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Bilateral thoracoscopic extended thymectomy versus sternotomy

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Abstract

Background: Complete open surgical resection is the standard treatment for thymoma and myasthenia gravis. We evaluated the feasibility of bilateral video-assisted thoracoscopic extended thymectomy, and compared it to surgery via sternotomy.

Methods: From 2011 to 2014, 43 patients undergoing thymectomy were divided into 2 groups: 23 underwent video-assisted thoracoscopic extended thymectomy, and 20 had thymectomy via sternotomy. The primary outcomes were postoperative pain score (visual analog scale) at 6, 12, 24, 48, and 72 h, and 1-month postoperatively, and morphine consumption in the first 48 h. Secondary outcomes were surgical and clinical results.

Results: There were no significant differences between the 2 groups in terms of demographics and preoperative clinical data. Compared to the sternotomy group, the video-assisted thoracoscopic thymectomy group had lower pain scores and morphine consumption at all time points, significantly less operative blood loss and chest drainage volume, and shorter hospital stay. The rates of improvement in myasthenia gravis were 85% and 86% in the video-assisted thoracoscopic thymectomy and sternotomy groups, respectively. No recurrence of thymoma was found in either group (median follow-up 27 months).

Conclusions: Our results seem to confirm that in selected cases, video-assisted thoracoscopic thymectomy allows complete resection of thymus and perithymic tissue, similar to sternotomy but with the known advantages of minimally invasive surgery including less pain and a good cosmetic result.

Keywords

Thymectomy, Thymus gland, Myasthenia gravis, Sternotomy, Thoracic surgery, video-assisted

Introduction

Complete surgical resection still represents the mainstay of treatment for thymoma and myasthenia gravis (MG).[1] Currently, median sternotomy is widely considered to be the standard approach for thymoma resection, but it is unacceptable, particularly to young female patients, because of significant esthetic sequelae. Thus in the last decade, several centers have proposed video-assisted thoracoscopic surgery (VATS) as an alternative to sternotomy for thymectomy, considering the reduced morbidity and better cosmetic results obtained with minimally invasive surgery compared to open techniques in the management of lung diseases.[2,3] Because complete resection of the thymus and surrounding fat tissue is the primary goal of surgery, the main concern is whether VATS can achieve the same clearance of thymic and fat tissue as sternotomy. Recently, we reported the feasibility of performing bilateral video-assisted thoracoscopic extended thymectomy (VATET) which has the advantage of amplifying the view of both cardiophrenic regions and facilitating complete resection of the thymus and surrounding mediastinal tissue.[4] Herein, we compared the surgical and clinical outcomes of bilateral VATET with those of

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open thymectomy to determine whether VATET could provide the surgical benefits of minimally invasive surgery without affecting the clinical results.

Patients and methods

This was a retrospective multicenter study conducted from January 2011 to November 2014. All consecutive patients undergoing extended thymectomy for management of thymus hyperplasia with MG or ofthymoma with or without MG were eligible. Patients who had a previous thoracic surgery procedure, used opiates preoperatively, had a history of chronic pain syndrome, and those undergoing induction therapy or with a diagnosis of thymic carcinoma or other mediastinal malignancies were excluded. Of the 53 patients who underwent thymectomy, 3 were excluded due to preoperative opioid use, 2 for history of chronic pain, 4 for incomplete data, and one for an intraoperative diagnosis of thymic carcinoma; thus 43 patients were analyzed, The patients were divided into 2 groups based on thymectomy performed via sternotomy or VATET. The operative approach was determined by the location and size of the thymoma, the surgeon's experience, and the patient's preference. Generally, small and early-Masaoka stage thymomas were resected by VATS while thymomas or hyperplasia >5 cm or advanced Masaoka stage thymomas (III–IV) and/or thymomas with suspected vascular invasion underwent sternotomy due to the difficulty of achieving complete resection with VATS. The 2 groups were compared to assess outcome differences. The primary outcome measures were pain score and morphine consumption. Secondary outcomes were mortality, major and minor morbidity, operative time, blood loss, chest drain duration, hospital stay, therapeutic response to thymectomy according to Myasthenia Gravis Foundation of America (MGFA) status, and recurrence of disease. The patients gave written consent for the operation and were aware that their data would be used for research purposes.

