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Surgical outcomes and reevaluation of treatment strategies for thymomas

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Abstract. Improved histological typing systems for thymic tumors and advances in induction and adjuvant therapy have created the need to reevaluate strategies for the management of thymoma. We retrospectively studied 73 patients with completely resected thymomas unassociated with myasthenia gravis. The World Health Organization (WHO) histologic classification, clinicopathological features and surgical outcomes were analyzed. Overall survival was 66.2% at 10 years, and the median survival time was 169 months. According to the Masaoka staging system, overall survival rates at 10 years were 94.7% in stage I, 76.1% in stage II, 30% in stage III and 0% in stage IV. In the WHO classification, overall survival rates at 10 years were 91.9% in types A and AB, 50.9% in type B2 and not achieved in type B3. The disease-free interval was slightly shorter in patients with B2 and B3 disease than in those with type A, AB and B1 disease. Advanced thymomas were significantly associated with type B2 and B3 ($p<0.01$). In stage III and IV disease, adjuvant or neoadjuvant therapy was associated with better survival as compared to no adjuvant therapy ($p=0.07$). On multivariate analysis, Masaoka stage III and IV disease and extended thymectomy indicated significant, negative and independent risk factors for survival ($p<0.01$). Masaoka stage I and II thymomas or WHO type A and AB thymomas have favorable prognoses and do not require postoperative adjuvant therapy. Patients with stage III and IV thymomas require additional therapy after surgery.

Introduction

Thymoma is a rare tumor derived from epithelial cells of the thymus. It is considered to be malignant due to the occasional invasion to surrounding organs and dissemination. Surgery remains the treatment of choice for thymoma, and postoperative radiation has been used as adjuvant therapy (1-3). Induction chemotherapy or chemoradiotherapy was suggested to improve outcomes, especially in advanced disease (4-7). However, the benefits of adjuvant radiotherapy in patients with Masaoka stage II disease (1,2,8) are controversial. The histological classification of thymoma remained controversial for a long period of time (9), but in 1999 the World Health Organization (WHO) Consensus Committee published a histological typing system for tumors of the thymus (10). Thymomas are now identified as A, AB, B1, B2 and B3 on the basis of the morphology of epithelial cells and the ratio of lymphocytes to epithelial cells. Numerous studies suggested that the WHO histological classification is useful for the prediction of outcomes (11-13). The addition of this new prognostic factor has therefore created the need to reevaluate treatment strategies for thymomas.

Patients and methods

Between 1985 and 2001, 73 thymomas, unassociated with myasthenia gravis (MG), were completely resected at the Kanagawa Cancer Center. Patients who had thymic cancer, carcinoids or non-curative surgery were excluded from this study. The extent of resection was determined by the operating surgeons on the basis of the patients' condition and extent of tumor. Thymomas were categorized according to the WHO classification (10). The histological diagnosis was based on the most significant component of each tumor. Pathological staging was performed according to the Masaoka staging system (8). In this retrospective study, the clinicopathological and prognostic relevance of the WHO histological classification for thymomas were examined, including the variables of age, gender, operation procedure, Masaoka staging system (I and II vs. III and IV) and WHO histological classification (A and AB vs. B1, B2 and B3; A, AB and B1 vs. B2 and B3). The surgical procedure for thymoma was classified into 3 groups: extended thymectomy (resection of the thymus, including the thymoma and the anterior mediastinal adipose tissue), thymectomy (resection of the thymus, including the thymoma) and tumor resection (resection of the tumor and a portion of the thymus) (14). Kaplan-Meier curves were plotted to evaluate overall and disease-free survival, and the log-rank test was used to compare survival between the groups. Each

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Table I. Patient characteristics.

Age	59.0 (18-86)
Gender	male 30, female 43
Masaoka stage	
I	19
II	41
III	10
IV	3
WHO classification	
Type A	3
Type AB	30
Type B1	18
Type B2	13
Type B3	6
Others	3
Extent of surgery	
Extended thymectomy	14
Thymectomy	47
Tumor resection	12

