

# **Case # 3**

# **Extensive Stage SCLC**

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# **Case #3 – Extensive Stage SCLC**

## ***Discussant: Pieter E. Postmus, MD***

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**A 59 year/old heavy smoking female is seen in clinics with a recent severe cough and breathlessness.**

- CT scan of chest and abdomen shows a large left suprahilar mass with bulky hilar & mediastinal adenopathy. Also, small bilobar hepatic metastases are seen.**
- MRI Brain - negative**
- Biopsies obtained by fiberoptic bronchoscopy reveal small cell lung cancer (SCLC)**
- CBC: Hgb 10.7; WBC 5,500; Platelets 180,000; Hepatic panel normal**
- ECOG performance status = 2**

# Case #3 – Extensive Stage SCLC

## Part I

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*Which chemotherapy regimen would you recommend at this time?*

- 1. Etoposide + carboplatin or cisplatin*
- 2. Topotecan (Hycamtin®) + cisplatin*
- 3. Oral topotecan + cisplatin*
- 4. Irinotecan with carboplatin or cisplatin*
- 5. Etoposide, carboplatin and paclitaxel*
- 6. Carboplatin + pemetrexed (Alimta®)*

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- 59-year-old female
- SCLC, extensive disease
- MRI brain negative
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# Staging of SCLC

- Accurate staging provides prognostic information and stage determines treatment strategies for all types of lung cancer
- The first staging system for SCLC was introduced in the 1950s by the Veterans' Administration Lung Study Group (VALSG) for use in their randomized clinical trials
- This simple system divided SCLC into two disease subgroups termed "Limited" and "Extensive" Disease:
  - Limited Disease (LD) was characterized by tumors confined to one hemi-thorax, although local extension and ipsilateral, supra-clavicular nodes could also be present if they could be encompassed in the same radiation portal as the primary tumor. No extra-thoracic metastases could be present
  - All other patients were classified as extensive disease (ED)

# Points of Uncertainty in Current Staging

- **Contralateral supraclavicular lymph nodes**
- **Pleural effusion**
- **Pericardial effusion**
- **Value of TNM**

# Available TNM Staging

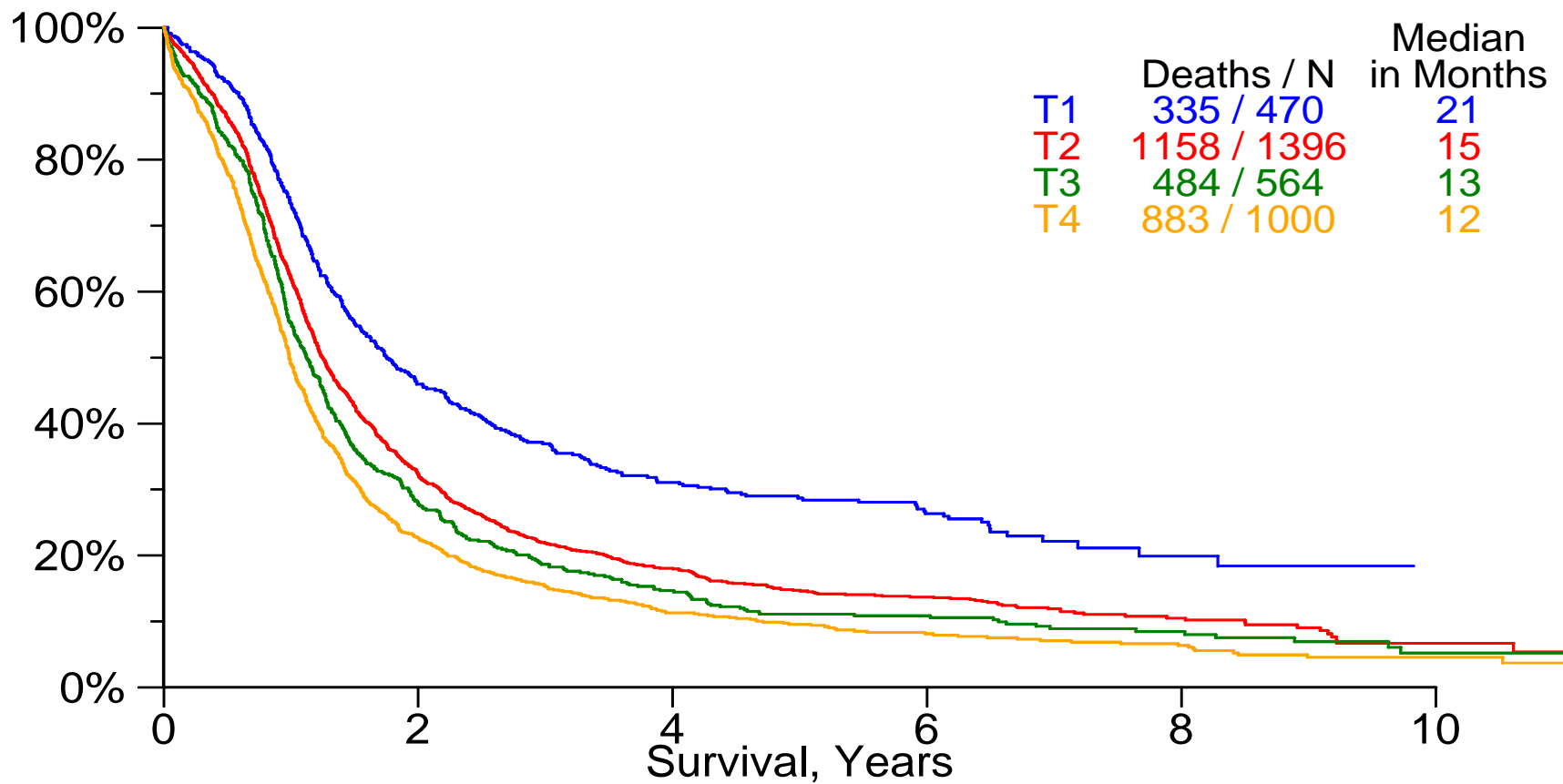
Summary of 12,620 small cell lung cancer cases from the IASLC international staging project database

	Clinical TNM	Pathological TNM	Clinical and Pathological TNM	cM1	Extensive or Limited Only	
Not Classified	<b>1819</b>	<b>127</b>	<b>193</b>	<b>1532</b>	<b>0</b>	<b>3671</b>
Extensive	<b>88</b>	<b>0</b>	<b>4</b>	<b>2998</b>	<b>2038</b>	<b>5128</b>
Limited	<b>1308</b>	<b>1</b>	<b>18</b>	<b>0</b>	<b>2494</b>	<b>3821</b>
Total	<b>3215</b>	<b>128</b>	<b>215</b>	<b>4530</b>	<b>4532</b>	<b>12620</b>

# Database

Type of Database	Available TNM Staging				Total
	Clinical TNM	Pathological TNM	Clinical and Pathological TNM	cM1	
Registry	<b>634</b>	<b>6</b>	<b>9</b>	<b>1720</b>	<b>2369</b>
Surgical Series	<b>31</b>	<b>67</b>	<b>3</b>	<b>5</b>	<b>106</b>
Clinical Trial	<b>1027</b>	<b>0</b>	<b>1</b>	<b>1556</b>	<b>2584</b>
Series	<b>742</b>	<b>2</b>	<b>31</b>	<b>596</b>	<b>1371</b>
Consortium	<b>240</b>	<b>11</b>	<b>171</b>	<b>263</b>	<b>685</b>
Institutional Registry	<b>541</b>	<b>0</b>	<b>0</b>	<b>390</b>	<b>931</b>
Surgical Registry	<b>0</b>	<b>42</b>	<b>0</b>	<b>0</b>	<b>42</b>
Total	<b>3215</b>	<b>128</b>	<b>215</b>	<b>4530</b>	<b>8088</b>

