

Value of Adjuvant Radiotherapy for Thymoma with Myasthenia Gravis after Extended Thymectomy

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Abstract

Background: The co-existence of myasthenia gravis (MG) and thymoma makes the surgical treatment more complicated and adjuvant radiation more controversial. The aim of this study was to investigate adjuvant radiotherapy for thymoma with MG after extended thymectomy.

Methods: A total of 181 patients with both MG and thymoma were recruited between 2003 and 2014 at Tongren Hospital, China. Among all the patients, 157 patients received radiation therapy after surgery (Group A); whereas the other 24 patients did not receive radiation therapy (Group B). According to the time that patients started mediastinal radiation therapy, we subdivided the 157 patients in Group A into subgroups (1-month subgroup, $n = 98$; 2-month subgroup, $n = 7$; and 3-month subgroup, $n = 52$). We then compared the effect of the mediastinal radiation therapy across these different groups using the survival rate, the rate of postoperative myasthenic crisis, and the complete stable remission (CSR) rate as the primary endpoints.

Results: There was a significant difference in the occurrence of postoperative myasthenic crisis between 1-month subgroup and Group B ($\chi^2 = 4.631$, $P = 0.031$). The rates of reaching CSR were 32.6% in 1-month subgroup, 25% in 3-month subgroup, and 22.7% in Group B, respectively. The overall survival rates of 1-month subgroup, 3-month subgroup, and Group B were 88.8%, 83.3%, and 77.3%, respectively. Analysis on the Kaplan-Meier survival curves demonstrated that within 8 years after surgery, there was no significant difference in aspects of overall survival and disease-free survival between 1-month subgroup and Group B, and between 3-month subgroup and Group B; over 8 years after surgery, the disease-free survival rates in 1-month subgroup, 3-month subgroup and Group B were 79.4%, 70.6%, and 55.3%, respectively.

Conclusions: Adjuvant radiation within 1 month after extended thymectomy may be helpful in controlling postoperative MG, such as decreasing the possibility of postoperative myasthenic crisis, and raising cumulative probabilities of reaching CSR.

Key words: Myasthenia Gravis; Prognosis; Radiotherapy; Thymectomy; Thymoma

INTRODUCTION

Thymoma is a kind of mediastinal tumors usually with an indolent growth pattern but malignant because of potential for local invasion, pleural dissemination, and even systemic metastases.^[1,2] Studies have revealed that the most important determinants of long-term survival in thymoma are completeness of resection, Masaoka stage, and Mueller-Hermelink histologic classification.^[3-6]

Thymomas are commonly associated with parathymic syndromes,^[7-9] one of the most common is myasthenia gravis (MG). In general, thymic tumors occur in approximately 20–30% of patients with MG and, in turn, MG occurs in 15–60% of patients with thymoma according

to different reports.^[9-11] The presence of MG gives thymomas some special pathological and clinical characteristics and may influence its prognosis.^[12,13] Adjuvant radiation therapy was suggested; however, there were still a lot of controversy. Our former studies revealed that some MG patients with thymoma experienced exacerbation of MG over 1 month after surgery and postoperative myasthenic crisis is the main

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cause of death for thymoma patients with MG.^[12] According to our experience, it seemed that adjuvant mediastinal radiation therapy within 1 month after extended thymectomy might not only decrease the incidence of postoperative myasthenic crisis but also might have impact on long-term outcome. The aim of this study was to investigate whether patients with MG and thymoma should receive mediastinal radiation therapy and the appropriate time after extended thymectomy.

METHODS

Ethical approval

Protocol of this study was reviewed and approved by the Human Research Ethics Board of Beijing Tongren Hospital, Capital Medical University. All patients gave written informed consent for this study.

Patients and study protocol

Between 2003 and 2014, 181 patients with MG and thymoma underwent extended thymectomy by video-assisted thoracoscopic surgery ($n = 172$) or the transsternal approach ($n = 9$).^[14] Briefly, thymoma was diagnosed by experienced neurologists according to both contrast-enhanced computed tomography and symptoms. MG was diagnosed according to standard clinical, pharmacologic, and electrophysiologic criteria. Anti-acetylcholine receptor (AChR) antibody titers were assayed by an immunoprecipitation method using human AChR antigen. Of all patients, 72.9% were positive for anti-AChR antibodies. Medicines used to control MG symptoms before surgery are shown in Table 1.

