

Operative Techniques in Early-Stage Lung Cancer

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Key Words

Lung cancer, thoracoscopic surgery, lobectomy, minimally invasive surgery, outcomes, survival

Abstract

Lung cancer is the most common cause of death by malignancy, responsible for more deaths than the next 4 causes combined and predicted to account for nearly 220,000 new cancer diagnoses and 160,000 deaths in 2009. The cornerstone of therapy for early-stage lung cancer is lobectomy and mediastinal lymph node dissection. Although lobectomy is considered the standard procedure, segmentectomy may be appropriate for selected patients. Conventional approaches to resection may be used, including posterolateral and muscle-sparing thoracotomy. However, minimally invasive lobectomy and segmentectomy procedures are now commonly used with superior outcomes. (*JNCCN* 2010;8:807–813)

Lung cancer is the most common cause of death by malignancy, responsible for more deaths than the next 4 causes combined and predicted to account for nearly 220,000 new cancer diagnoses and 160,000 deaths in 2009.¹ For patients with early-stage non–small cell lung cancer (NSCLC), lobectomy with mediastinal lymph node dissection is considered the optimal treatment.² Segmentectomy, anatomic sublobar resection of one or more bronchopulmonary segments, has a role in the management of some patients with early-stage NSCLC.^{2,3}

Thoracoscopic lobectomy has been successfully performed worldwide for more than a decade, has emerged as a reasonable option for the management of early-stage NSCLC,^{4,5} and is supported by evidence-based

treatment guidelines.² Advantages of thoracoscopic lobectomy compared with thoracotomy include less postoperative pain,^{6,7} better pulmonary function,^{7,8} shorter hospitalization,^{4–11} and improved delivery of adjuvant chemotherapy to eligible patients.^{12,13}

Despite these outcomes, the advantages of thoracoscopic lobectomy seem to be underused. From 1999 to 2006, only 20% of all lobectomies for NSCLC were performed thoracoscopically by the board-certified thoracic surgeons participating in the general thoracic surgery component of The Society of Thoracic Surgeons (STS) database.¹⁴ Recent assessment of morbidity after thoracoscopic lobectomy showed superior results for many outcomes compared with thoracotomy.^{15–22} This article analyzes the various strategies of surgical resection for patients with early-stage NSCLC.

Evidence for Lobectomy

The debate regarding the optimal resection technique for early-stage NSCLC was addressed in a prospective randomized trial conducted by the Lung Cancer Study Group (LCSG) comparing limited resection with lobectomy for patients with peripheral stage IA (T1N0) NSCLC documented at surgery.²³ In this study, 276 patients were randomized, with 247 eligible for analysis. Patients who underwent limited resection had a 75% increase in recurrence rates ($P = .02$) associated with a tripling of the local recurrence rate ($P = .008$). In addition, a 50% increase in cancer-specific death was seen ($P = .09$, one-sided) compared with patients who underwent lobectomy ($P = .10$, one-sided was the pre-defined threshold for statistical significance for this equivalency study).²³

This study established lobectomy as the preferred operation for patients with early-stage NSCLC. Nevertheless, some patients are considered poor candidates

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for lobectomy based on pulmonary function, previous resections, or other medical conditions. In these patients, limited resection procedures (segmentectomy, or nonanatomic wedge resection) have been used if negative surgical margins are achievable.

Is Segmentectomy Acceptable in Selected Patients?

Pulmonary segmentectomy was originally introduced more than 70 years ago for the treatment of benign lung conditions.²⁴ Later, Jensik et al.^{25,26} and Peters²⁷ independently suggested that anatomic pulmonary segmentectomy could be effectively applied to small primary lung cancers when acceptable surgical margins were achievable. Since then, numerous studies have been performed to define the indications for segmentectomy and identify the patients in whom the procedure would not result in increased risk for local recurrence, as shown in the LCSG trial.²³

Okada et al.²⁸ analyzed the outcomes of 1272 patients with lung cancer who underwent resection with lobectomy or segmentectomy. The authors concluded that segmentectomy was reasonable for patients with lesions smaller than 2 cm, with 5-year survival rates greater than 93%. In patients with tumors larger than 3 cm, the survival rate after lobectomy (81.3%) was considered superior to that after segmentectomy (62.9%). To better define the role of segmentectomy, Okada et al.²⁹ conducted a multi-institutional study involving 567 patients with clinical stage IA ($T < 2$ cm) NSCLC who underwent lobar or sublobar resection, with equivalent 5-year survival rates (83.4% vs. 85.9%, respectively), and concluded that segmentectomy should be considered in these patients. Neither study was able to define parameters for segmentectomy other than tumor size.

