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Original Research

Subxiphoid versus lateral intercostal approaches thoracoscopic thymectomy for non-myasthenic early-stage thymoma: A propensity score -matched analysis

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ABSTRACT

Background: Thymectomy is increasingly being performed via minimally invasive approaches. The present study aimed to assess the safety and feasibility of the subxiphoid approach to video-assisted thoracic surgery (VATS) compared with the lateral intercostal approach VATS.

Methods: Patients who underwent VATS thymectomy via subxiphoid and lateral intercostal approaches in our hospital between 2015 and 2018 were retrospectively analyzed. A series of perioperative outcomes, including clinical and surgical results, postoperative pain scores and cosmetic results, was compared in a propensity score matching analysis.

Results: A total of 98 patients diagnosed with non-myasthenic early-stage thymoma underwent complete thymectomy by VATS. Propensity score analysis revealed that 28 patients treated with the subxiphoid approach and 28 patients treated with the lateral intercostal approach had the same baseline characteristics. Compared with those in the lateral intercostal approach group, patients in the subxiphoidapproach group yielded lower pain scores and shorter postoperative hospital stays. Other advantages of the subxiphoid approach included decreased inflammatory cytokine response and superior cosmesis. There were no significant differences in postoperative complications between the two groups. All these patients recovered well when discharged. There were no perioperative deaths.

Conclusions: Our data suggest that subxiphoid and subcostal arch thoracoscopic radical thymectomy is a less invasive procedure for the treatment of non-myasthenic early-stage thymoma and provides a satisfactory cosmetic effect. Owing to the limitation ofour retrospective study, further prospective studies are needed to evaluate long-term and oncologic outcomes of subxiphoid approach VATS thymectomy.

1. Introduction

Video-assisted thoracic surgery (VATS) has been widely accepted as a minimally invasive alternative to conventional median sternotomy for thymectomy for the treatment of myasthenia gravis and early-stage thymoma [1–4]. Thymectomy involves the removal of all the soft tissues in the pre-vascular plane of the anterior mediastinum between the two phrenic nerves. In recent years, several less invasive approaches for performing thymectomy have been applied. These approaches include VATS thymectomy via a lateral intercostal approach, transcervical VATS thymectomy via a cervical incision and a subxiphoid VATS approach [2,5–9]. Among these, the lateral intercostal approach, including right side, left side and bilateral intercostal approaches, is the most frequently performed. Nevertheless, this approach does have some disadvantages. When approaching from one side of the chest, it is difficult to identify the contralateral phrenic nerve, and the risk of intercostal nerve injury resulting in postoperative chronic incision pain and numbness exists. Advantages of the subxiphoid approach over the lateral intercostal approach include a sufficient operative view of the cervical and bilateral pleural cavities, less pain and a better cosmetic effect. The subxiphoid VATS thymectomy approach can be divided into several techniques according to the incision design: the uniportal subxiphoid approach, the subxiphoid and subcostal arch approach, and a combination of the transthoracic and subxiphoid approaches. To increase maneuverability and reduce interference among devices, we have performed minimally invasive thymectomy using the subxiphoid and subcostal arch approach since October 2014.

The purpose of this study was to explore the initial findings of our

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experiences performing VATS thymectomy using the subxiphoid and lateral intercostal approach and to determine the safety and usefulness of the subxiphoid approach.

2. Methods

2.1. Patients and data collection

The current retrospective study was conducted from January 2015 to January 2018. All consecutive patients undergoing thymectomy for treatment of Masaoka stage I–II thymoma without myasthenia gravis were eligible. Our center has been performing thoracoscopic procedures for radical resection of thymoma since 2007. Due to the advantages of subxiphoid thymectomy, we began to adopt this technique for the treatment of early-stage thymoma in October 2014 using the same VATS selection criteria. All the surgeries were performed by two highlyexperienced surgeons (L.X and M.L.). Patients who had a previous thoracic surgery procedure, used opiates preoperatively, had a history of chronic pain syndrome or had a diagnosis of thymic carcinoma or other mediastinal malignancies were excluded. This study was approved by the Ethics Committee of the affiliated Cancer Hospital of Nanjing Medical University (no: JCH20140312). The work has been reported in line with the STROCSS criteria [10]. Individual patient consent was waived because of the retrospective nature of the study. From January 2015 to January 2018, a total of 178 patients underwent surgery for anterior mediastinal tumor at our hospital. Inorder to control the potential influence of subxiphoid VATS technique, the cases belong to surgeons' learning curves were excluded. According to the inclusion criteria, 98 patients were enrolled. All patients underwent the same preoperative evaluation, including standard cardiopulmonary function tests and neurological and radiological assessments (computed tomography (CT) or magnetic resonance). Contrast-enhanced CT scanning is routinely used to evaluate anterior mediastinal tumors in our department. Radiological studies showed a good correlation between the CT scan results and intraoperative findings. Particularly for Masaoka–Koga stage I–II disease, there was a high accuracy in determining whether the tumor would be resectable without the need for major vascular resection. Advanced-stage patients (Masaoka–Koga stages III and IV) and patients with tumors larger than 5 cm in diameter underwent a sternotomy thymectomy for oncological consideration.