Among all the patients, 157 received mediastinal radiation therapy after surgery (Group A); however, the other 24 did not receive adjuvant radiation therapy (Group B). According to the time when patients received mediastinal radiation therapy, the Group A could be subdivided into three subgroups: 1-month subgroup ($n = 98$, received

mediastinal radiation therapy within 1 month after surgery); 2-month subgroup ($n = 7$, received radiation therapy between 1 and 3 month after surgery); and 3-month subgroup ($n = 52$, received radiation therapy over 3 months after surgery). The main clinical features of the three subgroups before surgery are summarized in Table 1. It is noted that the number of patients in 2-month subgroup was only 7 and did not match with the other two subgroups at some clinical features. Hence, the following analyses did not involve this subgroup.

Finally, 159 patients were followed up from 15 months to 12 years: 89 in 1-month subgroup, 48 in 3-month subgroup, and 22 in Group B. There were three patients died during the follow-up period, among whom two patients died of heart diseases and one of a car accident). None of the death was relate to MG, thymoma, or radiation therapy.

Adjuvant radiation therapy

Total doses of adjuvant radiation therapy were 45 to 55 Gy in 25 to 30 fractions. Due to the very low frequency of lymph node metastases, the treatment plan should cover only the primary site of disease, and include nodal irradiation only in the presence of clinically evident lymph node involvement.

Clinical assessment

All thymic epithelial tumors were classified according to both of the WHO histologic classification^[15] and the Masaoka clinical staging system.^[16] Clinical and pathologic features of tumors, long-term survival rates, and pathological characteristics of nonneoplastic regions within the thymus of thymoma patients were assessed. Overall survival (calculated from the date of operation to death no matter what its cause is), and disease-free survival (counted as time to recurrence) were the primary endpoints for the radiation therapy. Survival was measured from the day of the operation until death or the last follow-up visit. Kaplan-Meier survival curves were further calculated and were used to compare different survival among groups.

Table 1: Comparisons of preoperative clinical features between Group A and Group B

Items	Group A ($n = 157$)			Group B ($n = 24$)
	1-month subgroup ($n = 98$)	2-month subgroup ($n = 7$)	3-month subgroup ($n = 52$)	
Gender (female/male, n)	53/45	5/2	24/28	15/9
Age (years), median (range)	51 (31–83)	53 (33–81)	46 (27–77)	47 (33–71)
Preoperative myasthenic crisis, n (%)	17 (17.3)	0	12 (23.1)	2 (8.3)
Disease duration (months), median (range)	5 (0.5–14.0)	3 (0.5–5.0)	3 (0.5–29.0)	3 (0.5–19.0)
Anti-AChR antibodies (+), n	68	6	39	19
Anticholinesterase, n (%)	76 (77.6)	5 (71.4)	44 (84.6)	20 (83.3)
Preoperation immunoglobulin, n (%)	36 (36.7)	1 (14.3)	21 (40.4)	7 (29.2)
Immunosuppressive drugs, n (%)	19 (19.4)	0	10 (19.2)	5 (20.8)
MGFA clinical classification, n (%)				
I	25 (25.5)	6 (22.3)	15 (28.8)	6 (25.0)
II	36 (36.7)	1 (14.3)	25 (48.1)	12 (50.0)
III	21 (21.4)	0	8 (15.4)	5 (20.8)
IV	8 (8.2)	0	5 (9.6)	1 (4.2)
V	5 (5.1)	0	2 (3.8)	0

AChR: Acetylcholine receptor; MGFA: Myasthenia Gravis Foundation of America.

The Myasthenia Gravis Foundation of America (MGFA) clinical classification was used to assess MG. Postthymectomy myasthenic crisis was defined as total postoperative mechanical ventilatory support for more than 48 h with no cardiopulmonary complications or cholinergic crisis. Complete stable remission (CSR) according to MGFA postintervention status^[17] was the other primary endpoint for the efficacy of the radiation therapy.

