Original Article

Who will benefit from thymectomy for myasthenia gravis? Is there any role for this procedure in elderly patients?

Ryo Otsuka, Kazuhiro Ueda, Toshiki Tanaka, Junichi Murakami, Masataro Hayashi, Kimikazu Hamano

Department of Surgery and Clinical Science, Division of Chest Surgery, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi, Japan

Contributions: (I) Conception and design: K Ueda; (II) Administrative support: K Hamano; (III) Provision of study materials or patients: R Otsuka, J Murakami; (IV) Collection and assembly of data: R Otsuka, T Tanaka, M Hayashi; (V) Data analysis and interpretation: R Otsuka, K Ueda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kazuhiro Ueda, MD. Department of Surgery and Clinical Science, Division of Chest Surgery, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. Email: uedakazu@m.kufm.kagoshima-u.ac.jp.

Background: The proportion of elderly patients with myasthenia gravis (MG) is increasing over time. Thoracoscopic extended thymectomy has been shown to achieve a superior short-term outcome to transsternal procedures. Therefore, the long-term clinical outcome should be re-examined, particularly in elderly patients.

Methods: We evaluated the long-term clinical outcomes after extended thymectomy in 30 MG patients with or without thymoma. Twenty-one (70%) patients underwent surgery by 65 years of age, and the remaining 9 (30%) underwent surgery after 65 years of age. Univariate and multivariate logistic regression analyses were used to determine the influence of various factors on the improvement in MG symptoms.

Results: The characteristics in the elderly patients were comparable to those in the younger patients, except for the age at surgery. Symptoms of MG improved in 4 of the 9 (44%) elderly patients and in 18 of the 21 (86%) younger patients (P=0.0192). One elderly patient who underwent transsternal thymectomy died suddenly on postoperative day 3, probably due to a MG crisis: no pathological abnormalities were detected by an autopsy. A multivariate analysis identified an age at thymectomy of <65 years (P=0.0237) and a duration from the onset to thymectomy of <1 year (P=0.0405) as independent factors associated with the improvement of MG symptoms. Indeed, 4 of the 5 (80%) elderly patients who underwent thymectomy within 1 year after the onset had a favorable long-term outcome.

Conclusions: Thymectomy can be an option even in elderly patients, provided the operation is performed early after the onset.

Keywords: Myasthenia gravis (MG); thymoma; thymectomy; thoracoscopy; elderly patients

Submitted Nov 03, 2018. Accepted for publication Nov 27, 2018.
doi: 10.21037/atm.2018.11.66
View this article at: http://dx.doi.org/10.21037/atm.2018.11.66

Introduction

Extended thymectomy is a first-line treatment for myasthenia gravis (MG) associated with thymoma, while it is optional for MG without thymoma (1). Since there may be some disease phenotypes in MG without thymoma, extended thymectomy has helped improve MG-related symptoms in select patients (1). Previous reports have suggested that a favorable long-term clinical outcome after thymectomy was found predominantly in patients with early-onset disease, with a short duration after MG onset, or with anti-acetylcholine-receptor antibodies (AchRAbs) (2-5). Unfortunately, there is no consensus regarding whether or not thymectomy should be performed in elderly patients, although some reports suggest that the long-term clinical outcome after thymectomy in elderly patients is comparable

Table 1 Characteristics according to age (≥65 or <65 years)

Variables	Total (n=30)	Elderly (n=9)	Younger (n=21)	P
Age (years)	53.1±18.0	70.8±3.1	45.5±16.3	
Gender (male/female)	9/21	2/7	7/14	0.54
Smoking history (yes/no)	7/23	1/8	6/15	0.30
PS (0/1/2/3)	16/9/2/3	6/1/0/2	10/8/2/1	0.19
BMI (kg/m^2)	22.2±3.4	22.5±2.7	22.1±3.7	0.79
VC (% of predicted)	98.8±20.1	103.1±16.8	97.0±18.6	0.45
Thymoma (present/absent)	11/19	3/6	8/13	0.80
Autoantibody (elevated/normal)	27/3	9/0	18/3	0.23
MGFA (I/II/III/IV/V)	5/19/4/1/1	2/5/2/0/0	3/14/2/1/1	0.45
Onset (<50/≥50 years)	10/20	0/9	10/11	0.0112
Length from onset to surgery (<1/≥1 year)	19/11	5/4	14/7	0.56
QMG score	12.4±4.8	12.3±6.5	12.5±4.0	0.90
Surgical approach (open/VATS)	4/26	2/7	2/19	0.35

