CALGB 30610

Thoracic Radiotherapy for Limited Stage Small Cell Lung Cancer

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Small Cell Lung Cancer

- Estimated 33,000 cases in 2013
  - ~ One-third limited stage
    - Impact of FDG-PET
  - Majority stage III (2-5% stage 1)
  - Evenly split M = F

- IASLC (AJCC v 7) Stage Prognostic
Survival by Stage

TABLE S2. Cox Multivariate Analysis of the IASLC Staging System for SCLC

<table>
<thead>
<tr>
<th>UICC6</th>
<th>Hazards Ratio</th>
<th>95% Confidence Interval</th>
<th>p</th>
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<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>1.000</td>
<td>(0.996–1.492)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IB</td>
<td>1.219</td>
<td>(1.025–1.424)</td>
<td>0.0548</td>
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<tr>
<td>Stage IIA</td>
<td>1.490</td>
<td>(1.166–2.033)</td>
<td>0.0002</td>
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<tr>
<td>Stage IIB</td>
<td>1.540</td>
<td>(1.584–2.178)</td>
<td>0.0023</td>
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<tr>
<td>Stage IIIA</td>
<td>1.858</td>
<td>(2.010–2.792)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Stage IIIB</td>
<td>2.369</td>
<td>(2.649–3.615)</td>
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<tr>
<td>Stage IVA</td>
<td>3.095</td>
<td>(3.653–4.947)</td>
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<tr>
<td>Stage IVB</td>
<td>4.251</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Age</td>
<td>1.014</td>
<td>(1.012–1.016)</td>
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<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>1.000</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Female</td>
<td>0.877</td>
<td>(0.842–0.913)</td>
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<tr>
<td>Ethnicity</td>
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<td>Caucasian</td>
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<tr>
<td>African American</td>
<td>0.939</td>
<td>(0.863–1.021)</td>
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<td>Hispanic</td>
<td>1.002</td>
<td>(0.932–1.072)</td>
<td>0.9852</td>
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<td>Chinese</td>
<td>0.823</td>
<td>(0.685–0.988)</td>
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<td>Non-Chinese Asian</td>
<td>0.843</td>
<td>(0.757–0.938)</td>
<td>0.0017</td>
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<td>Other</td>
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<td>(0.593–1.402)</td>
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<td>Marital status</td>
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<td>Married</td>
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<td>Unmarried</td>
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<td>Socioeconomic status</td>
<td>0.967</td>
<td>(0.952–0.982)</td>
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<td>Surgery</td>
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<td></td>
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<td>Yes</td>
<td>0.445</td>
<td>(0.386–0.513)</td>
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<td>Radiation</td>
<td></td>
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<tr>
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<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>Yes</td>
<td>0.722</td>
<td>(0.692–0.753)</td>
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<td>Chemotherapy</td>
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<tr>
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<td></td>
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<tr>
<td>Yes</td>
<td>0.379</td>
<td>(0.361–0.397)</td>
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Ou, Journal of Thoracic Oncology. 4(3):300-310,
<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Median OS (Months)</th>
<th>5-yr OS</th>
<th>Notes</th>
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<tr>
<td>INT 0096 1989-92</td>
<td>III</td>
<td>19 - 23</td>
<td>16 - 26%</td>
<td>BID v QD (45 Gy)</td>
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<td>NCCTG 1990-96</td>
<td>III</td>
<td>21</td>
<td>20 %</td>
<td>BID vs QD (50.4 Gy)</td>
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<td>CALGB 9235 1993-99</td>
<td>III</td>
<td>21</td>
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<td>Tamoxifen (50 Gy QD)</td>
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<td>RTOG 9609 1996-98</td>
<td>II</td>
<td>24</td>
<td>---</td>
<td>PET 45 BID</td>
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<td>ECOG 2596 1997-98</td>
<td>II</td>
<td>16</td>
<td></td>
<td>PET 63 Gy QD</td>
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<td>SWOG 9713 1998-99</td>
<td>II</td>
<td>17</td>
<td></td>
<td>Adj paclitaxel (61 Gy QD)</td>
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<tr>
<td>SWOG 0222 2003-06</td>
<td>II</td>
<td>21</td>
<td></td>
<td>Tirapazemine (61 Gy QD)</td>
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</table>
Small Cell Lung Cancer

- Progress has been slow!!!
  - Third generation chemotherapy
    - **Substituting Irinotecan**: extensive disease in Japan is an exception
    - **Adding Paclitaxel**: PET more toxic than ET
  - Targeted agents
    - Bevacizumab toxic in limited stage (SWOG)
Targeted therapy

- Bevacizumab + RT
Untreated ES-SCLC Enrollment

Chemo 4-6 cycles SD, PR, CR PCI Allowed

Stratify Cis vs Carbo 6 Cycles vs <6 Randomize

Sunitinib 37.5 mg/d Until Progression

Progression Until Progression (Crossover allowed)
Progression Free Survival

Median Progression Free Survival –
  sunitinib 3.77 mo
  placebo 2.30 mo
Stratified Log-Rank Test
1-sided p = 0.0372
HR = 1.53
90% CI: 1.03 - 2.27

