Role of Radiotherapy in Small Cell Lung cancer

Thanarpan Peerawong
Radiology Department, Faculty of Medicine, Prince of Songkhla University
Content

• Natural history
• Staging
• Role of radiotherapy
• Conclusion
Small cell lung cancer

- 15% of lung cancer
- 2/3 mets at presentation
- Central lesion with extensive lymphadenopathy
- Chemotherapy: main treatment
- Outcome: Untreat: L-SCLC 12wk., E-SCLC 5wk.

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>MS(mo)</th>
<th>2yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-SCLC</td>
<td>60-75%</td>
<td>18-24</td>
<td>25-50%</td>
</tr>
<tr>
<td>E-SCLC</td>
<td>20-35%</td>
<td>6-12</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

DeVita et al. Principles and Practice of Oncology, 2008
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Manifestation</th>
<th>Frequency (%)</th>
<th>Correctable</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIADH</td>
<td>Hyponatremia</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>ANP or AVP syndrome</td>
<td>Hyponatremia</td>
<td>15</td>
<td>Yes</td>
</tr>
<tr>
<td>Lambert-Eaton syndrome</td>
<td>Myasthenia gravis-like symptoms</td>
<td>1-3</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibody to VGCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic ACTH or CRH production</td>
<td>Ectopic Cushing's syndrome</td>
<td>5</td>
<td>Rarely</td>
</tr>
<tr>
<td>Cancer-associated retinopathy</td>
<td>Visual loss</td>
<td>&lt;1</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropic hormone; ANP, atrial natriuretic peptides; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; SIADH, syndrome of inappropriate antidiuretic hormone; VGCC, P/Q-type voltage-gated calcium channels.
Veterans’ Affairs Administration Lung Cancer Study Group (VALG)

- **limited disease (LD)**
  - defined as tumor confined to one hemithorax with or without loco-regional adenopathies that could be included in a single radiation field

- **Extensive disease (ED)**
  - having escaped from the previous stage parameters, including the presence of hematogenous metastasis and malignant pleural effusion

Alvarado-Luna G et al. Transl Lung Cancer Res 2016
VA/TNM

LD: T1–3N0–3M0
ED: M1 or T3-4 due to multiple lung nodule that too extensive or too large to cover by acceptable radiation plan

** LS: T1-2N0M0

Alvarado-Luna G et al. Transl Lung Cancer Res 2016
Halperin EC et al. Perez & Brady's Principles and Practice of Radiation Oncology 2013
SCLC: treatment scheme

<table>
<thead>
<tr>
<th>SL</th>
<th>Sx</th>
<th>CMT+TRT</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>CMT</td>
<td>PCI</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>CMT</td>
<td>sTRT</td>
<td>sPCI</td>
</tr>
</tbody>
</table>

Radiotherapy have role in every stage
Rationale of RT in SCLC

• LD: TRT improve 3yr OS 5.4% (9%->14%)
• ED: TRT improve 2yr OS 10% (3%->13%)
• Both: PCI improve 3yr OS 5.4% (15.3%->20.7%)

SCLC is chemo-sensitive and radiosensitive tumor. So, the radiotherapy is given to remove chemo-resistant cells. Repopulation triggered by neoadjuvant chemotherapy may inhibit the effectiveness of subsequent radiotherapy.

Slotman BJ et al. Lancet 2015
Brade AM et al. J Clin Oncol. 2006
Thoracic radiotherapy in LD

• Timing to start radiotherapy
• Dose and Fractionation
• Treatment volume
Neoadjuvant Vs concurrent chemotherapy

- JCOG 9104: PE regimens x 4 cycles (n 231)
- Arm 1) concurrent RT 45/30 BID starting day 2
  Arm 2) sequential RT 45/30 BID : pretreatment volumes
- PCI 24/16 BID if CR/near CR
- 3yr OS concurrent 30% vs. sequential 20% (NS); 5yr OS 24% vs 18% (NS)
- After adjustment, hazard ratio for death in concurrent arm 0.7 (SS).

Early versus late concurrent

- 5 randomized trials: cisplatin-based CMT
  - 2yr OS better if early RT (HR 0.73, SS)
  - 5-year OS also better (HR 0.65, SS)
  - Benefit if RT started within 30 days of chemotherapy.

