Locally Advanced NSCLC

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Introduction to ACRODeck

- The goal of ACRODeck is to introduce standard treatments of oncologic malignancies for early radiation oncology residents

- Please note that there is often considerable variation in standard treatment recommendations

- Moreover, the landscape of oncology is ever-changing; for practice changing landmark studies and feedback, please email: resident@acro.org
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Clinical Presentation and Differential Diagnosis

- Advanced lung cancer typically presents with symptoms of cough, dyspnea and weight loss
  - Hemoptysis, hoarseness, brachial plexopathy, SVC syndrome, and Horner’s syndrome may also be present

- Differential Diagnosis:
  - Neoplasm (NSCLC, SCLC, metastases)
  - Infections (fungal, bacterial, parasitic)

Locally advanced lung cancer is typically defined as stage III disease.
If a pleural effusion is present, thoracentesis with cytology should be performed: if positive, this is M1a disease.

Initial Workup

- **H/P & Labs**
  - Focus on smoking history, occupational exposures, weight loss
  - Counsel regarding smoking cessation
  - CBC, CMP, PFTs

- **Imaging**
  - CT chest and abdomen (must include liver and adrenals)
  - PET CT
  - MRI Brain for stage II+ disease
  - Consider MRI of spine/thoracic inlet for superior sulcus tumors and those abutting the spine, subclavian vessels, or brachial plexus

- **Invasive mediastinal staging**
  - Typically done via EBUS, EUS, or mediastinoscopy
  - Can be done during the same procedure as the primary resection, with evaluation of frozen mediastinal pathology prior to lung resection

- **Bronchoscopy**
  - Done prior to surgical resection

- **Biopsy**
  - Typically done via bronchoscopy or CT guidance
PFTs and Surgery

- Pulmonary Function Tests should measure:
  - FEV1 (Forced Expiratory Volume in 1 second)
  - DLCO (Diffusion Capacity of Carbon Monoxide)

- Generally, FEV1 ≥ 80% predicted with DLCO ≥ 80% predicted indicates a low risk for surgery, and needs no further testing
  - If either number is < 80% of predicted, further testing is required to calculate “Predicted Postoperative Pulmonary Function”
Pathologic Mediastinal Lymph Node Evaluation

- **Endobronchial Ultrasound (EBUS)**
  - Can access nodes near the airways

- **Cervical Mediastinoscopy**
  - Can access nodes near the airways
  - Inserts scope through an incision above the sternum

- **Endoscopic Ultrasound (EUS)**
  - Can access nodes near the esophagus
  - Only modality that can reach levels 8-9

- **Anterior Mediastinoscopy (Chamberlain Procedure)**
  - Only modality that can reach levels 5-6
  - Inserts scope through an incision in the parasternal 2nd left intercostal space

Different techniques allow access to different nodal stations
Pathologic Mediastinal Lymph Node Evaluation

Consider performance status and comorbidities before pathologic mediastinal staging

<table>
<thead>
<tr>
<th>Lymph Node Levels</th>
<th>2</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8-9</th>
<th>10</th>
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<tbody>
<tr>
<td>EBUS-FNA</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUS-FNA</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy: Cervical</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinoscopy: Chamberlain</td>
<td></td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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NEJM
Staging

- Nodal Staging:
  - N1: double digit LN levels
    - 10 – 14
  - N2: single digit LN levels
    - Excluding N3 disease
  - N3: contralateral LN levels and/or the level 1 station

N2 disease is at least Stage III
Treatment Summary

**Definitive ChemoRT**
- Radiotherapy: 60 Gy in 30 fx
- Chemotherapy: Carboplatin and Paclitaxel
- Immunotherapy: Durvalumab

**Surgery**
- Surgery: VATS Lobectomy + Mediastinal Lymph Node Dissection
- R0
  - Chemotherapy: Cisplatin Doublet
  - ± Immunotherapy
- R1 / R2
  - Chemotherapy: Cisplatin Doublet
  - ± Radiotherapy
Definitive ChemoRT → IT

