Value Dossier on Thoracic Surgery
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CONCISE SUMMARY

Despite extraordinary progress made in the areas of prevention, early detection, and treatment, cancer remains the second leading cause of death in the United States, with an annual mortality of more than 500,000 Americans. Lung cancer is the third most common cancer, with newly diagnosed cases expected to exceed 215,000 in the U.S. this year. Only prostate and breast cancer have a higher incidence rate. Often diagnosed in later stages, lung cancer is the leading cause of cancer mortality, accounting for approximately 30 percent of all cancer deaths. Globally, lung cancer claimed the lives of an estimated 1.3 million people in 2005 alone.

SEARCH CRITERIA

The Medline (PubMed) and EMBASE clinical databases were searched by IRS, using strategies appropriate to each database. PubMed was searched using the following terms: Bronchoscopy*, Thoracoplasty, Thoracoscopy*, Thoracostomy, Thymectomy, Thymoma/Surgery, Pulmonary Disease, Chronic Obstructive/Surgery*, Pneumonectomy*, or Emphysema/Surgery* and yielded 7931 results. Subject terms marked with an * were required to be major subject areas of the reference. A second search using the terms “Thoracic Surgery, Video-Assisted” returned 1471 results. The total results for these two searches was 8274 references. Limiting these references to studies on English manuscripts on humans that were either meta-analyses, practice guidelines, HTA’s or randomized controlled trials reduced the number of results to 433 references.

Two relevant health technology assessments were obtained from searches of inahta.org using the terms thoracoscopy or VATS. Searches of the PubMed database using the terms thoracoscopy or VATS and meta-analysis returned one systematic review. References provided by IRS which directly compared the outcomes of VATS versus open lung surgeries included one meta-analysis and five review articles. Thus, the total number of articles with pertinent results regarding VATS versus open lung surgeries include one meta-analysis, two health technology assessments, and six systematic and non-systematic reviews. Tables 10 and 11 are summaries of these references.

For this report, one meta-analysis, and six systematic reviews were selected for comparison of efficacy, safety, quality of life, and economic outcomes for VATS versus open lobectomy surgeries. These reports vary in the strictness of their inclusion criteria. Hence, while there is overlap in the individual studies included in different reviews, there are also many differences.

Furthermore, there have only been four RCTs investigating VATS versus open lobectomy; the majority of studies included in either the meta-analysis or the systematic reviews are non-RCTs. Therefore, the various outcomes reported are likely influenced by selection bias, and this is an important limitation.

Of these reports, the two that analyze individual studies and report composite results are the meta-analysis by Cheng et al and a systematic review by Whitson et al. The remainder of systematic reviews report results from individual studies and draw qualitative conclusions from these data. The composite results from the reports by Cheng et al and Whitson et al form the foundation of this analysis. These results, which include efficacy, safety, quality of life, and economic outcomes, are specifically outlined in the tables on pages 63-69. Pertinent qualitative conclusions made by the other reports are addressed in the text.

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BACKGROUND INFORMATION
- Anatomy and Physiology of the Lungs
- Lung Cancer
Lungs. The right lung is shorter, broader, and has a larger bronchi, blood vessels, lymphatics, and nerves enter the hilum, or root, on the medial side. This is where the only point of attachment for each lung is at the vertebra, the trachea divides into the right and left primary bronchi. The bronchi branch into smaller and smaller passages until they terminate in tiny air sacs called alveoli. The cartilage and mucous membrane of the primary bronchus are similar to that in the trachea. As the branching progresses through the bronchial tree, the amount of hyaline cartilage in the walls decreases until it is absent in the smallest bronchioles. As the cartilage content decreases, the amount of smooth muscle increases. The mucous membrane also undergoes a transition from ciliated pseudostratified columnar epithelium to simple cuboidal epithelium to simple squamous epithelium. The alveolar ducts and alveoli consist primarily of simple squamous epithelium, which permits rapid diffusion of oxygen and carbon dioxide. Exchange of gases between the air in the lungs and the blood in the capillaries occurs across the walls of the alveolar ducts and alveoli. The two lungs, which contain all components of the bronchi, bronchioles and alveoli. The primary bronchi are similar to that in the trachea. The left lung has two lobes. Each lung is enclosed by a double-layered serous membrane, called the pleura. The visceral pleura is firmly attached to the surface of the lung. At the hilum, the visceral pleura is continuous with the parietal pleura that lines the wall of the thorax. The small space between the visceral and parietal pleurae is the pleural cavity. It contains a thin film of serous fluid that is produced by the pleura. The fluid acts as a lubricant to reduce friction as the two layers slide against each other, and it helps to hold the two layers together as the lungs inflate and deflate (see figure 2).

**Figure 1:** Anatomy of the left lung, showing the bronchi, bronchioles and alveoli.

**Figure 2:** Illustration of the lungs, showing the anatomy of the pleura.

**LUNG CANCER**

Lung cancer is a malignant tumor of the lungs. Cancers originating in the lung are divided into two major types: Non-small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC).

**Non-small Cell Lung Cancer (NSCLC)**

NSCLCs account for 85 to 90% of lung cancers and are classified according to cell type within the cancer and the cells’ appearance microscopically. There are two major types of NSCLCs. The first, known as non-squamous carcinoma, includes adenocarcinoma, large-cell carcinoma, and other cell types. This is the most common type of lung cancer within the United States and is the most frequently occurring cell type among nonsmokers. Non-squamous carcinoma is usually found in the outer region of the lung. The second type of NSCLC is known as squamous cell, or epidermoid carcinoma, and is generally associated with smoking. Squamous cell carcinoma begins in the squamous cells lining the respiratory tract passages in the middle of the lungs near the bronchi.

**Small Cell Lung Cancer (SCLC)**

SCLC, also known as oat cell cancer, oat cell carcinoma, or small cell undifferentiated carcinoma, accounts for 10 to 15% of all lung cancers. Most SCLC is caused by smoking. SCLC is “an anaplastic, highly malignant, and usually bronchogenic carcinoma composed of small ovoid cells with scanty cytoplasm.” Small cell lung cancer is distinct from the more common non-small cell lung cancer by its rapid doubling time, high growth fraction, early development of widespread metastasis, and dramatic initial response to chemotherapy and radiation. However, most patients die from recurrent disease. The cancer cells multiply rapidly, form large tumors, and metastasize to lymph nodes and other organs, such as bones, brain, adrenal glands, and liver. Therefore, surgery is rarely an option and never the sole treatment provided.

**ETIOLOGY**

**NSCLC**

The primary cause of lung cancer is tobacco smoking, and this feature is characteristic of as many as 90% of patients (78% of men and 90% of women). In addition, passive smoking or secondhand smoke accounts for up to 15% of lung cancers in persons who do not smoke. Other causes of lung cancer include exposure to asbestos and radon.

**SCLC**

Tobacco smoking is the primary cause of SCLC lung cancer. All lung cancer subtypes occur with increased frequency in uranium miners, but SCLC is the most common of these, and the incidence is further increased in miners who smoke. Exposure to radon, an inert gas resulting from the decay of uranium, is also purported to cause SCLC.
STATISTICS

Global Lung Cancer Statistics

Lung cancer is the most common cancer in the world with 1.2 million new cases diagnosed annually. Internationally, the highest rates of lung cancer in men occur in Europe—particularly eastern Europe—and North America. For women, North America and the European countries of Denmark, Hungary, Iceland, and the United Kingdom have the highest rates (see figure 3). In contrast, the lowest rates for both men and women are found in Africa and Asia. The poor prognosis associated with lung cancer translates into similar incidence and mortality patterns across all countries.8

US Lung Cancer Incidence and Prevalence

In 2008, lung cancer incidence rates were estimated to account for approximately 15% of all new cancers and 29% of all cancer deaths. Approximately 2 out of 3 people diagnosed with lung cancer are older than 65 years. Of the 215,020 estimated new cases of lung cancer annually, 53% are in men (114,690) and the remainder (100,330) occur in women.10, 11

In 2006, there were over half a million (535,700) hospitalizations which cited a diagnosis of lung cancer; this translates into a rate of 179.3 admissions per 100,000 population. Nearly 28 percent of lung cancer-related hospitalizations (149,900 admissions) were principally for lung cancer, accounting for $2.1 billion in hospital costs. In addition, there were 385,800 admissions for which lung cancer was a secondary diagnosis, accounting for an additional $4.0 billion in hospital costs (see table 1).12

Table 1: Characteristics of hospitalizations related to lung cancer compared to hospitalizations for all conditions, 2006.

<table>
<thead>
<tr>
<th>Hospital Stays Principally for Lung Cancer</th>
<th>Hospital Stays with a Secondary Diagnosis of Lung Cancer</th>
<th>Hospital Stays for All Conditions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>149,900</td>
<td>385,800</td>
<td>30,342,300</td>
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</table>

**UTILIZATION CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Mean Length of Stay, Days</th>
<th>Mean Cost Per Hospitalization</th>
<th>Aggregate Cost</th>
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<tbody>
<tr>
<td>7.5</td>
<td>$14,200</td>
<td>$2.1 Billion</td>
</tr>
<tr>
<td>5.9</td>
<td>$10,400</td>
<td>$4.0 Billion</td>
</tr>
<tr>
<td>5.1</td>
<td>$9,900</td>
<td>$297.6 Billion</td>
</tr>
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<table>
<thead>
<tr>
<th>% Admitted Through the ER</th>
<th>% Died in Hospital</th>
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<tbody>
<tr>
<td>41.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>60.2%</td>
<td>2.6%</td>
</tr>
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</table>

**PATIENT CHARACTERISTIC**

<table>
<thead>
<tr>
<th>Mean Age, Years</th>
<th>% 18 to 44 Years</th>
<th>% 45 to 64 Years</th>
<th>% 65 Years and Older</th>
<th>% of Patients Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.7</td>
<td>2.4%</td>
<td>34.6%</td>
<td>63.1%</td>
<td>53.6%</td>
</tr>
<tr>
<td>69.3</td>
<td>1.8%</td>
<td>29.7%</td>
<td>68.4%</td>
<td>52.8%</td>
</tr>
<tr>
<td>58.1</td>
<td>18.5%</td>
<td>30.2%</td>
<td>44.7%</td>
<td>46.4%</td>
</tr>
</tbody>
</table>

* Stays for neonates and maternal conditions have been excluded.

Figure 3: European age-standardized lung cancer incidence rates by gender, 2006.
Hospitalizations

The number of hospitalizations for which lung cancer was the principal diagnosis has remained largely stable between 1995 and 2006 (see figure 4). However, the number of hospitalizations for which it was the secondary diagnosis has increased by 15% over this time period.