Data including the demographics, surgical procedure, pathological diagnosis, perioperative complications, cosmetic evaluation and outcomes were collected and compared. Postoperative pain was assessed using a numerical rating score (NRS) ranging from 0 (no pain) to 10 (intolerable pain). A patient self-reported cosmetic satisfaction score was applied using a score from 0 to 100 to indicate a very dissatisfied status to a very satisfied status, respectively, when the patients were discharged.

2.2. Surgical technique

We performed thoracoscopic thymectomy strictly following the principles of minimally invasive resection that were published by the International Thymic Malignancy Interest Group [11].

2.2.1. VATS thymectomy using the subxiphoid and subcostal arch approach (S-VATS)

After intravenous induction, the patient was anesthetized and intubated with a single-lumen endotracheal tube. The patient was placed in the supine position on the operating table with the legs open. The surgeon stood between the patient's legs, and the assistant stood on the right side. A 3-cm observation port was made 1.5 cm below the lower edge of the xiphoid. The rectus abdominis muscle was separated vertically, and the retrosternal space was then bluntly separated with the surgeon's finger to extend the working space. Then, two 5-mm extra pleural thoracic ports under the bilateral costal arches were created

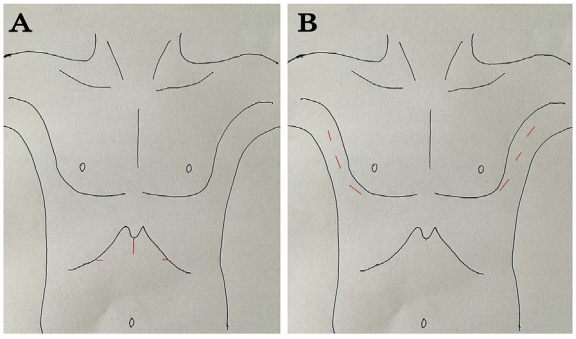

Fig. 1. Incisions resulting from the two VATS approaches. The camera port was extended to extract the resected specimens. A) The lateral intercostal approach; B) The subxiphoid approach (figure was modified from Yano et al.).

(Fig. 1A). A 10-mm, 30° oblique view rigid thoracoscope was inserted through the observation port. Carbon dioxide (CO_2) with 8 mmHg positive pressure was insufflated into the anterior mediastinum, helping to enlarge the retrosternal space. An ultrasonic scalpel and thoracoscopic grasping forceps were introduced into the bilateral operation ports. To ensure capsule integrity and en bloc dissection of the tumor, the surgeon took care to grasp the normal tissues but to not touch the tumor capsule. The primary surgical steps were as follows: First, the anterior border of the thymus was gradually dissociated along the retrosternal space to the thoracic outlet vertically and toward the bilateral diaphragm attachment point transversely. The adipose tissue at the bilateral cardiophrenic angle was also dissected. Second, the right pleural cavity was opened. Care was taken to fully visualize the innominate vein and superior vena cava junction prior to dissection of the thymic horn from the underlying innominate vein. The thymic veins were identified prior to draining into the innominate vein and meticulously ligated using an ultrasonic scalpel. Third, the left mediastinal pleura was opened along the left phrenic nerve. All the surrounding adipose tissue anterior to the left phrenic nerve was removed. Finally, the freed thymus and any attached mediastinal fat were placed into a specimen bag and removed via the subxiphoid observation port (the supplementary video provides the details). A chest tube was inserted into one subcostal arch port for drainage after the surgical field was evaluated. The subxiphoid and other subcostal arch incisions were sutured. An intraoperative view of thymectomy using the subxiphoid and subcostal arch approach is shown in Fig. 2.