- Concurrent chemoradiation
  - Chemotherapy = “Platinum-Doublet”
    - Carboplatin/Paclitaxel
    - Cisplatin/Etoposide
    - Carboplatin/Pemetrexed (For non-SqCC histology)
    - Cisplatin/Pemetrexed (For non-SqCC histology)
  - Radiation
    - 60 – 70 Gy (in 2 Gy fractions)

- Consolidative Immunotherapy
  - Durvalumab (for up to 12 months)
  - Only for those with no disease progression after chemoRT

ChemoRT has been historically preferred over surgery for N2/N3 disease. This preference is now controversial for N2 disease.
Radiation Dosing, per NCCN

- **Definitive RT**
  - 60 – 70 Gy (in 2 Gy fractions)

- **Preoperative RT**
  - 45 – 54 Gy (in 1.8 – 2 Gy fractions)

- **Postoperative RT**
  - **R0 Resection** (controversial since the publication of LungART)
    - 50 – 54 Gy (in 1.8 – 2 Gy fractions)
  - **ECE or R1 Resection**
    - 54 – 60 Gy (in 1.8 – 2 Gy fractions)
  - **R2 Resection**
    - 60 – 70 Gy (in 2 Gy fractions)
Radiation Simulation

Simulation

- 4DCT (± IV contrast)
  - IV contrast strongly recommended for nodal disease
- Supine, arms above head in an arm-board

Other motion management techniques include compression and DIBH
### Dose Constraints

<table>
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<tr>
<th>Organ at Risk (OAR)</th>
<th>Dose Constraint</th>
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</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Max ≤ 50 Gy</td>
</tr>
</tbody>
</table>
| Lung                | V$_{20Gy}$ ≤ 35%  
                     | Mean ≤ 20 Gy    |
| Heart               | V$_{50Gy}$ ≤ 25%  
                     | Mean ≤ 20 Gy    |
| Esophagus           | Max ≤ 105% of prescription  
                     | V$_{60Gy}$ ≤ 17%  
                     | Mean ≤ 34 Gy    |
| Brachial Plexus     | Max ≤ 66 Gy     |

V$_{20Gy}$ ≤ 30-40% has a radiation pneumonitis risk of around 15%
A contralateral esophageal sparing technique can be used to reduce the risk of esophagitis.

Radiation Toxicities

- **Acute:**
  - Fatigue
  - Skin Irritation
  - Cough
  - Esophagitis

- **Subacute**
  - Radiation Pneumonitis

- **Chronic:**
  - Chest Wall Pain
  - Rib Fracture
  - Cardiac Toxicity
  - Bronchopulmonary Hemorrhage/Fistula
  - Pulmonary Fibrosis
Radiation Pneumonitis

- Radiation pneumonitis typically presents 1 – 6 months after the completion of radiotherapy
  - Symptoms include cough, dyspnea, low-grade fevers, chest and pleuritic pain
  - Supplemental oxygen may be necessary

- The mainstay of treatment is steroids
  - There are a variety of dosing schedules, most including 40 – 60 mg steroids with a slow taper
    - Example 6-week schedule
      - Prednisone 60mg daily for 1 week
      - Prednisone 50mg daily for 1 week
      - Prednisone 40mg daily for 1 week
      - Prednisone 30mg daily for 1 week
      - Prednisone 20mg daily for 1 week
      - Prednisone 10mg daily for 1 week
Surgery (+ CHT ± PORT)

- **Surgery**
  - VATS lobectomy with a N1/N2 mediastinal lymph node dissection
    - However, both open surgeries and pneumonectomies are sometimes performed depending on tumor location and extent

- **Systemic Therapies (Given adjuvantly to stage II+, can be considered for stage IB)**
  - 4 cycles of cisplatin/pemetrexed (nonsquamous histologies)
  - 4 cycles of cisplatin/gemcitabine (squamous histologies)
  - Adjuvant osimertinib can be added for EGFR mutated
  - Immunotherapy may be added for patients PD-L1 ≥ 1%

- **Post-Operative Radiotherapy (PORT)**
  - Classically used in cases of N2 disease, margin positivity, and ECE
    - However, the use of PORT in completely resected N2 disease has become an area of marked controversy given the results of LungART (PMID 34919827)
  - Consider for R1 and R2 resections

A minimum of three N2 nodal stations are required for sampling during surgery.
Often, the purpose of neoadjuvant treatments is to allow for surgical resection.