Nakayama et al.³⁰ analyzed the outcomes of 63 patients with adenocarcinoma who underwent sublobar resection of clinical stage IA ($T < 2$ cm). In addition to limiting the analysis to adenocarcinoma, they further classified the tumors as either “air-containing type” (46 patients) or “solid-density type” (17 patients) according to the tumor shadow disappearance rate on high-resolution CT. After resection, 38 of the 46 air-containing tumors were found to be bronchoalveolar carcinomas. Furthermore, the 5-year survival rate for patients with air-containing

tumors was 95%, compared with 57% for those with solid-density tumors.

Currently, no consensus exists on selection criteria for sublobar resection. Although the studies mentioned earlier suggest that segmentectomy may be appropriate in selected patients with tumors smaller than 2 cm, the results have not been validated in North America or Europe. Because of poor pulmonary function, certain clinical situations may be appropriate for sublobar resection, and in these circumstances segmentectomy is preferred over nonanatomic wedge resection.² Sublobar resection may be the optimal therapy in patients who have poor pulmonary function and small lesions in the superior segment of the lower lobe, because lower lobectomy is poorly tolerated. In addition, patients with a history of previous pulmonary resections may be better candidates for sublobar resection than for lobectomy.

To improve patient selection for limited resection (as opposed to lobectomy), CALGB is conducting a phase III trial (CALGB 140503) of lobectomy versus sublobar resection for peripheral NSCLC of 2 cm or smaller. In this study, patients with pathologic stage IA ($T \leq 2$ cm), confirmed by intraoperative frozen section of appropriate N1 and N2 stations, are randomized to either lobectomy or sublobar resection, which could include either segmentectomy or nonanatomic wedge resection.

Thoracoscopic Approaches

Minimally invasive procedures using operative telescopes and video technology may be described as thoracoscopic procedures or video-assisted thoracic surgery (VATS). For clarity, the terms VATS or *thoracoscopic* should only refer to totally thoracoscopic approaches, where visualization is dependent on video monitors and rib spreading is avoided entirely. *Thoracoscopic lobectomy* is defined as the anatomic resection of an entire lobe of the lung, using a videoscope and an access incision, without the use of a mechanical retractor and without rib spreading. To be considered a viable alternative to conventional lobectomy, thoracoscopic lobectomy must be applied with the same oncologic principles: individual vessel ligation, complete anatomic resection with negative margins, complete hilar lymph node dissection, and appropriate management of the mediastinal lymph nodes.⁵

Thoracoscopic Lobectomy

Indications: The indications for thoracoscopic lobectomy are similar to those for lobectomy using the open approach: patients with known or suspected lung cancer (clinical stage I) that seems amenable to complete resection by lobectomy. Preoperative staging and patient selection for thoracoscopic lobectomy should be conducted as for conventional thoracotomy.^{2,5} Tumor size may preclude the option of thoracoscopic lobectomy in some patients, because some large specimens may not be amenable to removal without rib spreading; however, no absolute size criteria are used.

Contraindications: Absolute contraindications to thoracoscopic lobectomy include the inability to achieve complete resection with lobectomy; T3 or T4 tumors; active N2 or N3 disease; and inability to achieve single-lung ventilation. Relative contraindications include tumors that are visible at bronchoscopy, presence of hilar lymphadenopathy that would complicate vascular dissection (benign or malignant), prior thoracic irradiation, and the use induction therapy. Prior thoracic surgery, use of induction chemotherapy or radiation therapy, incomplete or absent fissures, and benign mediastinal adenopathy should not be considered contraindications.

