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ORIGINAL ARTICLE

Survival after extended thymectomy for thymoma

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Abstract

OBJECTIVES: Thymoma is a relatively rare tumour and is uniquely associated with autoimmune diseases such as myasthenia gravis (MG). However, the factors involved in the prognosis of thymoma remain under discussion.

METHODS: We retrospectively reviewed 162 patients who underwent extended thymectomy via median sternotomy for thymoma at our institute from 1976 to 2009. The histological subtype was classified according to the World Health Organization (WHO) histological classification system. Survival analysis was performed using the Kaplan–Meier method and the Cox proportional hazards model.

RESULTS: Tumours comprised 7 Type A tumours, 38 Type AB, 49 Type B1, 45 Type B2 and 23 Type B3. Various types of autoimmune diseases were comorbid in 66 patients. The median follow-up period was 94 months, and 14 patients experienced recurrence. Seven patients died of recurrent tumour, and 18 patients died of causes other than thymoma. The 10-year overall survival was 85.7%, and the 10-year disease-free survival (DFS) was 76.8%. The 10-year DFS was 62.5% for Type A, 86.3% for Type AB, 91.5% for Type B1, 77.1% for Type B2 and 26.3% for Type B3. In multivariate analysis, age, Type B3 and MG were determined as prognostic factors for survival. On the other hand, Masaoka's stage did not influence survival.

CONCLUSIONS: Type B3 classified by the WHO histological classification system is a poor prognostic factor for survival of thymoma after extended thymectomy. Association with MG is possibly an indicator of poor survival. Age is an independent prognostic factor, suggesting favourable prognosis of thymoma after surgical treatment. Considering thymoma is a rare tumour, it would be necessary to build a multi-institutional database as soon as possible.

Keywords: Thymoma • Extended thymectomy • Prognosis • World Health Organization histological classification system

THORACIC

INTRODUCTION

Thymoma is a relatively rare neoplasm arising from epithelial cells of the thymus. Its unique association with autoimmune diseases such as myasthenia gravis (MG) and pure red cell anaemia (PRCA) is well known [1, 2]. Thymoma exhibits malignant behaviour, invades adjacent organs and develops haematogenous or lymphogenous metastasis with progression. The standard treatment for thymoma is complete surgical resection. Although chemotherapy and/or radiotherapy have been adopted for locally advanced and metastatic diseases, the therapeutic effects of these treatments remain controversial [3]. Because of the rare incidence and favourable outcome of thymoma after surgical treatment in most patients, factors predicting survival after surgery remain unclear. To clarify the prognostic factors of thymoma, we retrospectively reviewed affected patients who had undergone extended thymectomy at our institute in the past 34 years.

MATERIALS AND METHODS

We reviewed the clinical charts of patients with thymoma who had undergone extended thymectomy via median sternotomy at our institute from 1976 to 2009. According to our institute's policy, resection of thymoma via lateral incision was performed until 1975. Then, in 1976, extended thymectomy via median sternotomy was adopted as the standard treatment because local recurrence after resection of thymoma was observed in several patients with early-stage disease who would otherwise have obtained a complete cure [4]. We recorded patient age, sex, history of MG or other autoimmune diseases and completeness of resection. Thymoma was classified according to Masaoka's staging system as follows: Stage I, macroscopically completely encapsulated, and microscopically no capsular invasion; Stage II, macroscopic invasion into the surrounding fatty tissue or mediastinal pleura, or microscopic invasion into the capsule; Stage III, macroscopic invasion into a neighbouring organ, i.e. the

pericardium, great vessels or lung; Stage IVA, pleural or pericardial dissemination; and Stage IVB, lymphogenous or haematogenous metastasis [5]. Adjuvant chemotherapy and/or radiotherapy were performed in most Stage III and IV patients. Histological diagnosis was performed based on the World Health Organization (WHO) histological classification system [6], and Type C tumour (thymic carcinoma and carcinoid) was not included because it is considered to have different aetiology.

Differences among the groups were assessed using Student's *t*-test or Pearson's χ^2-test. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan–Meier method, and difference in survival was determined by the log-rank test. Multivariate analysis was performed according to the Cox proportional hazards model to estimate hazard ratios with a 95% confidence interval (CI). A *P*-value of <0.05 was considered statistically significant. Statistic analysis was performed using JMP 6 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The study comprised 162 patients (83 men, 79 women; median age, 53 years; age range 15–83 years). The histological subtype in patients according to the WHO classification system was Type A in 7 patients, Type AB in 38, Type B1 in 49, Type B2 in 45 and Type B3 in 23. In addition, according to Masaoka's staging system, there were 76 patients with Stage I thymoma, 59 with Stage II, 14 with Stage III, 9 with Stage IVA and 4 with Stage IVB. Patients with advanced stage (Stage III/IV) were older than those with Stage I/ II (Table 1; $P = 0.005$). Distribution of stages differed among the histological subtypes ($P = 0.0004$). The relationship between Masaoka's stage and the WHO histological subtype is summarized in Table 2.

