Thymic Carcinoma: 30 Cases at a Single Institution

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Introduction: Thymic carcinoma is a rare and invasive mediastinal neoplasm that often metastasizes. It constitutes a heterogeneous group of tumors that displays different biologic behavior and prognosis. The clinical prognostic factors and treatment of thymic carcinoma are not yet standardized.

Methods: Thirty patients with thymic carcinoma have been treated at Nagoya City University Hospital since 1983. The clinical and pathologic data of these patients were retrospectively reviewed. Thirteen cases were considered to be unresectable or inoperable and received chemotherapy or chemoradiotherapy. Seventeen cases underwent resection; total in 7 cases and subtotal in 10 cases. Postoperative irradiation was added as adjuvant therapy in the tolerable cases. The most recent five cases received induction chemotherapy.

Results: In 17 of the 30 cases, the patients died. The survival periods in the death cases were from 2.4 to 78.1 months (mean, 32.4 months; median, 21.0 months). The observation periods in the 13 live cases were 6.3 to 232 months (average follow-up, 64.6 months). The 5-year survival rate was 47.5%, and median survival time (MST) was 49.0 months. Cases that underwent total resection showed significantly better prognosis than cases with subtotal resection ($p = 0.011$) and inoperable cases ($p = 0.002$). The cases that underwent subtotal resection showed significantly better prognosis than the inoperable cases ($p = 0.050$). The cases with hematogenous metastasis demonstrated significantly poorer prognosis ($p = 0.021$), but lymphogenous metastasis was not a significant predictor of poor prognosis. Only resectability was a significant prognostic factor in multivariate Cox regression analysis, and the hazard ratio was 5.123.

Conclusions: Resectability was the only prognostic factor in thymic carcinoma. We suggest the importance of preoperative precise evaluation to exclude unresectable Masaoka stage IVb disease and expect preoperative chemotherapy or chemoradiotherapy to improve the respectability.

Key Words: Thymic carcinoma.

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Thymic carcinoma is a rare and invasive mediastinal neoplasm that often metastasizes. It constitutes a heterogeneous group of tumors that displays different biologic behavior and prognosis. Chung et al. reported 305 patients with thymic carcinoma compiled from a Medline search from 1966 to 2000.[1] Kondo et al. reported 1320 patients with thymic epithelial tumors who were treated in 115 institutes in Japan from 1990 to 1994.[2] Their report included 186 thymic carcinomas. Other than these reports of the accumulation of cases from multiple institutions, only limited numbers of patients have been analyzed. Some reports suggested that tumor resectability, tumor stage, and tumor histology grading influenced the outcome.[3–5] Nevertheless, the clinicopathologic characteristics are still unclear. We treated 30 patients with thymic carcinoma from 1983 to 2006 at a single institution, and retrospectively reviewed their data to determine clinical prognostic factors and appropriate staging classification.

PATIENTS AND METHODS

Thirty patients with thymic carcinoma have been treated at Nagoya City University Hospital since 1983. The clinical and pathologic data of these patients were retrospectively reviewed. The study was approved by the Institutional Review Board of Nagoya City University Hospital. Written informed consent was obtained from all living patients and the families of deceased patients There were 16 men and 14 women, with a mean age of 59 years (median, 59.5) and a range between 33 and 84 years. Seventeen of 30 patients had clinical symptoms: chest pain ($n = 9$), facial or arm edema ($n = 4$), cough ($n = 2$), hoarseness ($n = 1$), and hemosputum ($n = 1$). No patients had concomitant paraneoplastic syndromes such as myasthenia gravis or pure red cell aplasia. Pretreatment evaluation of the tumor was done by physical examination, chest radiography, chest computed tomography (CT) scan and/or chest magnetic resonance imaging, abdominal CT scan, or brain CT scan to evaluate whether the lesions were resectable. In the six most recent cases, positron emission tomography was performed. Two patients underwent surgical resection without pretreatment biopsy because the tumor lesions were clinically diagnosed as noninvasive thymoma. For the other 28 tumors, pretreatment biopsy was performed. Cases with World Health Organization (WHO) classification type B3 thymoma (well-differentiated thymic carcinoma) and carcinoid tumors were excluded from the study. Treatment policy has changed transitionally. In the inoperable cases, intravenous chemotherapy has been se-

