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Subxiphoid versus Unilateral VATS Thymectomy for Thymomas: A Propensity Score-matching Analysis

Running head: Subxiphoid VATS thymectomy for thymomas

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Abstract

Background: The appropriate surgical approach of VATS for early-stage thymoma remains unclear. The present study aimed to explore the safety and feasibility of subxiphoid and subcostal arch thoracoscopic thymectomy in comparison with unilateral thoracoscopic thymectomy for treatment of early-stage thymoma.

Methods: The outcomes of 237 patients without myasthenia gravis who had undergone thoracoscopic thymectomy for Masaoka stage I and II thymoma from January 2015 to May 2019 at our center were retrospectively evaluated (subxiphoid and subcostal arch approach: 39; unilateral VATS approach: 198). A propensity score-matching analysis was generated to control for selection bias due to nonrandom group assignment in a 1:1 manner.

Results: There was no surgery-related mortality in included patients. Matching of patients according to propensity score resulted in a cohort that consisted of 39 patients in both groups. Patients had similar clinical characteristics in both groups. Compared with those in the unilateral group, patients in the subxiphoid group yielded lower pain scores at 24- and 72-hours post-operation, respectively ($P < 0.01$). In addition, the operation time was longer in the subxiphoid group (147.5 ± 43.6 min vs. 93.2 ± 33.8 min, $p < 0.01$). There were no significant differences in blood loss, total volume and time of drainage, complications or postoperative hospital stays between the two groups.

Conclusions: Subxiphoid and subcostal arch thoracoscopic thymectomy for early-stage thymoma appears to be a safe and feasible procedure. It is considered to be less invasive as it may cause minimal postoperative pain compared to the unilateral VATS approach.

Key words: subxiphoid and subcostal arch thoracoscopic thymectomy; thymoma; propensity score-matching analysis

The standard technique of thymectomy for thymomas is still a trans-sternal approach.

During the last decades, minimally invasive surgical techniques, such as video-assisted thoracoscopic surgery (VATS), play an important role in the management of thymic diseases, which provide access to the anterior mediastinum through the right or left side of the chest or through the subxiphoid area using a multiportal or uniportal approach and are associated with less intraoperative bleeding, lower rate of respiratory complications, shorter chest tube duration and shorter hospital stay, compared to the classical trans-sternal approach^{1,2}.

Previously, a unilateral approach was the most widely adopted technique and it is still commonly practiced³⁻⁵. However, this technique has limitations when the lesion extends to the contralateral side as it makes clear visualization of the contralateral phrenic nerve difficult. Thus, bilateral approaches and/or a subxiphoid approach have been added or performed depending on the localization of the lesion and preference of the surgical team. Within the last decade, the subxiphoid approach has been used successfully in many centers. Our team began performing this approach in 2015 using subxiphoid and subcostal arch incisions. In the present study, we aimed to explore the safety and feasibility of subxiphoid thoracoscopic thymectomy in comparison with unilateral thoracoscopic thymectomy for non-myasthenic early-stage thymoma.

Material and Methods

Study design and patient collection

Between January 2015 and May 2019, clinical data for all consecutive patients without myasthenia gravis who had undergone thoracoscopic thymectomy for Masaoka stage I and II thymoma were collected. Patients undergoing subxiphoid and subcostal arch thoracoscopic thymectomy were compared with those undergoing unilateral thoracoscopic thymectomy during the same period. Cardiac and pulmonary functions were evaluated preoperatively by 2-dimensional echocardiogram, electrocardiogram, and pulmonary function tests. Routine preoperative evaluation to

exclude distant metastases included thoracic and abdominal contrast computed tomography (CT) or positron emission tomography-CT scan, magnetic resonance imaging of the brain, and bone scintigraphy. Any ambiguities on the results were resolved by holding a multidisciplinary consultation to decide whether an operation was necessary. Patients with evidence of pleural adhesions or having had a previous thoracic surgery procedure were not eligible for VATS approach. Total thymectomy, with resection of all perithymic fat according to the Masaoka criteria, was performed in all patients⁶. Whether the subxiphoid or unilateral approach was used was determined by surgeon's preference. All procedures were performed by a single surgical team that mainly focuses on mediastinal disease. The study was approved by the First Affiliated Hospital of Guangzhou Medical University Research Ethics Committee.

