The Role of Surgery in the Management of Stage 3A Lung Cancer

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Henry Ford Hospital
No Disclosures
Stage 3A
Stage 3A
Stage 3A: Issues

• At any stage, lung ca potentially systemic
• 3A (N2) disease is very heterogenous
  – Unresectable
  – Potentially resectable
  – resected
• Data from one subgroup may not be applicable to another subgroup
• Staging accuracy, particularly “older” studies
• Therapy type/sequence different
  – Chemo a given
  – What is best local therapy?
Staging Modalities: Mediastinoscopy
Staging Modalities: EBUS
Lymph Node Map
The IASLC Lung Cancer Staging Project: A Proposal for a New International Lymph Node Map in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer

Rusch, Valerie W.; Asamura, Hisao; Watanabe, Hirokazu; Giroux, Dorothy J.; Rami-Porta, Ramon; Goldstraw, Peter; on behalf of the Members of the IASLC Staging Committee
doi: 10.1097/JTO.0b013e3181a0d82e
Albain KS, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

• RCT 396 pts with no progression of 3A following chemorads
• 202 resection/194 radiotherapy only
• Median survival NS (23.6 vs. 22.2 mos)
• Median progression free survival significant (12.8 vs. 10.5 mos)
• In subset analysis, OS was improved for patients who underwent lobectomy, but not pneumonectomy, versus chemotherapy plus radiotherapy.

• Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) non-small-cell lung cancer.

- 332 “unresectable” 3A who showed response to chemotherapy
- 167 randomized to resection/165 to radiation
- Median and 5 yr survival NS
- “The low morbidity and mortality of radiotherapy suggests that it is preferable for unresectable LN involvement.”
Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01


- RCT
- 43 pts with histologically confirmed N2 dz randomized to induction chemo followed by surgery or radiotherapy followed by consolidation chemo
- “The patient accrual to this trial made its results inconclusive, but several observations are notable. In this trial, histologic confirmation of N2 disease in the surgical and nonsurgical arms eliminated the usual biases from clinical staging. In this setting, [local control and survival were essentially equal between the surgical and RT arms.](https://example.com) The 3- and 5-year survival rates of nonsurgical therapy were comparable to published surgical trials of N2 disease.”
Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study
Betticher et al., Br J Cancer 2006;94:1099-106.

• 75 patients (from 90 enrolled) underwent tumor resection after induction chemo
• Median OS 35 mos in the 75 patients who underwent surgery; OS for all 90 was 28 mos
• Factors associated with OS, EFS and risk of local relapse and distant metastases were complete tumor resection and chemotherapy activity (clinical response, pathologic response, mediastinal downstaging).
Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival

- 92 pts with radiological response or stable disease after induction chemo for path proven ipsilateral N2 dz underwent surgical exploration with the aim of complete resection (complete resection 63 pts)
- Detection of multilevel compared to single level positive nodes at initial mediastinoscopy was related to lower 5YS (17% vs 39%; p < 0.005)
- Trend for a better 5YS in pts with mediastinal nodal downstaging compared to patients with persistent N2 dz (49% vs 27%; p = 0.095)
- In pts with persistent N2 dz, single level disease has a significantly better survival (37% vs 7% 5YS, p < 0.005)
- “Surgery after induction chemotherapy for stage IIIA-N2 NSCLC can be performed with an acceptable mortality and morbidity. Baseline single level N2 disease is an independent prognostic factor for long-term survival. Patients with mediastinal downstaging, but also a subgroup of patients with single level persistent N2 disease, after induction therapy have a rewarding survival.”
• 55 pts enrolled, histologically confirmed N2 (3A/3B)
• 4 cycles chemo/45 Gy hyperfractionated/resection if possible
• Overall mean survival 43 mos (estimated 5 yr survival 49%)
• downstaging had mean survival of 53 mos (estimated 5 yr survival 60%)
• “Neoadjuvant trimodal treatment for histologically proven N2 or N3 stage III non–small cell lung cancer is promising and can, like no other approach at present time, considerably improve 5-year survival rates up to 63% in selected patients.”
Trimodal Therapy for Histologically Proven N2/3 Non–Small Cell Lung Cancer: Mid-Term Results and Indicators for Survival

- 128 (120 completed) pts enrolled (87 with 3B dz)
- Complete/partial response eligible for resection (pts w stable dz deemed resectable also underwent resection)
- Pts with complete resection (n = 58) had 5yr survival rate of 43.1%, and median survival was 39 months (CI, 24 to 54 months)
- “in highly experienced centers, neoadjuvant chemoradiotherapy followed by complete resection is feasible and may offer a chance for long-term benefit and cure in carefully selected patients with advanced, stage III NSCLC”
Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery

- 144 pts (3A and 3B): 44 underwent resection
- XRT dose 60 Gy
- “On multivariate analysis, stage at the time of treatment (stage IIIA vs stage IIIB) and use of surgery were the only factors associated with improved outcome (P=.01 and P=.001, respectively).”
Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival

• Single center, chemo only (92 pts)
• 5 yr OS 33%
• Prognostic factors
  – Single level N2 at initial staging
  – Downstaging after therapy
  – Single level N2 after therapy

- Randomized path T1-3N2M0 to chemo/resection/XRT (170 pts) vs. chemo/xrt (171 pts) (both sequential)
- Overall, no statistical difference in OS (17 mos vs. 15 mos)
- Pts with ADC did better with resection (5 yr survival 20% vs. 7%, p=.017)
- Pts with T1N2 did better with resection (5 yr survival 36% vs. 17%)
Conclusions

• Paucity of comparable studies/data
• Surgical resection has a role in overall management of stage 3A NSCLC
• Selection, selection, selection!
  – Single station N2 does better
  – Downstaging N2 does better
  – Avoid pneumonectomy
  – Others?
• Stage, re-stage, N2 must be determined histologically!
• Experience (surgeon/institution) counts
• Multidisciplinary management is mandatory
Parting Thoughts

• Definition/impact(bias) of downstaging
• How much chemo (2 cycles vs. 4)?
• How much XRT?
RADIOCHEMOTHERAPY IN STAGE IIIA NSCLC

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Professor and Head
Division of Radiation Oncology
Stellenbosch University and Tygerberg Hospital
Cape Town
South Africa
I have no conflicts of interest to disclose
CONCURRENT RADIOCHEMOTHERAPY

STANDARD TREATMENT IN
LOCALLY ADVANCED, INOPERABLE
(STAGE III) NSCLC

Cochrane Database Systematic Review
O’Rourke et al, 2010

Chinese Meta-Analysis
Liang et al, Int J Cancer, 2010

IGR/MRC IPD meta-analysis
Auperin et al, JCO, 2010
CONCURRENT RADIOCHEMOTHERAPY IN LOCALLY ADVANCED (STAGE III) NSCLC

INCREASED TOXICITY?
RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin X 2 +/- Cetuximab

Paclitaxel
Carboplatin X 2 +/- Cetuximab

 Courtesy: Dr. B. Movsas, Discussant at ASTRO 2011
Overall Survival (%)

Months since Randomization

One-sided p-value, left tail

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>60 Gy</th>
<th>74 Gy</th>
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<tbody>
<tr>
<td>Dead</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>213</td>
<td>204</td>
</tr>
</tbody>
</table>

HR=1.45 (1.02, 2.05)\ p*=0.02

The higher dose arm fared worse!

