MANAGEMENT OF SMALL CELL LUNG CANCER

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Lung Cancer

Primary carcinoma of the lung was an uncommon cancer until the 1930s. At that time a dramatic increase in the incidence of lung cancer began that has not yet abated.

Although the overall incidence of lung cancer has dramatically increased over the past 30 years, the relative incidence of squamous cell carcinoma has decreased, and adenocarcinoma has become the dominant cell type—a phenomenon that has been temporally associated with the changes in tobacco blends and the use of filters in cigarettes.

Lung cancer is now the most common cause of cancer mortality in both males and females

WHO pathological classification

A. Squamous Cell Ca 30%

B. Small Cell Ca 20%

C. Adenocarcinama 40%:

- -Acinar
- -Papillary
- -Bronchoalveolar
- -Mucinous

D. Large Cell Ca

E. Mixed

Small cell lung cancer (SCLC)

- It is one of the most aggressive, fast growing tumors
- Without treatment the median survival is 6- 9 weeks

Staging

Limited or Extensive stage

1. Limited- tumour confined to ipsilateral thorax and nodes and able to fit in one radiation field.

2. Extensive- disease which can not fit in one radiation field

Staging

Points of uncertainty in current staging

- contralateral supraclavicular lymphnodes
- pleural effusion
- pericardial effusion
- value of TNM

PROGNOSTIC FACTORS

- Stage: limited vs exensive
- Histologic subclassification: poor if large cells are involved
- Metastasis
- Tumors with c-myc: more aggressive course
- N-myc: poor response to chemo
- p-53 Ab no correlation ? survival ! (cf NSCLC)
- Serum NSE: inversely related to survival algorithm:
- PI = zNSE + z(stage) + 2zPS, where PI represents the prognostic index, and z represents the regression coefficient. This algorithm segregated the patients into four groups with clearly different prognoses.
- **Cyfra 21-1 level over 3.6 ng/mL or a tissue polypeptidespecific antigen level over 140 U/Lsignificantly indicated a poor** survival rate.
- **Serum chromogranin level: poor prognosis**

Principals of Management Surgery

Surgery in Limited stage SCLC

- Fewer than 3% of patients with small-cell lung cancer (SCLC) present with super-limited, resectable disease
- If possible surgery should be offered.
- Adjuvant chemotherapy still to be administered with PCI in CR on post chemo assessment
- May have possible role in isolated thoracic relapse

Principals of Management Chemotherapy

- Mainstay of treatment, because of the chemo-responsiveness of the SCLC and frequent dissemination at the time of diagnosis

Principals of Management Chemotherapy

Response rates:

- 75-90% for limited stage
- 75% for extensive stage
- 50% of limited stage have complete response (CR)
- 25% CR for the extensive stage

Cytotoxic agents for SCLC

- Alkylating agents: **Cyclophosphamide 1500 mg/m2 IV q 3wk**
  Ifosfamide 5000 mg/m2 IV day 1 q 3wk
  Hexamethylmelamine
  Lomustine
- Vinca alkaloids: **Vincristine 2 mg IV q 3 wk**
  Vindesine
- Epipodophyllotoxin: **Etoposide 80 mg/m2 IV d1-3 q 3wk**
  Teniposide
- Platinum analogues: **Cisplatin 80 mg/m2 IV q 3wk, day 1**
  Carboplatin 300 mg/m2 day 1 q 3 wk
- Miscellaneous: **Doxorubicin 40 mg/m2 IV q 3 wk**
  Methotrexate
- **3rd generation drugs: ironotecan, topotecan, paclitaxel**

Platinum-based chemotherapy:

- TTP – 4-6 mths.
- Median Survival – 9-11 mths.
- 2 yr Survival - 5%

Platinum-based chemotherapy:

Carboplatin can be Substituted for Cisplatin*

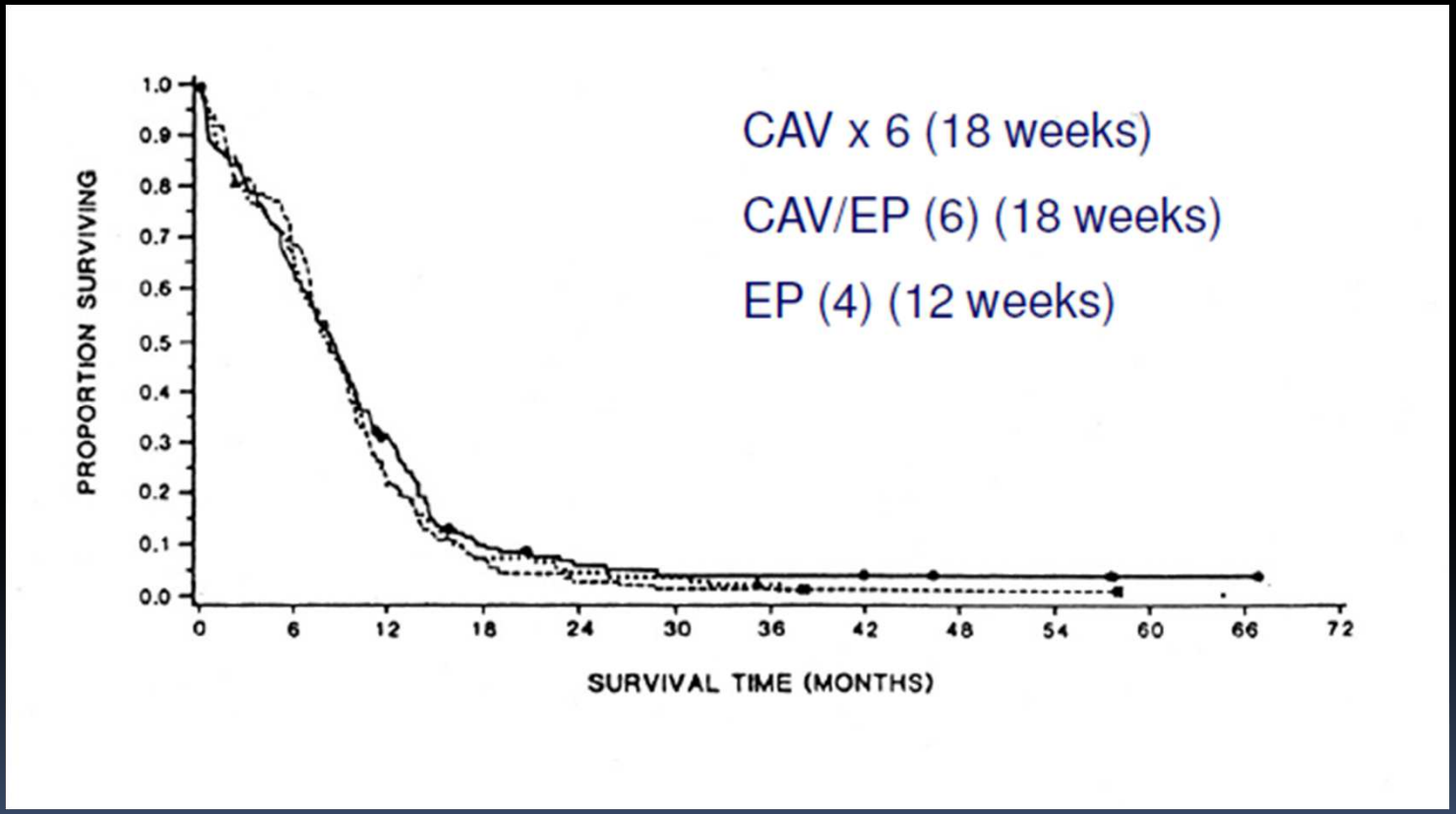
- 220 elderly or poor risk patients
- randomized to etoposide with either:
- – Carbo AUC 5 d1
- – Cisplatin 25 mg/m2 iv d1-3

Results

- Similar toxicity profiles and efficacy
- – (MST ~10 mos; 1 yr 35-40%)

*Okamoto et al, Abstract 7010, ASCO '05

EP BASED CHEMOTHERAPY- STANDARD OF CARE



Roth B, et al. J Clin Oncol 1992;10:282-291

Better Prognosis Platinum Regimens

Meta-analysis Cisplatin –

4.4% survival benefit at 1 year

Pujol; et al.Br J Cancer 2000

CbE equivalent to PE

Skarlos et al Ann Oncol 1994

Principals of Management Chemotherapy

Cisplatin-based:

Cisplatin 80 mg/m day 1 and etoposide 80 mg/m days 1, 2, 3

Cisplatin 25 mg/m days 1, 2, 3 and etoposide 100 mg/m days 1, 2, 3

Doxorubicin-based

Cyclophosphamide 1000 mg/m day 1 and doxorubicin 45 mg/m day 1

and vincristine 1.4 mg/m day 1

Ifosfamide-based

Ifosfamide 1200 mg/m days 1, 2, 3, 4 and etoposide 75 mg/m days 1, 2,3, 4 and cisplatin 20 mg/m days 1, 2, 3, 4

Mesna given along with ifosfamide.

Strategies to improve survival

- More drug combinations
- Alternate Chemotherapy
- Better drug combinations
- Addition of biologicals

More Drug Combinations

Randomised Phase III Trial

Etoposide and Cisplatin with or without Paclitaxel in ED- SCLC

N = 587, no prior treatment, P.S 0-1

Cisplatin 80mg/m2 D1-D3
Etoposide 80 mg/m2 D1-D3
6 cycles q3wkly

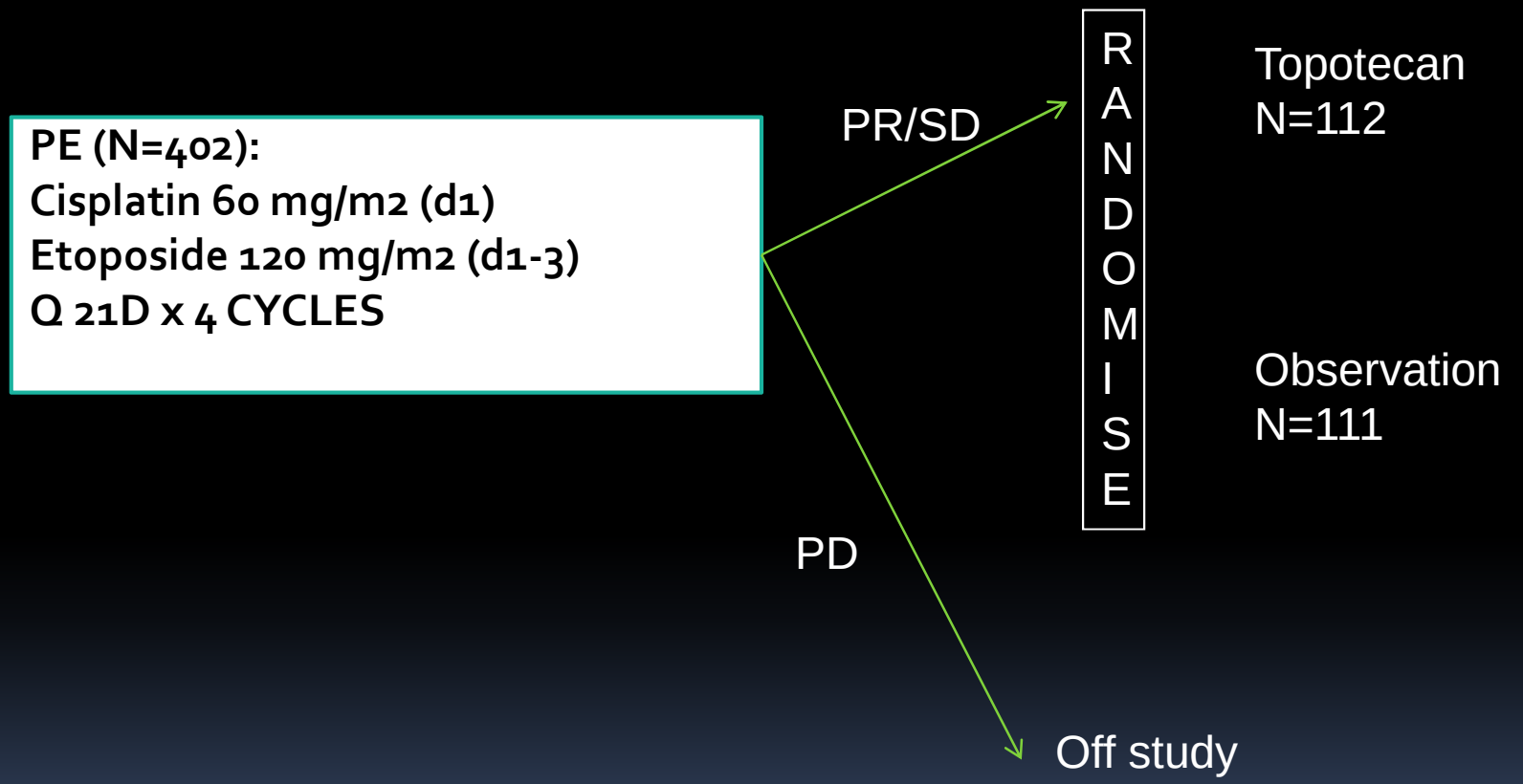
Cisplatin 80mg/m2 D1-D3
Etoposide 80 mg/m2 D1-D3
Paclitaxel 175mg/m2 D1

