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

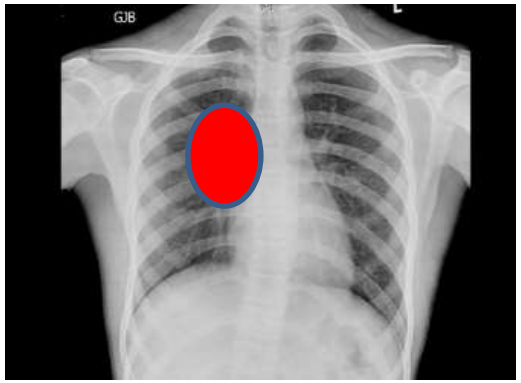
Small Cell Lung Cancer(SCLC)

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 7th 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



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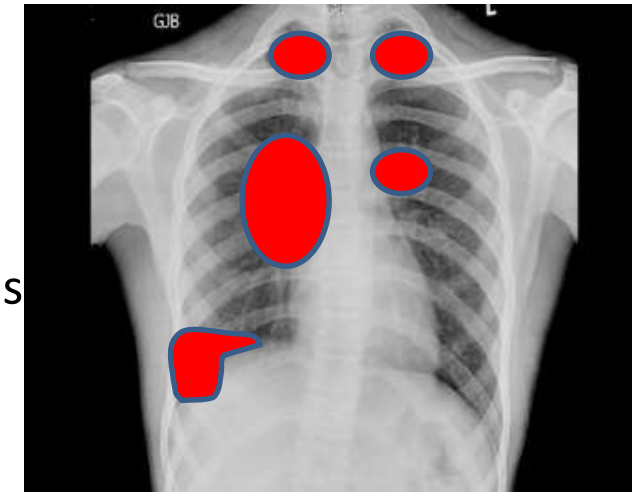
Pragmatic Staging

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



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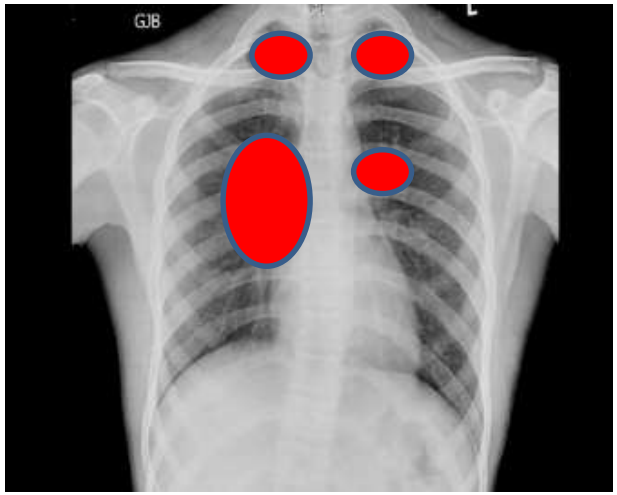
Pleural effusion is now extensive staging
Rest are still limited stage



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Pragmatic Staging

QUIZ

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Also TNM/ AJCC stage 7 edn
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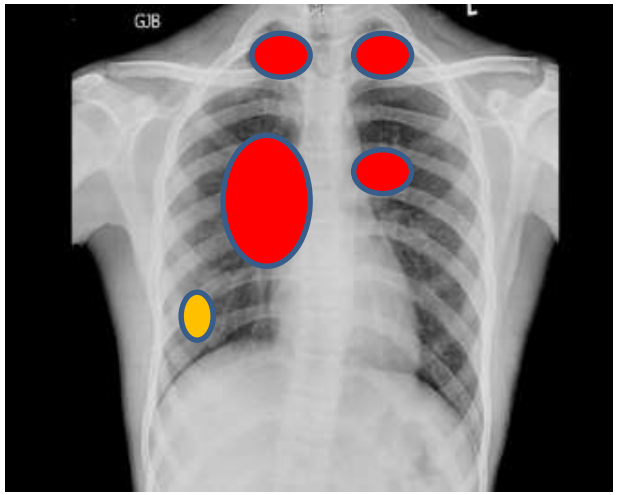
Rest are still limited stage
***Some T4 ?(Nodule in different lobe)**



