Myasthenia gravis in patients with thymoma affects survival rate following extended thymectomy

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Abstract. Thymomas are the most common adult tumors in the anterior mediastinal compartment, and a significant amount of thymomas are complicated by myasthenia gravis (MG). Extended thymectomy (ET) is the primary treatment method for thymomas and is used to completely resect possible ectopic thymus to avoid recurrence. Studies on the effect of MG in thymoma patients following ET are limited. The aim of the present study was to determine whether the presence of MG affects the prognosis of patients with thymoma. The present study consisted of 104 patients with thymoma that underwent ET; 61 men (58.7%) and 43 women (41.3%) (mean age, 54.6 years). In total, 38 patients had MG (36.5%). MG was most frequently observed in World Health Organization (WHO) classification type B2 thymoma compared with other types of thymoma. During the 5-year follow-up period, 11 patients succumbed to a recurrence of thymoma or respiratory failure due to MG. The overall 5-year survival rate in patients without MG or with MG was 89.1 and 76.0%, respectively. The overall survival (OS) rate in patients with Masaoka stages I + II and III + IV was 90.0 and 68.0%, respectively. The OS rate in patients with WHO type A + AB + B1 and type B2 + B3 was 96.9 and 76.8%, respectively. The patients with MG (P=0.026), Masaoka stages III + IV (P=0.008) and WHO type B2 + B3 (P=0.032) had a poorer prognosis compared with patients without these characteristics. Furthermore, multivariate analysis by Cox regression revealed that age [P=0.032; relative risk (RR)=1.097; 95% confidence interval (CI)=1.097-1.192] and MG (P=0.042; RR=0.167; 95% CI=0.037-0.940) significantly affected OS rate. In summary, ET is a reliable method for the treatment of thymoma. Long-term survival is expected for patients at early Masaoka stages, and for patients without MG. The prognosis of patients with thymomas with MG is poorer compared with patients without MG. The present findings provide useful information for the future management of patients with thymomas.

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Abbreviations: MG, myasthenia gravis; ET, extended thymectomy; WHO, World Health Organization; VATS, video-assisted thoracoscopic surgery; OS, overall survival

Key words: thymoma, myasthenia gravis, extended thymectomy, survival analysis

Introduction

Thymoma is a tumor originating from the epithelial cells of the thymus and is a relatively rare neoplasm with an incidence of 0.13 cases per 100,000 individuals per year (1,2). The prognosis of patients with thymoma largely depends on the Masaoka stage of disease and prognosis is poorer for patients with stage III or IV compared with patients with stage I and II tumors (3). The 10-year survival rates are 90, 70, 55 and 35% for stages I, II, III, and IV thymoma, respectively (4). Surgical resection is the primary treatment method for thymoma and a sternotomy is the optimal surgical procedure for thymoma, since it may not be possible to perform a complete thymectomy via thoracotomy on locally advanced lesions, particularly those that are stage III-IV (5,6). Normally, thymoma is a slow-growing tumor, but 40% of thymomas exhibit a locally invasive growth pattern. In addition, thymomas often result in the development of pleural dissemination and distant metastasis (7,8). Therefore, complete resection should be the primary goal during surgical treatment. The International Thymic Malignancies Interest Group recommends *en bloc* resection, also known as extended thymectomy (ET), including complete thymectomy and resection of the surrounding mediastinal fat, due to the possibility of macroscopically invisible invasion of the tumor (5). Due to the limited case number of thymomas, survival analysis following complete thymectomy based on large cohorts is limited. Therefore, gaining an improved understanding of survival prognosis may be beneficial for the management of the patients with thymoma.

Aside from disease stage, other factors that affect the outcome of patients following complete thymectomy remain largely unknown. Thymoma is frequently associated with parathymic diseases, including myasthenia gravis (MG) (9). MG is the most commonly associated paraneoplastic disease in thymoma patients and 30-50% of thymoma patients have

MG (10). However, whether MG is a determining factor for the outcome of patients with thymoma following complete thymectomy remains unknown. The present study demonstrated that the prognosis of patients with thymomas and MG is poorer compared with patients without MG. Therefore, MG status should be considered in the management of patients with thymomas.

