Combined treatment approach in management of limited stage SCLC

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Small cell lung cancer (SCLC) comprises about 15% of all lung cancers.

- rapid growth and early metastasis
- 10–25% of patients have brain metastases at diagnosis

- One third present with stage I-III disease (LS-SCLC)

- Excellent responses to CT and RT but few patients will be long term survivors
  - High risk of local relapse
  - High risk of distant spread (brain), 40–50% will develop them during the course of their disease
Pathology features

- Small round blue cell tumor
- Scant cytoplasm, high Nuclear/Cytoplasmic ratio
- All are reactive for keratin and epithelial membrane antigen
- Cytokeratin 7+ve, 20 –ve
- TTF-1 +ve
- Ki-67 proliferation high
- 75% have one more neuroendocrine markers
  - Chromogranin, synaptophysin, NSE
Historical but practical Staging

VA Lung Study Group (clinical / historical)

Limited Stage (~1/3 of cases)
• Confined to the ipsilateral hemithorax and within a single RT portal

Extensive Stage (~2/3 of cases)
• Disease outside of thorax or disease outside a single RT port (not including pleural effusion)
TNM classification

Better anatomic discrimination for measurement of outcome

8008 patients

Median survival (months)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>26</td>
</tr>
<tr>
<td>IB</td>
<td>21</td>
</tr>
<tr>
<td>IIA</td>
<td>15</td>
</tr>
<tr>
<td>IIB</td>
<td>12</td>
</tr>
<tr>
<td>IIIA</td>
<td>13</td>
</tr>
<tr>
<td>IIIIB</td>
<td>11</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
</tr>
</tbody>
</table>

Limited stage = T1-4 N0-3 M0

AJCC 7th Edition
How do we stage SCLC? officially AJCC but

NCCN Definitions

Limited Stage

• AJCC (8th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan
  • T N M stages same as NSCLC
  • Stage groupings same as NSCLC

Extensive Stage

• AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan
Presentation of SCLC

Predominantly central and bulky mediastinal lymph nodes location.
  • Hilar/Perihilar Mass on chest radiography

Superior Vena Cava Obstruction

Paraneoplastic Syndromes:
SIADH, Ectopic ACTH, Eaton-Lambert = proximal myopathy, Cerebellar ataxia
Role of surgery in very early stage SCLC

• Surgery in SCLC is not widely accepted but can be considered for very small biopsy-proven tumours (very limited disease)
  – Intraoperatively, a systematic nodal dissection should be carried out.
  – Sublobular resection is not recommended

• cT1N0M0, with confirmed negative mediastinal staging.

• SCLC may also be an incidental finding in patients undergoing surgery for a solitary pulmonary nodule, as seen in 4%-12% of cases
A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy.

**SCHEMA**

- **REGISTRATION**
- **INDUCTION CAV X 5**
- **OBJECTIVE RESPONSE**
- **RANDOMIZE**
  - Strata
    - CR vs PR
    - Size of residual
    - Performance Status
- **THORACOTOMY**
- **NO SURGERY**
  - **THORACIC AND BRAIN IRRADIATION**

**LCSG 832**

![Survival Probability Graph]

**Figure 1.** Schematic diagram of study design.

Lad T, Chest. 1994 Dec;106(6 Suppl):320S-323S
Resected T1T2N0 SCLC – Adjuvant Therapy

• Surgery alone provides poor outcomes, but in combination with chemotherapy, outcomes are reasonable
  – NCDB the 5-year OS rate of 954 patients who underwent R0 resection for pT1-2N0M0 SCLC was 47%.
• Multivariate analysis showed that adjuvant Chemotherapy or Chemotherapy + PCI were associated with improved survival.

Yang CF. J Clin Oncol. 2016 Apr 1;34(10):1057-64
## Front-line Chemo in SCLC Evolution

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Survival (months)</th>
<th>Type of Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>BSC</td>
<td>1.5</td>
<td>BSC</td>
</tr>
<tr>
<td>Green</td>
<td>CTX</td>
<td>4.0</td>
<td>mono-CT</td>
</tr>
<tr>
<td>Sandler</td>
<td>CTX+ CCNU+ MTX</td>
<td>7.2</td>
<td>1st -generation poly-CT</td>
</tr>
<tr>
<td>Roth</td>
<td>CAV</td>
<td>8.3</td>
<td>2nd-generation poly-CT</td>
</tr>
<tr>
<td>Eckardt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanna</td>
<td>PE</td>
<td>9.4-10.2</td>
<td>platinum-based poly-CT</td>
</tr>
</tbody>
</table>

Ardizzoni, ASCO 2007
Systemic treatment in stage I-III SCLC

- Cisplatin is the best radiosensitiser and has higher response rates
- Cisplatin-Etoposide can be delivered at full dose with thoracic RT with an acceptable toxicity profile
  - No change in systemic therapy in last 20 years.
  - No role for anthracyclines/ pemetrexed/ irinotecan
  - No role for chemotherapy dose intensification
  - Immune therapy: Trials underway!!
The Role of Radiotherapy