Data are expressed as the number or mean ± standard deviation. PS, performance status; BMI, body mass index; VC, vital capacity; MGFA, the Myasthenia Gravis Foundation of America; QMG score, Quantitative Myasthenia Gravis Score for Disease Severity; VATS, video-assisted thoracic surgery.

to that in younger patients (6,7), despite there being no definitive cut-off values for determining "elderly patients" in these reports.

According to the literature (8,9), the incidence rate of late-onset MG, particularly that in patients ≥65 years of age, increases strikingly with time, while the rate is constant in early-onset MG. Therefore, the long-term clinical outcome after thymectomy should be re-examined, particularly in elderly patients, in order to discuss the appropriate surgical indications in patients with MG.

Methods

Patients

This study was approved by the institutional review board (H30-072). In this study, 30 patients with ocular or generalized MG who underwent surgery in our institute between 2008 and 2016 were examined. We retrospectively reviewed the long-term clinical outcomes after extended thymectomy in these patients. The preoperative diagnosis was based on clinical features, the tensilon test, electromyography, and detection of AchRAbs. Anti-AchRAb levels were elevated in 27 patients, while they were not detected in the remaining 3 patients. However, anti-muscle specific kinase antibody was not detected in any of the 30 patients. Eleven patients had thymoma, and the remaining 19 did not. Extended thymectomy was performed for all patients by either transsternal (n=4) or thoracoscopic resection (n=25). Thoracoscopic resection was performed via a two-step procedure: dissection of the left-sided thymus and the surrounding fat tissues via three-port access in the right decubitus position, followed by dissection of the contralateral tissues via three-port assess in the left decubitus position. No patients underwent chemoradiotherapy. Twenty-one (70%) patients underwent surgery by 65 years of age, and the remaining 9 (30%) underwent surgery after 65 years of age. *Table 1* shows the characteristic variables in all of the patients, as well as the characteristics according to the age at operation (<65 *vs.* ≥65 years of age).

Clinicopathological data

All data, including the sex, age at the time of surgery, histology, medication, perioperative complications, and presence of MG symptoms, were obtained from the clinical and pathologic chart reviews. Clinical follow-up data were obtained by reviewing the hospital chart and through direct communication with patients or their family. Neurological

Table 2 The surgical outcome according to the age at operation (≥65 or <65 years)

Variables	Total	Group	
		Elderly	Younger
Postoperative status			
Complete stable remission	1	0	1
Pharmacologic remission	6	2	4
Minimal manifestations	13	2	11
Improved	2	0	2
Unchanged	7	4	3
Worsen	0	0	0
Died of myasthenia gravis	1	1	0
Overall outcome			
Improved/not improved	22/30	4/5	18/3*

*, P=0.0192 *vs.* elderly group.

signs were assessed using the Myasthenia Gravis Foundation of America (MGFA) classification (10) as follows: 0 (no symptoms) 1 (ocular signs and symptoms), 2 (mild generalized weakness), 3 (moderate weakness), and 4 (severe generalized weakness and/or respiratory dysfunction). Changes in MG-associated symptoms after thymectomy were classified into five groups according to the MGFA Postintervention Status classification (10): complete stable remission (CSR), pharmacologic remission (PR), minimal manifestations (MM), improved (I), and unchanged (U). We determined that the symptoms to be improved if the status was CSR, PR, MM, or I.

