Treatment of Stage 3A Lung Cancer

Gerard A. Silvestri MD,MS
Hillenbrand Professor of Thoracic Oncology
Medical University of South Carolina
Charleston, SC
Silvestri@musc.edu
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  - Exact Sciences
  - Integrated Diagnostics/Biodesix
  - Olympus America
  - Oncimmune
  - Oncocyte
  - Prolung
  - Veracyte
  - Veran
Outline

- What is stage III non-small cell lung cancer (NSCLC)?
- Review conventional treatment for stage III NSCLC
- Highlight early data for immunotherapy NSCLC
- Special Circumstances
Accurate staging is critical
- Treatment options are stage dependent
- Prognosis is based upon stage
- Enrollment in clinical trials by stage
- Provides a common language when discussing cases
- Allows for study of large cohorts of patients
<table>
<thead>
<tr>
<th>T (Primary Tumor)</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (Squamous or Adenocarcinoma)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤3 cm,</td>
</tr>
<tr>
<td>T1a(mi)</td>
<td>Minimally Invasive Adenocarcinoma</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤1 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;1 but ≤2 cm</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt;2 but ≤3 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;3 but ≤5 cm or tumor involving:</td>
</tr>
<tr>
<td></td>
<td>visceral pleura(^a), (PL1,2)</td>
</tr>
<tr>
<td></td>
<td>main bronchus (not carina), atelectasis to hilum(^a)</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt;3 but ≤4 cm</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt;4 but ≤5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt;5 but ≤7 cm</td>
</tr>
<tr>
<td></td>
<td>or invading chest wall, pericardium, phrenic nerve</td>
</tr>
<tr>
<td></td>
<td>or separate tumor nodule(s) in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor &gt;7 cm</td>
</tr>
<tr>
<td></td>
<td>or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine;</td>
</tr>
<tr>
<td></td>
<td>or tumor nodule(s) in a different ipsilateral lobe</td>
</tr>
<tr>
<td></td>
<td>T4 Inv</td>
</tr>
<tr>
<td></td>
<td>T4 Ipsi Nod</td>
</tr>
</tbody>
</table>
Stage IIIA

Key Feature:  

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>Additional nodule</th>
</tr>
</thead>
</table>
Case 1

- 79 yo F h/o COPD and tobacco use (20 pack-years) with growing RLL lung nodule (1.1 cm)
  - Mediastinoscopy
    - Positive N2 node
    - Adenocarcinoma, +KRAS
    - Stage?
  - cT1bN2M0
    - IIIA

<table>
<thead>
<tr>
<th>T/M</th>
<th>Label</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a ≤1</td>
<td>IA1</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>T1b &gt;1-2</td>
<td>IA2</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>T1c &gt;2-3</td>
<td>IA3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2</td>
<td>T2a Cent, Visc Pl</td>
<td>IB</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>T2a &gt;3-4</td>
<td>IB</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td></td>
<td>T2b &gt;4-5</td>
<td>IIA</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3</td>
<td>T3 &gt;5-7</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td></td>
<td>T3 Inv</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td></td>
<td>T3 Satell</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td>T4</td>
<td>T4 &gt;7</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td></td>
<td>T4 Inv</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td></td>
<td>T4 Ipsil Nod</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
</tr>
<tr>
<td>M1</td>
<td>M1a Contr Nod</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td>M1a Pl Dissem</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td>M1b Single</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td>M1c Multi</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
</tr>
</tbody>
</table>
Case 1, continued

- Concurrent chemoradiation
  - Carboplatin/Paclitaxel
  - Radiation (75 gray)

- Follow-up, 24 months later
Locally advanced NSCLC

Stage III lung cancer

<table>
<thead>
<tr>
<th>Type</th>
<th>IA1</th>
<th>IA2</th>
<th>IA3</th>
<th>IB</th>
<th>IIA</th>
<th>IIB</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IV A</th>
<th>IV B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>92</td>
<td>83</td>
<td>77</td>
<td>68</td>
<td>60</td>
<td>53</td>
<td>36</td>
<td>26</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Pathologic</td>
<td>90</td>
<td>85</td>
<td>80</td>
<td>73</td>
<td>65</td>
<td>56</td>
<td>41</td>
<td>24</td>
<td>12</td>
<td>-</td>
</tr>
</tbody>
</table>
Pathologic Stage (8th edition)

Overall survival, weighted by type of database submission (registry vs other)
Cox proportional hazards adjusted for age, sex, histotype, database type

Ref: Goldstraw J Thor Oncol 2016;11:39-51
Case 2

- 77 yo F h/o DM2 and tobacco use (35 pack-years) with hemoptysis
- CT: 4.6 cm subcarinal mass
- PET: negative for disease outside the chest

- EBUS
  - Level 7 + Adenocarcinoma (KRAS)
  - Stage?

- T2bN2M0
  - IIIA
Case 2, continued

- Not a surgical candidate
- Concurrent chemoradiation
  - Cisplatin/Pemetrexed
Question 1

- What further treatment recommendations for this patient?

1. no further treatment is required
2. continued chemotherapy until progression
3. adjuvant Immunotherapy
4. further treatment with chemotherapy and radiotherapy
Question 1

- What further treatment recommendations for this patient?

1. no further treatment is required
2. continued chemotherapy until progression
3. adjuvant Immunotherapy
4. further treatment with chemotherapy and radiotherapy
How does immunotherapy work?

• Signaling from dendritic cells or tumor cells can down-regulate T-cell activity

• Blockade of inhibitory signaling molecules on T-cells “re-activates” their anti-tumoral activity.

