Original Article

A Comparative Study of Video-Assisted Thoracoscopic Surgery Versus Median Sternotomy Thymectomy in Myasthenia Gravis

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Background: Thymectomy is a standard treatment for myasthenia gravis (MG) patients. Although there are different approaches for thymectomy available, the standard approach is still known as a median sternotomy. Currently, the video-assisted thoracoscopic (VATS) approach is increasing in popularity. It has shown benefits in less blood loss, less postoperative pain, and improvement of recovery after surgery. However, there are still controversies in the outcomes of these two approaches.

Objective: To compare perioperative and neurological outcomes of thymectomy between the median sternotomy approach and the VATS approach.

Materials and Methods: One hundred twenty-three patients underwent thymectomy between January 1, 2012 and December 30, 2020 and were enrolled in the present retrospective study. They were classified into two groups depending on the approach of the surgery. The perioperative and neurological outcomes were analyzed and compared between the two groups. The analyses were performed using students' t-test, Mann-Whitney test, chi-square, or Fisher's exact test.

Results: There were 72 patients in the median sternotomy group and 51 patients in the VATS group, and no death in both groups. There were also no significant differences between the two groups regarding surgical time, postoperative pain, postoperative complications, and neurological outcomes. Intraoperative blood loss, intercostal drainage volume and duration, and length of hospital stay were significantly less in the VATS group. Complete remission was significantly higher in VATS group. The median follows up time was significantly longer in the median sternotomy group.

Conclusion: The VATS approach for thymectomy had shown good outcomes, which were not inferior to the median sternotomy approach.

Keywords: VATS Thymectomy; MG; Thymoma; Thymectomy; Minimally invasive thymectomy; Myasthenia gravis; Left VATS thymectomy; Subxiphoid VATS thymectomy; Anterior mediastinal tumor; Anterior mediastinal mass

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Myasthenia gravis (MG) is an autoimmune disease producing an antibody that binds to the acetylcholine receptors in the neuromuscular junction and results in muscle weaknesses. The incidence of MG is 0.3 to 2.8 per 100,000 population[1].

Hence, the primary role in the treatment of MG is medication. A variety of medicines are being used for the treatment of MG. Mechanism of those medicines is immunosuppressive drugs and acetylcholine esterase inhibitor (ACHEI)[2-5].

According to SABISTON&SPENCER Surgery of the chest[6], 5% to 15% of patients with MG are found to have thymomas, and those 30% to 50% of thymomas are associated with clinical MG. The relationship between MG and thymoma provides the guidance for a treatment option of thymectomy. Furthermore, the previous research from The Quality Standards Subcommittee of the American Academy of Neurology shows that MG patients undergoing thymectomy are twice likely to attain complete remission[7].

The standard approach of thymectomy has been known as median sternotomy. Currently, minimally invasive surgery (MIS) demonstrates advantages

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Table 1. Neurological outcomes

Data	Total (n=84)	Median sternotomy (n=46)	VATS (n=38)	p-value
Complete remission (CR); n (%)	11 (13.1)	2 (4.4)	9 (23.7)	0.009
Time to CR; median (IQR)	24 (18, 33)	30 (24, 36)	24 (18, 30)	0.470
Pharmacologic remission (PR); n (%)	7 (8.3)	5 (10.9)	2 (5.3)	0.449
Time to PR; median (IQR)	22 (18, 47)	36 (22, 50)	16 (13, 18)	0.064
Minimal manifestation; n (%)	20 (23.8)	14 (30.4)	6 (15.8)	0.117
Improved; n (%)	28 (33.3)	16 (34.8)	12 (31.6)	0.757
Worsening; n (%)	8 (9.5)	6 (13.0)	2 (5.3)	0.284
Exacerbation; n (%)	9 (10.7)	6 (13.0)	3 (7.9)	0.503
Unchanged; n (%)	10(11.9)	3(6.5)	7(18.4)	0.094
Follow up time (month); mean±SD	44.7±28.1	53.9±29.6	33.6±21.7	0.001

VATS=video-assisted thoracoscopic; IQR=interquartile range; SD=standard deviation

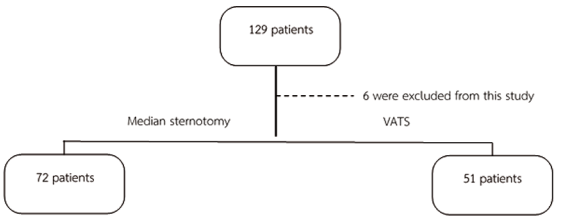

Figure 1. Flow of the study.

compared to the conventional method. For example, MIS has shown benefits in less blood loss, less postoperative pain, and can decrease the length of hospital stay. Nevertheless, there is a controversy over the neurological outcome of MIS surgery for thymectomy due to inadequate removal of the thymus gland.

