Editorial

Survival comparison between thymic carcinoma and thymic carcinoid: does it matter in clinical practice?

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Thymic carcinoma (TC), a cancer derived from thymic epithelial cells, was first recognized by Shimosato and associates in 1977 in a study of 8 squamous cell carcinomas of the thymus (1). Thymic carcinoid was initially described by Rosai and Higa in 1972 as a "mediastinal endocrine neoplasm", a separate entity from thymoma (2). Both TC and thymic carcinoid were previously categorized as Type C thymoma. However, in 2004, the WHO classification distinguished thymic carcinoid from TC, and the entity of thymic neuroendocrine tumor (TNET) was established (3). Thymic carcinoid, which includes low-grade typical carcinoid and intermediate-grade atypical carcinoid, is the main component of TNET. TNET also includes high-grade large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (4).

The article "*Comparison of clinical features and survival between TC and thymic carcinoid patients*," which was recently published in the *European Journal of Cardio-thoracic Surgery* by Zhao and associates (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai, China), compared the clinical characteristics and survival outcomes of between TC and TNET (5). The authors retrospectively analyzed a total of 287 patients with TC and 56 patients with TNET who were mainly treated by surgical resection in a single institution in China over 11 years. The TNET group only included typical and atypical carcinoids, and it was unclear whether high-grade neuroendocrine carcinomas (LCNEC and small cell carcinoma) were included in the TC group or excluded from the analysis. In both groups, most patients presented with advanced stage III–IV disease and were treated with a multidisciplinary approach such as adjuvant radiotherapy and chemotherapy in addition to surgery. Compared to the TC group, the TNET group included significantly more males, large tumors, and node disease. With respect to overall and disease-free survival (OS and DFS), the tumors shared a similar survival course (5-year OS: 80.7% for TNET and 60.7% for TC, P=0.159; 5-year DFS: 37.6% for TNET and 41.1% for TC, P=0.696), with a median follow-up of 47 months for TC and 55 months for TNET. Multivariate analyses showed that younger age, completeness of resection, and adjuvant radiotherapy were associated with OS, and the histological classification (TC or TNET) did not affect OS in this study. Propensity score matching produced 46 patients in each group and also showed no significant difference in OS or DFS between the two groups.

This was the largest single-institutional study to compare the prognosis between TC and TNET, and the results were consistent with those of a recent international database study by the International Thymic Malignancy Interest Group (ITMIG) and the European Society of Thoracic Surgeons (ESTS). In the joint ITMIG/ESTS database study, a total of 1,042 TCs and 205 TNETs including thymic carcinoids, LCNECs, and small cell carcinomas were retrospectively compared in terms of clinical characteristics and survival (6). The median OS was 6.6 years in TC and 7.5 years in TNET. In multivariate analyses, pathologic stage, resection status, and the use of radiotherapy were significant prognostic factors associated with OS and recurrence-free survival (RFS). However, the histology (TC or TNET) did

not influence either OS or RFS. Zao's study may provide external validation for the international database study, and the histology (TC or TNET) may not affect the prognosis for surgical cases. However, all previous comparative studies were conducted retrospectively, and a centralized histological review was not generally available. Other studies have shown contrasting results favoring TNET (7,8). Due to a selection bias, definitive conclusions could not be drawn regarding this comparison. Dose this survival comparison matter in clinical practice? The most clinically important aspect is the fact that TNET including thymic carcinoid, as well as TC, is a more biologically aggressive thymic epithelial tumor than thymoma. The main subgroup of TNET is not typical but rather atypical carcinoid, unlike NET in other organs. Although TC has been known as a high-grade malignancy, TNET is also a high-grade tumor which frequently tend to metastasize to regional lymph nodes and distant organs. In the largest ITMIG/ESTS studies of 205 TNET patients, the cumulative incidence of recurrence was 39% at 5 years, which was much higher than 8% reported in the recent ESTS database for all thymic malignancies (9). As the current Zao's study mentioned, compete surgical resection is essential to provide patients with localized thymic carcinoids a chance of cure (5,10,11), but the high risk of systemic relapse even after compete resection especially in advanced-stage disease emphasizes the needs for the development of drugs for those rare tumors.

The pharmacotherapeutic treatment of choice for thymic carcinoids has been very limited. However, a recent multicenter trial indicated that the long-acting somatostatin analogue pasireotide, either alone or in combination with the mammalian target of rapamycin (mTOR) inhibitor everolimus, might be a new treatment strategy for advanced or recurrent bronchopulmonary and thymic carcinoids (12). A global effort should be made to establish an effective multidisciplinary approach for these rare aggressive tumors.

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Footnote

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