

# SCLC: Combined modality therapy in limited stage disease

2<sup>nd</sup> International Thoracic Oncology Congress Dresden

18/9/2010 , Dresden

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# Combined therapy of LD-SCLC: Agenda

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- ◆ **Timing and fractionation of chest RT**
- ◆ **Role of PCI**
- ◆ **Role of surgery**
- ◆ **New prognostic factors**

# CT-RT guidelines for LD

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## ◆ PDQ

- Concurrent CT-RT (from 1° or 2° cycle)

## ◆ NCCN

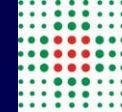
- Concurrent CT-RT (from 1° or 2° cycle)

## ◆ ESMO

- PE with early concurrent RT

## ◆ SIGN & NICE

- Consolidation RT after CT



# Early vs Late Thoracic RT in SCLC: Randomized studies

Reference	# Pts	RT start	RT dose	2-Year S.
Perry 1987	270	E week 0 L week 9	50 Gy	23% 30%
Murray 1993	308	E week 3 L week 15	40 Gy	40%* 34%
Work 1997	199	E week 0 L week 18	45 Gy	20% 19%
Jeremic 1997	103	E week 0 L week 6	54 Gy BID	34%* 26%
Takada 2002	231	E week 0 L week 13	45 Gy BID	55% 35%