Materials and methods

Patients. In total, 104 patients with thymoma were consecutively recruited to the present study between January 2005 and January 2010. All the patients were recruited at two centers (The First Hospital of Qinhuangdao, Qinhuangdao; the First Hospital of Jilin University, Changchun, China). The clinical characteristics of the patients were recorded, including gender, age, presence of MG, computed tomography (CT) of the chest, World Health Organization (WHO) type, Masaoka stage, myasthenic crisis presence and surgical treatment procedure. Follow-up was performed for all patients every 3 months through office visits or telephone interviews and the follow-up information consisted of postoperative MG status and physical examination. In addition, chest roentgenography and chest CT scans were performed every 6 months for the first 2 years following surgery and annually thereafter. The present study was approved by The First Hospital of Qinhuangdao Ethics Committee and all patients provided signed informed consent prior to participation.

Clinical and histological staging. The clinical stage of the tumors was evaluated according to the Masaoka staging system classification (11): Stage I, completely encapsulated and lacking microscopic capsular invasion; Stage II, microscopic capsular invasion or macroscopic invasion into mediastinal pleura or surrounding fatty tissue; stage III, macroscopic invasion into adjacent organs; stage IV, tumor with pleural or pericardial dissemination (IVa) or hematogenous or lymphogenous distant metastasis (IVb). The histological subtype of thymoma was defined according to the 2004 WHO histological classification (12). The WHO classification system categorizes tumors as follows: Type A, comprised of a homogenous population of neoplastic epithelial cells with spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes; type AB, foci possessing features of type A thymoma are admixed with foci rich in lymphocytes, the segregation of two patterns can be sharp or indistinct; type B1, resembles the normal functional thymus in that it combines large expanses with an appearance practically indistinguishable from that of normal thymic cortex, with areas resembling the thymic medulla; type B2, the neoplastic epithelial component appears as scattered, plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes, and perivascular spaces are common; type B3, comprised predominantly of epithelial cells with a round or polygonal shape that exhibit mild atypia admixed with a minor component of lymphocytes, and foci of squamous metaplasia and perivascular spaces are common. Masaoka stage and WHO classification were confirmed following histological examination of hematoxylin and eosin-stained sections (5 μm) derived from paraffin embedded blocks.

Surgical procedures. Two surgical procedures were used: Median sternotomy and video-assisted thoracoscopic surgery (VATS). ET was defined as the resection of the entire thymus and mediastinal fat tissue between the two phrenic nerves. For Masaoka stages III and IV, combined organ and tissue resection was required and performed.

Survival analysis. The date of surgery was considered at the time of diagnosis. The survival durations were calculated between the date of surgery and the date of death due to any cause or the last follow-up day in January 2015. Overall survival (OS) time was defined as the time between the date of diagnosis to date of death due to any cause.

Statistical analysis. The Kaplan-Meier method was used to estimate the probability of survival and the differences between survival in each group was analyzed by the log-rank test. Categorical variables were compared using the χ^2-test or Fisher's exact test. Multivariate analysis was performed using a Cox regression model. Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients characteristics. Out of the 104 patients, 63 were men and 41 were women. The mean age was 54.6 years (range, 20-79 years). As shown in Table I, all patients were divided into two groups based on whether or not the patient presented with MG. In addition, 30 patients presented with coronary disease, hypertension or diabetes. In total, 8 patients (7.7%) were WHO type A, 22 (21.2%) were AB, 17 (16.3%) were B1, 34 (32.7%) were B2 and 23 (22.1) were B3. According to the Masaoka staging system, 46 patients (44.2%) were diagnosed with stage I disease, 42 patients (40.4%) had stage II disease, 14 patients (13.5%) had stage III disease and 2 patients (1.9%) had stage IVa disease. In total, 38 patients (36.5%) had MG. In a comparison between the presence and absence of MG, the prevalence of MG was significantly higher in type B2 thymoma compared with other types of thymoma (P=0.019).

