Video-assisted thoracic surgery in lung cancer: Lung resection and mediastinal lymph node staging

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Published online: 15 February 2012
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Abstract Despite our ever-increasing ability to target the molecular and genetic pathways responsible for non-small cell lung cancer (NSCLC), anatomic surgical resection remains the mainstay of treatment for those without evidence of systemic disease. Although these procedures can be performed with relatively low mortality, the age and coexisting conditions of the population lends itself to a myriad of potential complications. Minimally invasive surgical approaches to the treatment of lung cancer hold the potential to offer curative resection to a much broader group of patients without compromising oncologic principles.

Keywords Non-small cell lung cancer · VATS · Lobectomy · Minimally invasive surgery

Introduction

Lung cancer remains one of the leading causes of cancer deaths in the United States accounting for 219,450 new cases and 159,390 deaths in 2009 [1]. NSCLC accounts for 80% of all cases. Although rates of heavy smoking have declined significantly since the 1964 Surgeon General's report, there are currently 94 million current or former smokers at risk for the disease [2]. More than half of NSCLC patients are older than 65 years at the time of diagnosis, with 30% older than 70 years [3–5]. Based on recent reports, we can expect increasing utilization of low-dose computerized tomographic screening with the hope of detecting earlier stage tumors [6]. Despite recent advances in multimodality therapies, anatomic surgical resection remains the standard of care for early-stage disease.

The 1995 publication from the Lung Cancer Study Group's (LCSG) prospective randomized trial of lobectomy versus limited resection for stage IA NSCLC reinforced the need for formal lobar resection in early-stage disease [7]. Sublobar resection was found to have increased risk of local/regional recurrence and higher 5-year mortality, with no evidence of preserved pulmonary function [7, 8]. The standard treatment therefore became rib-spreading thoracotomy with direct vision and formal anatomic resection. Although large series have demonstrated low mortality rates, perioperative morbidity rates have been as high as 32% [9–11]. It was in this environment with an ever aging and more comorbid population, that minimally invasive approach to resection was developed.

Hans Christian Jacobaeus described the first thoracoscopic procedure in 1910 [12]. The first reports of video-assisted thoracic surgery (VATS) pulmonary lobectomy were published in the early 1990s [13–15]. The theoretical advantages were less surgical trauma, improvements in

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post-operative pain, enhanced recovery, and less overall morbidity. Despite a growing body of evidence to support these advantages, 70% of lobectomies are still performed via thoracotomy [11]. As is the case with all minimally invasive surgical procedures, an initial learning curve exists. An en bloc resection of the target lobe must be performed using standard oncologic resection techniques isolating and separately dividing the arteries, veins, and bronchus and performing a mediastinal lymph node dissection for staging. This review will examine the evidence that VATS lobectomy decreases surgical morbidity without compromising oncologic principles for patients with early-stage NSCLC as well as the ever-expanding indications.

Minimally invasive (VATS) lobectomy definition

Although a full discussion of the techniques of VATS lobectomy is beyond the scope of this review, some critical elements exist. One key principle for the reduction of surgical trauma is the elimination of rib-spreading through the use of the thoracoscope for visualization. Although the original technical descriptions did not use rib-spreading, a study by Yim et al. [16] surveyed 33 thoracic surgeons worldwide and found that 70% of respondents utilized a rib spreader at one point during the procedure. The location and number of incisions was found to vary as well with 48% reporting use of a utility incision greater than 6 cm in length. The Cancer and Leukemia Group B study (CALGB 39802), which examined feasibility of VATS lobectomy for tumors $\leq$ 3 cm, established a unified technique and helped standardize the approach for VATS lobectomy [17•]. VATS lobectomy was defined by a 4–8 cm access incision with an additional two port incisions. Furthermore, videoscopic guidance was mandated and hilar dissection was performed without rib spreading. This study established the feasibility of VATS lobectomy in 127 patients with a mortality of 2.4% and severe complication rate of 7.4%. Long-term survival in this cohort was equivalent to historical controls.

Patient selection

Based on the National Comprehensive Cancer Network (NCCN) guidelines for patients with the pathologic diagnosis of NSCLC all patients should have a complete H&P (to include performance status), pathologic review, CT scan of the chest through the adrenals, baseline labs, smoking cessation counseling, and pulmonary function testing. Patients who are surgical candidates require clinical staging of the mediastinum to rule out metastatic disease. F18-fluorodeoxyglucose positron emission tomography (FDG-PET) is typically performed and surgical staging of the mediastinum by either endobronchial ultrasound (EBUS) or mediastinoscopy (CME) is necessary to determine the

status of lymph nodes that are either FDG avid or > 1 cm. Surgical staging of the mediastinum should be considered for any patient with T2 status, suspicion of N1 or N2 disease on CT scan, or clinical findings suggestive of advanced disease [18].

