Research Highlight

Efficacy of mediastinal lymph node dissection during thoracoscopic lobectomy

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Introduction

While the first description of thoracoscopy occurred as early as 1910 (1), the first successful attempts of video-assisted thoracoscopic (VATS) lobectomy for non-small cell lung cancer (NSCLC) did not take place until the early 1990s (2). As VATS lobectomy continues to gain acceptance as the less invasive alternative to open thoracotomy, extensive research has been conducted to compare its efficacy, postoperative outcomes and oncologic effectiveness to thoracotomy. Despite its many proven advantages, concerns regarding the oncologic effectiveness of VATS lobectomy remain as one of the major obstacles to its wider adoption (3). As an important assessment for accurate staging of NSCLC, adequate evaluation of lymph nodes, especially mediastinal lymph nodes, has been the center of the controversy.

Advantages of VATS *vs.* thoracotomy for lobectomy

The less invasive nature of VATS lobectomy, as compared to lobectomy via thoracotomy, is manifested in less morbidity, including less post-operative pain (4), reduced level of inflammatory response and preserved immune function (4-8), and fewer overall post-operative complications (9-12). Specifically, less post-operative pain with VATS lobectomy is evidenced by reduced amounts of analgesic use and fewer points on the 0-10 pain scale (4). A reduced level of inflammatory response and preserved immune function are demonstrated by lower levels of inflammatory mediators including IL-6 and C-reactive protein, as well as less reduction in levels of CD4 and natural killer cells (4-8). Pulmonary function tests on patients one and two weeks postoperatively have shown faster and improved recovery rates of FVC, FEV1 and vital capacity in VATS lobectomy compared with open lobectomy, supporting preserved pulmonary function (4). While mortality rates are often similar between VATS and open lobectomy, it is conceivable that less pain, reduced inflammation and preserved physiologic function will translate into fewer post-operative complications. This has been illustrated by several studies, including one prospective trial (13), 6 retrospective case control series (9,12,14,15) and one systematic review (7). These studies have shown that VATS lobectomy is associated with lower rates of post-operative complications, including air leak, arrhythmia and pneumonia. In fact, the utilization of the VATS technique has been demonstrated to be a stronger predictor of post-operative morbidity than age and pulmonary function after lobectomy (14,15). The potential to improve oncologic efficacy of VATS lobectomy is suggested in a study demonstrating superior compliance with adjuvant chemotherapy after VATS lobectomy (16). In their study, Petersen *et al*. found that as compared to open lobectomy, patients who underwent VATS lobectomy were more likely to receive planned adjuvant therapy, had fewer delays and reductions in planned doses (16).

Mediastinal lymph node dissection during lobectomy

Guideline recommendations

The controversy concerning the efficacy of mediastinal lymph node dissection (MLND) during VATS lobectomy originates from the lack of strict standards on the technique and extent of lymph node removal for MLN staging in all patients with NSCLC. Current practice guidelines by the National Comprehensive Cancer Network (NCCN) recommend the complete dissection of at least three

mediastinal nodal stations (N2) as defined by the most recent staging system (17,18). The European Society of Thoracic Surgeons (ESTS) has published similar guidelines, advising the removal of at least three hilar and interlobar nodes and three mediastinal nodes from three stations, in which the subcarinal station is always included (19). While mediastinal lymph node sampling (MLNS) is the standard of practice among most thoracic surgeons and groups participating in clinical trials in North America (20), debate continues on the efficacy of MLND *vs*. MLNS and focuses on local tumor control, detection of micrometastasis and effects on survival.

MLND *vs*. MLNS

Proponents of MLND argue that with complete removal of all resectable lymph nodes, the proportion of complete R0 resections is increased, leading to reduced local recurrence. This has been supported by several studies, in which the rates of local and overall recurrence were significantly reduced by MLND (19,21-23). Another potential advantage of MLND is more accurate tumor staging through detection of micrometastasis and skip lesions. In their study, Lardinois *et al*. demonstrated significantly higher number of mediastinal lymph nodes harvested by MLND compared with MLNS (17.3±5.3 *vs*. 7.2±2.5) (19). Despite the aforementioned potential advantages, whether MLND is associated with improved survival remains controversial. Some researchers argue that the perceived survival advantage of MLND is in fact a Will Rogers phenomenon - stage migration of patients due to an improved lymph node staging by a more extensive lymphadenectomy (21,24). In a retrospective review by Doddoli *et al*. comparing the effect of MLND (n=258) *vs*. MLNS (n=207) on overall survival of patients with Stage I NSCLC, MLND was found to be a favorable independent prognostic factor on survival (Hazard risk: 1.43, 95% CI 1.00-2.04; P=0.048) (23). Similarly, Lardinois *et al*. demonstrated longer disease-free survival in patients who underwent MLND *vs*. MLNS in stage I NSCLC (60.2±7 *vs*. 44.8±8.1 months, P<0.03) (19). Such results were supported by Keller *et al*. who reported an improved survival in patients who underwent MLND (median survival 57.5 months) *vs*. MLNS (median survival 29.2 months) in patients with Stages II and IIIa NSCLC. Of note, this survival advantage only applied to patients with right lung tumors (25). In a prospective randomized trial by Wu *et al*. comparing MLND *vs*. MLNS through thoracotomy for stages I-IIIA NSCLC (n=532), a significant survival advantage with MLND was again noted for stage I (5-year survival 82.16% *vs*. 57.49%, P=0.02) and IIIA NSCLC patients (26.98% *vs*. 6.18%, P<0.001) (22).

