Limited-Stage Small Cell Lung Cancer

Submitted to ABR 2015
Patient

- 64 year old gentleman
- Chief complaint: cough and increasing shortness of breath
History

• No pain, fevers, chills, night sweats. No weight loss, hemoptysis or other system complaints
• PMHx: HTN, HPL, NIDDM, BPH
• Meds: Aspirin, Amitriptyline, Atenolol, Benazepril, Clonidine, Hydrochlorothiazide, Simvastatin
• Allergies: NKDA
• Family Hx: sibling with Hodgkin lymphoma
• Social Hx: 45 years smoking, current 1-pk/day, No current EtOH (for several years), divorced, retired construction worker, No exotic travel history
History / Exam

• ROS: otherwise negative

• Exam:
  – Blood pressure 113/61, weight 210 pounds, pulse 72, afebrile
  – Lungs: slightly decreased breath sounds on right side. No crackles or wheezing auscultated.
  – Negative nodal and abdominal exam
• Labs: WNL

• PFTs:
  – FEV-1 of 2.64
  – DLCO of 52% of predicted

• Other imaging
  – CT Abdomen: negative
  – MRI Brain: negative
Patient

• Saw medical oncology and started cycle 1 of etoposide and carboplatin

• Referred to radiation oncology
Lung Cancer

• Worldwide
  – Most common cancer (1.35 million of 10.9 million cases)
  – Deadliest cancer (1.18 million of 6.7 million cancer-related deaths)

• US:
  – 2nd most common in men and women
  – Deadliest in men (90,330) and women (72,130)
  – More deaths than next three tumor sites combined (colorectal, breast and prostate)
Small Cell Lung Cancer

- 95% related to smoking
- Incidence declining in US
- Still accounts for approximately 20-25% of lung cancer cases (40,000 cases/yr) in US
- Classification: new WHO (2010) – only variant recognized is combined SCLC (c-SCLC)
- Association with paraneoplastic syndromes
  - ADH (SIADH), ACTH (Cushing’s)
  - Eaton-Lambert Syndrome (Lambert-Eaton myasthenic syndrome or LEMS)
- 2 clinical stages:
  - Limited: tumor confined to 1 hemithorax
  - Extensive: beyond 1 hemithorax
Limited Stage Small Cell Lung Cancer

• Only 25% of SCLC

• Survival:
  – 1960s: MRC trial; radiation superior to surgery (mean survival 6.5 vs. 10 months p= 0.04)
    • 1 yr, 2 yr and 5 yr survival of 22%, 10% and 4%
  – 1990s: NCI; chemoradiation with PCI
    • 1 yr, 2 yr and 5 yr survival of 83%, 43% and 19%
3 Questions

• Early 1990s:
  – 2 separate meta-analyses by Pignon et al (NEJM 1992) and Warde et al (JCO 1992) showed a 5.4% increase in overall survival with the addition of chemotherapy to radiation

• Timing of radiation and chemotherapy?
• Dosing and fractionation of radiation?
• With a >80% CNS metastases rate at 2 years, what is the role of prophylactic cranial irradiation (PCI)?
Phase III Study of Concurrent Versus Sequential Thoracic Radiotherapy in Combination With Cisplatin and Etoposide for Limited-Stage Small-Cell Lung Cancer: Results of the Japan Clinical Oncology Group Study 9104

By Minoru Takada, Masahiro Fukuoka, Masaaki Kawahara, Takahiko Sugiura, Akira Yokoyama, Soichiro Yokota, Yutaka Nishiwaki, Koshiro Watanabe, Kazumasa Noda, Tomohide Tamura, Haruhiko Fukuda, and Nagahiro Saijo for the Members of the Japan Clinical Oncology Group


