40th AROI-ICRO SUN PG Teaching Course on Lung Cancer
AIIMS Rishikesh

Combined treatment approach in management of limited stage SCLC

Dr Shagun Misra
Associate Professor
Department Of Radiotherapy,
SGPGIMS,Lucknow

Introduction

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

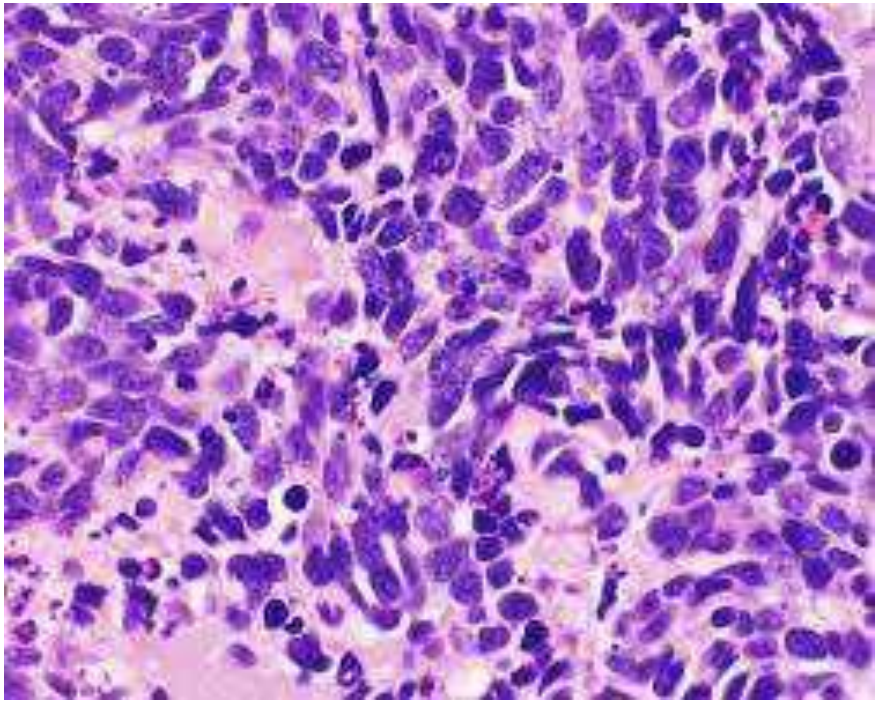
- One third present with stage I-III disease (LS-SCLC)

- 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)

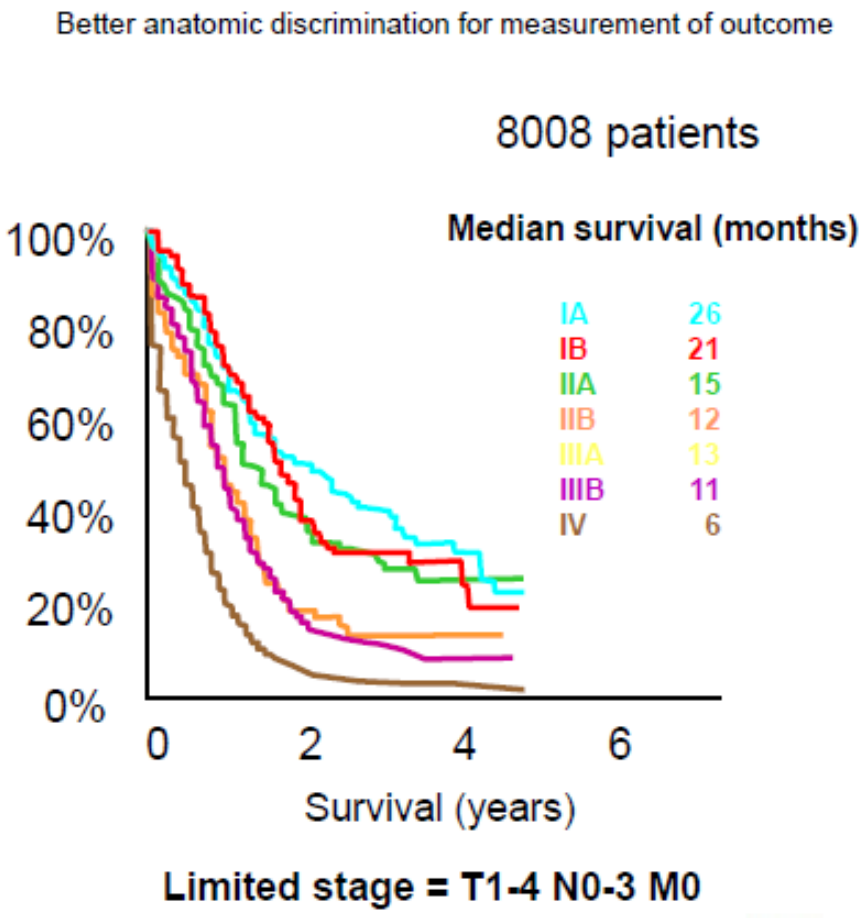
Limited Stage (~1/3 of cases)

