scientific reports

Check for updates

OPEN

Intercostal approach VATS is feasible for large-sized anterior mediastinal tumors

Lei Ke[1,4], Jiacong Liu[1,4], Yongfeng Shuai[2,4], Linhai Zhu[1,4]✉, Cheng He[1], Xuhua Huang[1], Wang Lv[1], Luming Wang[1]✉ & Jian Hu[1,3]✉

There is no consensus about whether relatively large mediastinal tumors (≥ 5.0 cm) are suitable for video-assisted thoracoscopic surgery (VATS). Therefore, this study aimed to compare the efficacy and safety of intercostal approach VATS for large-sized anterior mediastinal tumors (5.0–10.0 cm) with no invasion to the surrounding tissues and organs. A total of 129 patients with anterior mediastinal tumors who received surgery in our hospital between January 2018 and July 2022 were consecutively enrolled. Patients were divided into 2 groups based on mediastinal tumor diameter: Group A (tumor size between 1.0 and 4.9 cm) and Group B (tumor size between 5.0 and 10.0 cm). The primary endpoints were operation time, blood loss, and postoperative pain, and the secondary endpoints were the volume of drainage, drainage duration, postoperative hospital stay, and postoperative complications. Significant differences were found in the volume of drainage between the two groups (Group A: 218.4 ± 140.6, Group B: 398.9 ± 369.3, $P < 0.001$). However, no differences were found in operation time, blood loss, drainage duration, postoperative hospital stay and duration of postoperative oral analgesics ($P > 0.05$). In addition, there existed no significant differences in the postoperative complications. Intercostal approach VATS is regarded as a feasible and safe surgical method for large-sized anterior mediastinal tumors (5.0–10.0 cm) with no invasion to the surrounding tissues and organs.

Keywords Anterior mediastinal tumor, Intercostal approach video-assisted thoracoscopic surgery, Tumor size

Mediastinal masses are relatively rare during thoracic surgery diseases[1]. Most of mediastinal masses occur in the anterior compartment, including various different entities and showing a spectrum of clinical characteristics and symptoms[1]. Traditional thoracotomy is the main surgical method for treating anterior mediastinal tumors in the past. But in recent years, video-assisted thoracoscopic surgery (VATS) has been widely used as a minimally invasive alternative to traditional thoracotomy in clinical practice due to the advantages of minimal trauma, less intraoperative bleeding, mild pain, reliable therapeutic effect, rapid postoperative recovery, and consistent incision beauty requirements[2–7]. Minimally invasive approaches for excision of mediastinal mass include VATS via a lateral intercostal approach and a subxiphoid VATS approach, and the lateral intercostal approach VATS is the most common one[8].

VATS has become popular for mediastinal tumors. However, it is still difficult for a patient with a mediastinal tumor larger than 5.0 cm as a result of the narrow space in the anterior mediastinum[9]. There is still controversy over whether VATS is suitable for patients with a relatively large mediastinal tumor (≥ 5.0 cm). Kimura et al. think open thymectomy is proper in patients with thymomas > 5.0 cm because of the increase of technical difficulty and the risk of capsule injury[10]. While Odaka et al. demonstrated the feasibility of thoracoscopic thymectomy for thymomas ≥ 5.0 cm and Weng et al. revealed that VATS is a safe and effective approach for large thymomas (≥ 5.0 cm) with comparable surgical and oncological outcomes[11,12]. Until now, there are few studies focusing on mediastinal tumors ≥ 5.0 cm as an indication for VATS. Therefore, we conducted this study to evaluate the feasibility and safety of intercostal approach VATS for large anterior mediastinal tumors (5.0–10.0 cm) with no invasion to the surrounding tissues and organs.