The rate of hospital stays in 2006 across patient age is shown in figure 5. The total hospitalizations per 100,000 persons in the population for which lung cancer was either a principal or secondary diagnosis was 326.1 and 868.6, respectively. Patients over the age of 65 years were more likely to be hospitalized with a principal or secondary lung cancer diagnosis. These patients accounted for 253.3 (77.6%) of the hospitalizations with a lung cancer principal diagnosis and 708.8 (81.6%) of those with a lung cancer secondary diagnosis. Patients in the 45- to 64-year-old age bracket accounted for 69.3 (21.5%) of hospitalizations for principal diagnoses and 153.1 (17.6%) of hospitalizations for secondary diagnoses.

The rate of hospitalizations in 2006 across both gender and age is shown in figure 6. For patients older than 45 years of age, the rate of hospitalizations is higher for men than for women. In the 65+ year-old age group, the difference in the hospitalization rates between men and women for both principal and secondary diagnoses is more pronounced than in the 45 to 64 year-old age group. In the youngest age group, women have a slightly higher lung cancer hospitalization rate for both principal and secondary diagnoses.

Figure 4: Number of hospitalizations for lung cancer between 1995 and 2006.

Figure 5: The rate of lung cancer hospitalizations in 2006 as a function of age.

Figure 6: The rate of lung cancer hospitalizations in 2006 as a function of age and gender.
The hospitalization rate for lung cancer across geographic region within the United States is shown in figure 7. The Northeast observed the lowest hospitalization rate for principal diagnoses, whereas the South observed the highest. For secondary diagnoses of lung cancer, the West observed the lowest hospitalization rate while the Northeast observed the highest.

Figure 8 depicts the primary payers for lung cancer-related hospitalizations in 2006. Medicare was the primary payer for two-thirds of admissions, followed by private insurance, which was the primary payer for nearly a quarter of all lung cancer-related hospitalizations.

**Mortality**

Lung cancer is the leading cause of cancer deaths in both men and women. Lung cancer accounts for approximately 29% of all cancer deaths. In 2008, there were an estimated 161,840 deaths attributable to lung cancer. Of these, 114,690 were males, accounting for 31% of all cancer deaths among men. The remaining 100,330 were females, and comprised 27% of total deaths from cancer in women. These statistics reflect the fact that more people die from lung cancer than from breast, prostate, or colon cancer combined.

Although lung cancer deaths in men have been declining since 1991, they continue to rise among women and African Americans. Currently, men have a 1 in 13 chance of developing lung cancer, while women have a 1 in 16 chance. The rate of lung cancer increases with age. Currently, only 3% of all lung cancers are diagnosed in persons younger than 45 years. The average age at diagnosis is 71 years. Between 2001 and 2005, the median age of death for patients diagnosed with cancer of the lung or bronchus was 72 years.

The overall one-year survival rate between 1996 and 2004 from 17 SEER geographic regions was approximately 40% (the one-year mortality rate was 60%). The two-year survival rate was 25% (mortality rate of 75%). These one- and two-year survival rates have not improved in 10 years. Furthermore, the overall five-year survival rate is approximately 15% and has only improved marginally (see table 2). The five-year relative survival rates by ethnicity and gender are 13.4% for Caucasian men, 17.9% for Caucasian women, 10.4% for African American men, and 14.5% for African American women.

**1-Year Survival Rate**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>60.0%</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>66.0%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>20.7%</td>
</tr>
<tr>
<td>Uninsured</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

**2-Year Survival Rate**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>49.0%</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>50.0%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>36.9%</td>
</tr>
<tr>
<td>Uninsured</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

**5-Year Survival Rate**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>13.4%</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>17.9%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>10.4%</td>
</tr>
<tr>
<td>Uninsured</td>
<td>14.5%</td>
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</tbody>
</table>

**5-Year Survival Rate in Persons with Early Diagnosis/Treatment**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare</td>
<td>49.0%</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>50.0%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>36.9%</td>
</tr>
<tr>
<td>Uninsured</td>
<td>26.7%</td>
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</table>

**5-Year Survival Rate at an Early, Localized Stage**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate (%)</th>
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</thead>
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<tr>
<td>Medicare</td>
<td>13.4%</td>
</tr>
<tr>
<td>Private Insurance</td>
<td>17.9%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>10.4%</td>
</tr>
<tr>
<td>Uninsured</td>
<td>14.5%</td>
</tr>
</tbody>
</table>
LUNG CANCER DIAGNOSIS
- Screening and Early Detection
- Staging
LUNG CANCER DIAGNOSIS

SCREENING AND EARLY DETECTION

Lung cancer symptoms usually do not appear until the disease is in a late, non-localized stage. Approximately 85% of patients have advanced disease at diagnosis. Survival is strongly related to early diagnosis; patients without distant or loco-regional tumor spread who are treated with surgical resection have a five-year survival rate between 60% and 80%.

CURRENT SCREENING TECHNIQUES

Chest X Rays (Radiograph)
This is the most common screening technique for lung cancer. Generally, radiographs detect tumors in advanced stages. Radiograph films can distinguish the size, shape, and location of a tumor. However, this technique is limited in its ability to distinguish cancers from non-cancerous lesions.

Sputum Cytology
Sputum cytology has the ability to detect lung cancers not identified on chest x-rays. However, cytology cannot detect cancers that are located near the surface of the lungs. When positive, additional tests are required to determine the tumor location.

Bronchoscopy
Bronchoscopy affords an endoscopic view of the lungs via a flexible tube passed through the nose (or oropharynx in an intubated patient) and throat into the main airways of the lungs. If abnormalities are detected, a biopsy may be performed either through the bronchoscope, through the chest into the lung, by removal and examination of an enlarged lymph node in the neck, or by performing a surgical excision.

ADVANCES IN SCREENING

Spiral or Helical Computed Tomography (CT) Scan
CT captures images of the lung during a single breath hold. It generates a three-dimensional image of the lungs and has the ability to detect tumors in the earliest stage of disease, while patients are still asymptomatic. However, some experts are concerned that screening may lead to over-diagnosis or false-positive findings, resulting in unnecessary biopsies. Several large scale clinical trials are ongoing to determine the efficacy of CT scans in the early detection of lung cancer, and to clarify the relationship between early detection and mortality.

Two major studies are the Prostate, Colorectal, Lung, and Ovarian (PLCO) Cancer Screening Trial and the National Lung Screening Trial.

Laser Induced Fluorescence Endoscopy (LiFE)
The LiFE bronchoscope procedure is performed under light sedation with local anesthesia, and biopsies are taken from lungs areas that appear abnormal. This technique has the advantage of improved detection of bronchial lesions and early invasive malignancies, and it has the ability to identify angiogenic squamous dysplasia, a premalignant stage of cellular development.

Molecular Markers
Molecular markers are known protein or gene biomarkers detected in sputum samples that may aid in predicting and diagnosing lung cancer.

CURRENT STATUS OF SCREENING FOR LUNG CANCER

No lung cancer screening test exists that has been proven to reduce the mortality rate from lung cancer. This is in contrast to mammography for breast cancer, which has been shown to reduce cancer mortality rates. Currently, no standard screening method for lung cancer is recognized by any major medical organization. The United States Preventive Services Task Force (USPSTF) of the Agency for Healthcare Research and Quality (AHRQ) states: “...the evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with either low dose computed tomography, chest x-rays, sputum cytology, or a combination of these tests.”

At the present time, the National Comprehensive Cancer Network (NCCN) panel does not recommend the routine use of screening CT as standard clinical practice. Available data are conflicting. Thus, conclusive data from ongoing trials are needed to further inform the benefits and risks associated with screening for lung cancer with low-dose CT. However, if a screening strategy is used, then the I-ELCAP screening protocol should be followed.

“In medical research, as with many industries, technological progression is developed in response to patients’ needs. In the case of lung cancer, we are trying hard to catch up with the disease by developing a detection tool that can do for lung cancer what the mammogram has done for breast cancer.”

Fred R. Hirsch, M.D., Ph.D., Professor of Medicine, University of Colorado Cancer Center

STAGING

Revised International System for Staging Lung Cancer
The Revised International System for Staging Lung Cancer was adopted in 1997 by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer. These revisions provide greater prognostic specificity for patient groups. However, the correlation between stage and prognosis predates the widespread availability of PET imaging.

TNM Staging System
The system used to describe the growth and spread of non-small cell lung cancer (NSCLC) is the American Joint Committee on Cancer (AJCC) TNM staging system. The TNM system describes three key pieces of information:

T
Indicates the size of the primary tumor and whether it has grown into nearby areas

N
Describes how much the cancer has spread to regional lymph nodes

M
Indicates whether the cancer has metastasized (the most common sites of metastasis are the liver, bones, and brain)

TNM Definitions—Primary Tumor

tX Primary tumor cannot be assessed, or the tumor is proven by the presence of malignant cells in the sputum or bronchial washings but is not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 A tumor that is 3 cm or smaller in greatest dimension, is surrounded by lung or visceral pleura, and is without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T2 A tumor with any of the following features of size or extent:
- Larger than 3 cm in greatest dimension
- Involves the main bronchus and is 2 cm or larger distal to the carina
- Involves the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 A tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or, tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4 A tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or, separate tumor nodules in the same lobe; or, tumor with a malignant pleural effusion
TNM Definitions—Regional Lymph Nodes
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
- **N2**: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3**: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

TNM Definitions—Distant Metastasis
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis present (Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).)

AJCC Stage Groupings
The tumor information (T), lymph node involvement (N), and the metastasis assessment (M) are grouped into the following stages shown in table 3.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Occult Carcinoma, Tis, N0, M0</td>
</tr>
<tr>
<td>I</td>
<td>Stage I, T1, N0, M0</td>
</tr>
<tr>
<td>IA</td>
<td>Stage IA, T1, N1, M0</td>
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<tr>
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<td></td>
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Table 3: AJCC Stage Groupings
LUNG CANCER TREATMENT
- Care Path by Stage
- First-line Treatment Modalities (U.S. 2003)
- Treatment Approaches
- Surgical Procedures
- Additional Therapies
CARE PATH BY STAGE

**STAGE 0 NSCLC TREATMENT**
Clinical stage grouping: Tis, N0, M0
2.7% of NSCLCs

Standard treatment options:
1. Surgical resection using the least extensive technique possible (segmentectomy or wedge resection) to preserve maximum normal pulmonary tissue because these patients are at high risk for second lung cancers.
2. Endoscopic photodynamic therapy.

**STAGE I NSCLC TREATMENT**
Clinical stage grouping:
- T1, N0, M0 (Stage IA)
- T2, N0, M0 (Stage IB)

Stage IA 13% of NSCLCs 67% 5-year survival
Stage IB 23% of NSCLCs 57% 5-year survival

Standard treatment options:
1. Lobectomy or segmental, wedge, or sleeve resection as appropriate.
2. Radiation therapy with curative intent (for potentially operable patients who have medical contraindications to surgery).
3. Clinical trials of adjuvant chemotherapy after resection.
4. Chemoprevention trials.
5. Endoscopic photodynamic therapy (under clinical evaluation in highly selected T1, N0, M0 patients).