- 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



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

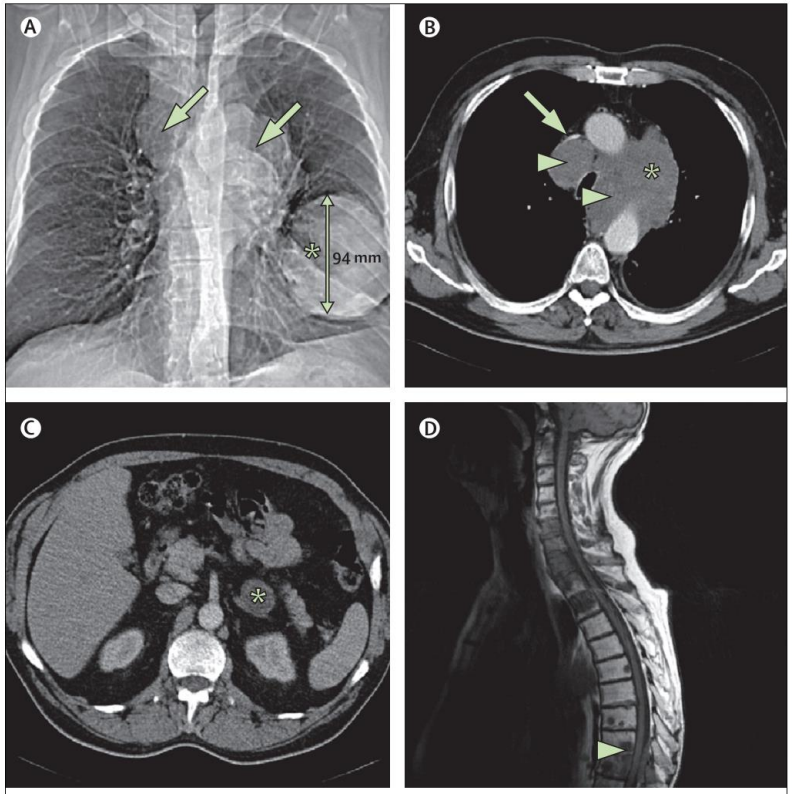
Presentation of SCLC

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

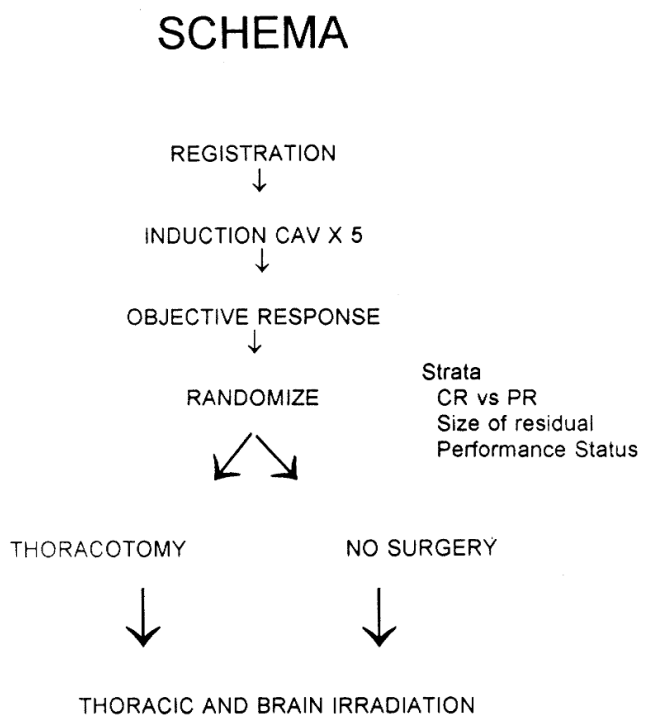
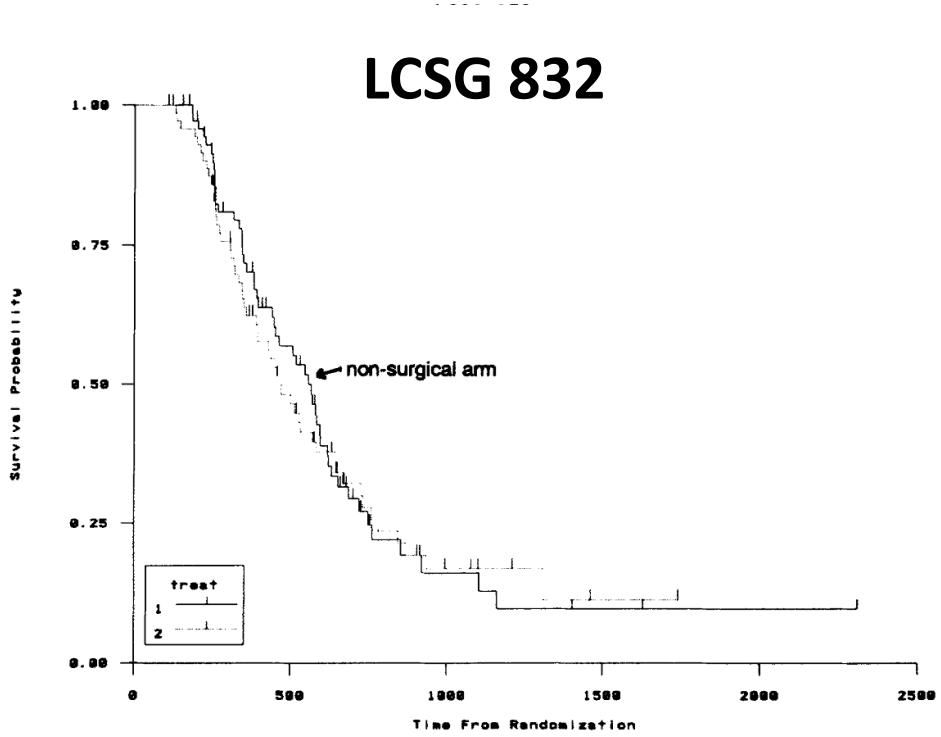
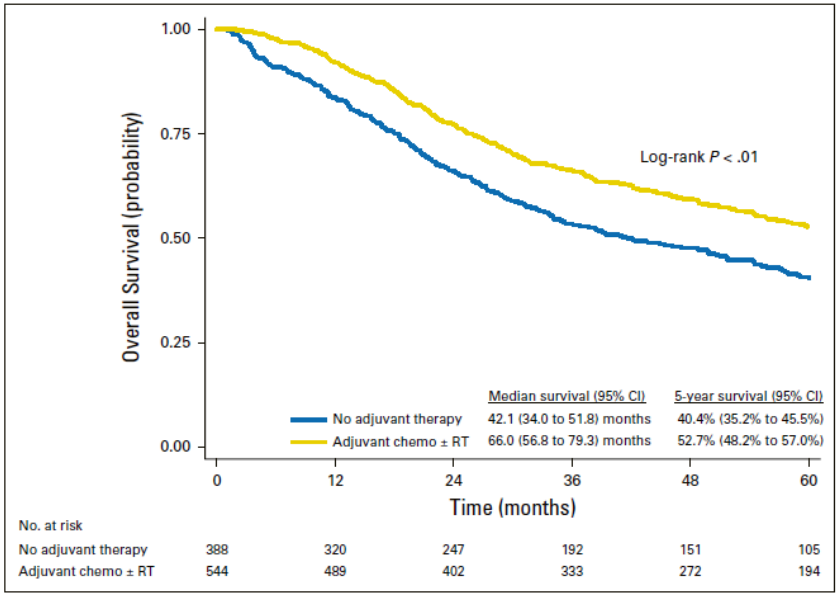


