Editorial

Treatment and prognostic factor for recurrent thymic epithelial tumors

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Thymic epithelial tumors (TETs) consist of thymoma and thymic carcinoma, and they tend to be treated fairly similarly despite they are histopathologically highly heterogeneous and officially recognized to be distinct according to the update of the WHO classification in 2004 (1). Surgery remains the cornerstone of therapy, and even though complete resection provides the best survival and opportunity of cure, approximately 10% to 30% of patients with TETs undergoing surgical resection developed recurrent diseases (2,3). A retrospective 10-year monoinstitutional analysis was conducted on 25 patients with first recurrence of disease progression by Banna *et al.* showed that combination chemotherapy could achieve high disease control rate in recurrent/progressive TET and confirmed the role of surgery in combination with chemotherapy (4).

Definition of progression-free survival and recurrence-free survival should be clarified when studies are to be conducted for prognosticators. Given that long-term survival is achievable with resection and recurrence may provide a more clinically relevant endpoint (5), only patients with completely resected thymoma and thymic carcinoma should be enrolled. Prognostic statements and treatment strategies for recurrence in TETs can therefore be made on the basis of greater patient collectives of those undergoing complete resection and longer follow-up.

Factors predicting recurrence and the optimal treatment for recurrent disease have been investigated, but patients undergoing incomplete resection were included (2,6,7). Banna *et al.* enrolled 25 patients, 20 of whom were thymoma and 5 thymic carcinoma treated either with surgery, or with chemotherapy and radiotherapy. Eleven patients were disease-free after the initial treatment because they underwent R0 resection. Although patients undergoing complete resection can experience long-term survival (8,9), recurrence is common in advanced disease, and often earlier and more distant, with lower progression-free survival in patients with thymic carcinoma (10,11). The tumor biology in patients undergoing R0 resection may be different from those undergoing incomplete resection. Among the 25 patients with recurrent disease, there were 4 stage II patients, 10 stage III patients, and 11 stage IV patients, and 11 of them underwent R0 resection. It is a common belief that invasion of aorta or pulmonary vessels by thymic epithelial tumors precludes complete resection, while invasion of innominate vein or superior vena cava (SVC) did not preclude surgery, and long-term survival could be anticipated if the tumor was radically resected as that invading the lung or pericardium (12,13). Tumor biology also contributes to the differences of recurrence-free survival in thymoma and thymic carcinoma. As thymoma is considered locally slowly growing more than hematogenously spreading, direct invasion into the lung might predispose to local or regional recurrence, whereas distant metastasis is commonly seen in thymic carcinoma at the time of diagnosis. Invasion of the innominate vein or SVC and the potential microscopic metastasis therefore poses a greater risk of recurrence than lung or pericardial invasion in patients with completely resected thymic carcinoma (12,13).

Banna *et al.* reported that 10 of 20 patients with recurrent thymoma were type B3. The tumor histology has been identified as one of the prognosticators of recurrent TETs (2,7). In most of the studies thymic carcinoma was categorized and analyzed along with thymoma, and few study focused on the association of tumor relapse with subtyping of thymic carcinoma (14). It is reported that the surgical outcome of patients with TETs depends on histologic classification and grade (7,14). We demonstrated that histologic classification and subtyping did not affect recurrence-free survival in patients with completely resected thymoma or thymic carcinoma (12,13).

Thymoma is usually comorbid with myasthenia gravis, which has been regarded as a positive prognostic factor for overall survival in TETs (15,16). On the other hand, the rare occurrence of myasthenia gravis with thymic carcinoma portends its invasiveness before diagnosis. The presence of myasthenia gravis enables timely diagnosis and complete resection for thymoma. Recurrent thymoma might also be associated with flare-up of myasthenia gravis. However, myasthenia gravis did not have protective effect on cumulative incidence of recurrence (17), and the timing and feasibility of surgical resection for recurrent thymoma may be affected by the existence of paraneoplastic syndrome. Besides myasthenia gravis, patients with multiple metastasis had a worse prognosis than single metastasis (18,19). Taken into consideration together, the performance status of patient with recurrent TET may impact on the feasibility of surgery and result in selection bias that the better prognosis in patients undergoing surgery for recurrent disease.

Banna *et al.* demonstrated that 7 of the surgically resected thymomas were type B3. Only one patient undergoing surgery at diagnosis and for first recurrence had subsequent recurrence. It has been reported histologic progression was noted in recurrent thymoma, and thymoma with cortical differentiate needed careful follow-up (20,21). This observation implies that the tumor behavior might be different between recurrent and progressive disease, and complete resection provides the only opportunity of long-term survival whatever the tumor histology is. Treatments for patients not suitable for surgery include chemotherapy, radiotherapy, and percutaneous cryoablation (22). Multiple combination with cytotoxic chemotherapeutic agents were reported in the study. Nonetheless, based on the meta-analysis by Hamaji *et al.* (23), and with the development of minimally invasive surgical approach and treatment modalities, complete resection for recurrent TETs should be considered in otherwise healthy patients (24,25).

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