Video-assisted thoracoscopy versus open approach in patients with Masaoka stage III thymic epithelial tumors

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Background: The treatment options for Masaoka stage III thymic epithelial tumors are diverse, mainly because the lesions infiltrate the neighboring organs, major vascular structures, with different scopes, extents, and manners. Surgical treatment is the main treatment for the patient in this stage. However, for minimally invasive or open surgery, the current controversy remains large. This study aimed to investigate the feasibility and indications of minimally invasive resection in the treatment of stage III thymic tumors.

Methods: Twenty-six patients with Masaoka stage III thymic tumors who underwent surgery were enrolled in the study. Among them, group A with 8 patients underwent thoracoscopic resection and group B with 18 patients (including one open-converted patient) underwent semi-sternotomy or full-sternotomy resection. The groups were compared with each other in terms of the characteristics of patients, tumors, and perioperative period.

Results: There were no significant differences in patients' characteristics, WHO classification, and complications between the two groups (P>0.05), but the tumors in group B were significantly larger than those in group A (P<0.05). In group B, the lesions infiltrated the superior vena cava and the phrenic nerve more frequently than that of group A (P<0.05). There was no significant difference between the two groups in the involvement of left innominate vein, pericardium, and lung (P>0.05). Tumor size, the involvement of superior vena cava and phrenic nerve were important factors in the determination of minimally invasive surgery for Masaoka stage III thymic tumor (P<0.05).

Conclusions: For Masaoka stage III thymic tumors, neighboring organs involved were noted to be important factors in successful minimally invasive tumor resection. Tumor size and involvement of phrenic nerve and superior vena cava were found to be the variables that hindered successful video-assisted thoracoscopy (VATS) resection. Thus, minimally invasive resection is acceptable in the treatment of selected cases of Masaoka stage III thymic tumors.

Keywords: Masaoka staging; minimally invasive surgery; thymic epithelial tumor; video-assisted thoracoscopy (VATS)

Introduction

Although thymic epithelial tumors are rare, they are the most common tumors in the anterior mediastinum (1). At present, the treatment decisions for thymic tumors are mainly based on the Masaoka-Koga staging system (*Table 1*) (2). Most tumors in stage I and II can be successfully and completely removed by minimally invasive surgery (3,4). However, for patients with stage III thymic tumors, the treatment is complex and diverse, including surgery, radiotherapy, targeted therapy, immunotherapy, etc. (5-8). In general, however, surgical treatment is the preferred option for resectable lesions, as numerous studies have demonstrated that complete resection of the tumor is the most important prognostic factor for thymic tumors (5,9,10). With the advancement of minimally invasive surgery, doctors have used video-assisted thoracoscopy (VATS) (10), even robotic VATS (11), to remove stage III thymic tumors. However, the open conversion rate is high at present. Moreover, there is still no consensus on criteria of enrollment of stage III thymic tumors for minimally invasive surgery, and no consensus on the best approach of minimally invasive surgery.

Herein, this study intended to investigate the feasibility of minimally invasive resection of stage III thymic tumors and to explore the surgical indications for minimally invasive resection of stage III thymic tumors.

Methods

Materials and methods

We retrospectively reviewed the recorded data of Masaoka stage III thymic tumor patients who underwent surgical resection between July 2015 and December 2018 at Jiangxi Provincial People's Hospital Affiliated to Nanchang University, Department of Cardio-thoracic Surgery. The institutional review board of our hospital approved this study. The number of ethics approval was 2014079. Authorized relatives of all the patients were consulted preoperatively to inform the disease information, the pros and cons of surgical procedure, as well as the risks and possible complications during and after the operation. Informed consent was obtained from all patients. Patients without myasthenia gravis (MG) of Osserman III or higher (12) required contrast-enhanced chest computed tomography (CT) within 1 month before the operation. Contrast-enhanced chest CT was not conducted in patients who complicated with MG of Osserman III or higher, but

chest magnetic resonance imaging (MRI) was required. Thus, the details of the involvement of the neighboring organs could be assessed more accurately, especially the invasion of large blood vessels.