lected with or without irradiation therapy. The cases were considered to be unresectable because of (1) apparent pleural or pericardial dissemination, (2) massive invasion of the great vessels or apparent invasion of the heart, or (3) hematogenous or cervical lymphogenous metastasis. Adjuvant chemotherapy has been considered an option for cases that underwent total resection, and was selected routinely in cases with subtotal resection and neuroendocrine carcinoma. Recently, paclitaxel and carboplatin have been selected for non-small cell carcinomas, and cisplatin-based regimens have been used for neuroendocrine carcinoma. In the most recent five cases, induction chemotherapy or chemoradiotherapy was performed before the operation. Postoperative irradiation was routinely added as adjuvant therapy in the tolerable cases that did not receive preoperative radiation therapy. Preoperative radiation therapy was limited to a dose of 40 Gy, and radical radiation was fully performed at a dose of 60 Gy. To determine the relation between resectability and prognosis, clear definitions of total resection and subtotal resection were necessary. We defined total resection as macroscopically and microscopically total resection of a tumor. For metastatic lymph nodes, we defined total resection if the lymph nodes with metastasis were located only in the anterior mediastinum and were resected en-block with the thymus and the tumor. We also regarded the cases with disseminations as subtotal resection even if all nodules were resected macroscopically. Because dissemination of thymic carcinoma was flat, it was difficult to distinguish from whitish pleural thickness. I believe that many thoracic surgeons are anxious about the resectability when dissemination nodules are removed macroscopically during operation and even after the operation. Only open biopsy or partial resection with residual large mass was not included in subtotal resection, and we regarded those cases as inoperable or unresectable.

Statistical analysis of survival was performed using the Kaplan-Meier and univariable log-rank test. Multivariate Cox regression analysis was performed. Statistical significance was defined as p less than 0.05.

RESULTS

The most common histologic type was squamous cell carcinoma (SqCC) ($n = 17$). SqCC was diagnosed as well-differentiated in five cases, moderate in five cases, moderate to poor in three cases, and poor in four cases. Other histologic types were neuroendocrine carcinoma ($n = 3$; two small-cell carcinoma and one large cell neuroendocrine carcinoma), adenocarcinoma ($n = 2$), poorly differentiated carcinoma without adenocarcinoma or SqCC features ($n = 2$), lymphoepithelioma-like carcinoma ($n = 1$), and two mixed subtypes (adenoid cystic carcinoma and SqCC, mucoepidermoid carcinoma and SqCC). Three tumors were diagnosed as carcinomas without subclassification. Clinical and pathologic staging were based on both the WHO classification[6] and the criteria described by Masaoka et al.[7] In the WHO classification, 2 cases were diagnosed as stage II disease, 14 cases were stage III disease, and 14 cases were stage IV disease. In the Masaoka classification, 2 cases were diagnosed as stage II disease, 13 cases were stage III, 7 cases were stage IVa, and 8 cases were stage IVb disease.

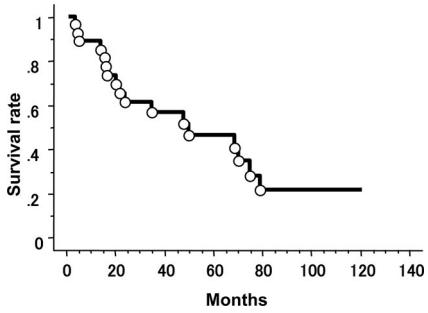

FIGURE 1. Overall survival of 30 cases. Five-year survival rate was 47.5% and median survival time (MST) was 49.0 months.

Seventeen of 30 cases died of cancer itself or from complications from cancer and its related treatment. The survival periods in the death cases were from 2.4 to 78.1 months (mean, 32.4 months; median, 21.0 months). The observation periods in the 13 live cases were 6.3 to 232 months (average follow-up, 64.6 months). Five-year survival rate was 47.5%, and median survival time (MST) was 49.0 months (Figure 1).