Surgical technique

Subxiphoid and Subcostal Arch Thoracoscopic Thymectomy

All patients were supine on the operating table with the surgeon standing between the patients' legs. The assistant was on the right side of the patient. A 3-cm incision was made at the lower edge of the xiphoid for setting the thoracoscope. The rectus abdominis muscle was dissected, and the posterior sternum space was created by finger dissection. Under the guidance of the operator's finger, two 5 mm extrapleural thoracic ports were created at the midclavicular line intersecting with the bilateral costal arch to introduce thoracoscopic grasping forceps and a harmonic scalpel. A 30-degree oblique, 10 mm thoracoscope was introduced through the subxiphoid incision. A pneumomediastinum was created by an 8cm H₂O positive pressure carbon dioxide (CO₂) insufflation to enlarge the retrosternal space and facilitate dissection of the tumor. Both the right-side and left-side mediastinal pleura were opened during the operation. The whole thymus with or without the thymoma and all the associated fat tissues were excised en-bloc. All specimens were placed in a plastic bag and removed from the mediastinum via the subxiphoid port. An 18-F drainage tube was

inserted into the mediastinum through the subxiphoid incision. (Figure 1)

Unilateral Thoracoscopic Thymectomy

The procedure was the same as previously described⁷. We did not use CO₂ insufflation in the cavity in unilateral VATS. The patient was tilted lateral in a semisupine position with a roll under the shoulder. The ipsilateral arm was held abducted over a padded L screen to expose the axilla for port placement. Three 10-mm ports were created. A 30 angled camera was placed in the most lateral 10-mm port. The surgical approach was exclusively from the side of the thymus to enable safe dissection under direct vision. The nontumoral part of the thymus and perithymic fat were dissected first and used for grasping and traction during dissection to minimize the risk of capsular damage. All specimens were safely removed via a specimen bag. Finally, an 18-F drainage tube was placed.

Postoperative course

All patients were transferred to the post-anesthesia care unit for recovery. Chest radiograph was performed for evaluation on the same day as surgery. Formal pain assessment for the study was carried out at 24 and 72 hours postoperatively by use of the visual analog scales (VAS: 0 is completely pain-free and 10 is hard to tolerate)⁸. Complications including pleural effusion, pneumothorax, subcutaneous emphysema, pulmonary atelectasis and inflammation after surgery were recorded. Criteria for pulmonary infection were a combination of the 3 following symptoms: 1. Infiltrate on chest X-ray, 2. Fever 3. Leukocytosis.

Primary Outcomes and Statistical Analysis

The primary outcomes were surgical mortality, rates of conversion to transsternal approach, operation time and blood loss. The secondary outcomes, including volume and duration of drainage, postoperative complications, postoperative pain and length

of hospital stay reflected efficacy. The propensity score-matched cohort was created using logistic regression to calculate propensity scores as proposed by Rosenbaum and Rubin⁹. Age, gender, body mass index (BMI), pulmonary function tests, comorbidity, tumor location(left/middle/right) and maximal tumor diameter were included in the model as potential baseline prognostic and risk factors. Using a 1:1 nearest neighbor matching algorithm that pairs patients with the closest propensity scores within a defined limit (calipers of width equal to 0.1), we found that the propensity score yielded 2 well-matched cohorts of 39 patients (logistic regression estimation algorithm). We compared standardized differences for all covariates between pre-match imbalance and post-match balance¹⁰. Continuous data are presented as mean standard deviation and were analyzed with 2-sample Student t tests for independent data. Categorical variables are given as a count and percentage of patients and compared with the χ^2 or Fisher exact test. P values<0.05 were considered statistically significant. All tests were 2-sided, with an α -level of 0.05. SPSS software (SPSS version 22.0; IBM Corp, Armonk, NY) and R (R version 2.15.3, 2013; The R Foundation, Vienna, Austria) were used for all statistical evaluations.

Results

From January 2015 to May 2019, a total of 237 patients with thymoma that underwent thoracoscopic thymectomy were included for analysis. Among those included, 39 patients underwent subxiphoid and subcostal arch approach, and 198 patients underwent unilateral approach. Comorbidities of these patients mainly included hypertension, diabetes mellitus, other cancer history and others. No perioperative mortality was recorded for any of the included patients. There were 3 and 2 patients for whom conversion to transsternal approach in subxiphoid and unilateral approach, respectively, were required. The reasons for conversion were: tumor penetrated the capsule (3), invaded pericardium and recurrent laryngeal nerve (1) and extensive pleural adhesions (1).

Matching of patients according to propensity score resulted in a cohort that consisted of 39 patients in each group. All demographic characteristics were comparable between the two groups. A dot plot of standardized mean differences for all covariates before and after matching is shown in Figure 2. The patients who underwent the subxiphoid approach had similar distributions to those that underwent the unilateral approach for age, gender, BMI, comorbidities, pulmonary function tests and maximal tumor diameter. Baseline characteristics of matched patients were shown in Table 1.