Statistical analyses

An unpaired Student's *t*-test was used to assess the relationships between discrete and continuous variables. The χ^2 test was used to compare discrete variables. Univariate and multivariate logistic regression analyses were used to determine the influence of various clinical factors on the improvement in MG symptoms. Using multivariate regression, independent predictors of improvements in MG symptoms were determined using all variables with a P value <0.1 as input. P values of <0.05 were considered to indicate statistical significance. The statistical analyses were performed using the Stata 12 software program (Stata Corp., College Station, TX, USA).

Results

The characteristics of the elderly patients were comparable to those of the younger patients (*Table 1*), except that 10 of the 21 (48%) younger patients had early-onset (at <50 years of age) disease, while none of the 9 (0%) elderly patients had early-onset disease (P=0.0112). The duration of operation was 205±89 min in the elderly patients and 243±62 min in the younger patients (P=0.19). The amount of intraoperative bleeding was 106±64 g in the elderly patients and 120±118 g in the younger patients (P=0.73).

The long-term surgical outcomes (median follow-up of 55.3 months) according to the age at operation (≥65 *vs.* <65 years) are summarized in *Table 2*. Among the elderly patients, the symptoms of MG did not improve in four of the nine patients. Furthermore, a 69-year-old female patient died suddenly on postoperative day 3; a postmortem autopsy showed no notable abnormalities, suggesting that the patient might have been affected by MG crisis. The patient had undergone surgery via median sternotomy for MGFA IIIb disease without thymoma. There were no notable postoperative complications in the current series, except for this patient. Overall, the symptoms of MG improved in 4 of the 9 (44%) elderly patients. In contrast, the symptoms of MG improved in 18 of the 21 (86%) younger patients (P=0.0192 *vs.* elderly patients). None of the elderly patients achieved complete stable remission.

Table 3 shows the results of a univariate analysis concerning the influence of various variables on the improvement of MG symptoms after thymectomy in the 30 total patients. An age at thymectomy of <65 years (P=0.0192), the presence of thymoma (P=0.0976), and a duration from the onset to thymectomy of <1 year (P=0.0086) were identified as possible factors associated with the improvement in the MG symptoms after thymectomy. A multivariate analysis including these factors identified an age at thymectomy of <65 years (P=0.0237) and a duration from the onset to thymectomy of <1 year (P=0.0405) as independent factors associated with the improvement of MG symptoms (*Table 4*).

Discussion

In the present study, we evaluated the long-term clinical outcomes after extended thymectomy in MG patients with or without thymoma. In the overall patients, an age at thymectomy ≥65 years and a duration from the onset to thymectomy of >1 year were independently associated with

Table 3 Results of a univariate analysis for the factors associated with the surgical outcome

Variables	Surgical outcome		P
	Improved	Not improved	
Age (years)	49.5±18.9	63.0±10.9	0.0683
Age (≥65/<65 years)	4/18	5/3	0.0192
Gender (male/female)	6/16	3/5	0.59
Smoking history (yes/no)	5/17	2/6	0.90
PS (0/1/2/3)	12/7/1/2	4/2/1/1	0.86
BMI (kg/m^2)	22.4±3.5	21.7±3.1	0.64
VC (% of predicted)	98.4±15.3	99.9±31.1	0.86
Thymoma (present/absent)	10/12	1/7	0.0976
Autoantibody (elevated/normal)	19/3	8/0	0.27
MGFA (I/II/III/IV/V)	4/13/3/1/1	1/5/2/0/0	0.43
Onset (<50/≥50 years)	8/14	2/6	0.56
Length from onset to surgery (<1/≥1 year)	17/5	2/6	0.0086
QMG score	12.2±4.8	13.3±5.1	0.61
Surgical approach (open/VATS)	2/20	2/6	0.26

Data are expressed as the number or mean ± standard deviation. PS, performance status; BMI, body mass index; VC, vital capacity; MGFA, the Myasthenia Gravis Foundation of America; QMG score, Quantitative Myasthenia Gravis Score for Disease Severity; VATS, video-assisted thoracic surgery.