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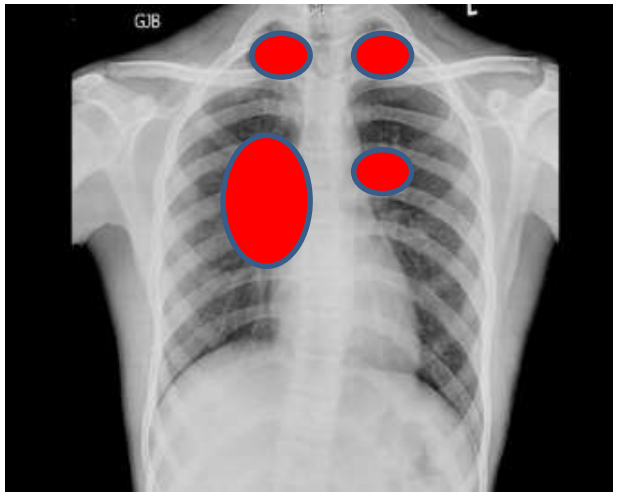
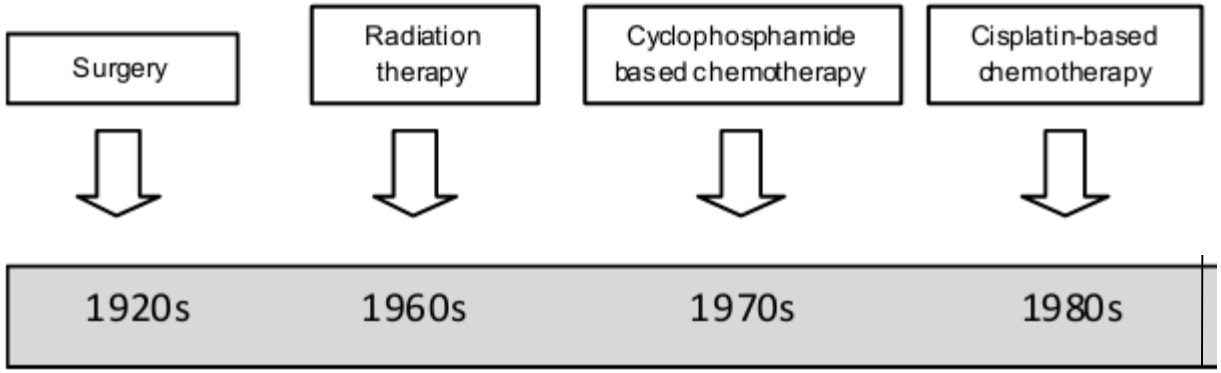
Lest Not Forget :
Rx in reasonable/tolerable radiotherapy port



Cancer Imaging. 2011; 11(1): 253–258. / NCCN guidelines

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

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

Wallace Fox, J.G. Scadding

The Lancet 1973

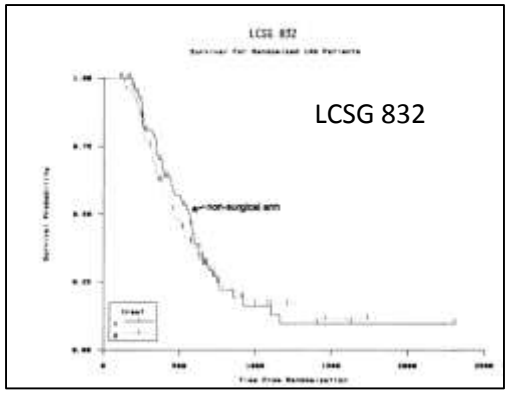
R0 in 50%
No survival benefit over RT
No CT
Historical study