Courtesy: Dr. B. Movsas, Discussant at ASTRO 2011
What’s **THE** reason that dose escalation is negative?

1) Dose Threshold?

2) **Toxicity**?

3) Table of Characteristics?

4) Technical factors?

5) Type of failure?

6) Result is actually TRUE?

7) Totally novel strategies?

**Courtesy: Dr. B. Movsas, Discussant at ASTRO 2011**
# RTOG 0617

Definitely, Probably, or Possibly Related to Treatment (using CTCAE Version 3.0)

<table>
<thead>
<tr>
<th>September 2011</th>
<th>Arm A: 60 Gy +/- Cetuximab (n=192)</th>
<th>Arm B: 74 Gy +/- Cetuximab (n=183)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>4</td>
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<tr>
<td>Worst non-hematologic</td>
<td>79 (41.1%)</td>
<td>14 (7.3%)</td>
</tr>
<tr>
<td>Worst overall</td>
<td>84 (43.8%)</td>
<td>45 (23.4%)</td>
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</table>

## Grade 5 Events

<table>
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<tr>
<th>(n=4)</th>
<th>(n=8)</th>
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</thead>
<tbody>
<tr>
<td>As scored by institution</td>
<td>2 Pulmonary</td>
</tr>
<tr>
<td>No significant difference</td>
<td>1 Thrombosis</td>
</tr>
<tr>
<td></td>
<td>1 Upper GI Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>1 Pulmonary Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>1 Pneumonia NOS</td>
</tr>
<tr>
<td></td>
<td>1 Esophageal</td>
</tr>
<tr>
<td></td>
<td>1 Death NOS</td>
</tr>
</tbody>
</table>

Courtesy: Dr. B. Movsas, Discussant at ASTRO 2011
## Locally Advanced NSCLC
### Acute High-Grade (≥ 3) Esophagitis

<table>
<thead>
<tr>
<th>Study/author</th>
<th>RT (Gy)</th>
<th>CHT</th>
<th>Sequence</th>
<th>Esophagitis</th>
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</thead>
<tbody>
<tr>
<td>RTOG 8808</td>
<td>60 (QD)</td>
<td>-</td>
<td>-</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>RTOG 8808</td>
<td>60 (QD)</td>
<td>PV</td>
<td>induction</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>RTOG 9204</td>
<td>63 (QD)</td>
<td>PE</td>
<td>induction</td>
<td>6%</td>
</tr>
<tr>
<td>RTOG 9015</td>
<td>69.6 (BID)</td>
<td>PV</td>
<td>concurrent</td>
<td>24%</td>
</tr>
<tr>
<td>RTOG 9106</td>
<td>69.6 (BID)</td>
<td>PE</td>
<td>concurrent</td>
<td>53%</td>
</tr>
<tr>
<td>RTOG 9204</td>
<td>69.6 (BID)</td>
<td>PE</td>
<td>concurrent</td>
<td>36%</td>
</tr>
<tr>
<td>LUN-27</td>
<td>60 (QD)</td>
<td>T</td>
<td>concurrent</td>
<td>17%</td>
</tr>
<tr>
<td>LUN-56</td>
<td>66 (QD)</td>
<td>TC</td>
<td>concurrent</td>
<td>25%</td>
</tr>
<tr>
<td>LUN-63</td>
<td>69.6 (BID)</td>
<td>TC</td>
<td>concurrent</td>
<td>26%</td>
</tr>
<tr>
<td>Jeremic et al</td>
<td>69.6 (BID)</td>
<td>CE</td>
<td>concurrent</td>
<td>10-15%</td>
</tr>
<tr>
<td>Jeremic et al</td>
<td>67.6 (BID)</td>
<td>TC</td>
<td>concurrent</td>
<td>17%</td>
</tr>
</tbody>
</table>
CONCURRENT RADIOCHEMOTHERAPY IN LOCALLY ADVANCED (STAGE III) NSCLC

Low-dose daily CHT leads to low toxicity

   Jeremic et al, 1996; 2001; 2005
   Koning CC et al, 2013

Hfx RT offers better LC and OS

   Mauguen et al, 2012
WHAT ABOUT STAGE IIIA NSCLC

• Lesser disease volume

• Greater chances for cure?

• More aggressive treatment justified?

• Surgery and/or CHT and/or RT
STAGE IIIA NSCLC

• Difference wrt inoperable stage III
  Anything applicable from previous?

• c vs p; T vs N; else..?
  for cN2 you do not need mediastinoscopy (PET?)

• Is it surgery vs RT question?
  CHT secured its position? Timing?

• Survival vs toxicity?
  Grade 3-5? Or just grade 5?
## STAGE IIIA NSCLC (prospective studies)

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
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<th>N</th>
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<tr>
<td>Shepherd</td>
<td>III</td>
<td>IIIA (N2)</td>
<td>15/16</td>
<td>RT</td>
<td>16.2/18.7</td>
<td>n.r.</td>
<td>0%</td>
</tr>
<tr>
<td>Johnstone</td>
<td>III</td>
<td>IIIA</td>
<td>29/32</td>
<td>CHT+S</td>
<td>19.4/17.4</td>
<td>70 (1yr)/66 (1yr)</td>
<td>7%/3%</td>
</tr>
<tr>
<td>Van Meerbeeck</td>
<td>III</td>
<td>III (N2)</td>
<td>167/165</td>
<td>CHT+S</td>
<td>16.4/17.5</td>
<td>15.7 (5yr)/14 (5yr)</td>
<td>9%/&lt;1%</td>
</tr>
<tr>
<td>Albain</td>
<td>III</td>
<td>IIIA</td>
<td>429</td>
<td>CHT/RT+S</td>
<td>23.6/22.2</td>
<td>27.2 (5yr)/20.3 (5yr)</td>
<td>8%/2%</td>
</tr>
<tr>
<td>Thomas</td>
<td>III</td>
<td>IIIA/B</td>
<td>264/260</td>
<td>CHT+RT (bid)/CHT+S</td>
<td>15.7/17.6</td>
<td>21 (5yr)/18 (5yr)</td>
<td>9%/5%</td>
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<tr>
<td>Gottfried</td>
<td>III</td>
<td>IIB (T3N0)</td>
<td>42/37</td>
<td>CHT+S</td>
<td>32.3/31.8</td>
<td>47 (3yr)/49 (3yr)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIIA/B (T4N0)</td>
<td></td>
<td>CHT+S+PORT (qd)</td>
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<tr>
<td>Sorenson</td>
<td>III</td>
<td>T1-3N2M0 (pN2)</td>
<td>170/171</td>
<td>CHT + S+ RT</td>
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<td>264</td>
<td>CHT+RT (bid)/ CHT+S</td>
<td>15.7</td>
<td>21 (5yr)</td>
<td>9%</td>
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<td></td>
<td>260</td>
<td>CHT+S+PORT (qd)</td>
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## STAGE IIIA NSCLC (retrospective studies)