[1]Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, China. [2]Department of Plastic Surgery, The Second Hospital of Yinzhou, Ningbo 315000, China. [3]Key Laboratory of Clinical Evaluation Technology for Medical Device of Zhejiang Province, Hangzhou 310003, China. [4]These authors contributed equally: Lei Ke, Jiacong Liu, Yongfeng Shuai and Linhai Zhu. ✉email: Linhai_zhu@zju.edu.cn; 1507144@zju.edu.cn; dr_hujian@zju.edu.cn

Patients and methods

Patient selection

This retrospective study initially included 129 patients with mediastinal masses who underwent intercostal approach video-assisted thoracoscopic surgery in the department of thoracic, the First Affiliated Hospital, Zhejiang University School of Medicine from January 2018 to July 2022. Patients were divided into 2 groups based on mediastinal tumor diameter: Group A (tumor size between 1.0 and 4.9 cm) and Group B (tumor size between 5.0 and 10.0 cm). This study was approved by the Medical Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (2022 IIT No. 1166). Every individual participant had signed an informed consent form, so we could utilize their information for this study. The flowchart of this study is shown in Fig. 1.

The main inclusion criteria for patients were: (I) age over 18 and under 80 years; (II) mediastinal tumor without myasthenia gravis; (III) mediastinal tumor with no invasion of surrounding tissues and organs; (IV) tumor diameter > 0 cm and ≤ 10.0 cm; (V) sufficient cardiopulmonary function to withstand surgery. The exclusion criteria were as followed (I) absence of preoperative imaging examination; (II) inability to tolerate single-lung ventilation; (III) suffered another malignancy; and (IV) distant metastases.

Each patient enrolled in our study was followed up through their regular examinations in the hospital. The follow-up was not completed until three months after surgery or after the study was terminated. The primary endpoints were operation time, blood loss, and postoperative pain, and the secondary endpoints were the volume of drainage, drainage duration, postoperative hospital stay, and postoperative complications.

Surgical procedures

Under general anesthesia, the patient was ventilated with double-cavity tracheal intubation during surgery and placed in a semi-lateral position at 30–45 degrees, cephalic and caudal down. This approach was performed through two ports: one observation port and one operation port. During surgery, those ports were determined according to the tumor's location. An incision between the 6th and 8th ribs of the midaxillary line was selected as the observation port, with a length of about 1.5 cm (Fig. 2A). A 3–4 cm incision between the 4th and 5th ribs of the anterior axillary line was selected as the operation port (Fig. 2B). After the incision of the bilateral mediastinal pleura, the exposed part was anterior to the internal thoracic vein, posterior to the front of the phrenic nerve, and the anterior mediastinal tissue was fully dissociated. We dissected the upper pole of the thymus and completely exposed the innominate veins. All patients underwent complete thymotomy and achieved R0 resection. The total thymic, tumor and adipose tissue from the diaphragmatic Angle of the heart were removed.

Statistical analysis

Continuous variables were expressed as the mean and standard deviation, and the t-test or Wilcoxon test was used to compare differences between groups. Categorical variables were expressed as frequencies and percentages, and the Pearson's chi-squared test or Fisher's exact test was used to compare differences between groups. All analyses were performed with SPSS software version 26.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Ethical approval

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2022 IIT No. 1166), in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines. Written informed consent was obtained from patients so that we could utilize their medical record information.

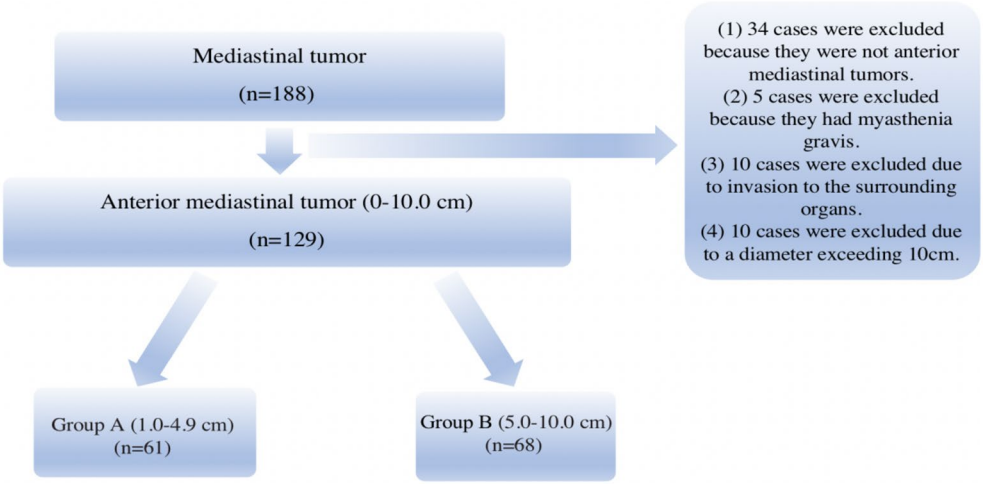

Figure 1. The flowchart of this study.

