Advances in Thoracic Surgical Oncology

Gita N. Mody, MD MPH
Assistant Professor
Division of Cardiothoracic Surgery
UNC Chapel Hill
UNC Lineberger Cancer Network
Research to Practice Lecture Series
July 28, 2021

Disclosures

Research funding and unpaid consulting from Sivan Ltd.
Research grant from American College of Surgeons
Learning Objectives

- Describe approaches to early stage lung cancer treatment based on tumor size and location
- Compare treatment strategies for advanced lung cancer
- Discuss the advantages of a multidisciplinary approach to the diagnosis and treatment of lung cancer

Outline of talk

- Early stage lung cancer
  » Lobar resections
  » Sublobar resections
  » Nodule localization
  » Minimally invasive surgery
  » SBRT

- Advanced stage lung cancer
  » Defining resectability
  » Neoadjuvant regimens
  » Adjuvant regimens

- Highlights from 101st AATS and ASCO 2021
Lung and Bronchus Cancer - Cancer Stat Facts.

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

Percent of Cases by Stage

- Localized (18%)
- Regional (22%)
- Distant (59%)
- Unknown (11%)
- Unstaged

5-Year Relative Survival

- Localized: 90.1%
- Regional: 33.1%
- Distant: 8.3%
- Unknown: 0.4%
Surgery for lung cancer overview

- **Stage I/II (localized):**
  - First line for medically operable
  - Adjuvant chemotherapy for stage II (>4cm or N1)

- **Stage IIIa (regional):**
  - Upfront for no mediastinal involvement (T4N0, T3-4N1)
  - After neoadjuvant for mediastinal involvement (T1-2,N2)

- **Stage IIIb/IV:**
  - Typically for diagnosis/palliation

Outline of talk

- **Early stage lung cancer**
  - Lobar resections
Lung cancer case presentation # 1

- 58yF current smoker
- Incidental RUL nodule on CT scan after MVC 3 years previously
- Enlarged to 3cm on serial CT scans

Lost to follow up
Developed symptoms
Staging PET showed avid hilar and mediastinal lymph nodes
Thoracic surgery is the mainstay of curative treatment of early stage lung cancer.

- >80,000 lung resection procedures are performed annually in the United States.

- Surgeries are increasing by 1.7% per year.


Images from https://www.mskcc.org/cancer-care/patient-education/about-your-thoracic-surgery
Lobectomy improves outcomes (long term survival, recurrence rates)


13

Lung cancer case presentation # 1

- Mediastinal staging (N2 nodes negative)
- Video Assisted Thoracoscopic Surgery (VATS) right upper lobectomy
- pT2a (3.5cm) N1
- Adjuvant chemotherapy
Outline of talk

• Early stage lung cancer
  » Lobar resections
  » Sublobar resection
    • Marginal pulmonary function
    • Multifocal disease

Segmentectomy has equivalent short-term survival to lobectomy.

|                  | 30-day mortality | Difference [95% CI]
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar resection</td>
<td>Sublobar resection</td>
</tr>
<tr>
<td>Overall</td>
<td>4/357 (1.13%)</td>
<td>2/340 (0.6%)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>1/87 (1.13%)</td>
<td>0/81 (0%)</td>
</tr>
<tr>
<td>61-70 years</td>
<td>2/42 (0.4%)</td>
<td>0/41 (0%)</td>
</tr>
<tr>
<td>71-80 years</td>
<td>1/111 (0.9%)</td>
<td>2/103 (1.9%)</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>1/37 (3.9%)</td>
<td>0/15 (0%)</td>
</tr>
</tbody>
</table>

Outline of talk

- Early stage lung cancer
  - Lobar resections
  - Sublobar resection
    - Marginal pulmonary function
    - Multifocal disease
  - Nodule localization
Lung cancer case presentation # 2

- 63yM w former smoking history
- Scan for restaging of lymphoma
- Increasing 2.5cm ground glass opacity in right lower lobe

Non-solid/small/central nodules may need intraoperative localization.

Preop CT Scan data is used to map nodule location during intraoperative bronchoscopy using electromagnetic sensors in pads on chest, bronchoscope tip.

Dye (blue, fluorescent) is injected at the mapped site.

Surgeon visualizes dye(s) intraoperatively.

New technology can be employed to simultaneously diagnose and localize nodules.


Novel approaches to localizing lesions are being developed.
Novel approaches to localizing lesions are being developed.