Patient characteristics

Twenty-six patients with thymic tumors underwent surgical resection with VATS or open approach. Eight patients had a complete VATS resection (group A), of which six patients underwent subxiphoid VATS operation, and two patients received subxiphoid combined right-sided VATS resection, as described in the surgical technique subsection. Eighteen patients who underwent open surgery had either a semi-sternotomy or a full-sternotomy (group B). One patient in group B was open-converted due to tumor invasion at the intersection of the left innominate vein and the superior vena cava. Group A had 8 patients, and group B had 18 patients.

Surgical technique

Patients in group A underwent full VATS resection, including six cases of subxiphoid VATS and two cases of subxiphoid combined right-sided VATS, and patients in group B underwent semi-sternotomy or full-sternotomy operation. The surgical technique was described as follows.

Subxiphoid VATS resection: implement single-lumen endotracheal intubation and general anesthesia in the supine position with legs separated, and the back was raised. An incision of 2–3 cm was made under the xiphoid process, with which tissues beneath the xiphoid was separated bluntly. Then take two 0.5–1 cm incisions under the left and right rib arches, respectively, the left one for separating forceps and the right for the ultrasonic scalpel. The thoracoscopy was placed in the subxiphoid incision, and the carbon dioxide was inflated into the mediastinum. Then cut the pleura on both sides, explore the chest cavity, and appraise invasion of the lung or hilar vessels; separate the fatty tissue and thymus from the subxiphoid incision along the pericardium, and carefully pay attention to the invasion of the pericardium, bilateral phrenic nerves, superior vena cava, and innominate vein. If the assessment was unresectable or without clear margin (R1 resection) under VATS, it converts to open surgery. If the invaded pericardium, lung tissue, and innominate vein were assessed to be resectable under VATS, the pericardium could be removed with an ultrasonic scalpel, and resection of invaded

964

Chen et al. VATS for Masaoka stage III thymic tumors

Table 1 Masaoka-Koga staging system

Stage	Definition
I	Macroscopically and microscopically completely encapsulated
IIA	Microscopic transcapsular invasion
IIB	Macroscopic invasion into the surrounding mediastinal fat tissue or grossly adherent to but not through the mediastinal pleura
III	Invasion into the neighboring organs
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastases

lung and innominate vein could easily be achieved with a thoracoscopic stapling device.

Subxiphoid combined right-sided VATS resection: add the following surgical procedure based on the above-mentioned subxiphoid VATS. The position should be changed to the supine position with the right chest padded up. The observation hole, the main operation hole, and the auxiliary operation hole were placed in the seventh intercostal space of the midaxillary line, the fourth intercostal space of the axillary line, and the fifth intercostal space of the midclavicular line, respectively. The right-sided VATS was mainly used to assist in cutting the invaded pericardium, separating the tumor and the invaded lung lobe.

Semi-sternotomy or full-sternotomy operation: patients were placed in the supine position. General anesthesia with single-lumen endotracheal intubation was implemented, the sternum was split from the upper end to the lower half or full sternal end. The bilateral mediastinum pleura were dissected, the mediastinal fat was removed within the phrenic nerves on both sides. The thymic tumor, aorta, pulmonary trunk, hilar vessels, innominate vein, superior vena cava, and pericardium were evaluated. The invaded phrenic nerves, innominate vein, and pericardium were removed directly. The superior vena cava was reserved, and the invaded wall was carefully dissected and sutured when less than one-third of SVC wall was invaded, or removed and reconstructed with PTFE graft when more than one-third of SVC wall was invaded.

Preoperative appraisal of CT and MRI was significant to ensure that radical resection, i.e., R0 resection, could be achieved. Regardless of whether the patient had MG or not, extended thymectomy was performed with an en bloc resection of the mediastinal fatty tissue and bilateral

mediastinal pleura. The specimen is always removed in a plastic bag with or without cutting apart the tumor tissue.