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<th>Phase</th>
<th>Stage</th>
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<th>MST (mos)</th>
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<tbody>
<tr>
<td>Uy</td>
<td>retrospective</td>
<td>IIIA (N2)</td>
<td>40</td>
<td>CHT/RT+S+CHT</td>
<td>40</td>
<td>52 (3yr)</td>
<td>7%</td>
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<td>Yap</td>
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<td>IIIA/B</td>
<td>33</td>
<td>CHT/RT+S</td>
<td>29.9</td>
<td>74 (2 yr)</td>
<td>&lt;1%</td>
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<tr>
<td>Taylor</td>
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<td>cIIIA</td>
<td>107</td>
<td>CHT +S (+ PORT) RT-CHT</td>
<td>31 27</td>
<td>33 (5yr)</td>
<td>30 (5yr) n.r.</td>
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<tr>
<td>Mac Manus</td>
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<td>IIIA</td>
<td>25</td>
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<td>26</td>
<td>32 (4yr)</td>
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<td>Seder</td>
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<td>IIIA</td>
<td>56 88</td>
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<td>n.r.</td>
<td>n.r.</td>
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<td>III N2</td>
<td>IIIA (N2)</td>
<td>15</td>
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<td>5%</td>
</tr>
<tr>
<td>Gottfried III</td>
<td>III</td>
<td>IIB (T3N0) IIA/B (T4N0)</td>
<td>42</td>
<td>CHT+S CHT+S+CHT</td>
<td>32.3</td>
<td>47 (3yr)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37</td>
<td></td>
<td>31.8</td>
<td>49 (3yr)</td>
<td></td>
</tr>
<tr>
<td>Sorenson III</td>
<td>III</td>
<td>T1-3N2M0 (pN2)</td>
<td>170</td>
<td>CHT + S + RT CHT + RT</td>
<td>17</td>
<td>20 (5yr)</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>171</td>
<td></td>
<td>15</td>
<td>16 (5yr)</td>
<td></td>
</tr>
<tr>
<td>Uy</td>
<td>retrospective</td>
<td>IIIA (N2)</td>
<td>40</td>
<td>CHT/RT+S+CHT</td>
<td>40</td>
<td>52 (3yr)</td>
<td>7%</td>
</tr>
<tr>
<td>Yap</td>
<td>retrospective</td>
<td>IIIA/B</td>
<td>33</td>
<td>CHT/RT+S</td>
<td>29.9</td>
<td>74 (2 yr)</td>
<td>1%</td>
</tr>
<tr>
<td>Taylor</td>
<td>retrospective</td>
<td>cIIIA</td>
<td>107</td>
<td>CHT+S (+ PORT) RT-CHT</td>
<td>31</td>
<td>33 (5yr)</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td></td>
<td>27</td>
<td>30 (5yr)</td>
<td></td>
</tr>
<tr>
<td>Jeremic</td>
<td>retrospective</td>
<td>cIIIA</td>
<td>177</td>
<td>RT-CHT</td>
<td>38</td>
<td>41 (5yr)</td>
<td>0</td>
</tr>
</tbody>
</table>
STAGE IIIA NSCLC
WHAT MATTERS BESIDE SURVIVALS

- About 30-50% pts receive inadequate or no surgery  
  *EORTC 08941; INT 0139*

- Lobectomy vs. pneumonectomy  
  *better results, lower mortality*

- Right-sided vs. left sided  
  *higher mortality*

- N status after induction  
  *N0-N1 after induction better than N2 after induction*
STAGE IIIA NSCLC
WHAT MIGHT MATTER AS WELL

- **WHO NEEDS LOBECTOMY**
  
  \( pT1-T2 \) better than \( pT3-T4 \) (Andre et al, 2000)

- **MORTALITY YOU CAN( NOT) AVOID**

  ARDS vs. pneumonitis, infection

- **WHETHER PET WOULD CHANGE THINGS**

  pre- and during the Tx (before ARDS comes)

- **TRADE-OFF BETWEEN T AND N COMPONENT**

  volumes, volumes, volumes – not sizes!! (more RT thinking!)
STAGE IIIA NSCLC
WHAT COULD MATTER AS WELL (I)

- Not only \( cN \) vs \( pN \), but No. of LN stations involved

\[
mN2 \text{ better than } cN2; \ L1 \text{ better than } L2+
\]

\[
mN2L1 > mNL2+ > cN2L1 > cN2L2+
\]

(34%) (11%) (8%) (3%) (5yr OS)

(Andre F et al, JCO, 2000)
STAGE IIIA NSCLC
WHAT COULD MATTER AS WELL (II)

- Location of T and LN important (Matsunaga, Proc ASCO, 2013)

  \( cN2\alpha \) – only involvement of UMLN in upper lobe T or only LMLN in lower lobe T

  \( cN2\beta \) – involvement of LMLN in upper lobe T +/- UMLN or involvement of UMLN in lower lobe T +/- LMLN

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>( cN2\alpha )</th>
<th>( cN2\beta )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>29.5%</td>
<td>0%</td>
<td>.0007</td>
</tr>
<tr>
<td>Cox PHM</td>
<td>HR: 0.426</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
STAGE IIIA NSCLC
WHAT COULD MATTER AS WELL (III)

• Histology may be important (Sorensen, Proc ASCO, 2013)

• CHT + S + RT (Arm A) vs CHT + RT (Arm B)

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>ADC</th>
<th>SQC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>20%</td>
<td>7%</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>HR: 0.60</td>
<td></td>
<td>.002</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

• Hard facts/trial data says radiochemotherapy
  *both survivals and toxicity*

• Wishful thinking say *PERHAPS* surgery
  *subgroup analysis, subset analysis, post-hoc blah-blah…*

• Even if there may be a role for surgery
  *currently nobody knows when and where for sure*

“Let it bleed” (Jagger-Richards) stays at home
Early Stage NSCLC: Imprimatur of Adjuvant Chemotherapy and Radiotherapy

Overview of Recent Data

Corey J Langer MD, FACP
Professor of Medicine
Director of Thoracic Oncology
Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA 19104
Disclosures: Past 10 yrs

• Grant/Research Support:
  – Bristol Myers Squibb, Pfizer, Imclone, Lilly, Schering-Plough Research Institute, SanofiAventis, Amgen, Cell Therapeutics, OrthoBiotech, Celgene, Vertex, Genentech, OSI, AstraZeneca, Pfizer, Medimmune, GSK

• Scientific Advisor:
  – Bristol Myers Squibb, Imclone, Sanofi-Aventis, Pfizer, GlaxoSmithKline, Pharmacyclics, Amgen, AstraZeneca, Novartis, Genentech, OSI, Savient, Bayer/Onyx, Abraxis, Clarient, Morphotek, Biodesix, AVEO, Synta

• Speakers Bureau: curtailed as of 12/10
  – Bristol Myers Squibb, Imclone, Sanofi-Aventis, Lilly, Genentech, OSI
Stage is Destiny!
## New Staging System (IASLC ‘07) instituted 2009

