

Limited-Stage Small Cell Lung Cancer

Submitted to ABR 2015

Patient

- 64 year old gentleman
- Chief complaint: cough and increasing shortness of breath

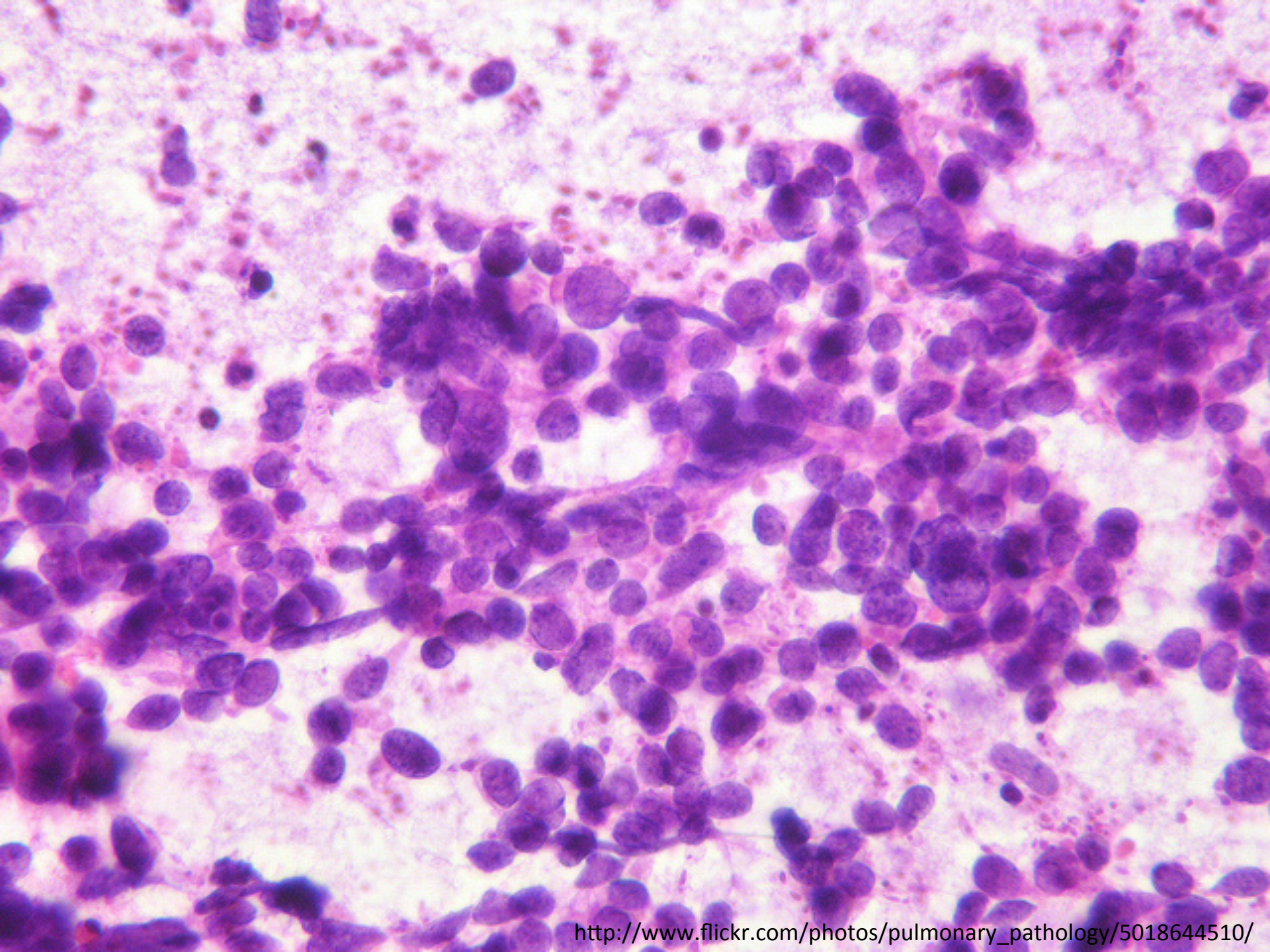
History

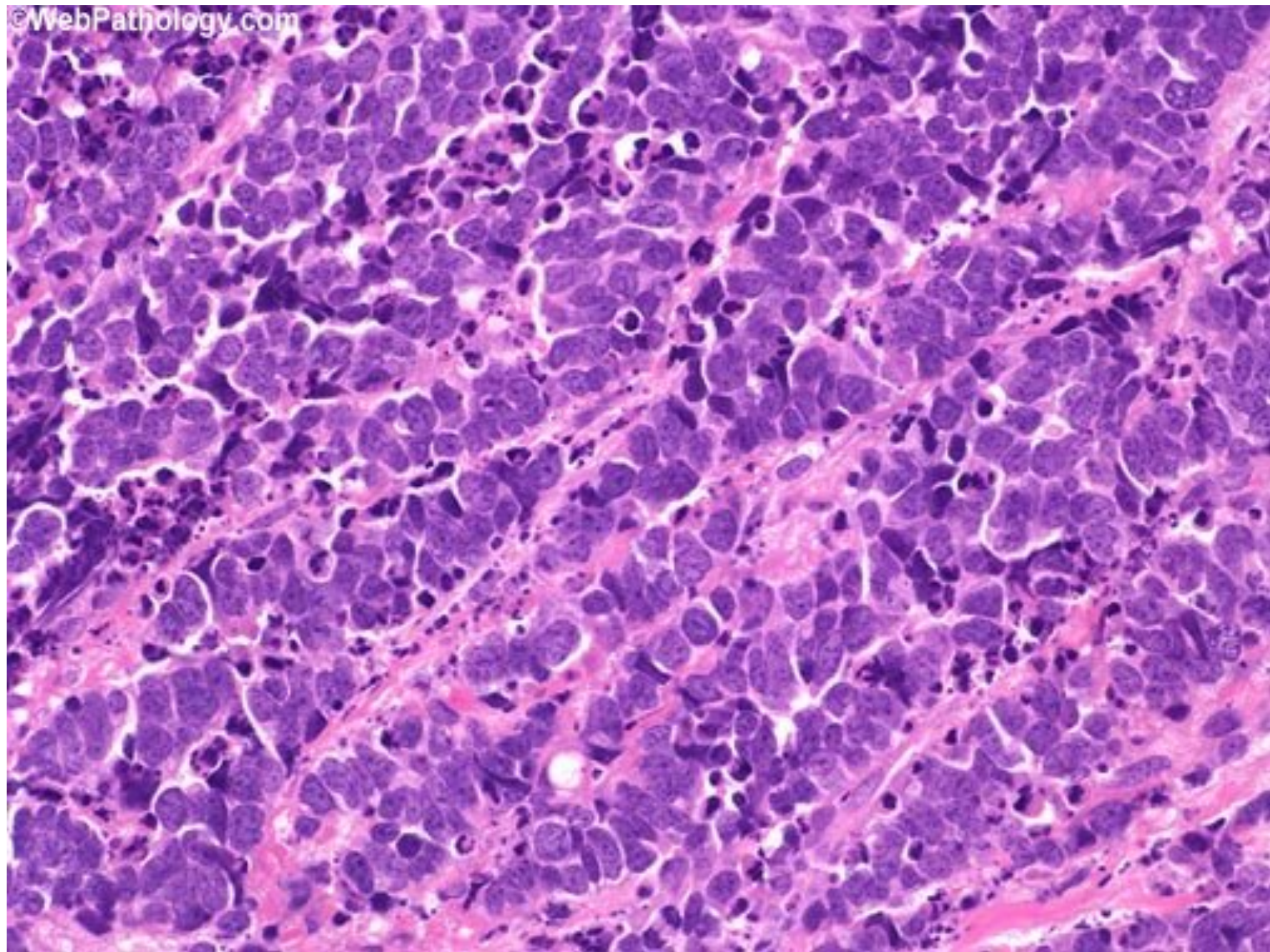
- No pain, fevers, chills, night sweats. No weight loss, hemoptysis or other system complaints
- PMHx: HTN, HPL, NIDDM, BPH
- Meds: Aspirin, Amitriptyline, Atenolol, Benazepril, Clonidine, Hydrochlorothiazide, Simvastatin
- Allergies: NKDA
- Family Hx: sibling with Hodgkin lymphoma
- Social Hx: 45 years smoking, current 1-pk/day, No current EtOH (for several years), divorced, retired construction worker, No exotic travel history