- Clinically introduced in Japan in September 2019 as first in human trials
- Kyoto and Fukuoka University investigators reported initial experience:
  » 19 lesions
    - 10 wedges
    - 6 subsegments
    - 2 segments
    - 1 wedge to lobectomy
  » Margin depth mean 10 (3-14) mm
  » No adverse events


Outline of talk

- Early stage lung cancer
  - Lobar resections
  - Sublobar resections
  - Nodule localization
  - Minimally invasive surgery
    - Video Assisted Thoracoscopic Surgery
    - Robotic Assisted Thoracoscopic Surgery

VIOLET establishes minimally invasive for early stage lung cancer resection.

Phase 2, in 9 centres (24 months recruitment)

All patients referred for lobectomy for lung cancer (100%) n=1312

Not eligible, 40%, n=525
Not recruited, 50% in phase 1 centres, 70% phase 2 centres in first 6 months, 50% thereafter, n=411

Eligible for VIOLET (60%)
336 randomised to:

168 VATS 168 Open surgery

Phase 1 & 2 patients (162+336) followed up after surgery, n=498

>95% followed to primary outcome (5 weeks), 80% followed to 1 year

VIOLET establishes minimally invasive for early stage lung cancer resection.

- **Study design**
  - cT1-3, N0-1 and M0 lung cancer
  - 56 months, 503 participants

- **Results favor VATS:**
  - less pain on VAS
  - less analgesic consumption
  - better physical function (EORTC QLQ-C30)
  - improved global health status
  - fewer complications
  - no difference in serious adverse events
  - hospital stay was shorter (4 vs 5 days)
  - lower 1 year readmission rates (29.0% vs. 35.9%)
  - Similar PFS (HR 0.74, 0.43 to 1.27; p=0.27)
  - Similar OS (HR 0.67, 0.32 to 1.40; p=0.282)

Lim E., et al. Video-assisted thoracoscopic versus open lobectomy in patients with early-stage lung cancer: One-year results from a randomized controlled trial (VIOLET). ASCO 2021 abstract

---

Robotic Assisted Thoracoscopic Surgery

Slide courtesy Dr. Jason Long, UNC.
Robotic technology may increase access to surgery for high risk patients.

Anatomic lung resections for primary lung cancer


- Society of Thoracic Surgery (STS) database analysis
- 634 Robotic, 2,200 VATS, and 562 open segments
- Robotic segments removed >=6 lymph nodes more commonly (34% vs. 14% vs 18%; p <0.001)
- Upstaging 6.2% (compared to 5.6% VATS, 8.2% Open, p = 0.049)

Outline of talk

- Early stage lung cancer
  - Lobar resections
  - Sublobar resections
  - Nodule localization
  - Minimally invasive surgery
  - SBRT

SBRT may be non-inferior to VATS lobectomy for operable stage IA NSCLC.

- STARS and ROSEL randomized trials
  - Lobectomy + MLND vs. SBRT in operable stage 1 lung cancer
  - Equivalent rates of progression
  - Higher 3-year overall survival (OS) for SBRT (95% vs 79%)
  - Variable use of VATS

- SBRT (n=80) vs. historical cohort VATS Lobectomy + MLND
  - OS 87% (95% CI: 79-95%) at 5 years (compared to 72%).
  - PFS 77% (95% CI: 68-87%) at 5 years.
  - Propensity score matched (age, gender, tumor size, histology, PS) comparison of SBRT vs VATS L-MLND showed non-inferiority.

Chang et al., Stereotactic ablative radiotherapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial. ASCO 2021 abstract.
Surgery for lung cancer overview

- **Stage I/II (localized)**
  » First line for medically operable
  » Adjuvant chemotherapy for stage II (>4cm or N1)

- **Stage IIIa (regional):**
  » Upfront for no mediastinal involvement (T4N0, T3-4N1)
  » After neoadjuvant for mediastinal involvement (T1-2,N2)

- **Stage IIIb/IV:**
  » Typically for diagnosis/palliation

Outline of talk

- **Early stage lung cancer**
  » Lobar resections
  » Sublobar resections
  » Nodule localization
  » Minimally invasive surgery
  » SBRT

- **Advanced stage lung cancer**
  » Defining resectability
Role of Surgery in stage III disease

Stage IIIa (T3N1, T4N0-N1)
- Location dependent and “resectable”
  - Tumors of chest wall (T3), proximal airway and mediastinum (T4) = surgical resection
  - T3 superior sulcus tumors: pre-operative chemoradiation followed by surgery
  - T4 superior sulcus tumors: definitive chemoradiation followed by immunotherapy

Surgical technology can be used to perform increasingly extended resections.

Surgical technology can be used to perform increasingly extended resections.

