisciplinary setting (13). An official TNM staging system for thymic epithelial neoplasms has recently been accepted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), the organizations responsible for defining stage classifications for tumors, based on the comprehensive analysis of a retrospective database created by ITMIG and the International Association for the Study of Lung Cancer (IASLC) that included more than 10,000 patients (14,15). In this comprehensive staging system, all Masaoka stage I, II, and some stage III thymic epithelial neoplasms are classified as TNM stage I tumors. Other notable stage groupings include TNM stage II, which is determined by pericardial invasion, and TNM stage III, which includes T3 and T4 tumors. These specific groupings are based on similar prognosis and survival data, and in an effort to assist in determining resectability, a major driver of the treatment strategy in advanced thymic epithelial neoplasms (16-18).

ITMIG and IASLC also proposed a lymph node map for use with the TNM staging system that incorporated retrospective data, preexisting lymph node classifications in the IASLC and American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)/American Society for Head and Neck Surgery (ASHNS) lymph node maps, and important lymph nodes defined by prior studies (19-21). In this lymph node map, specific anterior and deep regions are defined based on boundaries that outline the peripheral extent of surgical dissection in all planes, reflecting the technique used for thymic dissection, in which the specimen is removed *en bloc* (2).

Meurgey and colleagues evaluated a cohort of patients with thymic epithelial tumors at a single institution in an effort to determine the feasibility and the relevance for histologic subtyping of the consensus major and minor criteria recently proposed by ITMIG for the WHO classification and the new TNM staging system in a routine practice setting (22). In this study, not only were the updated histologic classification and new staging system feasible, but clinical and pathologic staging revealed the well-established correlation between histologic type and tumor stage is maintained when transitioning from the Masaoka-Koga system to the TNM staging system. It is important to note that the TNM system was constructed around the primary endpoint of overall survival; this is per TNM staging guidelines as for all other non-thymic TNM staged tumors. Some experts, however, have criticized the use of overall survival for thymic epithelial tumors. In contrast to other malignancies, thymic epithelial tumors tend to be less deadly and patients often present with multiple episodes of recurrence, usually requiring multidisciplinary management in the setting of chemo- and radio-sensitive tumors with prolonged survival. In this study by Meurgey and colleagues, WHO histological type and Masaoka-Koga stage, not TNM stage, were significantly associated with time to relapse; thus, the prognostic significance of the TNM staging system requires further validation in larger cohorts.

Although the feasibility of the TNM staging system is demonstrated in this study, several important limitations remain, such as the lack of meaningful information regarding the impact of tumor size and histologic type. The retrospective database included 5,796 cases with one-dimensional tumor measurements but only 231 with more than one measurement; thus, a meaningful analysis of the latter was unable to be performed due to small sample size. Attempts were made to identify relevant thresholds for tumor size. In the R0 cohort, a size of 9.5 cm was the best threshold but was not significant, and the only relevant threshold among the "any resection" cohort was 10 cm. Survival curves suggested a difference in the any R cohort; however, this was due to variations in outcomes of patients with incompletely resected lesions, and no significant difference was identified in the R0 patients. Other analyses stratifying with the Masaoka and Masaoka-Koga staging systems showed that lesion size was predictive only in R1 and R2 patients with advanced disease (stage III and IV). In terms of histologic type, the clinical outcomes for patients with specific T descriptors was similar for both thymoma and thymic carcinoma. However, there were a limited number of cases related to T4 disease, which prevented any meaningful assessment of outcomes based on histologic type. The limited number of thymic neuroendocrine neoplasms prevented a separate analysis of T categories, and these lesions were considered in the analyses of all patients. Because of the limited clinical utility of both tumor size and histologic type, these features were not considered further

 

in the stage classification. ITMIG is currently in the process of collecting a worldwide prospective database of patients with thymic epithelial malignancies. This database, being prospective, has the advantage of resolving the missing pieces of ITMIG's retrospective database, and that is getting multi-dimensional tumor measurements and more complete datasets on T and N status, which are not always completed in retrospective series and databases. It is anticipated that investigations involving larger prospective cohorts will not only enable the determination of the prognostic significance of the TNM system but also provide insight into the impact of tumor features, such as size and histologic type that could not be elucidated from the analyses of the retrospective database.

In summary, Meurgey and colleagues demonstrate the feasibility and the relevance for histologic subtyping of the consensus major and minor criteria recently proposed by ITMIG for the WHO classification and the new TNM staging system in a routine practice setting. Additionally, they show that the well-established correlation between histologic type and tumor stage is maintained when transitioning from the Masaoka-Koga system to the TNM staging system. However, the prognostic significance of the TNM staging system requires further validation in larger cohorts, at which time the potential impact of other features that could not be adequately assessed in the retrospective database could also be investigated.

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