Strategy for Thoracoscopic Lobectomy or Segmentectomy

The operative strategy for thoracoscopic lobectomy has been previously described.^{3,5,31-33} Briefly, single-lung anesthesia is established using a dual-lumen endotracheal tube or bronchial blocker. The patient is positioned in full lateral decubitus position with slight flexion of the table at hip level, which provides splaying of the ribs to improve thoracoscopic access and exposure. Port placement is a matter of surgeon preference. Most surgeons use 3 or 4 incisions, although lobectomy can usually be accomplished using only 2. The first incision, a 10-mm port access used predominantly for the thoracoscope, is placed in the 7th or 8th intercostal space in the midaxillary line. The second incision, an anterior access incision (4.5–6.0 cm) for dissection and specimen retrieval, is placed in the 5th or 6th intercostal space. No retractors of any kind are used.

Instrumentation for thoracoscopic lobectomy is critical to successful completion of the procedure. The thoracoscope should be a 30° angled scope to

optimize the ability to achieve panoramic visualization during dissection and to minimize competition with the operative instruments. A spectrum of surgical instruments may be used for dissection, including conventional instruments and dedicated thoracoscopic or laparoscopic instruments. Using curved instruments for retraction during dissection is especially beneficial because it will minimize the tendency for instruments to compete or collide with each other. Reticulating thoracoscopic (linear) mechanical staplers are used to control the vessels (2.0- or 2.5-mm staples), bronchus (3.5- or 4.8-mm staples), and fissure.

Individual vessel dissection is usually not performed through the fissure, but rather beginning with the anterior hilum and continuing posteriorly. For any anatomic thoracoscopic lobectomy, hilar dissection is begun with mobilization of the pulmonary vein. For upper lobectomy, the lung is reflected posteriorly and inferiorly to facilitate dissection. For lower lobectomy, the lung is retracted superiorly. Moving the thoracoscope to the anterior incision may improve visualization of the superior hilum and facilitate placement of the linear stapler for upper lobectomy, if introduced through the midaxillary port. At the completion of the procedure, the lobectomy specimen is removed using a protective bag to prevent port site recurrence. Complete mediastinal lymph node dissection is also performed, either before the resection or at the conclusion of the lobectomy.

The technique for thoracoscopic segmentectomy uses the fundamentals of thoracoscopic lobectomy previously reported.^{3,31,33} The standard segmentectomies performed with this technique include lingula-sparing left upper lobectomy, lingulectomy, superior segmentectomy, and basilar segmentectomy. Other individual segmental resections, such as posterior or anterior upper lobe segmentectomy, are feasible but less commonly performed.

The general strategy, instrumentation, and positioning of thoracoscopic segmentectomy are similar to those of thoracoscopic lobectomy. On establishing thoracoscopic access, full exploration is undertaken to exclude indications of unresectability, such as pleural carcinomatosis or other evidence of metastatic disease. For each anatomic sublobar resection, the segmental pulmonary vein of interest is the first hilar structure of interest. To improve access to the hilum,

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the pleura is divided at the pleural–parenchymal reflection, adding length to the hilum and exposing the vein for staple ligation using a linear endoscopic stapler. Subsequent dissection is dependent on the specific segments of interest. Parenchymal resection is then performed with the stapling device. Identification of the segmental borders for parenchymal division may be enhanced with temporary pulmonary reinflation; however, the visible venous anatomy of the exposed segments, including the segment being removed and the adjacent segment being preserved, will also guide this process.

Quality of Life After Thoracoscopic Lobectomy

The safety and efficacy of thoracoscopic lobectomy has been established for patients with early-stage lung cancer. Although no prospective, randomized series compare thoracoscopic lobectomy with conventional approaches, several published single- and multi-institutional experiences have concluded that thoracoscopic lobectomy is a reasonable strategy for patients with clinical stage I lung cancer.

Length of Stay and Chest Tube Duration

CALGB reported on the results of a multi-institutional series of 97 patients who underwent thoracoscopic lobectomy.¹⁰ In this series, mortality was 2%, operative time was 130 minutes, and median length of stay was 3 days. Onaitis et al.⁵ reported the results of thoracoscopic lobectomy in 500 consecutive patients. The 30-day mortality was 1%, with no intraoperative deaths. The conversion rate was less than 2%, and no cases were emergent. The median chest tube duration was 2 days and median length of stay was 3 days.

