Current Approaches for Limited Small Cell Lung Cancer

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Can we improve or personalize treatment?

- Limited
  - Histology/molecular targets
  - Systemic therapy
  - Radiation dose/fractionation
  - Radiation timing
  - Radiation volume
  - PCI
- Extensive
  - RT Oligometastatic
Intergroup Trial 0096
LSCLC 45 Gy QD or BID

45 Gy 3 wks BID

Thoracic radiation starting day 1 of cycle 1
Cisplatin – 60 mg/m² day 1
Etoposide – 120 mg/m² d 1,2,3
Cisplatin/etoposide q 3 week cycles
PCI: 25 Gy (2.5 Gy qd)

<table>
<thead>
<tr>
<th></th>
<th>45 Gy QD</th>
<th>45 Gy BID</th>
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</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>19 m</td>
<td>23 m</td>
<td>NS</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>16%</td>
<td>26%</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Local failure</td>
<td>52%</td>
<td>36%</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Local + distant</td>
<td>23%</td>
<td>6%</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>5%</td>
<td>4%</td>
<td>NS</td>
</tr>
</tbody>
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Increasing proportion of women

Increasing proportion of non-Hispanic blacks

TNM staging associated with prognosis

Increasing proportion extensive/Stage IV

Increasing proportion of patients being treated in community setting

NCDB Limited SCLC
Demographics 1992-2007

- Positive prognostic factors
  - low AJCC Stage
  - female gender
  - age < 70 yrs
  - non-Hispanic whites
  - surgery (Stage I/II)
  - radiation therapy
  - treatment facility type

- Non-prognostic factors
  - year treated

Can 18FDG-PET/CT help with decision making?

Complex….

- High SUVmax in primary
  - No prognostic difference in Stage I-III
  - Improved outcome in Stage IV
- Whole body metabolic tumor volume (SUV >3)
  - >127cc predicted poor survival
- Early CT or PET changes in Stage I-III
  - Improved survival if either reduced

C van der Leest et al, Lung Cancer 76;67-71, 2012
J van Loon et al, Radiother Oncol 99;172-75, 2011
Histopathology and Biologic Factors

- Proto-oncogenes and tumor suppressor genes
  - P53 mutation: 75%
  - Myc amplification: 15-30%
  - RB1: >90%

- Apoptosis pathways
  - Bcl-2 amplif: 80%
  - Telomerase overexp: >90%

- Cell cycle adhesion receptors
  - E-cadherin: 65%

Intergroup Trial 0096
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Recent advances in systemic therapy for SCLC

- Maintenance
- New agents
  - Irinotecan
  - Gemcitabine
  - Pemetrexed
  - Amrubicin
  - Picoplatin

- Targeted agents
  - GFR inhibitors
  - Anti-angiogenesis
  - Pro-apoptotic
  - Ant-CD56 antibody
  - Vaccines
  - Hedgehog Pathway

Intergroup Trial 0096
LSCLC 45 Gy QD or BID

45 Gy 3 wks BID

PE  PE  PE  PE → PCI

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PCI: 25 Gy (2.5 Gy qd)

*Turrisi A et al, NEJM 340:265-71, 1999*
Intergroup Trial 0096
LSCLC 45 Gy QD or BID

Dose/fractionation
Target
Timing

Thoracic radiation starting day 1 of cycle 1
Cisplatin – 60 mg/m^2 day 1
Etoposide – 120 mg/m^2 d 1,2,3
Cisplatin/etoposide q 3 week cycles
PCI: 25 Gy (2.5 Gy qd)

CALGB 30610/ RTOG 0538

**Eligibility**
- LSCLC
- No contralateral hilar or supraclav N
- ECOG PS 0-2

**Stratification**
- ECOG 0 vs. 1-2
- Weight loss
- Gender
- 3D vs. IMRT

**Accrual goal**
- 670-712

**Arm A: Standard**
- Cisplatin/Etoposide x 4 + Concurrent 45 Gy BID

**Arm B:**
- Cisplatin/Etoposide x 4 + Concurrent 61.2 Gy QD/BID

**Arm C:**
- Cisplatin/Etoposide x 4 + Concurrent 70 Gy QD

Approximately 80 patients per arm as of May 2012
CONVERT (EORTC/NCIC)

Eligibility
LSCLC
FEV1/KCO limits
V20 ≤ 35%
Reasonable RT port
ECOG PS 0-2

Stratification
ECOG PS 0-1 vs 2
Center
Na, Alk phos, LDH

Accrual goal 532

Arm A: Control
Cisplatin/Etoposide x 4-6 cycles
Concurrent 45 Gy BID 3 wks

Arm B: Experimental
Cisplatin/Etoposide x 4-6 cycles
Concurrent 66 Gy QD 33 fx

369/532 accrued as of May 2012. Anticipate closure late 2013
Omitting ENI in LSCLC: Evidence from a phase II trial

38 patients with involved field only (CT based)
No isolated nodal failures
2 nodal relapses with concurrent distant failure

Is involved-field RT based on CT safe in LSCLC?