<table>
<thead>
<tr>
<th>UICC6 T/M Descriptor</th>
<th>New T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 ( \leq 2 \text{ cm} )</td>
<td>T1a</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1 ( &gt; 2-3 \text{ cm} )</td>
<td>T1b</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 ( 3 \text{ to } \leq 5 \text{ cm} )</td>
<td>T2a</td>
<td>IB</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 ( &gt;5-7 )</td>
<td>T2b</td>
<td>IIA</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 ( \geq 7 \text{ cm} )</td>
<td>T3</td>
<td>IIB</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T3</td>
<td>IIB</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td>T3</td>
<td>IIB</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1 (ipsilateral Lung)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (pleural effusion)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (contralateral Lung)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
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<th>N3</th>
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<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
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<td>T1b</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (3 to ≤ 5 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt; 5-7)</td>
<td>T2b</td>
<td>IIA</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (≥ 7 cm)</td>
<td>T3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
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<tr>
<td>M1 (ipsilateral Lung)</td>
<td>T4</td>
<td>IIIA</td>
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</tr>
<tr>
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<td>IV</td>
<td>IV</td>
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<td>IV</td>
</tr>
</tbody>
</table>
Early Stage NSCLC

- 225,000 New Dx yearly
- 1/3 treated surgically for stage I-III A disease
- ~50% destined to relapse, usually in < 1-3 years: 37,500 “preventable” deaths yearly
- Prognosis: stage dependent

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>60 – 70%</td>
</tr>
<tr>
<td>II</td>
<td>40 – 60%</td>
</tr>
<tr>
<td>IIIA</td>
<td>20 – 30%</td>
</tr>
</tbody>
</table>
Platinum-Based Adjuvant Trials in Resected NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>N. of Patients</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMJ meta</td>
<td>1394</td>
<td>0.87 (0.74-1.02)</td>
</tr>
<tr>
<td>IALT</td>
<td>1867</td>
<td>0.86 (0.76-0.98)</td>
</tr>
<tr>
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</tr>
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<td>344</td>
<td>0.63 (0.60-1.07)</td>
</tr>
<tr>
<td>ANITA</td>
<td>840</td>
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</tr>
<tr>
<td>LACE meta</td>
<td>4584</td>
<td>0.89 (0.82-0.96)</td>
</tr>
</tbody>
</table>

NEJM 00; JNCI 03; EuroJTS 04, NEJM 04; NEJM 05; ASCO 04+06; Lancet Oncology 06
Platinum-Based Adjuvant Trials in Resected NSCLC: Longterm Results

<table>
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</table>

NEJM 00; JNCI 03; EuroJTS 04; NEJM 04; NEJM 05; ASCO 04+06; Lancet Oncology 06
LACE: Trials and patients

- 5 trials including 4,584 patients
- Median follow-up: 5.1 years (3.1 – 5.9)
- 80% male
- Median age 59 years, 9% ≥ 70 years old
- Pathological Stage:
  - IA: 8%, IB: 30%, II: 35%, III: 27%
- Surgery: 31% pneumonectomy
- Histology:
  - 49% squamous cell,
  - 39% adenocarcinoma, 12% other

Survival curve

Chemotherapy
No chemotherapy

Absolute difference
at 3 years: 3.9% ± 1.5%
at 5 years: 5.3% ± 1.6%

Survival (%)
Time from randomization (Years)
0 1 2 3 4 5 ≥ 6
CT effect & stage

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>102 / 347</td>
<td>1.41 [0.96;2.09]</td>
<td></td>
</tr>
<tr>
<td>Stage IB</td>
<td>509 / 1371</td>
<td>0.92 [0.78;1.10]</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>880 / 1616</td>
<td>0.83 [0.73;0.95]</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>865 / 1247</td>
<td>0.83 [0.73;0.95]</td>
<td></td>
</tr>
</tbody>
</table>

Test for trend: p = 0.051

CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin+vinorelbine (13% of stage IA patients versus ~43% for other stages)

### Stage-Specific Hazard Ratios

**Recent Adjuvant Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>IB &lt; 4 cm</th>
<th>IB &gt; 4 cm</th>
<th>II</th>
<th>IIIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>0.95</td>
<td>0.95</td>
<td>0.93</td>
<td>0.79</td>
</tr>
<tr>
<td>BR-10</td>
<td>1.73</td>
<td>0.66</td>
<td>0.59</td>
<td>N/A</td>
</tr>
<tr>
<td>ANITA</td>
<td>1.10</td>
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<td>0.92</td>
<td>0.92</td>
<td>0.83</td>
<td>0.83</td>
</tr>
</tbody>
</table>

- **Red**: Negative
- **Green**: Positive
- **Yellow**: Indeterminate
- **Blue**: Not studied
Potential Benefit from Adjuvant Systemic Therapy

- Patients cured with local regional therapy
- Patients with residual micrometastases resistant to adjuvant therapy
- Patients with residual micrometastases sensitive to adjuvant therapy

Prognostic Markers?

Predictive Markers?
Therapeutic Implications

• Short course adjuvant, platinum-based therapy has emerged as standard practice in resected stage Ib-IIIa NSCLC

• Ongoing controversies re:
  – Molecular Selection
  – Influence of Age on Outcome
  – Ideal platinating agent: carbo vs cisplatin
  – Choice of partner agent
  – Impact of Stage
  – Role of targeted agents
  – Utility of RT in IIIA (N2)
Therapeutic Implications

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  – Choice of partner agent
  – Impact of Stage
  – Role of targeted agents
  – Utility of RT in IIIA (N2)
NSCLC as an investigational venue

- Adjuvant period constitutes an excellent opportunity to test new systemic approaches, including targeted therapy, vaccines and immunotherapy
  - Microscopic, undetectable disease burden (more likely to benefit c/w “gross” metastatic NSCLC)
  - Current therapeutic plateau with adjuvant cisplatin-based chemotherapy
    - New cytotoxics unlikely to confer additional Tx benefit
  - Window of opportunity
    - E1505 testing Bevacizumab: 100% accrued (closing Sept ’13)
    - Radiant trial – Erlotinib vs Placebo: fully accrued ‘10; results pending
    - MAGE vaccine trial: closed to accrual; results pending
ECOG 1505: Adjuvant Bevacizumab

**ELIGIBLE:**
- Resected IB^\(^{-}\)IIIA
- \(\geq\) Lobectomy
- No prior chemo
- No planned XRT
- No h/o CVA/TIA
- No ATE w/in 1 yr

**STRATIFIED:**
- Stage
- Histology
- Gender
- Chemo regimen*

**RANDOMIZE**

- Chemotherapy x 4 cycles
- Chemotherapy x 4 cycles
- Plus Bevacizumab x 1 year

*Investigator Choice of 4 chemo regimens

- DDP + either VNR, DOC, GEM, PEM

^ Revised to exclude IB < 4cm

> Closed to accrual 9-13; n = 1500
RADIANT Trial: Adjuvant Trial of Erlotinib in NSCLC

Stage IB, II, or IIIA NSCLC*
Complete surgical resection
And subsequent adjuvant chemo
No prior or concurrent neoadjuvant or adjuvant
N=1654