Similar data in two meta-analysis from 1992:

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Dead/No. Entered</th>
<th>CT + RT</th>
<th>CT</th>
<th>O - E</th>
<th>Variance</th>
<th>Relative Risk (CT + RT:CT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen (Gösterlin)</td>
<td>69/69</td>
<td>74/76</td>
<td>11.2</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sydney (Rosenthal)</td>
<td>44/45</td>
<td>48/49</td>
<td>-8.2</td>
<td>21.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCI (Bunn)</td>
<td>46/48</td>
<td>46/49</td>
<td>-8.9</td>
<td>21.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECSG I (Birch)</td>
<td>123/153</td>
<td>111/142</td>
<td>-12.1</td>
<td>56.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>London (Souhami)</td>
<td>59/63</td>
<td>74/75</td>
<td>-7.9</td>
<td>32.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG (Kise)</td>
<td>43/47</td>
<td>46/56</td>
<td>4</td>
<td>21.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAKK (Joss)</td>
<td>35/36</td>
<td>32/34</td>
<td>0.6</td>
<td>16.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uppsala (Nöu)</td>
<td>22/26</td>
<td>31/31</td>
<td>-4.5</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB (Perry)</td>
<td>257/292</td>
<td>128/134</td>
<td>-20</td>
<td>75.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG (Creec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okayama (Ohnshi)</td>
<td>22/28</td>
<td>27/28</td>
<td>-4.8</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SECSG II (Birch)</td>
<td>116/154</td>
<td>140/168</td>
<td>-10.4</td>
<td>63.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GECTB (Lebeau)</td>
<td>14/19</td>
<td>12/17</td>
<td>1</td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>972/1111</td>
<td>890/992</td>
<td>-67.2</td>
<td>433.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \chi^2 \text{ of test for heterogeneity; } P = 0.15 \]

13 trials, 2140 pts.
5.4% 3 yr OS benefit

Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

The three-year survival rates were 14.3±1.1 percent in the combined-therapy group and 8.9±0.9 percent in the chemotherapy group (for a difference of 5.4±1.4 percent; \( P = 0.001 \) by stratified log-rank test). Each 1 bar denotes the standard deviation.

Sequential vs. Concurrent CTRT

Sequential CT-RT:
- smaller target volumes, leading to reduced toxicity.
- longer overall treatment times also increased the risk of tumor repopulation and the development of treatment-resistant clones.

Concurrent CT-RT
- reduces the risk of repopulation.
- possible radiosensitizing effect of chemotherapeutic agents.
- increases acute normal tissue toxicity
- might not be feasible in elderly patients or those with large tumors
Sequential vs. Concurrent CTRT

JCOG 9104

- N=231
- 4 cycles P+E with concurrent RT with cycle 1 OR sequential RT after cycle 4
- RT- 45 Gy/3 wks, 1.5 Gy b.i.d

- Underpowerd: 5% survival advantage with concurrent regimens
- Improved survival (median 27 vs. 20 months; p< 0.090) with concurrent treatment.
- significant increase in Grade 3 or greater leukopenia (85% vs.54%)
- similar rates of Grade 3 esophagitis in both arms

OS benefit at a cost of increased esophagitis
Control arm (45/25) may be a low bar to clear

Which Fractionation? CALGB 39808

Dose escalated 70GY Radiotherapy: CALGB 39808

- 2 cycles of paclitaxel + topotecan
- 70 Gy in 35 fractions with EP
- Phase II design, 63 patients
- 10% Grade 3/4 toxicity

Table 5. Comparison of INT-0096 and CALGB 39808

<table>
<thead>
<tr>
<th>Trial</th>
<th>INT-0096</th>
<th>CALGB 39808</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic radiotherapy regimen</td>
<td>45 Gy twice daily</td>
<td>70 Gy every day</td>
</tr>
<tr>
<td>Patient and tumor characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58%</td>
<td>54%</td>
</tr>
<tr>
<td>Weight loss &gt; 5%</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td>Age, years (median)</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Supraclavicular adenopathy</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Toxicity profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>87%</td>
<td>83%</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>32%</td>
<td>21%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median overall survival</td>
<td>20.3 months</td>
<td>22.4 months</td>
</tr>
<tr>
<td>2-year overall survival</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>2-year DFS</td>
<td>29%</td>
<td>31%</td>
</tr>
</tbody>
</table>

A 12% higher overall survival at 2 years in the once-daily group versus the twice-daily group was considered to be clinically significant to show superiority of the once-daily regimen.