Other studies have not confirmed such survival advantage of MLND. Early retrospective reviews demonstrated no difference in long-term survival after MLND *vs*. MLNS (26-28). A prospective randomized controlled trial by Sugi *et al*. comparing MLND *vs*. MLNS via thoracotomy for T1N0M0 (now T1aN0M0) lesions (n=115) revealed no significant differences in the recurrence rate (10% *vs*. 13%), 3-year (88.1% *vs*. 89.2%) or 5-year (81.4% *vs*. 83.9%) survival. The authors argued that because most recurrences occur distantly, better local control of disease does not translate into improved survival (29). Another prospective randomized controlled trial by Izbicki *et al*. comparing MLND to MLNS (n=169) showed that MLND did not improve survival in the overall group of patients (hazard ratio: 0.78, CI 0.47-1.24), although subgroup analysis showed an improvement in relapse-free survival (58.8% *vs*. 20.7%, P=0.037) in patients with pN1 or N2 disease with one lymph node level involvement (21). Most recently, the randomized, multi-institutional prospective trial by ACOSOG on MLND *vs*. systematic MLNS (Z0030) found no improvement on survival associated with MLND for patients with early-stage NSCLC. However, the authors still recommended MLND for all patients with resectable NSCLC, because of the potential benefits in more accurate staging with no increased mortality or morbidity (30).

Efficacy of MLND during VATS lobectomy

Technique

While the use of instruments may differ, the technique of MLND via VATS follows the same principles as the open approach. As described in detail by D'Amico *et al*., the most important lymph node stations are levels 2, 4, and 7 for a right upper lobectomy, level 5, 6, and 7 for left upper lobectomy and levels 7, 8, and 9 for lower lobectomies (in addition to the upper lymph node stations) (31).

Lymph node dissection may be performed prior to or following lobectomy, with superior exposure if performed prior to dissection of the hilum. The anterior paratracheal lymph node stations, which include levels 2 and 4, are bordered by the superior vena cava anteriorly, the trachea posteriorly, the pericardium medially, the azygos vein inferiorly and the junction of the innominate artery and the trachea superiorly. The right recurrent laryngeal nerve is at risk of injury during anterior

MLND and should be avoided by staying away from the innominate artery. Paratracheal lymph node dissection should be performed en bloc, with respect to the above mentioned borders, and may be performed with a combination sharp dissection, electrocautery, and other energy sources.

On the left side, the VATS approach with magnification facilitates dissection of level 5 and 6 lymph nodes with less risk of injury to the recurrent laryngeal nerve. Using the borders of the left phrenic nerve, the aortic arch, and the left pulmonary artery, all lymph node tissue in the aortopulmonary window should be readily resectable.

To perform subcarinal lymph node dissection (level 7), resection of all nodal tissue bordered by the two main bronchi, esophagus and pericardium is required. On the left side, retraction of the aorta is achieved using long, curved thoracoscopic instruments. Complete subcarinal lymph node dissection is achievable in all cases.

Safety and morbidity

As with open thoracotomy, potential complications from MLND during VATS lobectomy include injuries to the bronchial arteries, tracheobronchial tree and recurrent laryngeal nerves, prolonged air leak, hemorrhage and atrial fibrillation. There may also be risk of pulmonary edema by impairing the lymphatic backflow (23). Studies so far have demonstrated comparable operative mortality and morbidity of MLND by VATS *vs*. open lobectomy, indicating that MLND by VATS is a safe procedure (32).

Results

Several previous studies have examined the extent of MLND by VATS *vs*. open lobectomy. In one study by Kondo *et al*., thoracotomy was performed for reassessment of lymph nodes following MLND using VATS and yielded few additional lymph nodes (mean=1.3 LN, median 0) (33). Similarly, Sugi *et al*. found no difference between the numbers of lymph nodes dissected among VATS (mean=8.4±1.0) *vs*. open (mean=8.2±1.5) group during lobectomy (34). More recently, a retrospective review of 770 patients with cN0-pN2 NSCLC (VATS=450, open=320) by Watanabe *et al*. examined the total number of lymph nodes, number of lymph node stations, number of mediastinal nodes and mediastinal stations by VATS *vs*. open lobectomy, and found no difference in any of these categories (35).