Chemo: etoposide and cisplatin x4c

Table 3. Tumor Response According to Treatment Arm: Eligible Patients

<table>
<thead>
<tr>
<th>Result</th>
<th>Sequential Arm (n = 114)</th>
<th>Concurrent Arm (n = 114)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>31</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>Partial</td>
<td>74</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Overall</td>
<td>105</td>
<td>92</td>
<td>110</td>
</tr>
<tr>
<td>No change</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Progressive</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Importance of Timing for Thoracic Irradiation in the Combined Modality Treatment of Limited-Stage Small-Cell Lung Cancer

By Nevin Murray, Peter Coy, Joseph L. Pater, Ian Hodson, Andrew Arnold, Benny C. Zee, David Payne, Edmund C. Kostashuk, William K. Evans, Peter Dixon, Anna Sadura, Ronald Feld, Martin Levitt, Rafal Wierzbicki, Joseph Ayoub, Jean A. Maroun, and Kenneth S. Wilson for the National Cancer Institute of Canada Clinical Trials Group

Journal of Clinical Oncology, Vol 11, No 2 (February), 1993: pp 336-344

Fig 1. Study schema.

Fig 3. Overall survival: early TI v late TI.
• Timing of radiation and chemotherapy?

• Concurrent

• Start radiation within the first 4-6 weeks of starting chemotherapy (exception CALGB)
TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOThERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPoside

ANDREW T. TURRISI, III, M.D., KYUNGMAN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

BID: median 23 months, 2-yr 47%, 5-yr 26%
QD: median 19 months, 2-yr 41%, 5-yr 16%


CompliCation and No. of Radiation Treatments per Day

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>number (percent) of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Overall†
1 1 (0.5)
2 2 (1)
Myelotoxicity‡
1 2 (1)
2 7 (3)
Esophagitis
1 113 (56)
2 76 (37)
Other toxic effects
1 4 (2)
2 2 (1)

*Data were available for 203 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy.
†Overall rates are based on the grade of the most severe complication of any type that occurred in each patient.
‡Myelotoxicity was defined as any decrease in marrow-derived cells in the peripheral-blood counts.

Intergroup study 0096
A Pooled Analysis of Limited-Stage Small-Cell Lung Cancer Patients Treated with Induction Chemotherapy Followed by Concurrent Platinum-Based Chemotherapy and 70 Gy Daily Radiotherapy

CALGB 30904

Joseph K. Salama, MD,* Lydia Hodgson, MS,† Herbert Pang, PhD,‡ James J. Urbanic, MD,‡ A. William Blackstock, MD,‡ Steven E. Schild, MD,§ Jeffrey Crawford, MD,¶ Jeffrey A Bogart, MD,¶ and Everett E. Vokes, MD,# for the Cancer and Leukemia Group B

Journal of Thoracic Oncology • Volume XX, Number XX, XXX 2013

- Median follow up 78 months
- Median survival 19.9 months
- 5-yr OS pooled was 20%
- 2-yr PFS was 26%
• Dosing and fractionation for SCLC?

• Standard of care is 45 Gy delivered in 1.5 Gy fractions BID for 3 weeks

• There is growing evidence that doses >60 Gy may be effective in daily fractionation of 2 Gy with decreased grade 3+ esophagitis
PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

Anne Aupérin, M.D., Rodrigo Arrigada, M.D., Jean-Pierre Pignon, M.D., Ph.D., Cécile Le Pechoux, M.D., Anna Gregor, M.D., Richard J. Stephens, Paul E.G. Kristjansen, M.D., Ph.D., Bruce E. Johnson, M.D., Hiroshi Ueoka, M.D., Henry Wagner, M.D., and Joseph Aisner, M.D., for the Prophylactic Cranial Irradiation Overview Collaborative Group*


