ES-SCLC
Joint Case Conference

Anthony Paravati
Adam Yock

Case

- 57 yo woman with 35 pack year smoking history presented with persistent cough and rash
- Chest x-ray showed a large left upper lobe/left hilar mass and CT of the chest showed a 8.3 cm left upper lobe mass and severe emphysema
- Endobronchial biopsy demonstrated small cell carcinoma
- CT/PET negative for metastatic disease
- MRI of the brain showed multiple (at least 5) scattered brain lesions

Case

- Tx
  - WBRT 30 Gy in 10 fx completed first
  - Cis/etoposide x 4 cycles following WBRT
  - Restaging PET/CT showed interval decrease in size of the lung mass without new metastases
  - Repeat MRI negative
  - Split course lung RT to 5500 cGy (20 Fx total)
  - Repeat MRI in several months later demonstrated 8 new brain lesions as well as an enhancing lesion in the cervical spinal cord C2-3
  - Stereotactic RT - 500 x 5 to new brain lesions
  - Opposed laterals to the C2-3 lesion 300 cGy x 10

Epidemiology

- Approximately 15% of lung cancers – small decrease over past 30 years, higher proportion of women

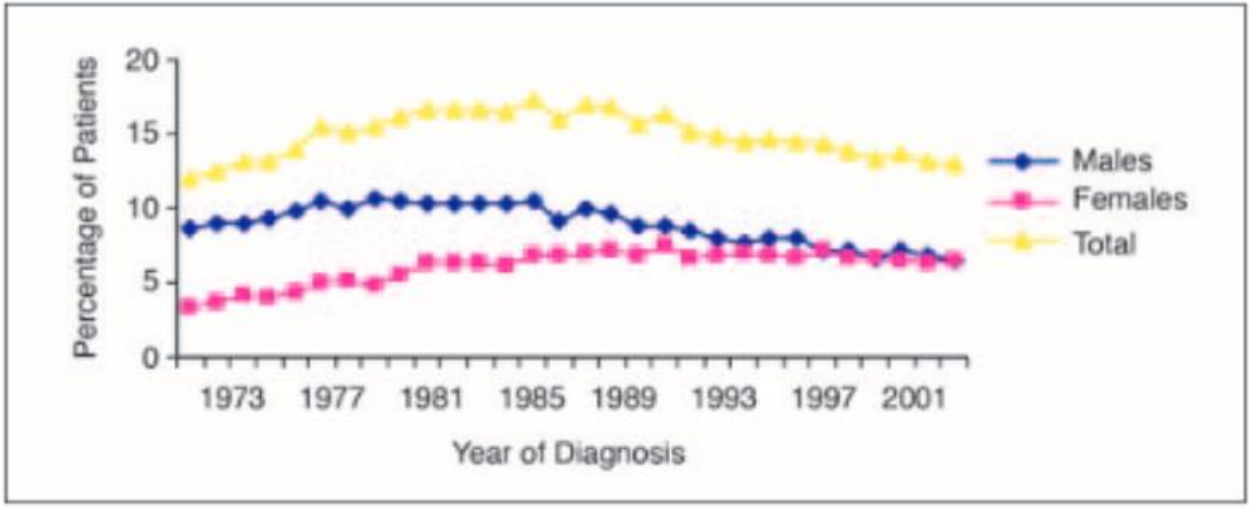


Fig 1. The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

Govindan, JCO 2006

Staging: officially AJCC but . . .

NCCN Definitions

Limited Stage

- AJCC (7th 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

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

Stage Distribution and Survival

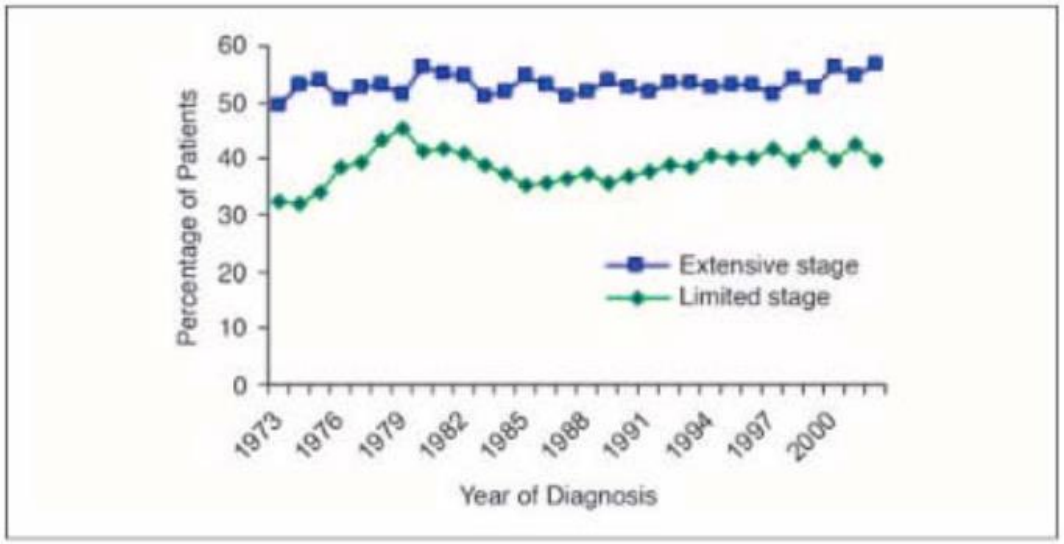


Fig 5. The diagnosis of small-cell lung cancer by stage.

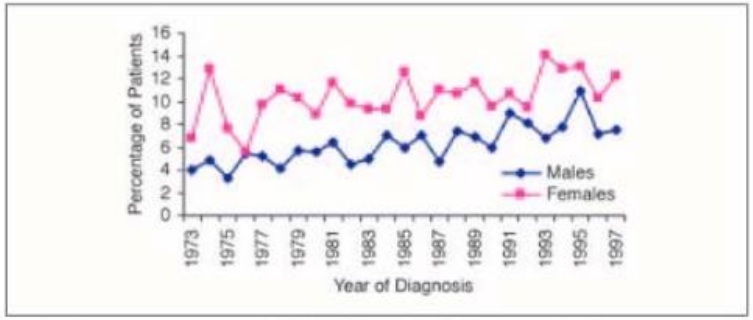


Fig 10. The all-cause survival trends in limited-stage small-cell lung cancer.

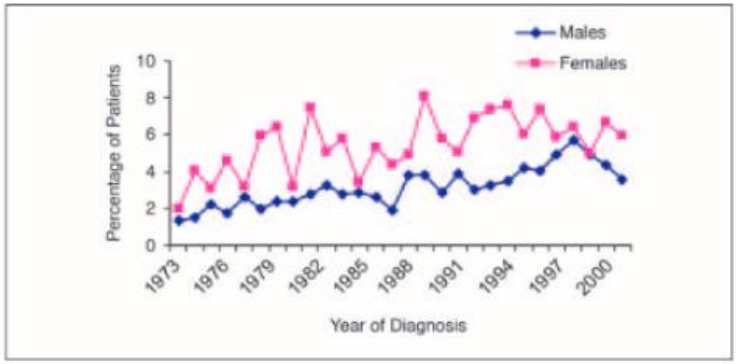


Fig 7. The all-cause survival trends in extensive-stage small-cell lung cancer.