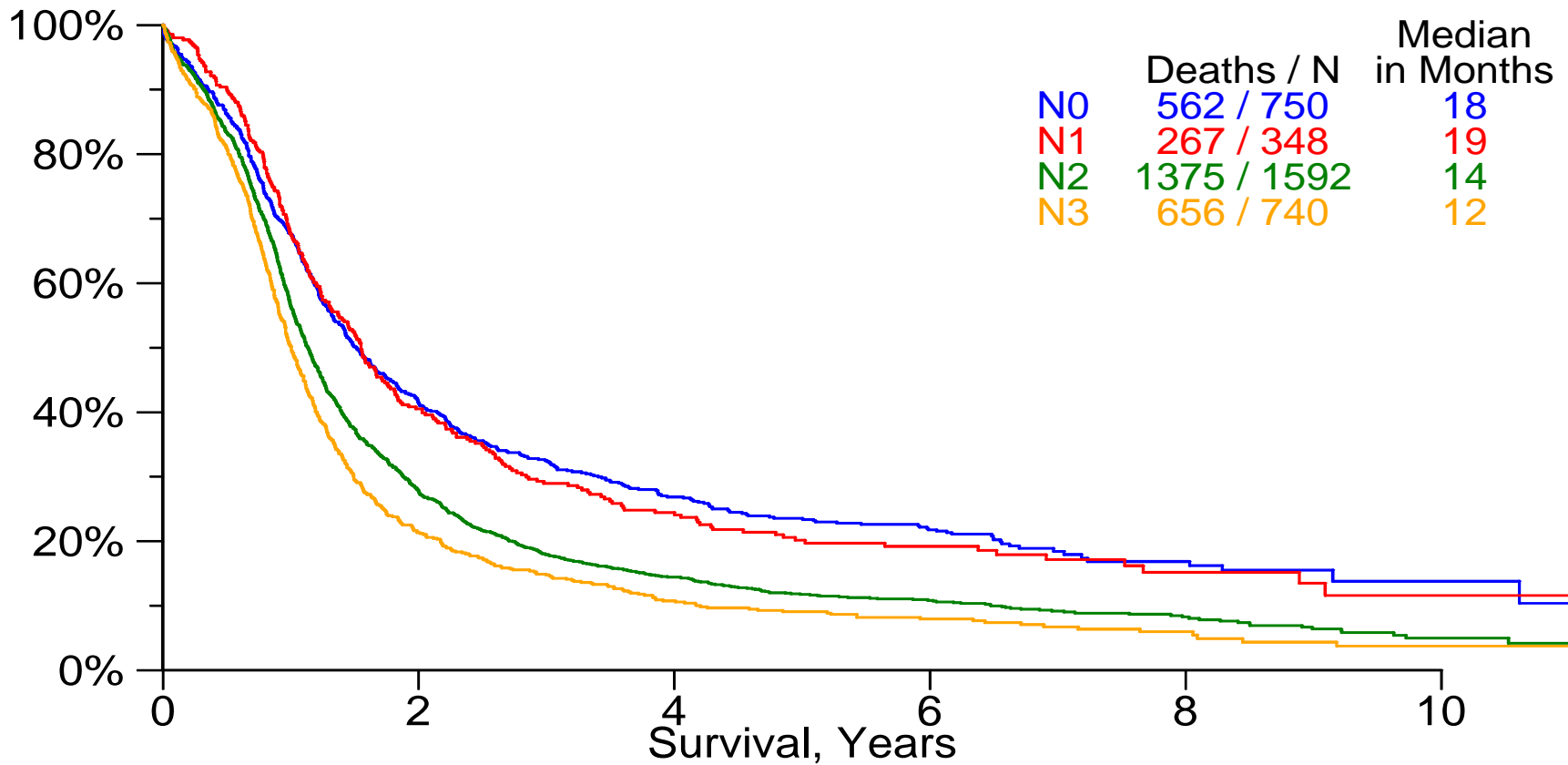
# Survival by Clinical T Stage



# Overall survival comparisons for clinical stage T1-T4 (any N) M0 small cell lung cancer, IASLC data

T Stage	N	1-Year Survival Rate	5-Year Survival Rate	Comparison	HR	P
T1	470	73%	29%			
T2	1396	62%	15%	T2 vs. T1	1.48	<0.0001
T3	564	55%	11%	T3 vs. T2	1.14	0.0185
T4	1000	49%	10%	T4 vs. T3	1.17	0.0055

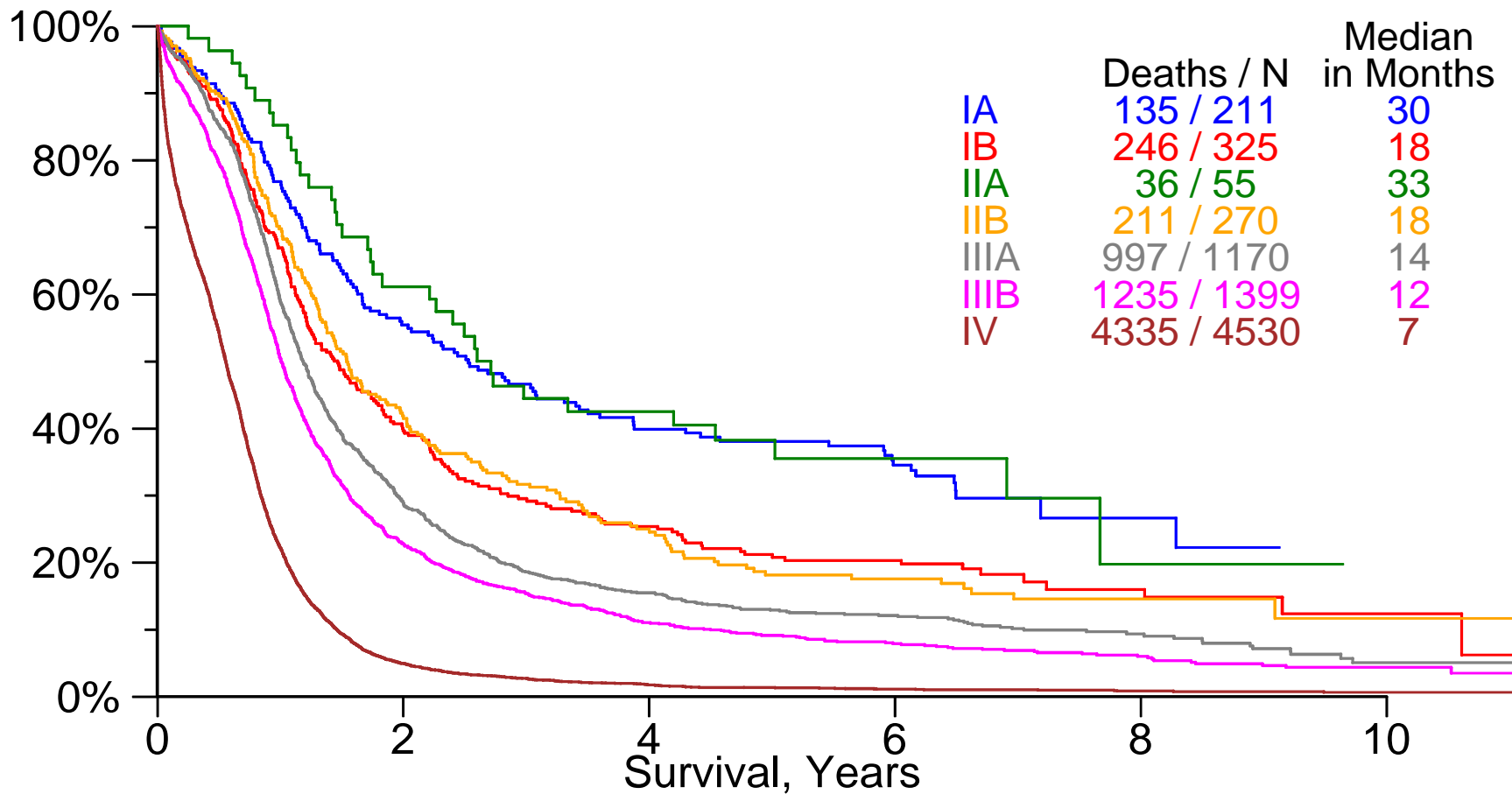
# Survival by Clinical N-Stage



# Overall survival comparisons for clinical stage N0-N3 (any T) M0 small cell lung cancer, IASLC database

N Stage	N	1-Year Survival Rate	5-Year Survival Rate	Comparison	HR	P
N0	750	68%	24%			
N1	348	68%	20%	N1 vs. N0	1.02	0.7552
N2	1592	56%	12%	N2 vs. N1	1.40	<0.0001
N3	740	50%	9%	N3 vs. N2	1.18	0.0006