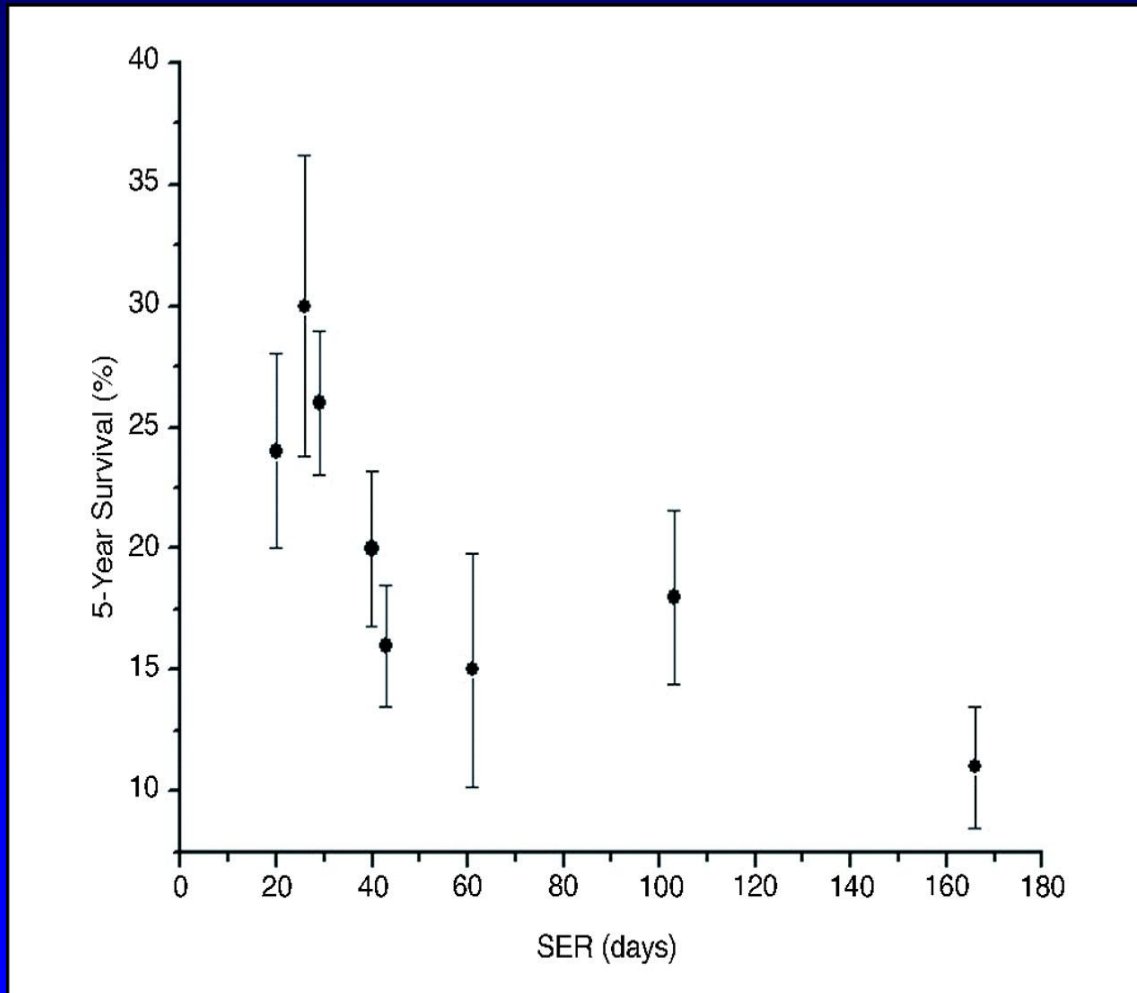
\* statistically significant difference

# Early versus delayed radiotherapy in SCLC

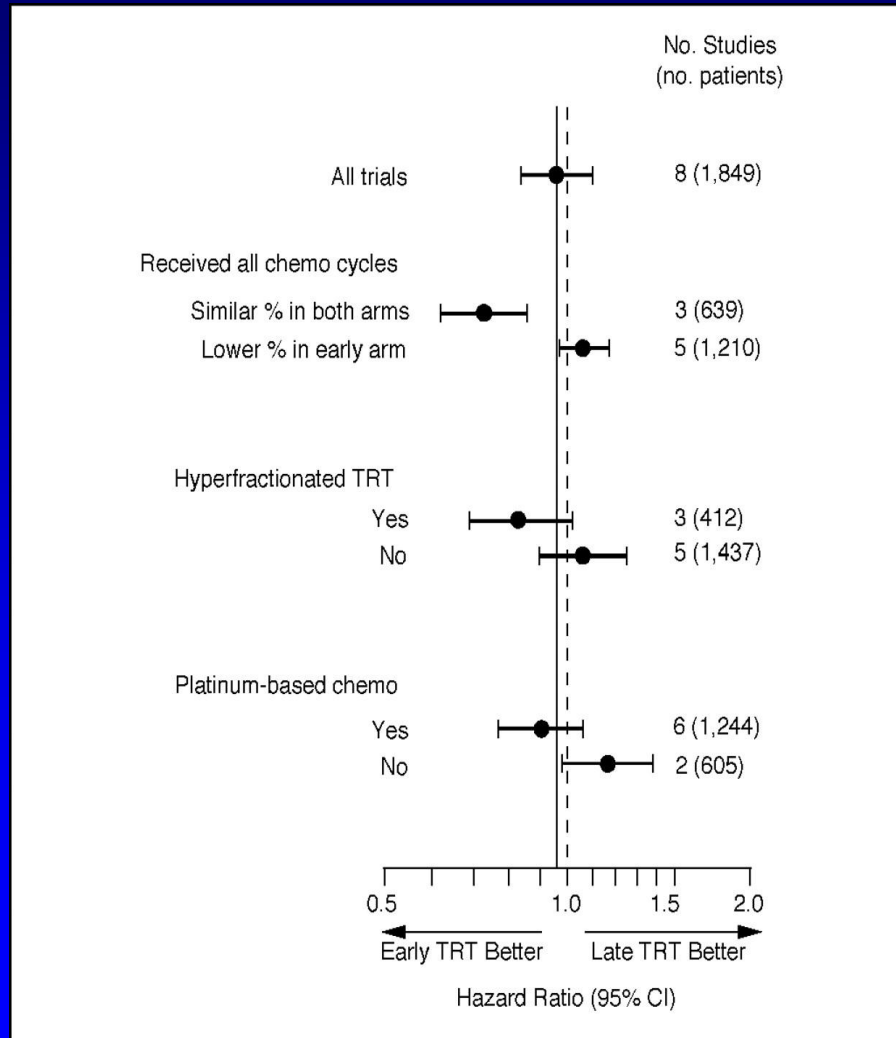
## Meta-analysis of 7 randomized studies:

- ◆ **Early RT: less than 30 days after starting CT versus**
- ◆ **Delayed RT: more than 30 days after starting CT**
  - at 2 years, 1 514 analyzed patients
  - at 5 years, 1 009 analyzed patients
- ◆ **No difference in 2 and 5 years overall survival**
- ◆ **Survival difference at 5 years for chemotherapy including cisplatin (640 patients) with early irradiation (RR = 0.9; p = 0.006)**

# Time from start of any treatment and the end of TRT (SER)



# Forest plot for treatment effect of early vs late TRT in LD-SCLC



# PE + TRT SDF vs BID in LD SCLC (Intergroup Trial 096)

- 417 pts
- LD SCLC
- m. age 62 yrs
- most PS 0-1
- 19% w.l.  $\geq 5\%$

**R**

PE<sub>x4</sub> + concurrent **single daily**  
TRT (1.8 Gy 5d/wk x 5 wks)  
+ PCI (25 Gy/10 fx) to CRs

PE<sub>x4</sub> + concurrent **twice daily**  
TRT (1.5 Gy bid 5d/wk x 3 wks)  
+ PCI (25 Gy/10 fx) to CRs

	<b>CR+PR</b>	<b>M.Survival</b>	<b>2-year Surv.</b>
<b>single</b>	87%	19 months	41%
<b>twice</b>	87%	23 months	47%*