*Enriched Population: FISH and/or IHC (+)

Arm A
Erlotinib qd × 2 years

Arm B
Placebo qd × 2 years

RANDOMIZE
RADIANT Trial: Adjuvant Trial of Erlotinib in NSCLC

Stage IB, II, or IIIA NSCLC*
Complete surgical resection
And subsequent adjuvant chemotherapy
No prior or concurrent neoadjuvant or adjuvant therapy

N = 1654

Arm A: Erlotinib qd × 2 years
Arm B: Placebo qd × 2 years

*Enriched Population: FISH and/or IHC (+)

Accrual Completed April, 2010
Vaccines

MAGE

Telomerase
MAGE-A3 Antigen
(melanoma antigen family A, 3)

• Truly tumor-specific
  – Not expressed on normal cells (RT-PCR)
  – Expressed by various tumor types
    • Lung 35-50%
    • Bladder 35%
    • Head & Neck 49%
    • Melanoma 74%

• Associated with poorer prognosis
  (Bolli et al., 2002; Gure et al., 2005)

• Member of a large family of genes (portfolio)
MAGE A3 ASCI* randomized phase II

- Stage pIIB or pII: double-blind, randomly assigned 2:1 to postoperative MAGE-A3 vaccination or placebo.
- Vaccination was started ≥6 weeks after surgery, with 5 vaccinations at 3-week intervals, followed by 8 vaccinations every 3 months.
- Other anti-cancer adjuvant therapy was not allowed.
- Primary endpoint was time-to-recurrence, other endpoints were recurrence rates at different times, and survival.

* antigen-specific cancer immune therapeutic
Vansteenkiste et al, ASCO 2006, abstract 7019
Disease-Free Interval

Vansteenkiste et al, ASCO 2006, abstract 7019
Efficacy Endpoints Overview

*Final analysis 05 Oct, 2006*

Cox regression model (95% confidence interval)
P-value from Cox regr. model adjusted for stratification covariates

HR with a 10% one-sided $\alpha$

- **Disease-Free Interval**
  - Hazard ratio $\text{HR} = 0.73$ (0.44 - 1.20) $P=0.107$

- **Disease-Free Survival**
  - Hazard ratio $\text{HR} = 0.73$ (0.45 - 1.16)

- **Overall Survival**
  - Hazard ratio $\text{HR} = 0.66$ (0.36 - 1.20)

« MAGE-A3 » better

« Control » better
Resectable NSCLC

Surgery

Pathological stage IB, II, IIIA

No chemotherapy

Chemotherapy (up to 4 cycles platinum based chemotherapy)

MAGE-A3 + AS15
Placebo

MAGE Trial Design (GSK sponsored)

MAGE-A3 + AS15
Placebo

MAGRIT Trial
MAGRIT: Phase III

- Largest lung cancer study EVER
- Began in October 2007
- Goal: 2270 patients from 400 centers in 33 countries in Europe, North and South America, Asia, Australia
- 2289 ultimately enrolled
## Enrollment Status: 6/10

<table>
<thead>
<tr>
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<th>Signed Consent</th>
<th>Results Known</th>
<th>MAGE-A3+</th>
<th>Randomized</th>
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<td>US</td>
<td>1521</td>
<td>1310</td>
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<td>161</td>
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<td>NA</td>
<td>1628</td>
<td>1464</td>
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<td>7447</td>
<td>6607</td>
<td>2233</td>
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Therapeutic Implications

- Short course adjuvant, platinum-based therapy has emerged as standard practice in resected stage Ib-IIIa NSCLC
- Ongoing controversies re:
  - Molecular Selection
  - Influence of Age on Outcome
  - Ideal platinating agent: carbo vs cisplatin
  - Choice of partner agent
  - Impact of Stage
  - Role of targeted agents
  - Utility of RT in IIIA (N2)
Should the pt receive adj RT?

1) Yes
2) No
3) Maybe
Adjuvant Radiotherapy: Meta-analysis 1998

- Individual data from 9 randomized trials including 2128 patients
- Treatment details (staging, surgery, RT) highly variable among series
- PORT: better local control: 29% fewer local recurrences - 195 LR vs 276 LR for no RT
- Overall HR = 1.21 (1.08-1.34) ~ survival decrement of 7% at two years (55% vs 48%)
- Increase risk greater for early stage patients (Stage I/II vs. III)

Lancet 25 July 1998
PORT Meta-analysis
Survival Curves

Figure 2: Kaplan-Meier curve for survival

Stewart et al Lancet 1998
PORT - Heterogeneity of Hazard

- No increased risk for patients with N2 disease
- Patients with the least to gain have the most to lose

Stewart et al Lancet 1998
PORT Meta-analysis

Methodologic Flaws

- Variable and unspecified staging
- Variable and unspecified interval between resection and PORT
- Inadequate RT
  - Suboptimal doses; large fields
  - Poor treatment planning
  - Outmoded techniques (e.g.: use of low-energy photons or $^{60}$Co for a substantial proportion of patients)
- Inclusion of $N_0$ patients
- Unpublished data (2 of 9 studies)
- Relatively short F/U (< 4 yrs)

Stewart et al Lancet 1998
Risks of PORT with Modern Technology

• Retrospective review
  – 202 patients treated with surgery and PORT for Stage II and III disease
  – Median dose 55 Gy
  – Actuarial rate of death from intercurrent disease was 13.5% compared to expected rate of 10%

Machtay et al JCO 2001
ANITA TRIAL: N2 Disease – Influence of RT

Survival Distribution Function

ANITA TRIAL: N2 Disease – Influence of RT

Survival Distribution Function

RT Effect? Or Serendipity?

# ANITA - PORT Evaluation

- PORT: 33% on obs, 22% on chemo
- For all Chemo > XRT = chemo/XRT > 0
- For N2 Chemo/XRT > chemo > XRT > 0

<table>
<thead>
<tr>
<th></th>
<th>XRT</th>
<th>Chemo</th>
<th>All pts MST</th>
<th>N2 MST</th>
<th>N2 5 yr OS</th>
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<td></td>
<td>No</td>
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<td>26mo</td>
<td>13mo</td>
<td>17%</td>
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<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>93mo</td>
<td>24mo</td>
<td>34%</td>
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<tr>
<td></td>
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<td>No</td>
<td>50mo</td>
<td>23mo</td>
<td>21%</td>
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<td>Yes</td>
<td>46mo</td>
<td>47mo</td>
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</table>

Plot of overall survival for N2 patients stratified by postoperative radiotherapy (PORT) use – SEER data

PORT Conclusions

- PORT has no role in N0 or N1 disease
- Role of PORT in N2 is controversial
  - Recent subset and retrospective analyses hint at benefit
  - Ongoing “Lung ART” trial in France
    - 700 pts with resected N2 randomized to PORT or not
    - Adjuvant chemo allowed 1st
    - Accrual sluggish
"Lung ART"

P.I. Dr Cécile Le Pechoux

Completely resected N2 NSCLC

Primary end-point: DFS  (Sample size: 700 patients)