History / Exam

- ROS: otherwise negative
- Exam:
 - Blood pressure 113/61, weight 210 pounds, pulse 72, afebrile
 - Lungs: slightly decreased breath sounds on right side. No crackles or wheezing auscultated.
 - Negative nodal and abdominal exam

- Labs: WNL
- PFTs:
 - FEV-1 of 2.64
 - DLCO of 52% of predicted
- Other imaging
 - CT Abdomen: negative
 - MRI Brain: negative





Patient

- Saw medical oncology and started cycle 1 of etoposide and carboplatin
- Referred to radiation oncology

Lung Cancer

- Worldwide
 - Most common cancer (1.35 million of 10.9 million cases)
 - Deadliest cancer (1.18 million of 6.7 million cancer-related deaths)
- US:
 - 2nd most common in men and women
 - Deadliest in men (90,330) and women (72,130)
 - More deaths than next three tumor sites combined (colorectal, breast and prostate)

Small Cell Lung Cancer

- 95% related to smoking
- Incidence declining in US
- Still accounts for approximately 20-25% of lung cancer cases (40,000 cases/yr) in US
- Classification: new WHO (2010) – only variant recognized is combined SCLC (c-SCLC)
- Association with paraneoplastic syndromes
 - ADH (SIADH), ACTH (Cushing's)
 - Eaton-Lambert Syndrome (Lambert-Eaton myasthenic syndrome or LEMS)
- 2 clinical stages:
 - Limited: tumor confined to 1 hemithorax
 - Extensive: beyond 1 hemithorax

Limited Stage Small Cell Lung Cancer

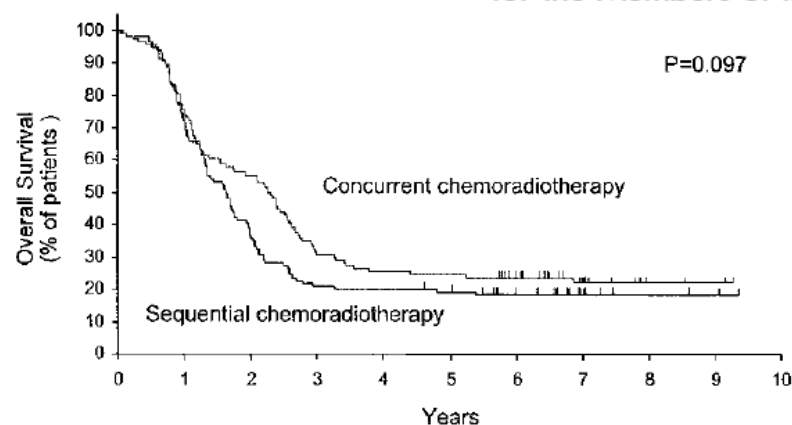
- Only 25% of SCLC
- Survival:
 - 1960s: MRC trial; radiation superior to surgery (mean survival 6.5 vs. 10 months $p=0.04$)
 - 1 yr, 2 yr and 5 yr survival of 22% 10% and 4%
 - Fox, et. al *Lancet* 1973; 2:63-65.
 - 1990s: NCI; chemoradiation with PCI
 - 1 yr, 2 yr and 5 yr survival of 83%, 43% and 19%
 - Johnson B, et. al. *JCO* 1996; 14:806-13.