# CALGB 30610/ RTOG 0538

• LD SCLC

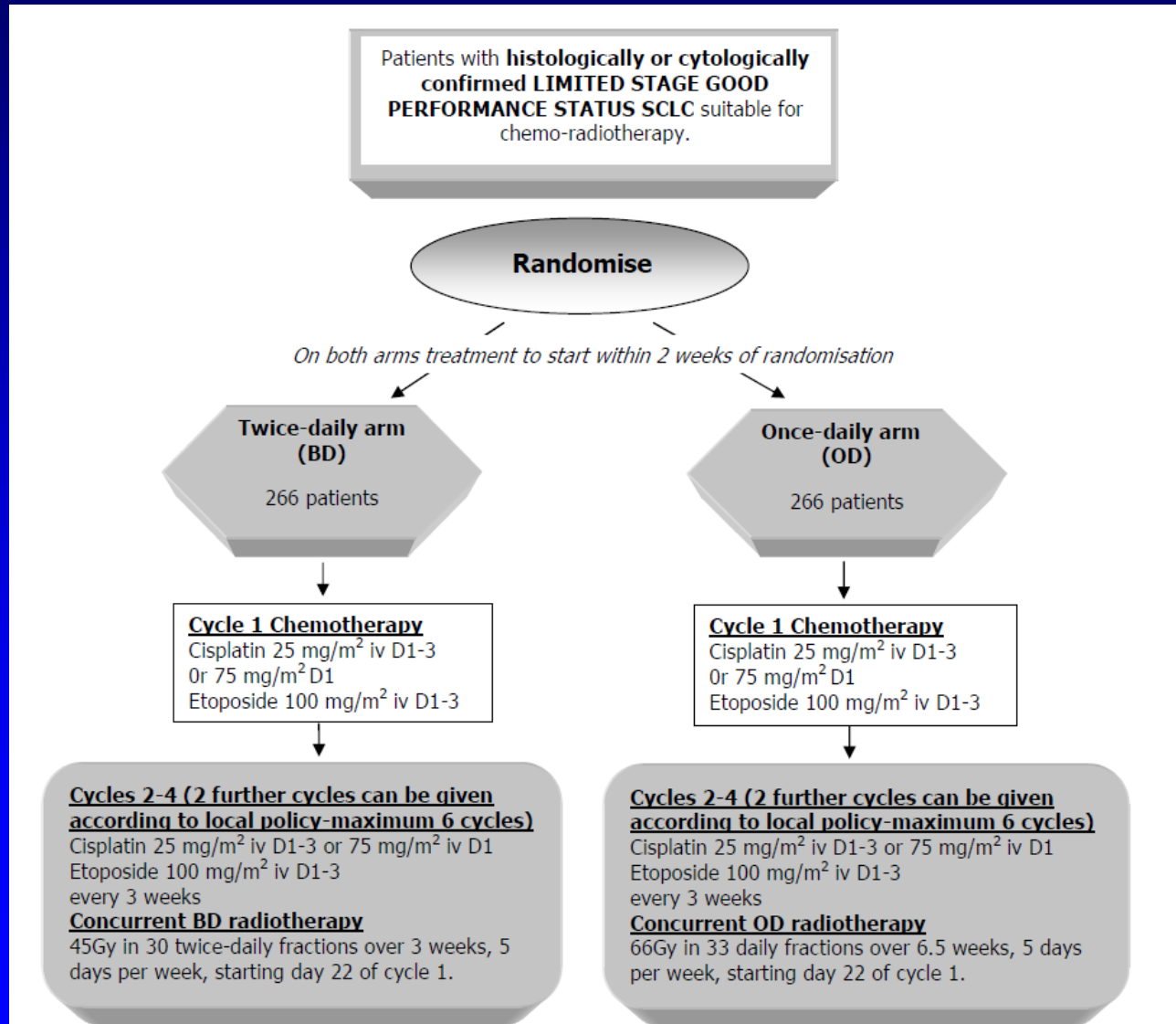
**R**

PE<sub>x</sub>4 + concurrent **twice daily**  
TRT 45 Gy (1.5 Gy bid 5d/wk x 3 wks)

PE<sub>x</sub>4 + concurrent **single daily**  
TRT 70 (2 Gy 5d/wk x 7 wks)

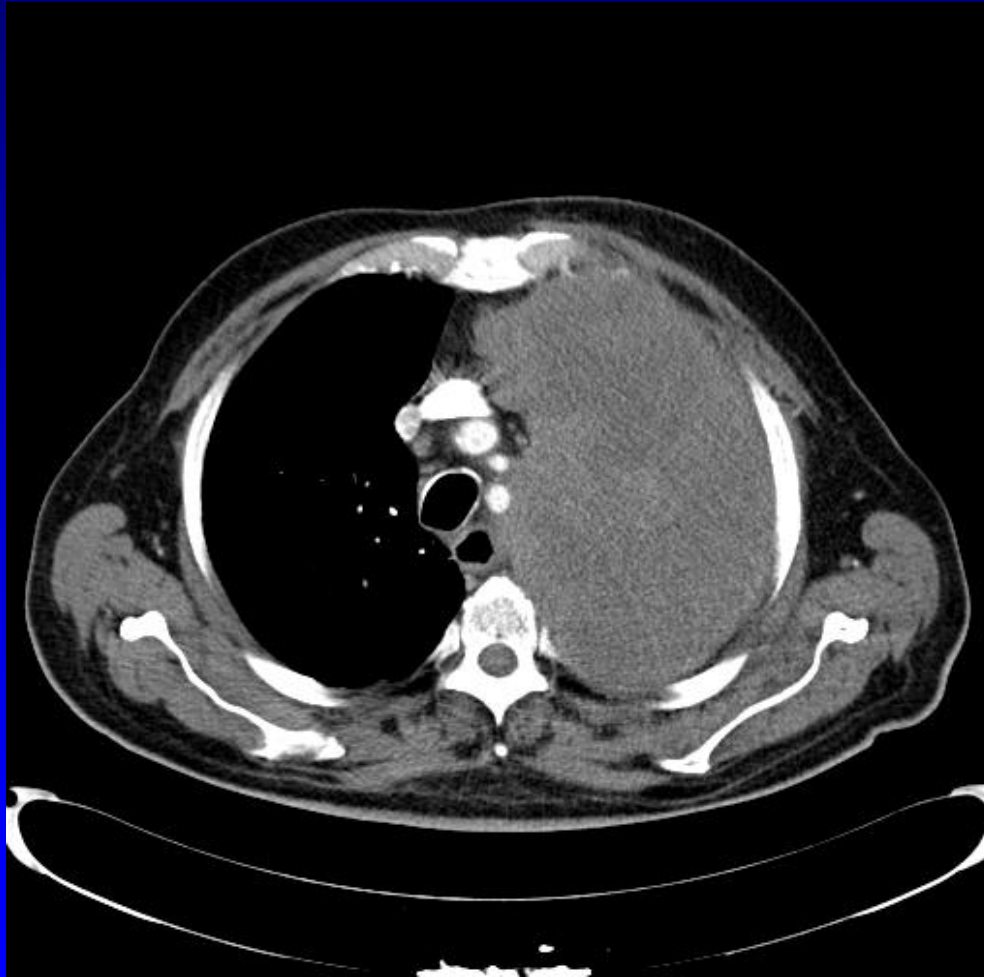
PE<sub>x</sub>4 + concurrent **mixed**  
TRT 61 (1.8 Gy daily for 16 days ->  
1.8 Gy twice daily for 9 days )

