Welcome to
Master Class for Oncologists

Los Angeles CA
October 3, 2008

Session 1:
1:30 PM - 2:15 PM
Innovations in The Surgical Treatment of Lung Cancer
Speaker:
Scott J. Swanson, MD

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Scott Swanson is a consultant to Ethicon Endo-Surgery

Off Label/Investigational Discussion
In accordance with Pri-Med Institute policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

1. What is the current standard of care for treatment of a 2.0 cm non-small cell lung cancer, specifically what operation is best?

1. Lobectomy
2. Segmentectomy
3. Wedge resection
4. Radiofrequency ablation
5. Stereotactic radiation

2. What are reported advantages of a VATS lobectomy over a thoracotomy and lobectomy?

1. Lower cost, decreased need for general anesthesia, technically easier
2. Shorter anesthetic, simpler to learn, less manipulation of lung during surgery
3. Less need for operative equipment, more lymph nodes removed, shorter operative time
4. Decreased pain, decreased length of hospital stay and lower peri-operative complications

3. What is the best treatment option for an otherwise fit 80 year old patient with a 3.5 cm non-small cell lung cancer?

1. Best supportive care
2. External beam radiation
3. Stereotactic radiation
4. VATS lobectomy
5. Radiofrequency ablation
4. What is the best treatment for stage IIIa non-small cell lung cancer in a fit patient with a 3 cm peripheral right upper lobe tumor and involvement of 4R and 7 identified by EBUS?

1. Induction therapy followed by re-staging and if mediastinal clearance then lobectomy and lymph node dissection. If no mediastinal clearance then further chemotherapy and possibly radiation therapy
2. Definitive chemoradiotherapy
3. Stereotactic radiation and chemotherapy
4. Lobectomy with radical node dissection followed by adjuvant chemotherapy
5. Induction therapy followed by pneumonectomy and radical node dissection

History of Surgery for Lung Cancer

• Evarts Graham (St Louis) reported the first successful pneumonectomy for lung cancer using a tourniquet technique in 1933
• Churchill (Boston, 1950) suggested lobectomy was a good option for surgical treatment of lung cancer
• Bonfil-Roberts and Claggett (NY, Minneapolis, 1972) reported that segmentectomy was reasonable for small lung cancers
• Currently lobectomy with lymph node dissection is the gold standard for surgical treatment of lung cancer

Innovations in the Surgical Treatment of Lung Cancer

• Thoracoscopic Technique
• Size of the resection – segmentectomy/wedge vs lobectomy
• Integrating chemotherapy, radiation therapy and surgery
• Surgery for special populations
  – Elderly
  – Severe Emphysema
• Alternatives to Surgery
  – Stereotactic Radiation – “Cyberknife”
  – Radiofrequency Ablation

Video-Assisted Thoracic Surgery or VATS

• Definition- via several small incisions (1-2cm) and videoscopic camera, lung surgery is performed with small instruments watching a TV monitor. No rib spreading is permitted
• Lewis (NJ) reported the first lobectomy using this technique in 1992
• Potential advantages – less pain, shorter hospital stay, less complications, improved pulmonary function, improved shoulder function, better cosmesis, decreased immune suppression and inflammation. Recently some evidence for improved long term survival

VATS Example – initial view right upper lobectomy

VATS Example – specimen removal
VATS Example – chest view after specimen removal

Survival following surgery for stage I NSCLC

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mani et al [10]</td>
<td>128</td>
<td>72</td>
</tr>
<tr>
<td>Williams et al [10]</td>
<td>401</td>
<td>71</td>
</tr>
<tr>
<td>Tanaseki et al [9]</td>
<td>129</td>
<td>71</td>
</tr>
<tr>
<td>Mounts et al [3]</td>
<td>725</td>
<td>68</td>
</tr>
<tr>
<td>Nazor et al [5]</td>
<td>506</td>
<td>65</td>
</tr>
<tr>
<td>Zhang et al [15]</td>
<td>752</td>
<td>64.6</td>
</tr>
<tr>
<td>Mounts [2]</td>
<td>805</td>
<td>63.5</td>
</tr>
<tr>
<td>Shimos et al [18]</td>
<td>288</td>
<td>61.7</td>
</tr>
<tr>
<td>Bedwinek et al [6]</td>
<td>439</td>
<td>58</td>
</tr>
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</table>

Mean 5-year survival rate: 64.8%

*(Published before the BLA; last appropriate sources are used for this analysis.)*