- Start of any treatment until the End of Radiotherapy (SER)
  - SER < 30 day: 5yr OS 20%
  - SER > 30 day: 5yr OS -1.8%/week

- Absolute benefit 10%

Pijls-Johannesma M et al Cancer Treat Rev. 2007
Disadvantage of early radiotherapy

- Survival benefit depend on complete CMT rate
  - NCI-C: MS early RT Vs late RT 21mo vs. 16mo: (86%)
  - LLCG: 14mo vs. 15mo: (69%Vs80%)
  - HeCOG: 17.5movs. 17.5mo:(71%Vs90%)

CCRT should limit to the PS(0-1)
If PS2 by tumor obstruction??

Spiro SG et al., J Clin Oncol. 2006
Skarlos DV et al Ann Oncol. 2001
Optimal dose schedule

• Historically: 1.8-2Gy/F TD 40-50Gy
• INT 0096: Hyperfractionation: 45Gy/30F 1.5 Gy bd
• CALGB 39808: Dose escalation: 70Gy/35F od
• 2 randomized study CONVERT, RTOG0538

<table>
<thead>
<tr>
<th><strong>CONVERT</strong></th>
<th><strong>RTOG 0538</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>532 729</td>
</tr>
</tbody>
</table>
| **Radiotherapy** | Arm A: 45Gy/30F (1.5Gy bd) start CMT day 22 of C1  
|             | Arm B: 66y/33F (2Gy od) start CMT day 22 of C1  |
| **CMT**     | Cis: 75mg/m2 or 25mg/m2 D1-3  
|             | Etoposide: 100mg/m2 D1-3  
|             | Every 21day for 4-6 cycles  |
| **IFRT**    | Yes  |
| **Definition** | CTV:GTV+0.5cm  
|             | PTV: CTV+0.8cm+1cmCC  |
|             | Cis: 80mg/m2 or Carbo: AUC5  
|             | Etoposide: 100mg/m2 D1-3  
|             | Every 21day for 4 cycles  |
|             | No (CTV+GTV plus POD)  |
|             | PTV1: initial until 44Gy  
<p>|             | PTV2: Re-CT during treatment  |</p>
<table>
<thead>
<tr>
<th></th>
<th>45Gy 1.5Gy bd (n 274)</th>
<th>66Gy 2Gy od (n 273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2yr OS</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Median OS</td>
<td>30mo</td>
<td>25mo</td>
</tr>
<tr>
<td>G3/4 neutropenia</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>G2 esophagitis</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>G3/4 esophagitis</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>G3/4 radiation pneumonitis</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Death from RT toxicity (3mo after RT)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Faivre-Finn C et al. ASCO Meeting abstracts J Clin Oncol 2016, 8504.
INT 0096: Hyperfractionation: 45Gy/30F 1.5Gy bd

CTV: GTV+ 1.5cm + ipsi hilum + mediastinum from the thoracic inlet to the subcarinal
Exclude: contra hilum + SPC

Convert
CTV: GTV+0.5cm
PTV: CTV+0.8cm+1cmCC

Steven E. Schild and Walter J. Curran Clinical Radiation Oncology, Chapter 43
Is IFRT possible?

- IFRT: reduced radiotherapy toxicity
- In SLC Controversy
  - Turrisi’s protocol: use as standard: ENI (RTOG 0538)
  - CONVERT study: Not permitted
- No RCT
- IFRT: INR (4-5%(0%,11%)) Ipsi SPC (L2-3), RUL
Impact of FDG-PET/CT

- 8% Downstage
- 19% Upstage
- 27% Change management

Pathological confirmation still need
Comparison of treatment outcomes between involved-field and elective nodal irradiation in limited-stage small cell lung cancer.

---

**Incidence of INF**

<table>
<thead>
<tr>
<th></th>
<th>IFI group (n = 50)</th>
<th>ENI group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without FDG-PET</td>
<td>3/23</td>
<td>0/16</td>
</tr>
<tr>
<td>With FDG-PET</td>
<td>0/27</td>
<td>0/14</td>
</tr>
</tbody>
</table>

Summary

• Start RT early as possible, compact
• IFRT or ENI depend on clinical situation
  • PET: IFRT
  • No PET: ENI or IFRT? Wait
• Dose: 45Gy/30Fs bd or 66G-70y/33-35Fs od
• Post CMT volume or re-CT sim
  • Post CMT: GTVp
  • Initial nodal involvement (cover level)
Thoracic radiotherapy in ED

• Considered systemic disease and poor prognosis
• MS 8-10mo 2yr-OS4-7%
• Historic treatment: EPx4-6