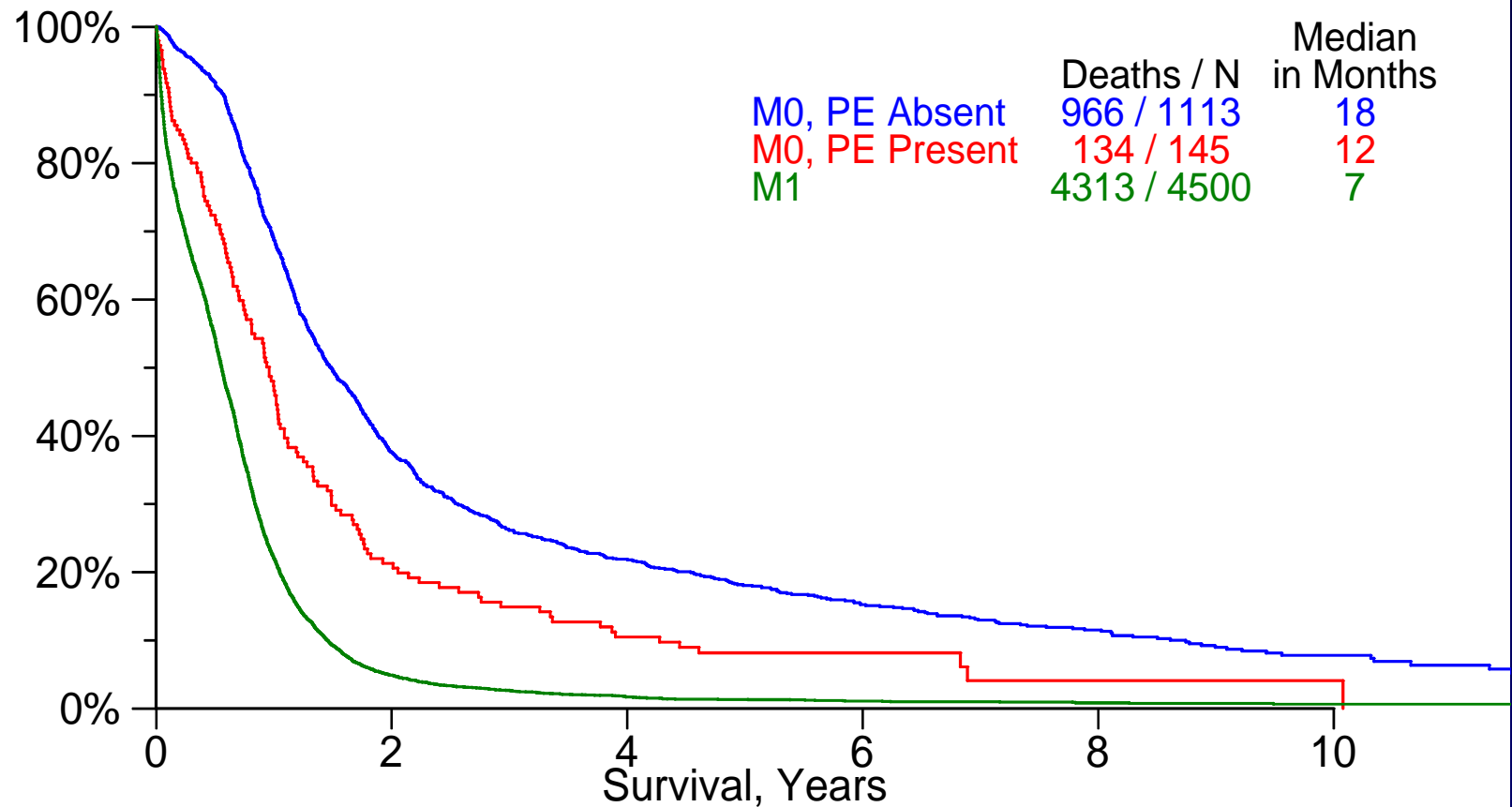
# Survival by Clinical TNM Category



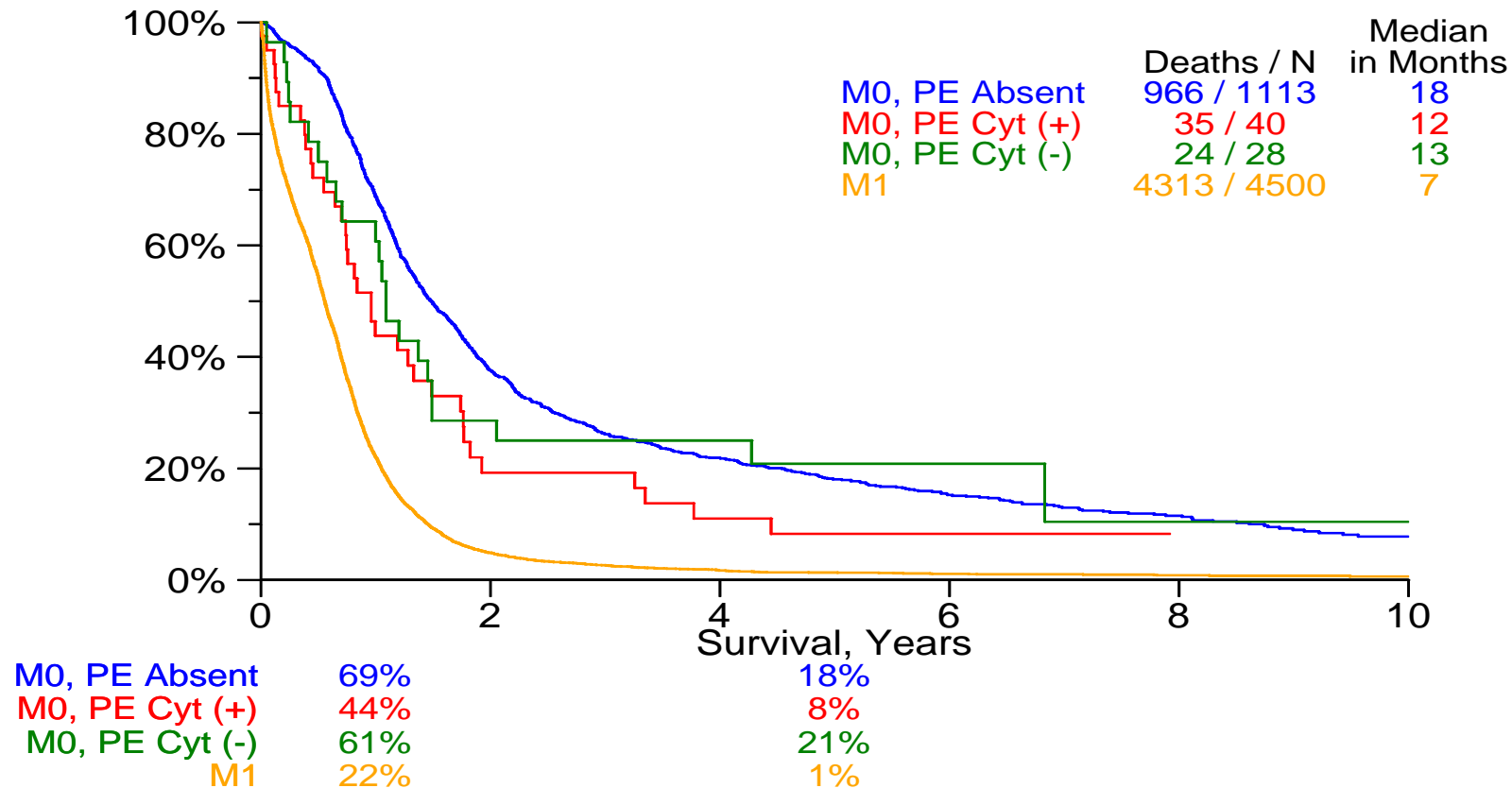
# Overall survival comparisons for clinical TNM stage category small cell lung cancer, IASLC database

Stage	N	1-Year Survival Rate	5-Year Survival Rate	Comparison	HR	P
IA	211	77%	38%			
IB	325	67%	21%	IB vs. IA	1.48	0.0003
IIA	55	85%	38%	IIA vs. IB	0.62	0.0075
IIB	270	70%	18%	IIB vs. IIA	1.57	0.0118
IIIA	1170	59%	13%	IIIA vs. IIB	1.32	0.0003
IIIB	1399	50%	9%	IIIB vs. IIIA	1.21	<0.0001
IV	4530	22%	1%	IV vs. IIIB	2.16	<0.0001

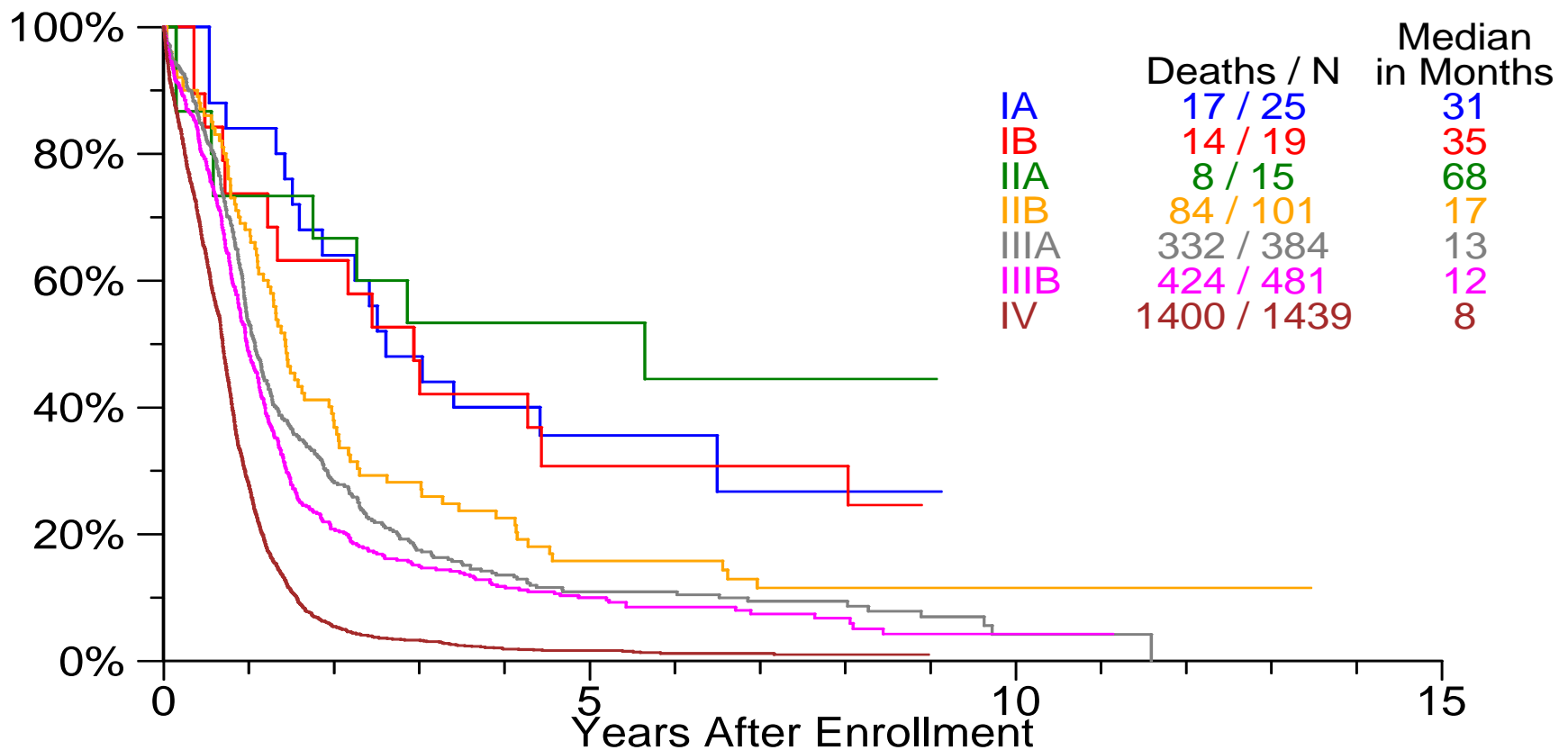
# Survival by pleural effusion status: all pleural effusions included