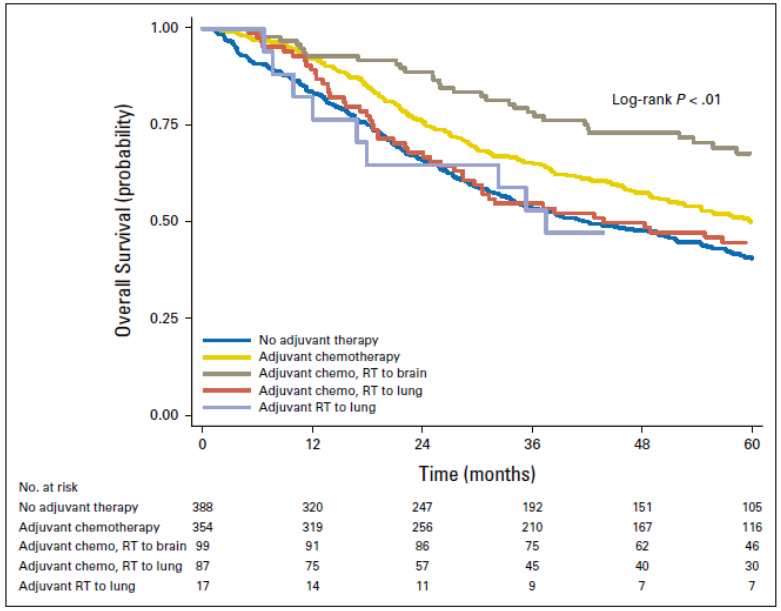
FIGURE 1. Schematic diagram of study design.



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

Author	Treatment	Survival (months)	
Green	BSC	1.5	BSC
Green	CTX	4.0	mono-CT
Sandler	CTX+ CCNU+ MTX	7.2	1st -generation poly-CT
Roth	CAV	8.3	2nd-generation poly-CT
Eckardt			
Hanna	PE	9.4-10.2	platinum-based poly-CT

Ardizzoni, ASCO 2007

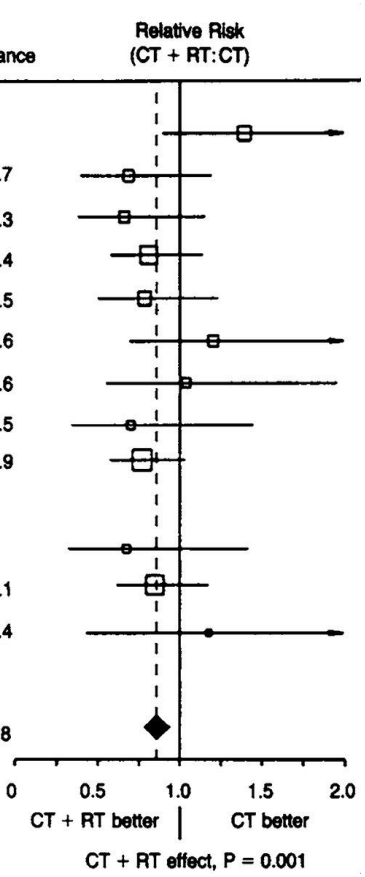
Systemic treatment in stage I-III SCLC

- 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

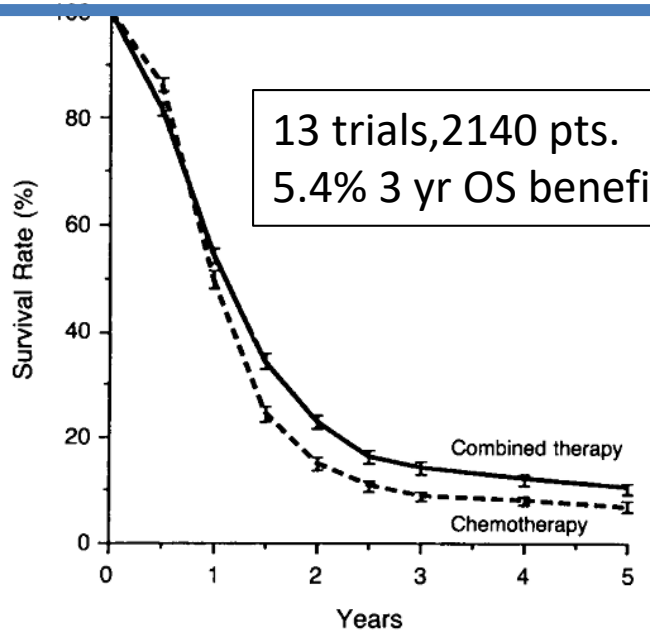
Similar data in two meta-analysis from 1992:

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



χ^2_{12} = 16.95 by test for heterogeneity; P = 0.15

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



No. at Risk						
Chemotherapy	992	475	138	78	63	47
Combined therapy	1111	575	236	143	110	81

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.