- 32 patients/12 years
- 56% major morbidity
- 3% 30 day mortality
- 1 year survival 73.6%
- 5 year survival 40.3%


doi: 10.1016/j.athoracsur.2015.05.131. PMID: 27000584.


doi: 10.1016/j.athoracsur.2015.05.131. PMID: 27000584.
Outline of talk

- **Early stage lung cancer**
  - Lobar resections
  - Sublobar resections
  - Nodule localization
  - Minimally invasive surgery
  - SBRT

- **Advanced stage lung cancer**
  - Defining resectability
  - Neoadjuvant regimens

Controversies in Stage IIIa (especially N2)

- SWOG 8805 (1995): established safety of induction concurrent CRT (45 Gy) in N2/N3 and/or T4
- RTOG 0229 (2012): 61.2Gy
- Intergroup 0139 (2009)
  - Induction chemoradiation -> if no progression, 1: surgery 2: continued radiotherapy
  - No overall survival advantage between two groups; Progression free survival better in surgery arm
  - Subgroup analysis: improved overall survival in patients receiving lobectomy, rather than pneumonectomy
- ESPATUE (2015)
  - Induction chemoradiation -> if tumors deemed resectable, 1: surgery 2: chemoradiation boost
  - No difference in 5 year overall survival

- Mediastinal clearance improves OS
- Surgical resection may be best indicated for large tumors with sterilized mediastinum

Surgery is increasingly considered in patients with advanced NSCLC.

- **Design**
  - Pooled analysis of 3 Swiss trials
  - IIIa (including single-multistation N2) and IIIb
  - Chemo (3 cycles cisplatin/docetaxel + surgery vs. chemo + sequential RT (44Gy) + surgery

- **Results**
  - 81% of 197 patients resected
  - 80% R0 including 30/36 extended resection (mostly chest wall)
  - OS 45% at 5 years and 28% at 10 years (similar in extended resection)


Outline of talk

- **Early stage lung cancer**
  - Lobar resections
  - Sublobar resections
  - Nodule localization
  - Minimally invasive surgery
  - SBRT

- **Advanced stage lung cancer**
  - Defining resectability
  - Neoadjuvant regimens
  - Adjuvant regimens
Immunotherapy improves pathologic response and retains surgical feasibility: CheckMate 816 (NCT02998528)

- **Study design**
  - 358 adults with resectable stage IIB–IIIA (AJCC 7th) NSCLC, ECOG PS 0-1, and no known EGFR/ALK alterations.
    - 64% IIla
  - randomized to preoperative immunotherapy + chemo (nivolumab 360 mg + platinum-doublet chemo Q3W 3 cycles) or chemo only

- **Results**
  - improved pathological complete response (pCR) and depth of pathologic response for all stages with neoadjuvant NIVO + chemo.

Spicer, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). ASCO 2021 abstract.
Immunotherapy improves pathologic response and retains surgical feasibility: CheckMate 816 (NCT02998528)

<table>
<thead>
<tr>
<th></th>
<th>NIVO + chemo</th>
<th>chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive surgery</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Minimally invasive</td>
<td>30%</td>
<td>22%</td>
</tr>
<tr>
<td>Conversion</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>77%</td>
<td>61%</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>17%</td>
<td>25%</td>
</tr>
<tr>
<td>R0 resection</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Viable tumor</td>
<td>10%</td>
<td>74%</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>184 min</td>
<td>217 min</td>
</tr>
<tr>
<td>LOS</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Surgical AEs</td>
<td>41%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Spicer, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum- doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). ASCO 2021 abstract.

Multidisciplinary evaluation can improve utilization of diagnostic capabilities.

Brittney Williams, MD MPH

Multidisciplinary evaluation can improve utilization of diagnostic capabilities.

Anatomic Pulmonary Resections  
N = 450  
January 2013 - December 2018

Primary Lung Cancer  
n = 343 (76.2%)  
Not Primary Lung Cancer  
n = 107 (23.8%)

Excluded  
n = 94  
Known metastatic disease (n = 53 [49.5%])  
Known infectious process (n = 37 [34.5%])  
Carcinoid (n = 2 [1.9%])  
Completion lobectomy (n = 1 [1.0%])  
Full response to chemotherapy (n = 1 [1.0%])

Included  
n = 13 (2.5%)  
Metastatic disease (n = 2 [15.4%])  
Infection (n = 6 [46.2%])  
Benign tumor (n = 2 [15.4%])  
Sarcoidosis (n = 1 [7.7%])  
Fibrous changes (n = 2 [15.4%])


References

• Questions

• Thank you