All patients underwent the same preoperative evaluation including standard cardiopulmonary function tests, neurologic and radiological assessments (computed tomography or magnetic resonance). All mediastinal masses diagnosed on computed tomography or magnetic resonance were evaluated by preoperative biopsies to exclude thymic carcinoma. In selected cases without a preoperative diagnosis but a high suspicion that the tumor was other than a thymoma (i.e. teratoma), an intraoperative biopsy was performed to obtain the diagnosis so as not to inadvertently perform a less than complete thymectomy for thymoma.

Diagnosis of MG was made on the basis of two or more of the following clinical findings: electromyographic result (decrement > 10% on repetitive stimulation), improvement in myasthenic symptomatology after anticholinesterase therapy, the level of antiacetylcholine receptor antibody (or anti-muscle specific kinase in the case of the negativity). The grade of MG was evaluated according to the MGFA classification. Neurologists determined the timing of surgery.

Patients in sternotomy group underwent a standard surgical approach.[1] The limits of resection included the diaphragm caudally, the thyroid orally, and the phrenic nerves laterally. Our novel technique of bilateral VATET has been reported previously.[4] Briefly, in cases of left thymoma, 3 ports were inserted through the 4th intercostal space on the median axillary line and through the 2nd–3rd and 6th intercostal spaces on the anterior axillary line. After incision of the mediastinal pleura, thymic dissection was performed cranially. The thymic veins and upper thymic poles were sectioned in that order, and thymic dissection was conducted caudally. A 4th 5-mm trocar was inserted through the 7–8th interspace in the posterior axillary line to resect the pericardiophrenic fat tissue. At the end of dissection, we opened the contralateral pleura and pushed the specimen into the right pleural cavity. The patient was placed in the left lateral decubitus position, and 3 or 4 ports were inserted in positions similar to the left side. Right thoracoscopy allows complete en-bloc thymic dissection of bilateral perithymic and pericardiophrenic fatty tissue. The specimen was removed through one of the incision ports or a utility incision in the case of a large specimen. A tube was placed in the mediastinum in the sternotomy group while in VATET group a chest tube, while in VATET group a chest tube, one for each side, was left in pleural space was left in pleural space. Patients were transferred to the surgical ward or intensive care unit, according to their clinical condition. They all received the same postoperative analgesia: subcutaneous morphine 10 mg 30 min before the end of the intervention, intravenous ketorolac 30 mg and paracetamol 1000 mg on awakening, and intravenous patient-controlled analgesia in the first 48 h postoperatively, allowing a maximum of 1 mg of morphine at 7-min intervals. If the visual analog scale (VAS) score surpassed 4, rescue analgesics were administered according to the standardized institutional protocol for pain treatment. After 48 h postoperatively, ketorolac was administered in case of pain. An example of VATET is reported in Figure 1.

Pain scores were assessed using VAS. The scores ranged from 0 (no pain) to 10 (intolerable pain). The data were recorded at 6, 12, 24, 48, 72 h, and 1 month after the operation. In addition, morphine consumption (in mg) was recorded at 6, 12, 24, 36, and 48 h postoperatively, as well as the additional rescue dose of morphine if required. Mortality, morbidity, operative time, blood loss, duration of chest tube drainage, intensive care unit