2 RCT:
• Distant-CR + local-CR/PR :54Gy/36F t
• Any response: 30Gy/10F

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>1yr OS</th>
<th>2yr OS</th>
<th>5yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeremic</td>
<td>11</td>
<td>46</td>
<td>28</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>65</td>
<td>38</td>
<td>9.1</td>
</tr>
<tr>
<td>Slotman</td>
<td>28</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Slotman BJ et al. Lancet 2015
Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis

A. Overall Survival

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slotman</td>
<td>0.840</td>
<td>0.694</td>
<td>1.016</td>
<td>-1.794</td>
</tr>
<tr>
<td>Jeremic</td>
<td>0.726</td>
<td>0.529</td>
<td>0.996</td>
<td>-1.985</td>
</tr>
<tr>
<td></td>
<td>0.808</td>
<td>0.686</td>
<td>0.951</td>
<td>-2.561</td>
</tr>
</tbody>
</table>

Random effects p=0.01
Q=0.598 df=1 p=0.439 I²=0%

0.5 1 2
Favours TRT  Favours No TRT

Significant increase G3/4 esophagitis 7%

B. Progression-Free Survival

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slotman</td>
<td>0.730</td>
<td>0.611</td>
<td>0.872</td>
<td>-3.475</td>
</tr>
<tr>
<td>Jeremic</td>
<td>0.797</td>
<td>0.578</td>
<td>1.100</td>
<td>-1.378</td>
</tr>
<tr>
<td></td>
<td>0.745</td>
<td>0.638</td>
<td>0.871</td>
<td>-3.708</td>
</tr>
</tbody>
</table>

Random effects p<0.001
Q=0.222 df=1 p=0.638 I²=0%

0.5 1 2
Favours TRT  Favours No TRT

no additional bronchopulmonary toxicity.

Summary

• TRT show benefit: DFS and OS
• Radiation induced immune response??
• Optimal dose fractionation: unknown
• Which patient will be survival benefit: unknown
• Should with caution and very select patient
Prophylactic cranial irradiation

• Brain metastases:
  • 20% at Dx, 40% at 1yr, 80% at autopsy
  • Median survival 3mo
  • Impact QOL than other metastatic site

• Rationale
  • BBB limits access for most water-soluble drugs
  • Small-volume tumors: not developed tumor-associated vasculature that allows chemotherapy access to established and contrast-enhancing metastases
  • PCI: ALL looked promising and suggested SCLC
Prophylactic Cranial Irradiation for Patients with Small-Cell Lung Cancer in Complete Remission

- 7 RCT, but 1 unpublished data: n 987 (4/7: <100, 14% ESSL)
- CR: CxR or bronchoscope or CT chest or CT brain
- Initial treatment: CMT or CMT+RT
- Dose: 24-40Gy/8-20F 2-3Gy/F

3yr: BM -25.3% DFS +8.8  OS +5.4%(15.3%>20.7%)
Higher RT dose: decreases more BM, But not survival

Benefit of PCI in ESSL

- 14% included in meta-analysis: CR
- EORTC 08993/22993
  - n 286 ESSLC + any response after CMT, Screen BM only symptom
  - PCI: 20-30Gy/5-12F: BED 25-39Gy start 4-6wk after CMT

Median survival +1.3mo (5.4mo>6.7mo)
1yr OS +14% (13.3%>27.1%)
PCI negative impact to sHRQOL

Slotman BJ, J Clin Oncol. 2008
Optimal dose regimen

• Higher RT dose: Decreases BM, But not survival
• PCI -> late neurotoxicity: CCRT, RT dose
• PCI99-01/ EORTC 00223-08004/ RTOG 0212
  • N 720, LSCLC, CR after CMT+RT
  • PCI 25Gy/10F Vs PCI 36Gy/18F or 36Gy/24F bd

Higher dose PCI: not sig. decrease BM But Higher mortality
Summary

• Dose
  • LD: 25Gy in 10Fs in CR, PR
  • ED: 20Gy in 5Fs
• Start early as possible: within 6 mo after initial CMT
• Benefit: 3yr OS +5%(LD), 1yr OS +15%(ED)
• Not recommend:
  • PS:3-4
  • impaired neurocognitive function
• Caution:
  • Age >60 yrs associated chronic neurotoxicity
  • PCI may not benefit: screen MRI q 3 mo (in ED)

Take home message

• Small cell lung cancer is aggressive and poor survival
• RT have role in every stage of disease
  • LD: early and short treatment time as possible
  • ED: Very Selection, beware additional complication without additional benefit
  • PCI: use with careful in extensive stage