Failure-Free Survival

CALGB 39802

![Failure-Free Survival Graph](image)

Disease-free survival in Stage I NSCLC

![Disease-Free Survival Graph](image)

VATS lobectomy results in 1100 pt - McKenna

VATS lobectomy – Outcomes

Cedars Sinai McKenna
VATS Lobectomy - Outcomes

CALGB 39802

- 6 intergroup centers, 11 surgeons, 127 pts
- T< 3cm, outer half, no N2
- 111/127 (87%) – stage I lung cancer
- Median procedure length – 130 min (47-428)
- 60 % had biopsy at time of procedure
- Median chest tube duration – 3d (1-14)
- Conversion 14/111 = 13%
- Mortality = 3/97 (3.1%)
- Morbidity = 8/97 (8.2%)
  - SVT – 5/97 (5.2%)
  - Bleeding – 2/97 (2.1%) – Rx = chest tube
  - Prolonged air leak – 1/97 (1%)


VATS Lobectomy Outcomes Comparisons

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Results</th>
<th>Common</th>
</tr>
</thead>
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<td>CALGB 39802</td>
<td>VATS</td>
<td>60 % had biopsy</td>
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Size of Resection for Lung Cancer

- Standard = lobectomy
- Increased usage of CT scans, changing epidemiology and more interest in screening programs has resulted in tumors being identified at a smaller size
- Data for superiority of lobectomy over wedge or segment is scarce
- New trial to re-examine this question – CALGB 140503

VATS Lobectomy Summary

- Current evidence would suggest that a lobectomy done using thoracoscopic or VATS approach is preferred for stage I and possibly stage II NSCLC
- Benefits of this approach include
  - Shorter hospital stay
  - Fewer peri-operative complications
  - Less pain
  - Better patient satisfaction
  - Potentially improved pulmonary function
  - Potentially better chemotherapy tolerance
- Long term survival is at least as good as with an open approach
- The operation does require technical competence

Lobectomy vs Wedge Resection

LCSG Trial

<table>
<thead>
<tr>
<th>Graph</th>
<th>Log rank test</th>
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Lobectomy vs Sublobar Resection for Stage I NSCLC

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<tr>
<th>Graph</th>
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</table>
Lobectomy vs Segmentectomy – Osaka Experience


**CALGB 140503**

- A phase III randomized trial of lobectomy vs sublobar resection for small (<2cm) peripheral NSLC – Nasser Altorki PI
- Major North American Trial – CALGB, ACOSOG, SWOG, NCIC, RTOG
- Patients with lung nodules < 2cm and peripheral on CT scan

**Objectives**
- Primary - determine disease-free survival
- Secondary
  - Determine overall survival
  - Pulmonary function at 6 months
  - Radiologic endpoints – PET predictors of outcome, CT f/u

**Peripheral = outer 1/3 by CT**
- Pure GGO and N2/N1 excluded
- Mediastinoscopy
  - to rule out N2 disease (within 6 wks of resection)

**Stratification**
- <1cm, 1-1.5cm, >1.5-2.0cm
- Histo- squamous, adeno, other
- Smoking status
  - never (<100cig)
  - former (>100 cigs and quit >1yr ago)
  - current (>100 cigs within 1yr or active)

**Accrual goal = 1297, opened in 6-07**

Operative Considerations

- Wedge/Segment – permissible by VATS
- Segment - individual vascular and bronchial dissection
- Margin
  - 2 cm or diameter of lesion
  - measured by surgeon on deflated lung and noted in record
- Frozen section- not mandated but encouraged
- Positive margin
  - failure
  - pts treated at surgeon’s discretion and followed

Size of surgical resection for stage I NSCLC Summary

- Standard of care for stage I NSCLC is a lobectomy
- However for tumors < 2cm consideration should be given for a segmentectomy (preferred) or wedge resection
- This should lead to improved pulmonary function and ability to have further surgery in the future should other tumors develop without compromising survival
- The best way to consider this option is in the setting of a clinical trial (CALGB 140503)

Multi-Modal Therapy for Stage IIIa disease

Multi-Modal Therapy for Stage IIIa disease

Lung Intergroup Trial 0139 Study Design

- No progression at re-evaluation
- No progression at re-evaluation
- No progression at re-evaluation
- No progression at re-evaluation

Surgical Resection
Continue RT to 61 Gy without interruption
CONSOLIDATION
cisplatin plus etoposide
X 2 cycles

Lobectomy following induction therapy is significantly superior to chemoradiation only