Supplementary video related to this article can be found at https://

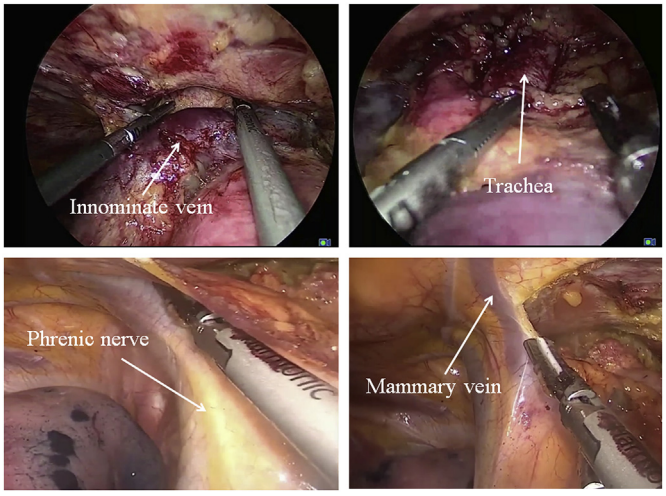

Fig. 2. Intraoperative photographs showing the main. Views of the left innominate vein (A), main trachea (B), phrenic nerve (C), and right mammary vein (D).

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2.2.2. VATS thymectomy using the lateral intercostal approach (L-VATS)

After intravenous induction, the patient was anesthetized and intubated with a double-lumen endotracheal tube. The patient was placed at 30–45° in a semi-supine position. The anterior mediastinal tumor was approached from the side of the right chest in most cases, but when the tumor was predominantly located on the left side, the approach was from the left chest. A 3-port approach was used, with one observation port and two main operation ports. An observation port of 0.5–1.0 cm was typically made in the 6th intercostal space at the anterior axillary line (Fig. 1B). This port was primarily used for placing the trocar lens of the thoracoscope into the thoracic cavity and was retained for the placement of the chest tube. Two main operation ports were placed in the 3rd intercostal space at the anterior axillary and in the 5th intercostal space at the midclavicular line. An ultrasonic scalpel was used for resection.

2.3. Postoperative management and evaluation

The majority of patients were extubated immediately postoperatively. For pain management, an opioid-sparing multimodal analgesic regimen was used. In short, 50 mg of indomethacin was administered in a suppository form to the patients immediately after surgery. All patients received patient-controlled analgesia with 0.2 mg/kg/h fentanyl and 0.1 mg/kg/h tramadol for 24–48 h. Postoperative pain scores at 6, 12, 24, 48 h and 1 month after the operation were assessed. Loxoprofen sodium hydrate was administered as a rescue analgesic when requested by patients with an NRS over 4. The chest drain was removed when drainage was less than 200 ml/day with no air leakage. Patients who were able to mobilize independently and appeared normal on chest radiography were discharged after chest tube removal.

2.4. Statistical analysis

Continuous variables were presented as either the mean ± standard deviation (SD) or as the median with interquartile range (IQR) as appropriate. The Student's t-test was applied to compare normally distributed variables, whereas the Mann–Whitney *U* test was used for non-normally distributed variables. Categorical data were analyzed using the Fisher's exact test. To minimize the impact of potential confounders and selection bias, propensity score analysis was used to compensate for the differences in baseline patient characteristics between the two groups of patients. A propensity score calculated by logistic regression, and covariates, including age, gender, body mass index (BMI), tumor size and Masaoka staging, were matched. A 1:1 nearest neighbor matching strategy was used to select the participants in the two groups of patients. All analyses were 2-tailed. *P*-values < 0.05 were considered statistically significant. All analyses were performed with the STATA 10 software package.

3. Results

The baseline clinicopathological characteristics, surgical procedures and outcomes of the patients with non-myasthenic early-stage thymoma were reviewed and are summarized in Table 1. From January 2015 to January 2018, a total of 98 patients were treated with the lateral intercostal approach and the subxiphoid approach to perform complete thymectomy.