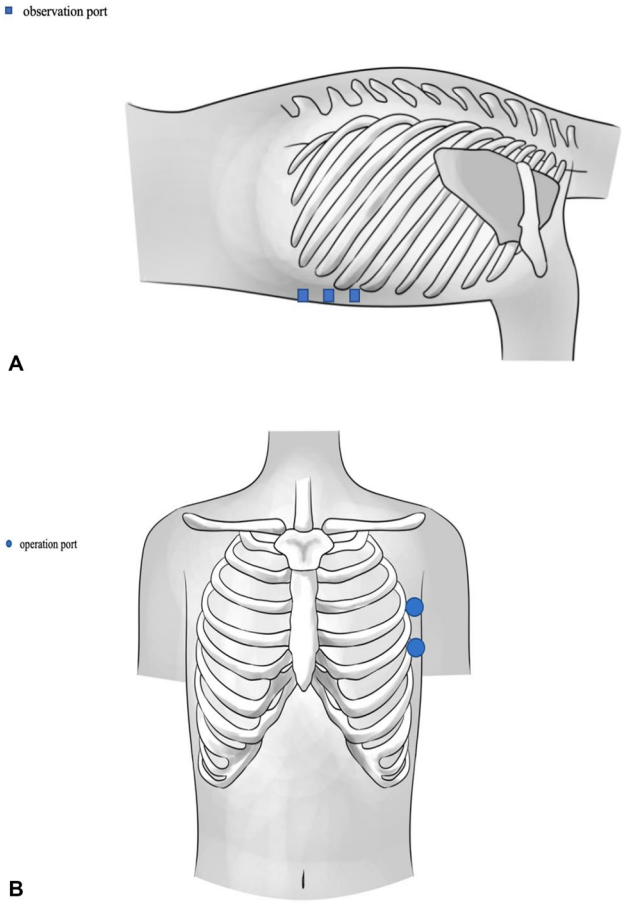

Figure 2. Operative conditions in the intercostal approach VATS. (**A**) Observation port, a selected incision between the 6th and 8th ribs of the midaxillary lineline according to the location of the mass, (**B**) operation port, a selected incision between the 4th and 5th ribs of the anterior axillary line according to the location of the mass.

Results

Patient characteristics

Eventually, a total of 129 patients were enrolled in our study between January 2018 and July 2022. These patients all received intercostal approach VATS. Based on tumor diameter, patients were divided into two groups: Group A (tumor size between 1.0 and 4.9 cm) and Group B (tumor size between 5.0 and 10.0 cm). The detailed characteristics of the two groups are shown in Table 1. There were no significant differences in age, BMI, sex, smoking status, drinking status, hypertension, diabetes mellitus, ASA status class and pathology ($P > 0.05$). There were differences in tumor diameter among the two groups (Group A: 2.88 ± 0.90, Group B: 6.96 ± 2.61, $P < 0.001$).

Intraoperative and postoperative outcomes

The operation time of Group A is shorter than that of Group B, but there was no statistically significant difference between them (Group A: 71.70 ± 29.53, Group B: 86.31 ± 31.01, $P > 0.05$) (Table 2). The blood loss (Group A: 20.00 ± 13.5,4 Group B: 21.76 ± 16.75, $P > 0.05$) and drainage duration (Group A: 2.28 ± 1.05, Group B: 2.81 ± 1.30, $P > 0.05$) of the two groups are similar. The volume of drainage in Group A was significantly smaller than Group B, and the difference is statistically significant (Group A: 218.44 ± 140.60, Group B: 398.99 ± 369.31, $P < 0.001$, Fig. 3). Between the two groups, there were no significant differences in postoperative hospital stay (Group A: 4.11 ± 1.78, Group B: 4.41 ± 1.82, $P > 0.05$) and duration of postoperative oral analgesics (Group A: 3.34 ± 1.05, Group B: 3.53 ± 1.13, $P > 0.05$). Both Group A and Group B underwent R0 resection, and none of these patients were converted to open chest surgery.