Table 4 Results of a multiple logistic regression analysis for the risk of treatment failure

Variables	Reference	Odds ratio	P
Length from onset to surgery	≥1 year	15.6	0.0237
Age at surgery	≥65 years	12.0	0.0405

an unfavorable outcome. When the analysis was restricted to the 9 elderly patients (≥65 years), 4 of the 5 (80%) patients who underwent thymectomy within 1 year after the onset had a favorable long-term outcome, while none of the remaining 4 patients who underwent thymectomy at more than 1 year after the onset had a favorable outcome. Therefore, our results suggest that extended thymectomy can help improve MG-related symptoms in select patients over 65 years of age who undergo surgery within 1 year after the onset, which is partly compatible with the findings of a previous report (2). Because the incidence of elderly patients with MG is increasing (8,9), a large-scale, comparative study between surgical and non-surgical therapy in elderly patients is warranted.

In accordance with a previous report (11), the MG-related outcomes were favorable in 10 of the 11 patients who had thymoma at the onset. However, the efficacy of thymectomy in non-thymomatous MG was shown to be inconsistent according to a previous meta-analysis (12). A more recent multi-institutional randomized study reported that thymectomy in combination with immunotherapy achieved a superior outcome, in terms of the QMG score, over immunotherapy alone in select patients; the inclusion criteria in that analysis comprised a patient age between 18 and 65 years, no thymoma, elevated AchRAb levels, and thymectomy within 5 years after the MG onset (13). However, the efficacy of thymectomy in elderly patients (≥65 years) without thymoma remains unclear. In our series, the clinical outcome was favorable in 10 of the 13 (77%) younger patients without thymoma and in 2 of the 6 (33%) elderly patients without thymoma (P=0.0671). Therefore, the eligibility for thymectomy of elderly patients without thymoma should be carefully determined based on the duration from the onset to operation.

In general, thymectomy is beneficial for the treatment of early-onset MG because a majority of patients with early-onset MG have a hyperplastic thymus, which directly contributes to the activation of AchRAb-specific T-cells, leading to the induction of MG symptoms. Therefore, the outcome after thymectomy in younger patients is generally better than that in elderly patients. However, we believe that a proportion of patients with late-onset MG may benefit from thymectomy even if they have no thymus abnormalities on computed tomography or magnetic resonance imaging. According to a previous report (14), thymoma appeared in some patients with late-onset MG after the long-term non-surgical treatment of MG, although they had not had apparent thymoma at the MG onset; such patients might have a subclinical thymus abnormality that may play a role in the occurrence of MG.

Another report suggested that the early initiation of treatment (<1 year after onset) for MG resulted in a better outcome than the late initiation of treatment (≥1 year after onset) (15), although the reason for this finding remains unclear. In our series, although the long-term surgical outcome in elderly patients was inferior to that in

younger patients, the outcome in patients with early-onset disease was statistically comparable to that in patients with late-onset disease. This discrepancy may be due to the proportion of patients who underwent thymectomy within 1 year after the onset being higher among patients with late-onset disease [75% (15 of the 20 patients)] than among patients with early-onset disease [56% (4 of the 9 patients)].

Regarding the surgical approach for extended thymectomy, our standard procedure shifted from a transsternal approach to a thoracoscopic approach during the study period. A previous meta-analysis suggested that a thoracoscopic approach is preferable to the transsternal approach because the thoracoscopic approach helps reduce the need for postoperative medication, operative blood loss, and postoperative hospital stay while achieving comparable long-term outcomes to the transsternal approach with regard to the complete stable remission rate (16). Favorable outcomes were also achieved by thymectomy via robotic surgery (17). In our series, the outcome was poor in both elderly patients who underwent transsternal thymectomy; indeed, the symptoms were not improved at all in one patient, and sudden death occurred early after the operation in the other patient. Further studies with more patients are necessary to clarify the influence of a less-invasive approach on the improvement of the surgical outcome, particularly in elderly patients.