Articles | December 1994

A Prospective Randomized Trial to Determine the Benefit of Surgical Resection of Residual Disease Following Response of Small Cell Lung Cancer to Combination Chemotherapy FREE TO VIEW

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

Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristine Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial With 5 Years' Follow-Up

By Stein Sundstrøm, Roy M. Bremnes, Stein Kaasa, Ulf Aasebø, Reidulv Hatlevoll, Ragnar Dahle, Nils Boye, Mari Wang, Tor Vigander, Jan Vilsvik, Eva Skovlund, Einar Hannisdal, and Steinar Aamdal for the Norwegian Lung Cancer Study Group

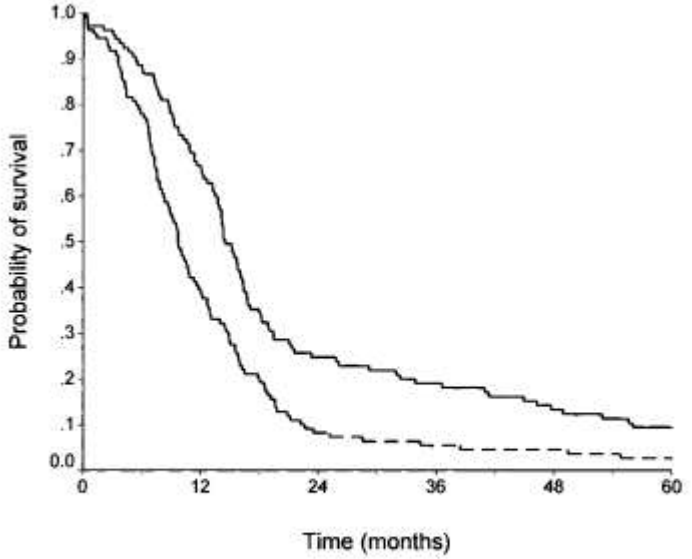


Fig 2. Overall survival of LD-SCLC patients (N = 214) according to treatment arm (*P* = .0001). CEV (dashed line), n = 109; EP (solid line), n = 105.

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

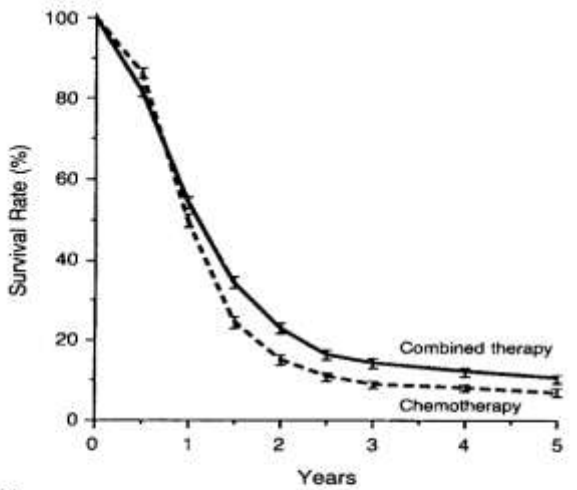


Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

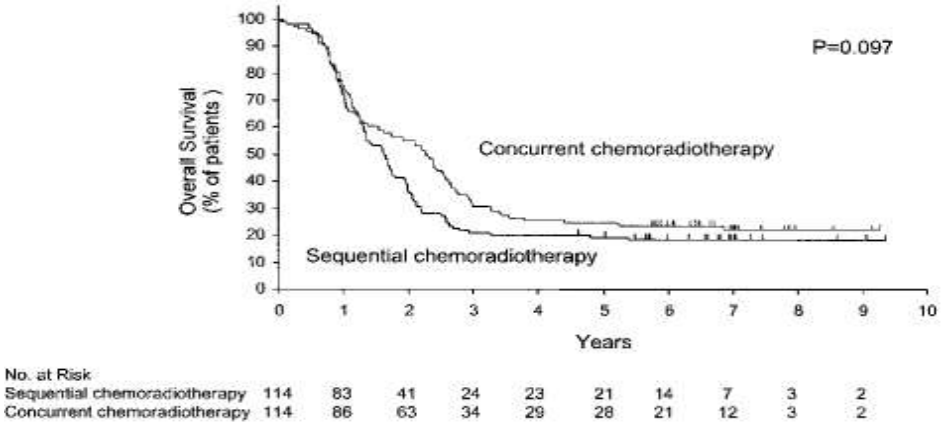
The three-year survival rates were 14.3±1.1 percent in the combined-therapy group and 8.9±0.9 percent in the chemotherapy group (for a difference of 5.4±1.4 percent; P = 0.001 by stratified log-rank test). Each I bar denotes the standard deviation.