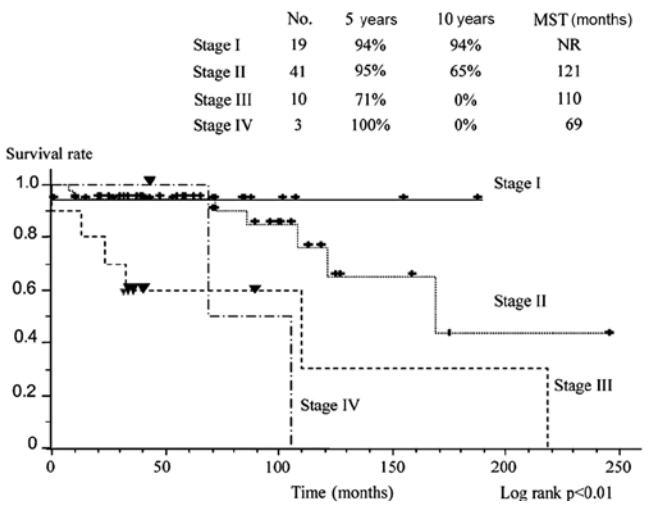

Figure 1. Overall survival curve according to the Masaoka staging system. MST, median suvival time; NR, no recurrence.

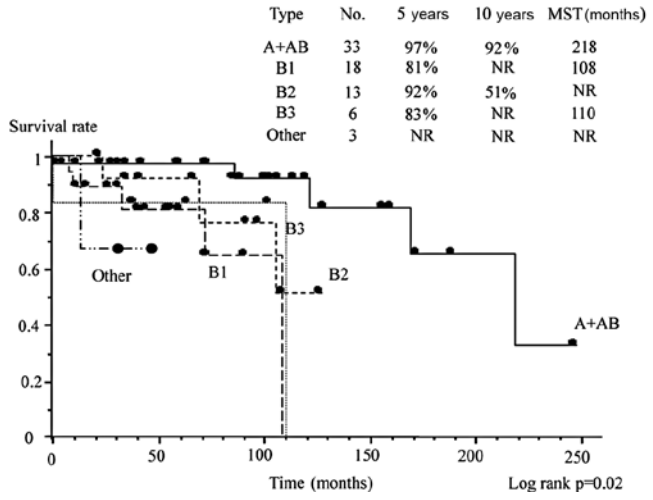

Figure 2. Overall survival curve according to the WHO classification. MST, median suvival time; NR, no recurrence.

variable was tested by the Chi-square and Fisher's exact tests. The Cox regression analysis was used for multivariate analysis of survival, performed with Stat View for Windows (version 5.0; SAS Institute Inc., Cary, NC, USA). Significance was defined as a $p<0.05$. Our institutional internal review board approved this retrospective study.

Results

The study group comprised 30 men and 43 women. Their median age was 59 years (range 18-86). Median follow-up was 80 months. Table I shows the clinical characteristics of the 73 patients. The overall survival rate was 89.8% at 5 years and 66.2% at 10 years. Median survival time (MST) was 169 months. A total of 16 patients succumbed to the disease, with only 3 patients deceased from tumor recurrence. The recurrences were locoregional or intrathoracic. Overall survival curves are plotted according to stage (Fig. 1). Survival was significantly better in patients with stage I and II disease than in those with stage III and IV disease. Fig. 2 shows survival according to the WHO classification. WHO type A and AB disease was associated with a more favorable survival than types B1, B2 and B3. Fig. 3 compares survival between patients with type A or AB disease compared to those with type B1, B2 or B3 disease. In the former group, the overall survival rate was 97% at 5 years and 92% at 10 years, with an MST of 218 months. By contrast, the overall survival rate in the latter group was only 86% at 5 years and 22% at 10 years, with an MST of 108 months. Survival was significantly worse in type B1, B2 and B3 disease than in type A and AB ($p<0.01$). Fig. 4 shows the distribution of patients according to the Masaoka staging system and WHO classification. A total of 81% of patients (48 cases) with stage I or II disease according to the Masaoka staging system had type A or AB disease according to WHO classification, and 83% of patients (10 cases) with stage III or IV disease were classified as having type B2 or B3 disease. Histologically, advanced thymomas were significantly associated with type B2 and B3 disease ($p<0.01$). Fig. 5 shows survival according to the extent of surgery. Extended thymectomy was associated with significantly worse survival than thymectomy and tumor resection. No differences were noted between total thymectomy and tumor resection. On multivariate analysis, stage III and IV disease and extended thymectomy were adverse, independent risk factors for survival ($p<0.01$). No recurrence occurred among patients with type A, AB or B1 disease (Fig. 6).