Statistical analysis

All analyses were performed with SPSS Statistics 19.0 (IBM Co., NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Discrete variables expressed as median (range) were compared using paired samples *t*-tests. The one-way analysis of variance (ANOVA) or the Mann-Whitney *U*-test was used to compare continuous variables among different groups. The Chi-square test was used to compare frequencies among different groups. A *P* < 0.05 was considered statistically significant.

RESULTS

There were no intraoperative deaths. The main operative complications include postoperative pneumonia, heart failure, severe bleeding, and injury to the phrenic nerve. The immunological and pathological features of different groups and subgroups at the time of surgery are shown in Table 2. Comparing with patients in Group B who did not receive radiation therapy, patients who received radiation therapy (in both 1-month subgroup and 3-month subgroup) did not show significant differences at surgical factors such as the length of surgery, operative complications, and intensive care unit stay.

Effect of the radiation therapy on myasthenia gravis

Postoperative myasthenic crisis occurred in 40 cases: 17 cases in 1-month subgroup, 14 in 3-month subgroup, and 9 in Group B as shown in Table 2. Compared with patients in Group B, patients in 1-month subgroup showed significantly lower occurrence of postoperative myasthenic crisis ($\chi^2 = 4.631$, *P* = 0.031). Moreover, the rates of reaching CSR were 32.6% in 1-month subgroup, 25.0% in 3-month subgroup, and 22.7% in Group B, respectively [Table 3]. Although analysis did not show significant results, it seems that the rate of CSR in 1-month subgroup was larger than those in 3-month subgroup and Group B. It needs to mention that the CSR in 1-month subgroup would reach up to 36%, while it would be <30% in 3-month subgroup and in Group B [Figure 1]. Moreover, there were 4 patients in 1-month subgroup, 1 patient in 3-month subgroup, and 2 patients in Group B whose MG was exacerbated after CSR had been achieved.

Effect of the radiation therapy on survival

The overall survival rates of 1-month subgroup, 3-month subgroup, and Group B were 88.8%, 83.3%, and 77.3%, respectively. No significant difference across the three groups was found. The number of death due to postoperative myasthenic crisis in the three groups was 3, 3, and 2. And recurrence in the three groups was 6, 4, and 4. Kaplan-Meier survival curves demonstrated that no significant difference at overall survival and disease-free survival across 1-month subgroup, 3-month subgroup, and Group B [Figures 2 and 3] within 8 years after surgery. As for the survival rates over 8 years after surgery, patients in 1-month subgroup (79.4%) or 3-month subgroup (70.6%) showed relatively higher disease-free survival rates than patients in Group B (55.3%).

Table 2: Comparisons of preoperative clinical features among 1-month subgroup, 3-month subgroup and Group B

Items	1-month subgroup (<i>n</i> = 98)	3-month subgroup (<i>n</i> = 52)	Group B (<i>n</i> = 24)
Length of surgery (min), mean ± SD	128.3 ± 61.7	130.3 ± 67.8	127.3 ± 63.2
Operative complications, <i>n</i> (%)	12 (12.2)	7 (13.5)	2 (8.3)
ICU (days), median (range)	3 (0–9)	3 (0–10)	3 (0–10)
Postoperative myasthenic crisis*, <i>n</i> (%)	17 (17.3)	14 (26.9)	9 (37.5)
WHO pathologic classification, <i>n</i> (%)			
A	0	0	1 (4.2)
AB	19 (19.4)	8 (15.4)	5 (20.8)
B ₁	26 (26.5)	14 (26.9)	6 (25.0)
B ₂	31 (31.6)	18 (34.6)	9 (27.8)
B ₃	22 (22.4)	12 (23.1)	3 (12.5)
Thymic carcinoma	0	0	0
Modified Masaoka clinical staging, <i>n</i> (%)			
I	16 (16.3)	11 (21.2)	9 (27.8)
II	53 (54.1)	28 (53.8)	13 (54.2)
III	29 (29.6)	13 (25.0)	2 (8.3)
IV	0	0	0
Pathology of paraneoplastic thymus, <i>n</i> (%)			
Involved thymus	69 (70.4)	38 (73.1)	15 (60.0)
Hyperplastic thymus	29 (29.6)	14 (26.9)	9 (27.8)
Microscopic thymoma	6 (6.1)	3 (5.8)	1 (4.2)
Unresectable cases	0	0	0

*Comparison between 1-month subgroup and Group 2, $\chi^2 = 4.631$, *P* = 0.031. SD: Standard deviation; ICU: Intensive Care Unit; WHO: World Health Organization.