**STAGE II NSCLC TREATMENT**
Clinical stage grouping:
- T1, N1, M0 (Stage IIA)
- T2, N1, M0 (Stage IIB)

Stage IIA >1% of NSCLCs 55% 5-year survival
Stage IIB 7% of NSCLCs 39% 5-year survival

Standard treatment options:
1. Lobectomy or pneumonectomy, or sleeve resection as appropriate.
2. Radiation therapy with curative intent (for potentially operable patients who have medical contraindications to surgery).

**STAGE IIIA NSCLC TREATMENT**
Clinical stage grouping:
- T1, N2, M0/T2, N2, M0/T3, N1, M0/T3, N2, M0

Stage IIIA 10% of NSCLCs 23% 5-year survival

Standard treatment options:
1. Surgery alone in operable patients without bulky lymphadenopathy.
2. Radiation therapy alone, for patients who are not suitable for neoadjuvant chemotherapy plus surgery.
3. Chemotherapy combined with other modalities.
4. Clinical trials of combined modality therapy.

**STAGE IIIA NSCLC TREATMENT: SUPERIOR SULCUS TUMOR**
Clinical stage grouping:
- T3, N0, M0 or T3, N1, M0

A special approach is merited for treatment of superior sulcus tumors

Standard treatment options:
1. Radiation therapy and surgery.
2. Radiation therapy alone.
3. Surgery alone (selected cases).
4. Chemotherapy combined with other modalities.
5. Clinical trials of combined modality therapy.

**STAGE IIIA NSCLC TREATMENT: CHEST WALL TUMOR**
Clinical stage grouping:
- T3, N0, M0 or T3, N1, M0

Selected patients with bulky primary tumors that directly invade the chest wall can obtain long-term survival with surgical management provided the tumor is completely resected.

Standard treatment options:
2. Surgery and radiation therapy.
3. Radiation therapy alone.
4. Chemotherapy combined with other modalities.
STAGE IIIB NSCLC TREATMENT (SEE FIGURE 12)
Clinical stage grouping: Any T, N3, M0/T4, any N, M0
Stage IIIB 20% of NSCLCs 5% 5-year survival
Standard treatment options:
1. Radiation therapy alone.
2. Chemotherapy combined with radiation therapy.
3. Chemotherapy and concurrent radiation therapy followed by resection.

STAGE IV NSCLC TREATMENT (SEE FIGURE 13)
Clinical stage grouping: Any T, any N, M1
Stage IV 27% of NSCLCs 1% 5-year survival
Standard treatment options:
1. External-beam radiation therapy, primarily for palliative relief of local symptomatic tumor growth.
2. Chemotherapy. The following regimens are associated with similar survival outcomes: Cisplatin plus vinblastine plus mitomycin; Cisplatin plus vinorelbine; Cisplatin plus paclitaxel; Cisplatin plus docetaxel; Cisplatin plus gemcitabine; Carboplatin plus paclitaxel.
3. Clinical trials evaluating the role of new chemotherapy regimens and other systemic agents. Initial results suggest newer nonplatinum-based chemotherapy regimens produce response and survival results like those produced by standard platinum-based regimens.
4. Endobronchial laser therapy and/or brachytherapy for obstructing lesions.
TREATMENT APPROACHES

Surgery, radiation therapy (RT), and chemotherapy are the three modalities commonly used to treat NSCLC. They can be used singly or in combination depending on disease severity.11

Other modalities are currently under investigation, although NCCN practice guidelines do not yet recommend their use as standard practice. These include photodynamic therapy and energy ablation systems (radiofrequency, microwave, and cryoblation).

MOST COMMON SURGICAL PROCEDURES

The most common surgical procedures for the treatment of lung cancer, along with their associated risks and benefits, are listed below.11

Lobectomy

Removal of one of the lobes of the lung. The patient’s lung function must be adequate before undergoing this procedure. The operation carries an overall mortality rate of 3% to 5%, and older patients have the highest risk.

Pneumonectomy

Removal of the entire lung. The procedure itself carries a mortality rate of 5% to 8%, with older patients having the highest risk. In such patients, recurrence almost always occurs.

Wedge Resection or Segmentectomy

Removal of only a small part of the lung. Consequently, nearly normal breathing function is preserved following the operation.

Video-assisted Thoracic Surgery

This is a minimally-invasive alternative to lobectomy.

THORACOTOMY PROCEDURES

The two basic types of thoracotomy surgery for the treatment of lung cancer are lobectomy and pneumonectomy. Lobectomy involves the removal of one of the lobes of the lung, while pneumonectomy involves the removal of an entire lung, for the purposes of both removing cancerous tissue and preserving surrounding tissue. Lobectomy and pneumonectomy are the procedures of choice for lung cancer since less aggressive pulmonary resections are associated with higher rates of locoregional recurrence and decreased long-term survival.12

Three basic thoracotomy approaches are utilized, and each must be performed in the operating room under general anesthesia. In limited anterior or lateral thoracotomy, a 6 to 8 centimeter intercostal incision is made. Then, after a large tidal volume, the lung is “popped out” through the incision and may then be biopsied. This approach is commonly used to diagnose diffuse interstitial lung disease, infectious diseases, or localized peripheral lung disease in immunosuppressed patients. Morbidity and mortality are very low, and patients require a chest tube for 24 to 48 hours following surgery. They often leave the hospital in three to four days.18

Open thoracotomy procedures are expected to decline over the period between 2005 and 2014 at a rate of 2.6% annually. The number of these procedures is expected to decline more rapidly during the second half of the forecast period, as thoracotomy is increasingly supplanted by less invasive thoracoscopy.18

PULMONARY RESSECTION

Anatomic resections of the lung, including pneumonectomy and lobectomy, are the standard operative techniques employed to treat both neoplastic and non-neoplastic diseases of the lung. Surgeons must be keenly familiar with the anatomy of the pulmonary vasculature, the bronchi, and the relation between the two. Posterior interlobar thoracotomy remains the standard incision for anatomic pulmonary resections. However, safe and complete resections can also be performed through a variety of smaller incisions, including posterior muscle-sparing, anterior muscle-sparing, and axillary thoracotomies. In the majority of cases, the thorax is entered at the fifth intercostal space, an approach that affords excellent exposure of the hilar structures. The anterior muscle-sparing thoracotomy is generally placed at the fourth intercostal space due to the more caudal positioning of the anterior aspects of the ribs. Although a sternotomy may be employed to gain access to the upper lobes, it does not provide adequate exposure of the lower lobes or the bronchi.18

SURGICAL PROCEDURES

RIGHT UPPER LOBECTOMY

Right Interlobar Fissure

Figure 14 shows the surgeon’s view of the right interlobar fissure. The fissures have been completed, and the segmental arteries to the upper, middle, and lower lobes have been identified. The posterior ascending branch to the upper lobe most commonly varies with respect to size and origin. This vessel may be absent or diminutive and may arise from the superior segmental branch to the lower lobe. The posterior segmental vein draining into the superior pulmonary vein (not seen) is clearly visualized in the right upper lobe, lateral to the pulmonary artery branches.18
is visible. Care should be taken not to injure this vessel during division of the fissure. It can be ligated via this approach if it cannot be adequately exposed from the fissure. Both the truncus anterior and the posterior ascending branch of the pulmonary artery lie directly anterior to the right upper-lobe bronchus, and care should be taken not to injure these vessels during bronchial encirclement. The bronchial arteries course along the medial and lateral edges of the bronchus intermedius. 19

RIGHT MIDDLE LOBECTOMY

Right Middle-lobe Bronchus
Figure 17 depicts the surgeon’s view of the right middle-lobe bronchus. Gentle posterior retraction of the basilar segmental artery to the lower lobe allows clear visualization of the origin of the middle-lobe bronchus.

Anterior Right Hilum
The surgeon’s view of the anterior right hilum is illustrated in figure 15. The apical venous branches of the superior pulmonary vein obscure the interlobar pulmonary artery and, to a lesser degree, the truncus anterior branch. Division of these venous branches during upper lobectomy improves exposure of the truncus anterior. The splitting of the main pulmonary artery into its two main branches may occur more proximally, and care should be taken to identify both branches before either one is divided. Another significant possible variation is a branch of the middle-lobe vein that arises from the intrapericardial portion of the superior pulmonary vein. 19

Posterior Right Hilum
Figure 16 shows the surgeon’s view of the posterior right hilum. The carina, right mainstem bronchus, right upper lobe, and bronchus intermedius are easily seen. The interlobar sump node has been removed and the fissure completed, and the posterior ascending branch of the pulmonary artery
RIGHT LOWER LOBECTOMY
Right Inferior Pulmonary Vein
The surgeon’s view of the right inferior pulmonary vein is illustrated in Figure 18. For encirclement of this vein, dissection may also have to be performed on its anterior surface. The branch to the superior segment can be seen overlying the origin of the superior segmental bronchus.

Right Fissure After Division
Figure 19 shows the surgeon’s view of the right fissure after division of the lower-lobe vessels. The decision of whether to divide the bronchi separately or to transect them with a single oblique application of the stapler depends on the proximity of the middle-lobe bronchus to the superior segmental and basilar bronchi.

LEFT UPPER LOBECTOMY
Left Interlobar Fissure
Figure 20 is an illustration of the surgeon’s view of the left interlobar fissure. The recurrent laryngeal nerve can be seen coursing lateral to the ligamentum arteriosum. The arterial branches supplying the left upper lobe between the apicoposterior segmental branch and the lingular branch can vary substantially in number and size. Another frequently encountered variation is a distal lingular branch that arises from a basilar segmental branch.

Anterior Left Hilum
The surgeon’s view of the anterior left hilum is shown in Figure 21. The apical branches of the superior pulmonary vein course anterior to the apicoposterior branches of the pulmonary artery. If additional vessel length is needed because of the presence of a central tumor, the pericardium may be entered and the vein divided at that location.
Left Fissure After Division

Figure 22 shows the surgeon’s view of the left fissure after division of the upper-lobe arteries. Care should be taken not to injure the pulmonary artery inadvertently when applying a stapler.

**LEFT LOWER LOBECTOMY**

Left Inferior Pulmonary Vein

Figure 23 depicts the surgeon’s view of the left inferior pulmonary vein. The left side, unlike the right side, affords only limited access to the subcarinal space. However, the length of the inferior pulmonary vein outside the pericardium is greater on the left side than on the right.

**Left Fissure After Division**

Figure 24 is an illustration of the surgeon’s view of the left fissure after division of the lower-lobe vessels. In this procedure, a single oblique transection of the entire left lower-lobe bronchus can be employed without any concern that a proximal bronchus will be compromised; this step would not be feasible in a right lower lobectomy because the right middle-lobe bronchus arises from the bronchus intermedius.

