Thymoma Patients With Pleural Dissemination: Nationwide Retrospective Study of 136 Cases in Japan

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Background. **Thymoma is a rare mediastinal tumor with relatively slow growth. However, advanced-stage cases with pleural dissemination are occasionally encountered. The outcome of surgical resection for thymomas with pleural dissemination has not been clearly determined.**

Methods. **We retrospectively investigated the clinical records of 2,835 patients with thymic epithelial tumors that were treated from 1991 to 2010 in 32 institutions that participated in the Japanese Association for Research on the Thymus. In this study, we analyzed the clinicopathologic factors and prognosis of thymoma patients with pleural dissemination who underwent surgical resection.**

Results. **The thymomas with pleural disseminations numbered 148 cases (5.2% in the 2,835 thymic epithelial tumors). Surgical resection was performed in 136 cases. Pathologic Masaoka stages were classified as IVA (n = 118) and IVB (n = 18). In Masaoka stage IVA disease, the small number of disseminated pleural nodules (10 or fewer) was related to the curative resection. The prognosis was also better in these cases than in those with greater than 10 disseminated pleural nodules (certified during the operation; $p = 0.0057$). Patients who underwent macroscopic total resection of disseminated nodules had a better prognosis than those with residual tumors ($p = 0.037$). In stage IVA cases with complete resection (n = 42), the efficacy of adjuvant chemotherapy, radiotherapy, or both was not demonstrated.**

Conclusions. **Macroscopic total resection of tumors appears to be a promising prognostic factor in Masaoka stage IVA thymomas. The number of disseminated pleural nodules correlated with resectability.**

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Thymoma is a rare mediastinal tumor, and because its progression is relatively slow, a large number of patients and long (>5 years) follow-up are required to determine the effect of any treatment. In the treatment for thymoma, only complete surgical resection has been considered as potentially curable [1, 2]. For the early-stage cases, there is no doubt that surgical resection is the treatment of choice. For the cases with pleural dissemination, there is a lack of consensus on treatment strategy, and complete surgical resection is generally considered difficult. Multimodality therapy (surgery, chemotherapy, and radiation) has been used for advanced thymomas. However, the efficacy of chemotherapy and radiotherapy for advanced or recurrent thymomas has not been determined [3–7]. In addition, it is difficult to plan clinical trials because of the rarity of thymomas with pleural dissemination.

The progression pattern for thymoma is different from that for tumors of other organs, which metastasize by lymphogenous or hematogenous routes. Thymomas often recur locally or as pleural dissemination. To improve survival, adjuvant therapies including preoperative or postoperative chemotherapy and radiotherapy for advanced thymomas have been suggested. However, the efficacies of adjuvant chemotherapy and radiotherapy have been controversial [1, 8–13].

In this retrospective study, the clinicopathologic factors and the prognosis of thymoma with pleural dissemination were studied using the data from multiple centers of the Japanese Association for Research on the Thymus for evaluating the efficacy of surgical resection and multimodality therapy.

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Patients and Methods

Patients

A retrospective review of clinical records was conducted at 32 institutions that participated in the Japanese Association for Research on the Thymus. The present study was approved by the Institutional Review Board of Nagoya City University Hospital and other institutions, and individual patient consent was not required for this retrospective study. There were 2,835 thymic epithelial tumors collected that were treated between 1991 and 2010. They included 2,423 thymomas, 306 thymic carcinomas, 64 neuroendocrine carcinomas, and 42 unknown thymic epithelial tumors.

In this study, 148 thymoma patients with pleural dissemination were extracted. They included 128 and 20 patients in Masaoka stages IVA and IVB, respectively. To clarify the efficacy of surgical resection, 12 patients who underwent biopsy only were excluded. We used the most recent revision of the World Health Organization histologic TNM classification and stage grouping of thymic epithelial tumors in 2004 [14] and the Masaoka staging system [15, 16]. In cases with disseminated pleural nodules (stage IVA) or lymph node involvement (stage IVB), if all of the pleural nodules or involved lymph nodes were completely resected, the operation was considered a macroscopically complete resection (MCR).

Statistical Analysis

Survival curves were analyzed by the Kaplan-Meier method and univariate log-rank test. Overall survival was calculated from the date of surgery to death. Disease-free survival was calculated from the date of surgery to the date of identification of the recurrent disease or death for any cause. The frequency distributions between groups were tested with the χ^2 test. Significance was defined as a probability value of less than 0.05. All of the data were analyzed with EZR software [17].

Results

The 136 patients ranged in age from 23 to 83 years, with a mean age of 52. They consisted of 51 men and 85 women. Using World Health Organization histopathologic classification of the tumors [12], thymomas were diagnosed as

Table 1. Prognostic Factors in Thymoma With Pleural Dissemination (n = 136)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test *p* Value
Sex	Male	51	87.3%	68.2%	0.572
	Female	85	81.3%	59.8%	
Age	≤60 y	95	89.3%	60.5%	0.462
	>60 y	41	68.4%	68.4%	
PS	0	98	83.8%	62.8%	0.823
	≥1	33	84.5%	57.1%	
WHO classification	A, AB, B1	31	73.1%	53.3%	0.371
	B2, B3	105	86.0%	65.4%	
Extrapleural pneumonectomy	–	128	85.3%	62.5%	0.633
	+	8	70.0%	70.0%	
MG	–	97	79.4%	58.0%	0.125
	+	39	92.6%	71.9%	
Adjuvant chemotherapy	–	93	84.5%	62.3%	0.690
	+	43	82.2%	62.2%	
Adjuvant radiotherapy	–	75	83.5%	60.6%	0.759
	+	61	81.9%	62.2%	
Adjuvant chemoradiotherapy	–	120	82.8%	61.7%	0.515
	+	16	84.8%	60.6%	
Preoperative Masaoka stage	I–III	27	87.0%	77.3%	0.173
	IVa, IVb	75	83.7%	56.6%	
Maximal tumor size	≤70 mm	68	85.1%	63.0%	0.762
	>70 mm	60	86.0%	60.8%	
Number of pleural dissemination	1–10	64	84.2%	80.2%	0.090
	≥11	35	85.0%	52.2%	
Resectability	MCR	46	82.6%	82.6%	0.064
	MRT	86	83.2%	53.9%	
Postoperative Masaoka stage	IVA	118	86.7%	62.5%	0.255
	IVB	18	67.8%	59.4%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.