Postoperative Pain

Demmy and Curtis⁶ reported on their results in a series of patients who underwent either thoracoscopic lobectomy or conventional thoracotomy. In this series, the percentage of patients reporting severe pain was 6% after thoracoscopic lobectomy and 65% after thoracotomy. Moreover, the percentage of patients reporting minimal or no pain was 63% after thoracoscopic lobectomy and 6% after thoracotomy. Other studies analyzing acute pain have concluded that thoracoscopic lobectomy causes either less pain or lower analgesia requirement in the early postoperative period.^{6–8}

Pulmonary Function

It is intuitive that diminished pain and smaller incisions should lead to better postoperative respiratory mechanics for patients undergoing minimally invasive lung resections. This is shown by testing performed immediately after surgery and up to 3 months postoperatively. In a prospective series of 47 patients assigned to either VATS lobectomy or axillary thoracotomy published in 1996, Tschernko et al.⁸ showed that at all time-points up to 72 hours after lung resection, the VATS group showed superior oxygen saturation. Furthermore, forced expiratory volumes over 1 second (FEV1) have been studied and compared. Nagahiro et al.⁷ showed that at 14 days postoperatively, the patients with VATS recovered 95% of their preoperative FEV1 compared with 80% for those undergoing thoracotomy. Findings from Nomori et al.¹¹ support the improved recovery of FEV1 in patients undergoing thoracoscopic lobectomies out to 3 months after surgery.

Postoperative Morbidity

Several studies have recently shown that the incidence of postoperative complications is lower after thoracoscopic lobectomy than with thoracotomy.^{15–22} One study, using a case-matched strategy, compared 122 patients undergoing thoracoscopic surgery and 122 undergoing thoracotomy.¹⁵ Overall, complications were lower in the thoracoscopic group (17.2% vs 27.9%; $P = .046$). Another retrospective, matched, case-control study focusing on elderly patients (aged 70 years) evaluated the perioperative outcomes after lobectomy with thoracoscopy and thoracotomy.¹⁶ After matching based on age, gender, presence of comorbid conditions, and preoperative clinical stage, each group comprised 82 patients. Thoracoscopic lobectomy resulted in a significantly lower rate of complications compared with thoracotomy (28% vs. 45%; $P = .04$). No patients undergoing thoracoscopic lobectomy had higher than grade 2 complications, whereas 7% of complications in the open lobectomy group were grade 3 or higher. No perioperative deaths were associated with thoracoscopic lobectomy compared with an in-hospital mortality rate of 3.6% associated with thoracotomy.

Whitson et al.²¹ analyzed the outcomes of 147 unmatched patients who underwent lobectomy, including 88 by thoracotomy and 59 by thoracoscopy.

Thoracoscopic lobectomy was associated with a lower incidence of pneumonia but showed no difference in other complications, including blood loss, atrial fibrillation, or number of ventilator days.

Using a prospective database, the outcomes of patients who underwent lobectomy at Duke from 1999 to 2009 were analyzed with respect to postoperative complications.¹⁷ Propensity-matched groups were analyzed based on preoperative variables and stage. Of the 1079 patients in the study, 697 underwent thoracoscopic lobectomy and 382 underwent lobectomy by thoracotomy.

In the overall analysis, thoracoscopic lobectomy was associated with a lower incidence of atrial fibrillation ($P = .01$), atelectasis ($P = .0001$), prolonged air leak ($P = .0004$), transfusion ($P = .0001$), pneumonia ($P = .001$), sepsis ($P = .008$), renal failure ($P = .003$), and death ($P = .003$). In the propensity-matched analysis comparing 284 patients in each group based on preoperative variables, 196 patients (69%) who underwent thoracoscopic lobectomy had no complications versus 144 patients (51%) who underwent thoracotomy ($P = .0001$). In addition, thoracoscopic lobectomy was associated with a lower incidence of atrial fibrillation (13% vs. 21%; $P = .01$), less atelectasis (5% vs. 12%; $P = .006$), fewer prolonged air leaks (13% vs. 19%; $P = .05$), fewer transfusions (4% vs. 13%; $P = .002$), less pneumonia (5% vs. 10%; $P = .05$), less renal failure (1.4% vs. 5%; $P = .02$), shorter chest tube duration (median 3 vs. 4 days; $P < .0001$), and shorter length of hospital stay (median 4 vs. 5 days; $P < .0001$).