G-CSF d4-d18
6 cycles q3wkly

MST 10.6 Vs 9.9 Mths.
More treatment related deaths in Paclitaxel arm

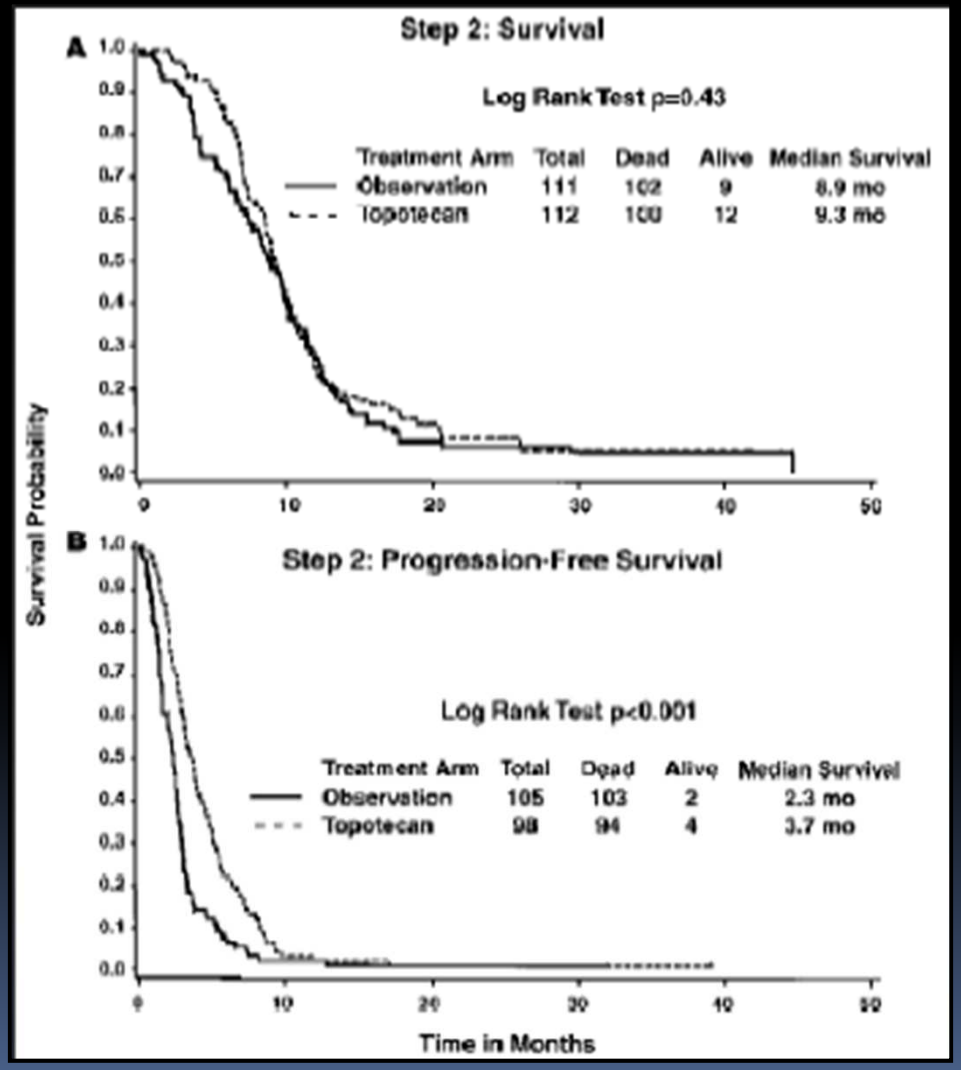
Neill at al. J Clin Oncol 2005

Consolidation with Topotecan after EP in ED SCLC



Schiller J, et al. J Clin Oncol 2001;19:2114-2122

Topotecan after EP



Schiller J, et al. J Clin Oncol 2001;19:2114-2122

Better Combinations

- Irinotecan plus cisplatin
- Irinotecan plus carboplatin
- Topotecan plus carboplatin
- Pemetrexed plus carboplatin

Cisplatin + Irinotecan Randomized Trials in Patients with ED-SCLC

JCOG 9511
Noda et al NEJM 346:85,2002

RANDOMISE

P -60 mg/m2 iv d 1
I -60 mg/m2 iv d 1, 8, 15
q4 wks X 6

N=154

P -80 mg/m2 iv d 1
E-100 mg/m2 iv d1,2,3
q3 wks X 6

North American /Australian
Hanna et al. JCO 24:2038 2006,

RANDOMISE

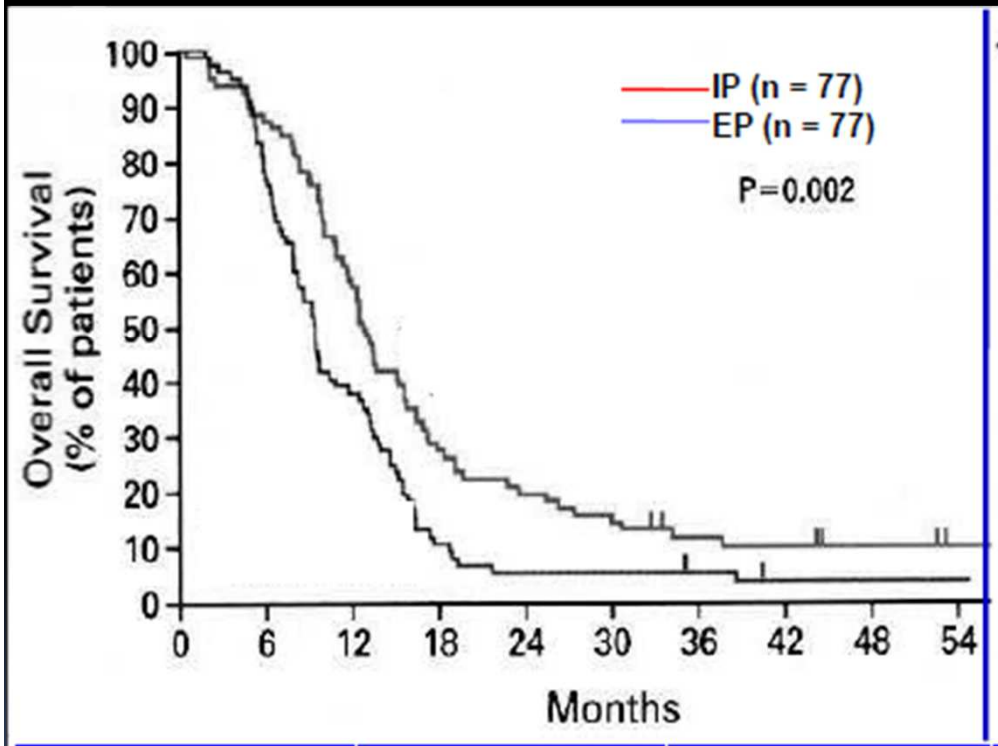
P: 30 mg/m2, d 1 & 8, q3wk +
I : 65 mg/m2, d 1 & 8, q3wk
Q 4 cycles

N = 331

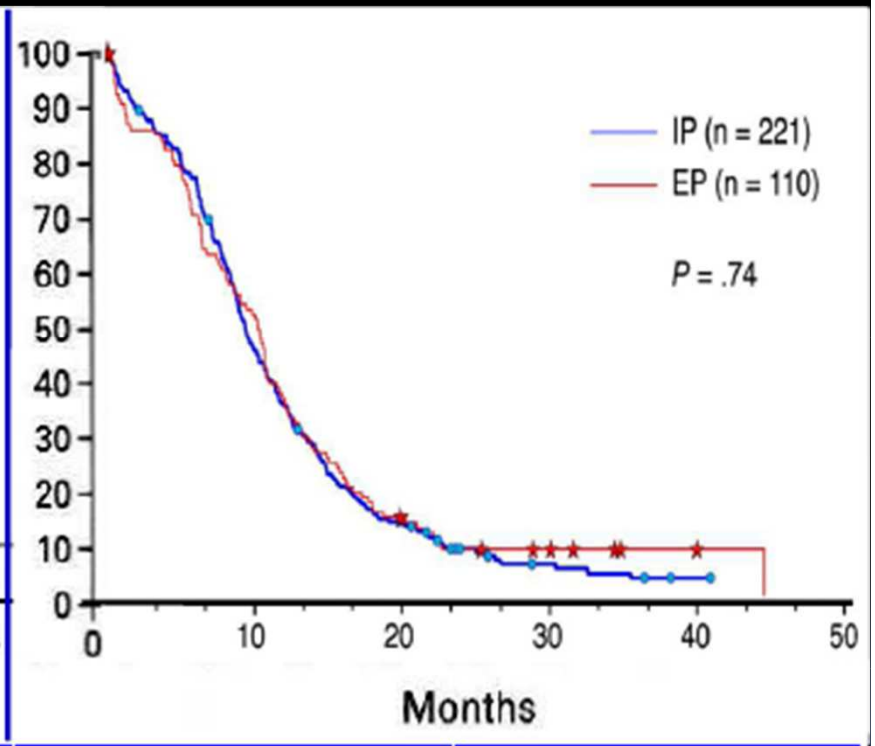
P -60 mg/m2 iv d 1
E-120 mg/m2 iv d1,2,3
q3 wks X 4