PACIFIC trial results

- Progression-free survival 16.8 months vs 5.6 months (HR 0.52; CI 0.42-0.65; p<0.001)

- Secondary endpoints
  - 12 month PFS: 55.9 vs 35.3%
  - Response rate 28.4% vs 16%
  - Ongoing response at 18 months: 72.3% vs 46.8%

Case 3: 75 year old woman with 70 pack years of smoking referred for an enlarging PET (+) mediastinal lymph node (after 6 month follow up CT). PFTs normal. No other nodules, masses, or areas of FDG uptake on PET scan.
What is the best next step?

- A. EBUS TBNA for lymph node sampling
- B. Serial follow-up imaging with Chest CT scans
- C. VATS for evaluation of level 6
- D. EUS FNA for lymph node sampling
What is the best next step?

- A. EBUS TBNA for mediastinal staging
- B. Serial follow-up imaging with Chest CT scans
- C. VATS for evaluation of level 6
- D. EUS FNA for lymph node sampling
Staging at level 5 and 6

- For the patients with a left upper lobe (LUL) cancer in whom invasive mediastinal staging is indicated, it is suggested that invasive assessment of the Aortopulmonary Window (APW) nodes be performed (via Chamberlain, VATS, or extended cervical mediastinoscopy) if other mediastinal node stations are found to be uninvolved

  (Grade 2B).

Case 1 continued: VATS performed

- Nodule in the left upper lobe seen and palpated (not appreciated on imaging)
- Wedge resection performed: frozen section NSLC
- Level 6: tumor deposit 2.5cm
- Total 1/26 lymph nodes (+)
- Lobectomy completed
Are all N2 nodes created equal?

- Nonrandomized evidence that involvement of a single, left level 5 mediastinal lymph node in patients with a left upper lobe tumor portends no worse of a prognosis than N1 disease.

- Median survival was 51.4 months (95% CI, 22.3 months–not reached) for patients with left upper lobe tumors and single-level N2 metastases and 49.4 months (95% CI, 25.4-89 months) for patients with left upper lobe tumors and N1 disease; 5-year survival was 42% in both groups.


Left upper lobe tumors and single-level N2 metastases vs. N1 disease

Log Rank P = 0.63

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Dead</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>43</td>
<td>30</td>
<td>49.4 months</td>
</tr>
<tr>
<td>N2</td>
<td>49</td>
<td>31</td>
<td>51.4 months</td>
</tr>
</tbody>
</table>

N2 disease

- In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), we recommend the treatment plan should be made with the input from a multidisciplinary team (Grade 1C)

- In patients with NSCLC who have incidental (occult) N2 disease (IIIA) found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumor is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested (Grade 2C)
Pancoast tumor

- Less than 5% of lung cancers
- Cancer in the superior sulcus
- Destructive lesions of the thoracic inlet
- Involvement of the brachial plexus and cervical sympathetic nerves (stellate ganglion)
- Mostly extrathoracic, involving the chest wall structures

Pancoast HK. *JAMA*. 1924. 83:1407-1411.

Foroulis et al. Journal of Thoracic Disease 20...
Symptoms

- Severe pain in the shoulder region radiating toward the axilla and scapula, with later extension along the ulnar aspect of the arm to the hand
- Atrophy of hand and arm muscles
- Horner syndrome (ptosis, miosis, hemianhydrosis, enophthalmos)
- Compression of the blood vessels with edema

Pancoast HK. *JAMA*. 1924. 83:1407-1411.
Question 3

In a patient with a Pancoast tumor the recommended treatment regimen should include?

1. chemotherapy with radiation therapy
2. Surgery followed by radiation
3. induction chemotherapy and radiotherapy followed by surgery
4. Radiation followed by surgery
Question 2

In a patient with a Pancoast tumor the recommended treatment regimen should include?

1. chemotherapy with radiation therapy
2. Surgery followed by radiation
3. Induction chemotherapy and radiotherapy followed by surgery
4. Radiation followed by surgery
Treatment

- Induction chemo-radiotherapy is the standard of care for any potentially resectable Pancoast tumor

- Complete tumor resection

- Anterior and posterior approaches to the thoracic inlet depending on location of the tumor (posterior - middle - anterior compartment of the thoracic inlet) and the depth/extent of invasion.

Unresectability

- Distant metastases, including a single brain metastasis
- Ipsilateral or contralateral mediastinal or supraclavicular nodes (N2/N3 disease)
- Involvement of the brachial plexus above the T1 (weakness of the intrinsic muscles of the hand is expected by sacrificing only the T1 nerve root, while sacrificing the C1 nerve root produces a permanent paralysis and severe disability of the dependent upper extremity)
- Involvement of more than 50% of the vertebral bodies;
- Invasion of the esophagus and/or trachea.

Prognosis

- Surgery associated with 5% mortality rate
- Complication rate varies from 7-38%.
- The overall 2-year survival rate after induction chemo-radiotherapy and resection varies from 55% to 70%, while the 5-year survival for R0 resections is quite good (54-77%). The main pattern of recurrence is that of distant metastases, especially in the brain.

Summary

- Standard of care for most patients with IIIA NSCLC is chemoradiotherapy.
- For select cases where patients with stage IIIA NSCLC are surgical candidates, a tumor board discussion is warranted weighing patient preferences, risks, and benefits of neoadjuvant chemoradiotherapy followed by surgery.
- Involvement of a single A-P window lymph node in patients with a left upper lobe tumor may portend a better prognosis than in other cases of stage IIIA disease.
- Tumor size has more prognostic impact than previously recognized, and a tumor > 7 cm is considered T4.
- Adjuvant Immunotherapy is now considered after definitive treatment.
- Induction chemo-radiotherapy should be standard of care for any potentially resectable Pancoast tumor.