Pignon J et al. N Engl J Med 1992;327:1618-1624.

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.

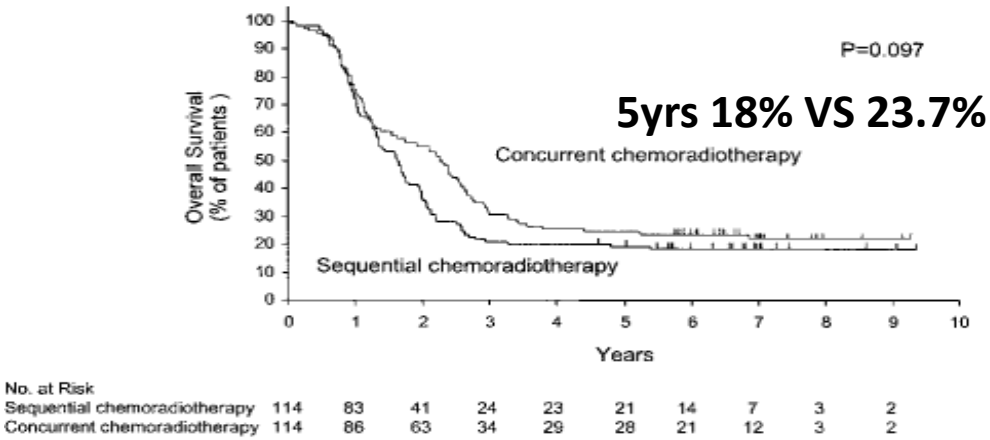
Concurrent CT-RT

- reduces the risk of repopulation.
- possible radiosensitizing effect of chemotherapeutic agents.
- increases acute normal tissue toxicity
- might not be feasible in el-derly 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

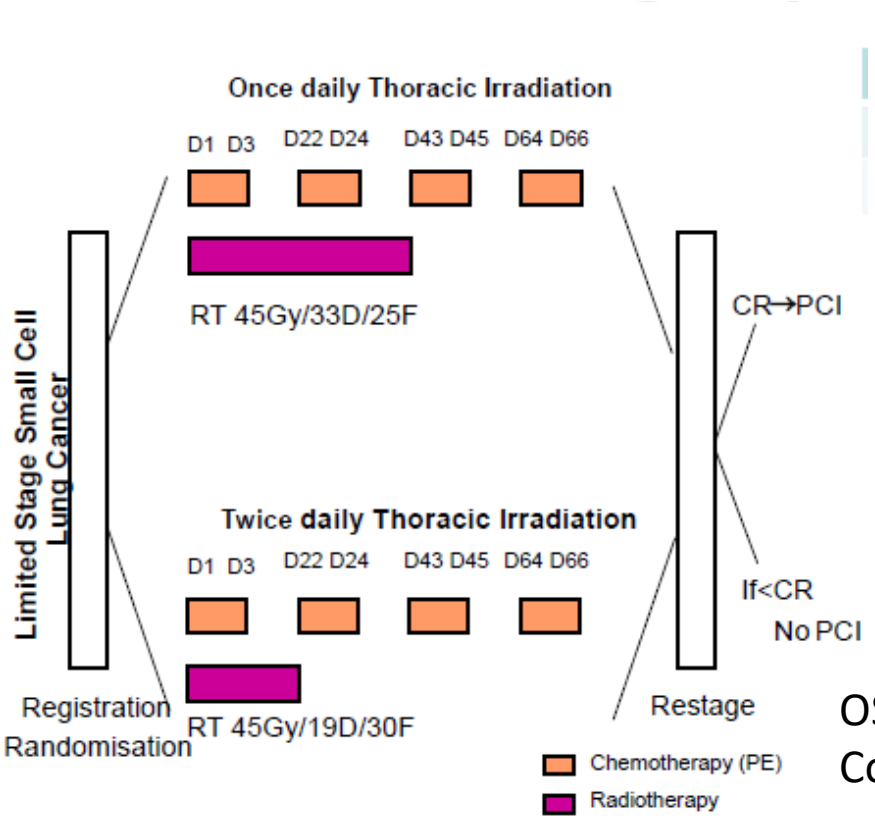


- Underpowerd: 5% survival advantage with concurrent regimens
- Improved survival (median 27 vs. 20 months; p< 0.090) with concurrent treatment.
- significant increase in Grade 3 or greater leukopenia (85% vs.54%)
- similar rates of Grade 3 esophagitis in both arms

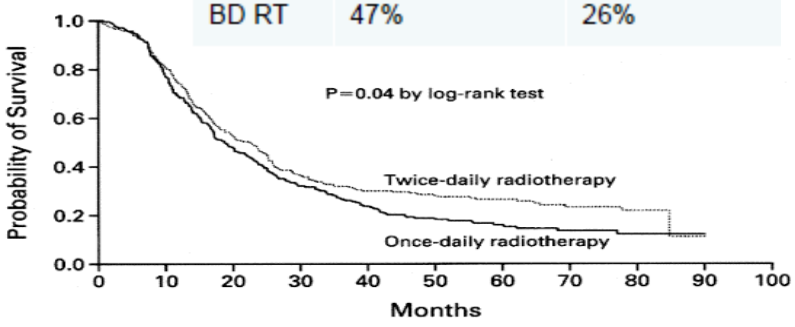
Takada M. J Clin Oncol. 2002 Jul 15;20(14):3054-60.

