Management of Limited Stage Disease: An Overview

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Small Cell Lung Cancer (SCLC)

Facts & Features

• 10-15% of all new Lung cancers
• Incidence is decreasing over decades
• Elderly (median age is 1 decade more than NSCLC)
• Almost synonymous with Smoking ( <3% are non-smokers)
• More than 90% are Heavy/ current smokers
• Early locoregional & Distant metastases
• Para-neoplastic syndromes common
• Aggressive disease
• Rx : Multi Disciplinary
• Relapses are common
• Salvage is difficult
Small Cell Lung Cancer (SCLC)

**Diagnosis & Staging**

- No different than NSCLC
- Use of PET-CT is recommended
- MRI brain is Preferred over CT Brain
- Staging : Changed Over years
- Present Recommendation : Use IASLC TNM/AJCC 7\textsuperscript{th} edn.

**Pragmatic Staging**

VALG (The Veterans Affairs Administration Lung Cancer Study Group)

- 1957 Two Stage classification
- **Limited disease** (LD/LS)\& Extensive disease (ED)
- Limited to **HEMITHORAX**
- **Rx in reasonable/tolerable radiotherapy port**
Small Cell Lung Cancer (SCLC)

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Pragmatic Staging

VALG 2 Stage, Modification by IASLC 1989
Limited disease (LD) includes Contralat. Hilar / mediastinal / supraclavicular nodes
*Pleural infusion was included (*wet disease)
Small Cell Lung Cancer (SCLC)

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Pragmatic Staging

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Pleural effusion is now extensive staging
Rest are still limited stage
Small Cell Lung Cancer (SCLC)

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*Some T4 ? (Nodule in different lobe)
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Lest Not Forget :
Rx in reasonable/tolerable radiotherapy port

Limited Stage SCLC
Treatment Evolution

- Combined Concurrent Chemoradiotherapy Is The Standard Of Care
- Surgery has very limited role
Limited Stage SCLC
Treatment Rules

• Combined Concurrent Chemoradiotherapy Is The Standard Of Care
  Surgery has very limited role

R0 in 50%
No survival benefit over RT
No CT
Historical study

MEDICAL RESEARCH COUNCIL COMPARATIVE TRIAL OF SURGERY AND RADIOThERAPY FOR PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF BRONCHUS: Ten-year Follow-up
The Lancet 1973
Wallace Fox, J.G. Scadding

A Prospective Randomized Trial to Determine the Benefit of Surgical Resection of Residual Disease Following Response of Small Cell Lung Cancer to Combination Chemotherapy
LCSG 832
Thomas Lad; Steven Piantadosi; Paul Thomas; David Payne; John Ruckdeschel; Giuseppe Giaccone

Induction CT (CAV)
Random
Sx Vs No Sx
Both receives thoracic RT
No benefit with addition of Sx
Limited Stage SCLC
Chemotherapy

**IMPORTANT DRUGS**

- CYCLOPHOSPHAMIDE
- DOXORUBICIN / EPIRUBICIN
- ETOPOSIDE
- PLATINUM (CISPLATINUM; CARBOPLATINUM)
- TOPOTECAN/IRENOTECAN
- VINCristINE

**OTHER DRUGS**

TKI
VEG
THALIDOMIDE
Limited Stage SCLC
Chemotherapy

**IMPORTANT DRUGS**

- CYCLOPHOSPHAMIDE
- DOXORUBICIN / EPIRUBICIN
- ETOPOSIDE  **SYNERGESTIC EFFECT**
- PLATINUM (CISPLATINUM; CARBOPLATINUM)
- TOPOTECAN / IRENOTECAN
- TAXEANS
- VINCristINE

**OTHER DRUGS**

TKI

VEG

THALIDOMIDE

436 Pts

EP is superior to CEV

In LD SCLC; OS (median) EP - 14.5 Vs CEV - 9 Months

Mascaux C Lung Cancer 30; 2000: 23-36
Limited Stage SCLC
CT with RT

A META-ANALYSIS OF THORACIC RADIOTHERAPY FOR SMALL-CELL LUNG CANCER
Jean-Pierre Pignon, M.D., Rodrigo Arriagada, M.D., Daniel C. Ihde, M.D., David H. Johnson, M.D.,