Adjuvant radiotherapy in stage II disease conferred no survival advantage as compared to no adjuvant radiotherapy (survival rate at 5 years, 95 vs. 75%, $p=0.17$). In stage III and IV disease, however, adjuvant or neoadjuvant therapy was associated with significantly better survival (100% at 5 years) than no adjuvant therapy (6 patients, 66.7%, $p=0.07$). Complete remission was observed in two patients in response to induction chemotherapy (cisplatin, vincristine, doxorubicin

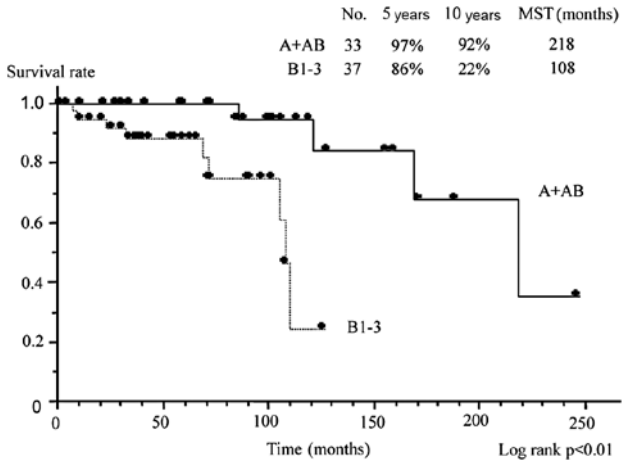

Figure 3. Overall survival curve according to the WHO classification A and AB vs. B1, B2 and B3. MST, median suvival time.

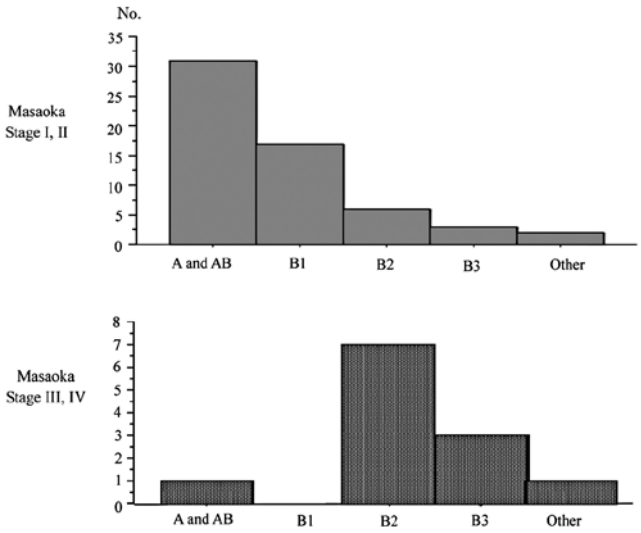

Figure 4. Distribution and relation between the Masaoka staging system and WHO classification.

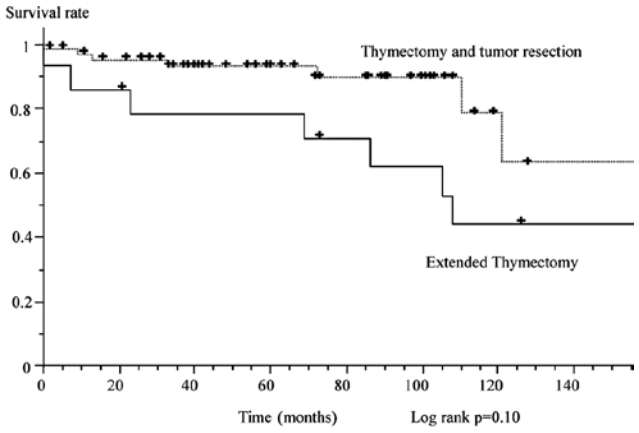

Figure 5. Overall survival curve according to the extent of the surgery.

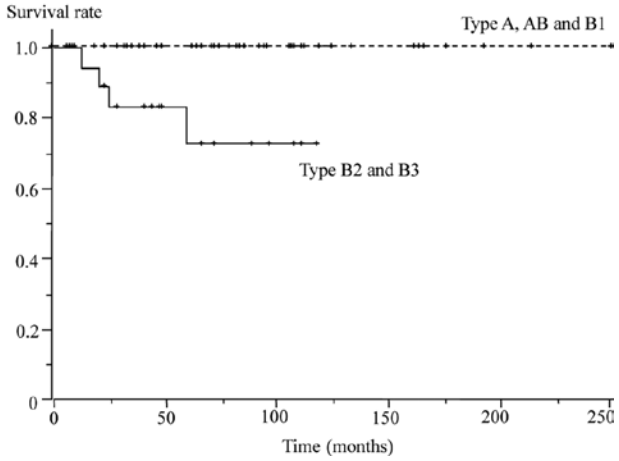

Figure 6. Disease-free survival curve according to the WHO classification.

and etoposide). No viable tumor cells were noted in the resected specimens.