**Surgery**

- Conformal RT
  - 54 Gy/27-30 fx

- No post-op RT

Pre or post-op chemotherapy allowed
Concomitant chemo not allowed

Sponsors: FNCLCC, IFCT, LARS-G, EORTC
ASTRO LUNG CANCER PANEL: Case Presentations

Moderator: Benjamin Movsas, M.D.
Herndon Chair in Oncology Research
Chairman, Radiation Oncology
Henry Ford Health System
“Opportunity paged me, beeped me, linked me, e-mailed me, faxed me, and spammed me. But I was expecting it to knock!”
Learning Objectives

- Debate re: controversy of the role of surgery in stage IIIA/pN2 NSCLC
- Analyze the role of adjuvant therapy in resected node positive NSCLC
- Recognize the emerging role of stereotactic body radiation therapy (SBRT) for early stage (central) NSCLC
Disclosure

• Research support from Varian, Inc. and Philips, Inc.
Our Expert Lung Panel

Dr. Zane Hammoud
Dr. Branislav Jeremic
Dr. Corey Langer
Dr. Ken Rosenzweig
Our Expert Lung Panel

Dr. Hammoud.....Chief of Thoracic Surgery at Henry Ford Health System

Dr. Jeremic.....Chief of Radonc, Stellenbosch University, Cape Town, South Africa

Dr. Langer.....Prof at U. of Penn and Director of Thoracic Oncology

Dr. Rosenzweig.....Chair of Radonc at Mount Sinai
1) Demographic Info:
I am a….

a) Medical student/Resident/Fellow
b) Radiation Oncologist
c) Medical Oncologist
d) Surgeon
e) Pulmonologist/other MD
f) Nurse
g) RT physicist
h) RT therapist/dosimetrist
i) Other
2) Demographic Info:
I work in….

a) An academic institution (ie, affiliated with a medical school)

b) A community setting
3) Demographic Info:
I work in....

a) United States
b) Canada
c) South America
d) Europe
e) Asia
f) Russia
g) Africa
h) Antarctica
i) Other
CASE #1

60 y/o male presents with cough.

No weight loss; KPS 90

CXR-- nodule medial R lung
CT-guided bx of R lung mass– NSCLC
Brain MRI-- negative
PET– uptake in R lung mass and R paratracheal LN
Mediastinoscopy-- +R4; neg L4 and level 7
Stage IIIA-- pN2

4) What is the optimal tx strategy?

a) Surgical resection + adjuvant tx
b) Definitive chemoRT
c) Preop chemo
d) Preop chemoRT
Stage IIIA-- pN2

5) For definitive chemoRT, what RT dose recommend?

a) 54-58 Gy
b) 60-66 Gy
c) 70-76 Gy
d) 78-82 Gy
Stage IIIA-- pN2

6) For preop chemoRT, what RT dose recommend?

a) 40 Gy  
b) 45 Gy  
c) 50 Gy  
d) 55 Gy  
e) 60 Gy
Stage IIIA-- pN2

7) Overall, which strategy would you recommend?

a) Definitive chemoRT
b) Neoadjuvant tx + surgery
Stage IIIA-- pN2
Overall, which strategy would you recommend?

1) Definitive chemoRT:  Dr. Jeremic
2) Neoadjuvant tx + surgery:  Dr. Hammoud

NOW........TO THE DEBATE!
Stage IIIA-- pN2
8) Now that you’ve heard the debate, which strategy would you recommend?

a) Definitive chemoRT
b) Neoadjuvant tx + surgery
Case #2:

65 y/o female presents with dyspnea.
No weight loss; KPS 90
CT– 5 cm Right lung mass and R hilar LN
PET– uptake in R lung mass and R hilar LN
Bx-- SqCCa
Patient s/p lobectomy

Pathology--
5.5 cm mod diff SqCCa with negative margins
2/3 positive hilar nodes
2 + R4 nodes
3 + level 7 LN s neg
(no ECE)
PS IIIA (T2N2M0 - margin):
9) What adjuvant treatment(s) would you recommend?

a) None – observation
b) Postop chemo
c) Postop RT
d) Postop chemo followed by RT
e) Postop concurrent chemoRT
PS IIIA (T2N2M0 - margin):
10) If use postop RT, what dose?

a) 40 Gy
b) 45 Gy
c) 50 Gy
d) 55 Gy
e) 60 Gy
f) 65 Gy
PS IIIA (T2N2M0 + margin):
11) What adjuvant treatment(s) would you recommend?

a) None – observation
b) Postop chemo
c) Postop RT
d) Postop chemo followed by RT
e) Postop concurrent chemoRT
PS IIIA (T2N2M0 + margin):  
12) If use postop RT, what dose?

a) 40 Gy  
b) 45 Gy  
c) 50 Gy  
d) 55 Gy  
e) 60 Gy  
f) 65 Gy
PS IIIA (T2N2M0 *neg* margin):

13) If you don’t recommend postop RT, why not?

   a) Based on PORT meta-analysis: postop RT associated with decreased OS
   b) Because of risks of postop RT
   c) Because this patient is margin neg: if + margin, would recommend
   d) Because with recent chemo data, RT not needed

To help us sort out the complex issues....DR. LANGER
PS IIIA (T2N2M0 neg margin):
14) Now that you’ve heard the expert, what adjuvant treatment(s) would you recommend?

a) None – observation
b) Postop chemo
c) Postop RT
d) Postop chemo followed by RT
e) Concurrent chemo RT
CASE #3

70 y/o male with long h/o smoking/COPD

CXR: Fullness in superior left hilar region
PET/CT: Uptake in 2 cm central lung lesion only
PATHOLOGICAL DIAGNOSIS:
Transbronchial biopsy: Squamous cell carcinoma, moderately differentiated

Clinical stage IA (central)
15) The standard of care in 2013 for a patient with resectable clinical stage (CS) I NSCLC is:

a) lobectomy/pneumonectomy
b) minimally invasive sublobar resection
c) stereotactic body radiation therapy (SBRT)
d) 3D conformal radiation therapy (3DCRT)
e) Radiofrequency ablation (RFA)
f) Observation
16) The standard of care in 2013 for a patient with medically inoperable CS I peripheral NSCLC is:

XX a) lobectomy/pneumonectomy
XX b) minimally invasive sublobar resection
c) stereotactic body radiation therapy (SBRT)
d) 3D conformal radiation therapy (3DCRT)
e) Radiofrequency ablation (RFA)
f) Observation
17) Medically inoperable
CS IA (T1N0M0):
If chose RT, what is optimal?

a) 3D conformal RT (3DCRT) to 60-63 Gy in std fx
b) 3DCRT to 66-70 Gy in std fx
c) 3DCRT in abbreviated fx (eg, 45 Gy/15 fx)
d) Hypofractionated Stereotactic Body RT (SBRT)
(eg, 48-60 Gy in 3-4 fx)
18) Medically inoperable
PERIPHERAL
CS IA (T1N0M0):
Regarding SBRT option:

a) Rx ~60 Gy in 3 fx
b) Rx ~48-50 Gy in 4-5 fx
c) Rx ~36-42 Gy in 6-7 fx
d) Rx ~30 Gy in 1 fx
e) SBRT is contraindicated
f) EBRT is a better/safer option
19) Medically inoperable
CENTRAL
CS IA (T1N0M0):
Regarding SBRT option:

a) Rx ~60 Gy in 3 fx
b) Rx ~48-50 Gy in 4-5 fx
c) Rx ~36-42 Gy in 6-7 fx
d) Rx ~30 Gy in 1 fx
e) SBRT is contraindicated
f) EBRT is a better/safer option

