Surgical Outcomes of Patients With Stage III Thymoma in the Japanese Nationwide Database

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Background. **To investigate the clinical characteristics and therapeutic outcomes of patients who underwent surgery for stage III thymoma in Japan.**

Methods. **Using the Japanese nationwide database, which contains the records of 2,835 patients with thymic epithelial tumors who underwent treatment between 1991 and 2010, we extracted and analyzed the records of those who underwent surgery for stage III thymoma.**

Results. **A total of 310 patients (170 males, 140 females; median age, 58 years) were analyzed. Involved sites were the lung in 194 (62.6%), the pericardium in 151 (48.7%), the great vessels in 126 (40.6%), the phrenic nerve in 84 (27.1%), and the chest wall in 7 (2.3%). Complete resection (R0) was achieved in 247 (79.7%) cases. Induction therapies were administered to 42 (13.5%) patients, and postoperative therapies were administered to 147 (47.4%). In R0 cases, 68 (27.5%) experienced recurrence. The pleural space was the most frequent site of recurrence (46; 18.6%). The 10-year overall and disease-free (in R0) survival rates were 80.2% and 51.6%, respectively. Multivariate analyses revealed that age ($p = 0.002$), male sex ($p = 0.017$), induction therapy ($p < 0.001$), and type B histology ($p = 0.037$) were independent adverse predictors for overall survival. Chest wall invasion was the only independent adverse predictor for disease-free survival, although the factor analysis was marginal for overall survival.**

Conclusions. **The outcomes of surgery for patients with stage III thymoma were favorable unless chest wall invasion was present; however, the role of complete resection and appropriate multimodal treatment plan require further investigation.**

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The treatment of stage III thymoma involves a variety of clinical approaches because of tumor invasion to the surrounding organs [1–6]. The gold standard therapy for this disease has not yet been established because of a shortage of data. Recently, the Japanese Association for Research on the Thymus (JART) conducted a nationwide study on thymoma with 2,835 patients. In the current study we retrospectively investigated the records of patients with stage III thymoma in this database. Our aim was to clarify the clinical characteristics and therapeutic outcomes of patients who underwent surgical resection for stage III thymoma.

Material and Methods

In 2012, a nationwide project to create a database for surgically treated thymic epithelial tumors was initiated by JART. The Masaoka staging system was applied to the classification of thymic epithelial tumors in this database [7]. For patients who underwent surgery before 2004, the diagnosis of thymic epithelial tumor was reviewed and confirmed by pathologists in each center according to the 2004 revision of the World Health Organization (WHO) classification [8]. Prior to the start of this study, the ethics review board of each institution examined and approved the research protocol, which adhered to the provisions of the Declaration of Helsinki. Finally, clinical data from 2,835 patients in 32 major centers in Japan between 1991 and 2010 were registered in the database.

In the current study, the records of patients with stage III thymoma who underwent surgery were extracted from the database. Patients with thymic carcinoma and neuroendocrine tumors were excluded. We retrospectively analyzed patient records for clinical characteristics and surgical outcomes.

To evaluate the sites of tumor invasion, we categorized the tumors into the following 5 sites of invasion: lung, pericardium, chest wall, phrenic nerve, and great vessels

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Acronyms and Abbreviations

CI = confidence interval
DFS = disease-free survival
DSS = disease-specific survival
HR = hazard ratio
JART = Japanese Association for Research on the Thymus
MG = myasthenia gravis
OS = overall survival
PFS = progression-free survival
PORT = postoperative radiotherapy
SD = standard deviation
SE = standard error
VATS = video-assisted thoracic surgery
WHO = World Health Organization

(superior vena cava, brachiocephalic vein, pulmonary artery, pulmonary vein, aorta, brachiocephalic artery, or heart). According to this categorization, the number of invaded sites was also evaluated.