Table 1: Age distribution by Masaoka's stage

Age	No. of patients	Masaoka's stage				
		I	II	III	IVA	IVB
Up to 49	66	32	23	4	5	2
50–59	41	25	15	0	1	0
60–69	29	13	10	5	0	1
70 and more	26	6	11	5	3	1

Table 2: Relation between Masaoka's stage and the WHO histological classification

Masaoka's stage	No. of patients	WHO classification					Complete resection (%)
		A	AB	B1	B2	B3	
I	76	3	18	31	19	5	76 (100%)
II	59	3	20	11	19	6	57 (96.6%)
III	14	1		4	3	6	10 (71.4 %)
IVA	9			3	3	3	2 (22.2%)
IVB	4				1	3	0 (0.0%)
Total	162	7	38	49	45	23	145 (89.5%)

Autoimmune disease was present in 66 patients (40.7%): MG in 53, hypothyroidism in 4, PRCA in 3, agammaglobulinaemia and Basedow disease in 2 and Felty syndrome and stiff-person syndrome in 1 patient each. Prevalence of MG was significantly higher in the early days (62.3% before 1990 vs. 14.9% after 1990, $P < 0.0001$). MG was more frequently associated with Type B1/ B2/B3 thymoma than with Type A/AB thymoma (Table 3; $P < 0.0001$). There was no relation between the association of MG and Masaoka's stage ($P = 0.37$).

All patients underwent extended thymectomy via median sternotomy. Two patients with Stage IVA also underwent extrapleural pneumonectomy of the diseased side. Complete resection was achieved in 145 patients (89.5%). Adjuvant therapy was performed in 24 (88.9%) of 27 patients with Stage III or IV thymoma: preoperative radiotherapy in 3, postoperative radiotherapy in 16, preoperative chemotherapy and postoperative radiotherapy in 1, postoperative chemoradiotherapy in 1 (in the order of chemotherapy and radiotherapy) and postoperative chemotherapy in 3. The regimen of chemotherapy was cyclophosphamide with steroid in one in the early days, and others received a platinum-containing regimen [cisplatin, doxorubicin, and cyclophosphamide (PAC) or doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC)]. Reasons for not performing adjuvant therapy were advanced age, operative morbidity or patient refusal.

Fourteen patients experienced recurrence. Of these, nine had recurrence after complete resection (Table 4), while only one had Stage I thymoma. The median interval from surgery to recurrence was 63 months (range, 5–134 months). Seven patients died of recurrent tumour, and the interval from recurrence to death ranged 5–95 months (median, 16 months). Eighteen patients died of causes other than thymoma: 2 died of malignant lymphoma and pneumonia, and 1 each died of PRCA, morbidity of coronary bypass surgery, bladder cancer, fulminant hepatitis, primary lung cancer, respiratory failure by MG, constrictive pericarditis probably due to postoperative radiation therapy, Parkinson disease, cerebral haemorrhage, glioblastoma, sepsis, sudden death, pulmonary embolism and insenescence.

The 5-year and 10-year OS were 94.7 and 85.7%, respectively, and the 5-year and 10-year DFS were 90.9 and 76.8%, respectively (Fig. 1). DFS curves according to the WHO histological subtype are shown in Fig. 2. The 10-year DFS was 62.5% for Type A, 86.3% for Type AB, 91.5% for Type B1, 77.1% for Type B2 and 26.3% for Type B3. There was a significant difference in the survival curve between Type AB and Type B3 ($P = 0.0008$), between Type B1 and Type B2 ($P = 0.026$) and between Type B1 and Type B3 ($P = 0.0001$), by the log-rank test. On the other hand, there was no difference between Type A and AB ($P = 0.16$), between Type A and B1 ($P = 0.10$) and Type AB and B1 ($P = 0.95$). DFS curves according to Masaoka's staging system are shown in Fig. 3. The 10-year DFS was 84.8% for Stage I thymoma, 80.4% for Stage II, 38.1% for Stage III and 38.1% for Stage IV. There was no difference in the survival curve between Stage I and Stage II ($P = 0.90$). Survival for Stage III disease was significantly worse than that for Stage I ($P = 0.0002$) and Stage II ($P = 0.002$). The 10-year DFS for patients who achieved complete resection was 79.7%, while that for patients with incomplete resection was 40.2% ($P < 0.0001$). The 10-year DFS for patients without MG was 83.0%, which was better than 68.3% for those with MG, with no significant difference ($P = 0.07$).

