Editorial

Next revision of the T descriptors in the TNM classification for thymic epithelial tumors: possibilities and problems

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The TNM classification of cancers proposed by the Union for International Cancer Control (UICC) is a widely accepted guide for predicting prognoses, selecting therapy and facilitating the development of new treatment strategies. In 2016, the UICC and American Joint Committee on Cancer (AJCC) applied the TNM cancer staging system to thymic epithelial tumors (1). In this edition, the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) staging committee proposed the classification (2-4). According to the new TNM classification, the T descriptor collectively defined tumors that are totally encapsulated, extend into the adjacent fat tissue, and invade the mediastinal pleura as T1 tumors. Only tumors that invade the pericardium are classified as T2. T3 and T4 tumors invade the lung, intrathoracic large vessels, and other tissues. In other words, the T descriptor defines the level of invasion to the adjacent organs, which is consistent with the philosophy of the Masaoka staging system. For a long time, this Masaoka staging system for thymoma and the other thymic epithelial tumors has been widely used in clinical practice (5-7). This Masaoka staging system is also divided into stage I and II according to the degree of local extension. The current TNM classification affected by Masaoka staging system is the first version that was accepted by UICC and AJCC. In the near future, a prospective review and evaluation will be implemented to validate these classifications. Thereafter, those results and proposals will be used to revise the classification, as has been done for cancers of other organs.

The general rules of the TNM system

The current TNM classification does not include tumor size as a T descriptor as same as Masaoka staging system. The staging committee mentioned that this was because the analysis of the IASLC/ITMIG database did not detect an association between the tumor size and the prognosis. Nevertheless, the general rules of the TNM system state in the TNM supplement (8) that the T descriptor defines the primary tumor based on the *size*, *location* and *degree of local invasion*. The tumor size is one of the most important prognostic determinants in the TNM classifications of many other cancers and can be determined before surgery using radiological imaging. This general rule was an essential principle when the TNM classification was revised. Following this rule, several studies revealed the prognostic impact of tumor size in patients with thymic epithelial tumors and sporadically already reported.

The prognostic impact of the tumor size in patients with thymic epithelial tumors

Wright *et al.* reported that patients with thymic epithelial tumors of >8.0 cm in size have a greater risk of recurrence in comparison to patients with tumors of <8.0 cm in size (9). Fukui *et al.* reported the prognostic significance of tumor size in cases of complete resection that were managed in their institute (10). They found that a tumor size of >4.0 cm was independently associated with worse recurrence-free survival. In their study, recurrence-free survival showed a significant decline as the tumor

size increased. Furthermore, according to a multivariate analysis, tumor size >4.0 cm was an independent prognostic factor for recurrence, and they concluded that tumor size was a good predictor of recurrence in patients with thymic epithelial tumors.

The prognostic impact of tumor size in patients with thymoma

In the analyses of the IASLC/ITMIG database, the relationship between tumor size and survival time was not investigated for each histological type. The prognoses and malignant behavior of thymic epithelial tumors can be quite different depending on the histological type. Considering these points, it should be conducted the analyses to be performed divided into each histological type when investigating the relationship between tumor size and prognoses regarding thymic epithelial tumors. Okumura *et al.* revealed the clinical importance of tumor size in patients with thymoma using a Japanese nationwide retrospective database (11). They found that higher incidence of recurrence over 5.0 cm and of tumor death over 8.0 cm. The Cox's proportional hazard model analysis showed that the tumor size was the independent factor to determine both recurrence-free survival (RFS) and disease-specific survival (DSS). They concluded that tumor size was an important prognostic factor. Based on the general rules of TNM system, this report was a highly important task. Nevertheless, this report also had some limitations; First, there were two cut-off values for the tumor size, so we were unable to judge which value was the true cut-off. Second, the cut-off value should be also presented based on the overall survival (OS). This is because any descriptors in the TNM staging system are usually applied to the results obtained by analyses of the OS. Although the ideal cut-off value for the tumor size might not be able to be derived in thymoma patients using the OS, it is important to show the differences in the cut-off values for the T descriptor between thymoma and other thymic malignancies. Third, while they did identify the prognostic importance of the tumor size in thymomas, thymic carcinoma and neuroendocrine tumor still need to be examined in order to elucidate the clinical relevance of the tumor size in these lesions. The tumor size is expected to similarly demonstrate prognostic influence in these two thymic malignancies as well. Regardless, the tumor size should be reflected in the T descriptors section of the forthcoming revision of the TNM classification on thymic epithelial tumors.

Problems in adopting tumor diameter as a T descriptor in the forthcoming TNM classification

On thymic epithelial tumors, prognoses and malignant behavior were quite different depending on the histological type, as mentioned above. On the other hand, in daily clinical practice surgical treatments are performed without a definitive pathological diagnosis. Based on this fact, the clinical TNM staging system should be common classification in all histological types, as it is in lung cancer. To establish common T descriptors, including tumor size, analyses to determine the cut-off values of tumor size should be conducted with patients divided into groups by histological type, as the malignant behavior of thymoma is unique. We recently reported the results of multimodality therapy for thymoma patients with pleural dissemination and showed a high rate of disease recurrence despite a good OS rate, indicating the dissociation of the OS and RFS (12). Given this unique malignant behavior of thymoma, we recommend that analyses should be conducted using the RFS or DSS in thymoma patients and the OS in patients with other thymic malignancies. When those devises were applied, it could be proposed as common T descriptors with good balance. It is expected that the prognostic impact of tumor size will be detected based on the largest cohort, and that an appropriate and reasonable revision that is useful for daily practice will be accomplished in the forthcoming TNM classification.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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