**LEFT PNEUMONECTOMY**

Posterior Left Hilum

Figure 25 shows the surgeon’s view of the posterior left hilum. The carina is located deep under the aortic arch. A left-side double-lumen tube or bronchial blocker may have to be withdrawn to afford better exposure of the proximal left mainstem bronchus. The orientation of the superior pulmonary vein and the pulmonary artery (anterior and superior to the bronchus, respectively) should be noted.
ADDITIONAL THERAPIES

ENERGY ABLATION SYSTEMS
- Used to treat solid lung cancer tumors.
- Experimental studies in rabbits have confirmed that lung RF ablation can be safely and effectively performed via a percutaneous, transthoracic approach. These studies have also prompted the start of clinical investigation.
- Pilot clinical studies have shown that RF ablation facilitates successful treatment of relatively small lung malignancies with a high rate of complete response and acceptable morbidity.
- The technique could represent a viable alternate or complementary treatment approach for patients with non-small cell lung cancer or lung metastases of favorable histotypes who are not candidates for surgical resection.
- RITA Medical System’s results of a multi-center prospective trial demonstrated a 92% survival rate following treatment RFA using their system.

ENERGY ABLATION Systems Recent Literature

PHOTODYNAMIC THERAPY
Photodynamic Therapy (PDT) is approved by the United States Food & Drug Administration (FDA) for the treatment of both early and late-stage lung cancer. PDT is a curative treatment for small primary non-small cell lung cancers growing in the tracheobronchial airways in patients who are not able to undergo surgery or radiotherapy. It is under investigation for patients with pleural spread of non-small cell lung cancer.

PHOTODYNAMIC THERAPY Recent Literature

TARGETED THERAPIES
Triton Biosystems is developing Targeted NanoTherapeutics (TNT) which ablates tumors using tiny magnetic spheres delivered systematically via attached monoclonal antibodies specific to tumor protein markers. The spheres infiltrate the tumors and are induced to heat with a localized, externally applied magnetic field.20

Molecular-based therapies targeting overexpressed growth receptors (EGFR, HER2/neu) by monoclonal antibody or small molecules are beginning to show clinical effectiveness. Additional agents targeting signal transduction pathways (e.g., farnesyl transferase inhibitors) for the RAS pathway as well as antisense oligonucleotide and gene therapies are all in advanced clinical testing stages. In combination with standard cytotoxic chemotherapy, they appear to enhance response rates.21, 22

Targeted Therapies Recent Literature
VIDEO-ASSISTED THORACIC SURGERY (VATS)

- Introduction and Background of VATS
- VATS Surgeries for Lung Cancer
INTRODUCTION AND BACKGROUND OF VATS

While lung volume reduction surgery has been performed using open procedures, the choice of procedure is increasingly becoming video-assisted thoracic surgery (VATS).

In 1991, the application of video technology to thoracoscopy revolutionized the procedure because it allowed several persons to both see the operative field simultaneously and to operate together as they would during an open procedure. In addition, the development of endoscopic instruments, particularly endoscopic staplers, enabled surgeons to perform major operations using minimally invasive techniques. The impact of this new technology was so profound that within a two-year period, traditional thoracoscopic techniques were largely abandoned in favor of video-assisted thoracic surgery (VATS).

Despite routine use in thoracoscopy, VATS is not currently used extensively for major pulmonary resection. VATS is an approved alternative for major pulmonary resection and has numerous advantages, including less clinically strenuous eligibility requirements, long-term survival rates equal to or better than those of open surgery, a more rapid recovery with an earlier return to activities, and significantly less postoperative pain.

Consumables costs for this surgery are a drawback and cost-effectiveness using various criteria is still being researched. A phase III trial sponsored by the National Cancer Institute is comparing laparoscopically assisted surgery and video-assisted thoracoscopy as less invasive options for esophageal cancer. The study will analyze various outcomes including side effects and recovery time.

Table 4 shows the volumes forecast for thoracoscopy (VATS) procedures for 2005 through 2014. Approximately 26,000 thoracoscopies were performed in the U.S. in 2005. The number of these procedures is expected to increase over the forecast period at a compound annual rate of 5.6% to reach an estimated 43,000 in the year 2014. Thoracoscopic procedures are expected to be utilized in more lung procedures due to improved instrumentation and broader acceptance of thoracoscopy by chest surgeons.

INDICATIONS AND CONTRAINDICATIONS

Diagnostic Indications
- Undiagnosed pleural effusion
- Indeterminate pulmonary nodule
- Undiagnosed interstitial lung disease
- Pulmonary infection in the immunosuppressed patient
- To define cell type in known thoracic malignancy
- To define extent of a primary thoracic tumor
- Nodal staging of a primary thoracic tumor
- Diagnosis of intrathoracic pathology to stage a primary extrathoracic tumor
- Evaluation of intrapleural infection

Therapeutic Indications

Lung
- Spontaneous pneumothorax
- Bulbous disease
- Lung volume reduction
- Persistent parenchymal air leak
- Benign pulmonary nodule
- Resection of pulmonary metastasis (in highly selected cases)
- Resection of a primary lung tumor (in highly selected cases)

Mediastinum
- Drainage of pericardial effusion
- Excision of bronchogenic or pericardial cyst
- Resection of selected primary mediastinal tumors
- Esophageal myotomy
- Facilitation of transhiatal esophagectomy
- Resection of primary esophageal tumors
- Thymic resection
- Ligation of thoracic duct

Pleura
- Drainage of a multiloculated effusion
- Drainage of an early empyema
- Pleurodesis

Contraindications
- Extensive intrapleural adhesions
- Inability to sustain single-lung ventilation
- Extensive involvement of hilar structures
- Preoperative induction chemotherapy or chemoradiotherapy
- Severe coagulopathy

Table 4: Thoracoscopy (VATS) procedure volumes forecast for 2005 through 2014.
VATS OPERATIVE PLANNING

Positioning and Port Placement

Patient preparation and positioning are similar for most VATS procedures. As a rule, the lateral decubitus position offers the best exposure, and it permits uncomplicated conversion to a thoracotomy if necessary.23

Instrumentation

Instrumentation for VATS is comprised of (1) video equipment, (2) endoscopes and thoracoports, (3) staplers, (4) thoracic instruments (e.g. lung clamps and retractors) modified for endoscopic use, and (5) various devices for tissue cauterization, including lasers. Because immediate conversion to thoracotomy is occasionally necessary, a basic set of thoracotomy instruments should be an integral part of a VATS instrument tray (see figure 26).23

Additional Considerations

Thoracoscopic lobectomy is being performed with increasing frequency, especially for early-stage lesions. This procedure employs two or three 1 cm ports and a utility thoracotomy (frequently in the axillary position) for instrumentation and removal of the specimen.25

Rib spreading is not necessary because visualization is achieved via the thoracoscope. The various thoracoscopic lobar resections are generally similar with regard to isolation and division of the hilar vessels and bronchi.25

Complete nodal dissections are also performed thoracoscopically.25

The main advantages of this approach seem to be reduced postoperative pain and earlier return to normal activity, but no randomized trials have shown these advantages to be significant.25

Because of the technical challenges associated with thoracoscopic pulmonary resections, surgeons should have a complete mastery of the hilar anatomy before attempting these procedures.25

Instruments Commonly Used During VATS

Images of the instrumentation commonly used during VATS procedures are shown in Figure 26. Modified trocar cannulas, called thoracoports (a), facilitate access to the pleural space. They are shorter than cannulas used in laparoscopy and have a corkscrew configuration on the outside that maintains their position on the chest wall. Instruments inserted through these ports include: endoscopic linear cutters that make incisions between two triple rows of staples (b). Nondisposable endoscopic lung clamps (c) are available in various shapes with serrations at the end or along the full length of the clamp. The sponge sticks (d) can be modified for endoscopic use as lung clamps or lymph node holders.

Figure 26: The instruments commonly used during VATS procedure.
Positioning of Instruments During VATS

Figure 27 shows the schematic for the typical positioning of instruments and the video camera for patients undergoing VATS for a lesion in the superior segment of the left lower lobe of the lung. Instruments are introduced through two port incisions made anteriorly at approximately the fifth intercostal space in the anterior axillary line and posteriorly parallel to and 2 to 3 cm away from the border of the scapula. For patients undergoing thoracoscopy for apical bullous disease in the left upper lobe of the lung, the camera port can be placed at the fifth or sixth intercostal space; one instrument port can be inserted in the axilla and the other port inserted higher on the posterior chest wall at approximately the third intercostal space.

VATS SURGERIES FOR LUNG CANCER

VATS WEDGE RESECTION


Consensus Panel Recommendations

For patients with clinical stage I non-small cell lung cancer undergoing lung lobectomy, VATS can be recommended:

1. To reduce overall postoperative complications (class IIa, level A evidence)
2. To reduce pain and overall functionality over the short term (class IIa, level B evidence)
3. To improve delivery of adjuvant chemotherapy delivery (class IIa, level B evidence)

For lobectomy in clinical stage I and II non-small cell lung cancer patients, with no proven difference in stage-specific 5-year survival compared with open thoracotomy (class IIb, level B evidence)

Operative Technique

Most pulmonary wedge resections are performed as true videothoracoscopic procedures using just three port incisions placed in the triangulated manner previously described. The pulmonary nodules to be removed are grasped with an endoscopic lung clamp (Pennington or Duval) inserted through one instrument port, and wedge resection is done with repeated applications of an endoscopic stapler inserted through the opposite port, as shown in figures 28 and 29. As the resection is performed, it is often helpful to introduce the staple through each of two instrument ports to obtain the correct angle for application to the lung. To prevent tumor implantation in the chest wall, small specimens (usually those resected with three or fewer stapler applications) are removed via the thoracopore. Larger specimens are placed in a disposable plastic specimen retrieval bag, which is then brought out through a very slightly enlarged anterior thoracopore incision.

When the wedge resections have been completed, intercostal blocks are performed under direct vision with a mediastinoscope aspiration needle, and a single chest tube is inserted through the inferior port after the videotoracoscope is withdrawn. The videotoracoscope can be placed through the anterior incision to check the position of the chest tube and to confirm reinflation of the lung after the double-lumen endotracheal tube is unclamped. The remaining incisions are then closed with sutures.

4. For lobectomy in clinical stage I and II non-small cell lung cancer patients, with no proven difference in stage-specific 5-year survival compared with open thoracotomy (class IIb, level B evidence)

Operative Technique

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When the wedge resections have been completed, intercostal blocks are performed under direct vision with a mediastinoscope aspiration needle, and a single chest tube is inserted through the inferior port after the videotoracoscope is withdrawn. The videotoracoscope can be placed through the anterior incision to check the position of the chest tube and to confirm reinflation of the lung after the double-lumen endotracheal tube is unclamped. The remaining incisions are then closed with sutures.