Cisplatin + Irinotecan Randomized Trials in Patients with ED-SCLC

JCOG 9511

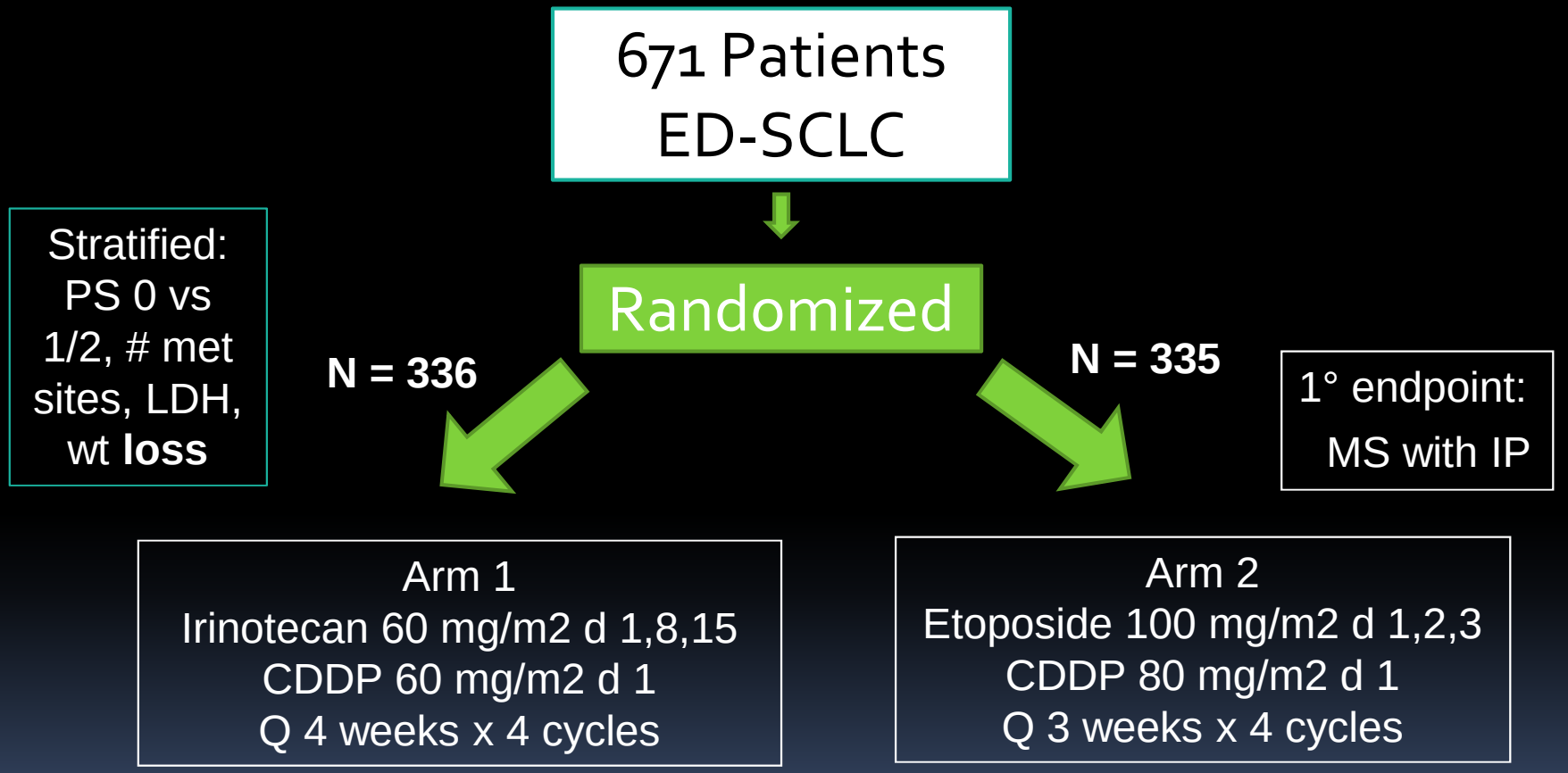


N AMER/AUS

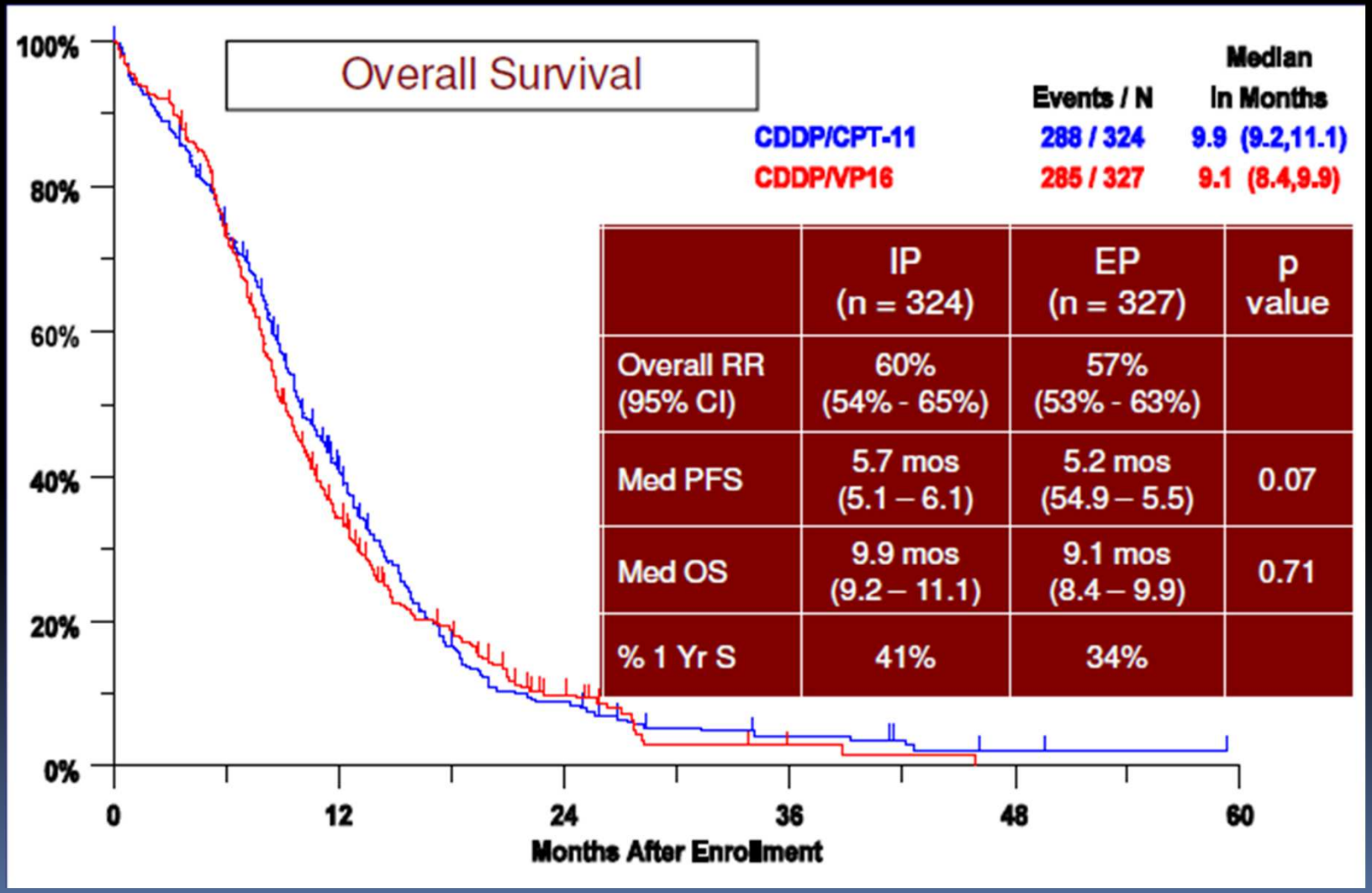


Survival	Irino + P	EP	Irino + P	EP
Median (95% c.i.)	12.8 m	9.4 m	9.3 m	10.2 m
% 1 yr	58.4%	37.7%	35%	35.2%
% 2 yr	19.5%	5.2%	8.0%	7.9%

S0124: IP vs EP
Natale et al, ASCO 2008, Abst 7512



S0124: Survival
Natale et al, ASCO 2008,



	IP (n = 324)	EP (n = 327)	p value
Overall RR (95% CI)	60% (54% - 65%)	57% (53% - 63%)	
Med PFS	5.7 mos (5.1 – 6.1)	5.2 mos (54.9 – 5.5)	0.07
Med OS	9.9 mos (9.2 – 11.1)	9.1 mos (8.4 – 9.9)	0.71
% 1 Yr S	41%	34%	

A randomised phase III trial
IV Topotecan/cisplatin versus cisplatin/etoposide ED-SCLC

- Chemo-naïve with confirmed
- ED-SCLC
- Male or female
- Age 18-75 yrs
- ECOG PS
- (0/1 vs 2)
- LDH

RANDOMIZE

Cisplatin/etoposide (n=346)
- Cisplatin: 75 mg/m2 IV d5
- Etoposide: 100 mg/m2/day IV d1-3

Topotecan/cisplatin (n=357)
- Topotecan: 1 mg/m2/day IV d1-5
- Cisplatin: 75 mg/m2 IV d1

Topotecan/[illegible]e (TE) (n=92)
- Topotecan: 1[illegible]n2/day IV d1-5
- Etoposide: [illegible]–1[illegible]mg/m2 IV d3-5

Cycles (maximum of 6)
repeated q21d

Heigener; ASCO 2008

Survival and Time to Progression (ITT)

Total number of deaths n (%)	**282 (84.4%)**	**283 (81.8%)**	
	Cis + Eto (PE) (n=334)	**Topo + Cis (TP) (n=346)**	**P-value**
Median survival (months) (95% CI)	**9.4 (8.1 – 10.8)**	**10.3 (9.3 – 11.3)**	**(unadjusted) 0.30**
1-year survival (95% CI)	**36.1% (30.9 – 41.4)**	**39.7% (34.5 – 44.9)**	**0.27**
Median TTP (months) (95% CI)	**6.0 (5.6 – 6.7)**	**7.0 (6.5 – 7.5)**	**0.004**