In Ramathibodi Hospital, the surgeons have been performing MIS surgery, known as video-assisted thoracoscopic surgery (VATS), for thymectomy since 2012. Therefore, the present study was conducted to compare postoperative outcomes as well as neurological outcomes between the median sternotomy, and the VATS approach.

Materials and Methods

Study design and patients

The present study was approved by the Ethics Committee of Ramathibodi Hospital (COA MURA2020/1565). The authors collected data from the hospital's electronic medical record. Inclusion criteria were MG patients who obtained thymectomy in Ramathibodi Hospital between January 1, 2012 and December 30, 2020. Patients younger than 18 years at the time of surgery, underwent thymectomy combined with other operations, redo-thymectomy, or had incomplete medical records were excluded.

All patients in Ramathibodi Hospital were diagnosed with MG by electromyography (EMG). The selected patients were classified into two groups by surgeon preference. The first group were the patients that underwent median sternotomy approach. The second group were the patients that underwent VATS thymectomy approach. Figure 1 shows the number and percentage of included patients in each group. Both groups were compared in the aspect of characteristic baseline, perioperative outcomes, pathology, and neurological outcomes.

Surgical procedures in the present study were done by seven attending cardiothoracic surgeons and residents. Surgical procedures in the present study were done by one of seven attending cardiothoracic surgeons in the unit or by residents under supervision.

Neurological outcomes

After thymectomy was done, 84 patients, with 46 patients in the median sternotomy group and 38 patients in the VATS group, were followed up at Ramathibodi Hospital as shown in Table 1. The patients that were not included were followed up at their rural hospitals.

The neurological outcomes in the present study were based on the definition from MG A Manual for the Health Care Provider[4] as shown in Table 2.

Statistical analysis

The demographic and preoperative data were collected and analyzed. Categorical variable was reported as frequency and percentage. Continuous data were reported as mean and standard deviation or median and interquartile range depending on data distribution. Two groups of data were compared using the student's t-test or Mann-Whitney test for continuous variables, and chi-square or Fisher's exact

Table 2. Neurological outcomes after thymectomy (MGFA postintervention status)

	Neurological outcomes after thymectomy (MGFA Postintervention status)
Complete remission (CR)	The patient has had no symptoms of signs of myasthenia gravis (MG) for at least 1 year and has received no therapy for MG during this time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic remission (PR)	The same criteria as for CR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal manifestation (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CR or PR do have a weakness that is only detectable by careful examination.
Improved (I)	A substantial decrease in pre-treatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in the QMG score.
Unchanged (U)	No substantial change in pre-treatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of maximum changes in QMG scores.
Worse (W)	A substantial increase in pre-treatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG scores.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy.

Performed with Stata v.14 (StataCorp LP). Statistics were significant with $p<0.05$.

test for categorical variables. All statistical analyses were performed with Stata, version 14 (StataCorp LP, College Station, TX, USA). Statistics were significant with a p-value less than 0.05.

Results

One hundred twenty-nine patients were enrolled in the present study. Six patients were excluded. The remaining 123 patients were included in the present study. The demographic and preoperative data are shown in Table 3. There were 31 men (25.2%) and 92 women (74.8%). The mean age was 45.2 (±SD 15.1) years. There was no significant difference in terms of symptom duration, preoperative medication, severity of symptoms, and underlying diseases except autoimmune disease. For the preoperative size of thymus on computerized tomography (CT) scan, four out of 123 patients did not undergo preoperative CT scan before surgery. Preoperative CT scan in 67.23% of patients (80 of 119 patients) could not demonstrate thymoma. The median size of the thymus gland in preoperative CT of the median sternotomy and VATS, were 2.9×3.0×3.9 cm and 2.2×1.4×2.0 cm, respectively. Albeit, the size of the thymus gland in the median sternotomy group was larger than in the vats, there was no significant difference except the width of the thymus gland.