Video-assisted thoracic surgery lobectomy is an acceptable approach in patients without anatomic or surgical contraindications. The absolute contraindications for VATS lobectomy are inability to tolerate single lung ventilation and pleural symphysis. Large tumors, > 4 cm, are a relative contraindication given that specimen retrieval usually requires some degree of rib spreading that may negate some of the benefits of VATS. Special patient populations in which VATS lobectomy has shown to have additional benefits are listed in Table 1.

For patients at highest risk for perioperative complications, VATS lobectomy has been shown to have advantages in selected series (Table 1). In patients with high preoperative comorbidities, Whitson et al. [19] reported fewer complications with equivalent OR times, blood loss, hospital length of stay, and survival rate. In patients in the seventh decade of life, a matched case-controlled study demonstrated patients undergoing VATS lobe had fewer severe complications and a shorter length of stay than their thoracotomy counterparts [20]. In this same age group, Demmy et al. [21] showed that patients undergoing open thoracotomy were more likely to be discharged to a skilled nursing facility or require home assistance than those undergoing VATS lobectomy. Similar results have been seen in smaller series of patients over the age of 80 [22, 23]. Studies comparing pulmonary function of VATS versus open lobectomy consistently demonstrate improved pulmonary function in patients undergoing VATS [24–28]. Nagahiro [25] found a quicker recovery in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) in the first 2 weeks following VATS lobectomy. Petersen et al. [29] examined the chemotherapy compliance between 100 patients undergoing VATS and open lobectomy. They found that patients undergoing VATS lobectomy received 75% or more of their

Table 1 Populations with defined benefit of VATS lobectomy

Population	Reference(s)
Stage IA NSCLC	[17•, 19, 30, 31••, 33, 39, 43, 47]
Elderly (age > 70 years)	[20, 23, 46, 56]
Poor pulmonary function*	[24–26]
High comorbidity	[19, 36]
Planned adjuvant therapy	[29]

*Defined as FEV1 < 0.8 L.

planned adjuvant regimen compared to only 40% in the thoracotomy group. In summary, VATS lobectomy has been shown to improve outcomes in patients with high comorbidities in highly selected series.

Oncologic results

In terms of recurrence, Sugi et al. [30] demonstrated in a randomized control trial that local recurrence rates were similar between VATS and thoracotomy lobectomy. The most recent meta-analysis pooled six trials that examined local recurrence and found similarly that there was no statistically significant difference (relative risk [RR]=0.64; 95% confidence interval [CI], 0.30 to 1.35; $P=0.24$) [31••]. This same analysis found that systemic recurrence was lower when comparing VATS to open lobectomy (RR=0.72; 95% CI, 0.34 to 0.95; $P=0.04$). With respect to 5-year survival, of the seven studies pooled in the analysis, VATS had an improved overall 5-year survival compared to open lobectomy (RR=0.72; 95% CI, 0.45 to 0.97).

Mediastinal lymph node staging

An early concern raised by opponents of VATS lobectomy was the adequacy of lymph node dissection. In order to examine the adequacy of lymphadenectomy, Sagawa et al. [32] performed VATS lobectomy with lymph node dissection followed by second surgeon performing a thoracotomy to access the number of residual lymph nodes. The authors found that with right and left sided VATS lobectomies, the rates of appropriate lymph node dissection were 97% and 98%, respectively. Similar results were seen in the American College of Surgeons Oncology Group (ACOSOG) Z0030 national cooperative trial, in which the number of lymph node stations sampled and lymph nodes removed were similar between VATS and open lobectomy [33]. Additional trials by Kirby [34] (VATS vs muscle-sparing thoracotomy) and Watanabe [35] (VATS+MLND vs open+MLND) also demonstrated similar numbers of lymph nodes dissected for each group. Furthermore, a large-scale analysis of the NCCN database has shown that there is no difference in

the number of lymph node stations sampled by either the VATS or open approach [36].

Performance of a complete mediastinal lymphadenectomy (MLND) at the time of pulmonary resection is controversial. Passlick et al. [37] have demonstrated an increased long-term survival in patients with MLND in which immunohistochemically detected lymph nodes were found. The American College of Surgeons Oncology Study Groups (ACOSOG) trial Z0030, which contained both VATS and open lobectomy, demonstrated that lobectomy+MLND can be performed safely with minimal increase in morbidity (38%) and mortality (1.4%) [33]. Long-term data from this cohort should help to answer the question as to the survival impact of MLND versus nodal sampling.

VATS lobectomy mortality

Current evidence suggests that VATS lobectomy can be performed for early-stage NSCLC with mortality results that are similar to the open approach [31••]. The largest reported series of VATS lobectomy by McKenna et al. includes 1048 resections for primary lung cancer with a mortality rate of 0.8% respectively [10], [38•]. Other large series report operative mortality rates from 0% to 2% [39, 40]. A secondary analysis of the ACOSOG Z0030 was performed comparing VATS to open lobectomy with similar operative mortality rates (0% and 1.6% respectively, $P=1.0$) [39]. Figures 1 and 2 demonstrate the pooled analysis of the morbidity and mortality of VATS versus open lobectomy.