In Cox regression analysis [Table 4 and Figure 4], after controlling variables, such as sex, age, Masaoka staging, and WHO classification, the outcome is the same as that of Kaplan-Meier survival curves.

DISCUSSION

This study suggested that adjuvant radiation therapy was effective for the MG symptoms in thymoma patients although it did not improve patients' survival. Hence, adjuvant radiation therapy may be applicable for thymoma patients with MG.

Previously, it is controversial whether thymoma patients undergoing surgery should receive postoperative adjuvant radiation.^[18-20] Adjuvant radiotherapy after complete surgical excision has previously been regarded as the standard of care. However, majority of experts questioned whether adjuvant radiation after complete resection was worth it in recent years.^[3-5,21] In their articles, they claimed that adjuvant radiation therapy had little influence on long-term, overall survival and even local control. Besides, adjuvant radiation therapy might increase risk of pulmonary toxicity.

For thymoma patients with MG, the presence of MG makes the surgical treatment more complex. The successful surgery

is only part of an interdisciplinary cooperation, which includes the perioperative treatment and postoperative long-term care for both MG and thymoma. Symptoms of MG might lead to early diagnosis of thymoma.^[13,22,23] Maybe this is why we did not have cases with MG having Stage IV thymoma since 2003. Even if thymoma invaded great vessels, the pericardium, or the lung in some cases, all operations were conducted by a complete resection with *en bloc* removal of all surrounding structures. However, complete resection could not avoid postoperative myasthenic crisis. In our series,

Table 3: Different postintervention status among 1-month subgroup, 3-month subgroup and Group B

Items	CSR (%)	Effective (%)
1-month subgroup (n = 89)	32.6	82.0
3-month subgroup (n = 48)	25.0	77.1
Group B (n = 22)	22.7	72.7

Comparisons among 1-month subgroup, 3-month subgroup and Group B, $P > 0.05$. CSR: Complete stable remission.

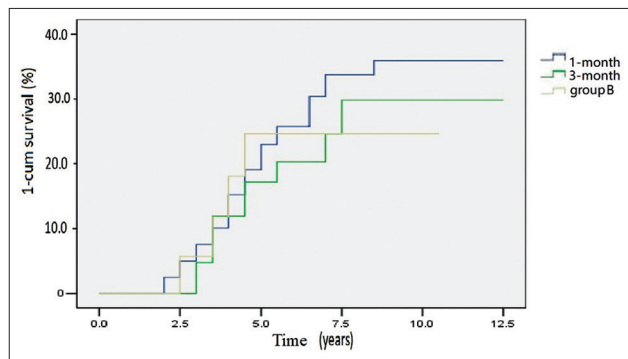


Figure 1: Comparison of CSR of myasthenia gravis after extended thymectomy (Wilcoxon statistic, $\chi^2 = 0.659$, $P = 0.719$). CSR: Complete stable remission.

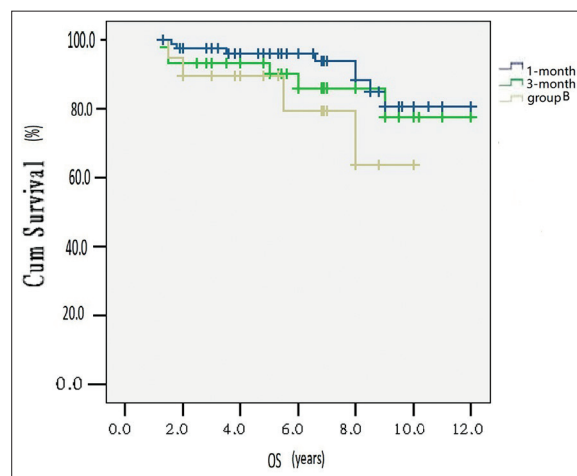


Figure 2: Comparison of overall survival of 1-month subgroup, 3-month subgroup and Group B (log-rank, $\chi^2 = 3.174$, $P = 0.075$). OS: Overall survival.