Govindan JCO 2006

ES-SCLC

- Majority of SCLC patients have extensive stage disease
- Disease is highly responsive to chemotherapy, but median survival is 8-13 months
- Multiple RCTs have evaluated chemotherapy combinations and timing. Two-drug regimens are better than single-drug regimens, but >2 is not very beneficial but more toxicity
- Platinum + Etoposide (4-6 cycles) remains standard first-line in most centers
- Can radiation help improve survival?

Treatment Overview

Limited stage disease

- Concurrent chemoRT – cisplatin/etoposide 4 cycles w/ thoracic RT (TRT) starting during cycle 1 or 2
- RT dose 45 Gy in 1.5 Gy fx BID
- If CR or near-CR achieved PCI

Extensive stage disease

- Upfront chemotherapy with cisplatin/etoposide
- +/- palliative RT
- For patients with good response, consider PCI
- If brain metastases at presentation WBRT is standard

Extensive Stage

- Jeremic et al. – 210 patients with extensive stage SCLC tx with cis/etoposide x 3 with local PR/CR and distant CR randomized to accelerated hyperfractionated RT (54 Gy/ 1.5 BID) with chemo vs 4 cycles chemo alone
- ChemoRT improved 5 yr OS (9.1 vs. 3.7%, p=0.041) and MS (17 vs. 11 mos)

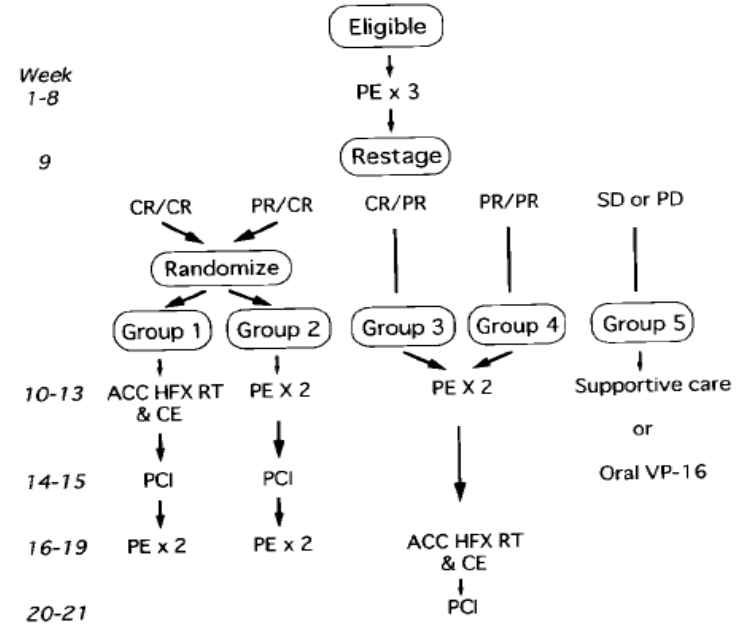
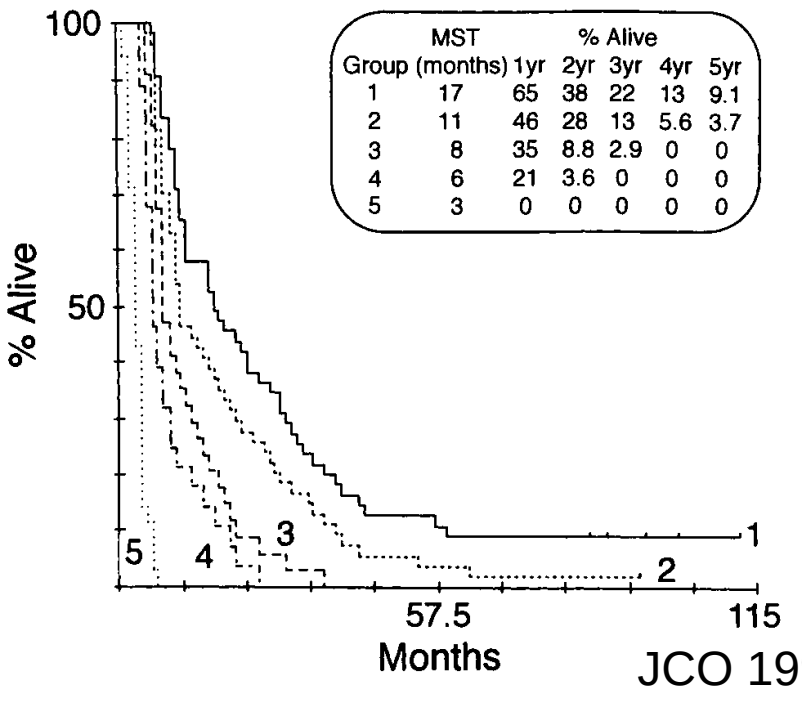


Fig 1. Treatment schema. VP-16, etoposide.