Progression Free Survival Time
(months from randomization)
Limited Stage Small Cell

• The Integration of Radiotherapy for LSCLC is a Unique Success Story in the Field
• Several positive phase III trials
  ▪ Adding RT to chemotherapy
  ▪ Timing of RT
  ▪ Altered Fractionation
• Few other examples where changing the radiotherapy regimen, in combination with chemotherapy, impacts Overall Survival
Limited Stage Small Cell
Impact of Thoracic Radiotherapy

Pignon et al  NEJM 92
• 13 Trials , >2000 patients
• 3 yr OS: 14.3 vs 8.9 %

Warde et al  JCO 92
• 2 yr OS: 16 vs 22%  (2 yr LC: 40 v 65 %)
• Toxic Death Rate ↑ 1.2%
Limited Stage Small Cell

Meta-analysis underestimates TRT impact?

- Antiquated Staging
- Cisplatin seldom utilized
- Modest TRT Dose: 35 - 50 Gy
- Sequential therapy in majority of trials
- 2D (CXR) Radiotherapy Planning
Radiobiology: Pre-clinical

- Radiation survival curves for SC lines characterized
- Large Cell variant less sensitive

Carney 1983
Dose / Fractionation

Twice-Daily Radiotherapy

- Hospital University of Pennsylvania
  - 45 Gy (1.5 BID) / 3 weeks (Cycle 1 PE)
  - Limited ENI / CT planning
  - 56% 2 year OS
  - 13% severe esophagitis (73% any)

Turrisi 1988
Intergroup Trial 0096 (ECOG)

45 Gy
1.8 Gy QD / 5 wks
CDDP VP-16  CDDP VP-16  CDDP VP-16  CDDP VP-16

45 Gy
1.5 Gy BID / 3 wks
CDDP VP-16  CDDP VP-16  CDDP VP-16  CDDP VP-16

PCI
INTERGROUP 0096

• Initially reported as a null trial (twice)
  • ASCO 1994 - initial report
  • ASCO 1996 - “final report”

• OS benefit emerged with 5 yr follow-up
  • 5-yr OS: 16 % (daily) vs 26% (twice-daily)
  • Gr 3/4 Esophagitis : 16% (daily) vs 32 % (twice-daily)

Turrisi NEJM 1999
INTERGROUP 0096

<table>
<thead>
<tr>
<th>Relapse</th>
<th>BID</th>
<th>QD</th>
<th>P value</th>
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<tbody>
<tr>
<td>Local alone</td>
<td>36%</td>
<td>52%</td>
<td>.058</td>
</tr>
<tr>
<td>Local + distant</td>
<td>6%</td>
<td>23%</td>
<td>.006</td>
</tr>
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</table>

“Local treatment significantly influences survival and failure patterns”
INT 0096: Clinical Impact

Patterns of Care

- 1998-99 (JCO 2003): 6% Patients Received BID RT, Median Daily RT = 50.4 Gy
- ASTRO Survey 2006: 28% would use 45 Gy BID

*Not* widely adopted in clinical trials (in U.S.)

- Acute Toxicity concerns?
- 45 Gy daily arm biologically appropriate comparison?

NCCN guidelines allow daily RT (60–70 Gy)

Movsas 2003   Kong 2007
• Randomized after cycle 3 PE
  • 50.4 Daily vs 48 Gy Twice -Daily
• 2 week RT treatment Interruption in BID arm
• No difference in survival b/w arms

Bonner 1999
Beyond 45 Gy BID?

Are there further therapeutic gains to be achieved by altering the delivery of thoracic RT?

- Traditional Dose Escalation

- Altered Fractionation Dose Escalation
Daily RT Dose Response?

- Data from early prospective trials did not suggest a dose response
  - NCI Canada: OS 25 Gy = 37.5 Gy (Seq)
  - FNCLCC: no dose response 45 - 65 Gy (Alt)

- Select retrospective studies suggest Dose response for daily RT
  - MGH: 5-yr OS 47% if > 50 Gy daily RT
  - Yale: 60 Gy RT – only 4% local failure

High Dose TRT: CALGB 8837

- Randomized phase I RT dose:
  - Cytoxan/PE X 3 → PE / RT
  - RT: BID or QD (56-70 Gy)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Median OS</th>
<th>6 Year OS</th>
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<tbody>
<tr>
<td>Daily</td>
<td>22</td>
<td>29.8 months</td>
<td>36 %</td>
</tr>
<tr>
<td>Twice Daily</td>
<td>25</td>
<td>24</td>
<td>20</td>
</tr>
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</table>

Median QD dose = 66 GY    BID MTD = 45 Gy

Choi JCO 98
Phase II: High Dose Daily RT

- 70 Gy tolerable (21% esophagitis, 6% pulmonary)
- Median survival 23 months (31 months if wt loss <5%)
- Encouraging outcomes considering delayed RT and absence of cisplatin, inclusion of PS 2 and weight loss