The results for each variable were expressed as mean ± standard deviation (SD). We analyzed relationships between combined treatments and clinical variables, and relationships between involved organs and resectability or recurrence. For categoric variables, the χ^2 test or Fisher exact test were used. For continuous variables, we used unpaired *t* tests. Kaplan-Meier curves were generated for overall survival (OS) and disease-free survival (DFS) in patients with complete resection. The 10-year OS and DFS were reported, including the standard error (SE). Univariate and multivariate analyses by Cox regression were used for the analysis of risk factors for OS and DFS. The clinical variables entered into the multivariate model were those considered significant based on the univariate analyses, on our experiences, or on previous reports. A stepwise forward procedure was used for the selection of the independent variables. The hazard ratios (HRs) for significant variables were reported with 95% confidence intervals (95% CIs). A *p* value of 0.05 or less was considered significant. The statistical analyses were performed with IBM SPSS Statistics, version 22 (IBM Corp, Armonk, NY).

Results

Patient Characteristics

The records of a total of 310 patients with Masaoka pathological (p)-stage III thymoma were extracted from the database of 2,835 patients with thymic epithelial tumors. During the postoperative follow-up period (mean, 2,240 days; range, 10 to 7,741 days), 39 patients died, 3 of whom died within 30 days after surgery.

Patient characteristics are listed in Table 1. The median age was 58 years. There were 170 (54.8%) males and 140 (45.2%) females. Involved sites were lung in 194 (62.6%), pericardium in 151 (48.7%), great vessels in 126 (40.6%), phrenic nerve in 84 (27.1%), and chest wall in 7 (2.3%) patients. Completeness of resection was R0 in 247 (79.7%), R1 in 33 (10.6%), R2 in 18 (5.8%), and unknown in 12 (3.9%) patients. Postoperative complications were observed in 74 (23.9%) patients. The frequency of tumor recurrence in R0 was 27.5% (68 patients).

Table 1. Patient Characteristics

Characteristic	Patients (n = 310)
Age, years (mean ± SD)	58.1 ± 13.1
Sex, n (%)	
Male	170 (54.8%)
Female	140 (45.2%)
With myasthenia gravis, n (%)	75 (24.5%)
Surgical approach, n (%)	
Open chest surgery	298 (96.1%)
VATS	12 (3.9%)
Surgical method, n (%)	
Thymectomy	266 (85.8%)
Tumor resection	33 (10.6%)
Debulking/biopsy	6 (1.9%)
Other	5 (1.6%)
Tumor size, cm (mean ± SD)	7.03 ± 3.04
Histology, WHO classification, n (%)	
A	15 (4.8%)
AB	39 (12.6%)
B1	46 (14.8%)
B2	112 (36.1%)
B3	94 (30.3%)
Other	4 (1.3%)
Type of invasion, n (%)	
Lung	194 (62.6%)
Pericardium	151 (48.7%)
Great vessels	126 (40.6%)
Phrenic nerve	84 (27.1%)
Chest wall	7 (2.3%)
Number of invaded sites (mean ± SD)	1.86 ± 1.01
1 site	137 (44.2%)
2 sites	82 (26.5%)
3 sites	62 (20.0%)
4/5 sites	21 (6.7%)
Any preoperative therapy, n (%)	56 (18.1%)
Preoperative steroid pulse	15 (4.8%)
Induction chemotherapy	29 (9.4%)
Induction radiotherapy	6 (1.9%)
Induction chemoradiotherapy	7 (2.3%)
Any postoperative therapy, n (%)	145 (46.8%)
Postoperative chemotherapy	14 (4.5%)
Postoperative radiotherapy	121 (39.0%)
Postoperative chemoradiotherapy	12 (3.9%)
Postoperative complications, n (%)	74 (23.9%)
Completeness of resection, n (%)	
R0	247 (79.7%)
R1	33 (10.6%)
R2	18 (5.8%)
Recurrence, n (%)	68 (27.5%)

VATS = video-assisted thoracic surgery; WHO = World Health Organization.