Heigener; ASCO 2008

Phase III Study
Pemetrexed/Carboplatin Versus etoposide/ Carboplatin ED-SCLC

Eligibility
- **ES-SCLC**
- **PS 0-2**
- **No prior chemo**

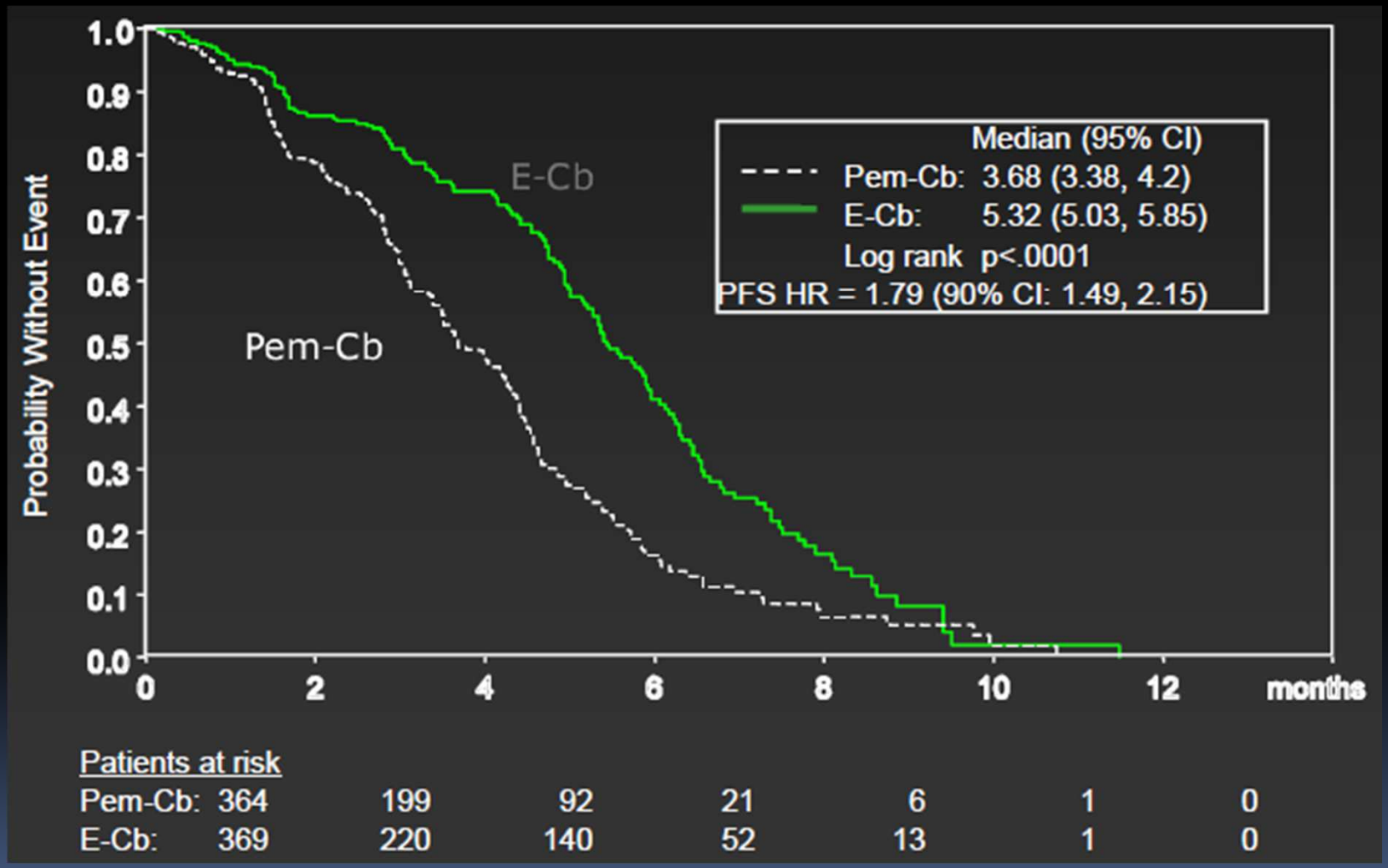
RANDOMIZE

Pem -500 mg/m2,d1
Cb – AUC 5 d1
Q 21 d X 6cycles
Prophylactic Folic acid,B12,dexamethasone

E 100 mg/m2 , d1,2,3
Cb – AUC 5 d1
Q 21 d X 6cycles

Socinski et al. ,ASCO 2008
Interim results of the Gales/ JMHO TRIAL

GALES / JMHO: Interim PFS Analysis



Socinski et al. ,ASCO 2008
Interim results of the Gales/ JMHO TRIAL

Newer agents - Amrubicin

Promising for 2nd line: Amrubicin

- Synthetic anthracycline
- Undergoing trials in 1st line
- There is concern about increased toxicity and especially in combination

Newer agents - Amrubicin

Phase II Studies of Amrubicin for the Treatment of Extensive-stage Small Cell Lung Cancer

Author	Type of Study	Drugs (doses)	Patient Population	No. of Patients (No. Assessable)	Overall Response§	Median Progression-free Survival	Median Survival
First-line Treatment							
Yana T et al[6]	Single arm	Amrubicin† (45 mg/m²/d, days 1 to 3)		35 (33)	76%	Not reported	11.7 months
Ohe Y et al[52]	Single arm	Amrubicin (40 to 45 mg/m²/d, days 1 to 3) AND cisplatin (60 mg/m² day 1)		44 (44)	89%	Not reported	13.6 months
Second-line Treatment							
Onoda S et al[7]	Single arm	Amrubicin (40 mg/m²/d, days 1 to 3)	Total	60	52%		11.2 months
			Sensitive	44	52%	4.2 months	11.6 months
			Refractory	16	50%	2.6 months	10.3 months
Ettinger DS et al[9]	Single arm	Amrubicin (40 mg/m²/d, days 1 to 3)	Refractory	75 (66)	17%	3.2 months	—
Inoue A et al[8]	Randomized	Amrubicin (40 mg/m²/d, days 1 to 3) OR topotecan (1.0 mg/m²/d, days 1 to 5)	Total	60 (59)			
			Sensitive				
			Amrubicin	17	53%	3.9 months	9.9 months
			Topotecan	19	21%	3.0 months	11.7 months
			Refractory				
			Amrubicin	12	17%	2.6 months	5.3 months
			Topotecan	11	0%	1.5 months	5.4 months
Jotte RM et al[10]	Randomized	Amrubicin (40 mg/m²/d, days 1 to 3) OR topotecan (1.5 mg/m²/d, days 1 to 5)	Sensitive				
			Amrubicin	50	35%	4.6 months	—
			Topotecan	26	4.3%	3.5 months	—

ASCO 2009

Principals of Management Radiotherapy

60% of the relapses after chemotherapy are in the thorax. TI reduces the risk of relapse by 50%

- Has role in SVCS and spinal cord compression

-High risk of brain metastases in SCLC(20% have brain involvement at diagnosis, 80% have brain involvement at death)- prophylactic cranial RT increases 3 year survival by 5% and is usually given if the patient is in CR post chemotherapy

Palliative RT – short course of irradiation to either the primary tumor or site of metastases can provide useful symptom control.

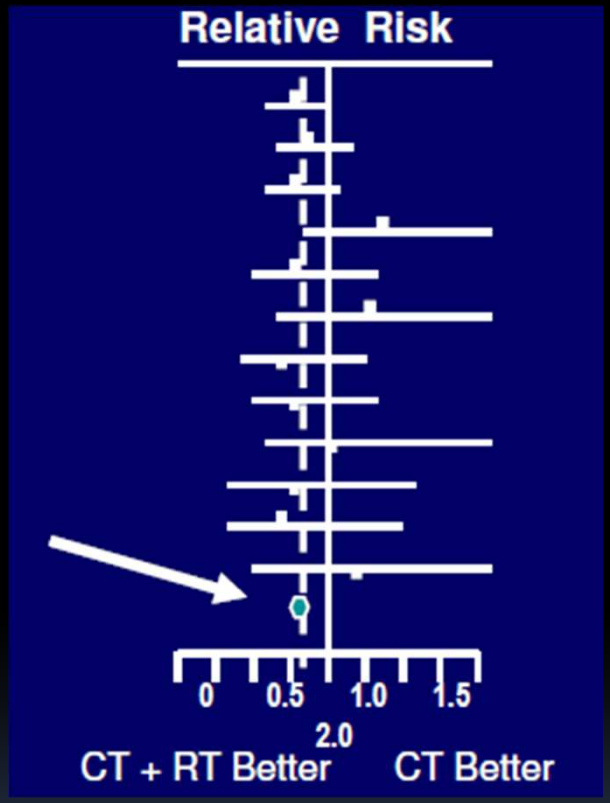
Despite the excellent response rates, cure is very unusual

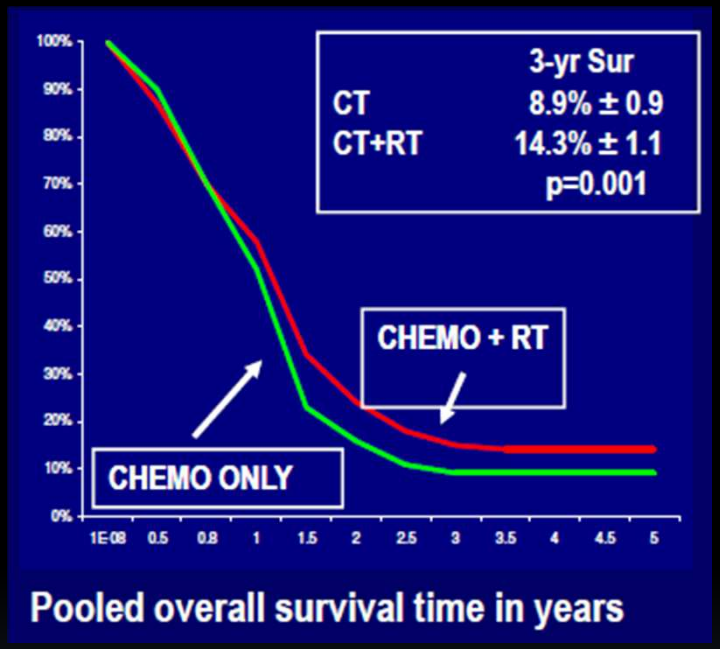
Median survival for Limited stage is 14 months and for extensive stage 7 months

SCLC: More than 1 disease

- Extremely chemotherapy sensitive
- Extremely chemotherapy resistant
- What are the biological differences?
- Many drugs are effective on chemotherapy sensitive cells
- No drugs are highly effective against the resistant clones
- Improved outcomes will come ONLY when we defeat the highly resistant clones

Thoracic Irradiation for LS SCLC





2 meta-analysis of thoracic XRT in LS SCLC:

1. Pignon et al. – NEJM ’92 : 3-year survival and prognostic factors
2. Warde and Payne – JCO ’92: 2-year survival, local control and toxicity