VATS lobectomy morbidity

As with open lobectomy, the most common complications seen following VATS lobectomy include arrhythmias, prolonged air leak, and pneumonia. In most series, atrial dysrhythmias remain the most common complication. Major complications such as pneumothorax, respiratory failure, and myocardial infarctions occur in less than 1% of cases. In the meta-analysis by Yan et al. [31••], no statistical differences with respect to prolonged air leaks, arrhythmias, or pneumonias were found when comparing VATS to

Fig. 1 Comparison of morbidity, VATS versus open lobectomy

Fig. 2 Comparison of mortality and survival, VATS versus open lobectomy

thoracotomy. The rates of surgical conversion to thoracotomy ranged from 0% to 15.7%. VATS lobectomy has been shown to reduce intraoperative blood loss and chest drain duration [41–43]. Several series have demonstrated a decreased hospital length of stay when compared to standard thoracotomy. In their large single-institution series, McKenna et al. [38•] reported morbidity rates of 15.3%.

Arrhythmias

Post-operative arrhythmias, particularly atrial fibrillation, are frequent complications of pulmonary resection often resulting in a prolonged patient stay. The pathogenesis of atrial fibrillation in the post-operative period is multifactorial in nature. Early proponents of minimally invasive pulmonary resection proposed that decreasing the surgical incisional trauma might lead to a decrease in atrial arrhythmias. This, however, has not proved to be the case reliably in all series [19, 27, 43–48]. The meta-analysis by Yan et al. [31••] found that the rate of atrial arrhythmias in VATS lobectomy was similar to that observed in the open procedure (RR, 0.99; 95% CI, 0.52–1.91; $P=0.98$). This suggests that the surgical incision is not the primary actor and that parenchymal and vascular dissection, neurohormonal mechanism, and denervation play a larger role in the arrhythmogenesis.

Chest tube drainage and air leaks

Regardless of the technique utilized, 30%–50% of patients have evidence of an air leak following pulmonary resection [49, 50]. Risk factors for development of a postoperative air leak are reduced pulmonary function, fragile lung parenchyma, pleural adhesions, and the use of steroids [51]. Prolonged air leak is typically defined as an air leak that persists ≥ 5 days or one that increases the hospital length of stay. Prolonged air leaks increase the risks of empyema, impact hospitalization costs, and may increase the rate of cardiopulmonary complications. In the meta-analysis by Yan et al. [31••], 10 studies were examined which compared the incidence of prolonged post-operative air leak [19,

27, 41, 43, 46–48, 52–54]. There was no difference seen between VATS and open lobectomy (RR=0.90; 95% CI, 0.52–1.55; $P=0.71$) [31••].

Chest drain duration following VATS lobectomy is more difficult to determine. Across the multiple randomized and nonrandomized trials, no clear consensus for the timing of chest drain removal exists. Although some trials support shorter chest drain time with VATS lobectomy versus open [42, 43], others show no difference [19, 25, 27, 45, 52]. A secondary analysis of the ACOSOG Z0030 showed fewer instances of chest drainage over 7 days (1.5% vs 10.8%, $P=0.29$) and the median total chest tube drainage was lower in the VATS group [39].

Postoperative pain and recovery

The postoperative recovery appears to be better for the VATS approach when compared to open lobectomy [55]. Postoperative pain as evidenced by visual pain scales, narcotic requirement, and sleep disturbances is less following VATS lobectomy [56]. Narcotic pain medication utilization has been shown to be significantly reduced in the early post-operative period (POD 1–7) [56]. Likewise, pain medication requirements have been seen to be lower at 3 weeks. Longer-term reductions in pain and severe pain have been found to be reduced at 3 months and persist at 1 year [42]. Of note, not all studies were consistent with the non-rib spreading technique of VATS lobectomy.

The quality of life following VATS lobectomy has also been examined [57, 58]. A prospective study of 100 patients undergoing surgery for lung cancer looked at quality-of-life questionnaires done preoperatively, and at 1-, 3-, 6-, and 12-month intervals [57]. Improved physical function was seen up to 12 months in patients who underwent VATS compared to open lobectomy. Additionally, pain favored VATS over thoracotomy even up to 12 months [41].

Learning curve

The feasibility of VATS lobectomy has been well established; the procedure has proven to be safe and can be

performed without compromising oncologic efficacy. Yet in the United States, only 30% of lobectomies are performed VATS [11]. One factor for this low penetrance into general thoracic practice is the technical complexity of the operation [59]. In 2006, Ferguson [60] compared the results of a single self-taught consultant surgeon to four surgical trainees. The effect of experience was demonstrated by the reduction in operative times and blood loss for the consultant over time. Similarly, for trainees, VATS lobectomy had no adverse impact on mortality, blood loss, or hospital length of stay.