3 Questions

- Early 1990s:
 - 2 separate meta-analyses by Pignon et al (NEJM 1992) and Warde et al (JCO 1992) showed a 5.4% increase in overall survival with the addition of chemotherapy to radiation
- Timing of radiation and chemotherapy?
- Dosing and fractionation of radiation?
- With a >80% CNS metastases rate at 2 years, what is the role of prophylactic cranial irradiation (PCI)?

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, Yutaka Nishiwaki, Koshiro Watanabe, Kazumasa Noda, Tomohide Tamura, Haruhiko Fukuda, and Nagahiro Saijo for the Members of the Japan Clinical Oncology Group



Journal of Clinical Oncology, Vol 20, No 14 (July 15), 2002: pp 3054-3060

Chemo : etoposide and cisplatin x4c

radiotherapy	114	83	41	24	23	21	14	7	3	2
radiotherapy	114	86	63	34	29	28	21	12	3	2

Table 3. Tumor Response According to Treatment Arm: Eligible Patients

Result	Sequential Arm (n = 114)		Concurrent Arm (n = 114)		P
	No. of Patients	%	No. of Patients	%	
Response					
Complete	31	27	45	40	.07
Partial	74	65	65	57	
Overall	105	92	110	96	.25
No change	3	3	1	1	
Progressive	4	4	1	1	
Could not be evaluated	2	2	2	2	

Importance of Timing for Thoracic Irradiation in the Combined Modality Treatment of Limited-Stage Small-Cell Lung Cancer

By Nevin Murray, Peter Coy, Joseph L. Pater, Ian Hodson, Andrew Arnold, Benny C. Zee, David Payne, Edmund C. Kostashuk, William K. Evans, Peter Dixon, Anna Sadura, Ronald Feld, Martin Levitt, Rafal Wierzbicki, Joseph Ayoub, Jean A. Maroun, and Kenneth S. Wilson for the National Cancer Institute of Canada Clinical Trials Group