Timing of Thoracic XRT in LD SCLC

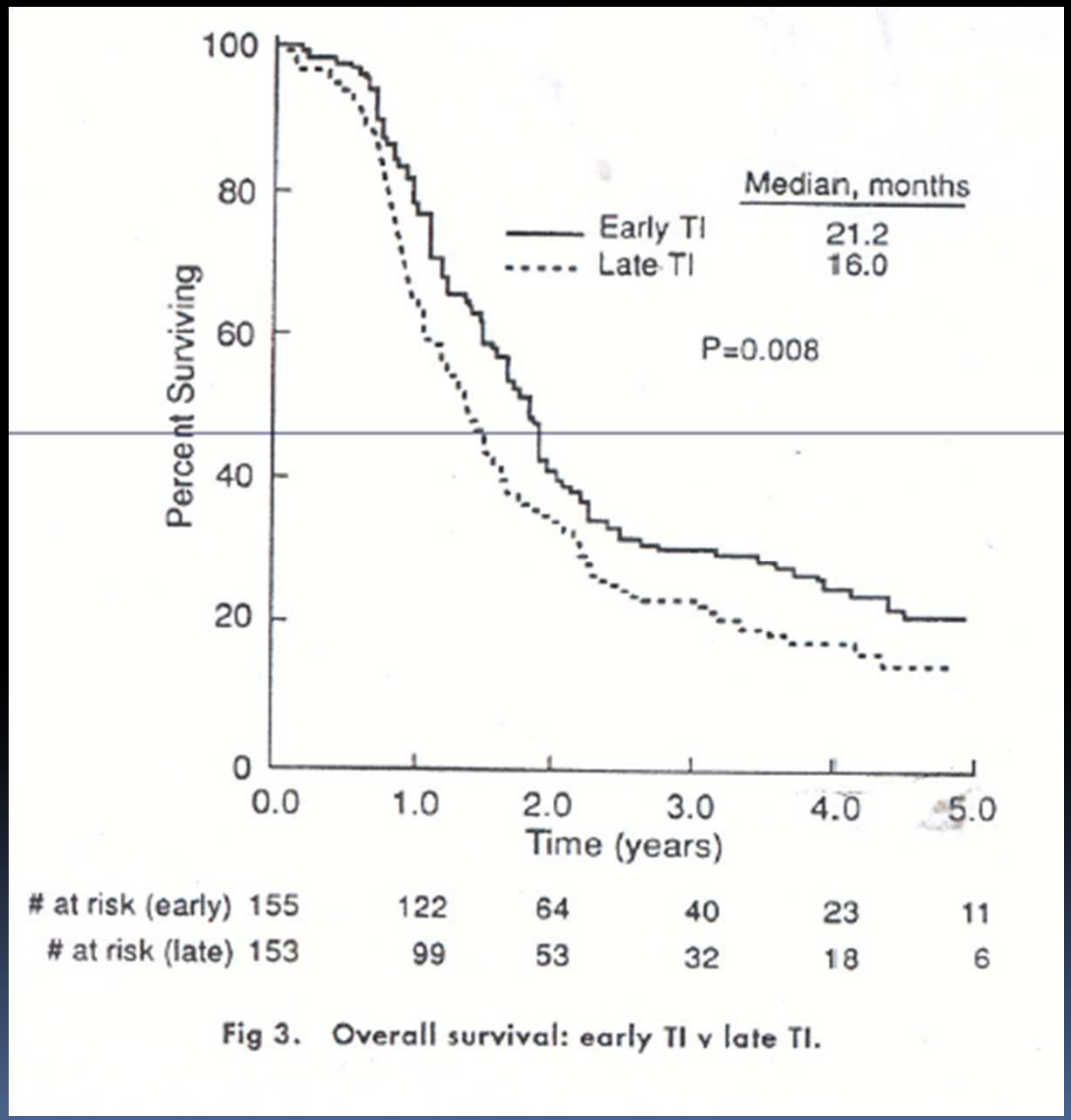


Fig 3. Overall survival: early TI v late TI.

Murray et al, JCO 1993;11:336-44

Multivariate Analysis for Survival for Patients with LD SCLC

Table 5. Multivariate Analysis for Survival

Variable	Hazard Ratio	95% CI	*P*
Sex			.0066
Male	1		
Female	0.72	0.57 to 0.91	
Chest radiotherapy			.0051
Sequential	1		
Concomittant	0.72	0.57 to 0.91	
PCI			< .0001
No	1		
Yes	0.52	0.41 to 0.65	
Lactate dehydrogenase			.0002
Grade 0	1		
Grade > 0	1.71	1.30 to 2.26	
Platelets			.0019
< 221 10^9/L	1		
≥ 221 10^9/L	1.44	1.14 to 1.81	

Abbreviation: PCI, prophylactic cranial irradiation.

Giaccone et al, JCO 2005;23:6854-64

Timing of Thoracic XRT in LD SCLC

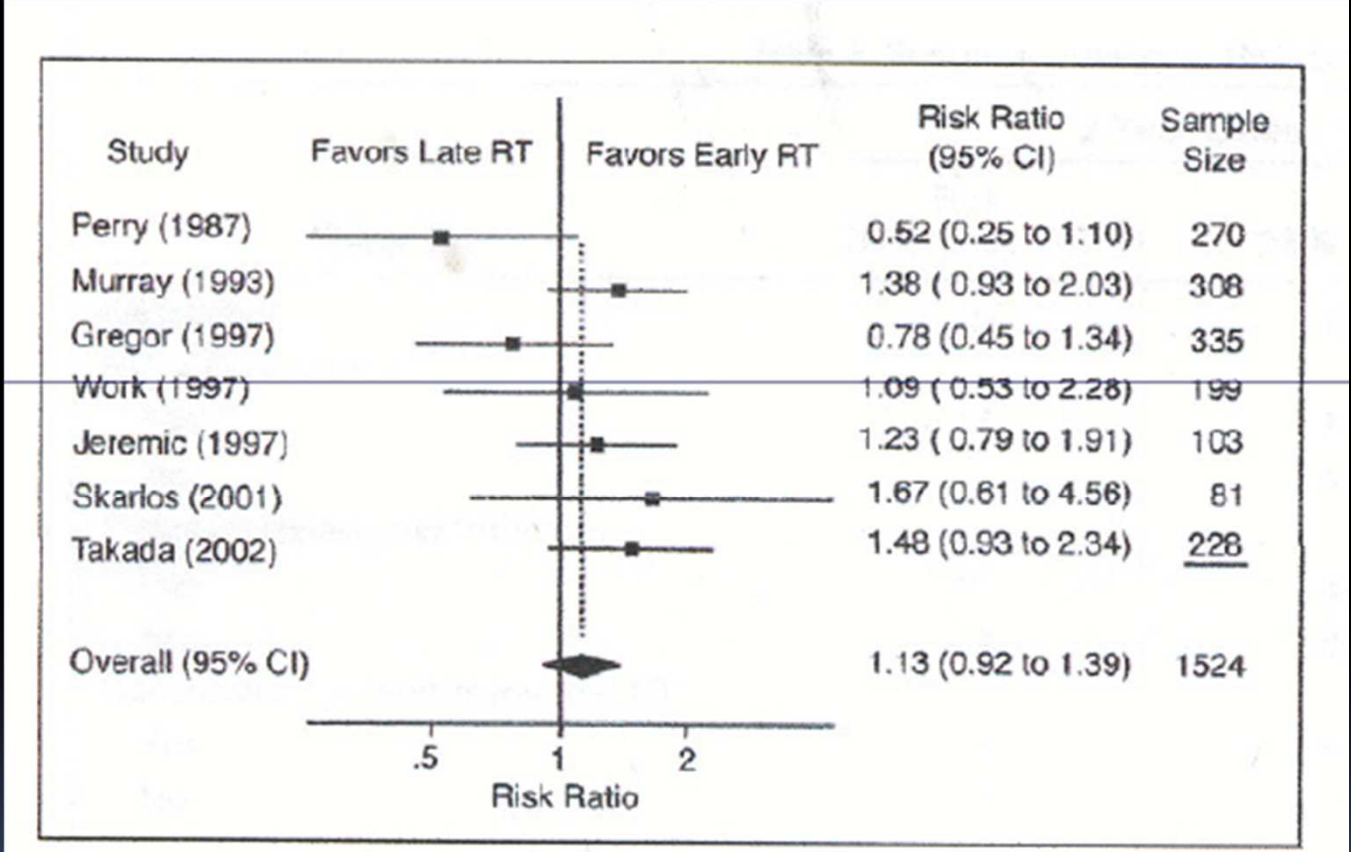


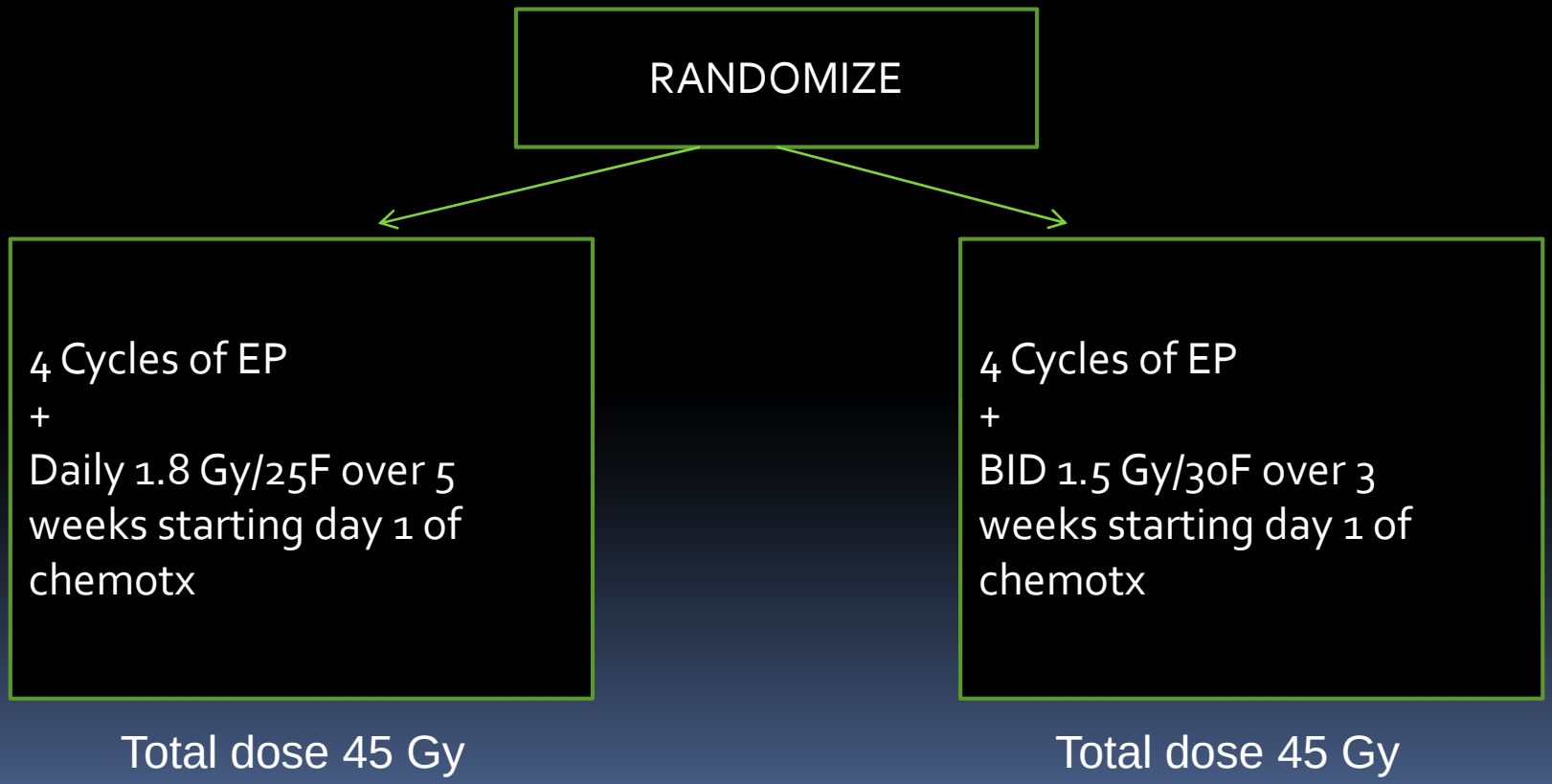
Fig 2. Three-year overall survival risk ratio forest plot for early v late thoracic radiation therapy (RT).