Which Fractionation? Intergroup 0096

Intergroup 0096



	2 year survival	5 year survival
OD RT	41%	16%
BD RT	47%	26%



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

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

Turrisi et al NEJM 340(4):1999;265-271

Which Fractionation? CALGB 39808

Dose escalated 70GY Radiotherapy: CALGB 39808

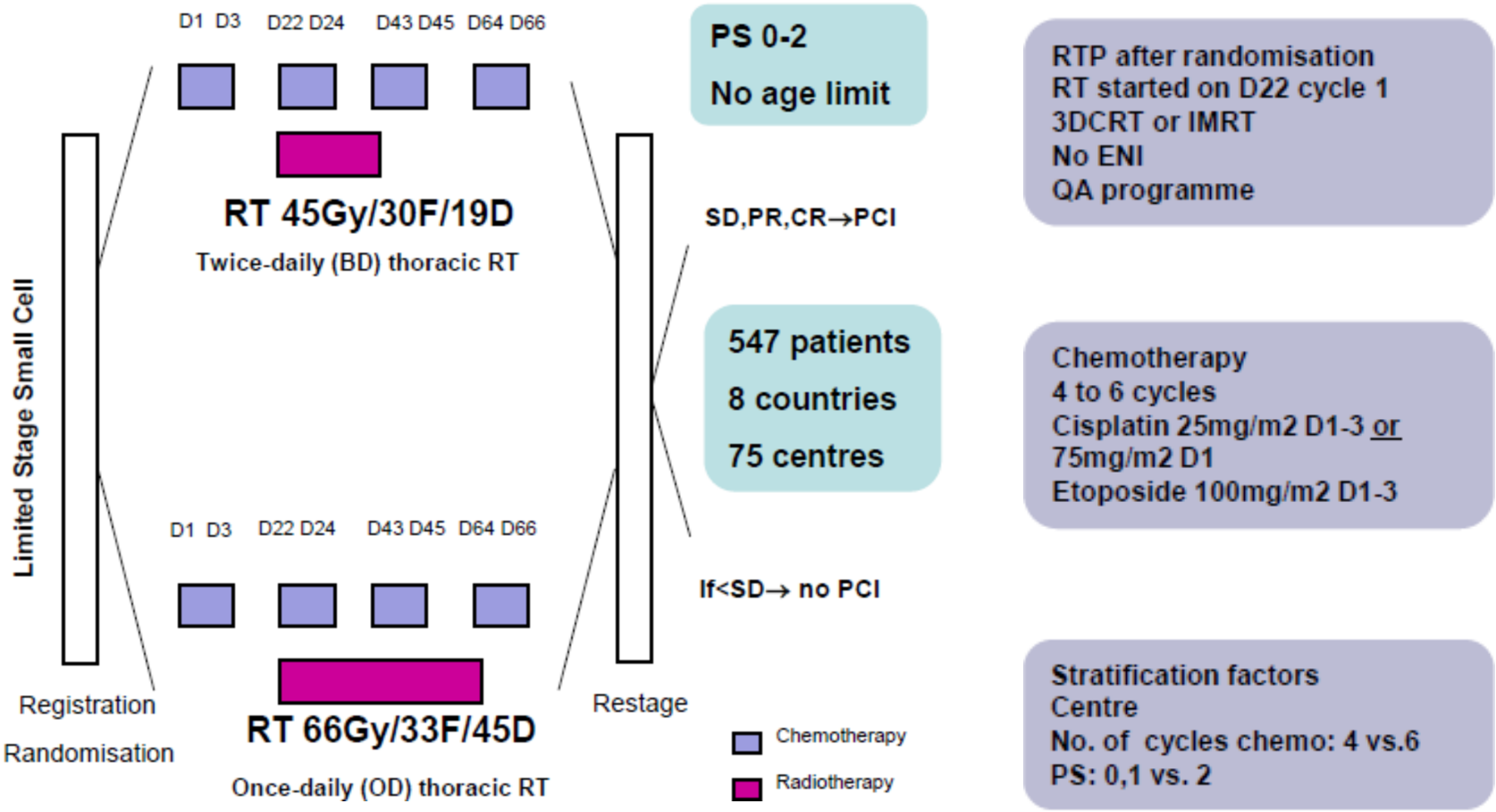
- 2 cycles of paclitaxel + topotecan
- 70 Gyin 35 fractions with EP
- Phase II design, 63 patients
- 10% Grade3/4 toxiciry

Table 5. Comparison of INT-0096 and CALGB 39808

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

Bogart JA. Int J Radiat Oncol Biol Phys. 2004 Jun 1;59(2):460-8.