Postoperative complications

The incidence of complications in Group B and in Group A was comparative (Group A: 4.92%, Group B: 8.82%). There was no statistically significant difference in pleural effusion, pneumothorax, chylothorax, subcutaneous emphysema and arrhythmias (Table 3). No life-threatening complications were observed in either group.

Variables	Group A (n = 61)	Group B (n = 68)	*P* value
Age (years, mean ± SD)	52.31 ± 13.76	51.85 ± 16.08	0.132
BMI (kg/m^2, mean ± SD)	24.39 ± 3.22	23.33 ± 3.13	0.772
Sex, n (%)			0.735
Male	35 (57.38)	37 (54.44)	
Female	26 (42.62)	31 (45.56)	
Smoking status, n (%)			0.138
Never	55 (90.16)	55 (80.88)	
Ever	6 (9.84)	13 (19.12)	
Drinking status, n (%)			0.442
Never	54 (88.52)	57 (83.82)	
Ever	7 (11.48)	11 (16.18)	
Comorbidity, n (%)			
Hypertension	10 (16.39)	17 (25.00)	0.230
Diabetes mellitus	4 (6.55)	2 (2.94)	0.421
ASA status class, n (%)			0.157
I	44 (72.13)	41 (60.29)	
II	17 (27.87)	27 (39.71)	
Tumor diameter (cm), mean ± SD (range)	2.88 ± 0.90 (1.0–5.0)	6.96 ± 2.61 (5.0–10.0)	**< 0.001**
Pathology			0.728
Thymic carcinoma, n (%)	3 (4.92)	5 (7.35)	
Type A thymic tumor, n (%)	4 (6.56)	10 (14.71)	
Type B1 thymic tumor, n (%)	3 (4.92)	4 (5.88)	
Type B2 thymic tumor, n (%)	3 (4.92)	1 (1.47)	
Type B3 thymic tumor, n (%)	3 (4.92)	1 (1.47)	
Type AB thymic tumor, n (%)	14 (22.95)	12 (17.65)	
Thymic hyperplasia, n (%)	6 (9.84)	5 (7.35)	
Thymic cyst, n (%)	18 (29.51)	22 (32.35)	
Teratoma, n (%)	7 (11.48)	8 (11.76)	

Table 1. Characteristics of the patients at baseline. *BMI* body mass index, *ASA* American Society of Anesthesiologists, *SD* standard deviation. Significant values are in bold.

Variables	Group A (n = 61)	Group B (n = 68)	*P* value
Operation time (min, mean ± SD)	71.70 ± 29.53	86.31 ± 31.01	0.513
Blood loss (ml, mean ± SD)	20.00 ± 13.54	21.76 ± 16.75	0.265
Drainage duration (days, mean ± SD)	2.28 ± 1.05	2.81 ± 1.30	0.254
Volume of drainage (ml, mean ± SD)	218.44 ± 140.60	398.99 ± 369.31	**< 0.001**
Postoperative hospital stay (days, mean ± SD)	4.11 ± 1.78	4.41 ± 1.82	0.470
Duration of postoperative oral analgesics (days, mean ± SD)	3.34 ± 1.05	3.53 ± 1.13	0.150
R0 resection, n (%)	61 (100.00)	68 (100.00)	NA
Conversion to open surgery, n (%)	0 (0.00)	0 (0.00)	NA

Table 2. Intraoperative and postoperative outcomes. *SD* standard deviation. Significant values are in bold.

Discussion

The main treatment method for mediastinal tumors is surgery, including traditional thoracotomy and VATS. Some scholars have compared the difference between minimally invasive surgery and open surgery in the treatment of early thymoma[13–16], they didn't focus on the size of the mass. A few researchers suggest VATS may have the same effect or be better than traditional open thoracotomy in treating small mediastinal masses[2,17]. Whitson et al. felt that VATS is ideally suitable for patients with mediastinal masses less than 3 cm[17], which can streamline the procedure. Jurado et al. thought VATS was safe and could achieve a comparable resection and postoperative complication profile[2]. However, in their research, we can hardly find large-sized mediastinal masses patients in the minimally invasive thymectomy cohort[2]. Studies report that there has been no consensus on the exact size of mediastinal tumor for which thoracoscopic surgery is suitable to be performed[9,10]. As we know, the space in the chest is fixed, the working space decreases as the size of the lesion increases. The special location and the complicating adjacent relationship of mediastinal tumors brought some difficulty to chief surgeons.