Data collection

The objective of the present study was to determine the feasibility and indications of minimally invasive resection in the treatment of Masaoka stage III thymic tumors. Age, gender, accompanied disease like MG, pathological results, tumor size, type of resected neighboring organs, duration of the operation, duration of postoperative hospital stay, reasons for open conversion, and complications were collected retrospectively. Three patients received preoperative chemotherapy, and all the patients underwent postoperative adjuvant chemotherapy. Routinely postoperative follow-ups were carried out for all patients.

Statistical analysis

The patients' characteristics were compared using Fisher's exact test, Pearson's χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. Pearson's χ^2 test was used to compare the differences between invaded neighboring organs between the two groups, with a value of $P<0.05$ considered statistically significant.

Results

There were 14 (53.8%) male and 12 (46.2%) female patients and the mean age of the patients was 47.2 years (range, 25–77 years). The mean size of the thymoma was 6.2 ± 2.2 cm (range, 2–12 cm). The mean length of postoperative stay (POS) was 12.6 ± 5.4 days (range, 5–32 days). No patient had redo VATS surgery for the treatment of hematoma or any other complications in group A. However, one patient in group B underwent a redo operation due to occlusion in the remained superior vena cava, and the superior vena cava was resected and reconstructed. According to the WHO histological classification, there were 1, 1, 2, 8, 4, 5 and 5 patient in A, AB, B1, B2, B2/B3, B3, and C, respectively. There were 14 (53.8%) patients with MG, of whom 8 patients underwent plasma exchange peri-operatively. Furthermore, MG patients experienced a much more prolonged POS than none-MG patients (15.1 ± 5.7 *vs.* 9.6 ± 3.1 days, t=3.02, P=0.006). Complete resection was achieved in all patients. The characteristics of patients in both groups are presented in *Table 2*.

Table 2 Characteristics of patients

Characteristics	Group A	Group B	P
Age ($\bar{x}$ ± s years)	55.5±16.5	43.6±13.5	0.063
Gender (male/female)	4/4	10/8	0.793
MG (+/−)	4/4	10/8	0.793
Preoperative therapy	0	3; VATS biopsy: 1; neoadjuvant: 3	0.220
Tumor size ($\bar{x}$ ± s cm)	5.2±1.4	6.7±2.4	0.125
POS ($\bar{x}$ ± s days)	11.0±4.4	13.3±5.7	0.330

MG, myasthenia gravis; VATS, video-assisted thoracoscopy; POS, postoperative stay.

Table 3 Potential factors affecting successful VATS resection for Masaoka stage III thymic tumor

Factors	Group A	Group B	P
Tumor size (>6/≤6 cm)	1/7	10/8	0.040
WHO subtype (A-AB/B_1-C)	2/6	0/18	0.027
Invaded organ (invaded/total)			
Pericardium	5/8	16/18	0.115
Lung	4/8	14/18	0.418
Phrenic nerve	0/8	7/18	0.039
Innominate vein	3/8	8/18	0.741
Superior vena cava	0/8	7/18	0.039

VATS, video-assisted thoracoscopy.

The potential factors affecting successful VATS resection for Masaoka stage III thymic tumor, including different invaded neighboring organs, was compared retrospectively. Pearson's χ^2 test demonstrated that the tumor size of bigger than 6 cm, invasion of phrenic nerve and involvement of superior vena cava would be the significant factors that hindered a successful VATS resection (*Table 3*).

No procedure-related mortality occurred. All patients completed follow-up, with a mean of 8 months (range: 2–18 months) for group A and 15 months (range: 3–36 months) for group B (P>0.05). All the patients underwent postoperative adjuvant chemotherapy and routine follow-ups. During the follow-up with brain MRI, CT scan of chest and abdomen, none of the patients developed recurrences; however, two patients were rehospitalized due to the onset of MG crisis. After treatment with plasma exchange and adjusting the drug treatment, including pyridostigmine bromide, prednisone, and tacrolimus, the symptoms were alleviated and stabilized, and the subsequent oral medication maintained to stable the symptoms. No tumor recurrence or metastasis was seen in all patients.