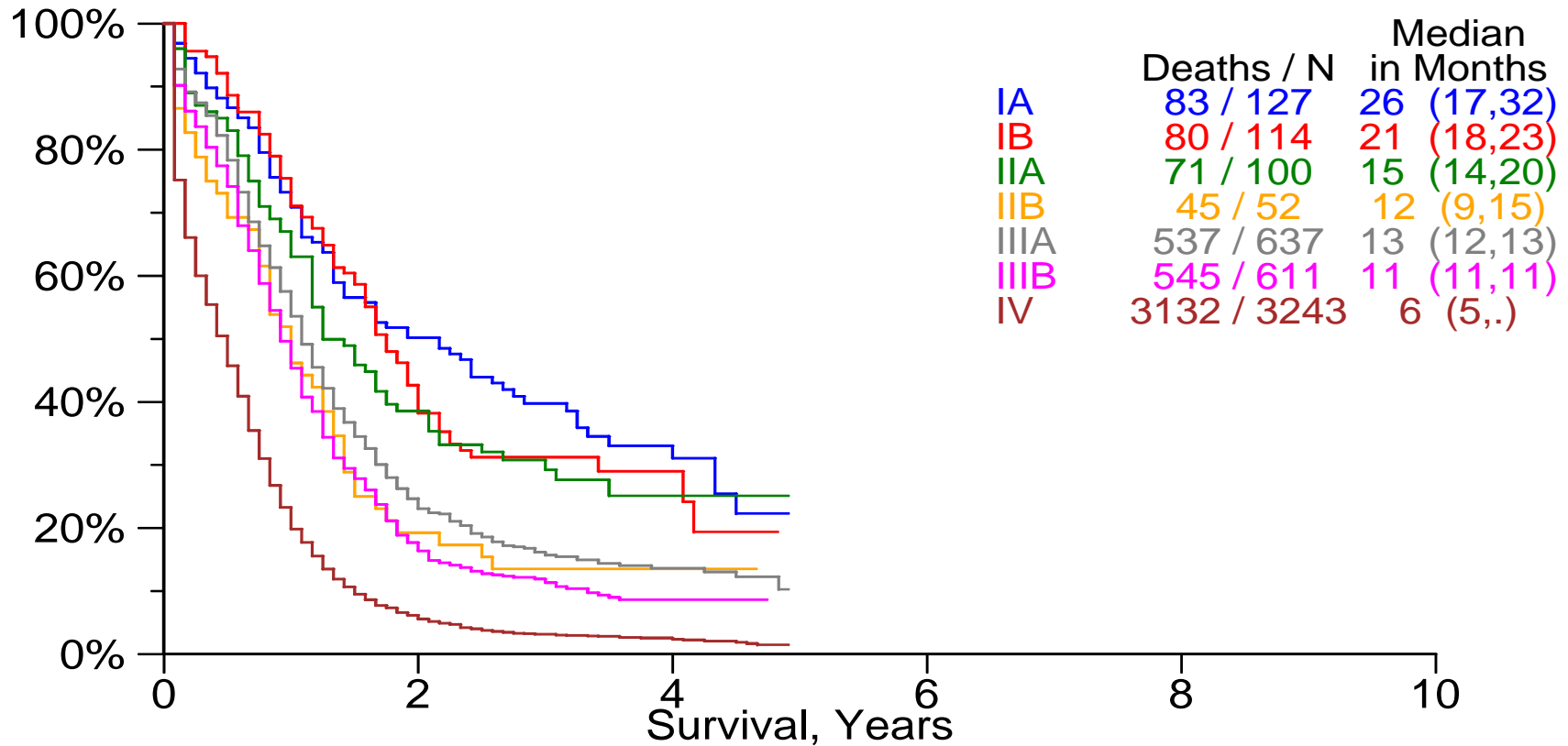
# Survival by pleural effusion status: only effusions with cytologic evaluation comparing cytology positive to cytology negative effusion



# Survival by IASLC proposed TNM stage



# Survival by IASLC proposed TNM stage in the SEER database



# Recommendations

- **TNM staging should be applied in SCLC**
- **Stratification by TNM stage be incorporated into clinical trials in Stage I-III SCLC.**
- **For prospective staging validation studies, more information must be collected to define N staging more clearly**
- **To determine whether there is a difference in prognosis for patients with cytology negative or positive pleural effusions and for patients with pericardial effusions.**

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- **SCLC, extensive disease**
- MRI brain negative
- Liver metastases
- PS 2

# Which staging procedures are needed?

ESMO guidelines *Ann Oncol* 2008; 19 suppl 2 41-42

Staging procedures should include medical history, physical examination, chest X-ray, complete blood count including differential count, liver and renal function tests, lactate dehydrogenase and sodium levels, and a CT scan of the chest and upper abdomen including the liver and adrenal glands.

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# Which staging procedures are needed?

ESMO guidelines *Ann Oncol* 2008; 19 suppl 2: 41-42

In patients with symptoms or abnormal physical examination suggesting metastasis additional tests may include bone scintigraphy, CT scan or MRI of the brain, and bone

Brain CT/MRI should be considered before starting treatment in patients without evidence of metastatic disease. The role of combined FDG–PET/CT scanning is not yet defined.

# Case #3 – Extensive Stage SCLC

## Part I

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*Which chemotherapy regimen would you recommend at this time?*

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- 3. Oral topotecan + cisplatin*
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# Front-line Chemo in SCLC Evolution

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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

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# Platinum vs Non-platinum Regimens

<b>19 trials (4054 patients)</b>	<b>CDDP</b>	<b>No- CDDP</b>	
<b>Toxic death rate</b>	<b>3.1</b>	<b>2.7 %</b>	
<b>Response rate</b>	<b>0.69</b>	<b>0.62</b>	<b>HR 1.35</b>
<b>Survival difference</b>	<b>2.6% at 6 months</b>	<b>HR 0.87</b>	
	<b>4.4% at 1 year</b>	<b>HR 0.80</b>	

# Cisplatin vs Carboplatin?

220 patients; ED >70 years or PS=3

	CDDP-VP16	CBDCA-VP
RO	73%	73%
PFS	5.3 m	4.7 m
OS	10.6 m	9.8 m

Okamoto, ASCO 2005

143 patients (61 ED)

RC	13%	19%
RP	47%	48%
Superv	10.4 m	10.4 m

Skarlos, *Ann Oncol* 1994

# SCLC:

## Any new Treatment Options?

### Chemotherapy

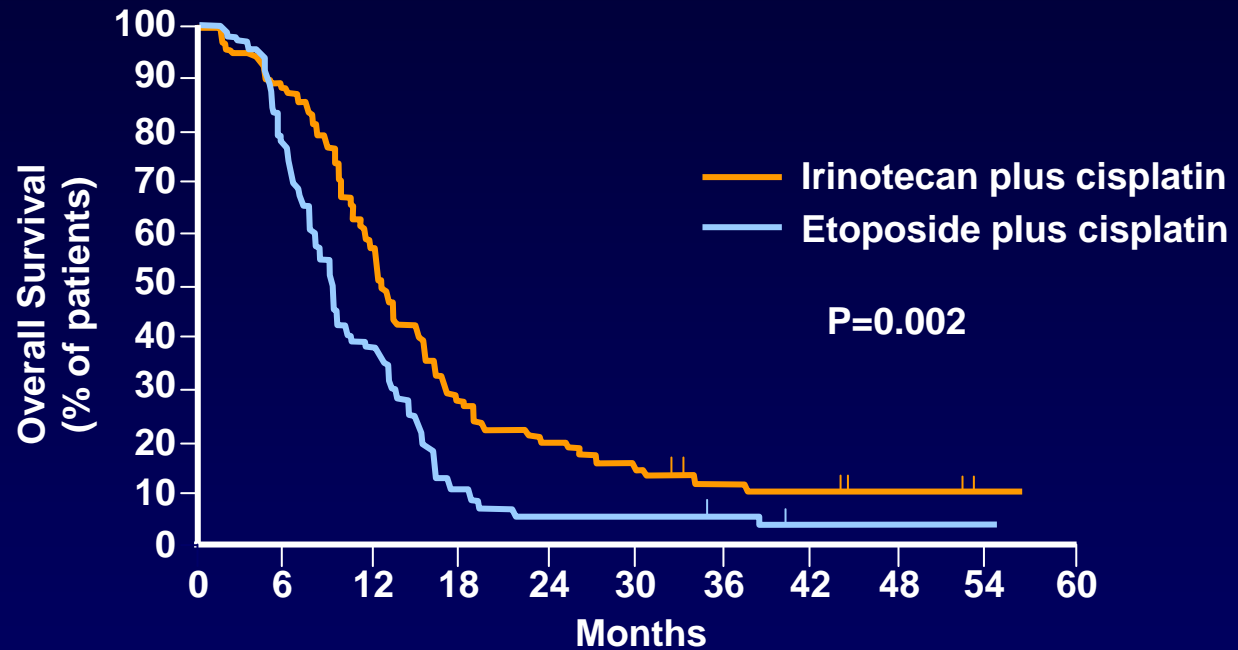
- **Topo I Inhibitors**
  - Irinotecan
  - Topotecan
  - Belotecan
- **Pemetrexed**

### Targeted Agents

- **Antiangiogenics**
  - Thalidomide
  - Bevacizumab
- **Anti C-Kit, EGFR...**

# Cis & VP-16 vs Cisplatin & Irinotecan

Irinotecan 60 mg/m<sup>2</sup> day 1, 8, 15 / Cisplatin 60 mg/m<sup>2</sup> day 1 q 21 x 4  
 Etoposide 100 mg/m<sup>2</sup> day 1-3 / Cisplatin 80 mg/m<sup>2</sup> day 1 q 21 x 4



No. at Risk

Irinotecan plus cisplatin	77	67	45	21	15	11	7
Etoposide plus cisplatin	77	60	29	9	4	4	3

## “ASCO 2008”

### Negative phase III studies of

- Pemetrexed in ED SCLC
- Irinotecan
- Topotecan
- no promising results of targeted agents

## “WCLC 2007”

### Negative phase III study of

- Thalidomide

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# Case #3 – Extensive Stage SCLC

## *Part II*

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Assuming a clinically significant response to induction chemotherapy would you recommend prophylactic cranial irradiation (PCI) for this patient with extensive stage SCLC?