13 trials
2140 patients

5.4 % overall survival at 3 years

Addition of RT Improves Survival
Limited Stage SCLC
CT with RT Sequencing

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,

N=231
4 cycles PE CCRT from cycle 1
Sequential RT after cycle 4 PE
RT- 45 Gy/3 wks, 1.5 Gy b.i.d

Improved survival (median 27 vs. 20 months; p< .10) in CCRT ( Though Underpowered)
No change in Gr 3 Oesophagitis
Significant increase in Grade 3 or greater leukopenia (85% vs.54%)
Limited Stage SCLC
CT with RT Sequencing

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  JCO(22) 2004: pp. 4837-4845

- Early TRT
  RT initiated within 9 weeks after starting chemotherapy
- Late TRT
  RT initiated after 9 weeks after starting chemotherapy

Survival RR for early TRT vs late TRT was 1.17
Absolute survival advantage 5.2% @2 year survival early TRT
Limited Stage SCLC
Thoracic Radiotherapy Volume

**PET CT based Staging / RT planning**

**Sixty patients**

**Volume:** Involved Primary/mediastinal nodes

30% of patients difference in the involved nodal stations between Pre-Rx 18 PET scans & CT scans

**Pattern of Relapse**

**Low rate of isolated nodal failures (3%)**

(in field and out field failures are same)

Low percentage of acute esophagitis

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**SELECTIVE NODAL IRRADIATION ON BASIS OF 18FDG-PET SCANS IN LIMITED-DISEASE SMALL-CELL LUNG CANCER: A PROSPECTIVE STUDY**

JUDITH VAN LOON, M.D.,* DIRK DE RUYSSCHER, M.D., PH.D.,* RINUS WANDERS, M.D.,*


<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Patients (n)</th>
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<tbody>
<tr>
<td>None</td>
<td>21 (35)</td>
</tr>
<tr>
<td>Local</td>
<td>9 (15)</td>
</tr>
<tr>
<td>In field</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Out of field</td>
<td>4 (6.7)</td>
</tr>
<tr>
<td>Both in field and out of field</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Isolated local</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Local and distant/nodal</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>Nodal</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>In field</td>
<td>8 (13.3)</td>
</tr>
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</tr>
<tr>
<td>Nodal and distant/local</td>
<td>18 (30.0)</td>
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<tr>
<td><strong>Distant</strong></td>
<td>34 (56.7)</td>
</tr>
<tr>
<td>Isolated distant</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Distant and local/nodal</td>
<td>15 (25.0)</td>
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<td>Isolated brain</td>
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Limited Stage SCLC
Thoracic Radiotherapy Volume

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Sixty patients

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30% of patients difference in the involved nodal stations between Pre-Rx 18 FDG-PET scans & CT scans

Pattern of Relapse
- low rate of isolated nodal failures (3%)
  (in field and out field failures are same)
- Low percentage of acute esophagitis
Limited Stage SCLC
Thoracic Radiotherapy Volume

Rx Volume: Pre chemo / Post chemo
  - Literature Data Not clear
  - Some used 2D / others 3D
  - Some pre chemo / other post Chemo

Ideally: Start RT day 1 of Cycle 1 (pre chemo)

Fallout: Increased Toxicity

Pragmatic: If volume large unable to deliver RT (post chemo)

Try to ensure: disease as seen on the CT scan (before @2 cycle)
Limited Stage SCLC
Thoracic Radiotherapy Dose Fractionation

Optimal Dose/ Fractionation of TRT is not known
High local failure with 45-50.4Gy @1.8 Gy OD
Community survey in USA ; pattern of care studies; 50 Gy@ 1.8 -2Gy ( 81 %)*

FREQUENCY OF THORACIC RADIOThERAPY WITH CHEMOTHERAPy IN LIMITED SMALL-CELL LUNG CANCER
TWICE-DAILY COMPARED WITH ONCE-DAILY THRACIC RADIOThERAPY
IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY
WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