Discussion

Masaoka stage III thymic tumors are a very heterogeneous disease. Treatments for thymic tumors of this stage are diverse and can be combined with varieties of treatment options, namely, multi-disciplinary treatment modes, such as surgery + adjuvant chemotherapy, surgery + adjuvant radiotherapy, surgery + adjuvant chemoradiotherapy, neoadjuvant chemotherapy + surgery, neoadjuvant chemotherapy + surgery + adjuvant chemotherapy, neoadjuvant chemotherapy + surgery + adjuvant radiotherapy, surgery alone, chemotherapy alone, etc. Studies have shown that this comprehensive treatment model could bring more benefits to patients, such as improving overall survival or disease-free survival (8,13). However, it can be found that surgery plays an important role in the treatment of stage III thymic tumors. Studies have shown that complete resection is the most important prognostic factor for stage III thymic tumors (9,14). Therefore, resectability of all stage III

thymic tumors should be evaluated preoperatively.

Surgical resection of stage III thymic tumors is more complicated and difficult than tumors in stage I–II. Tumors in stage III always invades the surrounding organs, including the lungs, pericardium and great blood vessels that enter and exit the heart. At the same time, the tumors tend to show invasive growth with aggressive infiltration into the invaded organs, which increases the difficulty of complete resection. Therefore, preoperative evaluation is very important, especially the relationship between tumors and neighboring organs, to determine which organs have been infiltrated, and the extent of involvements. In our center, patients with thymic tumors who complicate with MG of Osserman III or higher required a contrast-enhanced chest CT within one month before surgery. For patients receiving neoadjuvant therapy, the enhanced CT after the last neoadjuvant therapy was required; for patients with MG of Osserman III or higher, enhanced CT was abandoned, while chest MRI was required to assess the relationship between the tumor and peripheral organs (11).

If the stage III thymic tumor was evaluated as resectable, surgery was generally preferred. Generally, these types of tumors required a semi-sternotomy or a full-sternotomy approach. However, it had been reported that minimally invasive approaches could also successfully remove stage III thymic tumors (3,10,11). However, most of the stage III patients from these authors required an open conversion thoracotomy, resulting in a low rate of VATS surgery for stage III thymic tumors. The reason for the need for conversion was mainly due to the invasion of surrounding organs, which was difficult or impossible to handle under endoscopy. Studies showed that these affected peripheral organs mainly include the lungs, superior vena cava, aorta, pulmonary trunk, pericardium, chest wall, phrenic nerve, etc. (8). These invaded organs often required an en-bloc resection. Neoadjuvant radiotherapy and chemotherapy could lead to fibrosis of surrounding tissues and increase the difficulty of surgical resection. Therefore, patients undergoing neoadjuvant therapy had adopted sternotomy.

The surgical approach to stage III thymic tumors has been controversial. There is no consensus on the best surgical approach. So far, most patients received a sternotomy resection, mainly due to the imbalance of minimally invasive thoracoscopic techniques and the lack of consensus on minimally invasive resection of stage III thymic tumors. From our experience, tumors larger than 6 cm, and invasion of the phrenic nerve or superior vena cava were the main factors limiting the resection of stage III thymic tumors under the VATS approach. The WHO classification had no obvious effect on the choice of surgical approach. In terms of tumor size, 3 cm was once considered to be the boundary of minimally invasive thymectomy (15), and then 5 cm (10,11). We believe that with the advancement of VATS techniques, indications for VATS resection were expanding, and larger thymic tumors could be removed under minimally invasive surgery. As to the invaded peripheral organs, thymic tumors invading the phrenic nerve, superior vena cava, or aorta often need special attention to preserve nerves during operation, or need to undergo vascular reconstruction, or even need to remove the lesions and reconstruct blood vessels under extracorporeal circulation, so these lesions were not suitable for minimally invasive surgery. Therefore, we proposed that a thymic tumor of less than 6 cm, though invading the innominate vein, pericardium, and part of the lung tissue, could be considered for the minimally invasive removal of the tumor and resection of invaded organs. There was no need to rebuild the innominate vein or repair the pericardium. However, thymic tumors invading the superior vena cava or aorta, pulmonary trunk, etc., were either too difficult to remove by complete resection or require vascular reconstruction, therefore should be classified as a contraindication for minimally invasive surgery.