1. Yes
2. No

# Prophylactic Cranial Irradiation in CR

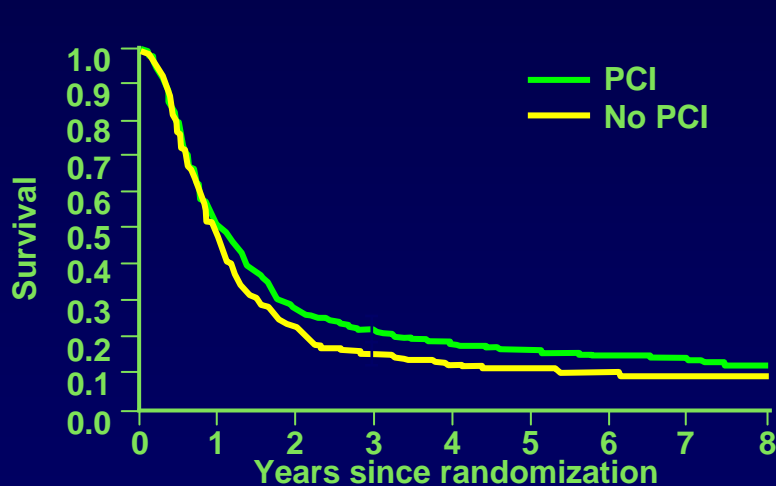
## HR

Overall survival 0.84 (0.73–0.97),  $p < 0.01$

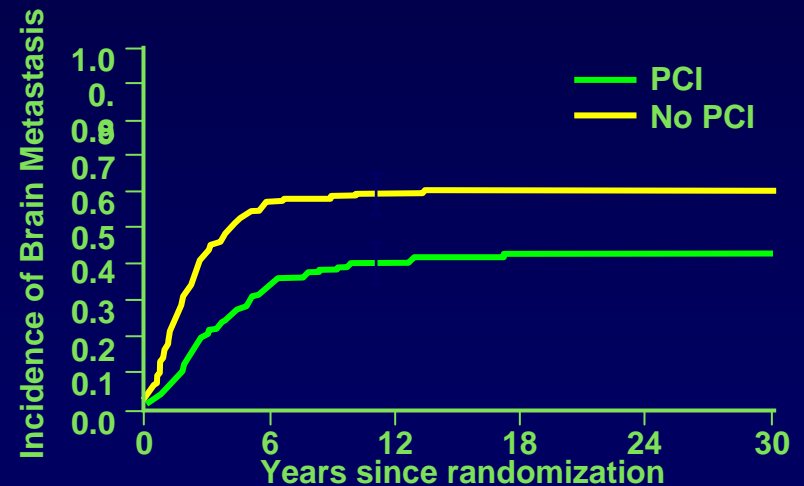
Disease-free survival 0.75 (0.65–0.86),  $p < 0.001$

Incidence of brain metastasis 0.46 (0.38–0.57),  $p < 0.001$

**5.4% absolute benefit in 3 year OS**



No. at risk		0	1	2	3	4	5	6	7	8
No PCI	461	224	103	61	44	34	23	19	15	
PCI	526	276	139	101	66	52	40	29	17	



No. at risk		0	6	12	18	24	30		
No PCI	457	171	88	57	41	32	21	18	4
PCI	524	248	133	96	66	52	40	29	17

# **Prophylactic Cranial Irradiation in Extensive Disease Small Cell Lung Cancer (EORTC 08993-22993)**

**Ben Slotman, Corinne Faivre-Finn, Gijs Kramert<sup>†</sup>, Elaine Rankin,**

**Michael Snee, Matthew Hatton, Pieter Postmus,**

**Laurence Collette, Murielle Mauer, Suresh Senan,**

**on behalf of the EORTC Radiation Oncology and Lung Cancer  
Groups**

# Background: Brain metastases (BM) in SCLC

- **High incidence: 18% at diagnosis; 80% at 2 years**
- **Major impact on physical and psychological functioning**
- **Poor response to systemic therapy and brain radiotherapy**
- **Prophylactic cranial irradiation (PCI) improves survival in patients in complete remission (Auperin et al., 1999)**

Does PCI have a role in patients with ED-SCLC after chemotherapy?

# Study Design



Stratification: Performance score and Institute

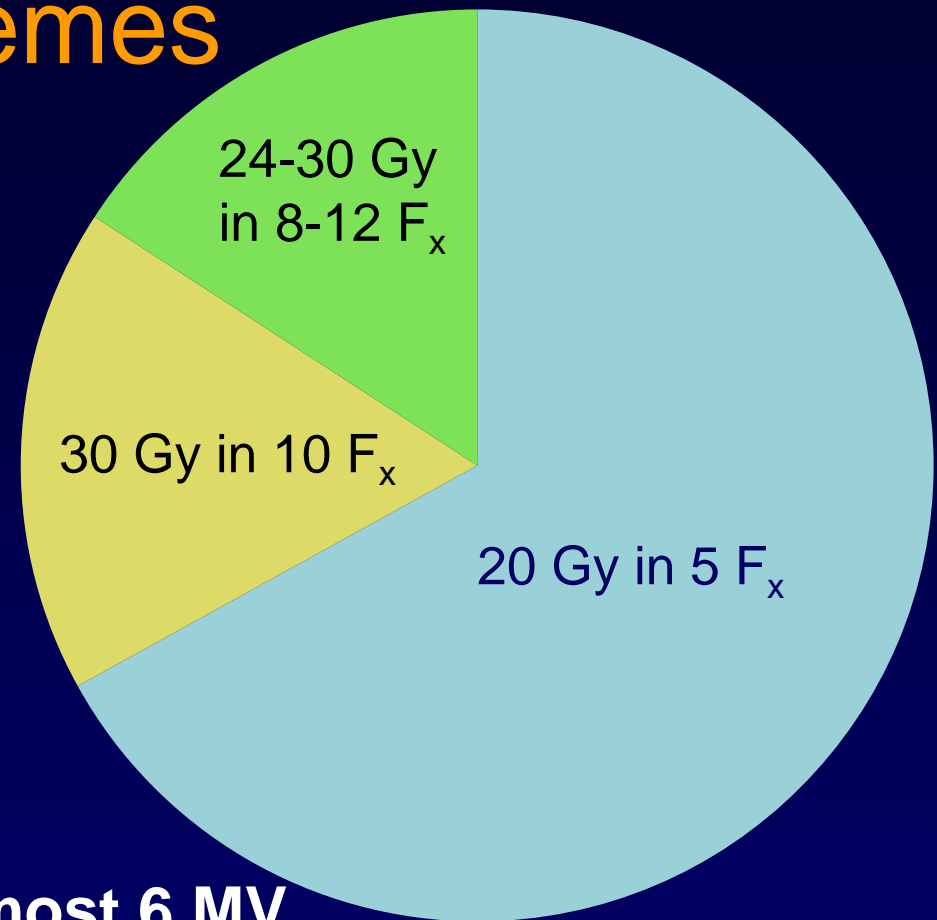
# Protocol Summary

- **Objective: to demonstrate a reduction in the risk of developing symptomatic brain metastases**
- **Study was sized to detect a hazard ratio of 0.44 with 80% power and 2-sided 5% significance**
- **286 patients accrued between February 2001 - March 2006**
- **IDMC review in December 2005: Continuation of recruitment until the planned sample size recommended**

# Patient Characteristics

	PCI (N=143)	Control (N=143)	Sign.
	N (%)	N (%)	
<b>Median Age (years)</b>	<b>62.0</b>	<b>63.0</b>	<b>N.S.</b>
<b>Range</b>	<b>37.0 - 75.0</b>	<b>39.0 - 75.0</b>	
<b>Gender</b>			<b>N.S.</b>
<b>male</b>	<b>97 (67.8)</b>	<b>82 (57.3)</b>	
<b>female</b>	<b>46 (32.2)</b>	<b>61 (42.7)</b>	
<b>WHO performance status</b>			<b>N.S.</b>
<b>WHO 0</b>	<b>52 (36.4)</b>	<b>52 (36.4)</b>	
<b>WHO 1</b>	<b>80 (55.9)</b>	<b>76 (53.1)</b>	
<b>WHO 2</b>	<b>11 (7.7)</b>	<b>15 (10.5)</b>	
<b>Median time since diagnosis (months)</b>	<b>4.2</b>	<b>4.2</b>	<b>N.S.</b>