Masaoka staging and WHO classification. The association between Masaoka stage and WHO classification was analyzed and is presented in Table II. The percentage of patients with Masaoka stages I, II, III and IVa was 42.3, 39.4, 16.3 and 1.9%, respectively. The percentage of patients with WHO type A, AB, B1, B2 and B3 was 7.7, 21.2, 16.3, 32.7 and 22.1%, respectively. The majority of patients with WHO type A, AB and B1 was observed at Masaoka stage I and II (44/47; 93.6%). However, thymomas classified as WHO type B2 and B3 subtype (16/19; 84.2%), which corresponded to Masaoka stage III and IVa, exhibited more invasive behavior and thus were considered more aggressive. The association between tumor size and Masaoka stage is indicated in Fig. 1A. The mean tumor size with Masaoka stages I and II was significantly smaller compared with tumors with Masaoka stages III and IV (P<0.001). No significant association was observed between tumor size and WHO classification (P=0.488) (Fig. 1B).

Table I. Characteristics of 104 thymoma patients with and without MG.

Characteristic	Total	Without MG	With MG	t/χ^2 value	P-value
Total patients, n	104 (100)	66 (64)	38 (37)		
Age at surgery, years	54.6±11.0	56.0±10.8	52.2±11.1	1.714	0.090
Gender, n (%)				1.849	0.174
Male	61 (59)	42 (64)	19 (50)		
Female	43 (41)	24 (36)	19 (50)		
Tumor size, cm	3.1±1.3	3.2±1.4	3.0±0.9	0.610	0.543
Surgical procedure, n (%)				0.865	0.352
Sternotomy	10 (10)	5 (8)	5 (13)		
VATS	94 (90)	61 (92)	33 (87)		
Myasthenic crisis, n (%)	8 (8)	0 (0)	8 (21)	7.538	0.006[b]
WHO histological classification, n (%)				11.83	0.019[a]
A	8 (8)	7 (11)	1 (3)	4.500	0.034[a]
AB	22 (21)	17 (26)	5 (13)	6.545	0.011[a]
B1	17 (16)	12 (18)	5 (13)	2.882	0.090
B2	34 (33)	14 (21)	20 (53)[c]	0.471	0.493
B3	23 (22)	16 (24)	7 (18)	2.130	0.144
Masaoka stage, n (%)				3.962	0.266
I	46 (44)	30 (45)	16 (42)	6.712	0.010[a]
II	42 (40)	28 (42)	14 (37)	4.677	0.031[a]
III	14 (14)	6 (9)	8 (21)	0.059	0.808
IVa	2 (2)	2 (3)	0 (0)		
Pathology of paraneoplastic thymus, n (%)				13.975	<0.001[b]
Involuted	87 (84)	62 (94)	25 (66)		
Hyperplastic	17 (16)	4 (6)	13 (34)		<0.001[b]
Radiotherapy, n (%)	49 (47)	25 (38)	24 (63)	6.185	0.013[a]
Recurrence, n (%)	3 (3)	1 (2)	2 (5)	92.346	<0.001[b]
Mortality, n (%)	11 (11)	3 (5)	8 (21)	9.013	0.003[b]

[a]P<0.05. [b]P<0.01. [c]Prevalence of MG was significantly higher in type B2 thymoma compared with other types of thymoma. MG, myasthenia gravis; VATS, video-assisted thoracoscopic surgery; WHO, World Health Organization.

Table II. Association between Masaoka stage and WHO histological classification.

		WHO histological classification, n					
Masaoka stage, n	Total patients, n	A	AB	B1	B2	B3	Mortalities
Total	104	8	22	17	34	23	11
I	46	4	9	6	17	8	1
II	42	4	11	10	6	10	3
III	14	0	2	1	10	4	6
IVa	2	0	0	0	1	1	1
Mortalities	11	0	1	0	5	5	-

WHO, World Health Organization.