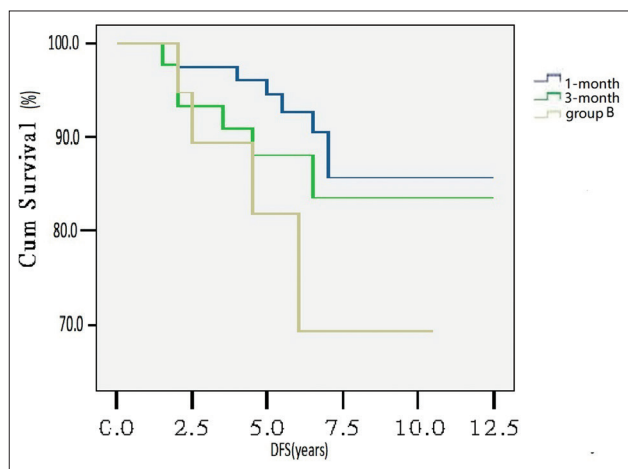


Figure 3: Comparison of disease-free survival of 1-month subgroup, 3-month subgroup and Group B (log-rank, $\chi^2 = 3.311$, $P = 0.069$). DFS: disease-free survival; WHO: World Health Organization.

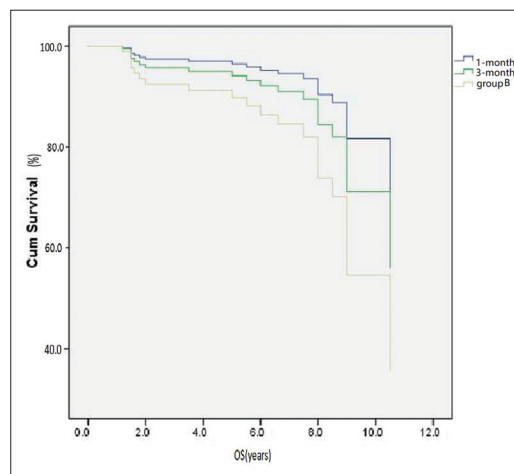


Figure 4: Demonstration of Cox regression analyses after controlling variables, such as sex, age, Masaoka staging and WHO classification (log-rank, $\chi^2 = 10.463$, $P = 0.401$). OS: Overall survival.

Table 4: Cox regression analysis between 1-month subgroup, 3-month subgroup and Group B

Items	B	SE	Wald	df	Significant	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Sex	-0.548	0.661	0.687	1	0.407	0.578	0.158	2.111
Age	1.244	0.799	2.426	1	0.119	3.470	0.725	16.601
Stage	0.032	0.419	0.006	1	0.939	1.033	0.454	2.347
Classification	-0.077	0.271	0.081	1	0.775	0.926	0.545	1.573
Group B*	-	-	3.958	2	0.138	-	-	-
1-month subgroup	-1.338	0.762	3.082	1	0.079	0.262	0.059	1.169
3-month subgroup	-0.741	0.869	0.728	1	0.394	0.476	0.087	2.616

–: Not available; *Group B includes 1-month subgroup and 3-month subgroup. SE: Standard error; CI: Confidence interval.

despite efforts to reduce postoperative myasthenic crisis, such as preoperative intravenous immunoglobulin, it still occurred in 22.1% (40/181) of cases. Actually, for most thymoma patients with MG, MG symptoms would be worsening over 1 month after surgery. Only a few patients with ocular MG could endure adjuvant radiation between 1 and 3 months after surgery. Having radiation therapy over 3 months after surgery might produce little influence in lessening the risk of postoperative myasthenic crisis ($P = 0.351$). By contrast, the incidence of postoperative myasthenic crisis in 1-month subgroup was significantly lower than that in patients did not receive radiation therapy ($P = 0.031$). This means that adjuvant radiation within 1 month after extended thymectomy might demonstrate a significant advantage to not having adjuvant radiation therapy.