The study included 28 patients who underwent subxiphoid approach thymectomy and 70 patients who underwent lateral intercostal approach thymectomy. Before matching, there were no significant differences between the two groups in terms of age, gender, disease stage or maximal tumor size. After 1:1 matching, all demographic characteristics were comparable between the two groups. There were no significant differences in the mean operative time (96 vs. 104 min, $P = 0.40$) or median intraoperative blood loss (50 (30–70) ml vs. 40 (30–70) ml, $P = 0.12$)). However, the white blood cell counts on postoperative day 1 (POD1) (9000 vs. 8600/μl, $P = 0.02$) and C-reactive protein (CRP) on POD1 (12.0 vs. 8.0 mg/dl, $P = 0.03$) were lower in the subxiphoid approach group than in the lateral approach group. The length of postoperative hospital stay was significantly shorter in the subxiphoid approach group than in the lateral approach group (4.6 and 3.6 days, respectively; $P = 0.01$). When comparing postoperative complications, no significant difference was observed ($P = 0.49$). However, in the lateral approach group, there were 2 patients with left phrenic nerve palsy postoperatively and 2 patients with transient paroxysmal atrial fibrillation (AF). One patient suffered from mild pneumonia. Postoperative complications were not experienced in the 28 patients treated using the subxiphoid approach. All these patients recovered well when discharged. There were no perioperative deaths.

There were statistically significant differences between the two groups with respect to postoperative pain. In addition to the primary endpoint of 6 and 12 h, comparing the subxiphoid approach with the lateral approach at 24 and 48 h, patients treated with the subxiphoid approach had less pain (NRS for 24 h, 3 (2–4) vs. 4 (3–5), $P = 0.03$; NRS for 48 h, 3 (2–3) vs. 4 (3–5), $P = 0.01$).

During the one-month follow-up visit, the subxiphoid approach group also reported relatively light pain (2 (1–2) vs. 2 (1–4), $P = 0.03$). In terms of cosmetic satisfaction, the subxiphoid approach patients reported higher cosmetic scores than the lateral approach group (95 ± 5.6 vs. 85 ± 7.6, $P < 0.01$).

4. Discussion

Complete resection is the standard of care for treatment of thymic masses. The completeness of thymoma resection is considered to be the most important determinant of survival [12]. Recently, VATS thymectomy for the treatment of early-stage thymoma has become much more popular. The incision wound resulting from lateral VATS thymectomy is relatively less noticeable than that from median sternotomy because of the small incision and the lateral location. Nevertheless, this approach has drawbacks, including difficulty in identifying the contralateral phrenic nerve, an insufficient operative field in the neck region and postoperative pain due to intercostal nerve injury. By contrast, intercostal nerve damage can be avoided in the subxiphoid approach, which is not conducted via the intercostal space. This approach represents further development of minimally invasive thoracic surgery and has been applied during metastasectomy, thymectomy and lobectomy [2,13,14]. In 2002, Hsu et al. performed subxiphoid video-assisted thoracoscopic extended thymectomy without intercostal or cervical incisions [15]. Because there are no intercostal nerves in the subxiphoid area, chronic chest wound pain can potentially be prevented by subxiphoid incisions; several studies have focused on this novel VATS approach [9,16–20]. In June 2007, our center converted from using median sternotomy to using lateral intercostal approach VATS thymectomy as the standard thymectomy approach for the treatment of early-stage thymoma. Subsequently, in October 2014, we converted from lateral VATS thymectomy to the subxiphoid approach via a skin incision made 1.5 cm below the xiphoid process using two 5 mm subcostal arch ports. Compared with subxiphoid single-port thymectomy, our procedure advantageously provides a more comfortable surgical manipulability because surgical instruments inserted into a single port interfere with each other, as ourselves as well as another group previously reported [17].

In the present study, the mean operation time, mean blood loss volume and mean chest tube drainage duration were similar between the groups. Although the comparison of postoperative complications between the groups was not significant, the complication rate was 7% (5/70) in the lateral approach VATS thymectomy group. This rate in the

Table 1
Patient characteristics, intra- and post-operative parameters.