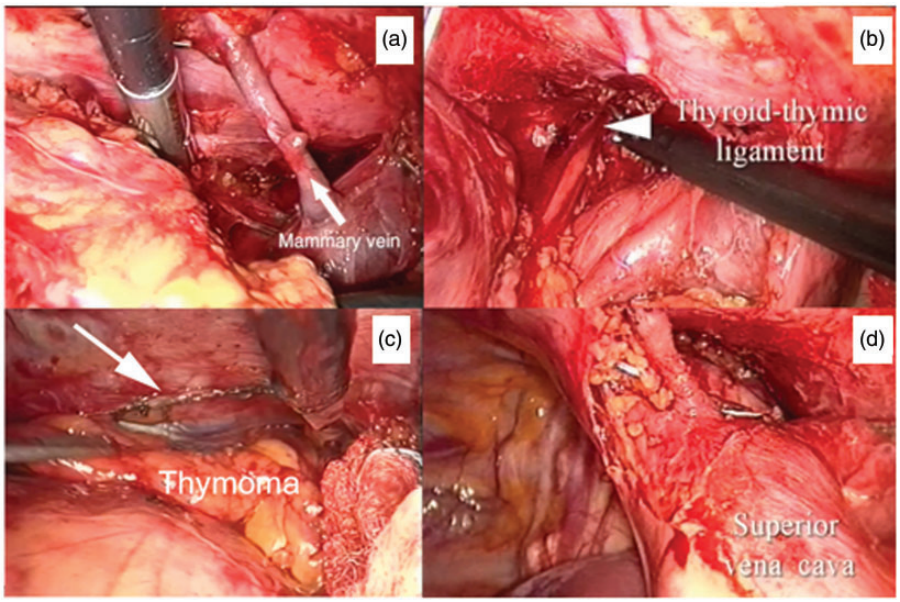

Figure 1. Intraoperative photographs showing the main steps in bilateral video-assisted thoracoscopic extended thymectomy. (a, b) After incision of the mediastinal pleura, thymic dissection is carried out cranially and then caudally to remove the thymoma with all mediastinal fatty tissue. (c) After completing the dissection, the contralateral pleura is opened (arrow), and the specimen is pushed into the right pleural cavity. (d) Right thoracoscopy allows complete resection of mediastinal fatty tissue on the right side.

and hospital length stay, scar discomfort, therapeutic response to thymectomy (MGFA status), and thymoma recurrence were recorded in all patients.

Data are reported as mean ± standard deviation for continuous variables and as number and percentages for categorical variables. Student's *t* test and the chi-square test were used to compare variables, as appropriate. The difference in VAS scores was evaluated by analysis of variance corrected with the Bonferroni post-hoc test. A *p* value <0.05 was considered statistically significant. MedCalc statistical software version 12.3 (MedCalc Software, Mariakerke, Belgium) was used for statistical analysis.

Results

The characteristics of the study population are summarized in Table 1. The VATET group were well-matched with the sternotomy group in terms of age, sex, forced expiratory volume in 1 s ($p = 0.8$), proportion of MG patients as well as MGFA classification, duration of medication ($p = 0.6$), and antiacetylcholine receptor antibody level. Thymoma was diagnosed in 6 patients in each group ($p = 0.9$) and no difference was found in Masaoka stage or tumor size. The VATET group compared to the sternotomy group, had lower postoperative VAS scores at 6 h (1.9 ± 0.6 vs. 2.6 ± 0.9, respectively), 12 h (1.8 ± 0.5 vs. 2.9 ± 1.2), 24 h (1.9 ± 0.8 vs. 3.7 ± 1.5), 48 h (1.8 ± 0.7 vs. 2.9 ± 0.7), 72 h (1.5 ± 0.6 vs. 2.2 ± 0.5), and 1 month (0.5 ± 0.6 vs. 0.9 ± 0.7). This difference was statistically significant ($p < 0.001$; Figure 2). The consumption of morphine was also lower in the VATET group compared to Sternotomy Group at 6 h (2.7 ± 0.9 vs. 4.1 ± 1.1 mg, respectively), 12 h (4.3 ± 0.6 vs. 13.3 ± 2.9 mg, respectively), 24 h (5.6 ± 1.4 vs. 17 ± 2.2 mg, respectively), 36 h (4.5 ± 1.1 vs. 16.8 ± 1.9 mg, respectively), and 48 h (3.4 ± 1.3 vs. 16.9 ± 2.1 mg, respectively). This difference was statistical significant ($p < 0.001$; Figure 3). No patient in the VATET group required a rescue dose of morphine, but it was required in 8 (40%) patients in the sternotomy group ($p = 0.003$). The surgical outcomes are summarized in Table 2. No surgical mortality or major morbidity was seen. No conversion from VATET to sternotomy occurred. Although minor complications were more frequent in the sternotomy group, the difference was not significant. Operative blood loss, chest drainage, intensive care unit stay ($p = 0.01$), and hospital stay ($p = 0.03$) were significantly less in the VATET group. Seven (35%) patients had post-sternotomy scar discomfort whereas all patients in the VATET group were satisfied with the cosmetic results ($p = 0.007$). Clinical outcomes are given in Table 3. Among MG patients, the postoperative MGFA status showed that the response to thymectomy was similar in both groups. We observed an improvement in pathologic MGFA status in 13 (62%) patients in the VATET group and 10 (71%) in the sternotomy group, the total improvement rate was 85% in the VATET group and 86% in the sternotomy group. In a median follow-up of 27 months (range 6–36 months), no thymoma recurrence was found in either group.