Clinicopathologic factors and prognosis are reported in Table 1. Gender and WHO T factor (primary tumor factor) did not influence prognosis statistically. N factor (regional lymph nodal factor) was also not a significant prognostic factor, although all five cases with lymphogenous metastasis died and had low 5-year survival rate (33.8%) and MST (40.0 months). M factor (distant metastasis factor) was also analyzed. In the group with hematogenous metastasis, all four cases died and no case experienced long survival with low MST (15.3 months). In the group without hematogenous metastasis, 13 cases died, and the 5-year survival rate was 58.3% and the MST was 69.7 months. The cases with hematogenous metastasis showed significantly poorer prognosis ($p = 0.021$) than those without hematogenous metastasis.

In stage classification, we have tried to classify in WHO (Figure 2*A*) and Masaoka stages (Figure 3*A*). In WHO classification, two cases of stage II survived without disease. Six of 14 cases with stage III disease died and their 5-year survival rate was 57.9% and their MST was 78.1 months. Eleven of 14 cases with stage IV disease died and their 5-year survival rate was 37.5% and their MST was 47.0 months. Prognosis in the cases with stage II or III was better than in the cases with stage IV disease, but it was not significant ($p = 0.064$) (Figure 2*B*).

In the Masaoka classification, two cases of stage II survived without disease. Five of 13 cases with stage III disease died, and the 5-year survival rate was 53.8%. MST was not predicted. Four of seven cases with stage IVa disease died and their 5-year survival rate was 64.3% and their MST was 68.0 months. All eight cases with stage IVb disease died and their 5-year survival rate was 25.0% and their MST was 15.3 months. There were no significant differences in prognosis among stage II + III, IVa, and IVb ($p = 0.115$) (Figure 3*B*).

TABLE 1. Clinocopathological Factors and Prognosis

	Number of Death Cases/Total Number of Cases	Five-Year Survival Rate (%)	Median Survival Time (mo)	Significance (log rank test)
Gender				
Male	8/16	46.2	49.0	$p = 0.889$
Female	9/14	49.2	47.0	
WHO classification				
T2	1/3	100	78.0	$p = 0.359$
T3	9/17	42.8	33.8	
T4	7/10	42.0	49.0	
WHO classification				
N0	12/25	49.0	49.1	$p = 0.302$
N1 + 2	5/5	33.8	40.0	
WHO classification				
M0	13/26	69.7	58.3	$p = 0.021$
M1	4/4	15.3	0	
WHO stage				
II	0/2	100	N/A	II + III vs. IV $p = 0.064$
III	6/14	57.9	78.0	
IV	11/14	37.5	47.0	
Masaoka stage				
II	0/2	100	N/A	II + III, IVa and IVb $p = 0.115$
III	5/13	53.8	N/A	
IVa	4/7	64.3	68.0	
IVb	8/8	25.0	15.3	
Histology				
High risk	11/20	69.7	50.5	$p = 0.281$
Low risk	3/7	68.0	64.3	
(Unknown)	(3/3)			
Resectability				$p = 0.002$
Total resection	1/7	100	N/A	TR vs. SR: $p = 0.011$
Subtotal resection	6/10	56.0	69.7	SR vs. IO: $p = 0.050$
Inoperable	10/13	14.1	23.0	TR vs. IO: $p = 0.002$

N/A, not available; TR, total resection; SR, subtotal resection; IO, inoperable.

Histologic classification of thymic carcinoma has been suggested by Suster and Rosai.[3] In this study, 7 cases were diagnosed in the low risk group and 20 cases were in the high-risk group. Three of seven cases in the low risk group died and the 5-year survival rate was 68.0%. Eleven of 20 cases in the high-risk group died and the 5-year survival rate was 69.7% and the MST was 50.5 months. There was no significant difference in the survival of these groups.

Resectability and prognosis were assessed in our study (Figure 4). We defined total and subtotal resection clearly, as stated in the materials and methods. Total resection was performed in six cases, and all six cases survived over 5 years. Subtotal resection (subtotal resection) was performed in 10 cases. Six of the 10 cases with subtotal resection died and their 5-year survival rate was 56.0% and their MST was 69.7 months. In the inoperable cases, 10 of 13 cases died and their 5-year survival rate was 14.1% and their MST was 23.0 months. The cases that underwent total resection showed significantly better prognosis than the cases with subtotal resection ($p = 0.011$) and the inoperable cases ($p = 0.002$). In addition, the cases that underwent subtotal resection showed significantly better prognosis than the inoperable cases ($p = 0.050$).

