Mini-Review

Clinical TNM staging of thymic epithelial malignancies

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Abstract: The International Thymic Malignancy Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC) formed the Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) to develop the first stage classification system for thymic epithelial tumors (TETs) which was published in the TNM Classification of Malignant Tumours issued by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), now in 8th edition. This system was developed from evidence-based analysis of the large ITMIG database of TETs, in conjunction with expert opinion. Until its publication in December 2017, there had been no universally accepted, standard means of classifying these tumors, although Masaoka-Koga staging system had most closely approached this standard. This brief article will summarize this new stage classification system for TETs, highlighting its differences with Masaoka-Koga and relevant next goals.

Keywords: TNM stage classification; thymic epithelial tumors (TETs); thymoma; thymic carcinoma

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In 2009, ITMIG and the International Association for the Study of Lung Cancer (IASLC) formed the Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) to develop the first staging classification system for thymic epithelial tumors (TETs). This committee of experts comprehensively analyzed the large ITMIG database of more than 10,000 patients with TETs to develop the first evidence-based stage classification system for TETs, supplemented by expert opinion where the data was deficient. All previous stage classification systems for these tumors had been based on much smaller groups of patients and were not universally accepted. The Masaoka-Koga Staging System (1,2) had come closest to universal acceptance, with ITMIG having endorsed it in 2011 as a bridge to the new classification system.

Masaoka-Koga primarily staged thymomas, as opposed to other thymic malignancies, differentiating stage I from Stage II tumors by whether or not there was transcapsular invasion. Stage III disease entails invasion of any neighboring organ, whether pericardium, great vessel, trachea, esophagus, or lung, for example. Pleural and pericardial metastases are deemed stage IVa and hematogenous and lymphogenous metastases are deemed IVb.

The new TNM stage classification system can be used for all thymic epithelial tumors and considers not only tumor characteristics, but also lymph nodal and metastasis characteristics, unlike Masaoka-Koga. It does not distinguish between fully encapsulated tumors and those that have invaded through the capsule into adjacent thymic tissue or mediastinal fat, because analysis of the ITMIG database revealed this distinction not to be clinically relevant. In addition, unlike TNM stage classification systems for most other malignancies, it provides no descriptor for tumor size, because tumor size was not found to be of clinical import. The "T" designation is based on the level of invasion, rather than size (3). The "N" descriptor draws a simple distinction between anterior or N1 and deep or N2 lymph nodes, describing prevascular (N1) and visceral (N2) lymphadenopathy, respectively, in the mediastinum and describing lymphadenopathy medial (N1) and lateral

(N2) to the common carotid arteries, respectively, in the neck (4). The "M" descriptor defines pleural and pericardial metastases as M1a and pulmonary nodules and more distant metastases as M1b (5). An additional difference from some earlier staging systems is that the TNM system can be used to stage all TETs, including thymic carcinomas and neuroendocrine tumors.

The stage grouping for the new TNM stage classification system for TETs classifies T1, T2, T3, and T4 tumors as stages I, II, IIIa, and IIIb respectively, provided there is no lymphadenopathy or metastatic disease. Upon development of N1 lymph nodes and/or M1a disease, regardless of the T descriptor, the TET is staged as stage IVa. Upon development of N2 lymph nodes and/or M1b disease, the TET is categorized as stage IVb (6). Currently, only stage IVb is universally deemed unresectable by thoracic surgeons. Potential for resection remains for the other stages, including stage IVa.

Analysis of the ITMIG database revealed an overall increased recurrence rate and death rate with increased TNM stage (6). An early validation study comparing Masaoka-Koga and TNM staging systems in a cohort of patients with TETs showed that many patients were down-staged from Stage II to Stage I, on account of the now deemed inconsequential distinction between tumors invading through and not invading through the capsule. Also, IVa patients as a group survived longer than Stage III patients (T3 and T4), presumably because of the relative ease of resectability of pleural and pericardial metastases, as opposed to invasive tumor into vital organs such as the aorta and pulmonary artery (7).

Principal limitations of the new TNM classification system for TETs include its derivation from a database, albeit the largest of its kind, with an underrepresentation of advanced tumors—the ITMIG database largely contains patients with surgically resectable disease. This actuality potentially diminishes the reliability of conclusions derived from the analysis regarding more advanced stages of disease. Also, at the present time, this staging system cannot be used for prognostic assessment.

The new TNM stage classification system for TETs, originally proposed in the *Journal of Thoracic Oncology* in 2014 (4) and subsequently published in the 8th edition of the TNM Classification of Malignant Tumours (8), represents the first official TNM staging classification system for TETs and should foster: (I) more consistent and effective communication between subspecialty disciplines to the benefit of patients; (II) further research avenues and enhanced reliability and reproducibility of results; and (III) ultimate development of a prognostic tool for TETs, which will continue to evolve with advances in therapy.

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Footnote

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