In multivariate analysis which compared age, completeness of resection, association with MG, Masaoka's stage (Stages III and

Table 3: Association of MG by the WHO histological classification and Masaoka's stage

	No. of patients	WHO classification					Masaoka's stage				
		A	AB	B1	B2	B3	I	II	III	IVA	IVB
MG+	54	1	3	16	25	8	29	17	2	4	1
MG–	108	6	35	33	20	15	47	42	12	5	3
% of MG	33.3	14.3	7.9	32.7	55.6	34.8	38.2	28.2	14.3	44.4	25.0

MG, myasthenia gravis.

Table 4: Summary of patients with recurrence

Case	Age/sex	WHO classification	Masaoka's stage	Resection	Recurrence	Interval from surgery to recurrence	Outcome	
1	58F	B2	I	Complete	Lung	134 months	Dead	16 months
2	50M	AB	II	Complete	Chest wall	71 months	Alive	32 months
3	55M	B1	II	Complete	pl	75 months	Dead	95 months
4	44F	B3	II	Complete	Liver	119 months	Dead	30 months
5	40F	B2	III	Incomplete	pl	37 months	Alive	92 months
6	22M	B3	III	Complete	Lung	26 months	Dead	8 months
7	47F	B3	III	Complete	Local	112 months	Dead	16 months
8	65M	B3	III	Complete	Local	79 months	Alive	4 months
9	72F	B3	III	Complete	Lung	55 months	Dead	64 months
10	42M	B1	IVA	Incomplete	pl	30 months	Alive	77 months
11	34F	B2	IVA	Complete	Local	52 months	Alive	26 months
12	47M	B2	IVA	Incomplete	pl	82 months	Alive	1 month
13	50F	B2	IVB	Incomplete	Liver	18 months	Dead	5 months
14	44F	B3	IVB	Incomplete	Neck LN	5 months	Alive	198 months

LN, lymph node; pl, pleural dissemination.

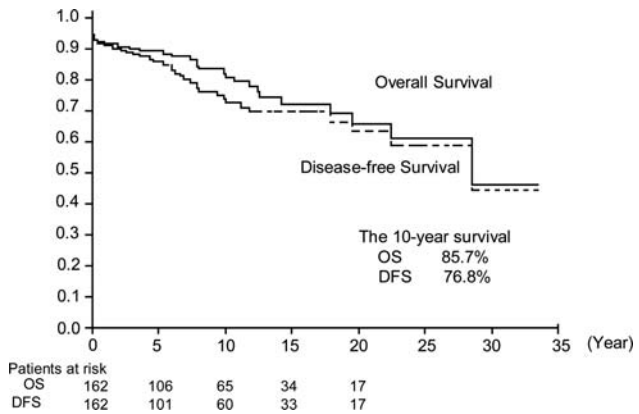

Figure 1: Survival of thymoma after extended thymectomy. The 10-year overall survival was 85.7%, and the 10-year DFS was 76.8%. DFS, disease-free survival.

IV vs. Stage I/II) and the WHO classification (Types B2 and B3 vs. Type A/AB/B1), age, association with MG and the WHO classification Type B3 were determined as prognostic factors for OS, and hazard ratios were 4.77 (age of 60–69, 95% CI 1.05–20.7, $P = 0.04$) and 21.0 (age of 70 and over, 95% CI 5.22–95.9, $P < 0.0001$), 3.02 (95% CI 1.05–9.44, $P = 0.04$) and 4.38 (95% CI 1.29–14.4, $P = 0.02$), respectively (Table 5). With regard to DFS, age, association with MG and the WHO classification Type B3 were also risk factors for recurrence among age, completeness of resection, association with MG, Masaoka's stage and the WHO classification, and hazard ratios were 7.41 (age of 70 and over, 95% CI 2.22–24.8, $P = 0.002$), 2.93 (95% CI 1.19–7.74, $P = 0.02$) and 3.54 (95% CI 1.22–10.1, $P = 0.02$), respectively.