Table 1. Clinical characteristics of 43 patients undergoing thymectomy.

Variables	Sternotomy ($n=20$)	VATET ($n=23$)	p value
Age (years)	47.5 ± 8.6	43.0 ± 9.8	0.6
Male	14 (70%)	16 (69%)	0.7
Myasthenia gravis	12 (60%)	15 (65%)	0.9
MGFA classification			
I	3	3	0.8
2a	4	5	0.6
2b	1	2	0.7
3a	1	2	0.8
3b	1	2	0.8
4a	1	1	0.5
4b	1	0	0.9
Antiacetylcholine receptor antibody (nmol L^{-1})	8.9 ± 2.7	10.3 ± 4.8	0.7
Size of specimen (cm)	7.3 ± 3.3	5.1 ± 5.9	0.09
Pathological diagnosis			
Thymic hyperplasia	8/20 (40%)	13/23 (56%)	0.4
Atrophic thymus	4/20 (20%)	1/23 (4%)	0.2
Thymoma	6/20 (30%)	6/23 (26%)	0.9
Normal thymus	2/20 (10%)	3/23 (14%)	0.5
Masaoka stage			
I	3 (50%)	4 (67%)	1.0
II	2 (16%)	2 (33%)	0.5
III	1 (4%)	0	1.0

MGFA: Myasthenia Gravis Foundation of America; VATET: video-assisted thoracoscopic extended thymectomy.

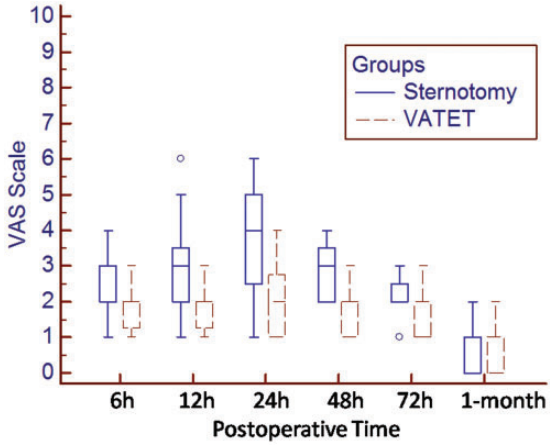

Figure 2. The visual analog scale (VAS) score was significantly lower in the video-assisted thoracoscopic extended thymectomy (VATET) group compared to the sternotomy group at all postoperative time points.

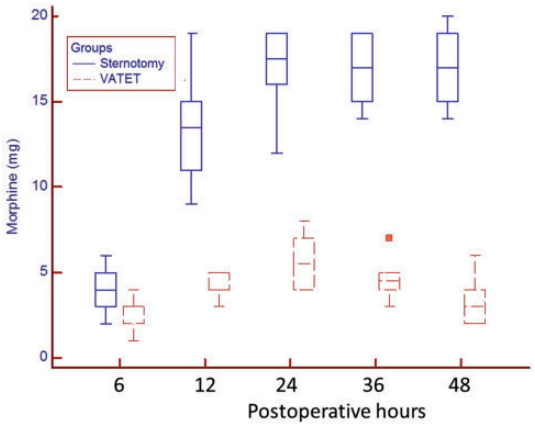

Figure 3. The consumption of morphine was lower in the video-assisted thoracoscopic extended thymectomy (VATET) group compared to the sternotomy group at all postoperative time points.