According to operative and anesthesia results, the operation time was longer in the subxiphoid group than the unilateral group (147.5 ± 43.6 min vs. 93.2 ± 33.8 min, $p < 0.01$). No significant differences were found in blood loss, total volume or time of drainage, postoperative complications, Masaoka staging, duration of postoperative hospital stay or conversion approach between the two groups. However, compared with the unilateral group, patients in the subxiphoid group yielded lower postoperative pain VAS scores at 24 (2.9 ± 1 VS. 5.6 ± 1.4 , $p < 0.01$) and 72 (2.2 ± 0.6 VS. 3.8 ± 1 , $p < 0.01$) hours after operation, respectively. (Table 2)

Comment

We herein showed minimally invasive thymectomy for anterior mediastinal tumors using the subxiphoid and subcostal arch approach compared with the unilateral VATS approach. With this propensity score-matched analysis, we demonstrated that subxiphoid approach was considered to be less invasive as it might cause minimal postoperative pain. Subxiphoid approach also provides an excellent view of the bilateral pleural cavities.

Trans-sternal approach has been the gold standard since Blalock first introduced

thymectomy for treatment of myasthenia in 1939¹¹. VATS thymectomy with a lateral intercostal approach has spread globally after being introduced for the first time in 1993¹². VATS thymectomy is currently the most frequently performed thoracoscopic procedure for thymoma or myasthenia gravis. We have conventionally performed VATS thymectomy using the lateral approach for more than 15 years. 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. Disadvantages of VATS approach included insufficient completeness of removal of the upper poles of the thymus with unilateral or bilateral VATS approach and risk of chronic pain after thoracoscopy^{13,14}.

The subxiphoid approach to thymectomy was first reported in 1999¹⁵. After that, subxiphoid VATS thymectomy with or without a transcervical incision has been reported which allows the surgeon to visualize both phrenic nerves very clearly and reach high into the anterior mediastinum under direct vision^{3,13,16}. We began to perform this technique in 2015, using the subxiphoid and subcostal arch incisions described by Zhou and colleagues¹⁷. The view from the subxiphoid approach was similar to the view from median sternotomy. To overcome the challenge of the working space, many surgeons have increased the working spaces by lifting of the sternum^{16,18,19}. We used CO₂ to maintain a sufficient surgical field after the retrosternal space is fully detached. The pressure of CO₂ is not higher than 8 mmHg. The space from the sternum to the heart was secured without relative complications. In our experience to date, low-pressure CO₂ insufflation within the mediastinum does not alter the patients' hemodynamic status regardless of continuity of the unilateral or bilateral pleura. Pleural tears also do not cause major difficulty during execution of the procedure. The operation time of the subxiphoid approach was longer than that of unilateral approach which may be the result of a lack of experience and the inherent learning curve of the surgical team. Compared with the conventional unilateral VATS

thymectomy, blood loss, total volume and time of drainage, surgical complications, length of postoperative hospital stay in our experience are not inferior, and our urgent conversion rate for bleeding is zero. Phrenic nerve injury might result in pulmonary functional loss and other related complications. So, we perform the thymectomy very carefully and mainly focus on the phrenic nerve and protect it. During the VATS surgery, if the tumor has obvious invasion and is closely related to phrenic nerve and separation is difficult, consider switching to thoracotomy. Therefore, there were no phrenic nerve injuries in the included patients.

The techniques of subxiphoid VATS approach differ among different institutes. Zielinski et al. developed the “maximal” transcervical-subxiphoid-video-thoracoscopic thymectomy, however the incisions were large and looked far less cosmetic than the unilateral approach¹³. Chung-Ping Hsu et al.¹⁶ used a subxiphoid incision plus a port for thoracoscope at 6th intercostal space. Using a classical thoracoscopic technique, the bilateral thymic lobes can be equally inspected and dissected. However, this procedure involves an intercostal incision and may thus cause intercostal nerve damage. Some studies reported the use of subxiphoid single-port VATS thymectomy^{20,21}. The limitations of this procedure are restricted maneuverability of dissecting instruments through the single port and the need for special instruments. In our institute, we use three ports: one subxiphoid incision and two subcostal arch incisions. The surgical maneuvers are smooth without the limitation of space. By omitting the intercostal incision, we found patients had less postoperative pain on 24 and 72 hours compared with those who underwent the unilateral VATS approach.

Mineo et al. suggested that dissection manoeuvres are safer from the left side because the superior vena cava lies outside of the surgical field. Thus the authors suggested that dissection of the peri-thymic fatty tissue around the left peri-cardiophrenic angle can be more readily carried out from the left side²².

Alternatively, surgeons who are using the right-sided approach have advocated that the superior vena cava can be clearly identified from the right and used as a landmark to dissect around the innominate veins. It is also comfortable for a right-handed surgeon to start at the inferior pole by allowing greater maneuverability of instruments in a wider right pleural cavity, especially in patients with cardiomegaly²³. In our study, the surgical side mainly depends on the tumor location, 89 patients underwent left approach.