Which Fractionation?CONVERT Trial

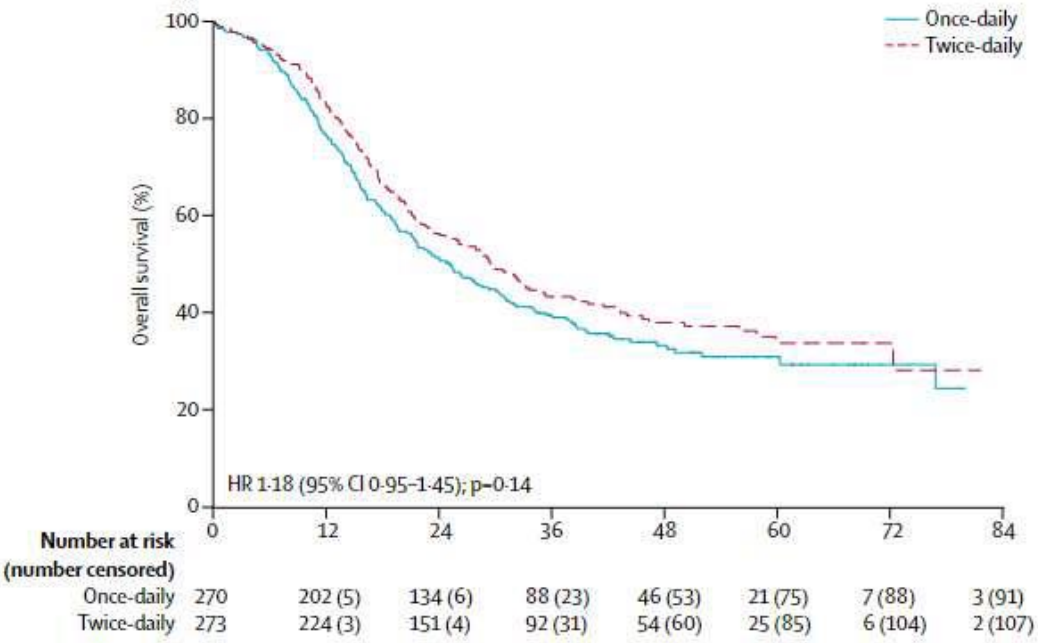


A 12% higher overall survival at 2 years in the once-daily group versus the twice-daily group was considered to be clinically significant to show superiority of the once-daily regimen.

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%,



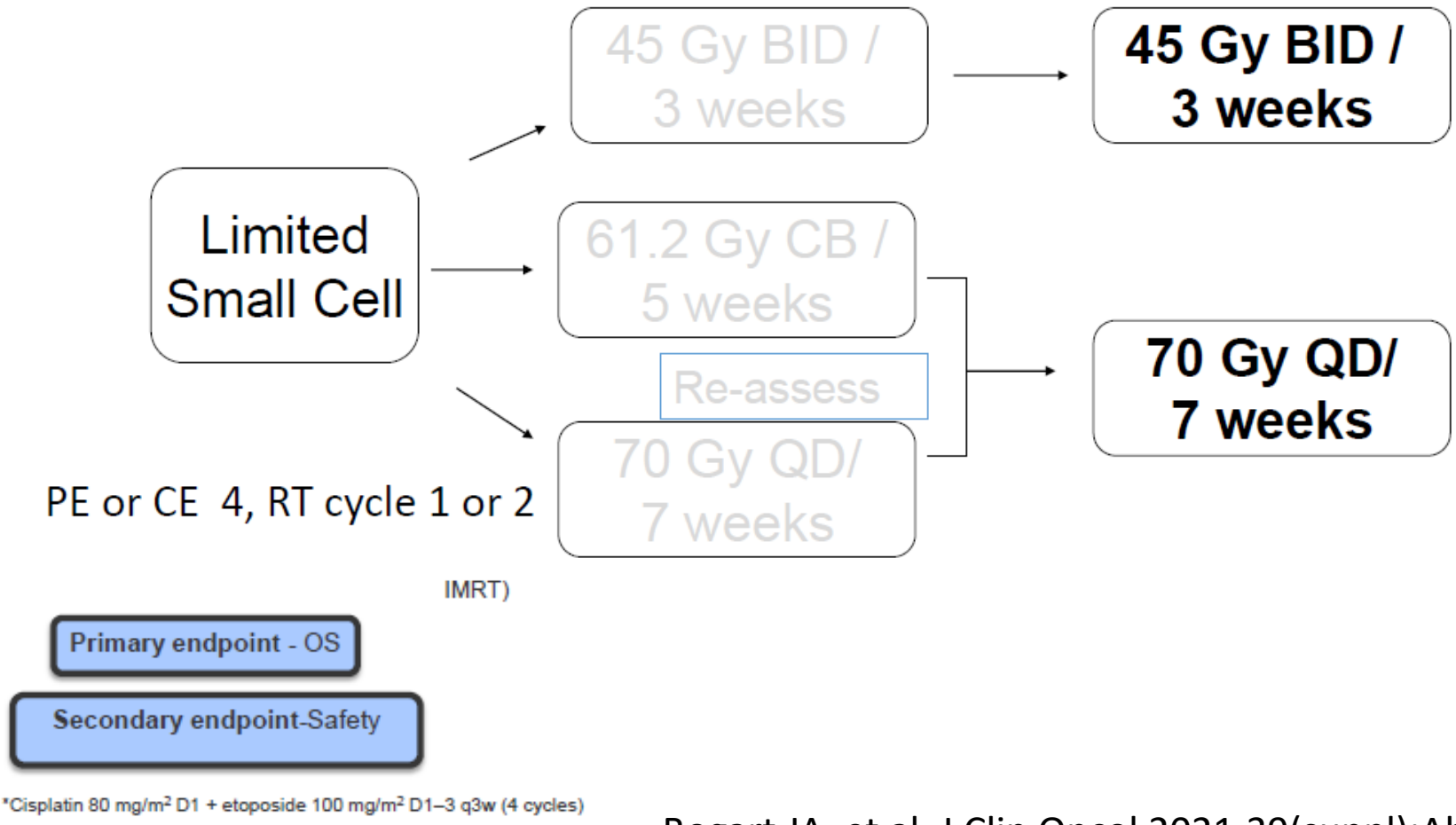
Toxicities similar and lower than expected

Survival in both arms was higher than previously reported

<u>BUT OD RT did not result in a superior survival or worse toxicity than BD RT</u>