Table 2. Surgical outcomes in 43 patients undergoing thymectomy.

Variables	Sternotomy ($n=20$)	VATET ($n=23$)	p value
Operative time (min)	137 ± 24	125 ± 13	0.8
Blood loss (mL)	136 ± 15	43 ± 8	<0.001
Drainage volume (mL)	867 ± 97	226 ± 29	0.003
Intensive care unit stay (days)	2.1 ± 0.9	0.2 ± 0.1	0.01
Hospital stay (days)	7 ± 2.6	5 ± 1.9	0.03
Atrial fibrillation	2 (10%)	0	0.4
Atelectasis	4 (20%)	1 (4%)	0.2
Transfusion	1 (5%)	0	0.4
Scar discomfort	7 (35%)	0	0.007

VATET: video-assisted thoracoscopic extended thymectomy.

Discussion

Since the first thymectomy reported in 1939,[5] there has been growing interest in developing minimally invasive approaches to reduce the morbidity and esthetic sequelae of sternotomy. Cooper and colleagues[6] and Calhoun and colleagues[7] proposed transcervical thymectomy with a special retractor to lift the sternum and enlarge the operative view of the anterior mediastinum. With increasing experience in VATS, several centers have attempted to replicate open thymectomy using a VATS procedure. Our group, with experience accumulated in the management of lung diseases,[8] moved from sternotomy to VATS for management of thymoma and MG.[3,4] However, concern about obtaining good cosmetic results should not reduce the ability to achieve radical resection of thymic tissue, which remains the

Table 3. Clinical outcomes in myasthenia gravis patients.

MGFA status	Sternotomy ($n=14$)	VATET ($n=21$)	p value
Complete stable remission	2 (14%)	5 (24%)	0.7
Pharmacological remission	0	0	
Minimal manifestations 0 (MM0)	1 (7%)	3 (14%)	0.9
Minimal manifestations 1 (MM1)	1 (7%)	0	0.8
Minimal manifestations 2 (MM2)	2 (14%)	3 (14%)	0.6
Minimal manifestations 3 (MM3)	6 (44%)	7 (34%)	0.8
Unchanged (U)	2 (14%)	3 (14%)	0.6
Worse (W)	0	0	
Death due to myasthenia (D)	0	0	

MGFA: Myasthenia Gravis Foundation of America; VATET: video-assisted thoracoscopic extended thymectomy.

primary objective of surgery. On the basis of this rationale, we compared our VATET technique with the standard thymectomy to determine whether the minimal invasive approach could improve the surgical outcomes without affecting the clinical results.

Firstly, we found a significant reduction in pain scores and opioid consumption after VATET compared to sternotomy, in agreement with previous experiences. The reduction in skin and chest wall incisions is the most likely explanation for pain reduction. The postoperative pain associated with myasthenia muscle weakness could reduce mobilization of the thoracic cavity and clearance of secretions, and increase the risk of pulmonary complications including hypoxia, atelectasis, and pulmonary infections. Reduced postoperative pain allows active coughing, faster recovery of respiratory function, and an earlier return to daily activity with fewer physical limitations, particularly important for MG patients who are younger, employed, and active. In addition, the smaller chest scar due to VATET is likely to increase acceptance of thymectomy among young women, and in theory, could reduce the morbidity related to sternotomy, such as sternal infection, nonunion and/or dehiscence, considering that MG patients are fragile due to immunosuppressant therapy.[9,10,11]