Faivre-Finn C. Lancet Oncol. 2017 Aug;18(8):1116-1125
Which Fractionation? CONVERT Trial

CONVERT: IMRT ~ 16-17%, PET staging ~ 57%, MRI Brain ~ 18%

Toxicities similar and lower than expected
Survival in both arms was higher than previously reported
BUT OD RT did not result in a superior survival or worse toxicity than BD RT

Faivre-Finn C. Lancet Oncol. 2017 Aug;18(8):1116-1125
Which Fractionation? CALGB 30610

Limited Small Cell

- 45 Gy BID / 3 weeks
- 61.2 Gy CB / 5 weeks
- Re-assess
- 70 Gy QD / 7 weeks

PE or CE 4, RT cycle 1 or 2

IMRT

Primary endpoint - OS
Secondary endpoint - Safety

* Cisplatin 80 mg/m² D1 + etoposide 100 mg/m² D1–3 q3w (4 cycles)

Which fractionation? CALGB 30610

**Conclusions** In patients with limited-stage SCLC, high-dose thoracic radiotherapy did not provide additional survival benefit over standard thoracic radiotherapy.

Reasonable Doses

- Turrisi Regimen (45Gy/30# bid)
- 60-70 Gy in 1.8 –2 Gy per fraction, once a day
Timing of concurrent CTRT

- Accelerated proliferation of tumour clonogens occurs during both radiotherapy and chemotherapy.

- A time interaction was suspected between chest irradiation and chemotherapy and, therefore, accelerated repopulation was postulated to be triggered by the first dose of any effective cytotoxic agent.

- Long-term survival, therefore, decreases with increasing time between the start of any treatment to the end of radiotherapy.
When to Deliver RT?

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

- Early TRT: Within 9 weeks starting chemotherapy and late TRT 9 weeks after chemotherapy.
- 5.2% increase in the 2-year survival of patients receiving early TRT.
- Greater difference was evident for hyperfractionated RT and platinum-based chemotherapy.

Fried DB, J Clin Oncol. 2004 Dec 1;22(23):4837-45.
The SER: Start date to End of RT

Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

Dirk De Ruysscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minkin, Rinus Wanders, Ludy Lutgens, Monique Hochstenbag, Liesbeth Boersma, Bradly Wouters, Guido Lammering, Johan Vansteenkiste, and Philippe Lambin

• The SER (time from start of any intervention to end of RT) was the most important predictor of outcome.
• 5-year survival rate more than 20% when SER <30 days
• Increased esophagitis with low SER
• Survival decrease of 1.86% per 1 week prolongation of SER

Survival at 5 years as a function of the time from the start of any treatment and the end of radiotherapy (SER)

Treatment Volumes?

- Two RCTs have compared Pre-chemotherapy vs. Post-chemotherapy volumes
  - SWOG study (started in 1979) used wide-field vs. limited-field 2-D planning
  - Chinese study used 3D planning
  - No differences in relapse rates or toxicity

- Post-chemo tumor volume but PRE-CHEMO nodal volume

- Dutch phase II data suggests that ENI is not required if a PET/CT is done for staging, but in the absence of PET/CT, isolated nodal relapse may be >10%.
Prophylactic cranial irradiation in stage I-III SCLC

Why PCI?
• Major risk of BMs-50 to 60%
• PCI reduces the risk BM by 50%
• PCI improves survival (6% @ 3 yrs)

_AuperinN EnglJ Med 1999_

When?
• After concurrent CTRT
• With consolidation thoracic RT if sequential CTRT is given

Standard dose/fractionation
• 25 Gyin 10 fractions

Prophylactic cranial irradiation in stage I-III SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>MRI</th>
<th>Survival</th>
<th>Brain Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI</td>
<td>No PCI</td>
</tr>
<tr>
<td>EORTC</td>
<td>286</td>
<td>Not required</td>
<td>27% (1-yr)</td>
<td>13%</td>
</tr>
<tr>
<td>Japan</td>
<td>224</td>
<td>pre, 3, 6, 9, 12, 18, 24 mo</td>
<td>11.6 mo (median)</td>
<td>13.6 mo</td>
</tr>
</tbody>
</table>

Prophylactic cranial irradiation in stage I-III SCLC

- PCI unequivocally ↓ brain mets, but is associated with cognitive decline
- Although PCI improved OS in the pre-MRI era, the impact of PCI in the context of MRI surveillance and early salvage therapy is unclear
- Randomized trials (SWOG S1827, EORTC PRIMALung) including LS and ES-SCLC are being opened or developed to validate/refute the Japanese trial results
- MRI surveillance and emerging strategies such as hippocampal-avoidance will continue to modify the risk/benefit ratio of PCI
Progress in stage I-III SCLC

- CT alone: <10%
- Seq CTRT: 10-15%
- ConCTRT: 20-25%
- BD CTRT: 25%
- CONVERT BD: 34%

5 year survival (%)
LS-SCLC: Take Home Messages

- Role of surgery for stage I-II SCLC not well defined, concurrent CTRT is a valid option
- Concurrent CTRT is the standard of care
  - Cisplatin etoposide is still standard in combination with RT
- Early thoracic RT is advocated:
- Several reasonable radiation fractionation
  - 45/30 BID, 70/35 (CALGB), 66/33 (CONVERT)
- PCI improves survival: Tread carefully in changing PCI practice in LS-SCLC
Thank You