Figure 27: Typical positioning of the instruments and the video camera during VATS.

Figure 28: VATS pulmonary wedge resection. A double-lumen endotracheal tube is used to render the lung partially atelectatic. The pulmonary nodule is lifted upwards with a lung clamp, and an endoscopic linear cutter is applied to the lung underneath.

Figure 29: VATS pulmonary wedge resection. A double-lumen endotracheal tube is used to render the lung partially atelectatic. The pulmonary nodule is lifted upwards with a lung clamp, and an endoscopic linear cutter is applied to the lung underneath.
VATS LOBECTOMY AND PNEUMONECTOMY

Although VATS lobectomy is less frequently performed than VATS pulmonary wedge resection, standard techniques have been developed for it. VATS pneumonectomy, on the other hand, is less well accepted. Both operations are done as video-assisted procedures using a utility thoracotomy, which facilitates insertion of standard thoracotomy instruments, extraction of the resected specimen from the pleural space, and performance of the technically complex aspects of the procedure, including dissection of the hilar vessels and the mediastinal lymph nodes.23

Although VATS lobectomy has not been proven to be equivalent to other procedures in oncological patients undergoing surgery, there is good evidence that it is safe in acute settings. Therefore, it should be performed to treat benign diseases (e.g. bronchiectasis). As with all minimally-invasive procedures, conversion to open thoracotomy is indicated if technical issues arise. Some authors advocate VATS lobectomy for low-grade malignancies (e.g. carcinoids) as well. It must be recognized, however, that although carcinoids have a lower malignant potential than non-small cell lung cancer, they are still malignancies and must be treated appropriately for optimal long-term outcome.23

VATS Lobectomy

Two approaches to lobectomy have been developed. One involves sequential anatomic ligation of the hilar structures, similar to a standard lobectomy, and the other involves mass ligation of the pulmonary vessels and the bronchus. Both approaches require at least two port incisions in addition to the utility thoracotomy incision.23

The sequential anatomic ligation approach has been well described and follows established surgical oncologic principles. Accordingly, it is a preferred method of performing VATS lobectomy. It must be noted, however, that VATS lobectomy is a procedure for which there is no accepted uniform definition. In a survey aimed at defining the criteria used by minimally-invasive thoracic surgeons for VATS lobectomy, the length of the utility incision ranged from 4 to 10 cm, the number of incisions ranged from three to five, and the use of rib spreading was variable.24

In an effort to standardize the approach at one institution, The Memorial Sloan-Kettering Cancer Center (MSKCC), VATS lobectomy was defined as an anatomic dissection that is performed entirely under thoracoscopic visualization, proceeds in an anterior-to-posterior fashion, employs a 4 cm utility incision, involves no rib spreading, and uses two thoracoscopic ports (one for the camera and one for retraction). This definition also includes nodal evaluation (either sampling or dissection) of levels 4, 7, and 9 on the right and levels 5, 6, 7, and 9 on the left.22

Robot-assisted VATS Lobectomy

To date, there have been only two published reports of the use of robotic technology during VATS lobectomy. One is a case report of a VATS left lower lobectomy performed with robotic assistance, and the other is a series of five patients, two of whom were converted to thoracotomy for technical reasons. It is clear from the lack of a substantial literature that a standardized approach has not yet been established. At MSKCC, however, they have developed a technique for robot-assisted VATS lobectomy that employs the da Vinci Surgical System as an adjunct to our standard VATS lobectomy technique. This robot-assisted approach has proven to be safer and feasible in more than 30 consecutive patients.24

There are several unique caveats that apply to robot-assisted VATS procedures. First, before attempting such a procedure, the operating surgeon, assistants, and all other operating personnel must be fully trained on the robotic surgical system being used. In the early stages of a center’s experience with a system, it is advisable to have a company representative present to help manage any complex technical issues that may arise. Second, care must be taken both during initial positioning and throughout the procedure to ensure that the arms of the robot do not collide with one another or the patient. Third, there must be constant communication between all team members and constant vigilance during the procedure. Un timely or unintended manipulation of any component of the robotic system during dissection around delicate hilar structures can be potentially disastrous and should be completely avoidable.23

VATS Lobectomy: Cost Considerations

It is difficult to estimate the cost-effectiveness of VATS procedures because the instrumentation, types of procedures performed, and surgical expertise with these operations are evolving. Initially, VATS procedures proved expensive for several reasons, including the cost of purchasing video and endoscopic equipment, the cost of disposable instrumentation, and the need for long operating times as surgeons and nursing staff gained experience with the procedures.23

Soon after VATS was introduced, a study from the Mayo Clinic compared the cost of performing VATS pulmonary wedge resections with that of thoracotomy. The VATS approach was associated with substantially shorter hospital stays but also with increased OR costs; hence, the use of VATS did not result in any significant overall savings. Since that study, however, as some VATS procedures (e.g. pulmonary wedge resection) have become standard operations and more reusable instrumentation has become available, the cost of VATS has fallen.24 Whether other more complex VATS procedures (e.g. thoracoscopic esophagectomy) are cost-effective remains to be determined.
HEALTH ECONOMICS
- Outcomes of Various Surgeries
- Costs of Lung Cancer
- Economic Burden of Disease
- Health Economics
- National Expenditures
OUTCOMES OF VARIOUS SURGERIES
HEALTH CARE UTILIZATION PROJECT DATA

Table 5 shows the data for outcomes of 36 lobectomy or pneumonectomy procedures from the 2006 national statistics. Table 6 provides the data from the 2006 national statistics for the outcomes of multiple specific diagnoses.

<table>
<thead>
<tr>
<th>36 Lobectomy or Pneumonectomy</th>
<th>Standard Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Discharges</td>
<td>3,805</td>
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<tr>
<td>LOS (Length of Stay), Days (mean)</td>
<td>0.2</td>
</tr>
<tr>
<td>LOS (Length of Stay), Days (median)</td>
<td>N/A</td>
</tr>
<tr>
<td>Charges $ (mean)</td>
<td>1,546</td>
</tr>
<tr>
<td>Charges $ (median)</td>
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</tr>
<tr>
<td>Cost $ (mean)</td>
<td>352</td>
</tr>
<tr>
<td>Cost $ (median)</td>
<td>N/A</td>
</tr>
<tr>
<td>Aggregate Costs</td>
<td>213,944,248</td>
</tr>
<tr>
<td>Aggregate Charges (the &quot;national bill&quot;)</td>
<td>213,944,248</td>
</tr>
</tbody>
</table>

Table 6: Data for the outcomes for multiple specific diagnoses from the 2006 national statistics.*

Table 7: Estimation of the PVLE among the adults 20 and older in 2010.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>PVLE, $ US</th>
<th>% of Total Cost</th>
<th>Deaths</th>
<th>PVLE/death $ US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (All Cancers)</td>
<td>392,373,675.00</td>
<td>100.00</td>
<td>657,005</td>
<td>216,701.00</td>
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<tr>
<td>Lung and Bronchus</td>
<td>38,953,476.028.00</td>
<td>27.36</td>
<td>185,202</td>
<td>210,330.00</td>
</tr>
</tbody>
</table>

Table 7: Estimation of the PVLE among the adults 20 and older in 2010.

COSTS OF LUNG CANCER

The cost of lung cancer deaths exceeds the cost of all other cancers for men aged 35 years and older. Recent trends suggest that overall cancer mortality has declined by approximately 1% per year. Reducing annual mortality rates by another 1%, starting in 2010, would reduce productivity costs of six costly cancers—lung, colon and rectum, female breast, pancreas, leukemia, and brain—by approximately $814 million per year. A reduction in lung cancer mortality would offer the greatest reduction in productivity costs, accounting for approximately $390 million in 2010 and $416 million in 2020. The total present value of lifetime earnings (PVLE) lost and the PVLE lost per death from cancer for adults 20 years and older for the year 2010 were estimated and are shown in Table 7. Lung cancer deaths accounted for more than 27% of the total costs (approximately $39 billion).
ECONOMIC BURDEN OF DISEASE

In this analysis, person-years of life lost (PYLL) due to cancer deaths for the years 2000 to 2020 were estimated and used to calculate the total value of life lost due to cancer deaths during this period. The projections are shown in Table 8. The reductions in this amount that would occur if cancer mortality rates declined during the period are also shown. The value of a year of life ($150,000) was based on previous estimates.

HEALTH ECONOMICS

The value of life lost from all cancer deaths in the year 2000 was $960.6 billion; lung cancer alone accounted for more than 25% of this total. The graph of projected value of life lost to lung cancer deaths in the United States is shown in figure 30. Projected annual decreases in cancer mortality rates of 2% reduced the expected value of life lost in the year 2020 from $433.4 billion to $289.4 billion for lung cancer.

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>&lt;65 years 610,855</td>
<td>65 years 635,080</td>
</tr>
</tbody>
</table>

Table 8: Person-years of life lost (PYLL) due to cancer deaths in the year 2000 by gender and tumor site.

Figure 30: The projected value of life lost due to cancer deaths in the United States.

NATIONAL EXPENDITURES


Table 9: National expenditures estimates, in 1996 dollars, for the medical treatments for the thirteenth most common cancers, based on cancer prevalence in 1996 and cancer-specific costs for 1995 through 1998.
VATS VERSUS OPEN SURGERY—LOBECTOMY

- Search Criteria
- Efficacy
- Safety
- Quality of Life
- Economic Factors
SEARCH CRITERIA

The Medline (PubMed) and EMBASE clinical databases were searched by IRS, using strategies appropriate to each database. PubMed was searched using the following terms: Bronchoscopy*, Thoracoplasty, Thoracoscopy*, Thoracotomy, Thymectomy, Thymoma/Surgery, Pulmonary Disease, Chronic Obstructive/Surgery*, Pulmonary Emphysema/Surgery* or Emphysema/Surgery* yielded 7931 results. Subject terms marked with an * were required to be major subject areas of the reference. A second search using the terms “Thoracic Surgery, Video Assisted” returned 1,471 results. The total results for these 2 searches was 8,274 references. Limiting these references to studies on English manuscripts on humans that were either meta-analyses, practice guidelines, or randomized controlled trials reduced the number of results to 433 references.

Two relevant health technology assessments were obtained from searches of inahta.org using the terms thoracoscopy or VATS. Searches of the PubMed database using the terms thoracoscopy or VATS and meta-analysis returned one systematic review. References provided by IRS which directly compared the outcomes of VATS versus open lung surgeries included one meta analysis and five review articles.

Thus, the total number of articles with pertinent results regarding VATS versus open lung surgeries include one meta analysis, two health technology assessments, and six systematic and non-systematic reviews. Tables 10 and 11 are summaries of these references.