Furthermore, CSR in 1-month subgroup was 32.6%, which is higher than those in Group 3-month subgroup and Group B. Figure 1 demonstrates that 4–5 years after surgery, the cumulative probability of achieving CSR in 1-month subgroup might reach up to 36%, which is higher than those in 3-month subgroup and Group B.

Furthermore, whether postoperative radiation therapy for patients having complete resection of thymoma could prolong their lives has been debated.^[24,25] Some experts questioned if routine adjuvant radiation therapy after complete resection would be helpful in long-term survival.^[26-28] In our study, Kaplan-Meier survival curves demonstrate that within 8 years after surgery, there was no significant difference in aspects of overall survival [Figure 2] and disease-free survival among three groups [Figure 3]. However, 8 years after surgery, there was a trend that the disease-free survival rate in 1-month subgroup (79.4%) has become higher than those in 3-month subgroup (70.6%) and Group B (55.3%). Hence, it seems that 8 years after surgery, adjuvant radiation within 1 month after extended thymectomy has an advantage over having radiation therapy over 3 months after surgery or without adjuvant radiation therapy.

After complete resection, patients with thymoma have a very low rate of recurrence.^[28-30] Unlike other malignant tumors, such as lung cancer, most recurrences or metastases of thymoma happened in pleural cavity. There were also occasional recurrences or metastases to lung or liver.

However, there was no lymph node metastasis detected in our study. Even if there were recurrences, because thymoma is an indolent disease, after undergoing re-resection, some patients might have a long-term survival.

The results of this study are actually part of a long-held discussion in the realm of management of thymoma with MG. Just because the co-existence of MG and thymoma is a rare condition, it is difficult to have prospective clinical trials to settle down the questions.

In conclusion, adjuvant radiation within 1 month after extended thymectomy may be helpful in controlling postoperative MG, such as decreasing the possibility of postoperative myasthenic crisis and raising cumulative probabilities of reaching CSR. Whether it might have influence in the prognosis of thymoma with MG needs to be further investigated in the future. In recurrences of thymoma patients with MG, no lymph node metastasis was detected.

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Conflicts of interest

There are no conflicts of interest.

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合并有重症肌无力的胸腺瘤手术后放疗的价值

摘要

背景：长期以来，关于胸腺瘤完全切除后辅助性放射治疗的争论一直存在。重症肌无力（MG）和胸腺瘤的共存使得手术治疗更加复杂，术后辅助放射更具争议性。本研究的目的是探讨MG胸腺瘤患者术后纵隔放疗的价值。

方法：2003年到2014年，181例合并有MG和胸腺瘤患者在北京同仁医院行胸腔镜胸腺扩大切除术，其中24例未接受术后辅助放疗（B组），157例患者术后进行纵隔放疗（A组）。根据术后放射治疗的开始时间，将术后纵隔放疗患者分为3个亚组：1月内放疗组， $n=98$ ；2月内放疗组， $n=7$ ；3月后放疗组， $n=52$ 。然后，我们利用生存率、术后肌无力危象发生率和完全缓解率（CSR）作为主要评价指标，对比纵隔放射治疗对不同组的影响。

结果：在术后肌无力危象发生方面，1月内放疗组和B组之间有显著性差异（ $\chi^2=4.631, P=0.031$ ）。达到CSR分别为：1月内放疗组为32.6%、3月后放疗组为25%，B组为22.7%。总生存率分别为：1月内放疗组为88.8%、3月后放疗组为83.3%，B组为77.3%。对比术后生存曲线表明，术后8年内各组间在总生存和无病生存方面无显著性差异。术后超过8年，1月内放疗组、3月后放疗组和B组的无病生存率分别是79.4%，70.6%和55.3%。

结论：胸腺扩大切除术后一个月内放疗在降低术后肌无力危象的发生和提高术后MG完全缓解率方面具有一定价值。