Journal of Clinical Oncology, Vol 11, No 2 (February), 1993: pp 336-344

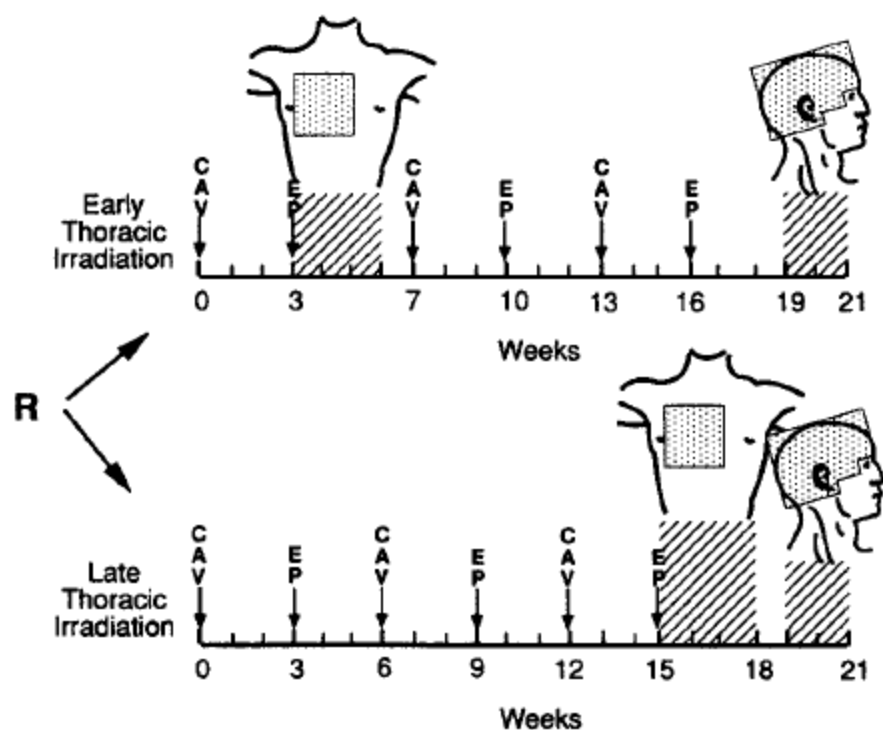
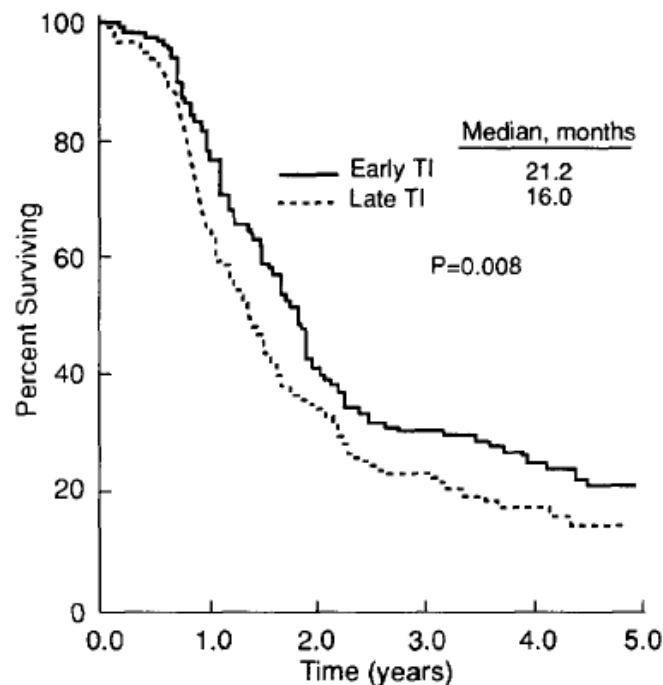


Fig 1. Study schema.



# at risk (early)	155	122	64	40	23	11
# at risk (late)	153	99	53	32	18	6

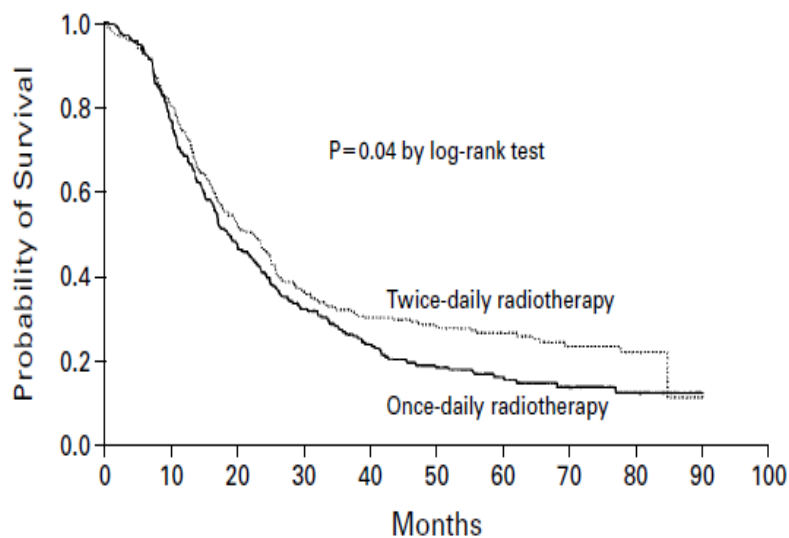
Fig 3. Overall survival: early TI v late TI.