# Radiotherapy schemes

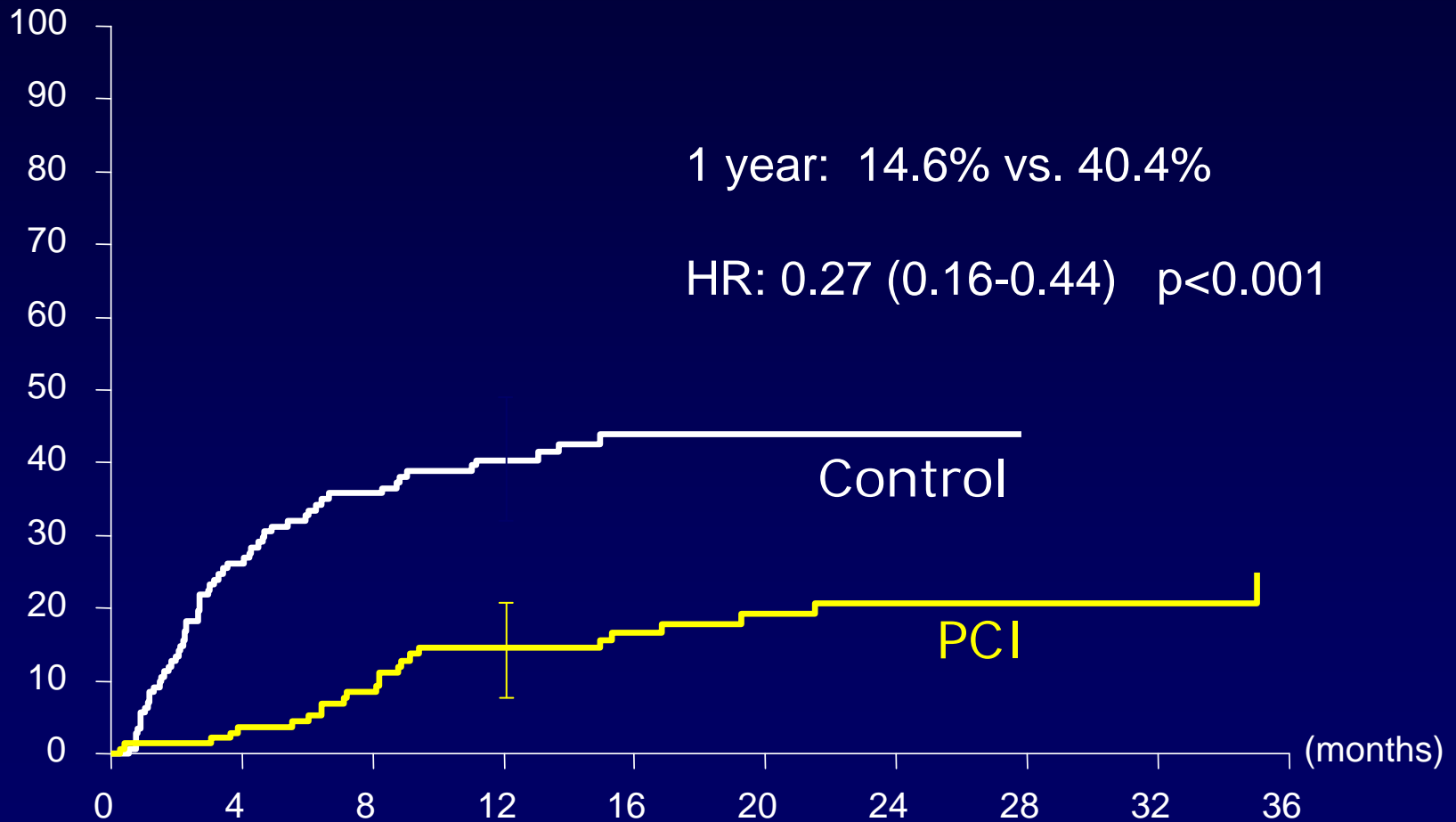


- 2 parallel-opposed fields, most 6 MV
- 1 stopped due to early progression
- 4 treatment interruptions (3 logistical, 1 refusal)

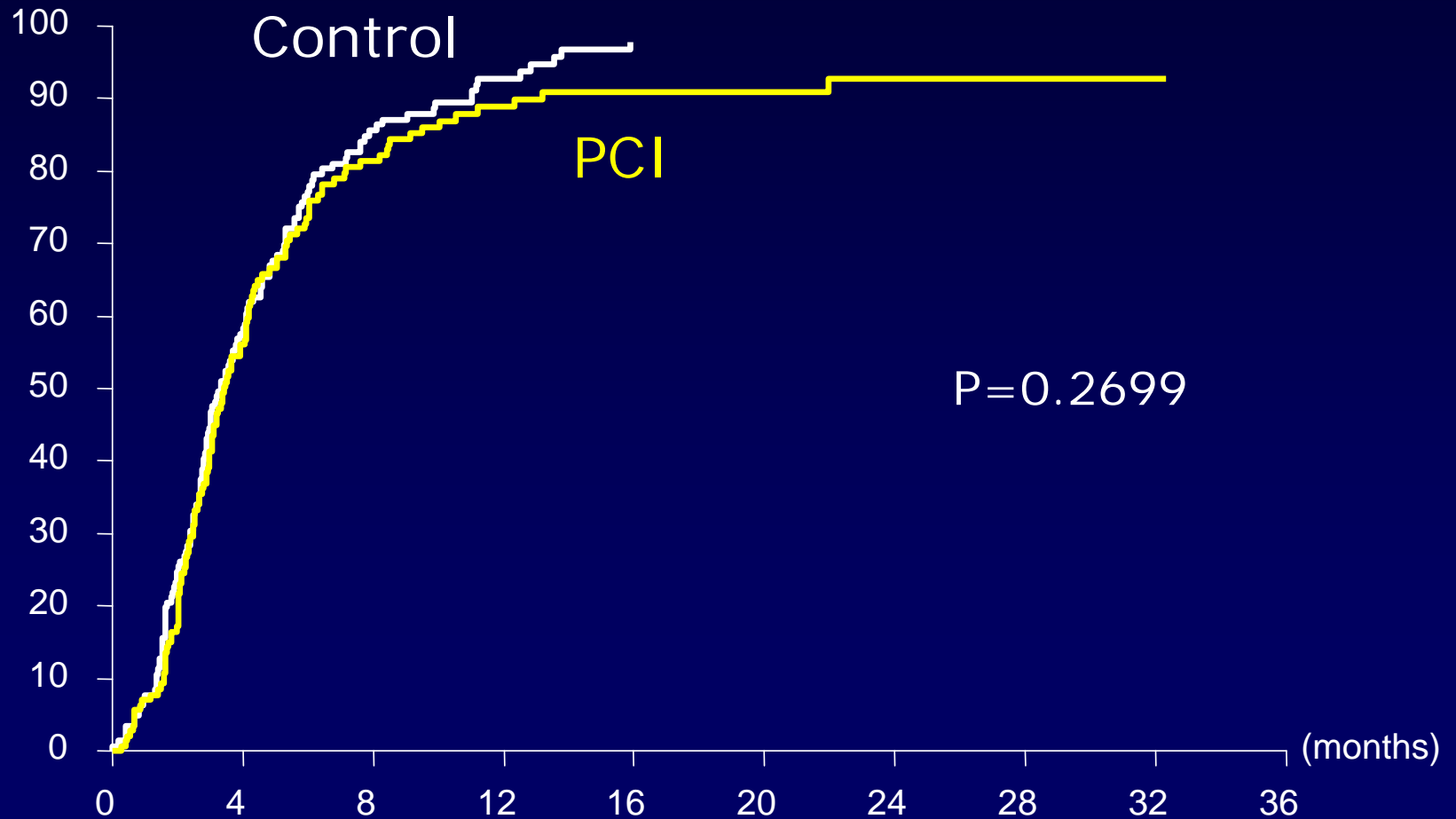
# Type of First Event

	PCI (N=143)	Control (N=143)
	N (%)	N (%)
No event	14 (9.8)	6 (4.2)
Symptomatic brain metastases - followed by extracranial progression	13 (9.1) 13	50 (35.0) 48
Extracranial disease progression - followed by brain metastases	109 (76.2) 11	85 (59.4) 9
Death due to other causes	7 (4.9)	2 (1.4)