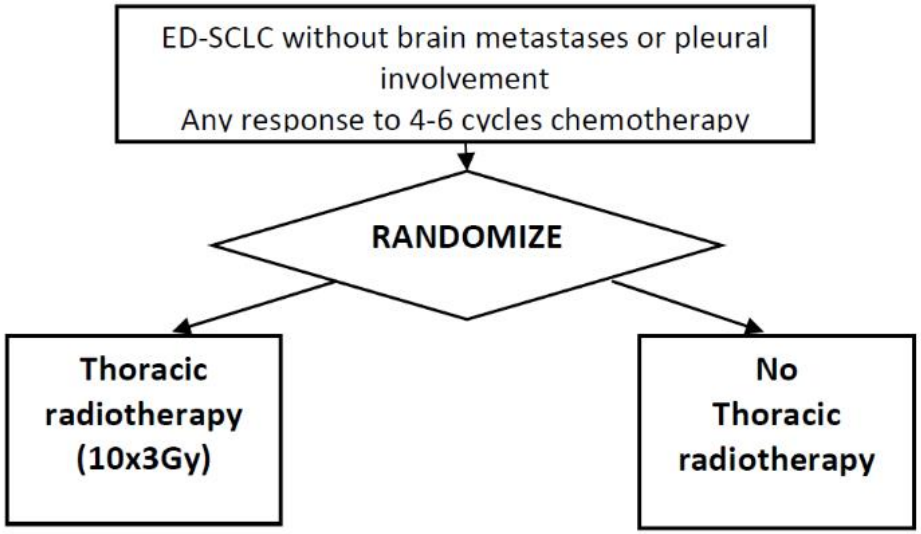


JCO 199

Slotman TRT trial – Lancet 2014

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**



All patients will receive PCI

PCI: 20/5, 25/10, 30/10-12-15

Lancet 2014

Slotman TRT trial – Lancet 2014

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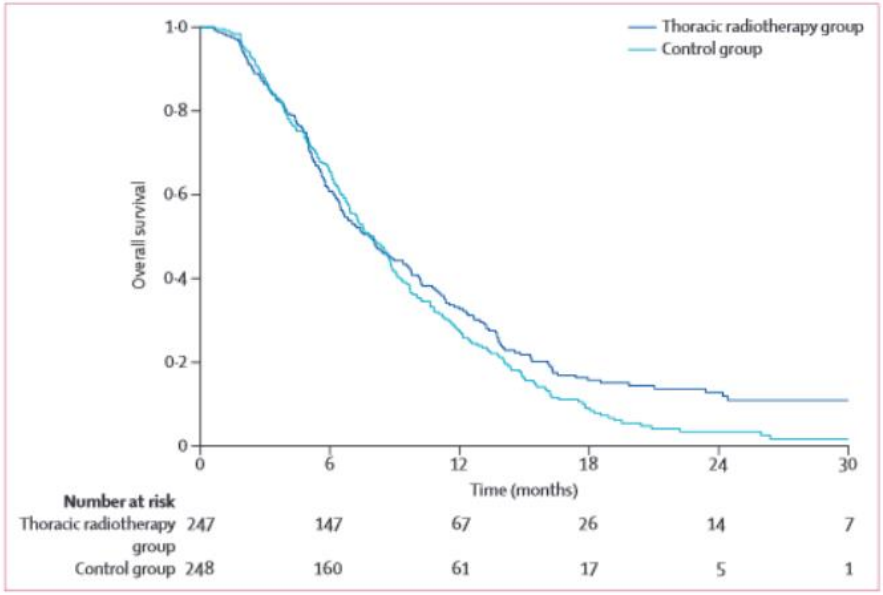


Figure 2: Kaplan-Meier curves for overall survival

1^0 Endpoint: 1-yr OS:

33% (TRT) vs. 28% (no TRT)

HR 0.84, p=0.066

2^0 Endpoint: 2-yr OS:

13% (TRT) vs. 3% (no TRT)

p=0.004

Median OS 8 months in both groups

Lancet 2014

Slotman TRT Trial – Lancet 2014

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Cough (grade 3)	0 (0·0%)	1 (0·4%)
Dysphagia (grade 3)	1 (0·4%)	0 (0·0%)
Dyspnoea (grade 3)	3 (1·2%)	4 (1·6%)
Oesophagitis (grade 3)	4 (1·6%)	0 (0·0%)
Fatigue (grade 3)	11 (4·5%)	8 (3·2%)
Fatigue (grade 4)	0 (0·0%)	1 (0·4%)
Insomnia (grade 3)	3 (1·2%)	2 (0·8%)
Nausea or vomiting (grade 3)	1 (0·4%)	0 (0·0%)
Headache (grade 3)	3 (1·2%)	2 (0·8%)

Table 2: Grade 3 and higher toxic effects

Slotman et al Lancet 2014

RTOG 0937 - PCI vs. PCI + TRT for ES-SCLC

RTOG 0937

Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extra-Cranial Irradiation for Extensive Disease Small Cell Lung Cancer (ED-SCLC)

SCHEMA (6/24/14)

S	**Response to Treatment**	**R**	**Arm 1: Prophylactic Cranial Irradiation**
T	1. Complete Response (CR)	**A**	2.5 Gy per fraction for a total of 25 Gy
R	2. Partial Response (PR)	**N**	
A		**D**	**Arm 2: Prophylactic Cranial Irradiation**
T		**O**	2.5 Gy per fraction for a total of 25 Gy
I	**Number of Metastatic Lesions**	**M**	and
F	1. 1	**I**	**Consolidative Radiation to**
Y	2. 2-4	**Z**	**Locoregional and Residual Metastatic Disease**
	Age	**E**	45 Gy at 3 Gy per fraction*
	1. <65		
	2. ≥65		*Acceptable alternative regimens: 30-40 Gy in 10 fractions

Patient Population: (See Section 3.0 for Eligibility) **[2/16/11]**
Patients with extensive disease small cell lung cancer, excluding CNS metastases; patients must have had radiographic evidence of 1-4 extra-cranial metastatic lesions **prior** to platinum-based chemotherapy AND have had radiographic partial or complete response to chemotherapy in a minimum of one site of disease and no progression in any site.

Primary Endpoint
Overall survival (death due to any cause)

Secondary Endpoints
- Comparison of treatment-related adverse events;
- Patterns of failure (see Section 11.4.2 and 11.4.3);
- Comparison of time to first failure;
- Evaluation of the percentage of the planned radiation dose to each site.

NRG ONCOLOGY

Advancing Research. Improving Lives.™

TO: Investigators participating in RTOG 0937: A Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone To Prophylactic Cranial Irradiation And Consolidative Extra-Cranial Irradiation For Extensive Disease Small Cell Lung Cancer (ED-SCLC)

FROM: Elizabeth Gore, MD

DATE: February 27, 2015

Effective immediately, RTOG 0937 will be closed to accrual. Patients still on the investigational arm (Arm 2) should discontinue and convert to appropriate standard of care.

Based on a review by the NRG Oncology Data Monitoring Committee of a planned protocol interim analysis, the study has crossed the futility boundary for the primary endpoint of overall survival. The overall survival for the investigational arm (Arm 2) did not exceed that of the control arm (Arm 1). The crossing of this futility boundary means that consolidation extra-cranial irradiation in addition to prophylactic cranial irradiation (PCI) cannot result in a survival benefit with further accrual or follow up of patients in this study.

Also noted is a disproportionate distribution of grade 4 and 5 toxicities. Out of the 40 patients in the PCI only arm, there were 16 deaths and no grade 4 or 5 toxicities. Out of the 39 patients in the arm receiving PCI plus consolidated irradiation there were 23 deaths and 7 patients with grade 4 or 5 toxicities.