- Timing of radiation and chemotherapy?
- Concurrent
- Start radiation within the first 4-6 weeks of starting chemotherapy (exception CALGB)

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

ANDREW T. TURRISI, III, M.D., KYUNG-MANN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

N Engl J Med 1999;340:265-71



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

COMPLICATION AND NO. OF RADIATION TREATMENTS PER DAY	GRADE						P VALUE
	0	1	2	3	4	5	
	number (percent) of patients						
Overall†							0.80
1	1 (0.5)	3 (1)	20 (10)	47 (23)	127 (63)	5 (2)	
2	2 (1)	0	19 (9)	51 (25)	128 (62)	6 (3)	
Myelotoxicity‡							0.70
1	2 (1)	9 (4)	19 (9)	43 (21)	129 (64)	1 (0.5)	
2	7 (3)	2 (1)	18 (9)	52 (25)	127 (62)	0	
Esophagitis							<0.001
1	113 (56)	19 (9)	38 (19)	22 (11)	11 (5)	0	
2	76 (37)	26 (13)	37 (18)	56 (27)	11 (5)	0	
Other toxic effects							0.20
1	4 (2)	18 (9)	119 (59)	46 (23)	12 (6)	4 (2)	
2	2 (1)	13 (6)	119 (58)	53 (26)	13 (6)	6 (3)	

*Data were available for 203 patients receiving once-daily radiotherapy and 206 patients receiving twice-daily therapy.

†Overall rates are based on the grade of the most severe complication of any type that occurred in each patient.

‡Myelotoxicity was defined as any decrease in marrow-derived cells in the peripheral-blood counts.¹⁰

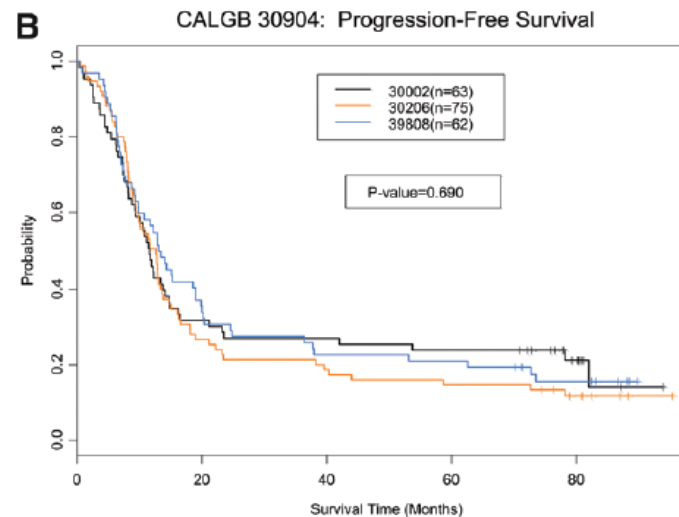
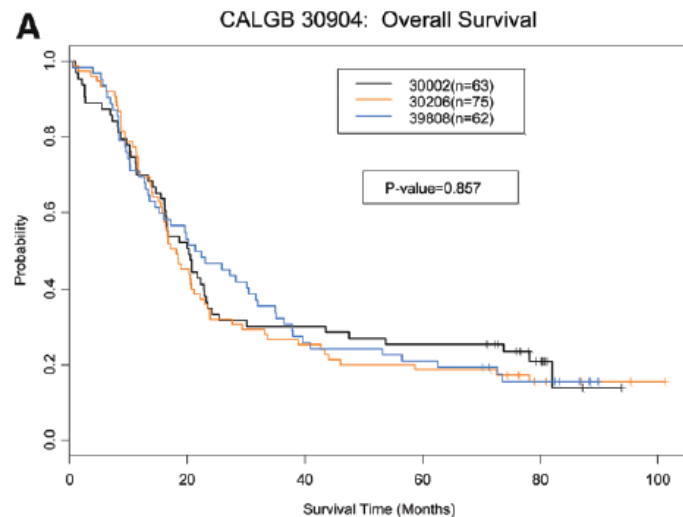
BID: median 23 months, 2-yr 47%, 5-yr 26%
 QD: median 19 months, 2-yr 41%, 5-yr 16%