Secondly, the VATET group had significant reductions in operative blood loss, chest drainage, and hospital stay. In theory, these findings could be interpreted as the indirect result of less invasive surgery. Some reports observed a significant reduction in operative blood loss during VATS thymectomy compared to sternotomy.[12–14] Others showed a shorter hospital stay and less opioid consumption after VATS thymectomy compared to sternotomy.[15–18] Furthermore, in a recent review, Zahid and colleagues[19] evaluated 14 studies including non-thymomatous MG patients and thymomatous patients with or without MG undergoing thymectomy through VATS vs. sternotomy, and concluded that VATS improved the cosmetic result and reduced the need for postoperative medication. However, our surgical outcomes should be considered with cautious. Although the difference was not significant, the VATET group had smaller and earlier stage tumors than the sternotomy group, because thymomas >5 cm and advanced Masaoka thymomas stages (III–IV) and thymomas with suspected vascular invasion were excluded from VATS. Thus VATET cases appear to be technically easier than open surgical cases, and that could affect surgical outcomes such as operative time, blood loss, chest drainage, and hospital stay.

Thirdly, minimally invasive surgery allowed complete resection of the thymus and surrounding tissue, similar to sternotomy. As reported by Jaretzki and colleagues,[1] the amount of tissue resected in each procedure remains the most objective parameter for estimation of surgical effect. The mean weight of specimens in our VATET group was similar to that in the sternotomy group, in agreement with other reports.[12,16] In addition, no significant differences were found in clinical outcomes. The response to thymectomy according to postoperative MGFA status was similar in both groups ($p=0.8$). In the VATET group we observed complete remission in 24%, improvement in pathologic MGFA status in 62%, and global improvement in 86% of cases. These data agree with reported global improvement rates ranging from 81% to 96%.[15] However, the VATET group had less risk of recurrence compared to the sternotomy group, due to smaller and earlier Masaoka stage tumors. This bias was due to the criteria of selection for VATET, which included small or non-invading tumors, in agreement with other studies.[9–11] Another limitation was the short follow-up (27 months, range 6–36 months) for evaluation of thymoma and/or MG recurrence. However, similar results have been reported in other studies with longer follow-up.[20–23] In a meta-analysis including 15 studies and involving 1003 MG patients, Ng and colleagues[24] compared VATS ($n=533$), transcervical ($n=449$), and infrasternal mediastinoscopic ($n=21$) procedures and found that VATS and transcervical surgery had comparable remission rates at the 10-year follow-up (35.4% vs. 38.1%, respectively). Similarly, Zahid and colleagues[19] found equivalent resolution of MG in patients undergoing VATS vs. sternotomy.

Finally, from a technical point of view, the main advantage of VATS compared to sternotomy is magnification of the operative view along the phrenic nerves,

near to the diaphragm and ribs. However, unilateral VATS may have several technical limitations as reported by Lee and colleagues.[25] Resection of tissue in the right cardiophrenic angle and within the confluence of the superior vena cava and innominate vein can be challenging using a left-sided approach, while a right-sided approach could limit resection of tissue in the left-sided cardiophrenic angle fat and/or at the level of the aortopulmonary window. To facilitate these manoeuvres, we performed bilateral VATS with the patient inclined forward at 60 degrees in the lateral decubitus position and the surgeon positioned cranially to the head of the patient. This position allowed a direct view of both pericardiophrenic angles and phrenic nerves without using special retractors or additional incisions, as reported by others.[26,27] The presence of a thymoma was a relative contraindication to VATET. During resection, great effort was made to leave the capsule intact and achieve complete dissection of perithymic and mediastinal fat to reduce the risk of recurrence. However, as mentioned above, the size of the tumor and the Masaoka stage were the main criteria for choosing the approach, and we suggest that sternotomy remains the strategy of choice for management of tumors >5 cm and/or advanced Masaoka stage thymomas.

Our results seem to confirm that in selected cases, VATET affords similar clinical results to sternotomy but with the well-defined advantages of minimally invasive surgery, such as reduced postoperative pain and good cosmetic results. The limited number of patients, differences between the two study groups due to the retrospective nature of study, and the brief follow-up could have affected our results which should be validated by larger prospective studies with longer follow-up.

Declaration of conflicting interests

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