MG developed postoperatively in 5 (6.8%) of the 73 patients. One patient each had stage I, III and IV disease, and 2 had stage II disease. According to the WHO classification, 1 patient had type AB disease, 2 had B1 and 2 patients had B2 disease. The mean time to the onset of MG was 16.4 months after surgery (range 5-31), with no recurrence of thymoma. The incidence of postoperative MG did not differ among the operative procedures (extended thymectomy, thymectomy and tumor resection; p>0.99). In 36 patients, anti-acetylcholine receptor antibodies were measured pre-operatively and were abnormally elevated in only 1 (50%) of 2 patients with postoperative MG and 7 (21%) of 34 patients without postoperative MG; a difference that was not significant (Fisher's exact test, p=0.40). The incidence of postoperative complications did not differ significantly among extended thymectomy, thymectomy and tumor resection (15.4 vs. 12.8%, p>0.99), but the operation time of extended thymectomy was significantly longer than with the other procedures (average 240 vs. 178 min, p=0.01).

Discussion

A number of thymomas are clinically asymptomatic (1) and difficult to detect on routine radiographic examinations at medical checkups due to their location. At the time of diagnosis, thymomas are often large. Tumor size is an important variable for staging many solid tumors (14), but not thymoma. In the Masaoka staging system, which is used internationally, staging is based primarily on the extent of tumor cells, i.e., invasion of the capsule and surrounding organs, dissemination of tumor cells and metastasis are the most important variables (8). This staging system is well known for its satisfactory relation to outcomes (1,2,8). In general, stage I and II disease exhibit favorable outcomes, where stage III and IV disease are occasionally associated with local recurrence, leading to the patient succumbing to the disease (2,8). Histological classifications were controversial (9) until the establishment of the WHO classification. Various studies have shown that the WHO classification is strongly related to outcomes, similar to the Masaoka staging system (8). In this series, we confirmed that type A and AB disease, according to the WHO classification was associated with a more favorable overall survival than was type B1, B2 and B3 disease. None of the patients with

type B1 disease succumbed. Type A, AB and B1 disease, thus, had more favorable outcomes than type B2 and B3, consistent with the results of previous studies (11-13,15,16).

Surgery remains the mainstay of treatment for thymomas, with thymectomy as the standard procedure (1). Thymomas can be accompanied by autoimmune disease, such as MG. Extended thymectomy is one surgical procedure for the treatment of MG (17). In previous studies, the incidence of postoperative MG in patients with thymoma without MG ranged from 1.5 to 28% (18-20). We previously performed extended thymectomy in patients with thymoma to prevent the postoperative development of MG. In this series, however, extended thymectomy was not more effective than standard procedures. Data from Japan indicate that resection of the thymus gland does not prevent postoperative MG (20). In our series, the results of pre-operative tests for anti-acetylcholine receptor antibodies did not predict the postoperative risk of MG. Thus, the use of extended thymectomy for thymomas remains controversial. No differences in postoperative complications among surgical procedures occurred, but prolonged surgery time may lead to increased costs and surgical stress on patients. Therefore, to ensure a definite surgical margin, total thymectomy appears to be the most appropriate procedure for thymomas.

The main site of recurrence of thymomas is the thoracic cavity. Adjuvant radiotherapy of the mediastinum were suggested to be useful for the decrease of the risk of local recurrence, even in stage II disease (8,21). In our study, adjuvant or neoadjuvant therapy did not improve overall or disease-free survival in patients with stage II thymoma, suggesting that adjuvant radiotherapy is not therapeutically useful for stage II disease. By contrast, adjuvant or neoadjuvant therapy was associated with more favorable outcomes in patients with stage III and IV thymomas. Numerous studies reported that induction therapy produces favorable results in advanced thymoma (2,4-7). In our series, 2 patients had complete pathological responses to induction chemotherapy. Induction therapy is thus anticipated to play a more significant role in the treatment of advanced thymomas. However, whether induction therapy should be indicated for the treatment of resectable stage III thymomas remains a matter of debate. In patients with unresectable thymomas, induction therapy can produce favorable outcomes. Nonetheless, prospective studies are required to confirm whether induction therapy is therapeutically useful.