Differences between ES-SCLC TRT trials

0937 Protocol – No OS Δ

- ES, no brain mets, 1-4 non-CNS metastatic lesions
- Completed 4-6 cycles of plat-based chemo
- No s/s of CNS mets
- **Negative Brain MRI**
- CT or PETCT after chemo
  - PR or CR in >= 1 site
- TRT: 45 Gy in 15
- PCI: 25 Gy in 10

Slotman Lancet 2015 – OS Δ

- ES – disease beyond hemithorax, hilar, mediastinal, SClav nodes
- Any response to 4-6 cycles of C/E
- **No CLINICAL e/o brain, leptomeningeal, pleural mets**
- **PCI doses**
  - **20 in 5, 25 in 10, 30 in 10, 12, 15**

PCI

PCI – Slotman 2007

The NEW ENGLAND JOURNAL of MEDICINE

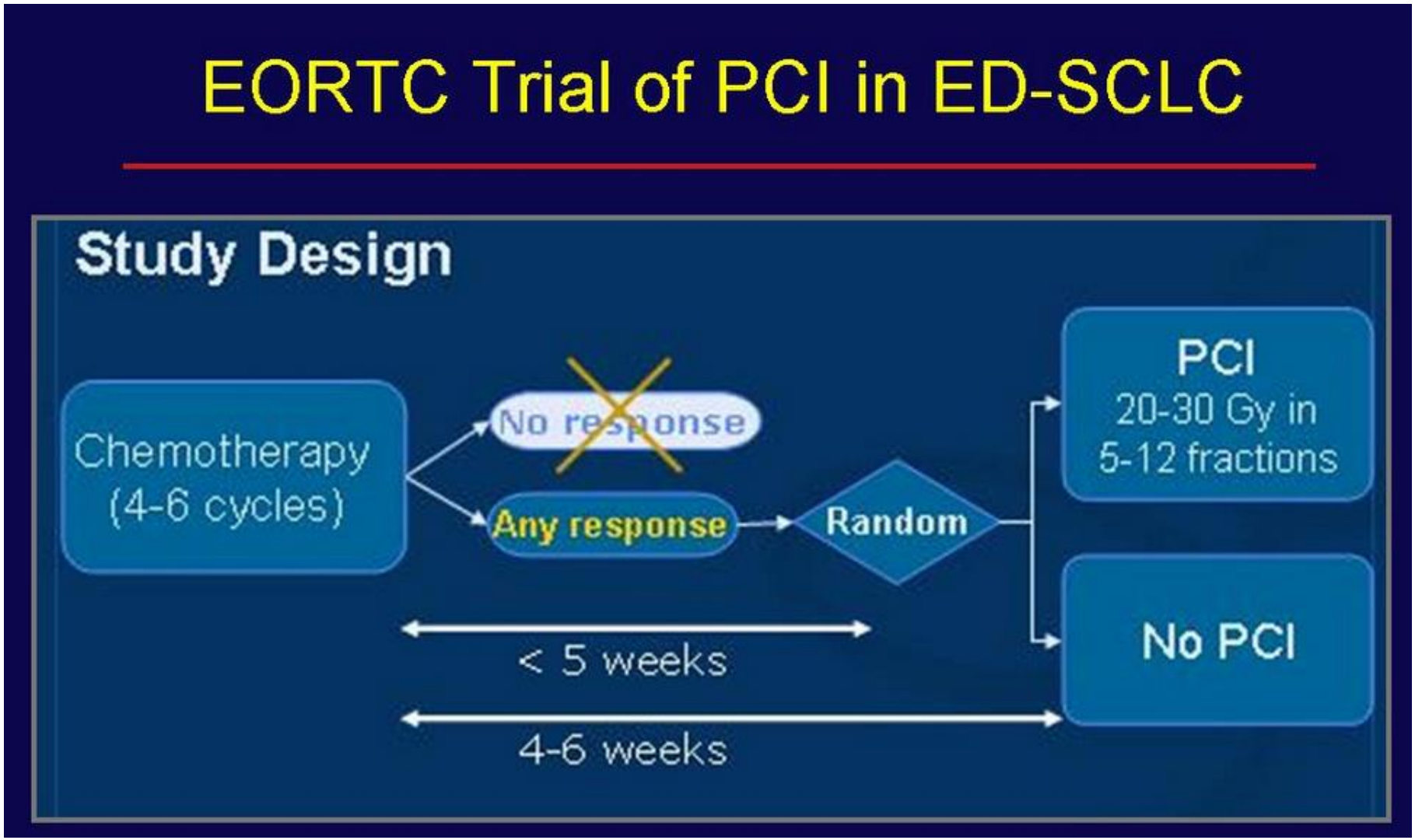
ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

- 286 patients with ES-SCLC randomized after any response to chemotherapy: PCI vs no PCI
- Several fractionations allowed: 20 Gy/5 and 30 Gy/10 most common
- Brain imaging was not part of standard staging and follow-up procedures, unless symptoms present

Slotman 2007

PCI trial Slotman B et al, NEJM 2007

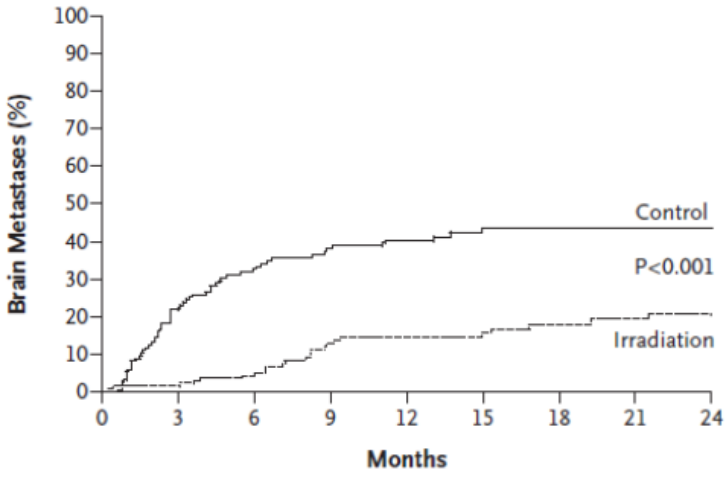


PCI trial Slotman B et al, NEJM 2007

EORTC

- 286 pts with ES-SCLC with PR or CR to chemotherapy and no e/o brain metastases randomized to PCI vs no further tx
- PCI reduced 1 yr incidence of symptomatic brain metastases (14.6 vs. 40.4%) and improved OS (27.1 vs. 13.3%)

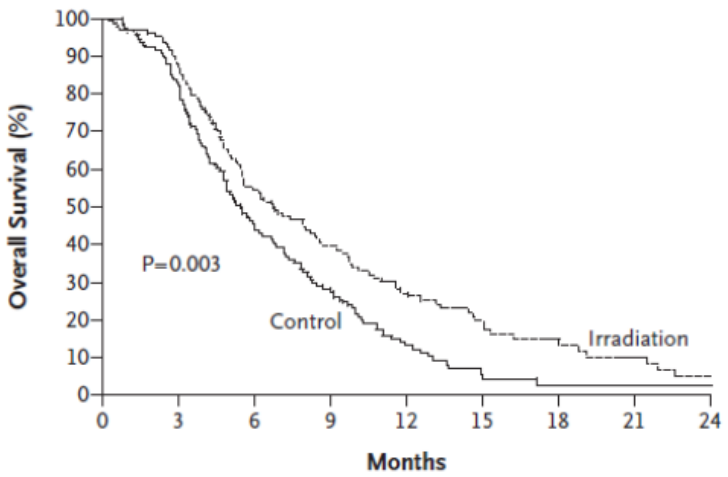
PCI in ES-SCLC



No. at Risk								
Control	143	94	48	29	11	2	1	1
Irradiation	143	119	66	38	24	16	10	5

Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).