**Neoadjuvant Treatment → Surgery**

- **Neoadjuvant Therapy**
  - Neoadjuvant chemoRT is an option
    - 45 Gy in 25 fx with platinum-doublet chemo
  - Neoadjuvant chemo-immunotherapy is another option, per Checkmate 816 (PMID: 35403841)
    - Nivolumab with platinum-doublet chemo
      - “Platinum-doublet” options:
        - Carboplatin/Paclitaxel (for any histology)
        - Cisplatin/Paclitaxel (for any histology)
        - Cisplatin/Gemcitabine (for SqCC Histology)
        - Cisplatin/Pemetrexed (for non-SqCC histology)

- **Surgery**
  - VATS lobectomy with a N1/N2 mediastinal lymph node dissection
  - However, both open surgeries and pneumonectomies are sometimes performed depending on tumor location and extent
Special Circumstances: Superior Sulcus Tumors

- Superior sulcus tumors are often in an eloquent location, with the brachial plexus and major vessels present
  - Surgical evaluation is critical to determine resectability
  - Get an MRI of primary site to evaluate local invasion

- For unresectable tumors:
  - Definitive chemoradiation → Durvalumab

- For potentially resectable tumors:
  1. Preoperative chemoradiation (45 Gy)
  2. Surgical re-evaluation with imaging (CT chest ± PET/CT ± MRI spine and thoracic inlet)
  3. Surgery
     - Followed by chemotherapy and immunotherapy (Atezolizumab or Osimertinib, based on PD-L1 and EGFR mutation status)
Recent immunotherapies have led to better prognosis.

**Prognosis**

- Lung cancer remains the most lethal cancer in the United States

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**Non-Small Cell Lung Cancer: 5-Year Survival Rates**

<table>
<thead>
<tr>
<th>Stage</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>B</th>
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<tbody>
<tr>
<td>1</td>
<td>92%</td>
<td>83%</td>
<td>77%</td>
<td>68%</td>
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<tr>
<td>2</td>
<td>60%</td>
<td>53%</td>
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<tr>
<td>3</td>
<td>36%</td>
<td>26%</td>
<td>13%</td>
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<tr>
<td>4</td>
<td>10%</td>
<td>&lt;1%</td>
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Source: American Cancer Society 2017
Review
Review #1: Nodal Anatomy

What is the marked lymph node station?

(A) 4  
(B) 5  
(C) 6  
(D) 7
Which of the following statements is true regarding the landmark study, RTOG 0617?

(A) Lung V5 was associated with grade 3 pneumonitis
(B) IMRT (vs. 3DCRT) was associated with lower rates of pneumonitis
(C) Dose escalation to 74 Gy was associated with improved OS
(D) IMRT was associated with improved overall survival
Review #3: PORT

In the post-operative radiotherapy trial Lung ART, what percent of patients were treated with IMRT?

(A) 91%
(B) 71%
(C) 41%
(D) 11%
Review #4: Dose Constraints

Per NCCN, what mean dose is allowed to the esophagus in a conventionally fractionated definitive chemoradiation plan for NSCLC?

(A) Mean ≤ 14 Gy
(B) Mean ≤ 24 Gy
(C) Mean ≤ 34 Gy
(D) Mean ≤ 44 Gy

V_{60Gy} < 17\% \text{ is also an accepted dose constraint for the esophagus}
Review #5: Adjuvant Therapy

Per the PACIFIC trial, the addition of Durvalumab after definitive chemoradiation resulted in which of the following?

(A) Improvement in PFS and OS for all patients
(B) Improvement in PFS only in patients with PD-L1 expression > 25%
(C) Increased Grade 3 Pneumonitis
The pattern of failure for advanced lung cancer is typically distant.