Multivariate Cox regression analysis was performed for WHO M factor (hematogenous metastasis), WHO stage, Masaoka stage, and resectability (total resection or subtotal resection or inoperable). Only resectability was a significant prognostic factor and the hazard ratio was 5.123 (Table 2).

DISCUSSION

We determined that resectability was the only prognostic factor in thymic carcinoma in this study. It has been reported that total resection of thymic carcinoma significantly

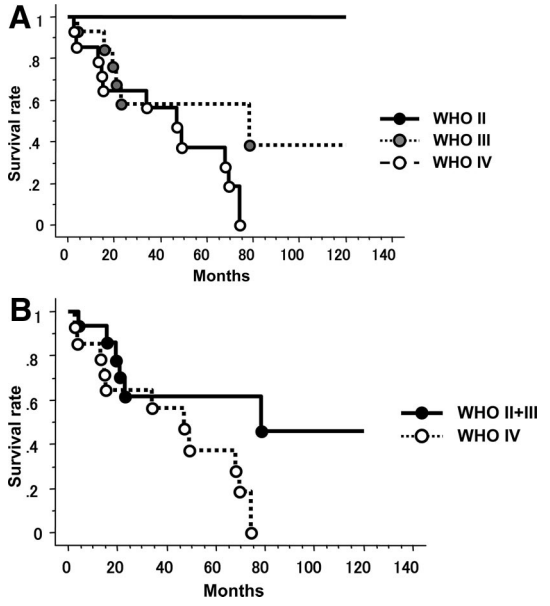

FIGURE 2. WHO stage classification and prognosis. *A*, Prognosis in three stages (II, III, and IV) were compared. *B*, Stages II and III were joined.

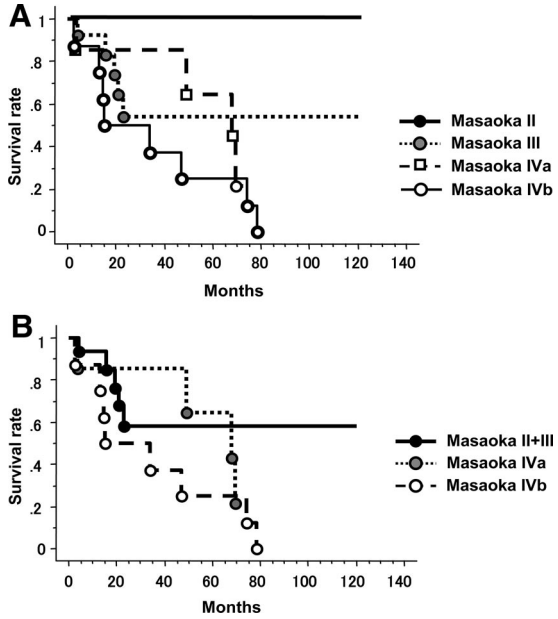

FIGURE 3. Masaoka stage classification and prognosis. *A*, Prognosis in four stages (II, III, IVa, and IVb) were compared. *B*, Stages II and III were joined.

increased survival rate.[2,4] In this study, many variations in treatment procedure were present, although most cases that underwent total resection or subtotal resection received irradiation therapy (15/17, 88%). We think the prognosis of those cases that underwent total or subtotal resection depended on the combination effect of resection and radiation therapy. Kondo et al. reported better prognosis in cases with total resection than in cases with subtotal resection or inoperable

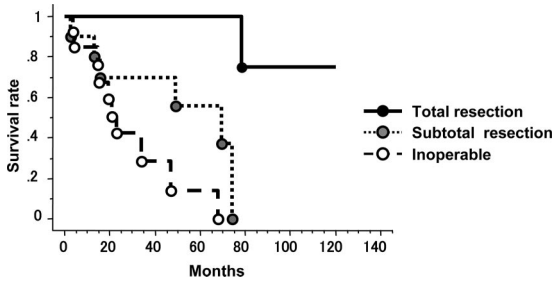

FIGURE 4. Resectability and prognosis. The cases that underwent total resection demonstrated significantly better prognosis than the cases with subtotal resection ($p = 0.011$) and the inoperable cases ($p = 0.002$). The cases that underwent subtotal resection also demonstrated significantly better prognosis than the inoperable cases ($p = 0.050$).