DISCUSSION

Factors involving the prognosis of thymoma remain under discussion because thymoma is a relatively rare tumour. Moreover, long-term follow-up is necessary to investigate prognosis because thymoma consists mainly of early-stage disease with favourable outcome. In this study, we retrospectively reviewed 162 cases spanning a period of up to 34 years to elucidate and specify the factors predicting prognosis of thymoma after surgical treatment. Furthermore, it is remarkable that the outcome of the surgical procedure in our series was almost uniform; all of our cases underwent extended thymectomy via median sternotomy. Because even patients with early-stage disease suffered from local recurrence after resection of thymoma via lateral incision [5], extended thymectomy via median sternotomy would be a reasonable approach considering the multicentric growth of thymoma in thymic tissue [7].

Since the WHO histological classification system of thymic tumours was published in 1999, many reports have suggested its applicability for predicting prognosis of thymoma [8, 9].

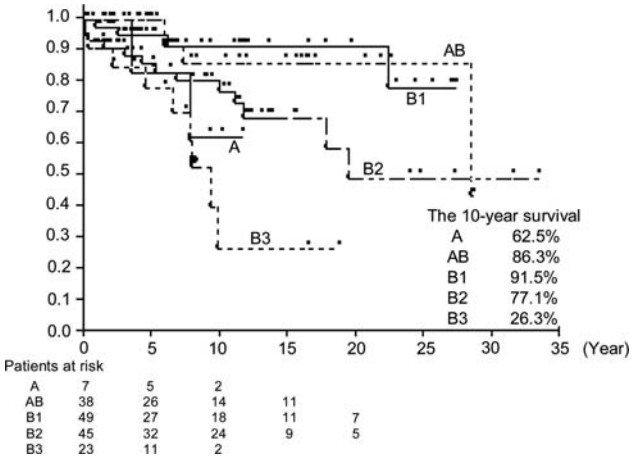

Figure 2: DFS according to the WHO histological classification system. There was a significant difference in survival curves between Type AB and Type B3 ($P = 0.0008$), between Type B1 and Type B2 ($P = 0.026$) and between Type B1 and Type B3 ($P = 0.0001$).

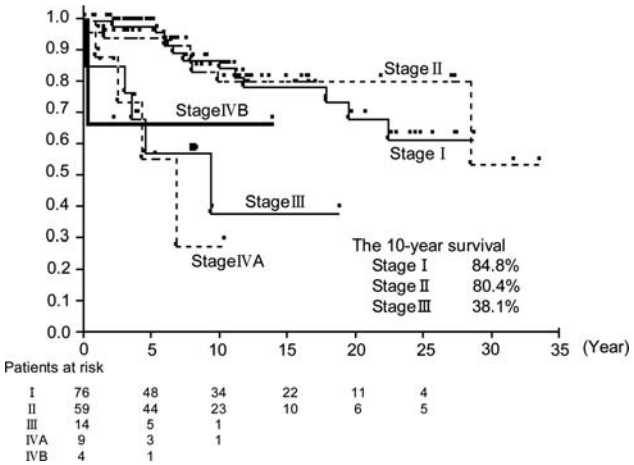

Figure 3: DFS according to Masaoka's stage. Survival for Stage III disease was significantly worse than that for Stage I ($P = 0.0002$) and Stage II ($P = 0.002$).

Masaoka's staging system has also been reported to reflect prognosis [10]. Our study revealed the relationship between the WHO histological classification and Masaoka's stage, and in the process determined that a shift from Type A to Type B3 in the WHO histological classification system is associated with increased invasiveness of thymoma. Univariate analysis showed that both the WHO classification and Masaoka's stage are predictive prognostic indicators. Type B3 thymoma had a significantly worse survival than Type AB and Type B1 thymoma, while survival for Stage III disease was significantly lower than that for Stage I and Stage II.

It remains controversial whether thymoma with MG has equivalent survival to that without. DFS without MG was 83.0% in 10 years (vs. 68.3% with MG), and the association with MG was one of the risk factors for recurrence and led to poor prognosis in multivariate analysis. Though MG has been considered to be a poor prognostic factor in previous reports [11], many recent studies reported that MG does not influence the survival [8, 10] or even is associated with better prognosis [9, 12, 13]. Kondo and Monden [12] suggested better prognosis of thymoma with MG because of the infrequency of Stage IVB disease and the early detection of thymoma during MG treatment. However, the frequency of MG did not change according to Masaoka's stage in our study. Furthermore, most reports suggesting MG would be accompanied with better survival did not adopt the WHO classification [12, 13], so they could not eliminate the influence of different prevalence of MG among the WHO classification. Our study also has the limitation that the prevalence of MG was higher before 1990 and unskilled treatment of thymoma and MG in the early days would be a part of explanation for a worse prognosis of thymoma with MG. It is necessary to further discuss whether MG would influence the survival of thymoma or not.