Let’s hear from Dr. Ken Rosenzweig
20) After the presentation, for medically inoperable CENTRAL CS IA (T1N0M0):
Regarding SBRT option:

a) Rx ~60 Gy in 3 fx
b) Rx ~48-50 Gy in 4-5 fx
c) Rx ~36-42 Gy in 6-7 fx
d) Rx ~30 Gy in 1 fx
e) SBRT is contraindicated
f) EBRT is a better/safer option
21) Is lung SBRT available at your institution at this time?

a) Yes
b) No
c) No – but will be available in the next 6-12 months
Case #4: Recurrent Disease

72-year-old male, who was diagnosed with squamous cell carcinoma of the left upper lobe in July of 2007. The diagnosis was made in China. He was staged as T4N0M0 due to suspected invasion of the aorta.

He received concurrent chemoRT to a dose of 61.2 Gy (with carboplatin and paclitaxel).

In October 2008, he developed recurrent disease adjacent to the left mainstem bronchus for which he received a second course of radiation therapy consisting of 54 Gy, combined with cetuximab. He was then placed on gefitinib.

More recently, he came to the US, and underwent evaluation including bronchoscopy, which revealed residual squamous cell carcinoma of the left upper lobe. FEV-1 = 2.8 Liters, 53% of predicted.
First course of RT in 8/07 (61.2 Gy)
Second course of RT in 10/08 (54 Gy)
22) Management??

a) Chemotherapy
b) More RT
c) Surgery
d) Other systemic therapy
e) Palliative care prn
Surgery 10/09

PROCEDURES PERFORMED:
1. Fiberoptic bronchoscopy
2. Diagnostic left thoracoscopy
3. Left intrapericardial pneumonectomy
4. Serratus muscle pedicle flap to bronchial stump
Pathology

Residual squamous cell carcinoma and moderate necrosis involving a 7 cm mass. Margins are negative.
Patient went home 6 days post-op
A 74-year-old woman presented to the emergency department two hours after the development of slurred speech and weakness of the left arm and leg. The blood pressure was 154/66 mm Hg, and the pulse rate was 70/minute. A neurologic examination revealed a right gaze preference, left hemiplegia, and a left hemisensory deficit. Computed tomography (CT) of the brain revealed no abnormalities, and the results of coagulation studies were normal. Tissue plasminogen activator was administered intravenously over a one-hour period for acute ischemia of the right middle cerebral artery. The blood pressure remained below 150/110 mm Hg during the infusion. Nine hours later, the patient became aphasic. A CT scan showed hemorrhagic infarction of the right frontal lobe. Blood extended into the lateral ventricles. She was treated with intermittent infusions of mannitol for one day. Although she regained a normal level of consciousness four days later, a dense left hemiparesis and sensory deficit persisted. She was discharged to a rehabilitation facility. Six weeks later, her neurologic deficits had not improved substantially.

The image shows a CT scan of the brain, highlighting a hemorrhagic transformation of a cerebral infarct.
23) PCI for stage III NSCLC (after good response to tx):

a) New std of care
b) Not std of care
c) Recommend in selected patients
d) Discuss benefits/risks with pts (ie, let pt decide)
24) PCI for LS-SCLC
(after good response to tx):

a) 25 Gy/10 fx
b) 30 Gy/15 fx
c) 36 Gy/18 fx
d) 36 Gy (at 1.5 Gy BID)
Staging Updates 7th Ed:
25) 7.5 cm LUL lesion with neg LNs

a) T2N0 (stage IB)
b) T2N0 (stage IIA)
c) T3N0 (stage IIA)
d) T3N0 (stage IIB)
Staging Updates 7th Ed:

7.5 cm LUL lesion with neg LNs

1) T2N0 (stage IB)
2) T2N0 (stage IIA)
3) T3N0 (stage IIA)
4) T3N0 (stage IIB)

(used to be #1)
Staging Updates 7th Ed:

26) 5 cm LUL lesion with neg LN and tumor nodule in LUL

a) T2N0M0 (stage IB)
b) T3N0M0 (stage IIB)
c) T4N0M0 (stage IIIB)
d) T2N0M1 (stage IV)
Staging Updates 7th Ed:
5 cm LUL lesion with neg LN
and tumor nodule in LUL

a) T2N0M0 (stage IB)
b) T3N0M0 (stage IIB)
c) T4N0M0 (stage IIIB)
d) T2N0M1 (stage IV)

(used to be #3)
Staging Updates 7th Ed:

27) 5 cm LUL lesion with neg LNs and tumor nodule in LLL

a) T2N0M1 (stage IV)
b) T3N0M1 (stage IV)
c) T3N0M0 (stage IIIA)
d) T4N0M0 (stage IIIA)
Staging Updates 7\textsuperscript{th} Ed:
5 cm LUL lesion with neg LN\textsubscript{s} and tumor nodule in LLL

\begin{enumerate}
\item T2N0M1 (stage IV)
\item T3N0M1 (stage IV)
\item T3N0M0 (stage IIIA)
\item T4N0M0 (stage IIIA)
\end{enumerate}

(used to be #1)
Staging Updates 7th Ed:
28) 5 cm LUL lesion with neg LN
and malignant pleural effusion

a) T2N0M1 (stage IV)
b) T3N0M0 (stage IIIB)
c) T4N0M0 (stage IIIB)
d) T4N0M1 (stage IV)
Staging Updates 7th Ed:
5 cm LUL lesion with neg LN
and malignant pleural effusion

a) T2N0M1 (stage IV)
b) T3N0M0 (stage IIIB)
c) T4N0M0 (stage IIIB)
d) T4N0M1 (stage IV)

(used to be #3; MPE now = M1a)
Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Early Stage Non-Small Cell Lung Cancer

Kenneth Rosenzweig, MD
Department of Radiation Oncology
Icahn School of Medicine at Mount Sinai
New York, NY
Disclosure

- President-elect – American Radium Society
Toxicity of Central Lung SBRT

- Timmerman, et al. *JCO* 2006
- 70 pts
- 20 Gy x 3 or 22 Gy x 3
- 14 patients had Grade 3 to 5 toxicity
  - 8 Grade 3/4 - ↓PFT’s, effusion, pneumonia
  - 6 toxic deaths – pneumonia, pericardial effusion, hemoptysis
  - Central tumors more likely to have toxicity

“*No fly zone*”
GTV/PT

VDistal Bronchus

Mainstem Bronchus

Esophagus

Relative dose [%]

Dose (cGy)