Similar results were obtained when the STS database was analyzed by Paul et al.¹⁸ All patients undergoing lobectomy as the primary procedure through thoracoscopy or thoracotomy were identified in the STS database from 2002 to 2007. After exclusions, 6323 patients were identified: 5042 thoracotomy and 1281 thoracoscopy. A propensity analysis was performed, incorporating preoperative variables, and the incidence of postoperative complications was compared. Matching based on propensity scores produced 1281 patients in each group for analysis of postoperative outcomes. After VATS lobectomy, 945 patients (73.8%) had no complications compared with 847 (65.3%) who underwent lobectomy through thoracotomy ($P < .0001$). Compared with open lobectomy, VATS lobectomy was associated with a lower incidence of arrhythmias

($n = 93$ [7.3%] vs. 147 [11.5%]; $P = .0004$), reintubation ($n = 18$ [1.4%] vs. 40 [3.1%]; $P = .0046$), and blood transfusion ($n = 31$ [2.4%] vs. $n = 60$ [4.7%]; $P = .0028$), and a shorter length of stay (4.0 vs. 6.0 days; $P < .0001$) and chest tube duration (3.0 vs. 4.0 days; $P < .0001$). No difference was seen in operative mortality between the groups.

Finally, Berry et al.¹⁹ reported a recent analysis of high-risk patients older than 70 years. During the study period, 338 patients older than 70 years (mean age 75.7 ± 0.2) underwent lobectomy (219 thoracoscopy, 119 thoracotomy). Operative mortality was 3.8% (13 patients) and morbidity was 47% (159 patients). Patients with at least 1 complication had increased length of stay (8.3 ± 0.6 vs. 3.8 ± 0.1 days; $P < .0001$) and mortality (6.9% [11 of 159] vs. 1.1% [2 of 179]; $P = .008$). Significant predictors of morbidity by multivariable analysis included age (odds ratio, 1.09; $P = .01$) and thoracotomy as a surgical approach (odds ratio 2.21; $P = .004$). Thoracotomy remained a significant predictor of morbidity when the propensity to undergo thoracoscopy was considered (odds ratio, 4.9; $P = .002$).

Administration of Adjuvant Chemotherapy

One of the most promising advantages associated with thoracoscopic lobectomy relates to the ability of patients to tolerate adjuvant therapy. A recent study compared the ability to deliver adjuvant chemotherapy in 100 patients who underwent complete resection for NSCLC through either thoracotomy or thoracoscopy.¹² Those undergoing thoracoscopic lobectomy had significantly fewer delayed (18% vs. 58%; $P < .001$) and reduced (26% vs. 49%; $P = .02$) chemotherapy doses. A higher percentage of patients undergoing thoracoscopic resection received 75% or more of their planned adjuvant regimen without delayed or reduced doses (61% vs. 40%; $P = .03$). Another group evaluating adjuvant chemotherapy received after VATS noted that 85% of patients received all cycles of planned chemotherapy, with or without some delay.¹³

Cost

A retrospective analysis of actual cost and prospectively collected health-related quality of life (QOL) outcomes was recently reported by Burfeind et al.³⁴

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Between 2002 and 2004, 113 patients underwent lobectomy through thoracoscopy or thoracotomy and completed QOL assessments both preoperatively and 1 year postoperatively. Cost-utility analysis was performed by transforming a global QOL measurement to an estimate of utility and calculating a quality-adjusted life year for each patient. Total costs (\$US) were significantly greater for the strategy of thoracotomy vs. thoracoscopy (\$12,119 vs. \$10,084, respectively; $P = .0012$). The use of minimally invasive techniques for the 50,000 lobectomies performed in the United States each year was estimated to represent a savings of approximately \$100 million.

Summary

Minimally invasive surgical resections have been shown to be safe and effective for patients with early-stage lung cancer. Thoracoscopic lobectomy is designed to achieve the same oncologic result as conventional lobectomy: complete hilar dissection and individual vessel control. The recognized advantages of thoracoscopic anatomic resection include less short-term postoperative pain, shorter hospital stay, faster return to full activity, preserved pulmonary function, and fewer postoperative complications. In addition, thoracoscopic lobectomy may preserve the immunologic response and improve compliance with adjuvant therapy. Although no prospective randomized studies have compared the thoracoscopic approach with conventional thoracotomy, the recent demonstration of superior postoperative outcomes using propensity-matched populations suggests that thoracoscopic lobectomy should now be considered the standard for patients with early-stage lung cancer.

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