Editorial

Validation of the latest WHO histological classification and the 8th TNM staging system for thymic epithelial tumors

Kazuo Nakagawa

Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan

Correspondence to: Kazuo Nakagawa, MD. Department of Thoracic Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Email: kznakaga@ncc.go.jp.

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Histological classification and staging systems are indispensable for performing accurate management and research in patients with malignant tumors. The World Health Organization (WHO) classification and the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification are the international standards for the histological classification and staging of malignant tumors. However, for thymic epithelial tumors (TETs), these systems were not available until 1999 (1) and 2017 (2), respectively, perhaps because of the rarity and unique biological behavior of these tumors.

To date, many histological classifications have been proposed for TETs. Several of these classifications were widely used when they were published (3). In 1961, Bernatz and colleagues classified thymoma into 4 histological subtypes according to the relative proportion of epithelial cells and lymphocytes: predominantly lymphocytic, mixed, epithelial, and spindle cell (4). In 1985, Marino and Müller-Hermelink developed a new histological classification of thymic epithelial neoplasm based on the morphologic and functional resemblance of neoplastic epithelial cells to normal thymic cortical and medullary epithelial cells: medullary, mixed, predominantly cortical, and cortical (5). Kirchner and colleagues then proposed well-differentiated thymic carcinoma (TC) as an organotypic low-grade carcinoma of the thymus (6). On the other hand, Moran and Suster presented 3 categories of TET based simply on the grade of histologic atypia: thymoma, atypical thymoma, and TC (7). While some studies showed that these classifications were useful for predicting clinical behavior, others disputed their clinical relevance. Thus, although several histological classifications for thymoma have been published, their clinical usefulness has been controversial. Against this background, the WHO histological classification of the thymus was published for the first time in 1999 (1), and was revised in 2004 (8). Since then, while there have been several reports regarding its prognostic significance, its low reproducibility has been an important issue. In 2014, the International Thymic Interest Group (ITMIG) consensus statement on the use of the WHO histological classification to refine histological criteria for better management, particularly, for prototypic and difficult-to-classify TETs, was published (9). More recently, the latest WHO histological classification of the thymus was published in 2015, and included the ITMIG consensus statement (10). To date, only one study has evaluated the clinical and prognostic relevance of the ITMIG consensus statement (11).

In terms of the staging of TETs, many staging systems have also been proposed (3). Among them, Masaoka's staging system from 1981 has been widely used for a long time (12). In 1994, Koga and colleagues modified Masaoka's staging system (13). However, there have been several arguments regarding these staging systems: i.e., the prognostic significance of capsular invasion, the prognostic significance of the division between stages I and II, and the prognostic diversity between various kinds of stage III tumors based on the involved organs (14,15). In 2017, the TNM staging system for TETs based on a proposal from the International Association for the Study of Lung Cancer (IASLC) and the ITMIG TET staging project (16) was established for the first time (2). In this staging system,

stages I and II of Masaoka's staging system were merged into a single stage I. Furthermore, tumor that invaded only the pericardium was reclassified as stage II. To date, only a few studies have evaluated the TNM staging system for TETs (17).

A recent study by Meurgey and colleagues assessed the ITMIG statement on the WHO histological classification and the 8th TNM staging system for TETs for the first time using a series of 188 TETs (18). Their study seems to be identical to the evaluation of the latest WHO classification (9). They demonstrated that the ITMIG consensus major criteria were identified in 100% of type A, AB, B1, and B2 thymomas. However, the value of the minor criteria was controversial because of their variable frequency among their cases. These might be more useful for tumors with a borderline histology. They suggested potential major criteria for type B3 thymoma, consisting of pink impression at low magnification, lack of intercellular bridges, and lack of expression of CD117 by epithelial cells. Furthermore, for difficult cases, they proposed that keratin or p63 immunohistochemical staining may be used to highlight the confluence of epithelial cells in type B1 and B2 thymomas, similar to TdT staining in type A and AB thymomas to evaluate the lymphocytic content. In their study, only 2 observers assessed ITMIG consensus major and minor criteria, and further studies on reproducibility are warranted to address potential interobserver variability.