Surgical procedure and mortalities. All patients underwent ET either by sternotomy (10 patients) or VATS (94 patients). In addition, combined resection with adjacent organs, including the lung (n=6), pericardium (n=5), left brachiocephalic (n=3)

Table III. Univariate and multivariate analysis for patients that underwent extended thymectomy for thymoma treatment.

	Univariate analysis			Multivariate analysis		
Characteristic	P-value	RR	95% CI	P-value	RR	95% CI
Gender	0.299	2.020	0.536-7.619	0.512	-	-
Age[a]	0.001	1.138	1.055-1.228	0.032	1.097	1.010-1.192
Tumor size[b]	<0.001	2.288	1.491-3.510	0.052	-	-
MG association	0.042	3.974	1.053-14.991	0.042	0.167	0.037-0.940
WHO classification[c]	0.046	2.054	1.011-4.172	0.084	-	-
Masaoka stage[d]	0.009	2.400	1.239-4.648	0.541	-	-
Surgical procedure[e]	0.003	0.145	0.041-0.510	0.574	-	-
Radiotherapy	0.026	0.175	0.038-0.814	0.322	-	-

[a]<60 vs. ≥60 years. [b]<3 vs. ≥3 cm. [c]Stage A vs. AB vs. B1 vs. B2 vs. B3. [d]Stage I vs. II vs. III vs. IVa. [e]Sternotomy vs. video-assisted thoracoscopic surgery. WHO, World Health Organization; CI, confidence interval; RR, relative risk; Y, yes; N, no.

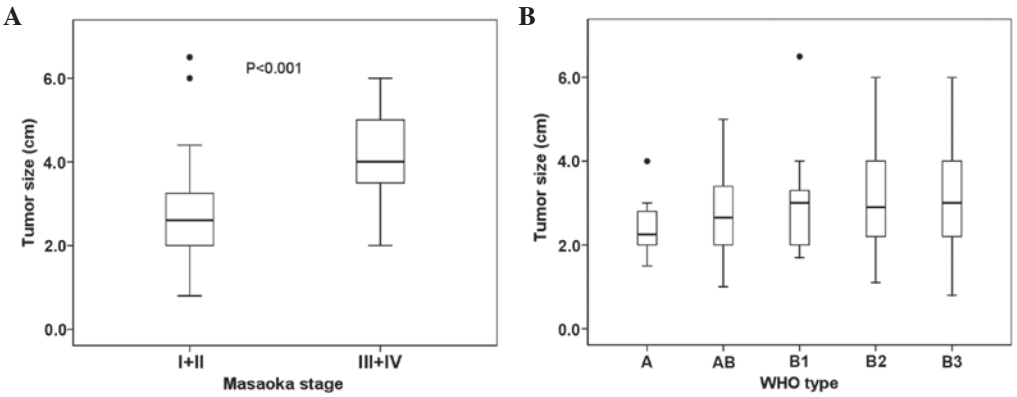

Figure 1. Tumor size divided according to Masaoka stage or WHO histological classification. (A) Association between tumor size and Masaoka stage. The tumor size in Masaoka stage I and II was significantly smaller compared with stages III and IV (P<0.001). (B) Association between tumor size and WHO histological classification. WHO, World Health Organization.