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

CLINICAL INVESTIGATION **Lung**

SELECTIVE NODAL IRRADIATION ON BASIS OF ^{18}FDG-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.,*

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 2, pp. 329–336, 2010

PET CT based Staging / RT planning

Sixty patients

Volume: Involved Primary/ mediastinal nodes

30% of patients difference in the involved nod stations betweenPre-Rx 18 PET scans & CT sca

Pattern of Relapse

low rate of isolated nodal failures (3%)

(in field and out field failures are same)

Low percentage of acute esophagitis

Recurrence	Patients (n)
None	**21 (35)**
Local	**9 (15)**
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
Nodal	**20 (33.3)**
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/local	18 (30.0)
Distant	**34 (56.7)**
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)

Limited Stage SCLC

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Selective nodal Irradiation

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Limited Stage SCLC

Thoracic Radiotherapy Volume

Rx Volume : Pre chemo / Post chemo

Literature Data Not clear
Some used 2D / others 3 D
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

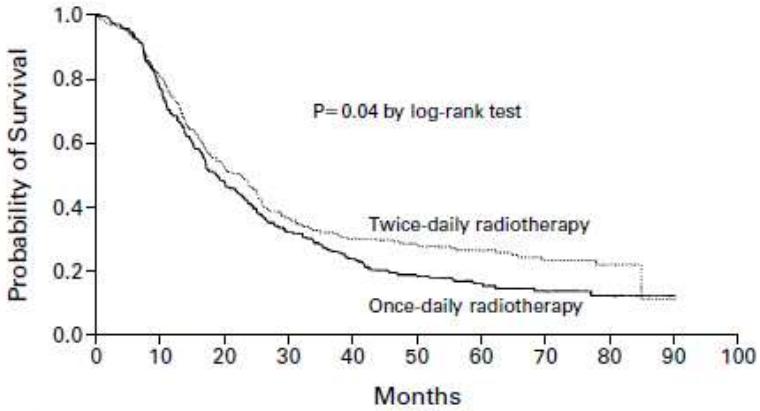
Community survey in USA ; pattern of care studies; 50 Gy@ 1.8 -2Gy (81 %)*

FREQUENCY OF THORACIC RADIOTHERAPY WITH CHEMOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER

TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III

January 28, 1999 The New England Journal of Medicine



TREATMENT GROUP	0–20 MO	20–40 MO	40–60 MO	60–80 MO	80–100 MO
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

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 56-60Gy

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

VOLUME 24 · NUMBER 7 · MARCH 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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***
Stage I	31%
Stage II	19%
Stage III	08%
Stage IV	02 %