Fried et al, JCO 2004;22:4837-45

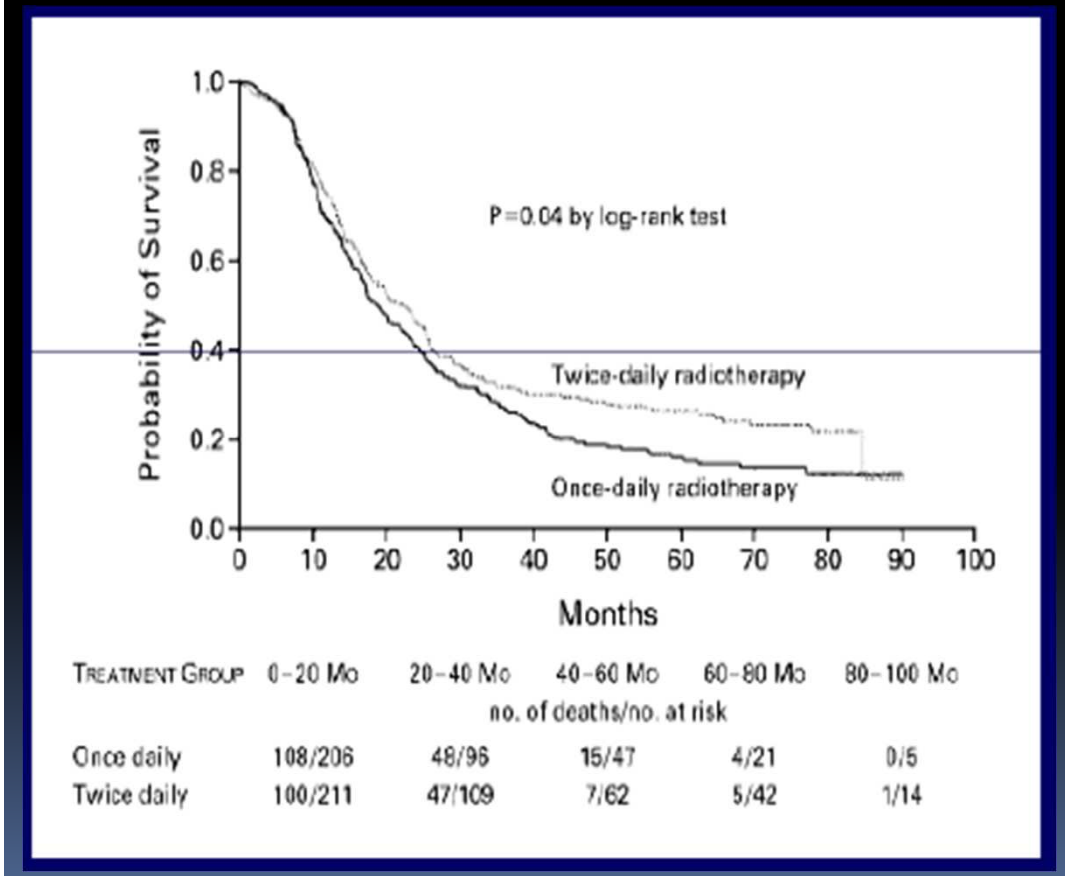
Turrisi et al: BID vs QD XRT in LS SCLC with Concurrent EP

(NEJM 1999; 340(4):265-271)

N = 417 patients with LS SCLC



Hyperfractionated Radiotherapy Improves Survival



	2 year OS (%)	5 year OS (%)
QD XRT	41%	16%
BID XRT	47%	26%

Reduction in local failure:

36% vs 52%

Increased toxicity:

Grade 3 esophagitis

27% vs 11%

But no increase in mortality

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

QD vs BID XRT in LD SCLC

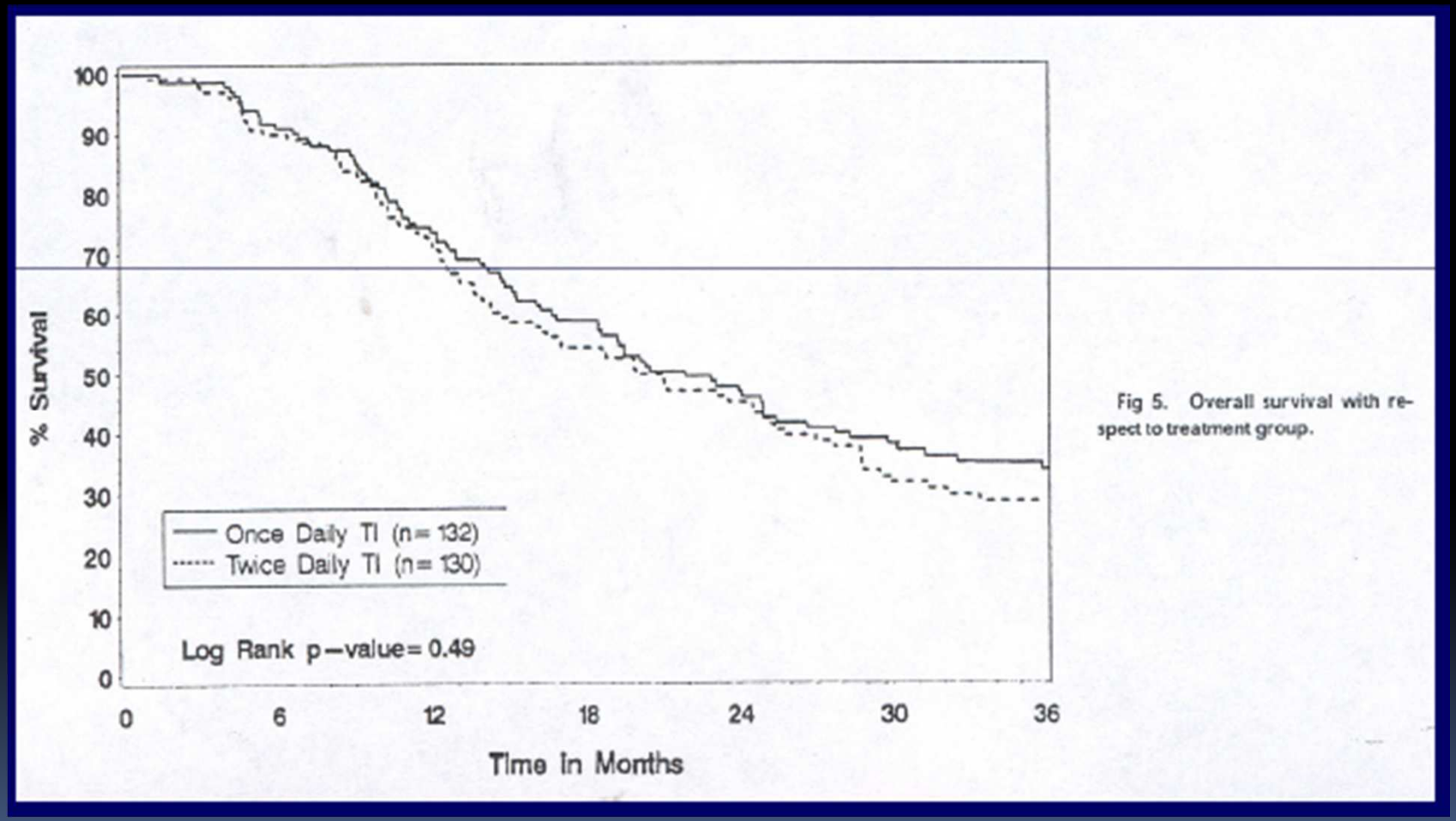


Fig 5. Overall survival with respect to treatment group.

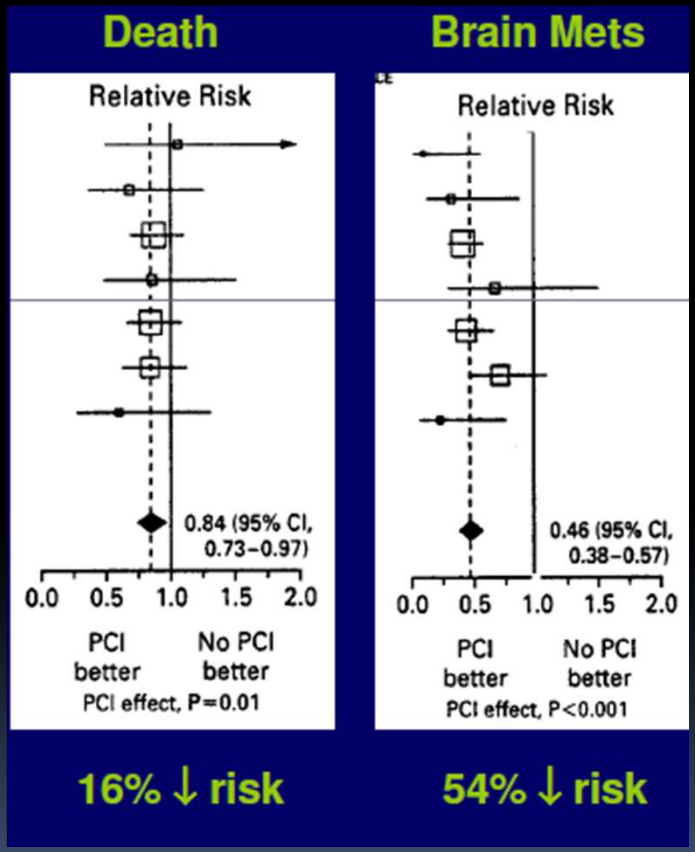
Bonner et al, JCO 1999;17:2681-91

Role of PCI

- It was frequently practiced in complete response (CR) and occasionally in good partial response (PR) patients, it was not unequivocally proved to produce superior survival
- Fear of toxicity: decline in neurocognitive function
- The issue was taken by meta-analysis by Perez et al(1981):
  - ↓ relative risk of death
  - absolute ↑se in 3yr survival by 5.4%
  - absolute ↑se in ds free survival by 8.8%
  - ↓cumulative risk for CNS metastasis
  - issue of toxicity was clearly discarded
- The current approach is to administer PCI at the time of achieving CR, but its timing becomes important to avoid administration concurrently with CHT, and thus more CNS toxicity

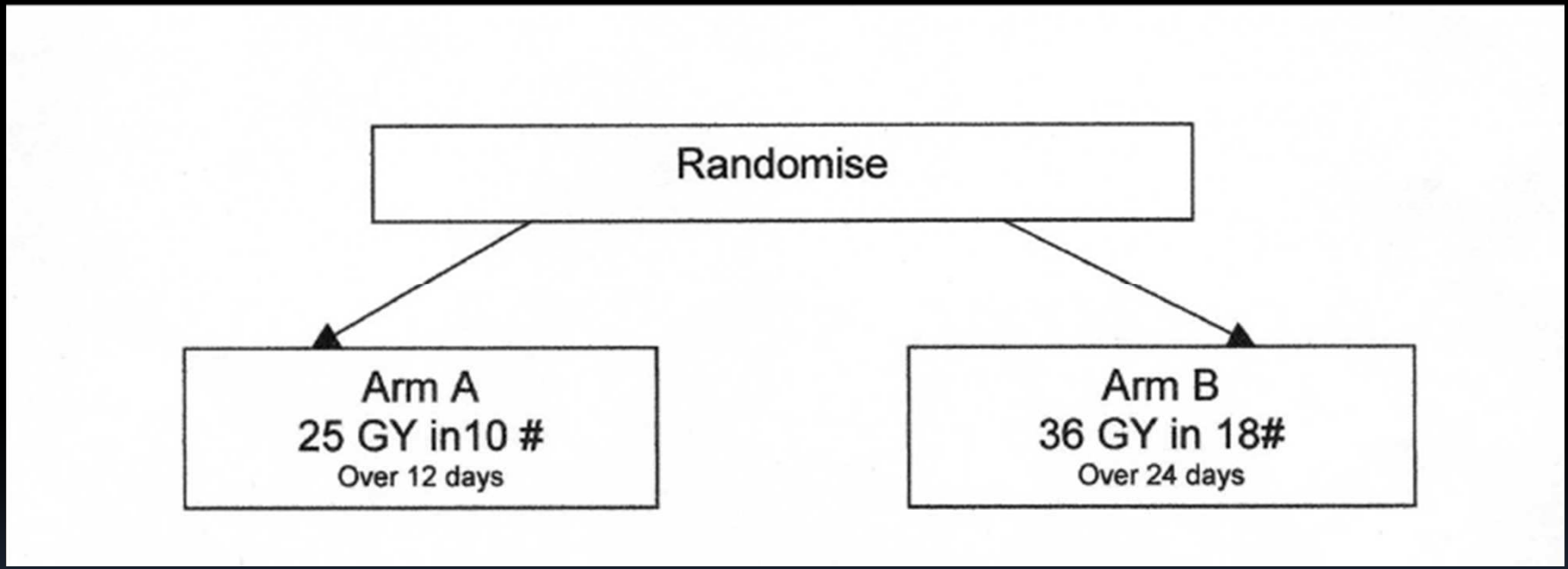
PCI in Small cell lung cancer
Local treatment in a systemic disease