Faivre-Finn C. Lancet Oncol. 2017 Aug;18(8):1116-1125

Which Fractionation?CALGB 30610

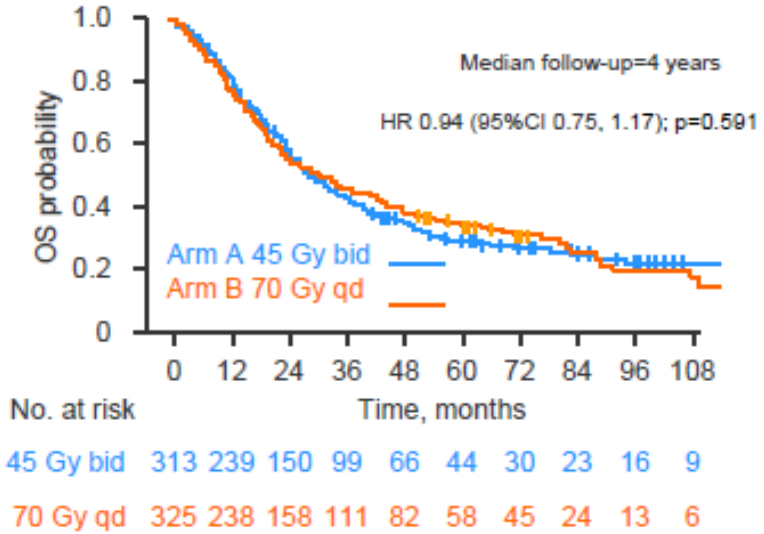


Bogart JA, et al. J Clin Oncol 2021;39(suppl):Abstr 8505

Which fractionation?CALGB 30610

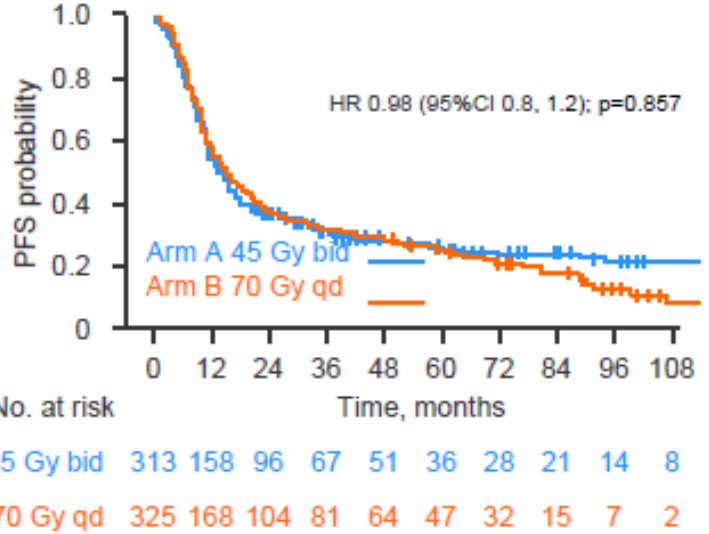
Overall survival

	mOS, mo (95%CI)	2-years OS, % (95%CI)	5-years OS, % (95%CI)
45 Gy bid	28.5 (25.4, 35.5)	58 (53, 64)	29 (23, 35)
70 Gy qd	30.5 (25.4, 41.1)	56 (51, 62)	34 (23, 35)



Progression-free survival

	mPFS, mo (95%CI)	2-years PFS, % (95%CI)	5-years PFS, % (95%CI)
45 Gy bid	13.5 (11.7, 15.8)	36 (31, 42)	25 (20, 31)
70 Gy qd	14.2 (11.9, 17.7)	36 (31, 42)	24 (20, 30)



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

Bogart JA, et al. J Clin Oncol 2021;39(suppl):Abstr 8505

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

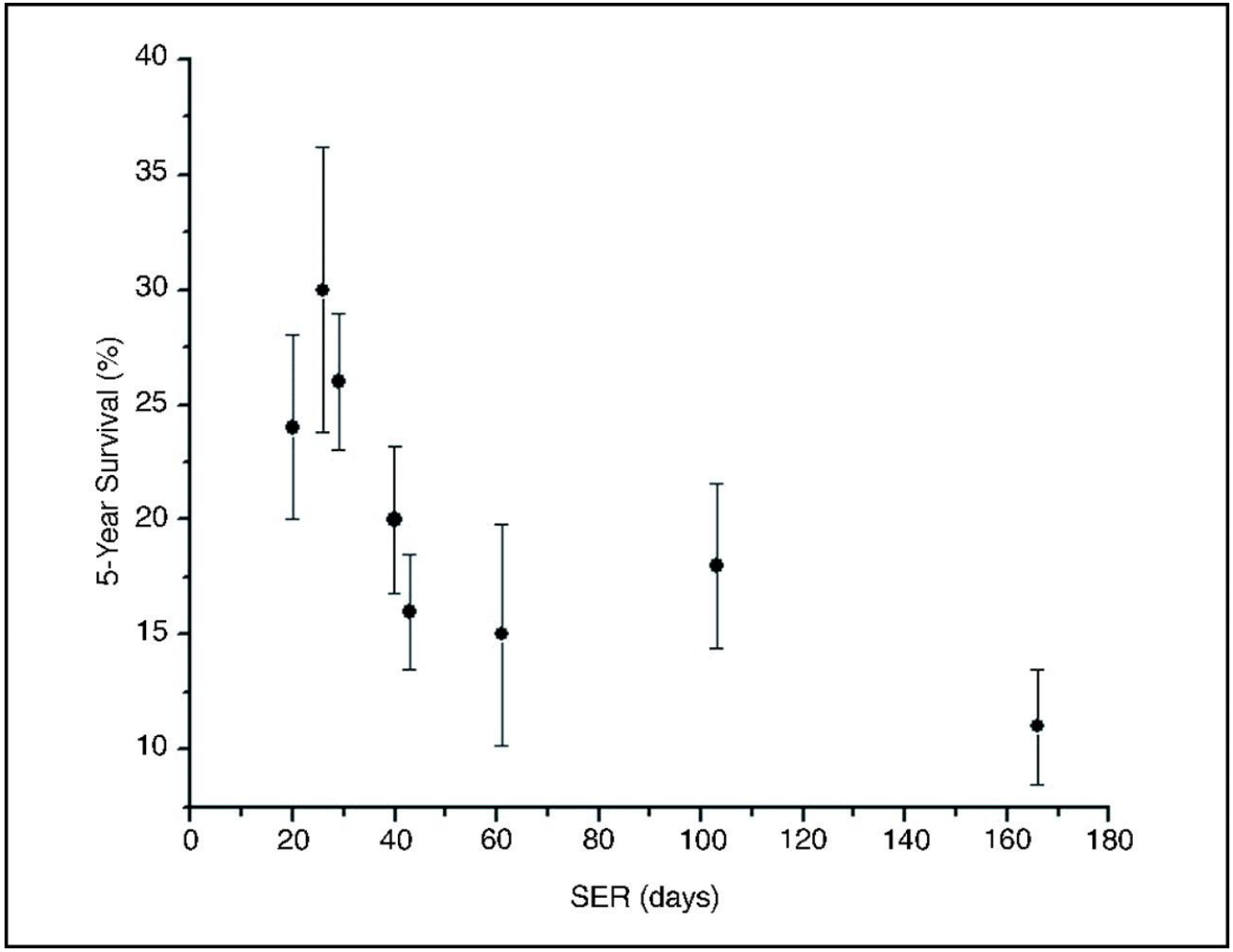
Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