STUDY LISTINGS

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
<th>Country</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Alam, Naveed</td>
<td>Video-assisted Thoracic Surgery (VATS) Lobectomy: the Evidence Base</td>
<td>JSLS</td>
<td>USA</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>2007</td>
<td>West, D.</td>
<td>Does video-assisted thoracoscopic lobectomy produce better tumor clearance compared to open lobectomy for non-small cell carcinoma of the lung</td>
<td>Interactive Cardiovascular and Thoracic Surgery</td>
<td>Scotland</td>
<td>Systematic Review</td>
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<td>2006</td>
<td>Wright, G.</td>
<td>Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials</td>
<td>Thorax</td>
<td>Australia</td>
<td>Systematic Review</td>
</tr>
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<td>2005</td>
<td>Banerjee, S.</td>
<td>Lung volume reduction surgery for emphysema</td>
<td>Ottawa Canadian Coordinating Office for Health Technology Assessment (CCTA)</td>
<td>Canada</td>
<td>Health Technology Assessment (Systematic Review with a meta-analysis performed)</td>
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<tr>
<td>2002</td>
<td>Babidge, W.</td>
<td>A systematic review of lung volume reduction surgery</td>
<td>ASERP-S</td>
<td>Australia</td>
<td>HTA based on Systematic Review</td>
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Table 10: Bibliographic summary of the studies used to compare VATS and open surgery with respect to efficacy, safety, quality of life, and economic outcomes.
Video-assisted thoracic surgery lobectomy has controversial advantages over traditional open surgical approaches. Subjective concerns such as pain, dyspnea, physical functioning, and overall satisfaction generally favor VATS but vary depending on survey timing. Independence, a major quality of life component, favors video-assisted thoracic surgery because fewer objective hospital and discharge resources are needed because pulmonary function, activity level, muscle strength, and walking capacity are better. Video-assisted thoracic surgery often hastens return to work and facilitates adjuvant chemotherapy or subsequent urgent surgical procedures. Video-assisted thoracic surgery-related quality of life benefits are amplified by advanced age (or other frailties) and reduced by advanced cancer stage or comorbid illness.

Methods: A systematic review of the Medline database. We looked for randomized controlled trials comparing VATS with open thoracotomy for lobectomy. We screened 17,923 studies. After independent review of the abstracts by 2 reviewers, we included 39 studies (only one randomized controlled trial) in our analysis. In aggregate, these 39 studies involved 3,256 thoracotomy and 3,114 VATS patients. The characteristics of the VATS approach, compared with thoracotomy, in terms of short-term morbidity and long-term survival. To identify relevant articles for inclusion in our analysis, we performed a systematic review of the Medline database. We looked for randomized controlled trials, observational studies, and case series that reported outcomes after VATS or thoracotomy lobectomy for NSCLC. For statistical testing, we used a two-sided approach (Alpha=0.05) under the hypothesis that VATS lobectomy is superior to thoracotomy lobectomy. We screened 17,923 studies. After independent review of the abstracts by 2 reviewers, we included 39 studies (only one randomized controlled trial) in our analysis. In aggregate, these 39 studies involved 3,256 thoracotomy and 3,114 VATS patients. The characteristics of the two groups were not significantly different. Compared with thoracotomy, VATS lobectomy was associated with shorter chest tube duration, shorter length of hospital stay, and improved survival (at 4 years after resection), all statistically significant. Compared with lobectomy performed by thoracotomy, VATS lobectomy for patients with early-stage NSCLC appears to favor lower morbidity and better short-term survival.

Results: Baseline prognosis was similar. Conclusion: In expert hands, VATS lobectomy appears to be a safe procedure. However, the published evidence is thin and ongoing study is required, preferably with standardization of VATS techniques.

## Table 11

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Abstract summaries of the studies used to compare VATS and open surgery with respect to efficacy, quality of life, and economic outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Demmy, Todd</td>
<td>Video-assisted thoracic surgery lobectomy has controversial advantages over traditional open surgical approaches. Subjective concerns such as pain, dyspnea, physical functioning, and overall satisfaction generally favor VATS but vary depending on survey timing. Independence, a major quality of life component, favors video-assisted thoracic surgery because fewer objective hospital and discharge resources are needed because pulmonary function, activity level, muscle strength, and walking capacity are better. Video-assisted thoracic surgery often hastens return to work and facilitates adjuvant chemotherapy or subsequent urgent surgical procedures. Video-assisted thoracic surgery-related quality of life benefits are amplified by advanced age (or other frailties) and reduced by advanced cancer stage or comorbid illness.</td>
</tr>
<tr>
<td>2008</td>
<td>Flores, Raja M.</td>
<td>Video-assisted thoracic surgery (VATS) lobectomy provides a minimally invasive approach for the management of early-stage lung cancer. Questions about the safety of VATS lobectomy and its adequacy as a cancer operation compared with open thoracotomy have hindered its universal acceptance among thoracic surgeons. Evidence suggests that VATS lobectomy can be safely performed and is an adequate cancer operation for early-stage non-small cell lung cancer. Video-assisted thoracic surgery (VATS) versus open thoracotomy (OTH) for lobectomy are lacking in the literature.</td>
</tr>
<tr>
<td>2008</td>
<td>Whitson, Bryan</td>
<td>Video-assisted thoracic surgery (VATS) lobectomy has been touted to provide superior outcomes, compared with thoracotomy, for patients with early-stage non-small cell lung cancer (NSCLC). However, supporting data are limited to case series and small observational studies. We hypothesized that a systematic review of the literature would enable a more objective evaluation of the evidence in order to determine the potential superiority of the VATS approach, compared with thoracotomy, in terms of short-term morbidity and long-term survival. To identify relevant articles for inclusion in our analysis, we performed a systematic review of the Medline database. We looked for randomized controlled trials, observational studies, and case series that reported outcomes after VATS or thoracotomy lobectomy for NSCLC. For statistical testing, we used a two-sided approach (Alpha=0.05) under the hypothesis that VATS lobectomy is superior to thoracotomy lobectomy. We screened 17,923 studies. After independent review of the abstracts by 2 reviewers, we included 39 studies (only one randomized controlled trial) in our analysis. In aggregate, these 39 studies involved 3,256 thoracotomy and 3,114 VATS patients. The characteristics of the two groups were not significantly different. Compared with thoracotomy, VATS lobectomy was associated with shorter chest tube duration, shorter length of hospital stay, and improved survival (at 4 years after resection), all statistically significant. Compared with lobectomy performed by thoracotomy, VATS lobectomy for patients with early-stage NSCLC appears to favor lower morbidity and better short-term survival.</td>
</tr>
<tr>
<td>2007</td>
<td>Cheng, Davy</td>
<td>Objectives: This meta-analysis sought to determine whether video-assisted thoracic surgery (VATS) improves clinical and resource outcomes compared with thoracotomy (OPEN) in adults undergoing lobectomy for non-small cell lung cancer (NSCLC). Methods: A comprehensive search was undertaken to identify all randomized (RCT) and nonrandomized (non-RCT) controlled trials comparing VATS with OPEN thoracotomy, available up to April 2007. The primary outcome was survival. Secondary outcomes included any other reported clinical outcome and resource utilization. Odds ratios (OR), weighted mean differences (WMD), or standardized mean differences (SMD), and their 95% confidence intervals (95% CI) were analyzed as appropriate. Results: Baseline characteristics were similar for VATS and OPEN. VATS may be more favorable for VATS (more females, smaller tumor size, less advanced stage, histology associated with peripheral location and with more indolent disease) than for OPEN in non-RCT but not RCT. Postoperative complications were significantly reduced in the VATS group when both RCT and non-RCT were considered in aggregate.</td>
</tr>
<tr>
<td>2007</td>
<td>Alam, Naveed</td>
<td>A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was whether a VATS lobectomy produces an equivalent cancer outcome and cancer clearance compared to an open lobectomy. VATS lobectomy can be safely performed and is an adequate cancer operation for early-stage non-small cell lung cancer. There is evidence that patients experience less pain with VATS, but that length of hospital stay is similar. Conclusion: In expert hands, VATS lobectomy appears to be a safe procedure. However, the published evidence is thin and ongoing study is required, preferably with standardization of VATS techniques.</td>
</tr>
<tr>
<td>2007</td>
<td>West, D.</td>
<td>Background: Video-assisted thoracic surgery (VATS) lobectomy provides a minimally invasive alternative for management of early stage non-small cell lung cancer (NSCLC). However, adequately powered well-balanced studies comparing VATS with open thoracotomy are lacking in the literature. Questions about the safety of VATS lobectomy and its adequacy as a cancer operation compared with open thoracotomy have hindered its universal acceptance among thoracic surgeons. Evidence suggests that VATS lobectomy can be safely performed and is an adequate cancer operation for early-stage non-small cell lung cancer. However, there have been no previously published systematic reviews. Methods: We performed a systematic review of the literature on VATS lobectomy to assess these questions. The Medline database was queried and the papers analyzed. Results: Four randomized control trials, 11 case-control series, and 10 case series were reviewed. A variety of VATS techniques are used, making generalization of results difficult. The weight of this evidence suggests that VATS lobectomy can be safely performed and is an adequate cancer operation for early-stage non-small cell lung cancer. There is evidence that patients experience less pain with VATS, but that length of hospital stay is similar. Conclusion: In expert hands, VATS lobectomy appears to be a safe procedure. However, the published evidence is thin and ongoing study is required, preferably with standardization of VATS techniques.</td>
</tr>
<tr>
<td>2006</td>
<td>Wright, G.</td>
<td>Background: Surgery is considered the treatment of choice for patients with resectable stage I and II (and some patients with stage IIIA non-small cell lung cancer (NSCLC), but there have been no previously published systematic reviews. Methods: A systematic review and meta-analysis of randomised controlled trials was conducted to determine whether surgical resection improves disease specific mortality in patients with stage I, II, and IIIA NSCLC compared with non-surgical treatment, and to compare the efficacy of different surgical approaches. Results: Eleven trials were included. No studies had untreated control groups. In a pooled analysis of these trials, 4-year survival was superior in patients undergoing resection with stage I-IIA NSCLC who had complete mediastinal lymph node dissection compared with lymph node sampling (hazard ratio estimated at 0.78 (95% CI 0.65 to 0.93)). Another trial reported an increased rate of local recurrence in patients with stage I NSCLC treated with limited resection compared with lobectomy. One small study reported a survival advantage among patients with stage IIA NSCLC treated with chemotherapy followed by surgery compared with chemotherapy followed by radiotherapy. No other trials reported significant improvements in survival after surgery compared with non-surgery. Conclusion: It is difficult to draw conclusions about the efficacy of surgery for locoregional NSCLC because of the small number of participants studied and shortcomings of the trials. However, current evidence suggests that complete mediastinal lymph node dissection is associated with improved survival compared with node sampling in patients with stage I-IIA NSCLC undergoing resection.</td>
</tr>
</tbody>
</table>