Some limitations should be acknowledged. First, the study was retrospective and the comparison was based on historical controls. In addition, even though the propensity-score matching method was used, selection bias for both minimally invasive techniques, based on size, location and the relationship with other tissues still existed; risk-adjusted analysis was merely for hypothesis generation. The tumor location is a major factor affecting the surgical approach. In the subxiphoid approach, tumors in the middle position account for most, which might be one reason for this approach. Second, the handling of the forceps could be difficult due to obesity or to a sternal anomaly caused, for example, by pectus excavatum. Special attention should go to the visualization of the innominate vein. Sternal traction might help in these cases. Third, a small bleeding/hematoma may occur on the surface of the retrosternal area after the blind detachment. This bleeding may contaminate the thoracoscope, thus cleaning of the thoracoscope is frequently required. Fourth, we used VAS score for patients in the early post-operative period to demonstrate the advantage of subxiphoid approach. Due to the limited records, we will record morphine equivalents administered in the post-operative period as a second measure to further corroborate the VAS results.

We conclude that subxiphoid and subcostal arch thoracoscopic thymectomy for early-stage thymoma appears to be a safe and feasible procedure. Compared to the

unilateral VATS approach, subxiphoid approach is considered to be less invasive as it may cause minimal postoperative pain. The subxiphoid incision also provides an excellent view of the bilateral pleural cavities. Further prospective study on this topic is warranted.

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Table 1. The characteristics of the included patients.

Variables	Before propensity score matching			After propensity score matching		
	Subxiphoid approach (n=39)	Unilateral approach(n=198)	P value	Subxiphoid approach (n=39)	Unilateral approach(n=39)	P value
Gender(male/female)	20/19	99/99	0.89	20/19	19/ 20	1
Age(year)	48±14	47±14	0.70	48±14	52±15	0.31
BMI(kg/m2)	23.2±3.1	23.1±3.3	0.95	23.1±3.1	22.8±3.1	0.63
Pulmonary Function						
FEV1(L)	2.7±0.7	2.6±0.8	0.67	2.7±0.7	2.5±0.7	0.31
FVC(L)	3.4±0.7	3.3±0.8	0.61	3.4±0.8	3.2±0.7	0.4
Comorbidity	10	38	0.36	8	9	1
hypertension	6	20		6	6	
diabetes mellitus	6	14		5	3	
myasthenia gravis	4	12		3	2	
other cancer history	2	10		2	3	
others	2	20		2	2	
Maximal tumor diameter (cm)	6.7±2.9	5.9±2.8	0.15	6.7±2.9	6.9±2.6	0.6
Location(left/middle/right)	5/30/4	84/33/81	<0.01	5/30/4	17/7/15	<0.01

BMI, body mass index; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

Table 2. Surgical outcomes of the included patients.

Variables	Before propensity score matching			After propensity score matching		
	Subxiphoid approach (n=39)	Unilateral approach(n=198)	P value	Subxiphoid approach (n=39)	Unilateral approach (n=39)	P value
Operation time(min)	147.5±43.6	103.5±58.7	<0.01	147.5±43.6	93.2±33.8	<0.01
Blood loss(ml)	35.8±42.4	65±211.7	0.08	35.8±42.4	55.9±210	0.58
Total drainage(ml)	341.3±411.1	379.8±377.2	0.62	341.3±411.1	338.6±314.1	0.98
Times of drainage removal(day)	1.8±1.5	1.5±1.7	0.31	1.8±1.5	1.3±1.3	0.1
Complications	10	22	0.02	10	5	0.24
pleural effusion	5	13		5	1	
pneumothorax	1	3		1	0	
subcutaneous emphysema	2	10		2	4	
pulmonary inflammation	3	4		3	1	
Masaoka staging			0.11			1
Stage I	23	88		23	22	
Stage II	16	110		16	17	
Postoperative pain (VAS score)						

24h	after	2.9±1	5.8±1.3	<0.01	2.9±1	5.6±1.4	<0.01
operation							
72h	after	2.2±0.6	4±1	<0.01	2.2±0.6	3.8±1	<0.01
operation							
Hospital	stay	4.2±2.1	3.9±2.6	0.42	4.2±2.1	3.7±2.3	0.31
after operation							
Conversion	to	3	2	0.03	3	1	0.62
transsternal							
approach							

VAS, visual analogue scale.

Figure Legends

Figure 1: Thoracoscopic extended thymectomy via subxiphoid and subcostal arch approach: the camera was introduced into the anterior mediastinum via the subxiphoid incision; a 45-cm long thoracoscopic grasping and a 45-cm-long harmonic scalpel were introduced into the anterior mediastinum through the bilateral costal arch ports.

Figure 2: Dot plot of standardized mean differences for all covariates before and after matching. BMI, Body mass index.