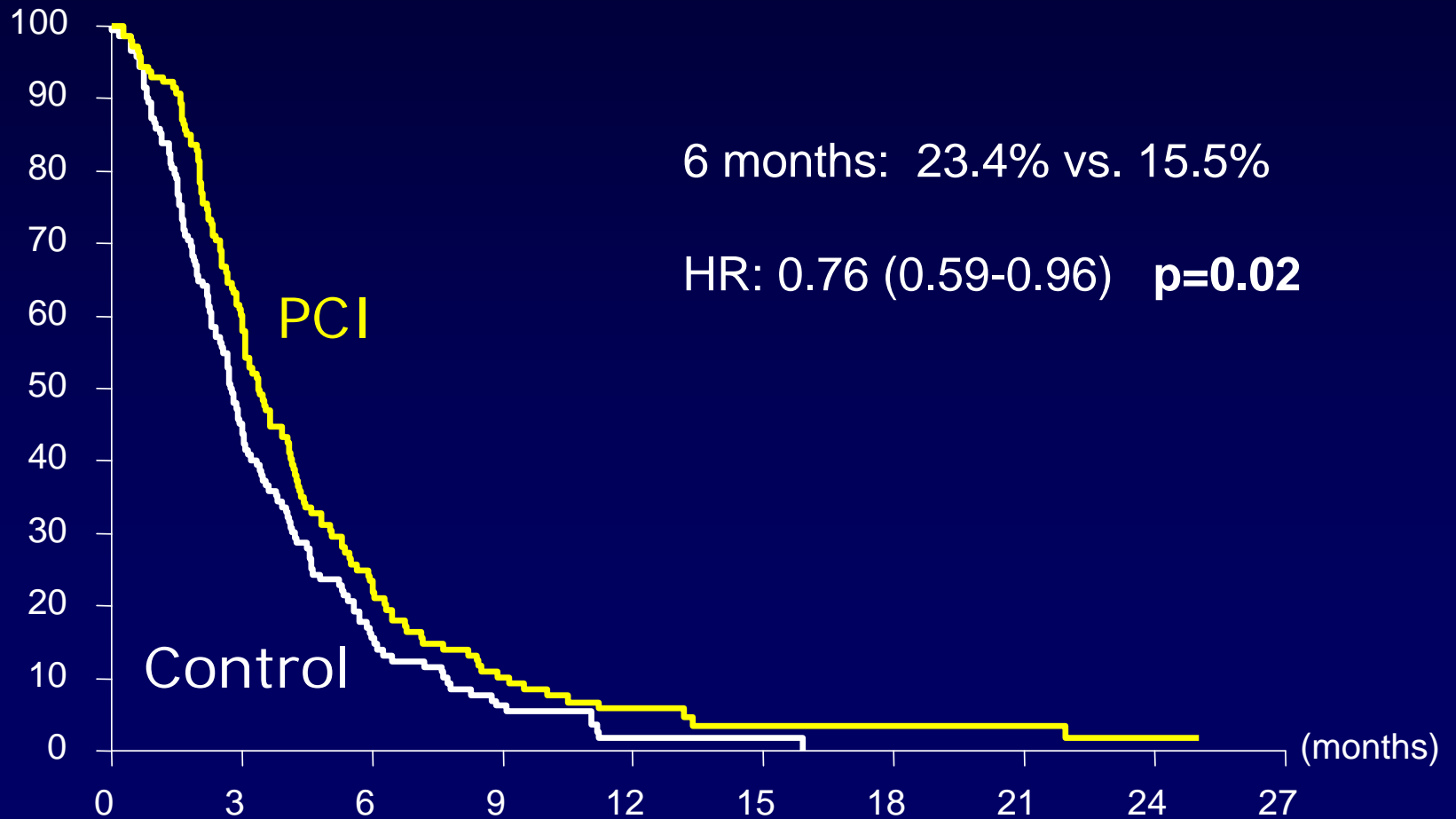
# Symptomatic Brain Metastases



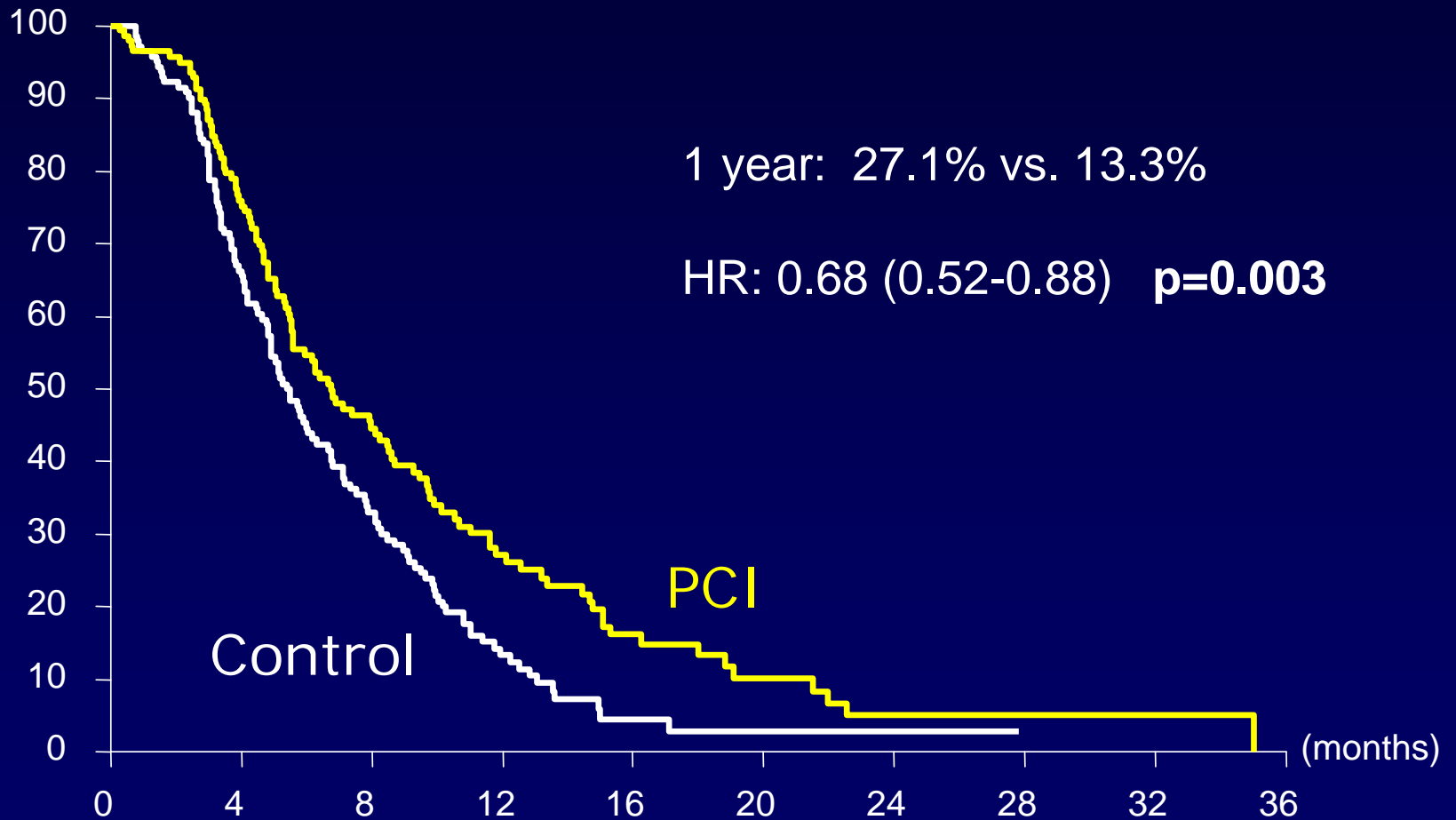
# Extracranial Progression



# Failure-free Survival



# Overall Survival



# Summary

- **PCI significantly reduces the risk of symptomatic brain metastases ( $p < 0.001$ ; HR = 0.27; 14.6 vs. 40.4% at 1 yr)**
- **No difference for the time to extra-cranial progression**
- **PCI significantly prolongs failure-free survival and overall survival (Overall survival:  $p = 0.003$ ; HR = 0.68 ; 27.1 vs. 13.3% at 1 yr)**
- **PCI is well tolerated and does not adversely influence QoL/global health status**

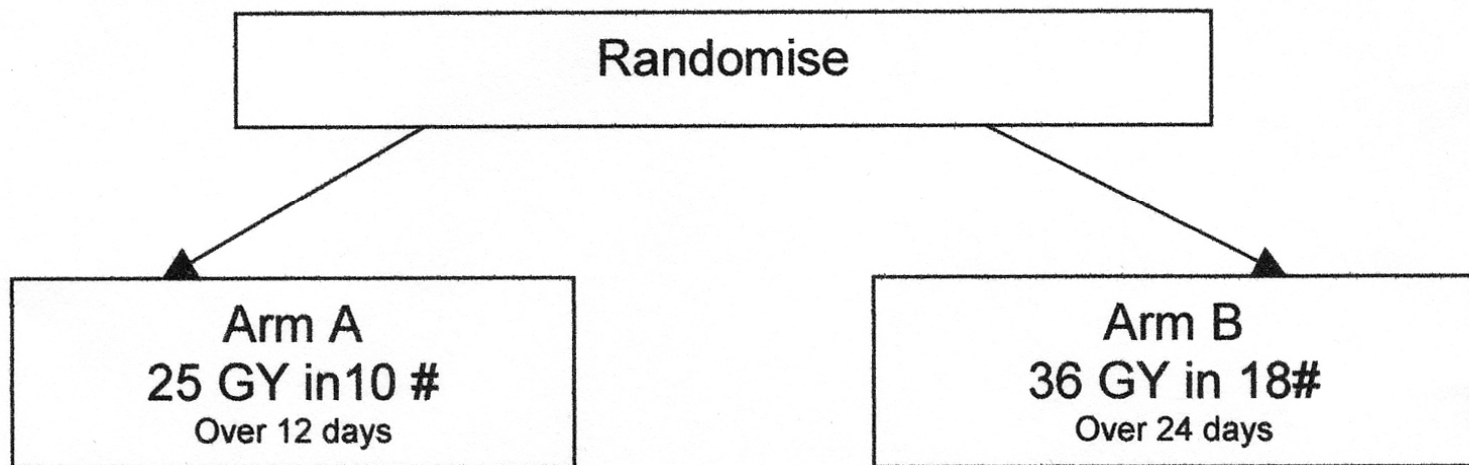
# PCI

## DOSE ?

# PCI OI-EULINT1

## High VS. Standard Dose PCI

### In LS SCLC Complete Responders



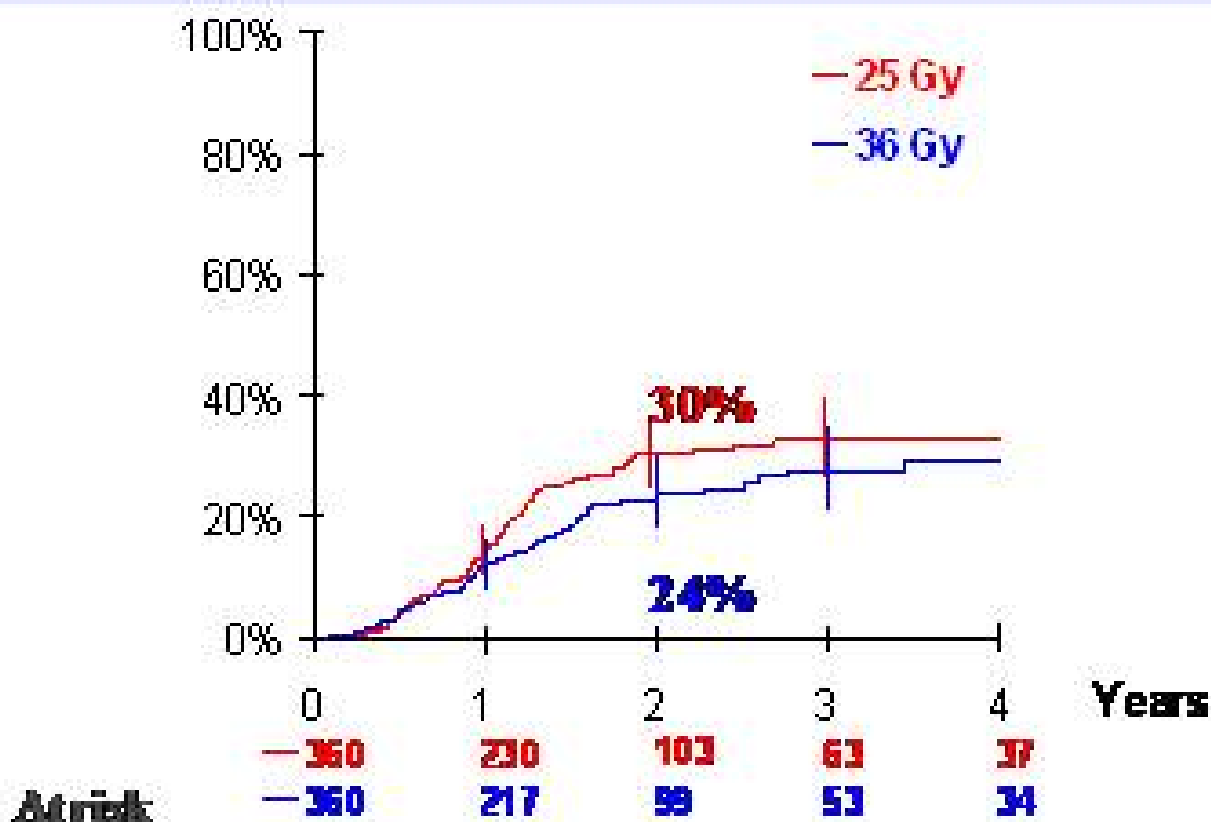
Primary endpoint : incidence of brain metastases at 2 years  
Secondary endpoints: survival, QoL