INT0139 Trimodality Arm Overall Survival by Pathologic Nodal Status

Pathologic N0 (pN0)
Pathologic N1 (pN1, not evaluable)
No surgery (pN2)

p = 0.03941

INT0139 Trimodality Arm Comparison of Overall Survival Between Nodal Status at Surgery

- T4N0 a: 36.1% vs. 23.6%
- T4N1-2 vs. 42.8%
- No surgery: 8.9%

Nodal Downstaging Predicts Improved Survival Following Induction Therapy for Stage III disease

Lung Intergroup Trial 0139/RTOG 9309 Conclusions

- N0 status at surgery significantly predicts greater 5-year survival
- The trimodality approach is not optimal when a pneumonectomy is required due to high mortality risk
- Surgical resection after C/RT can be considered for fit patients if lobectomy is feasible
Nodal downstaging, complete resection and lack of complication predict improved outcome in stage IIIa.

Adjuvant chemotherapy for stages IB-IIIa ANITA Trial

Douillard et al

ACCP guidelines for Stage IIIa (N2) NSCLC

• If N2 disease is found at surgery and complete resection is possible
  – Resection followed by chemotherapy and possibly RT
• If N2 disease is found prior to resection refer for multimodality therapy
  – Induction therapy followed by surgery should only be done as part of a clinical trial
• Pt should not have pneumonectomy following chemoradiation
• Surgery or radiation only is not recommended
• Primary treatment should be chemoradiation

Treatment of Stage IIIa NSLC

Summary

• Controversial
• ACCP guideline to recommend definitive chemoradiotherapy as primary treatment choice (may be improved by adding surgical resection in appropriate patients) is not justified by the data
• Induction therapy followed by surgery which does not involve a pneumonectomy (may) give(s) the best outcome
• When (mediastinal lymph nodes are no longer involved) downstaging after induction therapy occurs are those patients will show most are most likely to benefit from surgical resection therefore consider role of re-staging (VATS, EBUS, EUS)
• If N2 disease is determined at the time of resection particularly if single station disease and/or in setting of negative PET scan and with the results of studies such as ANITA, surgeon should consider lobectomy and complete mediastinal node dissection followed by adjuvant chemotherapy

Surgery for Special Populations

• Limited pulmonary reserve
• Elderly – pts >70

Limited Pulmonary Reserve

• High Risk is variable definition
  – Pre-operative FEV1 < 50% predicted
  – Predicted postoperative FEV1 < 800 ml following lobectomy
  – Pre-operative DLCO < 50% predicted
  – VO2 max < 15 ml/m2

• Conventional treatment for high risk subjects is best supportive care, chemotherapy or radiation therapy if symptomatic
Innovative Treatment for High Risk Patients

• Further work-up with quantitative v/q scan to determine if surgical target is providing significant amount of functioning lung
• Surgical treatment options include:
  – Wedge
  – Wedge and brachytherapy
  – Segmentectomy
  – Lobectomy
• VATS approach is particularly helpful in this setting – avoids pain issues and transecting muscles providing respiratory function
• Alternative treatments – radiofrequency ablation and stereotactic radiation

Innovative Treatment for High Risk Patients

• Evidence basis for treatment decisions in this setting is limited
• VATS lobectomy or segmentectomy is preferable particularly if v/q scan suggests minimal function in target lung (< 10%)
• Wedge + brachytherapy does appear to decrease local recurrence rates relative to wedge alone
  Landreneau Ann Thorac Surg Feb 2006
  – Current ACOSOG trial is ongoing to confirm this
• Alternative treatments (cyberknife, RFA) may be feasible but evidence to date suggests increased local recurrence vs. surgical resection
  • ACOSOG trial is ongoing to examine feasibility of RFA in high risk patients

Innovative Treatment for Elderly Patients

• Data is limited in this setting
• SEER-data suggests if pt is over 71 then wedge and lobectomy have similar survival outcomes
  Mery et al. Chest July 2005
• VATS lobectomy is feasible and has excellent outcomes
  Shaw, Swanson et al Ann Thor Surg March 2007
• Alternative treatment in this population has not been examined

Innovative Treatment in Special Populations - Summary

• Surgical treatment appears feasible and relatively safe although careful diagnostic work-up and surgical expertise is important
• Minimally invasive options may be particularly useful
• Alternative treatment may be of benefit but adequate data is currently not available to make informed decisions

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Questions & Answers

Thank you for attending Master Class for Oncologists