Editorial

The International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems for thymic epithelial tumors and large-scale retrospective data

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Thymic epithelial tumors are rare tumors. However, they are the most common tumor of the anterior mediastinum (1). A lot of studies analyzed retrospective clinical data of patients with thymoma from single-institute (2). Recently some studies analyzed large-scale retrospective clinical data (more than 1,000 patients) of thymic epithelial tumors including thymoma and thymic carcinoma from multiple institutes (3-5). The studies in Japan analyzed 1,320 patients with thymic epithelial tumors treated surgically from 115 institutes during the period from 1990 through 1994 and 2,835 patients with thymic epithelial tumors treated surgically during the period from 1991 through 2010 (3,4). The study by the European Society of Thoracic Surgeons (ESTS) database analyzed 2,151 patients with thymic epithelial tumors treated surgically from 35 institutions during the period from 1990 to 2010 (5). Large-scale retrospective data can clarify the biology and the therapy for thymic epithelial tumors. In this article "*Comparison of the Masaoka-Koga staging and the International Association for the Study of Lung Cancer/the International Thymic Malignancies Interest Group proposal for the TNM staging systems based on the Chinese Alliance for Research in Thymomas retrospective database*" by Liang *et al*., the Chinese Alliance for Research in Thymomas (ChART) collected the retrospective data of 2,370 patients treated at 18 hospitals in China during 1992 to 2012. Of these, 1,198 patient data were used to compare Masaoka-Koga staging and the International Association for the Study of Lung Cancer (IASLC)/the International Thymic Malignancies Interest Group (ITMIG) proposal for the TNM staging systems. As there are few reports which judged the validity of the IASLC/ITMIG proposal for the TNM staging systems using large-scale data now, report of Liang *et al*. has an excellent value.

The clinical staging system for thymoma was first introduced by Bergh and associates in 1978 (6), later modified by Wilkins and Castleman (7), and confirmed by Masaoka and associates in 1981 (8). The Masaoka classification is now the most widely accepted and is an excellent predictor of the prognosis of thymoma (2,3). However, several articles have pointed out some problems and have suggested that an update of the system is desirable (9). To correct them, the ITMIG proposed the Masaoka-Koga stage classification system (10). The Masaoka system refers more vaguely to capsular invasion-definition between stage I and II. The Masaoka-Koga system defined stage I as "grossly and microscopically completely encapsulated tumors including tumors with invasion into but not through the capsule" and stage IIA as "tumor with microscopic transcapsular invasion", and stage III included tumors with microscopic involvement of mediastinal pleura.

However, many studies do not provide appreciable prognostic separation between stages I and II in the Masaoka or Masaoka-Koga system (11,12), as Liang *et al*. showed that differences in cumulative incidence of recurrence (CIR) between stage I and stage II were statistically significant, and that no statistical significance was detected in differences of overall survival (OS) between stage I and stage II. In the Masaoka or Masaoka-

Koga system, the presence of local invasion (T factor) is strongly emphasized in comparison with lymphogenous and hematogenous metastasis (N and M factors) because of the rarity of lymphogenous and hematogenous metastasis in thymoma. However, it is necessary to determine how N or M factors influence prognosis to establish a TNM system classification of thymic epithelial tumors, including thymic cancer and carcinoid (13).

Now there is no an official-stage classification system for thymic malignancies. In 2009, both the ITMIG and the IASLC recognized the need for a consistent stage classification system for thymic epithelial tumors. A Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established collaboratively by IASLC and ITMIG. IASLC led discussions and received approval from AJCC and UICC to develop proposals for stage classification of thymic malignancies that would help define thymic stage classification in the 8th edition of the stage classification manuals. ITMIG assembled a retrospective global database of 10,808 patients with thymic malignancies from 105 sites worldwide, carried out statistical analysis and proposed the TNM classification for thymic epithelial tumors (14).

T1 includes tumors that were classified as stage I or II in the Masoaka or Masaoka-Koga stage classification systems, because there is no significant difference of recurrence and OS between stage I and II in the Masoaka or Masaoka-Koga stage classification systems. However, there is a slight difference in CIR in patients from Japan submitted by the JART. The TD-SPFC decided, to gain more prospective data for further testing, to subcategorize T1 into T1a (no mediastinal pleural involvement) and T1b (involvement of the mediastinal pleura) (12). Liang *et al*. showed that there was a significant difference in CIR between T1a and T1b tumors, which confirmed the result of JART data. T2 (the pericardium invasion) cases resulted in a worse rate of recurrence and survival in patients than T1 cases. Recurrence in T2 cases was lower than that in T3 cases, although there was no significant difference of OS between T2 cases and T3 cases (12). Liang *et al*. showed that there was no significant difference in CIR and OS between T2 and T3 cases. Some investigators think that as stage III thymoma is highly heterogenous in terms of the involved organs, the classification should divide the subgroups according to prognosis (15). The TD-SPFC analyzed CIR and OS of stage III cases in terms of involvement of each single structure (pericardium, lung, great vessels, etc.), the number of different structures involved and possible combinations. However, there were no apparent differences (12). There was a trend to worse OS between T4 cases and T3 cases (there was no significant difference) because the number of patients available for analysis with T4 involvement was limited (12). Liang *et al*. showed that there was significant difference in OS between T3 cases and T4 cases.

In terms of N factor, the JART has conducted the best analysis of the incidence and location of node metastases from thymic malignancies. Lymph node metastases were seen in 2% of thymomas, 27% of thymic carcinomas, and these node metastases were seen most often in anterior mediastinal lymph nodes N1 (89% of thymoma, 69% of thymic carcinomas) (16). Liang *et al*. showed that there was a significant difference in OS between N0 cases and N1–2 cases. However, the results of Liang *et al*. (comparing N0 cases with N1–2 cases) cannot estimate a prognostic feature of N factor. The TD-SPFC demonstrated that the recurrence and survival outcomes of patients with N1 involvement are similar to those of patients with M1a involvement, and that the outcomes of patients with N2 and M1b involvement (or both) are similar. The N1 and M1a cases were grouped into the stage group IVA and the N2 and M1b cases into stage group IVB (17).

Since now some organs like ITMIG collect large-scale retrospective and prospective data for thymic epithelial tumors with multi-institutes, analyze them and judged the validity of the IASLC/ITMIG proposal for the TNM staging systems like the report of Liang *et al*. The repeat of this process will make an excellent TNM classification for thymic epithelial tumors.

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Footnote

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