5 yr OS
OD Vs BD
16% Vs 26%
Gr. 3 Oeso. 11% vs 27 %
( p <0.001)

* SEER DATA 2003 Movsas et al
Limited Stage SCLC
Thoracic Radiotherapy Dose Fractionation

Pragmatic: Difficult to offer BD doses (logistics, toxicity)

• INCREASED DOSE /FRACTION (Reduce no of days) = Use of 2 Gy
• INCREASED TOTAL DOSE = Use of dose 56-60 Gy

CONVERT TRIAL
Con Chemo (EP 4-6 cycles) RT starting Day 22
45 Gy @1.8 Gy BD / 3 wks VS 66 Gy @2 Gy OD / 6.6 wks
End Point = Overall Survival

CALGB 30610/RTOG 538 TRIAL
Con Chemo (EP 4 cycles) RT starting Day 1
45 Gy@1.8 Gy BD 3 weeks VS 70 Gy @ 2 Gy/ 7 wk OD VS 61.2Gy @1.8 Gy OD 16 days followed by 1.8 Gy BD 9 days (Con Boost) *
End Point = 2 year & median Overall Survival
(Planned interim Analysis)
Limited Stage SCLC
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End Point = 2 year & median Overall Survival

*10 March 2013
Limited Stage SCLC
OPTIMAL INTEGRATION: SER TIME

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 Ruyscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minken, Rinus Wanders,

<table>
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<tr>
<th>VOLUME 24</th>
<th>NUMBER 7</th>
<th>MARCH 1 2008</th>
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<tbody>
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<td>Journal of Clinical Oncology</td>
<td>Original Report</td>
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SER : Start of any intervention (CT) to End of Radiotherapy
Rapidly accelerating Tumors
Hypothesis: Does Early RT Helps In Increased OS
Short SER is Better: For TUMOR (Toxicity Also Increased)
8 RCT studies (2 Omitted because no time difference, no OS reported, 1 used Doxorubicin (low efficacy, higher toxicity)

TUMOR : Short SER RR 0.62 {95% CI 0.49-.80 (p=.0003)}
Higher OS 5 yr 20% MORE if SER less than 30 days
(Each week loss of OR by 1..83%)
Limited Stage SCLC
TOXICITY: Non Hematogenous

**Acute:** (COMMON)

- Esophagitis:
- Dermatitis
- Cough
- Fatigue

**Subacute/late:**

**LUNG**
- Pneumonitis/Fibrosis

**ESOPHAGUS**
- Stricture
- Perforation

**CARDIAC**
- Pericarditis
- Coronary artery disease

**NEUROLOGICAL**
- Lhermitte’s syndrome,
- Brachial plexopathy

**OTHERS**
- Rib fracture
Limited Stage SCLC
Prophylaxis Cranial Radiotherapy

• Sanctuary site
• Almost Essential { in CR or near CR}
  ( except in Progressive disease)
• Preferably Early after completion CTRT

• Dose = 25 Gy-30 Gy / 10 - 15 Fr/ 2-3 weeks
Limited Stage SCLC

Prognostic factors

Patient Related
- Age
- Comorbidity
- Performance status

Tumor related
- Stage of disease
- Biochemistry (serum Na+, LDH, Alk Pos)

Treatment related
- Timing of Radiotherapy (Thoracic & Cranial)
- Chemotherapy
- Overall treatment Time

Expected 5 yr survival*

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* SEER data 1988-2001
Limited Stage SCLC

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Conclusions

• CESSATION OF HABITS
• ADEQUATE STAGING(IMAGING)
• MULTI DISCIPLINARY APPROACH
• MAINTING OF TIME TREATMENT INTENSITY (INCLUDING NUTRITION)
• TIMELY MANAGEMENT OF TOXICITY (HEMATOGENOUS/NON HEMATOGENOUS)
Limited Stage SCLC
TIMELINES

Cycle 1  Cycle 2  Cycle 3  Cycle 4  Cycle 5  Cycle 6
TRT  IDEAL  TRT  PRAGMATIC  TRT  NOT IDEAL  TRT  POOR  PCI
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Acknowledgements
Dr Shagun
Dr Arpita

Thoracic DMG