This study has its limitations. First, the number of cases is small, and no cases of aortic or pulmonary trunk invasion were enrolled because these patients were considered as not suitable for surgical resection in our institution. Second, the short-term follow-up time doubted the effectiveness of the VATS resection and the long-term effects under the minimally invasive approach need to be further explored.

Conclusions

In summary, we compared the treatment of stage III thymic tumors with different surgical approaches. It is proved that the minimally invasive approach can be used as a treatment for selected Masaoka stage III thymic tumors that invade the innominate vein, pericardium, and lung with limited extents. However, those who invade the superior vena cava and phrenic nerve are not suitable for minimally invasive approach. Also, those with tumors of greater than 6 cm should not be considered for the minimally invasive approach or should be carefully evaluated preoperatively for VATS. However, the study lacks large-sample and long-term follow-up. Multi-Center research is needed to prove the results.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board of our hospital (No. 2014079). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived due to the retrospective nature of the study.

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References

1. Bhora FY, Chen DJ, Detterbeck FC, et al. The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A thymic epithelial tumors staging project: A proposed lymph node map for thymic epithelial tumors in the forthcoming 8th edition of the TNM classification of malignant tumors. J Thorac Oncol 2014;9:S88-96.

2. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: Modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int 1994;44:359-67.

3. Toker A. Standardized definitions and policies of minimally invasive thymoma resection. Ann Cardiothorac Surg 2015;4:535-39.

4. Toker A, Erus S, Ziyade S, et al. It is feasible to operate on pathological masaoka stage I and II thymoma patients with video-assisted thoracoscopy: Analysis of factors for a successful resection. Surg Endosc 2013;27:1555-60.

5. Modh A, Rimner A, Allen PK, et al. Treatment modalities and outcomes in patients with advanced invasive thymoma or thymic carcinoma: A retrospective multicenter study. Am J Clin Oncol 2016;39:120-25.

6. Owen D, Chu B, Lehman AM, et al. Expression patterns, prognostic value, and intratumoral heterogeneity of PD-L1 and PD-1 in thymoma and thymic carcinoma. J Thorac Oncol 2018;13:1204-12.

7. Serpico D, Trama A, Haspinger E, et al. Available evidence and new biological perspectives on medical treatment of advanced thymic epithelial tumors. Ann Oncol 2015;26:838-47.

8. Shintani Y, Inoue M, Kawamura T, et al. Multimodality treatment for advanced thymic carcinoma: Outcomes of induction therapy followed by surgical resection in 16 cases at a single institution. Gen Thorac Cardiovasc Surg 2015;63:159-63.

9. Hamanaka K, Koyama T, Matsuoka S, et al. Analysis of surgical treatment of masaoka stage III-IV thymic epithelial tumors. Gen Thorac Cardiovasc Surg 2018;66:731-5.

10. Odaka M, Tsukamoto Y, Shibasaki T, et al. Thoracoscopic thymectomy is a feasible and less invasive alternative for the surgical treatment of large thymomas. Interact Cardiovasc Thorac Surg 2017;25:103-8.

11. Marulli G, Maessen J, Melfi F, et al. Multi-institutional european experience of robotic thymectomy for thymoma. Ann Cardiothorac Surg 2016;5:18-25.

12. Jayam Trouth A, Dabi A, Solieman N, et al. Myasthenia Gravis: A Review. Autoimmune Dis 2012;2012:874680.

13. Ried M, Marx A, Götz A, et al. State of the art: Diagnostic tools and innovative therapies for treatment of advanced thymoma and thymic carcinoma. Eur J Cardiothorac Surg 2016;49:1545-52.

14. Okuma Y, Horio H, Hosomi Y, et al. The potency of curative-intent treatment for advanced thymic carcinoma. Lung Cancer 2014;84:175-81.

15. Marulli G, Rea F, Melfi F, et al. Robot-aided thoracoscopic thymectomy for early-stage thymoma: A multicenter European study. J Thorac Cardiovasc Surg 2012;144:1125-30.