* SEER data 1988-2001

Limited Stage SCLC

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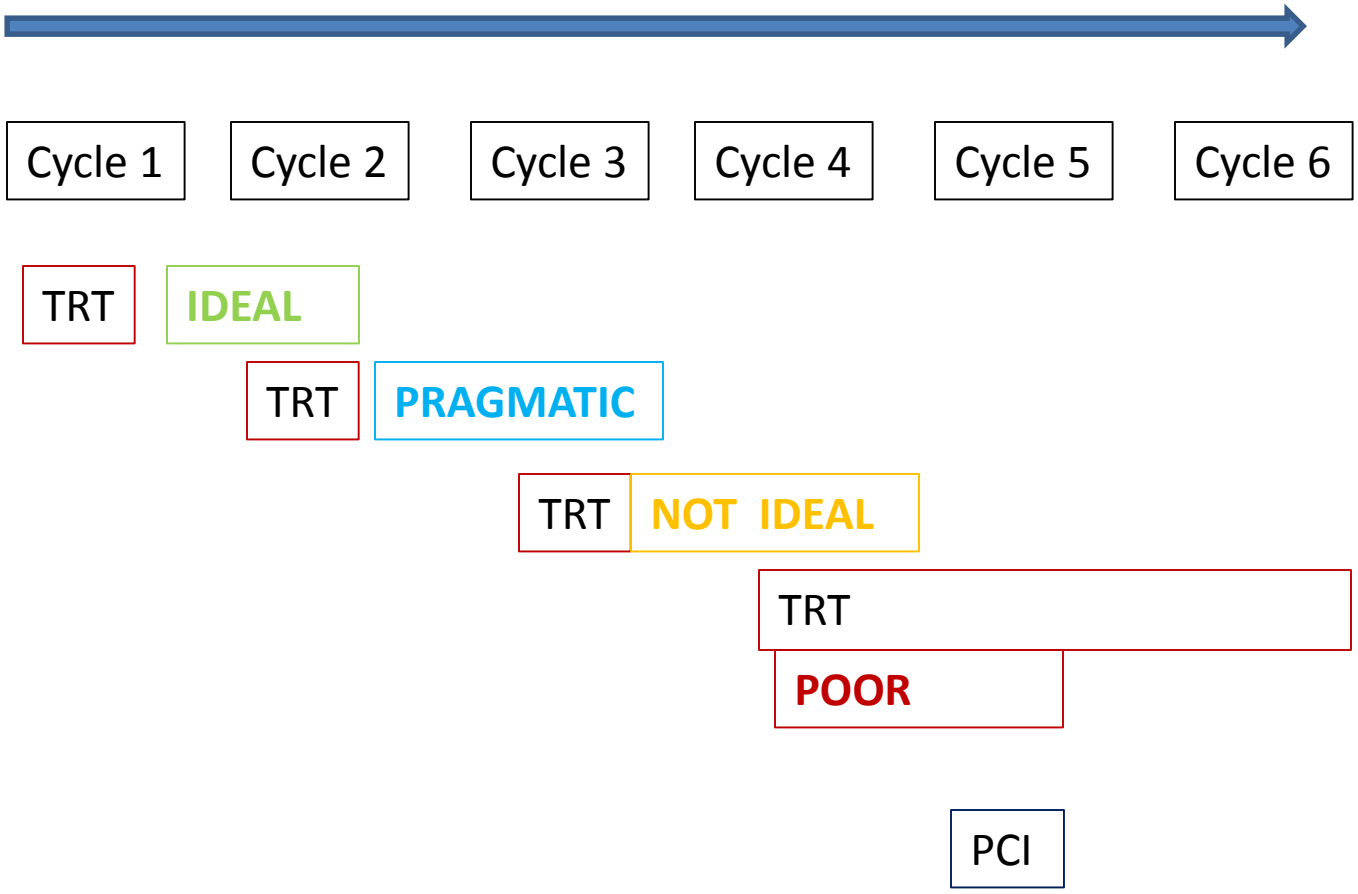
* SEER data 1988-2001

Conclusions

- CESSATION OF HABITS
- ADEQUATE STAGING(IMAGING)
- MULTI DISCIPLINARY APRROACH
- MAINTING OF TIME TREATMENT INTENSITY(INCLUDING NUTRITION)
- TIMELY MANAGEMT OF TOXICITY (HEMATOGENOUS/NON HEMATOGENOUS

Limited Stage SCLC

TIMELINES



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Dr Arpita

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