Data from the recent ACSOG Z0030 trial (n=752, VATS=66, open=686) has also confirmed the efficacy of MLND by VATS procedure by demonstrating similar number of LN removed and LN stations assessed (36). So far, few studies have disputed the efficacy of MLND by VATS, with one study by Delinger *et al*. (VATS=79, open=464) showing a fewer number of LN sampled by VATS compared to thoracotomy (7.4±0.6 *vs*. 8.9±0.2, P=0.03) and fewer number of N2 nodes (2.5±3.0 *vs*. 3.7±3.0, P=0.004) (37). In a recent study analyzing data from the NCCN Database by D'Amico *et al*. with a more balanced number of VATS *vs*. open patients (n=388, VATS=199, open=189), VATS and thoracotomy were found to result in similar number of mediastinal lymph node resections (median=4 for both groups) and N2 nodes (median=3 for both groups). The percentage of patients with at least three MLN stations assessed, as recommended for the guidelines, was also similar in the VATS *vs*. open group (66% *vs*. 58%, P=0.12) (38).

Correlation between clinical and pathological staging

In addition to the extent of MLND, the correlation between clinical and pathological staging has been examined by previous investigations and was found to be comparable for VATS *vs*. open MLND. In the study by Sugi *et al*., the incidence of upstaging from N0 to N1 and N2 disease was found to be 4.2% and 2.1%, respectively, for MLND via VATS, and 5.8% and 1.9% for open (P=0.47) (34). This is similar to the research by Denlinger *et al*., in which 1.3% of patients with clinical N0 or N1 disease and treated with VATS had pathologic N2 disease, as opposed to 3.9% treated with thoracotomy (P=0.5) (37). Although the study by Watanabe *et al*. reported higher rates of upstaging for both VATS and open groups of patients with Stage I NSCLC with rate of 20.1% (N0 to N1 or N2 disease) for VATS and 30.3% for open MLND, there was no significant difference between the two groups (32). In the NCCN Database study by D'Amico *et al*., the rate of upstaging from N0 to N1, N2 and N3 disease was 6.4%, 2.3% and 0%, respectively, for MLND via VATS and 6.9%, 7.6% and 0% for thoracotomy (P=0.24). The rate of downstaging from N2 to N1 and N0 disease was 0% and 29%, respectively, for VATS and 8.7% and 17.4% for thoracotomy (P=0.99) (38).

Disease-free survival and overall survival

The definitive proof of efficacy for MLND via VATS lobectomy lies in its impact on rate of both disease-free and

Table 1 Summary of recent studies on the disease-free and overall survival of patients with lobectomy via VATS *vs.* thoracotomy

Study	Disease-free survival (VATS *vs.* thoracotomy)	Overall survival (VATS *vs.* thoracotomy)
Sugi (2000)[34]	-	3 yr: 90% *vs.* 93% (P=0.74) 5 yr: 90% *vs.* 85%
Watanabe (2008)[35]	5 yr: 60.9% *vs.* 49.6% (P=0.714)	5 yr: 45.4% *vs.* 41.1% (P=0.83)
Denlinger (2010)[37]	-	3 yr: 83.3% *vs.* 74.5% (P=0.43)
Flores (2009)[9]	-	5 yr: 79% *vs.* 75% (P=0.08)

overall survival. Previous researches have shown equivalent, if not superior, survival rates of VATS lobectomy as compared to thoracotomy (9,35,39,40). In their prospective randomized trial comparing oncologic results of VATS *vs.* open lobectomy, Sugi *et al.* revealed similar 3- and 5-year survival rates (90% *vs.* 93% and 90% *vs.* 85%, respectively) for patients with clinical stage IA lung cancer (34). Additional retrospective analyses and systemic reviews have confirmed these findings (9,39), while one meta-analysis reported a significantly improved 5-year survival rate (RR=0.72, CI 0.45-0.97) associated with VATS lobectomy for early-stage NSCLC (40). A summary of recent studies can be found in *Table 1*.

Conclusions

In conclusion, VATS lobectomy has both physiologic and biologic advantages over open thoracotomy. While controversy still exists concerning its oncologic effectiveness, especially its efficacy in MLND, research to date has confirmed its feasibility, safety, as well as equivalent outcomes as compared to open thoracotomy. In the future, research may help resolve the controversy over the extent of MLND and contribute further to the adoption of VATS lobectomy.

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