- 108 patients IF treated only, 55-56 Gy BID, concurrent or sandwiched with cis/etop chemo
- 28/78 (36%) failures LRF
  - In field 16 (57%)
  - Out of field 10 (36%)
  - In and out 2 (7%)

B Xia et al, Rad Oncol 102:258-62, 2012
Is involved-field RT based on CT safe in LSCLC?

- 108 patients IF treated only, 55-56 Gy BID, concurrent or sandwiched with cis/etop chemo
- 28/78 (36%) failures LRF
  - In field 16 (57%)
  - Out of field 10 (36%)
  - In and out 2 (7%)
- All 5 (4.6%) isolated nodal relapses were in supraclav

B Xia et al, Rad Oncol 102:258-62, 2012
Locoregional failures following involved field radiation in LSCLC

- Cumulative LRF rate: 2 yrs 29%, 5 yrs 38%
- Approx 70% of LRF were out of field
- 85% of LRF were within 6 cm of 95% isodose line

Study Design

LD-SCLC Treatment-naïve
N=219

Initial arm (n=111)
EP: Etoposide 100mg/m² D1-3
Cisplatin 70mg/m² D1, q3 w
TRT: 52.5 Gy/25 fx (2.1 Gy/fx, once daily)

Delayed arm (n=108)
TRT

1:1*

PCI for patients with PR or CR

- Primary end point: Complete response rate (WHO criteria)
- Secondary end point: ORR, OS, PFS, and toxicity (NCI-CTC ver. 2.0)

*Stratified by the institute
Response evaluation: every 2 cycles during treatment, every 3 mo. for 1 Y, and then every 6 mo.
**1st versus 3rd Cycle TRT + Cisplatin-Etoposide in L-SCLC**

- **1st Cycle arm** (n=111)
  - EP: Etoposide 100mg/m^2 D1-3
  - Cisplatin 70mg/m^2 D1, q3 w
  - TRT: 52.5 Gy/25 fx (2.1 Gy/fx, once daily)

- **3rd Cycle Delayed arm** (n=108)
  - EP: Etoposide 100mg/m^2 D1-3
  - Cisplatin 70mg/m^2 D1, q3 w
  - TRT: 52.5 Gy/25 fx (2.1 Gy/fx, once daily)

- **Enrollment between 2003 and 2010 (7 years)**
- **Median Follow Up is 59.4 months (about 5 years)**

- **Primary end point**: Complete response rate (WHO criteria)
- **Secondary end point**: ORR, OS, PFS, and toxicity (NCI-CTC ver. 2.0)

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LD-SCLC Treatment-naïve
N=219

PCI for patients with PR or CR

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Park K et al, Proc ASCO 2012. Abst #7007
Efficacy Comparisons

Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Initial Arm (n = 111)</th>
<th>Delayed Arm (n = 108)</th>
<th>95% CI of the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>40 (36.0%)</td>
<td>41 (38.0%)</td>
<td>(-14.7%, 10.9%)</td>
</tr>
<tr>
<td>PR</td>
<td>62 (55.9%)</td>
<td>56 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4 (3.6%)</td>
<td>4 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5 (4.5%)</td>
<td>5 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>91.9%</td>
<td>89.8%</td>
<td></td>
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Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>P</th>
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<tbody>
<tr>
<td>Initial arm</td>
<td>24.1 months</td>
<td>0.69</td>
</tr>
<tr>
<td>Delayed arm</td>
<td>26.8 months</td>
<td>0.90 (95% CI: 0.18-1.82)</td>
</tr>
</tbody>
</table>

2-yr OS rate: Initial arm 50.7%, Delayed arm 56.0%
5-yr OS rate: Initial arm 24.3%, Delayed arm 24.6%

Locoregional Failure

Initial TRT: Delayed TRT

P = 0.14

Distant Failure

Initial TRT: Delayed TRT

P = 0.96

Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Initial arm</td>
<td>12.4 months</td>
<td>0.60</td>
</tr>
<tr>
<td>Delayed arm</td>
<td>11.2 months</td>
<td>0.90 (95% CI: 0.37-1.84)</td>
</tr>
</tbody>
</table>