Multivariate analysis revealed that the WHO classification Type B3 carried an increased risk of recurrence and was a poor prognostic factor. Type B2 and Type B3 tumours are supposed to be of more aggressive nature than others [8, 14], and division of Type B3 from Type B2 in the analysis showed that only Type B3 thymoma held an increased risk compared with Type A/AB/B1.

Table 5: Multivariate analysis of survival

	OS			DFS		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age						
Up to 49	1			1		
50–59	2.98	0.99–9.58	0.05	1.55	0.60–3.91	0.35
60–69	4.77	1.05–20.7	0.04	1.81	0.51–5.78	0.34
70 and more	21.0	5.22–95.9	<0.0001	7.41	2.22–24.8	0.002
Incomplete resection	5.42	0.67–31.3	0.10	4.80	0.66–26.2	0.11
Association with MG	3.02	1.05–9.44	0.04	2.93	1.19–7.74	0.02
Masaoka's stage						
I/II	1			1		
III	1.63	0.37–6.48	0.50	2.69	0.74–8.89	0.12
IV	0.15	0.01–2.29	0.17	1.08	0.15–9.56	0.94
WHO classification						
A/AB/B1	1			1		
B2	1.96	0.71–5.55	0.19	1.54	0.60–4.01	0.37
B3	4.38	1.29–14.4	0.02	3.54	1.22–10.1	0.02

CI, confidence interval; DFS, disease-free survival; MG, myasthenia gravis; OS, overall survival.

In contrast, completeness of resection and Masaoka's stage failed to show any impact on survival or recurrence. Considering the trend that progression of Masaoka's stage was associated with a shift of the WHO classification, Masaoka's stage would not affect the survival if the influence of the WHO classification, especially that of Type B3, was excluded by multivariate analysis. However, it would be possible that the impact of Masaoka's stage was underestimated due to relatively small population of Stage III/IV disease in this study. As to completeness of resection, while Margaritora *et al.* [9] insisted on the importance of complete resection, completeness of resection exhibited no/little impact on survival in some multivariate analyses [8, 15], and this study is consistent with them. Age is the strongest prognostic factor, which can be explained by relatively long survival (5–95 months) after recurrence. Long survival after recurrence could also lead to little impact of complete resection on survival. Of the 25 deaths in this study, only 7 patients (28.0%) died of thymoma. On the other hand, as many as 18 patients died of causes other than thymoma. Similarly, the previous study demonstrated that thymoma was responsible for only 23.1–37.9% of all deaths during the follow-up period [8, 16]. Thymoma is frequently associated with secondary malignancies, and the risk of secondary malignancies also increases with advancing age [17]. In fact, the prognosis of thymoma after surgery is so good, with a 10-year OS of 85.7%, that many patients died of causes other than thymoma, which leads to the result that age is an independent prognostic factor.

Recurrence of thymoma could lead to exacerbation of autoimmune disease. Evoli *et al.* [18] reported that 18 of 115 patients with invasive thymoma experienced recurrence, of whom 10 (55.6%) showed an association with the onset/aggravation of autoimmune disease. Any potential risk of exacerbating autoimmune disease should be avoided because it can severely impair patient quality of life. In addition, once recurrence has occurred, the disease cannot be cured even if long-term survival is achieved through aggressive surgery [19]. Minimizing recurrence by extended thymectomy would be important, especially in young patients, because thymoma has good prognosis.

This retrospective study spans a long period of time. Because no determined regimen was specified as adjuvant chemotherapy and radiotherapy, the impact of adjuvant therapy on survival cannot be discussed. This is an institutional report, and the relatively small number of recurrence or death events during the study period is another limitation of our study. However, this study revealed findings that suggest favourable prognosis of thymoma after a long follow-up period. Since thymoma is a rare tumour, every single-institutional study has the same limitations. For this reason, there is an urgent need to build a multi-institutional database, which would offer an insight into the treatment of thymoma.

In conclusion, we confirmed that the WHO classification system reflects survival of thymoma after extended thymectomy and that Type B3 tumour has poor prognosis. Association with MG is a possible risk factor for recurrence and poor prognosis. Age is an independent prognostic factor, suggesting favourable prognosis of thymoma after surgical treatment.

Conflict of interest: none declared.

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