Some structures are unapproved or rejected
Update of Indiana Experience

- Fakiris, et al., *IJROBP* 2009
- Median f/u of 50 months
- Central tumors had similar overall survival to peripheral tumors at 24 months
  - Median survival 33 mo vs. 24 mo (p=0.7)
VU Experience

- 63 centrally located tumors
  - 37 central hilum and 26 pericardial/mediastinal
- Dose: 60 Gy/8 fractions
- No definitive grade 4 or 5 toxicity
- Pericardial tumors not associated with cardiovascular deaths
- Compared to 445 peripheral tumors
  - Local control similar in both groups (90 – 92%)
  - Overall survival slightly better in central tumors
Erasmus Experience (Rotterdam)

- Nuyttens, et al., *Radiother Oncology* 2012
- 58 tumors in 56 patients
- Multiple fractionations schemes
- PTV dose reduced in 21 patients to protect organs at risk
  - No Grade 4 or 5 toxicity
- Trend toward improved 2-year local control for $\text{BED}_{10} > 100$ Gy
  - 85% vs. 88% (p = 0.4)
Yale Experience

• Rowe, et al., *J Thor Oncol*, 2012
• 51 tumors in 47 patients
  – 40 central, 11 mediastinal
• Typical dose: 50 Gy in 4 fractions
• Toxicity
  – 1 Grade 5 hemoptysis, 4 Grade 3 dyspnea
• Local control
  – \( \text{BED}_{10} > 100 \text{ Gy} \): 94%
  – \( \text{BED}_{10} < 100 \text{ Gy} \): 80% (\( p=0.02 \))
MSKCC Experience

- Modh, et al., ASTRO 2013 (Abstract #78)
- 107 patients with central tumors
- Typical dose 45 Gy in 5 fractions
- Grade 3 or worse toxicity: 12%
  - Two treatment related deaths
- 2-year rate of local control
  - $\text{BED}_{10} > 100$ Gy: 88%
  - $\text{BED}_{10} < 100$ Gy: 69% (p=0.1)
Systematic Review

- Senthil, et al., *Radiother Oncology*, 2013 (VU)
- Review of twenty publications
  - 563 central tumors receiving SABR
  - Toxicity
    - Grade 5: 2.8%
      - $\text{BED}_3$ of 210 Gy cut-off (3.6% vs. 1%)
    - Grade 3 – 4: 8.6%
Systemic Review: Which BED?

• For tumor control $>100 \text{ Gy } \text{BED}_{10}$ probably necessary
  – 50 Gy/5 fractions
  – 60 Gy/8 fractions

• For toxicity $<210 \text{ Gy } \text{BED}_{3}$
  – 50 Gy/5 fractions = 217 Gy BED$_3$
  – 60 Gy/8 fractions = 210 Gy BED$_3$

Senthi, et al., 2013
RTOG 0813

- Phase I/II dose escalation study
- Nine levels
  - Level 1: 40 Gy in 5 fractions
  - Level 9: 60 Gy in 5 fraction
- Closed September, 2013
  - One year wait for toxicity results
  - ? ASCO 2015
## Normal Structure Constraints: Esophagus

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<tr>
<th>Institution</th>
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<tbody>
<tr>
<td>RTOG 0813</td>
<td>27.5 Gy (5.5 Gy/fx) &lt; 5 cc</td>
</tr>
<tr>
<td></td>
<td>(D_{\text{max}}: 105%)</td>
</tr>
<tr>
<td>Erasmus (Rotterdam)</td>
<td>(D_{\text{max}}: 7) Gy/fraction</td>
</tr>
<tr>
<td>Beaumont</td>
<td>4 fractions: (D_{\text{mean}} \leq 30.5) Gy</td>
</tr>
<tr>
<td>MSKCC</td>
<td>3 fractions: (D_{\text{max}} \leq 30) Gy</td>
</tr>
<tr>
<td>UT Southwestern</td>
<td>3 fractions: (D_{\text{max}} &lt; 25.2) Gy, (D_{5\text{cc}} &lt; 17.7) Gy</td>
</tr>
<tr>
<td>Washington U</td>
<td>3 fractions: (D_{\text{max}} \leq 27) Gy</td>
</tr>
<tr>
<td>JCOG 0403</td>
<td>40 Gy (\leq 1) cc, 35 Gy (\leq 10) CC</td>
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## Normal Structure Constraints: Bronchial Tree

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<tr>
<td>RTOG 0813</td>
<td>18 Gy (3.6 Gy/fx) &lt; 4 cc</td>
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<td>$D_{\text{max}}$: 105%</td>
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<tr>
<td>Erasmus (Rotterdam)</td>
<td>$D_{\text{max}}$: 12 Gy/fraction</td>
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<tr>
<td>Beaumont</td>
<td>4 fractions: $D_{\text{max}} \leq 34$ Gy</td>
</tr>
<tr>
<td>MSKCC</td>
<td>3 fractions: $D_{\text{max}} \leq 30$ Gy</td>
</tr>
<tr>
<td>UT Southwestern</td>
<td>3 fractions: $D_{\text{max}} &lt; 30$ Gy, $D_{4\text{cc}} &lt; 15$ Gy</td>
</tr>
<tr>
<td>Washington U</td>
<td>3 fractions: $D_{\text{max}} \leq 30$ Gy</td>
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<tr>
<td>JCOG 0403</td>
<td>40 Gy $\leq 10$ cc</td>
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## Normal Structure Constraints: Heart

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<td>RTOG 0813</td>
<td>32 Gy (6.4 Gy/fx) &lt; 15 cc, D(_{\text{max}}): 105%</td>
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<tr>
<td>Beaumont</td>
<td>4 fractions: D(_{\text{max}}) ≤ 36 Gy</td>
</tr>
<tr>
<td>UT Southwestern</td>
<td>3 fractions: D(<em>{\text{max}}) &lt; 30 Gy, D(</em>{15\text{cc}}) &lt; 24 Gy</td>
</tr>
<tr>
<td>Washington U</td>
<td>3 fractions: D(_{\text{max}}) ≤ 30 Gy</td>
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<tr>
<td>JCOG 0403</td>
<td>48 Gy ≤ 1 cc, 40 Gy ≤ 10 cc</td>
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## Normal Structure Constraints: Great Vessels

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<tr>
<td>RTOG 0813</td>
<td>47 Gy (9.4 Gy/fx) &lt; 15 cc</td>
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<td>(D_{\text{max}}\cdot 105%)</td>
</tr>
<tr>
<td>Beaumont</td>
<td>4 fractions: (D_{\text{max}} \leq 36) Gy</td>
</tr>
<tr>
<td>UT Southwestern</td>
<td>3 fractions: (D_{\text{max}} &lt; 45) Gy, (D_{10cc} &lt; 39) Gy</td>
</tr>
<tr>
<td>JCOG 0403</td>
<td>40 Gy \leq 1 cc, 35 Gy \leq 10 cc</td>
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</table>
Conclusions

• Treatment of central tumors still remains a challenge, but experience has increased

• Difficult to achieve acceptable $\text{BED}_{10}$ and still keep normal tissue dose constraints acceptable
  – 50 Gy/5 fractions a good compromise

• Await results of RTOG 0813

• Use daily cone beam imaging to verify