No. at Risk								
Control	143	115	58	36	15	3	2	1
Irradiation	143	119	67	44	26	17	11	6

Figure 3. Overall Survival.

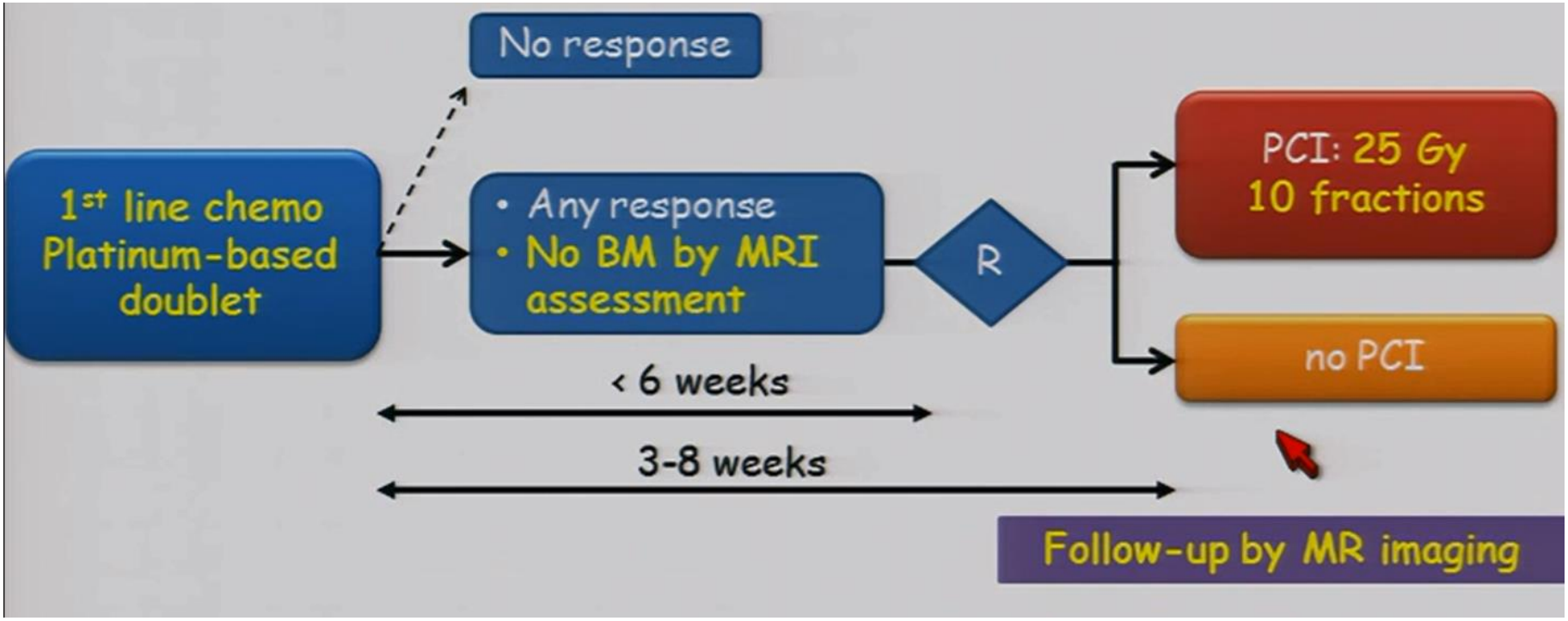
Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman 2007

Concerns re: Slotman PCI – NEJM 2007

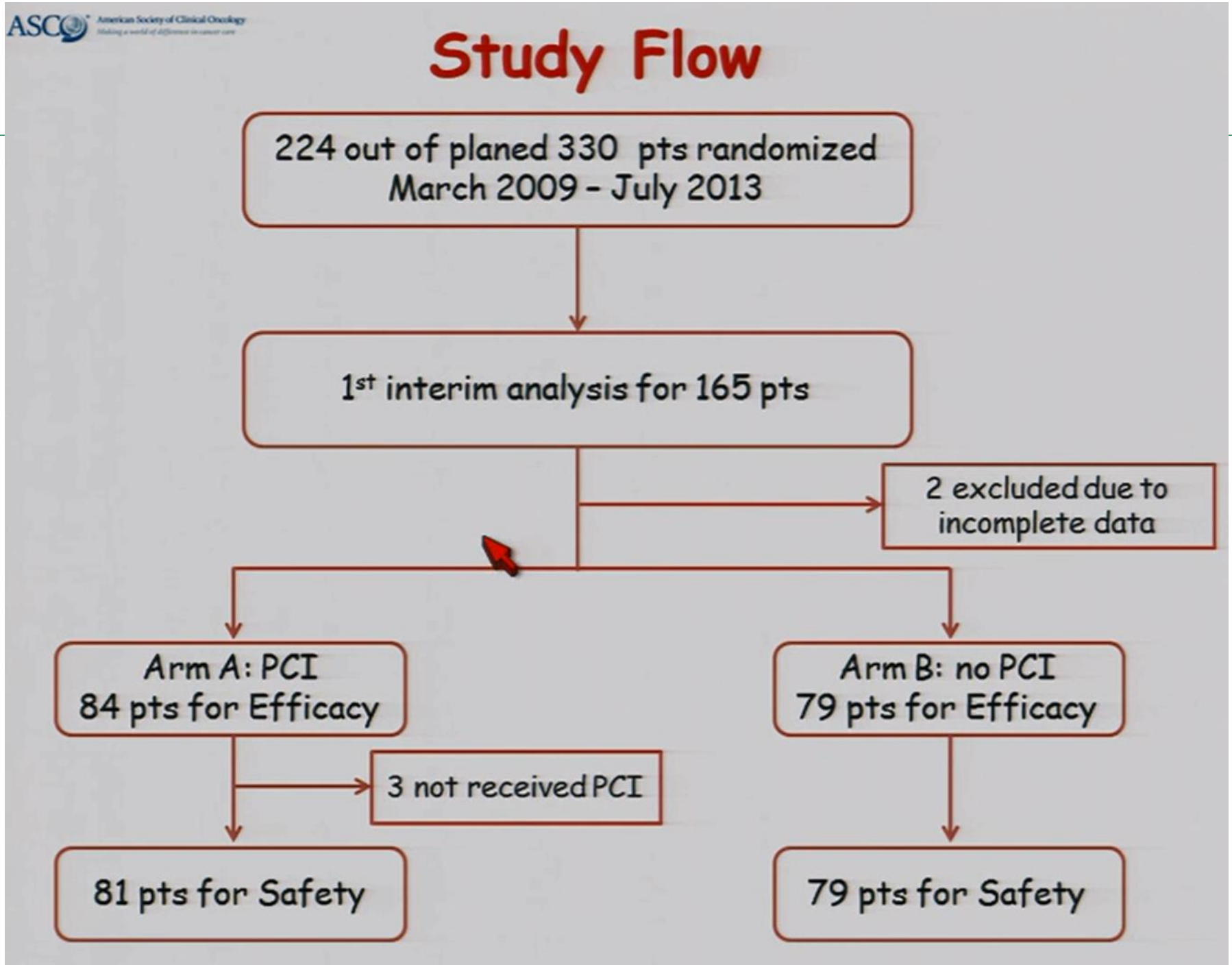
- Lack of imaging assessment to confirm absence of brain mets at study enrollment
- Use of 1st line chemo other than platinum (they let hospitals decide chemo)
- Lack of follow-up imaging assessment for BM (also left this to hospitals)
- Various radiation doses/fractionation in PCI treatment arm