# Inclusion criteria

- **Histologically proven limited-stage SCLC**
- **Complete response to induction therapy (established on at least a chest X-ray)**
- **Brain CT-scan or MRI at <1 month pre-randomisation**
- **Baseline QOL and neurological assessment**
- **Age  $\leq 70^*$ , WHO performance status  $\leq 2$**
- **PCI starting as soon as possible after CR**
- **Informed consent**

\* except in the US, no age limit

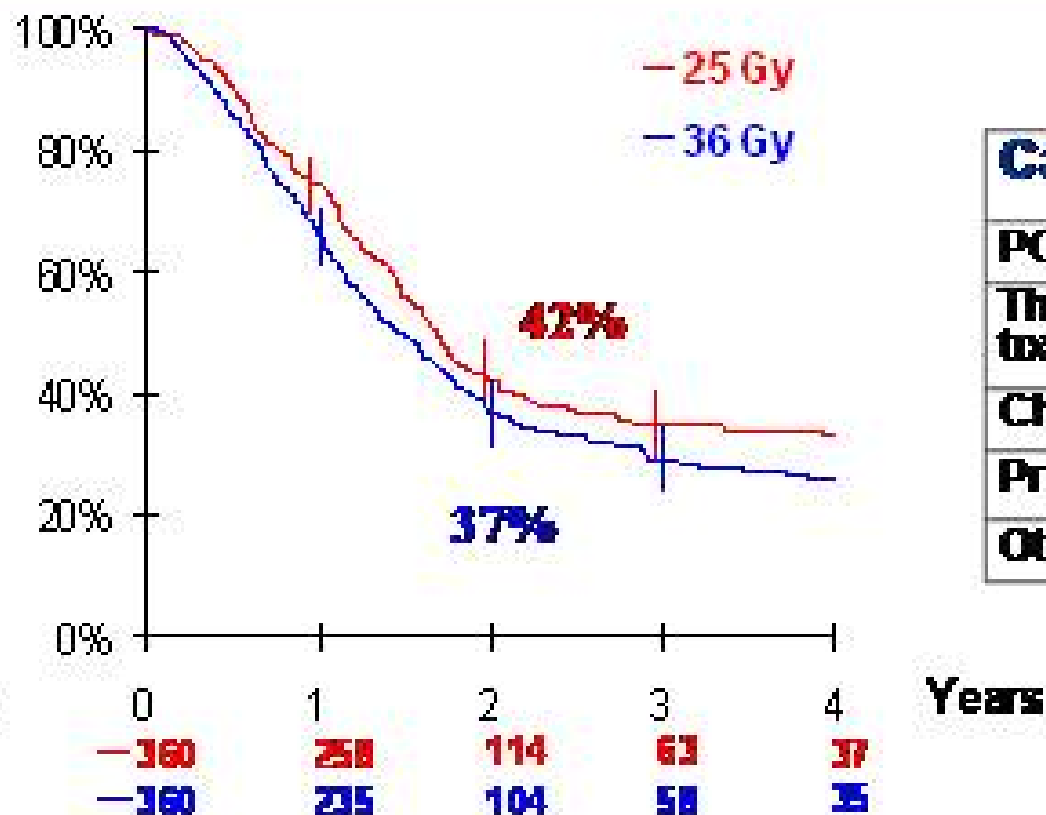
# Brain metastasis incidence



143 brain metastases observed before March 1<sup>st</sup> 2007

HR of brain metastasis in 36 Gy versus 25 Gy: 0.77 (0.55-1.08), p=0.13

# Overall survival



Cause of death	25 Gy	36 Gy
PCI toxicity	1	1
Thoracic irradiation toxicity	1	3
Chemotherapy toxicity	4	0
Progression	184	216
Other	27	29

466 deaths observed before March, 1<sup>st</sup> 2007

HR of death in 36 Gy versus 25 Gy: 1.22 (1.02-1.47), p=0.03

## **Conclusion**

**PCI with a total dose of 25 Gy  
remains the standard of  
care in limited-stage SCLC.**

**Part III: A major response resulted following therapy with etoposide + carboplatin (4 cycles). Patient did well for 4 months and then the cough recurred and disease progression was documented in lung and liver.**

**Which second-line chemotherapy would you suggest?**

1. Rechallenge with induction regimen
2. Cyclophosphamide + doxorubicin + vincristine (CAV)
3. Topotecan + cisplatin
4. Oral topotecan
5. Oral etoposide

ESMO Guidelines *Ann Oncol*  
2008; 19 suppl 2: 41-42

## **second-line chemotherapy**

Patients with good performance status relapsing after response to first-line chemotherapy should be considered for second-line chemotherapy as second-line chemotherapy increases survival [II, B]. No second-line regimen has proved superior to others with regard to survival.

# Chemotherapy for Relapsed Small Cell Lung Cancer: A Systematic Review and Practice Guideline

*J Thor Oncol* 2007; 2: 348

- The evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed SCLC is limited. The selection of patients for treatment with second-line therapy should be dependent on the treatment-free interval, the extent of response to first-line therapy, residual toxicity from first-line therapy, and the PS of the patient.
- There is currently no standard second-line chemotherapy regimen for patients who fail to respond to or who relapse shortly after first-line therapy. Clinical trials are needed to determine the optimal treatment regimen.

- There is insufficient evidence to recommend a specific chemotherapy regimen. Nevertheless, in the opinion of the lung cancer disease site group, patients who relapse three or more months after having completed first-line chemotherapy may benefit from re-treatment with the same regimen that induced their initial response. This would generally mean re-treatment with EP. Alternative regimens may include CAV or Cb and etoposide.

- Topotecan is a possible alternative for patients who initially respond to chemotherapy and who have a response duration of 45 days or longer.
- Topotecan may be administered orally or intravenously. Available evidence has not yet established a superior mode of administration, and each has different benefits and toxicities. Oral administration is associated with a higher incidence of grade 3/4 diarrhea, whereas IV administration may result in a higher frequency of grade 3/4 neutropenia.

# SCLC

## Treatment at relapse: Is it worthwhile??

- Survival longer than with supportive care?
- Is it effective as palliative therapy (symptom improvement) ?
- Are there specific approaches for specific sites?
- Has it a role for the development of therapy?

# SCLC

## Chemotherapy versus BSC

therapy	MS from start 1st-line (wks)	no. pts	response rate (%)	MS from start 2nd-line (wks)
short + 2nd-line	38	105	25.6	20
short + BSC	30	106	-	11
long + 2nd-line	42	114	18.7	15
long + BSC	38	112	-	12

P < 0.001

# RCT Oral Topotecan vs BSC in Relapsed SCLC

Relapsed  
SCLC

N = 141

Stratify:

PS 0/1 vs 2

Gender

TTP (<60  
vs >60 d)

Liver mets

R  
A  
N  
D  
O  
M  
I  
Z  
E

Oral Topotecan 2.3  
mg/sqm/day 1-5 q 3wk

BSC

Primary end point: Survival

Secondary: QoL, ORR, 6 mo  
survival

# Survival and TTP (ITT)

	Topo + BSC (n = 71)	BSC Alone (n = 70)
Median survival (95% CI)	<b>25.9 wk</b> (18.3, 31.6)	13.9 wk (11.1, 18.6)
6-Month survival (95% CI)	<b>48.8%</b> (37.1, 60.5)	25.7% (15.5, 35.9)
Median TTP (95% CI)	16.3 wk (12.9, 20.0)	

# Recurrent SCLC

## Effect of Radiotherapy

year of study	type of study	dose (Gy)	no. pts LD/ED	RR in radiation port (%)	median surv. (mo.)
1977 <sup>1</sup>	retrospective	21 - 51	23 11/12	52	3
1983 <sup>2</sup>	retrospective	40	25 8/17	64	4
1991 <sup>3</sup>	retrospective	60 (11) 45-55 (14) 38-42 (11)	36 27/9	77	4

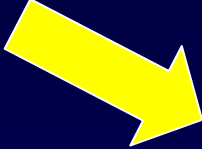
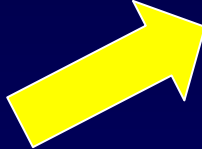

<sup>1</sup> Ihde DC et al. *Radiology* 1977; 132: 443

<sup>2</sup> Ochs JJ et al. *Cancer Treat Rep* 1983; 67: 1123

<sup>3</sup> Salazar OM et al. *Int J Radiat Oncol Biol Phys* 1991; 21: 645

# Recurrent SCLC

## Prognostic Factors for Response to 2nd Line

- **Response to initial therapy  $\geq$  partial**  

  - **Duration of response  $>$  3 months**  

  - **No response and/or early progression ( $<$  3 months)**  

- Sensitive**
- Refractory/resistant**

# Promising for 2nd Line: Amrubicin

- **Synthetic Anthracycline**

- **Phase II**

- Relapsed SCLC, RR 79%

*Yana ASCO 1998*

- Amrubicin + cisplatin, first line ED, RR 88%, median survival 14.1 months

*Ohe ASCO 2004*

- Amrubicin + Irinotecan, unable to demonstrate MTD or RD due to toxicity

*Kurata ASCO 2005*

**Part III: A major response resulted following therapy with etoposide + carboplatin (4 cycles). Patient did well for 4 months and then the cough recurred and disease progression was documented in lung and liver.**

**Which second-line chemotherapy would you suggest?**

1. Rechallenge with induction regimen
2. Cyclophosphamide + doxorubicin + vincristine (CAV)
3. Topotecan + cisplatin
4. Oral topotecan
5. Oral etoposide

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