### Table: Study CALGB 39808

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Induction</th>
<th>RT</th>
<th>Concurrent</th>
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<tbody>
<tr>
<td>CALGB 39808</td>
<td>63</td>
<td>Paclitaxel Topotecan x2</td>
<td>70 Gy</td>
<td>Carboplatin Etoposide x3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 weeks</td>
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Bogart 2004
## 39808/ 0096 Comparison (*2-yr FU)

<table>
<thead>
<tr>
<th></th>
<th>INT 0096 (45 Gy BID)</th>
<th>C 39808 (70 GY QD)</th>
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<tbody>
<tr>
<td>Male</td>
<td>58 %</td>
<td>54 %</td>
</tr>
<tr>
<td>Wt loss &gt; 5%</td>
<td>18 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Age (med)</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Med. OS</td>
<td>20.3* mo</td>
<td>22.4 mo</td>
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<tr>
<td>2-yr OS</td>
<td>44 %</td>
<td>48 %</td>
</tr>
<tr>
<td>2-yr DFS</td>
<td>29 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Esophagitis (3+)</td>
<td>32 %</td>
<td>19 %</td>
</tr>
</tbody>
</table>

* ~ 2-yr follow-up (ASCO 1994)

39808: Novel induction, Cycle 3 TRT, No Cisplatin
High Dose Concomitant Boost

• Improved control in H&N SCC (RTOG)
• Phase I (RTOG 9712) defined 61.2 Gy/PE as MTD in LSCLC
• Phase II completed (RTOG 0239) with acceptable toxicity (18% Esophagitis)
  ▪ Preliminary report 2yr-OS 37%, 80% LC

I = large field,  X = boost field

Avoids BID “large field” TRT

Komaki 2005, 2009
# High Dose TRT Regimens

<table>
<thead>
<tr>
<th>RT Regimen</th>
<th>Nominal Dose</th>
<th>BED</th>
<th>BED-time</th>
<th>Relative BED</th>
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</thead>
<tbody>
<tr>
<td>INT 0096</td>
<td>45 Gy twice-daily</td>
<td>52</td>
<td>43</td>
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</tr>
<tr>
<td>CALGB</td>
<td>70 Gy daily</td>
<td>82</td>
<td>63</td>
<td>~ 1.5</td>
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<tr>
<td>RTOG</td>
<td>61.2 Gy conc boost</td>
<td>72</td>
<td>57</td>
<td>~ 1.4</td>
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</table>

- Higher *predicted* efficacy with CALGB & RTOG regimens
- 70 Gy represents > 50% nominal dose escalation

(BED = biologic equivalent dose)
Phase III: CALGB 30610/ RTOG 0538

Limited Small Cell

45 Gy BID / 3 weeks

61.2 Gy CB / 5 weeks

70 Gy QD / 7 weeks

PE x 4 → PCI
Cycle 1 TRT

Experimental TRT Arm

Primary Endpoint = OS

Re-assess

45 Gy BID / 3 weeks

vs
Phase III: CALGB 30610/ RTOG 0538

Limited Small Cell

45 Gy BID / 3 weeks

61.2 Gy CB / 5 weeks

Re-assess

70 Gy QD/ 7 weeks

45 Gy BID / 3 weeks

70 Gy QD/ 7 weeks

Primary Endpoint = OS

PE x 4 → PCI
Cycle 1 or 2 TRT

VS
Status of Phase III trials

• CALGB 30610
  • Accrued 360 + patients / 700+
  • No significant difference in toxicity
    • CB arm dropped 3/2013
RTOG 0617 (Stage III NSCLC)

Stratify
3D v IMRT
PS 0 v 1
PET Y / N
Histology

Randomize

Carboplatin Paclitaxel weekly
XRT : 60 Gy in 6

Carboplatin Paclitaxel weekly
XRT : 74Gy in 7.5 weeks

Carboplatin Paclitaxel/Cetuximab
XRT : 60 Gy in 6

Carboplatin Paclitaxel/Cetuximab
XRT : 74Gy in 7.5 weeks

Adjuvant Carboplatin Paclitaxel

Adjuvant Carboplatin Paclitaxel Cetuximab

n = 500
RTOG 0617 (Stage III NSCLC)

Stratify
3D v IMRT
PS 0 v 1
PET Y / N
Histology

Carboplatin Paclitaxel weekly
XRT : 60 Gy in 6 weeks

Carboplatin Paclitaxel/Cetuximab
XRT : 60 Gy in 6 weeks

June, 2011 : 74 Gy Arms Closed
(Futility Analysis)

Adjuvant Carboplatin Paclitaxel

Adjuvant Carboplatin Paclitaxel Cetuximab
Major Amendments

- Allow RT to be given with either 1\textsuperscript{st} or 2\textsuperscript{nd} cycle of chemotherapy
- Reduced to 2 arm trial
- Allow Registration after 1\textsuperscript{st} cycle of chemotherapy
- Planning to allow substitution of carboplatin for cisplatin
Summary

• Optimizing thoracic RT critical in LSCLC

• 45 Gy BID not widely accepted and Protracted High dose QD RT now routinely used in practice without sufficient evidence
  • Are the results of RTOG 0617 for NSCLC a lesson learned? 74 Gy + chemo not better than 60 Gy +chemo
  • CALGB and CONVERT critical test for dose escalation paradigm