### Table 11 (cont'd)
Technology Lung volume reduction surgery (LVRS) using buttressing (reinforcing) or no buttressing staples or laser; unilateral or bilateral; however; staged or simultaneous procedures; and median sternotomy (MS) or video-assisted thoracoscopic surgery (VATS). Dis- eased Emphysema is a chronic obstructive pulmonary disease (COPD) that mainly affects adults older than 65. It causes shortness of breath and reduces quality of life (QoL). Issue LVRS is one treatment option for patients with severe emphysema. It is an expensive pro- cedure with a high risk of postoperative death. It may be used as a bridge to lung trans- plantation or when transplantation is unavailable. There is a need to compare LVRS with medical management, and compare different types of LVRS procedures. Methods and Re- sults A meta-analysis was performed to derive statistical summaries. The relative benefit and harm were determined by examin- ing the impact on QoL, mortality, shortness of breath, and pulmonary function, and com- parisons made with treatment. Seven randomized controlled trials (RCTs) involving 1,412 patients and comparing LVRS with medical management, were identified. Four RCTs and 10 cohort studies comparing different LVRS procedures were identified: implications for Decision Making There is no reduction in the overall death rate at about two years. LVRS is a palliative treatment that improves QoL, lung function, and exercise tolerance. It increases the risk of short-term death compared with medical management alone. For cer- tain patients, LVRS offers a survival advantage compared with medical management. These patients whose exercise capacity is low. Other patients are at high risk of death after LVRS. These are pa- tients who have a forced expiratory volume in one second that is no more than 20% of the predicted value, and who have a homogenous distribution of emphysema in the lung, or a carbon monoxide diffusing capacity that is no more than 20% of the predicted value. There is no definite advantage to any one LVRS procedure, in terms of clinical outcomes or in-hospital costs. The US National Emphysema Treatment Trial (NETT) shows that the total cost, six months after surgery, was less with VATS compared with the MS procedure.

Table 11 (cont’d)

Table 11

LOBECTOMY

For this report, one meta-analysis27 and six systematic reviews28–33 were selected for comparison of efficacy, safety, quality of life, and economic outcomes for VATS versus open lobectomy surgeries. These reports vary in the strictness of their inclu- sion criteria. Hence, while there is overlap in the individual studies included in different reviews, there are also many differences. Furthermore, there have only been four RCTs investi- gating VATS versus open lobectomy; the majority of studies included in either the meta-analysis or the systematic reviews are non-RCTs. Therefore, the various outcomes reported are likely influenced by selection bias, and this is an important limitation. Similar studies have been done to analyze individual studies and report composite results are the meta- analysis by Cheng et al. and a systematic review by Whitson et al. The remainder of systematic reviews report results from individual studies and a detailed review of surgery.

Table 12 (cont’d)

Table 12


Background: During the early part of this century a number of surgical procedures were used in an attempt to palliate the dyspnea of severe emphysema. The first was lobectomy, which was succes- sful and carried a high risk of mortality. Emphysema is usually a heterogeneous process. In the 1950s Brantigan introduced the notion of resecting the bulla in bullous emphysema. This procedure is still in use today. The surgeon is limited in their assessment of the function of the remaining lung. In the early 1990s Cooper resuscitated and modified Brantigan’s approach, which is now recognised as a useful treatment for diffuse emphysema. The hypothesis was that resection of the most seriously damaged areas of hyperinflated lung, using a bronchial stapler, would result in improvement in the function of the remaining lung and so lessen dys- pnoea. A variety of different approaches to this surgery have been proposed, being via median sternotomy, thoracostomy or with a video-assisted thoracoscopic (VATS) technique. These are both unilateral and bilateral approaches, with equivalent benefits being achieved using unilateral surgery in appropriately selected patients. The areas for surgical removal are identified prior to surgery by computed tomography and radiouclide ventilation-perfusion scanning. Meth- ods for sealing the site of resected lung include the use of staples or a laser (Neodymium:YAG), however prolonged air leak is a common postoperative complication. Attempts to overcome this have been to use buttressing materials along the staple line, most commonly bovine pericardium, but collagen also has been suggested as a cheaper option. Lung Volume Reduction Surgery (LVRS) is a procedure that requires appropriate selection of patients who have been suitably, informed of the risks of this procedure. They are encouraged to participate in a pulmonary re- habilitation program both prior to, and after surgery. For patients with end-stage emphysema, surgical therapy in the form of pulmonary resection for the only option. The patient selection criteria for LVRS are rigorous, involving both functional and radiological assessment. The number of patients who qualify for LVRS is a small percentage of those originally assessed. To date, few long-term studies have been performed up to two years post surgery with most se- ries suffering from large losses to follow-up. Methods: Literature up to and including September 2005 was included for review, and of the 70 articles retrieved on LVRS, only 13 were comparative studies. All original published studies on Lung Volume Reduction Surgery were identified by searching SilverPlatter Medline (WinSpirs); Ovid Current Contents; The Cochrane Collection (The Cochrane Library CD–1998, Issue3); and Lexis-Nexis Embase. Human studies, specifically pa- tients with any distribution of emphysema (upper, lower and diffuse) were included in this review. Bullous emphysema of all types was excluded. English language papers detailing randomised- controlled clinical trials, case series or case reports were included. Results: The studies were either Level II or Level III evidence, that is, randomised or unrandomised controlled trials. However, only one study compared LVRS with another method of treatment. This study compared patients who were selected for but denied LVRS due to changes in government funding arrangements in the United States. Despite higher earlier mortality in the LVRS group, at three years, improve- ment in pulmonary function was still apparent in the LVRS group, and mortality was less than in those denied the procedure. Other studies compared the different LVRS procedures, and also variations on the procedures, such as staple versus laser, stapling with and without buttressing, and unilateral versus bilateral lobectomy. Pulmonary function parameters were used most com- monly to indicate postoperative improvements. Stapling appeared to provide greater improve- ment in the short-term, while butturing of the staple line offered no clear improvement. There are no significant differences were found between bovine pericardium or collagen. Mortality of the procedure is often significant, reports vary between 0% and 28%. The most common adverse outcome is arterial air leak, occurring in about 50% of cases in in-study periods. Other complications, which generally occurred in less than 10% of cases, included pneumonia, delayed pneumothorax, respiratory failure and wound infection. Re-operation was also necessary in a small number of cases due to pleural space problems, including bleeding. Conclusion and Recommendations: No one technique appears to be the most safe and efficacious for LVRS and the ability to suffer from significant harm is considerable to follow-up and insufficiently long in the individual trials. The reviewer suggests that both bilateral and unilateral LVRS using stapling-excision and median sternotomy in highly selected cases, to be a safe and reasonable efficacious procedure for treatment of diffuse emphysema. Similar results have been obtained using stapling-excision. Laser ablation by VATS, despite producing encouraging results in bullous emphysema produced higher one-year mortality, frequent late pneumothorax and less functional improve- ment than stapling excision in diffuse emphysema. This procedure is not recommended as a safe and efficacious treatment for diffuse emphysema at this time. Two large multi-centre trials have been set up in both America and Canada to assess surgical treatments of LVRS and compare them to medical management. Results from these studies are still a few years away.
EFFICACY

Efficacy is evaluated in terms of survival at a given time point after surgery, as well as various measurable outcomes such as cancer recurrence rates, pulmonary function, and reduction in delays for planned adjuvant chemotherapy. The time point at which overall survival is evaluated, as well as the types of complications evaluated, vary across studies. When studies did not report results for specific areas, the corresponding table sections were omitted.

Cheng et al. found that the incidence of death did not differ significantly between VATS and open lobectomy at one year or three years. However, there was a significant reduction in mortality at five years. Because of the sparse number of RCTs available, these outcomes were largely influenced by nonrandomized trial data.27

In contrast, Flores et al. found that there was no significant difference between VATS and open surgery in RCTs studied with respect to 5-year survival rate.28 Cheng et al. also performed an aggregate analysis on the 20 trials reporting death at any time point, defining this as the “maximum follow-up” time point, and found a statistically significant 29% reduction in the odds of death at this time point.27 Whitson et al. found that the overall rate of complications following VATS versus open lobectomy are also evaluated in terms of complications. The complications selected by individual studies varied widely. Those selected for aggregate analysis by Whitson et al. and/or by Cheng et al. included the overall complication rate, chest tube duration, hospital length of stay (also used to evaluate costs), incidence of atrial fibrillation, pneumonia, persistent air leak, pulmonary complications, blood loss, and 30-day post-operative mortality. These outcomes are summarized in table 13.

Cheng et al. found that the overall complication rate was significantly reduced in the VATS group compared with the open group (OR 0.48, 95% CI 0.34-0.70). This result was comparable in both randomized and nonrandomized trials.27 Similarly, Whitson et al. found that the overall rate of complications following VATS versus open lobectomy significantly favored the VATS approach.29

Cheng et al. reported that the duration of chest tube placement was reduced by approximately one day in the VATS group compared to the open group.32 This is similar to the decrease of 1.5 days for chest tube duration for VATS surgery compared with open surgery found by Whitson et al.33 In addition to the significant decrease in the number of days of drainage, Cheng et al. reported that the mean volume of chest tube drainage was also significantly reduced (-106 mL, 95% CI -206 to -7 mL).

The rates of local and distant cancer recurrence were not found to be significantly different for VATS versus open surgery. VATS surgeries were associated with significantly shorter delays in planned adjuvant chemotherapy than open surgery. However, it is important to note that these data were only reported in a single trial.34 Similar to Cheng et al., Flores determined that there was no significant difference in the cancer recurrence rates.

SAFETY

In contrast, Flores et al. found that there was no significant difference between VATS and open surgery in the RCTs studied with respect to the length of hospital stay, blood loss, or chest tube duration.29

Comparisons of VATS to open surgery for lobectomy are also evaluated in terms of complications. The complications selected by individual studies varied widely. Those selected for aggregate analysis by Whitson et al. and/or by Cheng et al. included overall lung cancer recurrence, total number of complications, chest tube drainage, hospital length of stay, post-operative mortality, incidence of atrial fibrillation, pneumonia, persistent air leak, pulmonary complications, bleeding, and 30-day post-operative mortality. These outcomes are summarized in table 13.

Cheng et al. found that the overall complication rate was significantly reduced in the VATS group compared with the open group (OR 0.48, 95% CI 0.34-0.70). This result was comparable in both randomized and nonrandomized trials.27 Similarly, Whitson et al. found that the overall rate of complications following VATS versus open lobectomy significantly favored the VATS approach.29

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The rates of local and distant cancer recurrence were not found to be significantly different for VATS versus open surgery. VATS surgeries were associated with significantly shorter delays in planned adjuvant chemotherapy than open surgery. However, it is important to note that these data were only reported in a single trial.34 Similar to Cheng et al., Flores determined that there was no significant difference in the cancer recurrence rates.