TABLE 2. Multivariate Cox Regression Analysis

Factors	Significance (*p*)	Hazard Ratio
WHO classification M factor	0.604	1.548
WHO stage	0.630	1.546
Masaoka stage	0.205	2.030
Resectability	0.003	5.123

cases.[2] Tseng et al. also reported better prognosis in cases with complete resection and poor prognosis in cases with tumor invasion of the great vessels.[4] In this study, we also demonstrated better prognosis in the cases with total resection. In addition, the cases with subtotal resection demonstrated better prognosis than the inoperable cases. We speculated that the difference between Kondo's report and our study depended on the definition of total resection and subtotal resection. Kondo et al. defined total resection as a condition in which no tumor remained macroscopically. In our study there were two cases with small number of dissemination nodules (Masaoka IVa stage) and they showed better prognosis. Probably such cases that underwent macroscopically total resection were included in the total resection group in Kondo's study. We included such cases with dissemination in the group with subtotal resection even if all nodules were resected macroscopically, because dissemination nodules of thymic carcinoma was flat and it was difficult to distinguish from whitish pleural thickness. I believe many thoracic surgeons are not confident of the resectability, whether total resection is performed or not during operation and even after the operation. From these experiences we have defined the macroscopic total resection of pleural dissemination as subtotal resection. In addition, radiation therapy was performed for all cases with subtotal resection in our study. This effect may have contributed to improve prognosis of the cases with subtotal resection.

Although resectability was the only prognostic factor with a high hazard ratio (5.123), it is not an original prognostic factor. Whether resection is performed or not is evaluated by preoperative assessment and perioperative findings and these assessments are important. We think that righteousness of these assessments which we have performed was demonstrated. We cannot improve the prognosis of inopera-

ble cases even if they undergo subtotal resection. There was a poor prognosis for the cases with Masaoka Stage IVb disease that underwent subtotal resection. Two cases with Masaoka stage IVb disease died 2.4 and 13.3 months after subtotal resection. Therefore, we do not recommend partial resection of unresectable tumors (inoperable cases) as debulking surgery. It is necessary to determine the real operative indication to improve the operative result. In this study, we could not strictly determine the inoperable indications. Nevertheless, we consider that Masaoka stage IVb disease should be excluded from the operative indication.

In addition, to improve the resectability, we expect preoperative chemotherapy. Chemotherapy has been reported to be effective in thymic carcinoma.[8,9] Recently, the effect of doublet chemotherapy consisting of carboplatin and paclitaxel has been reported.[10–12] We performed preoperative chemotherapy or chemoradiotherapy in our most recent four cases. No cases showed any complications of preoperative adjuvant therapy. It was not possible to evaluate whether the preoperative chemotherapy or chemoradiotherapy had a positive effect on survival.

Because a new WHO classification of malignant thymic epithelial tumor was published in 2004,[6] we adapted 30 cases with thymic carcinoma to the WHO classification and the Masaoka classification. There have been no thymic carcinoma specific stage classifications. We have so far used the Masaoka classification that was created for thymoma.[7] In this study, we compared the WHO classification and the Masaoka classification. Thymic carcinoma is usually diagnosed with the advanced stages. In our study, most cases (28 of 30 cases, 93%) were diagnosed with WHO stage III or IV. If we use the WHO classification, the distribution of cases trends toward advanced stages. On the other hand, Masaoka stage classification divides stage IV into stages IVa and IVb, and the distribution is better balanced. In the relationship between stage and prognosis, both the WHO and Masaoka classifications did not demonstrate statistical significance in prognosis by single and multivariate analysis. More accumulation of cases will be necessary to evaluate the relationship between stage and prognosis. New original stage classification for only thymic carcinoma may be necessary.

It is necessary to add the limitations of our study, for example, it was retrospective and it covered for long periods. In addition, many different treatments have been given for cases.

In conclusion, resectability was the only prognostic factor in thymic carcinoma. To increase the resectability, we suggest the importance of precise preoperative evaluation to exclude unresectable Masaoka stage IVb disease and expect preoperative chemotherapy or chemoradiotherapy to improve the respectability.

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