1-yr PFS rate: Initial arm 51.8%, Delayed arm 48.1%
2-yr PFS rate: Initial arm 28.0%, Delayed arm 23.5%
Meta-Analysis of Timing of Chest RT in LSCLC

If chemo compliance similar then early RT (before day 49) associated with improved 5-yr survival

9 trials with 2,304 patients

De Ruysscher D et al, Abst M019.03, WCLC 2011
• V20 decreased from 71 to 36%
• NTCP decreased from 44 to 16%

Green 45 Gy
Red 49.5 Gy
Brown 22.5 Gy
Thoracic radiation starting day 1 of cycle 1
Cisplatin – 60 mg/m² day 1
Etoposide – 120 mg/m² d 1,2,3
Cisplatin/etoposide q 3 week cycles

PCI: 25 Gy (2.5 Gy qd)

45 Gy 3 wks BID

PE

PE

PE

PCI

Prophylactic Cranial Irradiation (PCI)

5.4% Absolute improved survival at 3 yrs

Auperin A et al, NEJM 1999;341:524-526
RTOG 0212: Impact of PCI on Chronic Neurotoxicity

264 evaluable patients

- No difference in QOL between doses
- Neurocognitive decline by 12 months
  - 62% 25 Gy arm
  - 85-90% 36 Gy arms
- Higher toxicity if age > 60 yrs

Standard of care for PCI for LSCLC:
25 Gy in 10 fractions

Wolfson A et al, IJROBP 2011;81(1):77-84
Who benefits from PCI?

- Initial response to chemoradiation in LSCLC predicts interval to developing brain metastases

<table>
<thead>
<tr>
<th>Response</th>
<th>PCI</th>
<th>BM-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Yes</td>
<td>640 days</td>
</tr>
<tr>
<td>No</td>
<td>482 days</td>
<td></td>
</tr>
<tr>
<td>Not CR</td>
<td>No</td>
<td>273 days</td>
</tr>
</tbody>
</table>

- No prospective study in LSCLC has looked at role of PCI in non-CR

F Manapov et al, J Neurooncol 2012 (ePub)
Decreased Brain Metastases with Early vs Late PCI for LSCLC

Thoracic RT 54 Gy qd + early PCI

<table>
<thead>
<tr>
<th>PCI</th>
<th>N</th>
<th>Brain Metastases N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>41</td>
<td>3 (7.3%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Late</td>
<td>45</td>
<td>9 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

B Sas-Korczynska et al, Strahlenther Onkol, 186:315-9, 2010
Role of Radiation Therapy in ESCLC RTOG 0937

Accrual Goal
Eligible
ESCLC
PS 0-2
No CNS mets
1-3 sites of mets
CR or PR to chemo
Stratify
Response
1. CR
2. PR
Number of Met Sites
1. 1
2. 2-3

Arm 1: PCI
2.5 Gy in 10 fx

Arm 2: PCI
2.5 Gy 10 fx +
Consolidative RT to Locoregional and Residual Metastatic Disease
45 Gy in 15 fx or 40 Gy in 10 fx

4-6 cycles platin-based chemo
Post-chemotherapy consolidation thoracic RT for ESCLC

- Phase II study of 40 Gy/15 fractions thoracic RT if objective response to chemotherapy (carbo or cisplatinum). All got PCI.
- Involved field RT to pre-chemo regions by CT (No PET)
- 32 evaluable patients
- RT tolerated well
- Median OS 8.3 months
- 16/32 (50%) failed in chest
  7/16 (44%) failed in field

D Yee et al, Rad Oncol 102:234-38, 2012
## Can we improve or personalize treatment?

<table>
<thead>
<tr>
<th></th>
<th>Limited</th>
<th>Extensive</th>
</tr>
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<tbody>
<tr>
<td>Histology/molecular targets</td>
<td>Not yet</td>
<td>RT Oligometastatic</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>Not yet</td>
<td></td>
</tr>
<tr>
<td>Radiation dose/fractions</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>Radiation timing</td>
<td>Cycle 1-3</td>
<td></td>
</tr>
<tr>
<td>Radiation volume</td>
<td>???</td>
<td>Time/dose</td>
</tr>
<tr>
<td>PCI</td>
<td>Early/late</td>
<td></td>
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<td></td>
<td></td>
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</table>