A Pooled Analysis of Limited-Stage Small-Cell Lung Cancer Patients Treated with Induction Chemotherapy Followed by Concurrent Platinum-Based Chemotherapy and 70 Gy Daily Radiotherapy

CALGB 30904

Joseph K. Salama, MD, Lydia Hodgson, MS,† Herbert Pang, PhD,† James J. Urbanic, MD,‡ A. William Blackstock, MD,‡ Steven E. Schild, MD,§ Jeffrey Crawford, MD,|| Jeffrey A Bogart, MD,¶ and Everett E. Vokes, MD,# for the Cancer and Leukemia Group B*

Journal of Thoracic Oncology • Volume XX, Number XX, XXX 2013



- Median follow up 78 months
- Median survival 19.9 months
- 5-yr OS pooled was 20%
- 2-yr PFS was 26%

- Dosing and fractionation for SCLC?
- Standard of care is 45 Gy delivered in 1.5 Gy fractions BID for 3 weeks
- There is growing evidence that doses >60 Gy may be effective in daily fractionation of 2 Gy with decreased grade 3+ esophagitis

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

ANNE AUPÉRIN, M.D., RODRIGO ARRIAGADA, M.D., JEAN-PIERRE PIGNON, M.D., PH.D., CÉCILE LE PÉCHOUX, M.D., ANNA GREGOR, M.D., RICHARD J. STEPHENS, PAUL E.G. KRISTJANSEN, M.D., PH.D., BRUCE E. JOHNSON, M.D., HIROSHI UEOKA, M.D., HENRY WAGNER, M.D., AND JOSEPH AISNER, M.D.,
FOR THE PROPHYLACTIC CRANIAL IRRADIATION OVERVIEW COLLABORATIVE GROUP*

N Engl J Med 1999;341:476-84

TRIAL	ENROLLMENT PERIOD	MEDIAN FOLLOW-UP yr	INDUCTION THERAPY	TOTAL DOSE/ NO. OF FRACTIONS (DOSE/FRACTION)	MEDIAN TIME BETWEEN START OF INDUCTION THERAPY AND ENROLLMENT	NO. OF PATIENTS	NO. OF PATIENTS SURVIVING
					mo		
UMCC ²⁹	1977–1980	18.5	CT	30 Gy/10 (3 Gy)	3.6	29	2
Okayama ³⁰	1981–1986	11.7	CT or CT plus RT	40 Gy/20 (2 Gy)	2.5	46	4
PCI-85 ⁵	1985–1993	8.4	CT or CT plus RT	24 Gy/8 (3 Gy)	5.3	300	32
Danish–NCI (unpublished)	1985–1991	8.8	CT	24 Gy/8 (3 Gy)	4.4	55	7
UKCCCR–EORTC ¹⁵	1987–1995	3.5	CT or CT plus RT	8–36 Gy/1–18†	NA	314	54
PCI-88 ³¹	1988–1994	5.1	CT or CT plus RT	24 Gy/8 (3 Gy)	5.1	211	37
ECOG–RTOG ³²	1991–1994	3.9	CT or CT plus RT	25 Gy/10 (2.5 Gy)	NA	32	5

END POINT	NO. OF PATIENTS		RELATIVE RISK (95% CI)	P VALUE	HETEROGENEITY (P VALUE)	RATE IN THE CONTROL GROUP OVER A 3-YR PERIOD	ABSOLUTE BENEFIT AT 3 YR
	TREATMENT GROUP	CONTROL GROUP					
							percent
Overall survival	526	461	0.84 (0.73–0.97)	0.01	0.95	15.3	+5.4
Disease-free survival	526	461	0.75 (0.65–0.86)	<0.001	0.96	13.5	+8.8
Cumulative incidence of brain metastasis	524	457	0.46 (0.38–0.57)	<0.001	0.14	58.6	–25.3
Cumulative incidence of other metastases	325	332	0.89 (0.69–1.15)	0.37	0.51	45.6	–3.8
Cumulative incidence of local or regional recurrence	323	334	0.97 (0.75–1.26)	0.84	0.45	45.1	–1.0

Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial

Cécile Le Péchoux, Ariane Dunant, Suresh Senan, Aaron Wolfson, Elisabeth Quoix, Corinne Faivre-Finn, Tudor Ciuleanu, Rodrigo Arriagada, Richard Jones, Rinus Wanders, Delphine Lerouge, Agnès Laplanche, on behalf of the Prophylactic Cranial Irradiation (PCI) Collaborative Group*

Lancet Oncol 2009; 10: 467-74

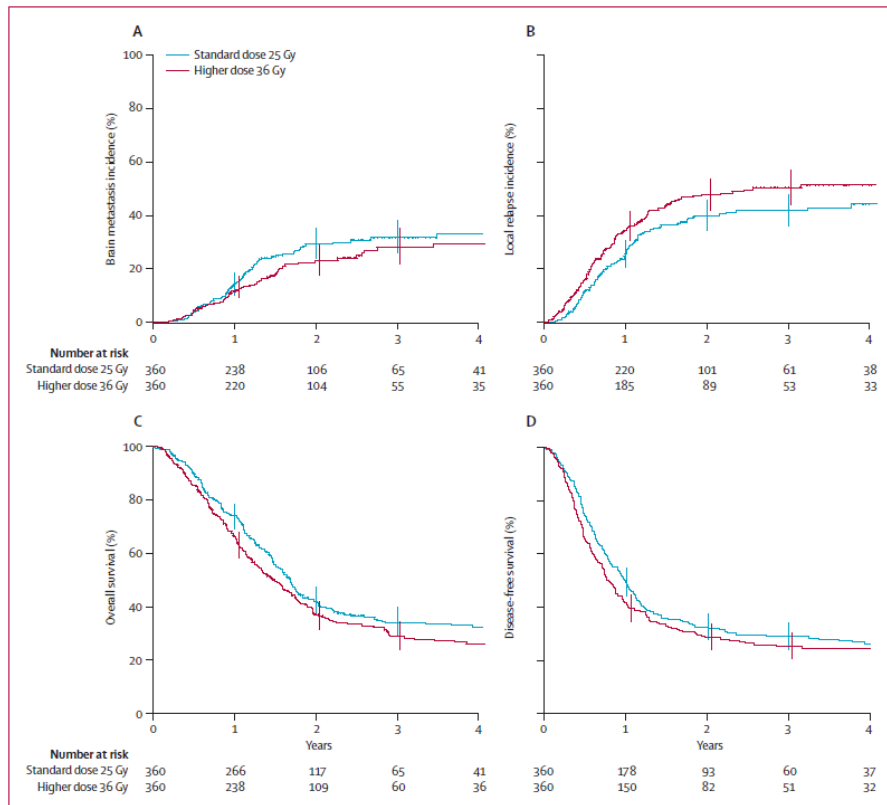


Figure 2: Kaplan-Meier curves showing total incidence of brain metastasis (A), local relapse (B), overall survival (C), and disease-free survival (D)

- Median follow up 39 months
- No difference in brain mets between high dose vs low dose groups (29% vs 23%, $p=0.18$)
- Worse 2-yr survival in high dose group (37% vs 42%, $p=0.05$)
- Conclusion: no benefit to high dose PCI

- Role of PCI?
- Should be done in patients with response to chemoradiation
- 25 Gy in 10 fractions is standard of care and higher doses appear worse

Patient

- Right paratracheal mass treated to 5940 cGy in 180 cGy fractions with concurrent etoposide and carboplatin
- PCI to 3600 cGy in 20 fxns according to RTOG 0212
- Right lung mass treated to 4800 cGy in 4 fractions between ~1 year later
- Died 5 years later
 - in the interim, underwent adrenalectomy, RT to cerebellar metastasis