Group variable	Before Propensity score matching			After Propensity score matching		
	Lateral approach	Subxiphoid approach	*P*-value	Lateral approach	Subxiphoid approach	*P*-value
Patients (n)	70	28		28	28	
Age (years)	54.8 ± 8.6	58.2 ± 10.0	0.10	56.2 ± 9.5	58.2 ± 10.0	0.45
Gender (M/F)	26/44	16/12	0.11	11/17	16/12	0.29
BMI (kg/m^2)	23.4 ± 2.6	22.7 ± 3.8	0.30	24.1 ± 4.3	22.7 ± 3.8	0.20
Maximal tumor diameter (cm)	3.6 ± 1.3	3.2 ± 1.6	0.20	3.4 ± 1.6	3.2 ± 1.6	0.64
Masaoka staging						
Stage I	28	14	0.38	10	14	0.42
Stage II	42	14		18	14	
Operation time (min)	116 ± 36	104 ± 29	0.12	96 ± 40	104 ± 29	0.40
Intraoperative blood loss median (IQR), (ml)	40 (30–80)	40 (30–70)	0.36	50 (30–70)	40 (30–70)	0.12
WBC on POD 1median (IQR) (/ul)	9000 (7600–12000)	8600 (8200–10800)	0.01	9000 (8100–11200)	8600 (8200–10800)	0.02
CRP on POD 1 (mg/dl)	12.5 ± 7.2	8.0 ± 6.3	0.01	12 ± 7.4	8.0 ± 6.3	0.03
Drainage duration (day)	2.1 ± 1.3	1.8 ± 1.6	0.34	2.4 ± 1.4	1.8 ± 1.6	0.14
Postoperative hospital stay (day)	4.3 ± 1.6	3.6 ± 1.2	0.04	4.6 ± 1.6	3.6 ± 1.2	0.01
Postoperative complications ±	5/65	0/28	0.32	2/26	0/28	0.49
Phrenic nerve paralysis	2	0		0	0	
Pneumonia	1	0		1	0	
Atrial fibrillation	2	0		1	0	
Mortality	0	0		0	0	

M, male; F, female; BMI, body mass index; CRP, C-reactive protein; WBC, white blood cell count; POD, postoperative day; median (25th, 75th percentile) as the IQR; Atrial fibrillation, AF.

lateral approach group was approximately that reported in a previous Japanese study (11/140) [21]. In this study, 2 patients developed left phrenic nerve palsy after surgery. The phrenic nerve was injured because of difficulty in identifying the contralateral nerve from the right lateral approach. No corresponding postoperative complications occurred in the subxiphoid approach group, and this result was consistent with those of other studies [9,17]. In addition, a lower invasiveness of the subxiphoid approach was demonstrated by the comparison data of postoperative white blood cell counts and levels of C-reactive protein. When the subjective evaluation of pain scores and cosmetic results were evaluated, pain sensations were more severe in the lateral intercostal approach group, especially during the 24 to 48 postoperative hours. Moreover, the patients who underwent subxiphoid approach VATS thymectomy reported less pain at the 1-month post-surgical follow-up. Intercostals nerve compression or injury can be avoided by the subxiphoid approach, possibly explaining why less postoperative pain occurred [13,22]. Lateral approach VATS patients always developed intercostal nerve paralysis or neuralgia lasting for months or sometimes for a lifetime as a post-thoracotomy pain syndrome [23]. The length of hospital stay was longer in the lateral approach group. We believe that this result was due to hospital discharge being delayed for some lateral approach group patients because of pain and the fact that patients in the subxiphoid approach group experienced less postoperative pain.

4.1. Limitations

Our study had several limitations. First, the retrospective nature of the study and the fact that it was performed at a single institution may have led to potential bias. Even after careful matching by propensity scoring, selection bias might not have been completely avoided. Second, the follow-ups of the subxiphoid approach and lateral approach groups were short. Considering the indolent nature of thymoma and the need for more than 10 years of follow-up, more data and longer observations for validation are required. Third, the evaluation of inflammation-related indicators was limited because of the retrospective nature of the study. Continuous detection of objective inflammation-related indicators is needed to confirm the reduced trauma of the subxiphoid approach. Fourth, our study had a small sample size after propensity score matching, possibly influencing the results in the subxiphoid approach group. Therefore, these results should be interpreted with caution. In the future, larger case series with longer periods of follow-up will be required to confirm the safety and oncological results of this subxiphoid procedure.

5. Conclusions

The findings in the present study suggest that subxiphoid approach video-assisted thoracoscopic thymectomy is safe and effective for the treatment of early-stage thymoma. Its merits over the lateral intercostal approach include a better operative view, less pain and superior cosmesis.

Ethical approval

This study was approved by the Ethics Committee of the Affiliated Cancer Hospital of Nanjing Medical University (Nanjing, China). All patient surgical data in the study were approved for extraction from the database.

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Author contribution

Louqian Zhang and Ming Li drafted the manuscript; Lin Xu and Qin Zhang contributed to the conception and design of the work; Feng Jiang and Zhi Zhang contributed to collection clinical data. Louqian Zhang contributed to the generous assistance with statistical analysis. Lin Xu did the critical revision of the article.

Conflicts of interest

There is no conflict of interest in the submission of this manuscript.

Research registration unique identifying number

researchregistry4345.

Guarantor

Lin Xu.

Data statement

All data included in this study are available upon request by contact with the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.01.011.

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