Dirk De Ruysscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minken, 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

De Ruysscher, D. et al. J Clin Oncol 2006; 24:1057-1063

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



De Ruysscher, D. et al. J Clin Oncol 2006; 24:1057-1063

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

Le Pechoux. Lancet Oncol 2009 & Ann Oncol2011

Prophylactic cranial irradiation in stage I-III SCLC

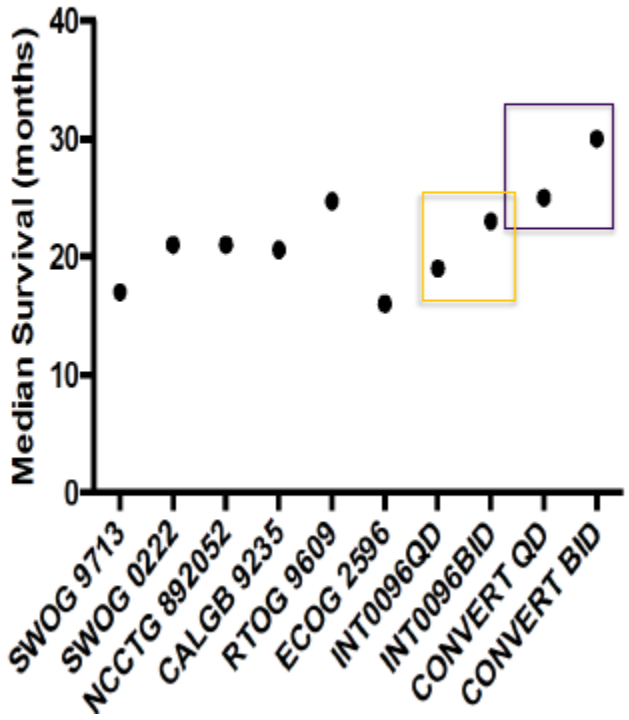
Study	n	MRI	Survival		Brain Mets	
			PCI	No PCI	PCI	No PCI
EORTC	286	Not required	**27 %** (1-yr)	**13%**	15%	40%
Japan	224	pre, 3, 6, 9, 12, 18, 24 mo	**11.6 mo** (median)	**13.6 mo**	33 %	59%

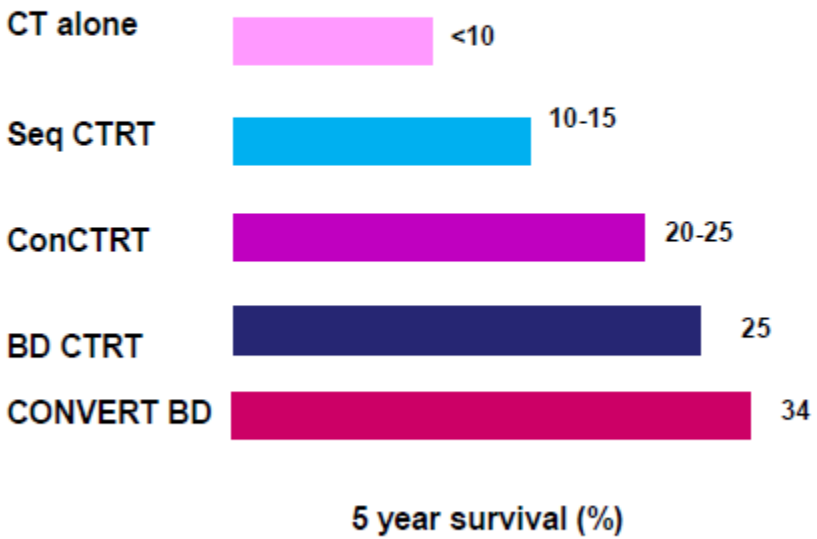
Slotman, Ben, et al. *New England Journal of Medicine357.7 (2007): 664-672*
Takahashi, Toshiaki, et al. *Lancet Oncology18.5 (2017): 663-671*

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





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