<table>
<thead>
<tr>
<th>Trial</th>
<th>Enrollment Period</th>
<th>Median Follow-up</th>
<th>Induction Therapy</th>
<th>Total Dose/No. of Fractions (Dose/fraction)</th>
<th>Median Time between Start of Induction Therapy and Enrollment</th>
<th>No. of Patients</th>
<th>No. of Patients Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMCC</td>
<td>1977–1980</td>
<td>18.5</td>
<td>CT</td>
<td>30 Gy/10 (3 Gy)</td>
<td>3.6</td>
<td>29</td>
<td>2</td>
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<tr>
<td>Okayama</td>
<td>1981–1986</td>
<td>11.7</td>
<td>CT or CT plus RT</td>
<td>40 Gy/20 (2 Gy)</td>
<td>2.5</td>
<td>46</td>
<td>4</td>
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<tr>
<td>PCI-85</td>
<td>1985–1993</td>
<td>8.4</td>
<td>CT or CT plus RT</td>
<td>24 Gy/8 (3 Gy)</td>
<td>5.3</td>
<td>300</td>
<td>32</td>
</tr>
<tr>
<td>Danish–NCI</td>
<td>1985–1991</td>
<td>8.8</td>
<td>CT</td>
<td>24 Gy/8 (3 Gy)</td>
<td>4.4</td>
<td>55</td>
<td>7</td>
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<tr>
<td>UKCCCR–EORTC</td>
<td>1987–1995</td>
<td>3.5</td>
<td>CT or CT plus RT</td>
<td>8–36 Gy/1–18†</td>
<td>NA</td>
<td>314</td>
<td>54</td>
</tr>
<tr>
<td>PCI-88</td>
<td>1988–1994</td>
<td>5.1</td>
<td>CT or CT plus RT</td>
<td>24 Gy/8 (3 Gy)</td>
<td>5.1</td>
<td>211</td>
<td>37</td>
</tr>
<tr>
<td>ECOG–RTOG</td>
<td>1991–1994</td>
<td>3.9</td>
<td>CT or CT plus RT</td>
<td>25 Gy/10 (2.5 Gy)</td>
<td>NA</td>
<td>32</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. of Patients</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Heterogeneity (P Value)</th>
<th>Rate in the Control Group over a 3-Yr Period</th>
<th>Absolute Benefit at 3 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>Control Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>526</td>
<td>461</td>
<td>0.84 (0.73–0.97)</td>
<td>0.01</td>
<td>0.95</td>
<td>15.3</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>526</td>
<td>461</td>
<td>0.75 (0.65–0.86)</td>
<td>&lt;0.001</td>
<td>0.96</td>
<td>13.5</td>
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<tr>
<td>Cumulative incidence of brain</td>
<td>524</td>
<td>457</td>
<td>0.46 (0.38–0.57)</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>58.6</td>
</tr>
<tr>
<td>metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cumulative incidence of other</td>
<td>325</td>
<td>332</td>
<td>0.89 (0.69–1.15)</td>
<td>0.37</td>
<td>0.51</td>
<td>45.6</td>
</tr>
<tr>
<td>metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of local</td>
<td>323</td>
<td>334</td>
<td>0.97 (0.75–1.26)</td>
<td>0.84</td>
<td>0.45</td>
<td>45.1</td>
</tr>
<tr>
<td>or regional recurrence</td>
<td></td>
<td></td>
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</table>

*For a more detailed analysis of the trial results, please refer to the original publication. The table summarizes the key findings, including the number of patients, relative risk, p-value, and the rate in the control group over a 3-year period.
• Median follow up 39 months
• No difference in brain mets between high dose vs low dose groups (29% vs 23%, p=0.18)
• Worse 2-yr survival in high dose group (37% vs 42%, p=0.05)
• Conclusion: no benefit to high dose PCI
• Role of PCI?

• Should be done in patients with response to chemoradiation

• 25 Gy in 10 fractions is standard of care and higher doses appear worse
Patient

- Right paratracheal mass treated to 5940 cGy in 180 cGy fractions with concurrent etoposide and carboplatin
- PCI to 3600 cGy in 20 fxns according to RTOG 0212
- Right lung mass treated to 4800 cGy in 4 fractions between ~1 year later
- Died 5 years later
  - in the interim, underwent adrenalectomy, RT to cerebellar metastasis