Perioperative findings and postoperative outcomes are shown in Table 4. The surgical time of the VATS group tends to be longer, but it was not statistically different. Intraoperative blood loss was significantly higher ($p<0.001$) in the median sternotomy group at median 200 mL (IQR 100, 300) versus median 30 mL (IQR 10, 100) in the VATS group. Same as intraoperative blood loss, chest drainage volume, chest tube duration, and length of hospital stay were significantly higher in the median sternotomy group. In terms of mean postoperative pain, the VATS group had a lower average of postoperative pain but with no statistical significance.

In the VATS group, six patients had been converted to median sternotomy since two patients had an injury to the innominate vein. The third patient could not tolerate one lung ventilation. The fourth patient was due to bleeding from the mid pericardium, and the last two patients were because of camera problems.

For the postoperative complications, fourteen patients had postoperative complications. The most common complication was phrenic nerve injury in five out of 16 patients. The second was postoperative infection in four out of 16 patients. The third and the fourth were subcutaneous emphysema and pneumothorax, with two patients in each complication. The rests were reintubation and pulmonary embolism, and chylothorax with one patient in each complication. The detail of complications is shown in Table 4. The reason for reintubation was inadequate reversal of muscle relaxant. There was no statistically significant difference in each complication between median sternotomy, and VATS groups.

The pathologic report is shown in Table 5. There was no significant difference in thymus size and histopathology of the thymus gland between the two

Table 3. Demographic and preoperative data

Data	Total (n=123)	Median sternotomy (n=72)	VATS (n=51)	p-value
Sex: male; n (%)	31 (25.2)	17 (23.6)	14 (27.5)	0.629
Age (year); mean±SD	45.2±15.1	45.9±14.8	44.1±15.5	0.483
Underlying disease; n (%)				
Diabetes mellitus	18 (14.6)	9 (12.5)	9 (17.6)	0.426
Hypertension	34 (27.6)	22 (30.6)	12 (23.5)	0.391
Dyslipidemia	17 (13.8)	10 (13.9)	7 (13.8)	0.979
Hyperthyroid	7 (5.7)	3 (4.2)	4 (7.8)	0.447
Hypothyroid	1 (0.8)	1 (1.4)	0 (0.0)	0.999
Asthma	2 (1.6)	1 (1.4)	1 (2.0)	0.999
Autoimmune	6 (4.9)	0 (0.0)	6 (11.8)	0.004
Other	14 (11.3)	10 (13.9)	4 (7.8)	0.298
History of MG crisis; n (%)	19 (15.5)	12 (16.7)	7 (13.7)	0.657
Symptom duration; median (IQR)	12 (5, 24)	12 (4, 36)	12 (6, 24)	0.924
Symptom at time of surgery; n (%)				
MG crisis	4 (3.3)	4 (5.6)	0 (0.0)	0.141
Generalize MG	98 (79.7)	58 (80.6)	40 (78.4)	0.773
Ocular MG	21 (17.1)	10 (13.9)	11 (21.6)	0.265
MGFA; n (%)				0.566
MGFA I	19 (15.5)	11 (15.3)	8 (15.7)	
MGFA IIA	49 (39.8)	30 (41.7)	19 (37.3)	
MGFA IIB	48 (39.0)	26 (36.1)	22 (43.2)	
MGFA IIIA	1 (0.8)	0 (0.0)	1 (1.9)	
MGFA IIIB	2 (1.6)	1 (1.4)	1 (1.9)	
MGFA IV	1 (0.8)	1 (1.4)	0 (0.0)	
MGFA V	3 (2.4)	3 (4.2)	0 (0.0)	
Dose of prednisolone (mg); median (IQR)	30 (15, 40)	30 (15, 40)	30 (18, 40)	0.514
Dose of azathioprine (mg); median (IQR)	100 (50, 100)	75 (50, 100)	100 (50, 100)	0.337
Dose of mestinon (mg); median (IQR)	180 (180, 240)	180 (180, 240)	180 (180, 240)	0.311
Dose of cellcept (mg); median (IQR)	1,500 (1,500, 2,000)	1,500 (1,500, 2,000)	1,500 (250, 2,000)	0.543
Thymoma on preoperative CT; n (%)	n=119; 39 (32.8)	n=68; 21 (30.9)	n=51; 18 (35.3)	0.612
Thymoma size on peroperative CT; median (IQR)				
Width (cm), n=56	2.5 (1.7, 4.1)	2.9 (2.0, 4.7)	2.2 (1.4, 2.7)	0.028
Length (cm), n=52	2.6 (1.4, 4.1)	3.0 (2.0, 4.4)	1.4 (1.2, 3.5)	0.093
Height (cm), n=27	3.4 (1.8, 4.7)	3.9 (2.0, 5.0)	2.0 (1.8, 3.8)	0.287