- Meta Analysis:
  - 7 trials, 987 pts 1977 - 1991:
  - Only one trial (32 pts) used Plat Etop
- 3 yr intracranial relapse 25% ↑se in dfs and OS by 5%



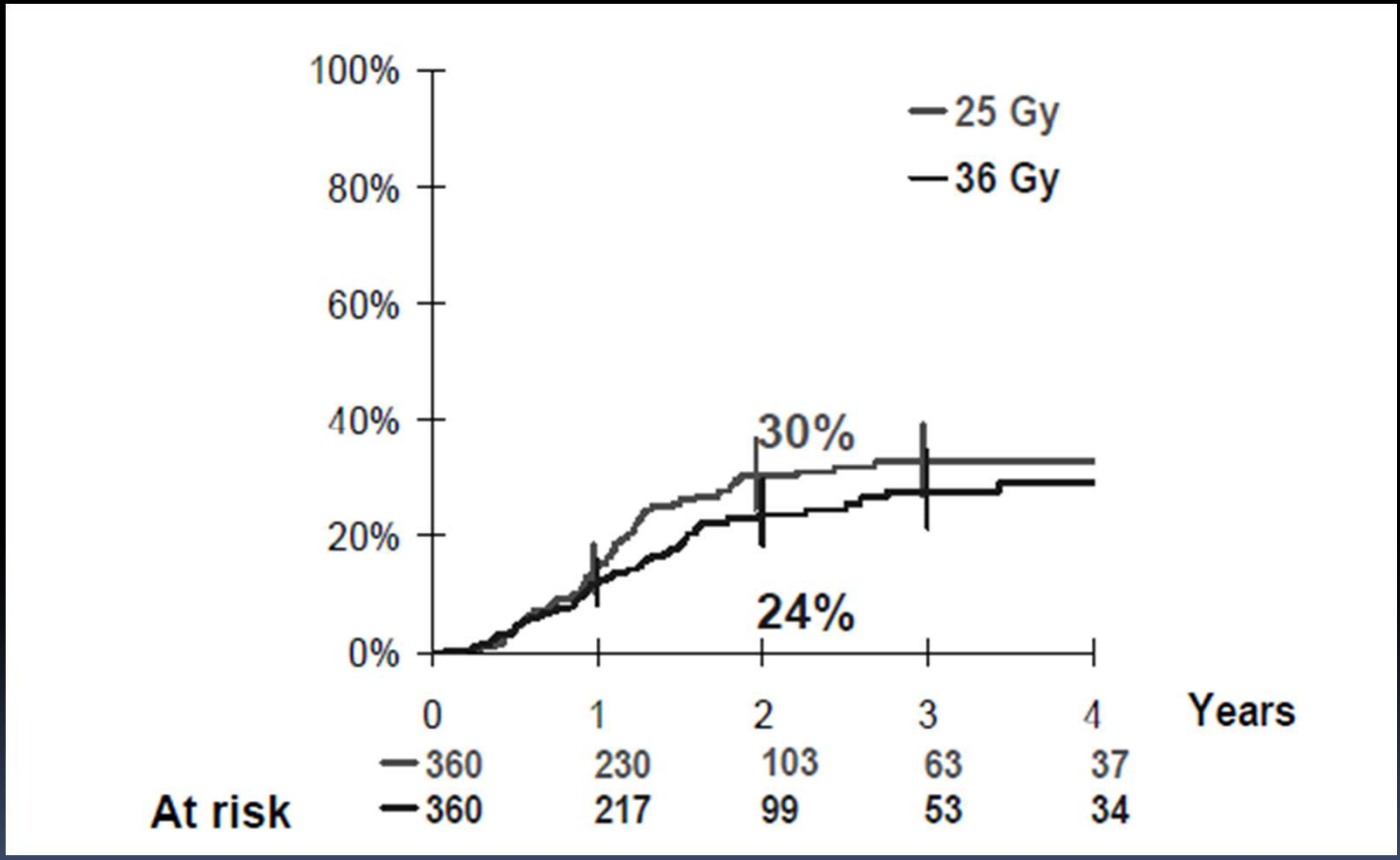
Auperin et al, N Engl Med. 1999; 341(7):476

PCI OI-EULINT1
High VS. Standard Dose PCI
In LS SCLC Complete Responders



Primary endpoint : incidence of brain metastases at 2 years
Secondary endpoints: survival, QoL

Brain metastasis incidence



Primary endpoint : incidence of brain metastases at 2 years
HR of brain metastasis in 36 Gy versus 25 Gy: 0.77 (0.55-1.08), p=0.13

PCI with a total dose of 25 Gy remains the standard of care in LD SCLC

PCI in ED SCLC

PCI reduces incidence of symptomatic brain metastases

- Well tolerated
- Does not adversely affect QOL
- Should be routinely offered in patients with ED-SCLC who respond to systemic therapy

PCI in ED SCLC

ED SCLC, PS 0-2

- Response following 4-6 cycles chemo
- Randomized to PCI vs Observation
  - PCI: 20-30 Gy in 5-12 fractions
- Baseline brain imaging NOT mandated unless symptoms warranted imaging

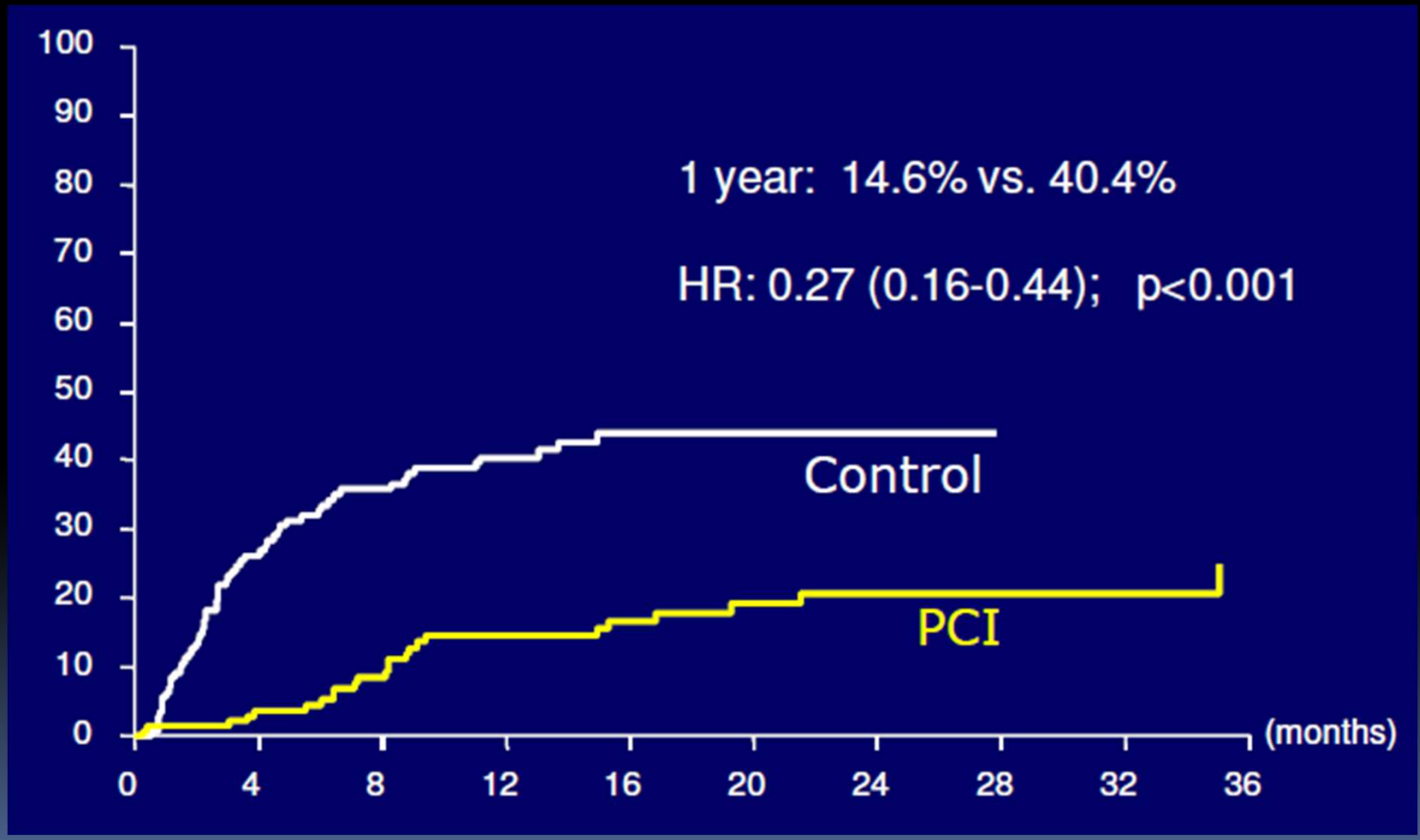
Slotman et al, ASCO 2007,abst 4

PCI in ED SCLC: Patient Characteristics

Variable	PCI	Control
N	143	143
PS 0-1	92.3%	89.5%
Persistent 1° disease	75.5%	76.9%
Bone mets	22%	26%
Lymph nodes	50%	47%
"Other sites of mets"	64%	82%
No mets present	30.8%	27.3%
Received 20 Gy in 5 fx	~67%	-----