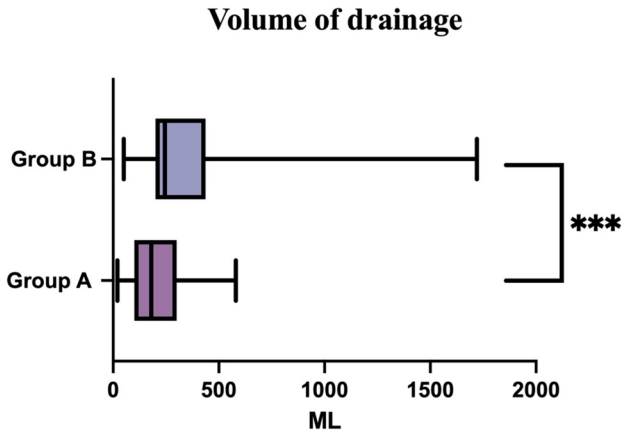

Figure 3. Violin plot of volume of drainage. ***, $P < 0.001$. Group A (1.0 ~ 5.0 cm), Group B (5.0 ~ 10.0 cm).

Variables	Group A (n = 61)	Group B (n = 68)	*P* value
Overall complication, n (%)	3 (4.92)	6 (8.82)	0.601
Pleural effusion, n (%)	1 (1.64)	2 (2.94)	1.000
Pneumothorax, n (%)	1 (1.64)	1 (1.47)	1,000
Pulmonary infection, n (%)	0 (0.00)	0 (0.00)	NA
Chylothorax, n (%)	0 (0.00)	1 (1.47)	1.000
Subcutaneous emphysema, n (%)	1 (1.64)	3 (4.41)	0.621
Arrhythmias, n (%)	0 (0.00)	1 (1.47)	1.000
Phrenic nerve palsy, n (%)	0 (0.00)	0 (0.00)	NA
Hoarseness, n (%)	0 (0.00)	0 (0.00)	NA
Postoperative bleeding, n (%)	0 (0.00)	0 (0.00)	NA
Re-surgery, n (%)	0 (0.00)	0 (0.00)	NA

Table 3. Postoperative complications.

Many researchers thought traditional thoracotomy was still suited for large-sized masses. Kimura et al. chose traditional thoracotomy in patients with mediastinal tumor > 5 cm in principle for VATS may increase the technical difficulty and the risk of capsule injury, the authors thought that VATS for large tumor may cause pleural spread due to invasion of the capsule during the procedure[10]. Ye et al. indicated that the size of mediastinal tumor may affect tthe success of VATS, the minimally invasive approaches[6]. Traditional thoracotomy can offer good exposure of the surgical field to surgeons, facilitate resection of the affected structure in advanced cases and satisfy the oncology concerns[12,18]. However, it can also cause large wounds, large intraoperative blood loss and high postoperative complications, affect postoperative recovery[7,19,20]. So there are many surgeons trying to remove large tumors with minimally invasive surgery. Gossot et al. reported that VATS was appropriate for large intrathoracic masses with some experience and suitable instrumentation[21]. Takeo et al. thought VATS is indicated for patients with tumors larger than 5 cm[9]. Odaka et al. demonstrated the decreased the feasibility and safety of VATS for mediastinal tumor ≥ 5 cm, and they also pointed out that VATS and thoracotomy have comparable oncological outcomes[11]. Agatsuma et al. reported that a mediastinal tumor diameter of 5 cm or larger was not a risk factor for a positive surgical margin in in thoracoscopic surgery[7]. Marshall et al. outline the instrumentation and techniques adopted for mediastinal operation, and then they suggested that VATS was feasible for complex mediastinal masses[22].Compared with traditional thoracotomy, VATS can achieve less blood loss, shorter hospital stay and similar oncological results[6,7]. The lateral intercostal approach VATS is the most common approach in thoracoscopic surgery[8,23], which is characterized by the small size and lateral location.