VATS=video-assisted thoracoscopic; MG=myasthenia gravis; MGFA=Myasthenia Gravis Foundation of America; CT=computerized tomography; IQR=interquartile range; SD=standard deviation

groups. The most common histopathology was thymic hyperplasia in 50 out of 123 thymus glands (40.6%). The incidence of thymoma was 34.9%, which was greater than the review that the authors have already mentioned before.

The neurological outcome is shown in Table 1. Thirty-nine patients were excluded from the analysis because they were not followed up by Ramathibodi Hospital. The total remission in the present study was 21.4% with 18 out of 84 patients. Conversely, there was more complete remission in the VATS group at nine versus two patients (p=0.009) but more pharmacological remission in the median sternotomy group at five versus two patients (p=0.449). The other neurological outcomes were not significantly different. There was no death in the present study. The median of follow up time was significantly longer in the median sternotomy group at 53.9±29.6 months versus 33.6±21.7 months (p=0.001).

Discussion

Thymectomy is widely accepted in the standard treatment of MG[4]. It had shown benefits overcoming medication treatment alone. According to Gronseth

Table 4. Perioperative findings and complication

Data	Total (n=123)	Median sternotomy (n=72)	VATS (n=51)	p-value
Surgical time (minute); mean±SD	135±44	130±46	143±40	0.115
Blood loss (mL); median (IQR)	100 (50, 250)	200 (100, 300)	30 (10, 100)	<0.001
Convert to open; n (%)	-	-	6 (11.8)	-
Immediate extubating; n (%)	119 (96.7)	69 (95.8)	50 (98.0)	0.641
Chest drainage volume (mL); median (IQR)	360 (160, 600)	360 (265, 705)	270 (100, 525)	0.023
Chest tube duration (day); median (IQR)	2 (2, 3)	3 (2, 3)	2 (2, 3)	0.001
Postoperative pain; mean±SD				
24 hours	3.0±1.6	3.2±1.7	2.7±1.4	0.099
48 hours (n=122)	2.3±1.6	2.4±1.6	2.2±1.6	0.521
72 hours (n=109)	1.7±1.5	1.8±1.6	1.5±1.2	0.189
Length of hospital stay (day); median (IQR)	4 (3, 5)	4 (3, 6)	3 (3, 4)	0.001
Postoperative complication; n (%)				
Pneumothorax	2 (1.6)	1 (1.4)	1 (2.0)	0.999
Phrenic nerve injury	5 (4.1)	2 (2.8)	3 (5.9)	0.648
Reintubation	1 (0.8)	0 (0.0)	1 (2.0)	0.415
Postoperative infection	4 (3.3)	1 (1.4)	3 (5.9)	0.306
Subcutaneous emphysema	2 (1.6)	0 (0.0)	2 (3.9)	0.170
Pulmonary embolism	1 (1.4)	1 (1.4)	0 (0.0)	-
Chylothorax	1 (0.8)	0 (0.0)	1 (2.0)	0.415

VATS=video-assisted thoracoscopic; IQR=interquartile range; SD=standard deviation

Table 5. Pathology report

Data	Total (n=123)	Median sternotomy (n=72)	VATS (n=51)	p-value
Thymus size; mean±SD				
Width (cm)	9.5±3.4	9.9±3.7	8.9±2.9	0.118
Length (cm)	6.8±2.1	6.8±2.3	6.7±1.9	0.684
Height (cm)	2.3±1.2	2.4±1.3	2.1±1.0	0.143
Histopathology report; n (%)				
Thymic hyperplasia	50 (40.6)	27 (37.5)	23 (45.1)	0.398
Involuted thymus	28 (22.8)	16 (22.2)	12 (23.5)	0.865
Thymic cyst	2 (1.6)	0 (0.0)	2 (3.9)	0.170
Thymolipoma	3 (2.4)	1 (1.4)	2 (3.9)	0.569
Thymoma				
• A	7 (5.7)	7 (9.7)	0 (0.0)	0.041
• AB	8 (6.5)	4 (5.7)	4 (7.8)	0.717
• B1	7 (5.7)	5 (6.9)	2 (3.9)	0.698
• B2	15 (12.2)	11 (15.3)	4 (7.8)	0.214
• B3	6 (4.9)	4 (5.6)	2 (3.9)	0.679
• C	0 (0.0)	0 (0.0)	0 (0.0)	-
Other	1 (0.8)	0 (0.0)	1 (2.0)	0.415
Thymoma size; median (IQR)				
Width (cm)	4 (3, 7)	4 (3, 7)	4 (2, 7)	0.735
Length (cm)	3 (2, 6)	3 (2, 6)	3 (3, 4)	0.864
Height (cm)	2 (1, 3)	2 (2, 3)	1 (1, 3)	0.482