JAPANESE PCI TRIAL presented at ASCO 2014, NOT PUBLISHED



Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint:	Overall Survival
Secondary endpoints:	Time to BM (evaluated every 3 months) Progression-Free Survival (PFS) Safety Mini Mental State Examination (MMSE)


ASCO American Society of Clinical Oncology
Study Flow
224 out of planed 330 pts randomized
March 2009 – July 2013
1st interim analysis for 165 pts
2 excluded due to incomplete data
Arm A: PCI
84 pts for Efficacy
Arm B: no PCI
79 pts for Efficacy
3 not received PCI
81 pts for Safety
79 pts for Safety

1st line Chemotherapy

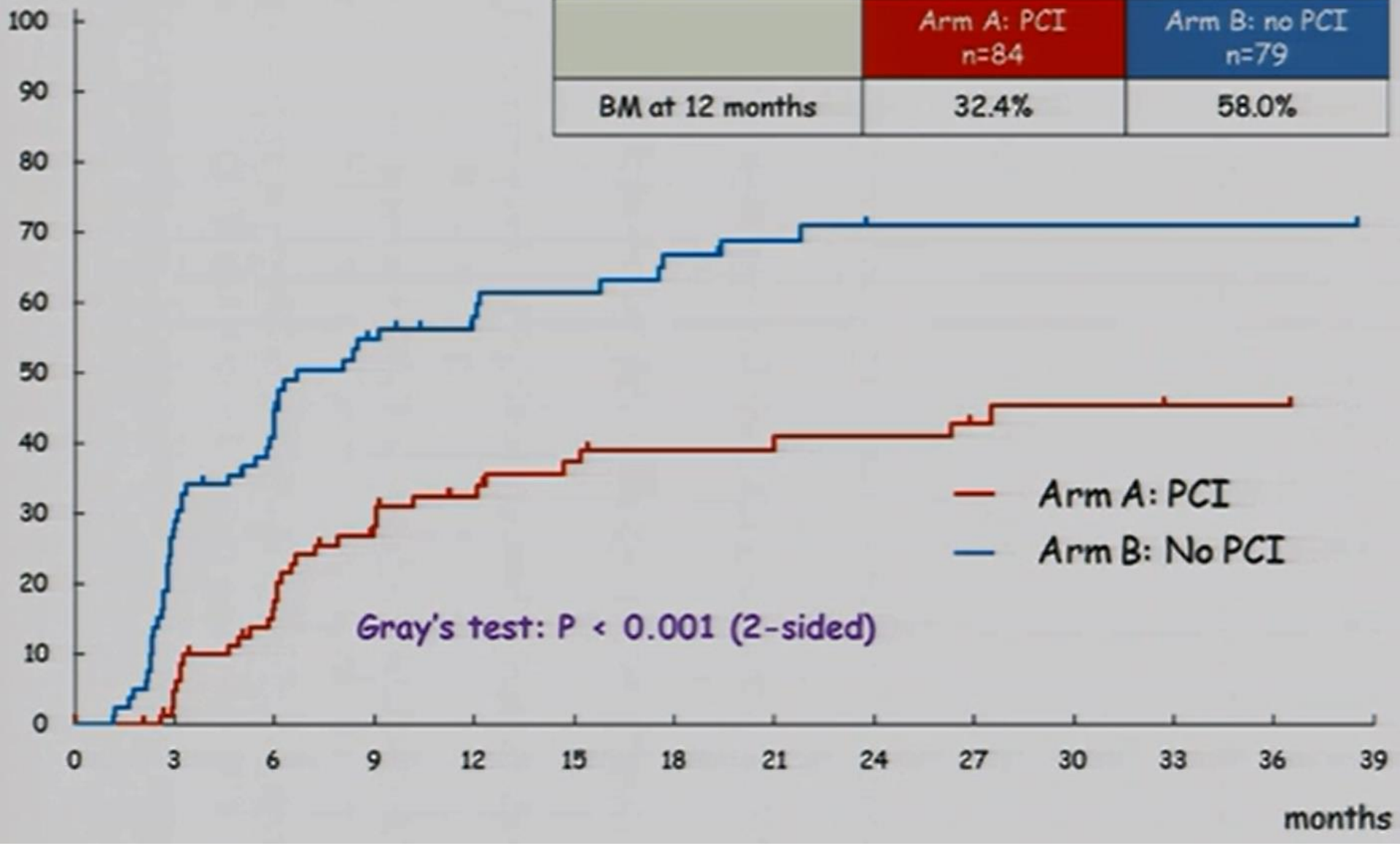
Regimen	Arm A PCI n=84	Arm B no PCI n=79	Total n=163
CDDP+irinotecan	32	26	58
CBDCA+etoposide	28	29	57
CDDP+etoposide	12	15	27

Japanese PCI trial - Results

- In July 2013, a preplanned interim analysis was conducted for the survival data of 163 pts from 41 centers
- The study was terminated because of futility; with a median follow-up of 9.4 months and 111 observed deaths,
  - **median OS was 10.1 months for PCI (n=84**
  - **and 15.1 months for Obs (n=79),**
  - (HR=1.38, 95%CI= 0.95-2.01; stratified log-rank test, P=0.091)
- Bayesian predictive probability of showing superiority of PCI over Obs was 0.01%
- PCI significantly reduced the risk of BM as compared to Obs (32.4% vs 58.0% at 12 months; Gray's test, P<0.001)
- PFS was comparable between the two arms (median, 2.2 vs. 2.4 months; HR=1.12, 95%CI=0.82-1.54)
- No significant difference in AEs greater than Grade 2 was observed between the two arms
- Conclusions: PCI after response to chemotherapy had a negative impact on OS in pts with ED-SCLC. Clinical trial information: 000001755