Training in VATS lobectomy is offered in most US cardiothoracic training programs today. There are also 6-month to 12-month fellowships that specialize in advanced VATS procedures. For practicing thoracic surgeons, there are technical courses offered by professional societies and other practicing surgeons. Most surgeons feel that it takes about 50 VATS lobectomies to be comfortable with the procedure [44]. Specific technical concerns do exist. Bleeding from the pulmonary artery can occur more easily and be more difficult to control [61]; however, the rate of major bleeding is less than 1%.

Conversion rates from VATS to open lobectomy range from 0% to 15.7% [55]. Reasons for conversion include technical factors such as failure to progress and uncontrollable bleeding, which tend to decrease with experience. However, anatomic factors such as extent of tumor, mediastinal involvement, calcified lymph nodes, and complete fusion of the fissures do persist.

Immunomodulation

The biologic impact of VATS versus open lobectomy has been examined in multiple *in vivo* trials [53, 62–64]. VATS lobectomy was associated with reduced impairment of cell-mediated immunity as demonstrated by improved postoperative CD4 counts, natural killer cell function, and improved cellular cytotoxicity [62, 64]. Likewise, smaller increases in acute phase reactants (interleukin 6, C-reactive protein) were seen with VATS when compared to thoracotomy [53, 65]. Although these findings may explain the improved recovery seen with VATS lobectomy, whether this translates into long-term survival is unknown.

Chest wall involvement and other advanced resections

The effects of avoid rib spreading with thoracotomy is touted as one of the main advantages to the VATS approach. Chest wall involvement has classically been felt to be a contraindication to VATS, given the need for en bloc resection with the involved portions of rib. There is, however, evidence that each intercostal nerve that is protected from rib spreading improves postoperative pain. By removing only the involved ribs and limiting trauma from retraction

of the chest wall some surgeons feel there may be a functional recovery advantage for the patient. Yendamuri et al. [66] reported their experience with three patients who underwent thoracoscopic lobectomy with en bloc chest wall resection. Two patients had undergone neoadjuvant therapy prior to resection and one required a reexploration for a chest wall hematoma. All patients were off of narcotic pain medications by 3 weeks postoperatively. This procedure is not appropriate for patients requiring large chest wall resection (> 4 ribs) or post-scapular resection requiring reconstruction.

Bronchoplastic (sleeve) procedures for central lung cancers are routinely performed for parenchymal preserving curative resection [67]. Small series of VATS bronchoplastic resections have been published [68]. Authors describe the multiple technical challenges inherent in this approach. Currently it is limited to hilar tumors without evidence of vascular invasion. Additionally, VATS has been extended to pneumonectomy as well as sublobar resection [69, 70].

Robotic lobectomy

Experience with utilizing robotic technology for lobectomy is still evolving and the data are not as robust as for the VATS approach. Proponents for developing this procedure emphasize that the three-dimensional visualization, improved degrees of freedom of the instruments, and ease of fine dissection facilitate the performance of VATS lobectomy. At this point, the published experience is limited to small series [71, 72].

As with all robotic procedures, a steep learning curve exists. Gharagozloo et al. [72] published their experience with 100 robot-assisted lobectomies. The technique included utilizing the robot for the mediastinal, subcarinal, and hilar dissection followed by conversion to VATS lobectomy through an access incision for division of vascular, parenchymal, and bronchial structures. In their experience the morbidity and mortality were 21% and 3%, respectively.

Some notable disadvantages to robotic lobectomy are the difficulty in lung manipulation, insertion of staplers, and requirement for a skilled assistant as the surgeon is remote from the operative field. However, there have been over 1500 robotic surgical systems sold in the United States, and as more thoracic surgeons begin adopting robotics for mediastinal procedures such as thymectomy, we can expect this field to continue to expand [73].

Conclusions

Lung cancer remains one of the predominant causes of cancer death in the United States today. With the emerging evidence for low-dose CT screening, and the large

population of current and former smokers at risk, we will hopefully begin seeing larger numbers of patients with early-stage disease. Although no large randomized controlled trial exists, there is a growing body of evidence to support that video-assisted thoracic surgery lobectomy is oncologically equivalent to thoracotomy, has similar mortality rates, and may be superior with respect to surgical morbidity. It may be advantageous in elderly and high-risk populations but this is reported only in highly selected series. It is important to recognize that, as with all highly technical procedures, a learning curve exists and a certain level of expertise is necessary to obtain the results equal to those reported from high-volume centers of excellence.

Disclosure No potential conflicts of interest relevant to this article were reported.

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