VATS=video-assisted thoracoscopic; IQR=interquartile range; SD=standard deviation

et al[7], MG patients that underwent thymectomy are twice as likely to attain medication-free remission, 1.6 times as likely to become asymptomatic, and 1.7 times as likely to be improved. The approach to thymectomy can be performed by various techniques such as median sternotomy, transcervical, thoracoscopic, or VATS in either left sided, right sided, or subxiphoid, and Robotic. Even though the gold standard in the approach of thymectomy is median sternotomy, the VATS approach is more popular based on the result of studies[8-13] showing that the VATS approach had less blood loss, less postoperative pain, and less length of stay. There is still one considerable concern about the completeness of resection compared to median sternotomy, which residual of the thymus gland might affect the neurological outcome.

According to the result of the present study, the demographic and preoperative data between the two groups are comparable. Even if the width of the thymus size was slightly larger in the median sternotomy group, it does not affect the approach. However, one concern was the underlying disease, which the VATS groups had more autoimmune disease than the median sternotomy group. The patients who had an autoimmune disease might need immunosuppressive drugs after the operation. Thus, the authors could not classify them into the remission group. Conversely, there are three out of six patients, who needed immunosuppressive drugs to control symptoms preoperatively.

Both VATS groups had shorter length of stay and chest tube duration, less intraoperative blood loss, and less first 24-hour postoperative pain. These results are similar to the other studies[8-11,13,14] since median sternotomy approach is required to cut the sternum. This procedure has more bleeding from the raw surface from the bone, more pain from cutting the bone, and larger skin incision. The conversion rate in the present study is 11.76% with six out of 51 patients. Compared with Xie et al[8], the conversion rates are 0% to 11.8%. However, only three patients were converted to an open approach due to surgical technique, which was bleeding. The rest were converted due to camera and ventilation problems. The postoperative complications were found in 16 patients with five patients in the median sternotomy group and eleven patients in the VATS group. The complication was higher in the VATS approach, as the present study center started the VATS approach in 2012, and there was a learning curve in the initial period of surgery. Nevertheless, there is no significant difference between the two groups.

In connection with neurological outcomes, the remission rate tended to be higher in the VATS group, and the time to remission tended to be shorter. However, the exacerbation was higher in the median sternotomy group with synchronously as the follow up time. For this reason, the longer follow up time, the higher chance of symptom exacerbation. The present study remission rate is quite lower compared to other studies[9,11,14]. After reviewing the electronic medical record, some patients examined by the neurologist did not have weakness symptoms, but they usually asked the doctor for ACHEI when they felt like the symptoms had occurred. This group of patients had to be categorized as Minimal Manifestation. Even though the remission rate was lower than other research, there was no difference in the overall neurological outcomes in the present study.

Limitation

Since the present study was a retrospective study, observational and selection biases are inevitable. The learning curve of VATS thymectomy also affects the outcome. The lack of AChR-Ab data is also a limitation. The most affected outcome is follow-up time because in the initial period of the VATS approach, there were fewer cases than nowadays. Another limitation that should not be neglected is the status of the neurological outcomes. As discussed above, most patients usually asked for ACHEI even though they had no symptoms. In the future, an extended study on this topic could be done to minimize the confounding factors.

Conclusion

From the results of the present study along with other studies, the VATS approach for thymectomy is as effective as of the median sternotomy approach.

What is already known on this topic?

Thymectomy by VATS approach has more benefit in intraoperative blood loss and postoperative recovery.

What this study adds?

Thymectomy by VATS approach provides the same neurological outcomes compared to the median sternotomy approach. Complete remission rate tended to be higher in the VATS approach.

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Conflicts of interest

The authors declare no conflict of interest.

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