OVERALL SURVIVAL

Table 12: Overall survival rates as a function of the time post-surgery. Significant differences between VATS and open surgery are shown in bold. OR = odds ratio, 95% CI = confidence interval, WMD = weighted mean difference.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Studies</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>VATS open pValue</td>
<td>98.2%, 91.2%, 0.28</td>
<td>OR 0.78, 95% CI 0.54-1.77</td>
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<tr>
<td>2 Year</td>
<td></td>
<td></td>
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<tr>
<td># Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VATS open pValue</td>
<td>91.6%, 84.9%, 0.12</td>
<td></td>
</tr>
<tr>
<td>3 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Studies</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>VATS open pValue</td>
<td>87.2%, 81.6%, 0.18</td>
<td>OR 0.109, 95% CI 0.60-1.77</td>
</tr>
<tr>
<td>4 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VATS open pValue</td>
<td>88.4%, 71.4%, 0.003</td>
<td></td>
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<tr>
<td>5 Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Studies</td>
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<td></td>
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<tr>
<td>VATS open pValue</td>
<td>80.1%, 65.6%, 0.064</td>
<td>OR 0.1-0.67, 95% CI 0.47-0.97</td>
</tr>
<tr>
<td>Maximum Follow-Up</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Studies</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>VATS open pValue</td>
<td></td>
<td>OR 0.71, 95% CI 0.54-0.93</td>
</tr>
</tbody>
</table>

Table 13: Outcome measures for VATS versus open surgery lobectomy. Significant differences between VATS and open surgery are shown in bold. OR = odds ratio, 95% CI = confidence interval, WMD = weighted mean difference.
Although Cheng et. al.\(^27\) reported that blood loss was significantly reduced for VATS versus open lobectomy, they found that the following were not significantly reduced: incidence of excessive blood loss (OR 0.45, 95% CI 0.13-1.60), incidence of re-exploration for bleeding (OR 0.10, 95% CI 0.01-2.00), or the number of patients transfused (OR 0.59, 95% CI 0.14-2.49).\(^27\) In contrast, Flores et. al. found that there was no significant difference between VATS and open surgery in the RCTs studied in regards to blood loss and chest tube duration.\(^29\)

The differences in the rates of atrial fibrillation, pneumonia, and persistent air leak for VATS versus open surgery were all determined to be statistically non-significant.\(^27\)\(^29\) However, Cheng et. al. reported that pulmonary complications were significantly less common in the VATS group compared with those who underwent open lobectomy.\(^27\) Cheng et. al. also found that there was no significant difference in 30-day mortality rate following surgery with VATS versus open lobectomy.\(^27\)

### Table 14: Complications as a function of VATS versus open surgery lobectomy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Complications Rate</td>
<td># Studies</td>
<td>20</td>
</tr>
<tr>
<td>VATS</td>
<td>16.4%</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>31.2%</td>
<td></td>
</tr>
<tr>
<td>pValue</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td># Studies</td>
<td>16</td>
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</tr>
<tr>
<td>VATS</td>
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<td></td>
</tr>
<tr>
<td>Open</td>
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<td></td>
</tr>
<tr>
<td>pValue</td>
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</tr>
<tr>
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<tr>
<td>VATS</td>
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</tr>
<tr>
<td>Open</td>
<td>13.3%</td>
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</tr>
<tr>
<td>pValue</td>
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Significant differences between VATS and open surgery are shown in bold.

\(^1\)OR = odds ratio; \(^2\)CI = confidence interval; \(^3\)WMD = weighted mean difference.

### Table 14 (cont): Complications as a function of the time post-surgery

<table>
<thead>
<tr>
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<tr>
<td>Persistent Air Leak</td>
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<tr>
<td>VATS</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>pValue</td>
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<td></td>
</tr>
<tr>
<td>Pulmonary Complications</td>
<td># Studies</td>
<td>5</td>
</tr>
<tr>
<td>VATS</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>pValue</td>
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<td></td>
</tr>
<tr>
<td>Blood Loss</td>
<td># Studies</td>
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</tr>
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<tr>
<td>Open</td>
<td>5.7%</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td># Studies</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>VATS</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>pValue</td>
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<tr>
<td>Mortality Within 30 Days of Surgery</td>
<td># Studies</td>
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</tr>
<tr>
<td>VATS</td>
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<td></td>
</tr>
<tr>
<td>Open</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>pValue</td>
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<td></td>
</tr>
</tbody>
</table>

Significant differences between VATS and open surgery are shown in bold.

\(^1\)OR = odds ratio; \(^2\)CI = confidence interval; \(^3\)WMD = weighted mean difference.
QUALITY OF LIFE

Many different quality of life (QOL) assessment tools exist for characterizing this important outcome. Standardization of the QOL forms has resulted in general agreement for several specific survey forms. Demmy et al. specifically mention 20 such forms and note that additional forms exist. Whitson et al. do not address QOL outcomes, but Cheng et al. report numerous QOL assessment outcomes, some of which were significantly superior in patients undergoing VATS compared to open lobectomy (severe postoperative pain, postoperative pain up to one year following discharge from the hospital, and analgesic requirements; statistical values are shown below).

Severe Postoperative Pain
OR 0.03 CI 0.00–0.30 (1 non-RCT)

Analgesic Requirements (total dose requirements)
SMD –4 units 95% CI –7 to –1 units (4 non-RCTs)

However, other QOL assessment outcomes (life scores for overall quality of life, overall impression of operation, overall incidence of postoperative pain, satisfaction related to wound numbness, shoulder strength at three months, overall patient-reported physical scores at 3 years follow-up) were not significantly different between these two groups of patients. The statistical values are reported below.

Life Scores for Overall Quality of Life
WMD 8.8 points 95% CI –2.4 to 20.0 (1 non-RCT)

Overall impression of operation
SMD 0.32 95% CI –0.12 to 0.75 (2 non-RCTs)

Overall Incidence of Postoperative Pain
OR 0.47 95% CI 0.17–1.29 (2 non-RCTs)

Satisfaction Related to Wound Numbness
WMD –0.2 95% CI –0.63 to 0.23 (1 non-RCT)

Overall Patient-Reported Physical
WMD 1.40 points CI –5.23–8.03 points function scores at 3 years follow-up (1 non-RCT)

The importance of these outcomes is difficult to interpret because, with the exception of analgesic requirements, they were drawn from only one or two studies.

Demmy et al. found that, of the subjective measures of QOL reported in 12 separate studies, improved pain control was the most common benefit, and this, in turn, positively influenced other secondary outcomes. The authors conclude that “…there is sufficient objective evidence to reassure patients and physicians that VATS lobectomy is noninferior in terms of long-term cancer survival and superior in terms of certain dimensions of QOL.”

Flores et al. also found that patients tend to experience less pain with VATS lobectomy procedures.29

ECONOMIC FACTORS

Cheng et al. reported that the operating time was 16 minutes longer for patients undergoing VATS, but their mean hospital length of stay was significantly shorter by 2.6 days.27 Although the total costs for surgery and hospitalization were significantly higher for VATS than for open lobectomy, the values were based on the standardized mean difference from two small studies which evaluated differences in costs retrospectively. Moreover, they were performed in two different care settings and used different definitions for cost.27

Whitson et al. reported that the length of the hospital stay following VATS lobectomy was approximately 5 days shorter than that for open lobectomy.21

<table>
<thead>
<tr>
<th>Mean Hospital Length of Stay (days)16</th>
<th>Whitson (2008)</th>
<th>Cheng (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Studies</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>VATS</td>
<td>8.3, 95% CI (6.9–9.8)</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>13.3, 95% CI (8.5–17.1)</td>
<td></td>
</tr>
<tr>
<td>*p Value</td>
<td>.016</td>
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</table>

<table>
<thead>
<tr>
<th>Surgical Length of Time*</th>
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<td># Studies</td>
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<td>VATS</td>
<td>24</td>
</tr>
<tr>
<td>Open</td>
<td></td>
</tr>
<tr>
<td>*p Value</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Costs for Surgery and Hospital Stay*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># Studies</td>
<td>2</td>
</tr>
<tr>
<td>VATS</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td></td>
</tr>
<tr>
<td>*SMD 0.72, 95% CI 0.21–1.12 P = 0.0005 See note C (below)</td>
<td></td>
</tr>
</tbody>
</table>
What are the key statistics about lung cancer?

Cancer incidence, mortality, and prevalence


Current Surgical Diagnosis and Treatment, 11th Edition 2003 NY, McGraw Hill; Chapter 19; David Jablons, Robert B. Cameron, MD, Kevin Turle, MD. Neoplasms of the Lung.

Current Surgical Diagnosis and Treatment, 11th Edition 2003 NY, McGraw Hill; Chapter 19; David Jablons, Robert B. Cameron, MD, Kevin Turle, MD. Neoplasms of the Lung.


SOURCES FOR FIGURES AND TABLES

Figures

Figure 1. http://www.nlm.nih.gov/medlineplus/ency/images/page103.htm (copyright 2005, A.D.A.M., Inc.)

Figure 2: http://www.cancercontrol.org/figures/section-22


Table 2: ACS: Detailed Guide: Lung Cancer What Are the Key Statistics for Lung Cancer? http://www.cancer.org/docroot/CRI/content/CRI什麼Section-22

Table 3: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/HCPatientFriendlyPage#Section-22


Table 5: Data for the outcomes by 36 lobectomy or pneumonectomy procedures from the 2006 national statistics.

Table 6: Data for the outcomes for multiple specific diagnoses from the 2006 national statistics.


Table 8: JNCI Journal of the National Cancer Institute 2008 100(24): 1755-1762.


Tables 10-11: Bibliographic summary of the studies used to compare VATS and open surgery with respect to efficacy, safety, quality of life, and economic outcomes.

Table 12: Overall survival rates as a function of the time post-surgery.

Table 13: Outcome measures for VATS versus open surgery lobectomy.

Table 14: Complications as a function of VATS versus open surgery lobectomy. Complications as a function of the time post-surgery.

Table 15: Resource utilization and costs.

Table 16: Economic outcomes.

Table 17: Table 1: Resource utilization and costs.

Table 18: Table 2: Economic outcomes.

Table 19: Table 3: Economic outcomes.

Table 20: Table 4: Economic outcomes.

Table 21: Table 5: Economic outcomes.

Table 22: Table 6: Economic outcomes.

Table 23: Table 7: Economic outcomes.

Table 24: Table 8: Economic outcomes.

Table 25: Table 9: Economic outcomes.

Table 26: Table 10: Economic outcomes.

Table 27: Table 11: Economic outcomes.