Several limitations associated with the present study warrant mention. First, the sample size is too small to determine the real role of thymectomy in the elderly patients or the predictors of treatment failure. Second, our subjects had various phenotypes of MG, including thymoma, ocular type, and cases with no detectable autoantibodies, which can compromise the accurate detection of differences between the younger and elderly patients. Finally, the follow-up length was relatively short (median, 55.3 months) for an evaluation of the long-term outcomes after thymectomy. A large-scale study with a long-term follow-up is mandatory to clarify the current topics.

In conclusion, thymectomy is feasible, even in elderly patients, provided the operation is performed early after the onset.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board (H30-072).

References

1. Cataneo AJ, Felisberto G Jr, Cataneo DC. Thymectomy in nonthymomatous myasthenia gravis - systematic review and meta-analysis. Orphanet J Rare Dis 2018;13:99.
2. Mineo TC, Ambrogi V. Outcomes after thymectomy in class I myasthenia gravis. J Thorac Cardiovasc Surg 2013;145:1319-24.
3. Ando T, Omasa M, Kondo T, et al. Predictive factors of myasthenic crisis after extended thymectomy for patients with myasthenia gravis. Eur J Cardiothorac Surg 2015;48:705-9; discussion 709.
4. Leuzzi G, Meacci E, Cusumano G, et al. Thymectomy in myasthenia gravis: proposal for a predictive score of postoperative myasthenic crisis. Eur J Cardiothorac Surg 2014;45:e76-88; discussion e88.
5. Blalock A, Mason MF, Morgan HJ, et al. Myasthenia gravis and tumors of the thymic region. Report of a case in which the tumor was removed. Ann Surg 1939;110:544-61.
6. Tsuchida M, Yamato Y, Souma T, et al. Efficacy and safety of extended thymectomy for elderly patients with myasthenia gravis. Ann Thorac Surg 1999;67:1563-7.
7. Abt PL, Patel HJ, Marsh A, et al. Analysis of thymectomy for myasthenia gravis in older patients: a 20-year single institution experience. J Am Coll Surg 2001;192:459-64.
8. Matsuda M, Dohi-Iijima N, Nakamura A, et al. Increase in incidence of elderly-onset patients with myasthenia gravis in Nagano Prefecture, Japan. Intern Med 2005;44:572-7.
9. Somnier FE. Increasing incidence of late-onset anti-AChR antibody-seropositive myasthenia gravis. Neurology 2005;65:928-30.
10. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000;55:16-23.
11. Blalock A, Mason MF, Morgan HJ, et al. Myasthenia gravis and tumors of the thymic region. Report of a case in which the tumor was removed. Ann Surg 1939;110:544-61.

12. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review) report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:7-15.
13. Wolfe GI, Kaminshi HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med. 2016; 375:511-22.
14. Sugawara M, Wada C, Okawa S, et al. Long-term follow up of thymus in patients with myasthenia gravis. J Neuroimmunol 2010;221:121-4.
15. Beghi E, Antozzi C, Batocchi AP, et al. Prognosis of myasthenia gravis: a multicenter follow-up study of 844 patients. J Neurol Sci 1991;106:213-20.
16. Zahid I, Sharif S, Routledge T, et al. Video-assisted thoracoscopic surgery or transsternal thymectomy in the treatment of myasthenia gravis? Interact Cardiovasc Thorac Surg 2011;12:40-6.
17. Ricciardi R, Melfi F, Maestri M, et al. Endoscopic thymectomy: A neurologist's perspective. Ann Cardiothorac Surg 2016;5:38-44.

Cite this article as: Otsuka R, Ueda K, Tanaka T, Murakami J, Hayashi M, Hamano K. Who will benefit from thymectomy for myasthenia gravis? Is there any role for this procedure in elderly patients? Ann Transl Med 2019;7(1):4. doi: 10.21037/atm.2018.11.66