Time to Brain Metastasis

	Arm A: PCI n=84	Arm B: no PCI n=79
BM at 12 months	32.4%	58.0%



Post-Study Radiotherapy for Appeared BM

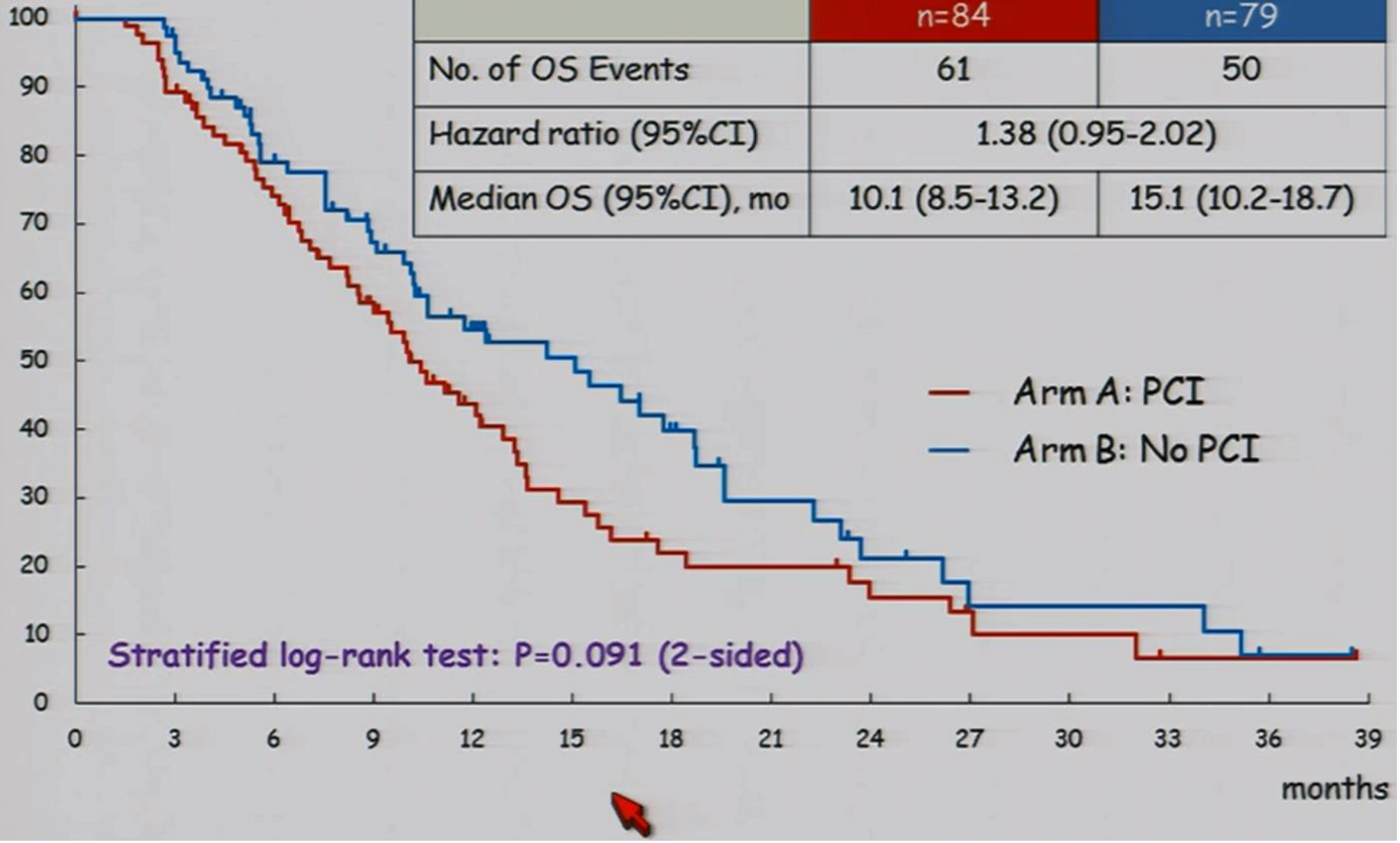
	Arm A: PCI N=84	Arm B: no PCI N=79
appeared new BM	32 pts	51 pts
Whole Brain Irradiation (WBI) Radiation dose, median	1 pt 25 Gy	31 pts 30 Gy
Stereotactic radiosurgery (SRS)	9 pts	6 pts
WBI + SRS	0 pt	4 pts
% radiotherapy for appeared BM	31.3%	80.4%

Post-Study Chemotherapy After PD

	Arm A: PCI	Arm B: no PCI
2nd line chemotherapy	68 (82%)	70 (89%)
Single agent	48	49
Platinum-based doublet	15	18
Cisplatin + irinotecan + etoposide	4	3
Other	1	0
3rd line chemotherapy	36 (43%)	42 (53%)
Single agent	24	29
Platinum-based doublet	9	13
Other	3	0
4th line chemotherapy	13 (16%)	21 (27%)
Single agent	6	13
Platinum-based doublet	7	7