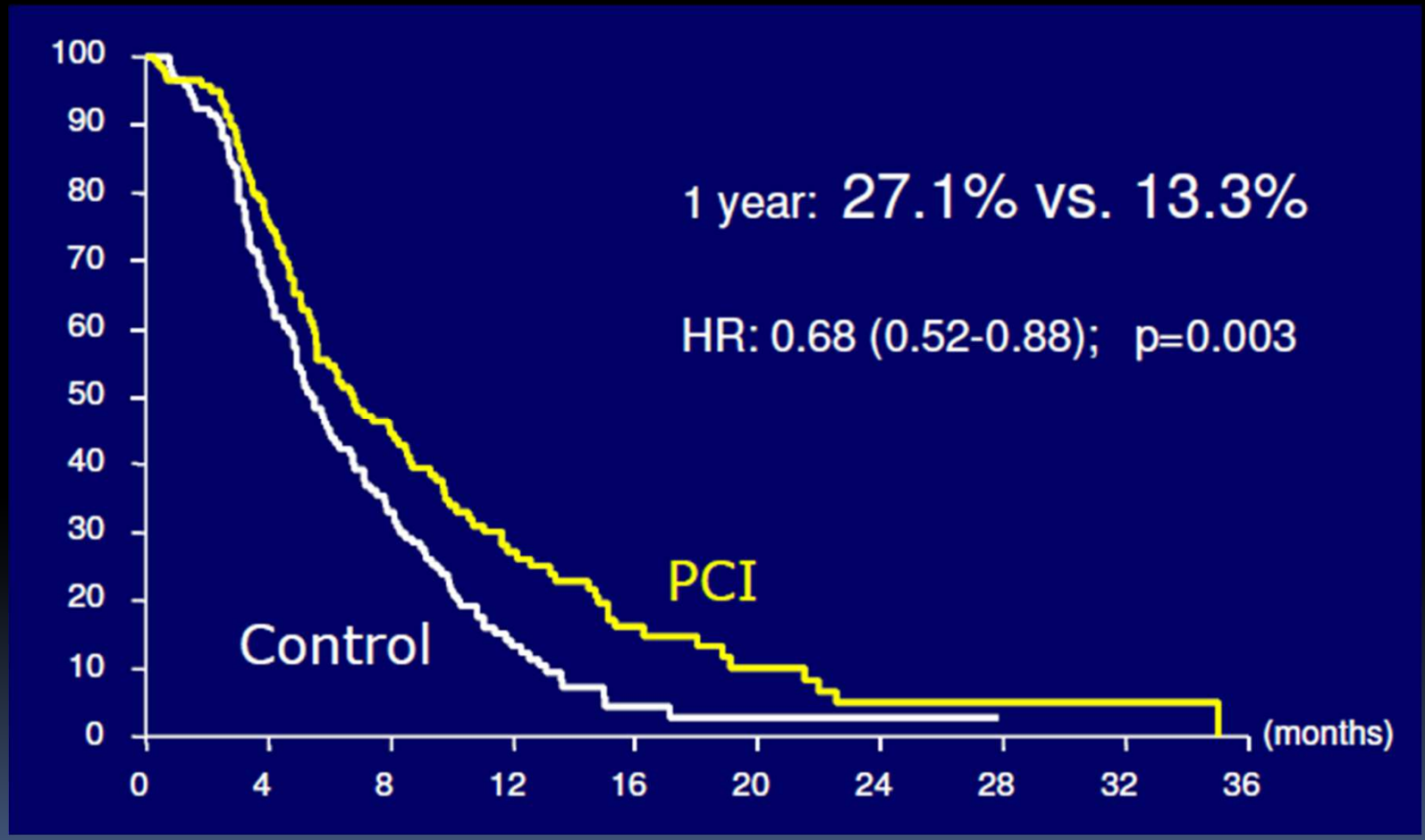
Slotman et al, ASCO 2007,abst 4

Symptomatic Brain Metastases incidence



Slotman et al, ASCO 2007,abst 4

Survival from Randomization



Slotman et al, ASCO 2007,abst 4

Thoracic RT in ED

Next step….

Wait and see ? no

- PCI ? Yes/ 25 Gy
- Thoracic control is a problem:
  - –75% persisting thoracic disease after initial chemotherapy
  - –90% thoracic disease progression after at 1 year after initial chemotherapy

Is there a role of thoracic radiotherapy in ES SCLC ?

SCLC – ED
ROLE OF THORACIC RADIOTHERAPY

- 3 cycles of EP and CR at distant sites /any response intrathoracically

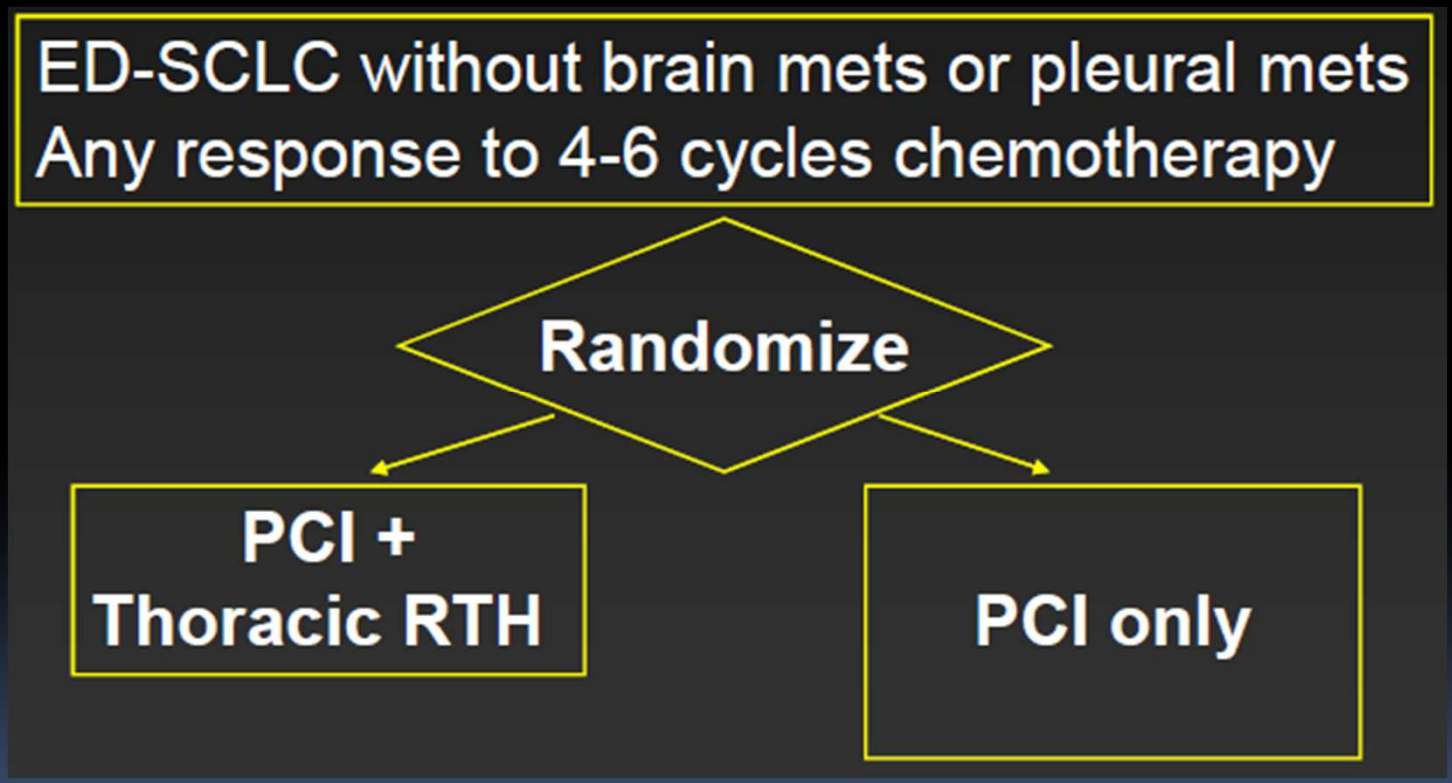
  - Thoracic radiotherapy at 54Gy/18#s and low dose chemotherapy and 2 cycles of PE

  - An additional 4 cycles of PE

    - MS 17 mths Vs 11 mths
    - 5yr 9.1% Vs 2.7% p=0.041
    - First relapse 13 mths Vs 9mths

Jeremic et al; JCO 1999

Proposed randomized phase II trial
Dutch Lung Cancer Study Group

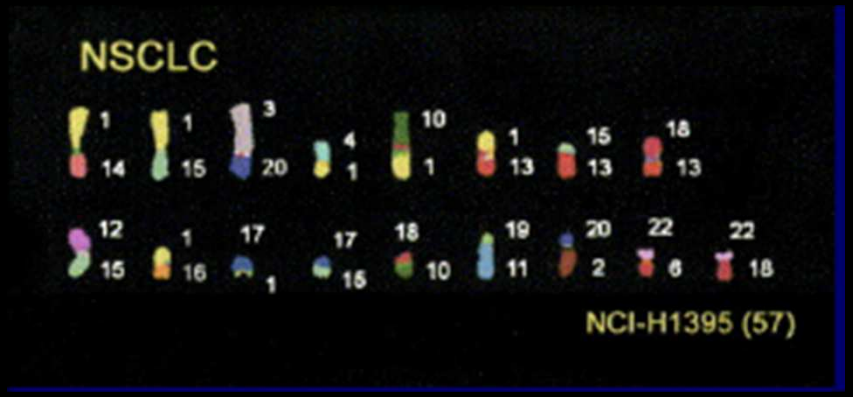


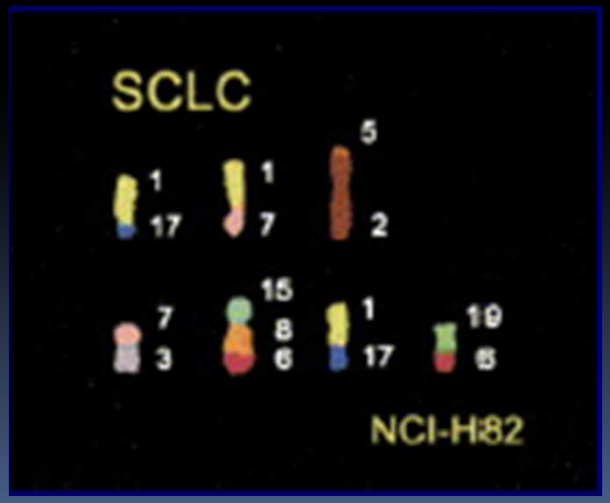
Treatment of Recurrent Small Cell Lung Cancer

- Possible Chemotherapy Agents:
  - topotecan (Hycamtin): only FDA-approved drug for recurrent disease
  - oral etoposide (VP-16)
  - paclitaxel (Taxol)
  - irinotecan/CPT-11 (Camptosar)
  - CAV
  - others in clinical trials
- Palliative radiation to relieve symptoms

Complexity of Lung Cancer defined by chromosomal painting

Complex disease
- Not a single agent responsible for disease as in polio or small pox.
- Not a single gene responsible like cystic fibrosis or sickle cell anemia





SCLC and Anti-angiogenic Trials

Study	Target	Agent	Schema	Result
NCI-C/ EORTC	MMP	Marimastat	+/- Maintenance	Negative
Bayer		BAY 12-9566	+/- Maintenance	Negative
ECOG	VEGF	BEV (B)	Chemo + B	Positive
CALGB			Chemo + B	Negative
HOG			Chemo + B	Negative
United Kingdom	Vascular stabilizer	Thalidomide	Chemo +/- T	Negative
NCI-C	VEGFR TKi	ZD 6474	+/- Maintenance	Negative
SWOG	VEGFR TKi	Sorafenib	Monotherapy	Negative

SCLC and Targeted Agents

Study	Target	Agent	Schema	Result
Rudin	Bcl-2	Oblimersen	Chemo +/-	Negative
ECOG	MTOR	CCI-779	+/- Maintenance	Negative
HOG	EGFR	Gefitinib	Monotherapy	Negative
Johnson Krug Dy	C-Kit	Imatinib	Monotherapy Monotherapy Monotherapy	Negative Negative Negative
EORTC	GD-3	BEC2/BCG	+/- Maintenance	Negative
SWOG	Proteo-some	Bortezomib	Monotherapy	Negative
SWOG	RAF/VEGF	Sorafenib	Monotherapy	Negative

Conclusion
first line therapy

- SCLC is an aggressive but highly sensitive disease.
- Etoposide/Cisplatin (carboplatin) standard of care in SCLC
- The results of Newer combinations i.e. with Irinotecan and topotecan are promising.
- PCI is accepted and improves survival
- Thoracic radiation in LS to be initiated as early as possible

  Improved outcomes will come ONLY when

  we defeat the highly resistant clones
- Role of Thoracic RT in ED appears promising in maintenance.