At this time, a more interesting issue is the frequency of discordance between histological subtypes based on the previous WHO classification (1999 or 2004 version) and those based on the ITMIG statement. Meurgey and colleagues did not describe the details in their study, particularly with regard to the conversion rate from type B1 to type B2 or from type B2 to type B1, as well as from type B3 to TC or TC to type B3. There is a simplified histological classification: low-risk (type A, AB, and B1) and high-risk (type B2 and type B3) thymoma (8). Accordingly, the accurate distinction between type B1 and type B2 thymoma seems to be important. In fact, the frequency of type B1 and type B2 thymoma was different in previous studies (10). Furthermore, different studies have shown various differences in prognosis between type B1 and type B2 thymoma (10). Ruffini and colleagues demonstrated that high-risk thymoma did not significantly differ from low-risk thymoma in terms of overall survival or disease-free survival, and identified the lack of a central review of pathology specimens in their study as a main issue (19).

In terms of staging systems, as Fukui and colleagues mentioned in their study (17), the frequency of each stage is heterogeneous in the present study. More than 80% of the patients were assigned to stage I, whereas only 2% of the patients were assigned to stage II and no patients were assigned to stage IIIb. They also demonstrated for the first time that a significant correlation between histological subtype and stage at diagnosis was maintained after restaging according the new TNM classification. With respect to the treatment strategy, they pointed out a major issue regarding how to identify patients who could benefit from postoperative radiation therapy based on the new TNM staging system.

Although the reproducibility of the WHO histological classification will be improved with the application of the ITMIG consensus statement, further evaluation will be needed in various countries or institutions all over the world. There are still several issues regarding the histological classification and staging of TETs. First, the ITMIG consensus statement recommended that combined thymoma should not be used as a classification. For tumors that consist of several histological subtypes, all of the histological subtypes should be listed beginning with the predominant subtype. For statistical and study purposes, thymoma components of 10% or less in a thymoma can be disregarded and the tumor can be classified according to the predominant component. This rule is not applicable to type AB thymoma. Furthermore, for tumors that consist of TC and thymomas, the histological subtype is defined as TC regardless of the predominant subtype. However, for type B3 thymoma—the most aggressive histological subtype of thymoma—this rule does not seem to be appropriate, as with TC. One study suggested that tumors in which type B3 thymoma was recognized should be classified as type B3 thymoma (20). The definition of the histologic subtype that consists of type B3 and other subtypes of thymoma should be investigated further. Second, the ITMIG consensus statement proposed calling tumors that appear to be B3 thymomas under hematoxylin and eosin (H&E) staining, but which show two features of TC, i.e., CD5/CD117 expression and lack of TdT+ T cells, "B3/TC borderline tumors". At present, in routine clinical practice, whether patients with TET are diagnosed with thymoma or TC can affect the treatment strategy. Although such B3/TC borderline tumors might be rare, the prognosis of patients with such borderline tumor should be investigated in the near future to determine the optimal treatment for these patients. Third, the ITMIG consensus statement noted that type A thymoma included small subsets of aggressive

tumors. Whether such type A thymoma with aggressive behavior should be considered a type A variant, such as type A1–3, or a type B3 variant is also an important issue that should be evaluated in the near future.

In the 8th TNM classification, tumors that invade only the pericardium have been newly assigned to stage II. However, the frequency seems to be very low. Furthermore, a finding of invasion of the pericardium alone cannot be detected by preoperative radiological work-up. In addition, there was a statistically significant difference in disease-free survival, but not overall survival, between stage II and stage III (16). These findings raise the question of whether or not stage II in which the tumor invades only the pericardium is clinically meaningful. The new TNM staging system for TETs needs to be further evaluated.

Precise histological classification and staging systems are indispensable for optimal management and research. TETs are rare tumors with unique biological behavior, and their malignant potential is quite heterogeneous. In addition, histological classification and staging systems for these tumors are relatively new compared to those for other malignant tumors. Evaluations and proposals from studies such as that by Meurgey and colleagues (18) can help to make the WHO histological classification and the TNM staging system of TETs more robust and worthwhile.

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Footnote

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