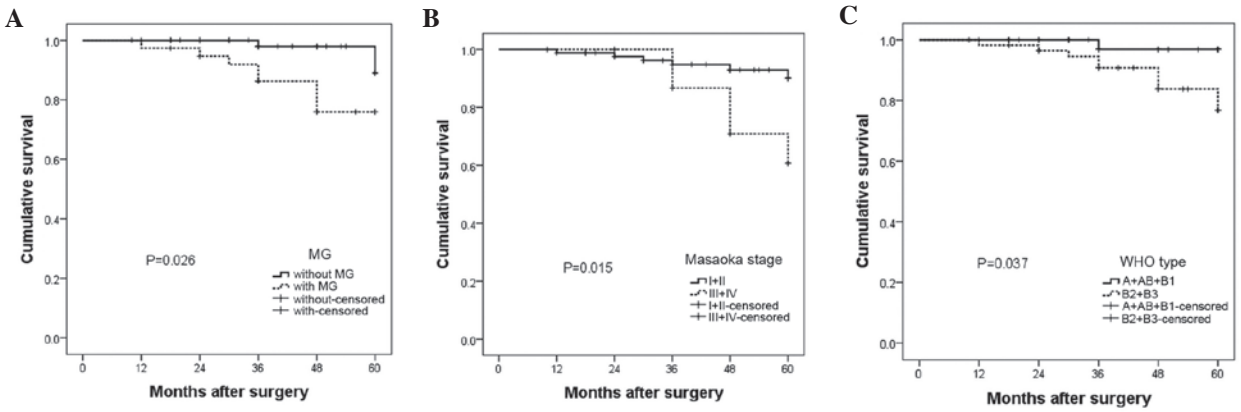

Figure 2. Overall survival curves following surgery according to MG diagnosis, Masaoka stage and WHO histological classification. (A) The overall survival rates in patients with and without MG; (B) the overall survival rates in patients according to Masaoka stage; (C) the overall survival rates in patients according to WHO histological classification. MG, myasthenia gravis; WHO, World Health Organization.

or partial superior vena cava (n=2), was also performed if required. There were no perioperative mortalities, but in 7 patients perioperative myasthenic crisis occurred in the group with MG. In addition, 18 patients (17.3%) had postoperative complications, including 10 patients with MG that experienced assisted breathing with a ventilator due to myasthenic crisis. In addition, 4 patients contracted pneumonia, 2 had pulmonary embolisms and 2 had surgical wound infections. There were 11 mortalities during the 5-year follow-up period. The mortality-associated causes consisted

of recurrence of thymoma in 3 patients and respiratory failure due to MG in 8 patients. The mortality rate in patients with MG was significantly higher compared with patients without MG (P=0.003).

OS rates. The OS rate at 5 years was 89.1 and 76.0% in patients without MG and with MG, respectively (Fig. 2A). The OS rate was 90.0 and 68.0% for patients with Masaoka stages I + II and III + IV, respectively (Fig. 2B). The OS rate was 96.9 and 76.8% in WHO types A + AB + B1 and B2 + B3, respectively (Fig. 2C). Therefore, patients with MG (P=0.026), stages III + IV (P=0.015) and WHO type B2 + B3 (P=0.037) had a poorer prognosis compared with patients without these characteristics.

To determine the factors that affect patient outcome, Cox regression analysis was performed (Table III). Univariate analysis revealed that age (P=0.001), tumor size (P<0.001), MG association (P=0.042), WHO type (P=0.046), Masaoka stage (P=0.016) and surgical procedure (P=0.003) significantly affected the OS rate of patients. Multivariate analysis revealed that age (P=0.013) and MG association (P=0.037) significantly affected OS rate of patients.

Discussion

Although, thymomas are the most common adult tumors in the anterior mediastinal compartment, it is a rare neoplasm with an overall incidence of 0.13 cases per 100,000 individuals per year (13-15). A recent study based on a large cohort of patients with thymomas revealed that the 10-year OS rate was 0.73 (95% confidence interval 0.69-0.75) (16). The same study reported that Masaoka stages III + IV, incomplete resection and non-thymoma histology (a diagnosis of thymic carcinoma or neuroendocrine thymic tumors) had a significant affect in increasing recurrence and in worsening survival rates of patients (16). Therefore, although the OS rate was relatively high, a cure for advanced thymomas remains a challenge (17,18). Surgical resection is considered as the primary treatment of thymoma, with a reported operative mortality of 2% and a complication rate of ~20% (5). Complications may include blood vessel damage, postoperative myasthenic crisis and pain, and wound infection (5). Although the role of surgical resection in the treatment of thymoma is clear, the factors that affect the outcome of patients following surgery are not fully determined. MG is the most commonly associated paraneoplastic disease in thymoma patients, but the affects of MG post-operatively remain unclear. The present study compared the outcome of patients with or without MG following surgery. The present results clearly demonstrated that MG is an important factor that should be considered in the management of patients with thymoma.