In conclusion, the outcomes of surgery for thymomas are satisfactory. Patients with Masaoka stage I or II disease or WHO type A or AB disease have favorable prognoses and do not require adjuvant therapy. Patients with stage III or IV thymomas should receive adjuvant therapy in addition to surgery. As for the extent of surgery, thymectomy is the procedure of choice for the management of thymomas.

References

1. Shields TW: Thymic tumors. In: Tymic Tumors. Shields TW, Locicero J III and Ponn RB (eds). General thoracic surgery, fifth edition. Lippincott Williams and Wilkins, Philadelphia, pp2181-2205, 2000.
2. Cowen D, Richaud P, Mornex F, *et al*: Thymoma. Results of a multicentric retrospective series of 149 non-metastatic irradiated patients and review of the literature. FNCLCC trialists. Federation Nationale des Centres de Lutte Contre le Cancer. Radiother Oncol 34: 9-16, 1995.
3. Hejna M, Haberl I and Raderer M: Nonsurgical management of malignant thymoma. Cancer 85: 1871-1884, 1999.
4. Igawa S, Murakami H, Takahashi T, *et al*: Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. Lung Cancer 67: 194-197, 2010.
5. Kim ES, Putnam JB, Komaki R, *et al*: Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 44: 369-379, 2005.
6. Rea F, Sartori F, Loy M, Calabrò F, Fornasiero A, Daniele O and Altavilla G: Chemotherapy and operation for invasive thymoma. J Thorac Cardiovasc Surg 106: 543-549, 1993.
7. Berruti A, Borasio P, Gerbino A, *et al*: Primary chemotherapy with adriamycin, cisplatin, vincristine and cyclophosphamide in locally advanced thymomas: a single institution experience. Br J Cancer 81: 841-845, 1999.
8. Masaoka A, Monden Y, Nakahara K and Tanioka T: Follow-up study of thymomas with special reference to their clinical stages. Cancer 48: 2485-2492, 1981.
9. Shimosato Y: Controversies surrounding the subclassification of thymoma. Cancer 74: 542-544, 1994.
10. Rosai J: World Health Organization International Histological Classification of Tumours. Histological Typing of Tumours of the Thymus. 2nd edition. Springer-Verlag, New York, 1999.
11. Rena O, Papalia E, Maggi G, *et al*: World Health Organization histologic classification: an independent prognostic factor in resected thymomas. Lung Cancer 50: 59-66, 2005.
12. Kondo K, Yoshizawa K, Tsuyuguchi M, *et al*: WHO histologic classification is a prognostic indicator in thymoma. Ann Thorac Surg 77: 1183-1188, 2004.
13. Okumura M, Ohta M, Tateyama H, *et al*: The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. Cancer 94: 624-632, 2002.
14. Pollock RE, Doroshow JH, Khayat D, *et al*: UICC Manual of Clinical Oncology. 8th edition. Wiley-Liss, NY, 2004.
15. Zisis C, Rontogianni D, Tzavara C, *et al*: Prognostic factors in thymic epithelial tumors undergoing complete resection. Ann Thorac Surg 80: 1056-1062, 2005.
16. Detterbeck FC: Clinical value of the WHO classification system of thymoma. Ann Thorac Surg 81: 2328-2334, 2006.
17. Masaoka A, Yamakawa Y, Niwa H, *et al*: Extended thymectomy for myasthenia gravis patients: a 20-year review. Ann Thorac Surg 62: 853-859, 1996.
18. Namba T, Brunner NG and Grob D: Myasthenia gravis in patients with thymoma, with particular reference to onset after thymectomy. Medicine 57: 411-433, 1978.
19. Rosenow EC III and Hurley BT: Disorders of the thymus. A review. Arch Intern Med 144: 763-770, 1984.
20. Kondo K and Monden Y: Myasthenia gravis appearing after thymectomy for thymoma. Eur J Cardiothorac Surg 28: 22-25, 2005.
21. Nakahara K, Ohno K, Hashimoto J, *et al*: Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. J Thorac Cardiovasc Surg 95: 1041-1047, 1988.