Editorial

New histological classification and staging of thymic malignancies: ITMIG consensus statements and the 8th TNM staging system

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Thymic epithelial tumors are rare malignancies, and their pathological classification has been refined for many times. In 1961, Bernatz *et al.* have subtyped thymic malignancies according to lymphocytes and epithelial component; however, the concept of thymic carcinoma was not introduced (1). All tumors arising in the thymus were referred as "thymoma". In 1978, Rosai and Levine have first described the malignant nature of "thymoma" (2). They defined thymoma as benign tumors that originate from thymic epithelial cells. Most of the tumors are encapsulated but sometimes invade other organs or metastasize despite their histology. These tumors are described as malignant type I (without histological atypia) and type II (accompanied by moderate to marked histological atypia). In 1985, Marino and Müller-Hermelink have introduced a new system of classification of thymic malignancies according to their similarities with normal epithelial cells and have evaluated the prognostic relevance of the new classification (3). Further, In 1999, Rosai has compiled the WHO classification (4) on the basis of cellular components (spindle cells, epithelial cells, and lymphocytes) and histological atypia. According to that classification, thymic carcinoma was referred as type C, which included many subtypes. In the revision of the WHO classification in 2004, it was further sub-divided into a different entity as "thymic carcinoma (TC)." Thymic malignancies are now classified into A, AB, B1, B2, B3, and TC, considering not only histology but also staging and disease-free survival. Subsequently, the biological feature of TC was elucidated as the loss of thymic functions, which cause immunological complications in thymoma patients, including myasthenia gravis, pure red-cell anemia, and Good syndrome. Further, the key drugs for chemotherapy are different for TC and thymoma. Meanwhile, histological features of each subtype are based on the single spectrum; therefore, some cases are difficult to classify. To avoid discordance between pathologists, the International Thymic Malignancy Interest Group (ITMIG) conducted a review of "borderland tumor" by 18 pathologists and published a consensus statement of major and minor criteria for differentiating each subtype (5). These recommendations were reflected in the revision of the WHO classification in 2016.

The staging system of thymic malignancies has been widely based on the specialized classification, not the TNM classification for a long time. In 1981, Masaoka *et al.* first described the Masaoka staging system, which is reported to be correlated with prognosis. Further, Koga *et al.* revised this system to Masaoka-Koga Staging system (6,7). This new staging system is based on the clinical outcomes of 91 patients treated at a single institution (6) and irrelevant to the TNM staging axis. Because there has been demand for novel grading system, several TNM systems have been introduced. The Thymic Domain of the Staging

and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC) and ITMIG conducted a retrospective surveillance of more than 10,000 cases of thymic malignancies and proposed a novel TNM staging system (5,8). The American Joint Committee on Cancer/Union Internationale Contre le Cancer Consortium (AJCC/UICC) approved this new system in the 8th TNM staging classification.

Recently, Meurgey *et al.* have reviewed the cases that met the criteria proposed by the ITMIG and reclassified them according to new TNM staging system as an alternative to the Masaoka-Koga system in 188 cases of thymic malignancies (9). Consequently, 100% of type A, AB, B1, and B2 thymoma and 87% of TC met the major criteria. However, a proportion of thymic malignancies with minor criteria varied between types of thymic malignancies and ranged from 0% to 22%. The new staging systems were applied to 152 patients, and 84% of them were classified into stage I. Correlation between stage at diagnosis and histology was also reported in the new TNM staging system.

Although the high prevalence of primary criteria proved the external validity of the ITMIG recommendations, some of the minor criteria were not observed in the majority of each subtype (9). Thus, the frequency of minor criteria must be revealed to reduce the inter-observer discordance of diagnosis. The report by Meurgey *et al.* provides valuable data regarding the frequency of minor criteria. A previous study has reported that the discrepancy between the expert and non-expert diagnosis of thymic malignancies considering the ITMIG consensus criteria was 22% (10). Histopathological assessment in this study was performed by two pathologists with disparity in experience. This aspect conforms to daily-practice; however, they did not reveal the difference between the pathologists' opinion. Therefore, further research is warranted to examine the dissolving effect of the ITMIG consensus criteria on diagnosis imparity.

Immunohistochemical criteria, which constitute a part of minor criteria of the ITMIG consensus recommendations, may contribute to the objective of classification. CD5, c-kit, and Glut-1 have been used for differentiating B3 thymoma and TC. Meurgey has proposed p63 staining to be useful to detect epithelial components in B1 and B2 thymoma (9). The antibody of p63 is also applied to detect the basal cell of the prostate and squamous cell differentiation of non-small cell lung cancer. Therefore, it is easy to implicate p63 immunostaining into routine practice. However, specificity analysis must be conducted to find better marker.

Chemotherapy and/or radiotherapy are applied to manage patients with distant metastasis and also other factors that impede surgical resection. In such cases, treatments are occasionally initiated on the basis of biopsy findings. However, there are some criteria that would be difficult to confirm in small amount of tissue. For example, 13% of TC (n=2) in the reported study did not present with definite atypia; however, immunohistochemical criteria and infiltrative growth pattern led to the diagnosis of TC (9). This growth pattern could be dismissed when only biopsy specimens were available. In the study of Meurgey *et al.*, surgically resected specimens and biopsy or fragmented specimens were primarily used, which were reviewed only in nine percent of the cases (n=17). Further comparison of the histology of biopsy and resected specimens and review of major or minor criteria would enable us to evaluate these morphological and immunohistochemical criteria, whether they are applicable in routine practice. Additionally, their investigation included a small number of cases of TC (n=20) and advanced stage (Stage IVa/b, n=5). The biological characteristics of thymoma and TC are different, and the analysis of patients in advanced stages would impact the decision in palliative-intent chemotherapy. An investigation at international level is required to reveal the clinical behavior of these rare diseases.

Some cases with stage III disease in the Masaoka-Koga system were reclassified into stage I or II according to the 8th TNM staging system. Meurgey *et al.* have revealed a significant difference in time to relapse between stages of Masaoka-Koga system; however, the gap was narrowed by new staging system using TNM classification (9). Recently, a retrospective study conducted in China has also reported that the variance between stages in relapse ratio and overall survival became insignificant when re-staged considering the 8th TNM-based staging compared with that considering the Masaoka-Koga staging system (11). These results may have stemmed from the expansion of stage I disease. Stage I in the new TNM-based system comprises T1bN0M0 disease, which was previously treated as stage III. The study has reported significant difference in relapse and survival between patients with T1aN0M0 and T1bN0M0 diseases (11). These studies indicate that resectability plays a crucial role in patients' prognosis.

The retrospective study by Meurgey *et al.* has revealed the ITMIG consensus statements on the histology of thymic malignancies, which appropriately reflects the pathological findings of each subtype (9). Therefore, consensus criteria must be assessed henceforth whether

they benefit the diagnosis regardless of observer experience. Surgical resectability has impact on prognosis assessment even when applying the 8th TNM staging system. Further investigations on a large number of cases are required, with international collaborations, to reveal the characteristics of thymic malignancies, which is a rare cancer, to stratify of prognosis using N and M factors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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