Thymomas usually occur in the sixth decade of life and have no significant gender predilection (19-22). In the present study, the median age of the patients was 54.6 years, which was 5 years younger than in other studies (19). The ratio of men to women in the present study was 1/1.4, which was within the range of results from other studies (19,20). Masaoka stages are characterized by the degree of invasion by the tumor through the capsule into surrounding tissue structures, and is an important prognostic factor in determining the most beneficial therapeutic method for a patient (11). In the 104 thymoma patients in the present study, there were 16 (15.4%) patients with Masaoka stage III + IV. The patients all had successful surgical resection of the entire thymus, mediastinal fat tissue between the two phrenic nerves and adjacent organs, including the lung (n=6), pericardium (n=5), left brachiocephalic (n=3) and partial superior vena cava (n=2). However, there remained 3 recurrent cases at stage III (3/14; 21.4%). Detterbeck (23) reported that the average recurrence rate at stage III was 30%, which is higher compared with the present results. The average tumor size increased with the elevated Masaoka stage in the present study, and 5-year OS rates were 90.0 and 68.0% at stages I + II and stages III + IV, respectively, and the survival rate at stages III + IV was slightly lower compared with stages I + II.

MG occurs in 15-60% of patients with thymoma, according to various studies (24-26). In the present results, thymoma patients with MG accounted for 36.5% of the patients. In the majority of studies, the incidence of MG in thymoma patients is the highest in WHO type B2 (21,27,28). In the present study, the incidence of MG in type A, AB, B1, B2 and B3 was 2.6, 13.2, 13.2, 52.6 and 18.4%, respectively. The prevalence of MG was significantly different in type B2 thymoma compared with that in other types of thymoma. In the 38 patients that had thymoma with MG, muscle weakness relief following surgery was 77.8%, which is similar to the 81.1% reported by Yu *et al* (29). However, 1 out of 66 (1.5%) patients without preoperative MG developed postoperative MG in the present study. This percentage was significantly lower compared with the 4.8% reported by Sun *et al* (30). During the surgery that the present patients underwent, ET was performed and the ectopic thymus was removed. In the MG group, the paraneoplastic thymus in 31.5% patients was hyperplastic, while it was only hyperplastic in 6.1% of patients in the group without MG. This suggests that MG development does not always result from thymoma. Therefore, the paraneoplastic thymus or ectopic thymic tissue may be important in MG development, which should be addressed in future studies.

There is controversy regarding whether or not MG affects the prognosis of thymomas (26,31). This debate is critical to guide future management of patients with thymoma. In the present study, survival analysis revealed that the 5-year survival rate of thymoma patients with MG (76.0%) was reduced compared with patients without MG (89.1%) (P=0.026). In addition, multivariate analysis by Cox regression demonstrated that MG (P=0.042) and age (P=0.032) were independent prognostic factors for survival. However, in a previous study performed in 228 patients, it was revealed that the prognosis was similar between patients with (90.0%) and without MG (89.3%) (31). The variance in the present and previous results are probably due to varying severities of MG, and different Masaoka stage, diagnosis methods and treatment procedures.

In summary, the present results clearly demonstrate that ET is a reliable method for the treatment of thymoma. Similarly to previous reports, the incidence of MG was significantly different in WHO type B2 thymoma compared with other types of thymoma. In addition, it is also possible that MG in certain thymoma patients was not caused by thymoma, but by the paraneoplastic thymus. Long-term survival may be expected not only for patients at early Masaoka stages, but also

for patients without MG, and the prognosis of patients with thymoma with MG is poorer compared with patients without MG. Therefore, the present findings provide useful information for the future management of patients with thymomas.

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