In order to determine whether lateral intercostal approach VATS is feasible for large mediastinal masses, we conducted this study. This study compared the results of different mediastinal tumor sizes after thoracoscopic surgery to determine whether tumors of different sizes can be operated by thoracoscopic surgery. In our study, patients with tumors less than 5 cm in diameter had a lower surgical time than patients with tumors larger than 5 cm in diameter. The postoperative drainage volume in group A was significantly lower than that in group B. The remaining intraoperative and postoperative outcomes were not significantly different between patients with tumor diameter greater than 5 cm and those with tumor diameter less than 5 cm. R0 resection was performed by intercostal approach VATS in all mediastinal tumors less than 10 cm in diameter, and no cases were converted to thoracotomy, which ensured its safety and the integrity of tumor resection. It was found in our study that in

intercostal approach VATS for mediastinal masses less than 10 cm, the size of the mass had no significant impact on the surgical outcome. This is similar to the results of some previous studies[7,9,11,21]. The longer drainage and operation time may be caused by the larger operation scope. We believe that the larger the tumor, the longer the surgical time, and the greater the drainage volume.

There are several limitations in this study. Firstly, it was conducted in a single center, the sample size of this study might not be sufficient. Secondly, heterogeneity of patients may affect results, we sought to minimize selection bias by continuously enrolling patients who met inclusion criteria. Additionally, we didn't compare the difference of the two group in other pathways of thoracoscopic surgery and the influence of location is ignored. Finally, postoperative follow-up period was too short to evaluate oncology outcomes.

In conclusion, intercostal approach VATS is regarded as a feasible and safe surgical method for anterior mediastinal tumors with size ≤ 10.0 cm. And large-sized anterior mediastinal tumors (5.0–10.0 cm) with no invasion to the surrounding tissues and organs should be considered as an indication for intercostal approach VATS. Further study is still needed to confirm our conclusion and evaluate long-term and oncologic outcomes.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Received: 26 May 2024; Accepted: 16 July 2024
Published online: 26 July 2024