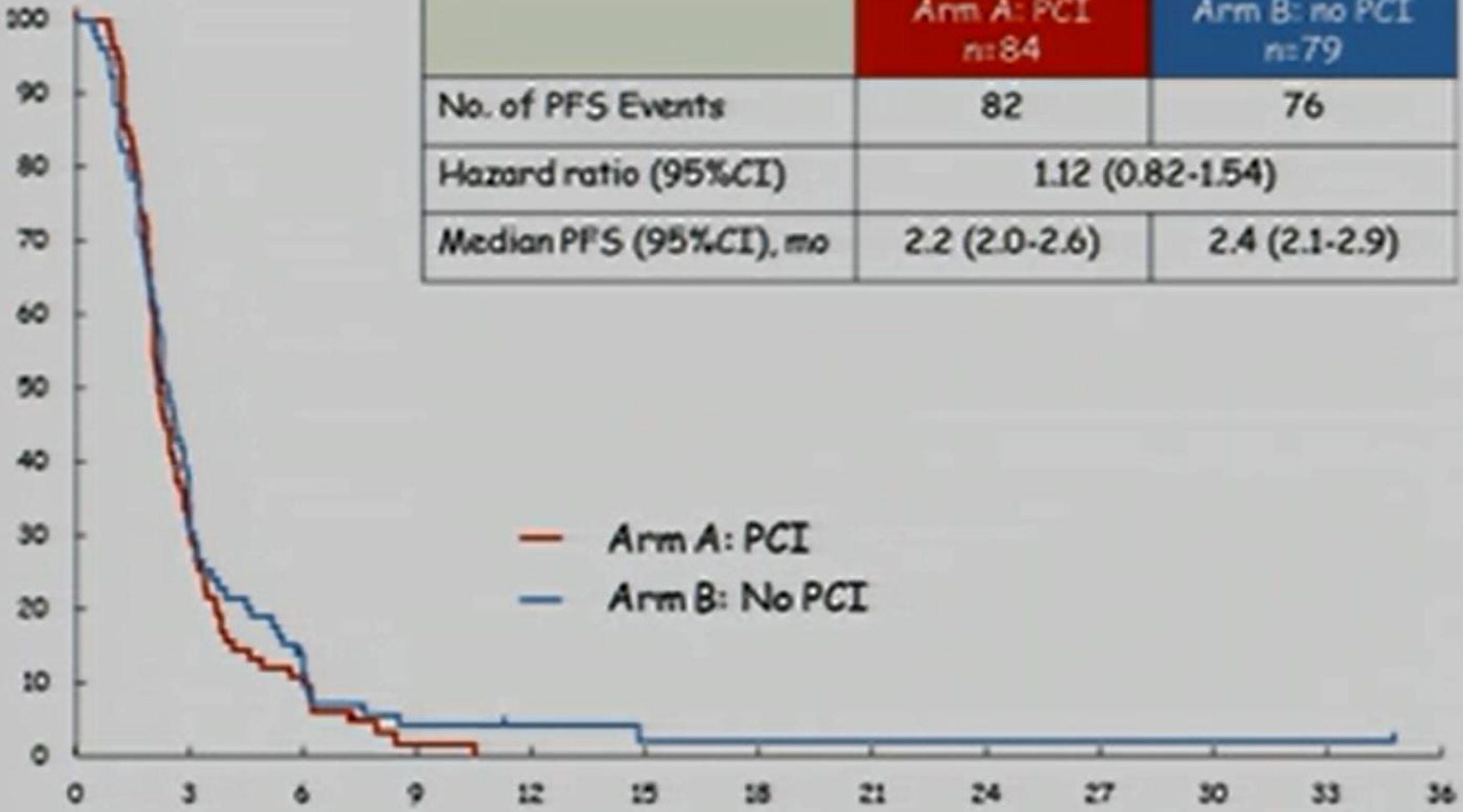
Overall Survival

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of OS Events	61	50
Hazard ratio (95%CI)	1.38 (0.95-2.02)	
Median OS (95%CI), mo	10.1 (8.5-13.2)	15.1 (10.2-18.7)



Progression-Free Survival

	Arm A: PCI n:84	Arm B: no PCI n:79
No. of PFS Events	82	76
Hazard ratio (95%CI)	1.12 (0.82-1.54)	
Median PFS (95%CI), mo	2.2 (2.0-2.6)	2.4 (2.1-2.9)



Concerns re: Slotman PCI – NEJM 2007

- Lack of imaging assessment to confirm absence of brain mets at study enrollment
- Use of 1st line chemo other than platinum (they let hospitals decide chemo)
- Lack of follow-up imaging assessment for BM (also left this to hospitals)
- Various radiation doses/fractionation in PCI treatment arm

Japanese trial vs Slotman PCI

- From March 2009, pts with ED-SCLC who had any response to first-line platinum doublet chemotherapy were randomized to either PCI (25Gy/10 fractions) or observation (Obs) alone
- The patients were required to prove the absence of BM by MRI prior to enrollment
- The primary endpoint was OS and a planned sample size of 330 was determined to detect the hazard ratio (HR) of 0.75 at a significance level of 0.05 and a power of 80%
- Secondary endpoints included time to BM (evaluated every 3 months by imaging), progression-free survival (PFS), and adverse effects (AEs)

Treatment Volumes --

Multimodal Therapy for Limited Small-Cell Lung Cancer: A Randomized Study of Induction Combination Chemotherapy With or Without Thoracic Radiation in Complete Responders; and With Wide-Field Versus Reduced-Field Radiation in Partial Responders: A Southwest Oncology Group Study

By Merrill S. Kies, Joaquin G. Mira, John J. Crowley, T. Timothy Chen, Richard Pazdur, Petre N. Grozea, Saul E. Rivkin, Charles A. Coltman, Jr, John H. Ward, and Robert B. Livingston

JCO 1987

Omitting Elective Nodal Irradiation and Irradiating Postinduction Versus Preinduction Chemotherapy Tumor Extent for Limited-Stage Small Cell Lung Cancer

Interim Analysis of a Prospective Randomized Noninferiority Trial

Xiao Hu, MD[1]; Yong Bao, MD[1]; Li Zhang, MD[2]; Ying Guo, MD[3]; Yuan Yuan Chen, MD[1]; Kai Xin Li, MD[4]; Wei Hua Wang, MD[5]; Yuan Liu, MD[6]; Han He, MD[7]; and Ming Chen, MD[1]

Cancer 2011

- 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

- 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%.

RTOG 0937 – treatment planning/target volumes

- GTV – post chemo imaging
  - Lymph nodes if > 1 cm or PET positive
  - Separate GTVS for each extra-cranial site
- CTV – GTV + 0.5 recommended
  - GTV plus 0 – 1 cm allowed
- PTV – “in most cases CTV + 1.5 cm=PTV”
  - May reduce to 0.5 if breath hold or gating or ITV approach used to eefine GV with 4dCT
- 3DCRT
  - IMRT allowed

Dose Constraints

Organ	Dose Constraint	
Lung	V20 ≤ 30% MLD < 20Gy	
Liver	≥ 700 cc < 18 Gy	
Each Kidney	V18 < 25 %	
Spinal cord/Brachial plexus	Maximum dose 36 Gy	
Heart/Pericardium	Maximum dose 105% prescribed dose AND V45 < 30%	
Esophagus	Maximum dose 105% of prescribed dose	
Small Bowel	Dose (Gy)	3 Gy/Fx Recommended Maximum Volume
	30	150 cc
	35	100 cc
	40	50 cc
	45	1 cc

ES – SCLC Take Home Messages

- Extensive Stage:
  - Double platinum-based chemotherapy
  - In patient, with a response , consider thoracic radiotherapy with PCI (maybe not PCI after Japenese trial published)

- Limited Stage:
  - Chemotherapy (with early RT)
  - Several reasonable radiation fractionations
    - 45/30 BID, 70/35 (CALGB), 60/30, 40/15 (NCIC BR-6)
  - PCI in responders

Prophylactic Cranial Irradiation Overview Collaborative Group

- PMID 10441603 -- "Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group." (Auperin A, N Engl J Med. 1999 Aug 12;341(7):476-84.)
  - Meta-analysis. Individual data of 987 patients from 7 randomized trials. Patients with complete remission. Extensive disease in 12-17%.
  - Outcome: 3-year OS PCI+ 21% vs. PCI- 15% (absolute benefit 5%, SS). 3-year LC 33% vs. 59% (SS). DFS also improved
  - RT dose: larger doses (8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy) led to greater decrease in risk of mets, but no impact on survival
  - Timing: decreased risk of mets with earlier administration after induction chemo
  - Conclusion: PCI improves overall survival, DFS and control of brain metastases
  - Critique: 4/7 trials had <100 patients, ~14% had extensive disease, dose-fractionation not uniform