References

1. Carter, B. W., Marom, E. M. & Detterbeck, F. C. Approaching the patient with an anterior mediastinal mass: A guide for clinicians. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **9**(9 Suppl 2), S102–S109 (2014).
2. Jurado, J. *et al.* Minimally invasive thymectomy and open thymectomy: Outcome analysis of 263 patients. *Ann. Thorac. Surg.* **94**(3), 974–982 (2012).
3. Ng, C. S. H., Wan, I. Y. P. & Yim, A. P. C. Video-assisted thoracic surgery thymectomy: The better approach. *Ann. Thorac. Surg.* **89**(6), S2135–S2141 (2010).
4. Batirel, H. F. Minimally invasive techniques in thymic surgery: A worldwide perspective. *J. Vis. Surg.* **4**, 7 (2018).
5. Numanami, H. *et al.* Thoracoscopic thymectomy using a subxiphoid approach for anterior mediastinal tumors. *Ann. Thorac. Cardiovasc. Surg. Off. J. Assoc. Thorac. Cardiovasc. Surg. Asia* **24**(2), 65–72 (2018).
6. Ye, B. *et al.* Surgical techniques for early-stage thymoma: Video-assisted thoracoscopic thymectomy versus transsternal thymectomy. *J. Thorac. Cardiovasc. Surg.* **147**(5), 1599–1603 (2014).
7. Agatsuma, H. *et al.* Video-assisted thoracic surgery thymectomy versus sternotomy thymectomy in patients with thymoma. *Ann. Thorac. Surg.* **104**(3), 1047–1053 (2017).
8. Zhang, L. *et al.* Subxiphoid versus lateral intercostal approaches thoracoscopic thymectomy for non-myasthenic early-stage thymoma: A propensity score -matched analysis. *Int. J. Surg. (London, England)* **67**, 13–17 (2019).
9. Takeo, S. *et al.* Outcome of an original video-assisted thoracoscopic extended thymectomy for thymoma. *Ann. Thorac. Surg.* **92**(6), 2000–2005 (2011).
10. Kimura, T. *et al.* The oncological feasibility and limitations of video-assisted thoracoscopic thymectomy for early-stage thymomas. *Eur. J. Cardio Thorac. Surg. Off. J. Eur. Assoc. Cardio Thorac. Surg.* **44**(3), e214–e218 (2013).
11. Odaka, M. *et al.* Thoracoscopic thymectomy is a feasible and less invasive alternative for the surgical treatment of large thymomas. *Interact. Cardiovasc. Thorac. Surg.* **25**(1), 103–108 (2017).
12. Weng, W. *et al.* Video-assisted thoracoscopic thymectomy is feasible for large thymomas: A propensity-matched comparison. *Interact. Cardiovasc. Thorac. Surg.* **30**(4), 565–572 (2020).
13. Tseng, Y.-C. *et al.* Is thymectomy necessary in nonmyasthenic patients with early thymoma?. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* **8**(7), 952–958 (2013).
14. Toker, A. *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.* **27**(5), 1555–1560 (2013).
15. Gu, Z.-T. *et al.* Comparison of video-assisted thoracoscopic surgery and median sternotomy approaches for thymic tumor resections at a single institution. *Surg. Laparosc. Endosc. Percutaneous Tech.* **25**(1), 47–51 (2015).
16. Zielinski, M. *et al.* Resection of thymomas with use of the new minimally-invasive technique of extended thymectomy performed through the subxiphoid-right video-thoracoscopic approach with double elevation of the sternum. *Eur. J. Cardio Thorac. Surg. Off. J. Eur. Assoc. Cardio Thorac. Surg.* **44**(2), e113–e119 (2013).
17. Whitson, B. A. *et al.* Thoracoscopic thymectomy: Technical pearls to a 21st century approach. *J. Thorac. Dis.* **5**(2), 129–134 (2013).
18. Detterbeck, F. C. Clinical value of the WHO classification system of thymoma. *Ann. Thorac. Surg.* **81**(6), 2328–2334 (2006).
19. Pennathur, A. *et al.* Comparison of surgical techniques for early-stage thymoma: Feasibility of minimally invasive thymectomy and comparison with open resection. *J. Thorac. Cardiovasc. Surg.* **141**(3), 694–701 (2011).
20. Hsu, C. P. Subxiphoid approach for thoracoscopic thymectomy. *Surg. Endosc.* **16**(7), 1105 (2002).
21. Gossot, D. *et al.* Thoracoscopic resection of bulky intrathoracic benign lesions. *Eur. J. Cardio Thorac. Surg. Off. J. Eur. Assoc. Cardio Thorac. Surg.* **32**(6), 848–851 (2007).
22. Marshall, M. B. *et al.* Video-assisted thoracoscopic surgery for complex mediastinal mass resections. *Ann. Cardiothorac. Surg.* **4**(6), 509–518 (2015).
23. Suda, T. *et al.* Video-assisted thoracoscopic thymectomy versus subxiphoid single-port thymectomy: Initial results. *Eur. J. Cardio Thorac. Surg. Off. J. Eur. Assoc. Cardio Thorac. Surg.* **49**(Suppl 1), i54–i58 (2016).

Author contributions

L.K. and J.L. made the concept and design. L.Z., C.H., and X.H. obtained and analyzed the clinical data. L.K., J.L., and Y.S. drafted the manuscript. W.L., L.W., and J.H. critically revised the manuscript for important intellectual content. All authors contributed to the article and reviewed the manuscript.

Funding

This research was supported by the Key R&D Program of Zhejiang (Grant Numbers 2022c04030), the Zhejiang Province Major Science and Technology Special Program Project (Grant Numbers 2020C03058), the Zhejiang Province Lung Tumor Diagnosis and Treatment Technology Research Supported by the Center (Grant Numbers

JBZX-202007), the Zhejiang Provincial Traditional Chinese Medicine (Integrated Traditional Chinese and Western Medicine) Key Discipline (Grant Numbers 2017-XK-A33), the Zhejiang Provincial Natural Science Foundation (Grant Numbers LY19H160039).

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to L.Z., L.W. or J.H.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.