# CONVERT: Concurrent **ON**ce-daily **VER**sus twice-daily **RadioTherapy**



# Is concurrent CT-RT always feasible?

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# Limitation to the use of concurrent CT-RT in SCLC-LD

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- ◆ Tumor volume and location
- ◆ Occult extensive disease
- ◆ Poor PS and comorbidities
- ◆ Rapidly growing and aggressive tumors
- ◆ Logistics
- ◆ Advanced age

# Eligibility for concurrent CT-RT of locally advanced LC

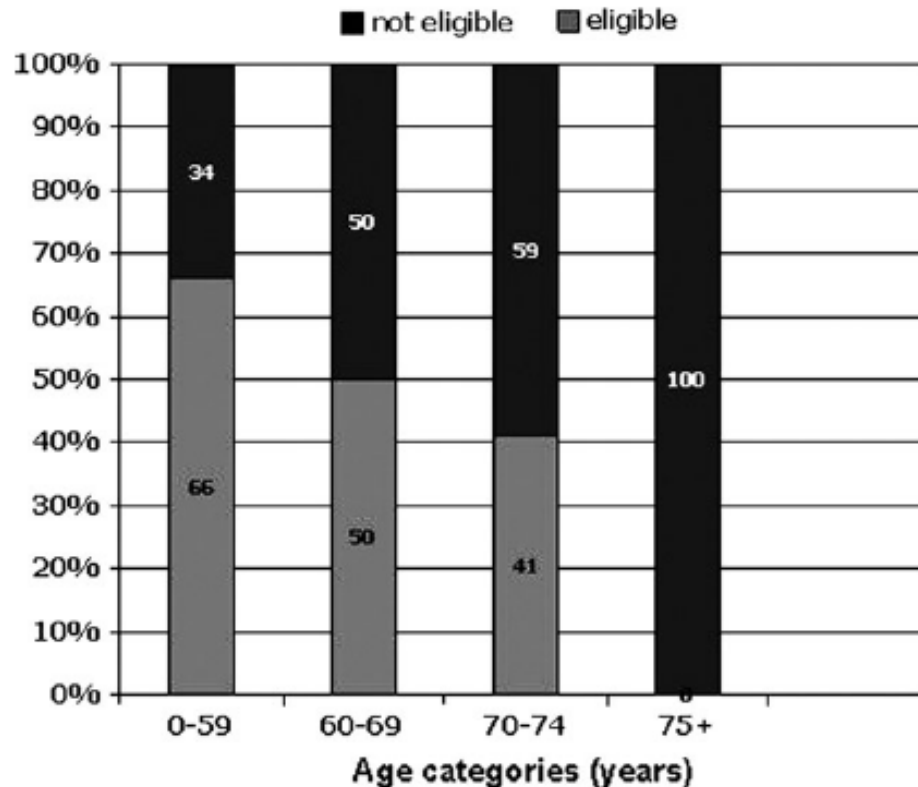


Figure 3. Percentage patients eligible for concurrent therapy.

711 pts (143 SCLC) locally advanced stage LC  
assessed for possible concurrent CT-RT

# Combined CT-RT in elderly SCLC

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- ◆ In the meta-analysis (Pignon, NEJM '92) trend toward adverse outcome for pts > 70 years by adding RT to CT
- ◆ In 0096 trial (Yuen, Cancer 2000) worse survival and higher fatal toxicity (10%) for pts > 70 yrs
- ◆ In the NCCTG trial (Schild, Cancer 2005) more toxicity (pulmonary g4 6% and toxic deaths 5.6%) in pts > 70 yrs

# PCI in SCLC-LD:

## ESMO Recommendations '09

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- ◆ **Patients with SCLC-LD achieving a major response should be offered prophylactic cranial irradiation as it reduces risk of cerebral metastases and improves survival (I, A)**

# Meta-analysis of 7 trials of PCI vs No-PCI in SCLC

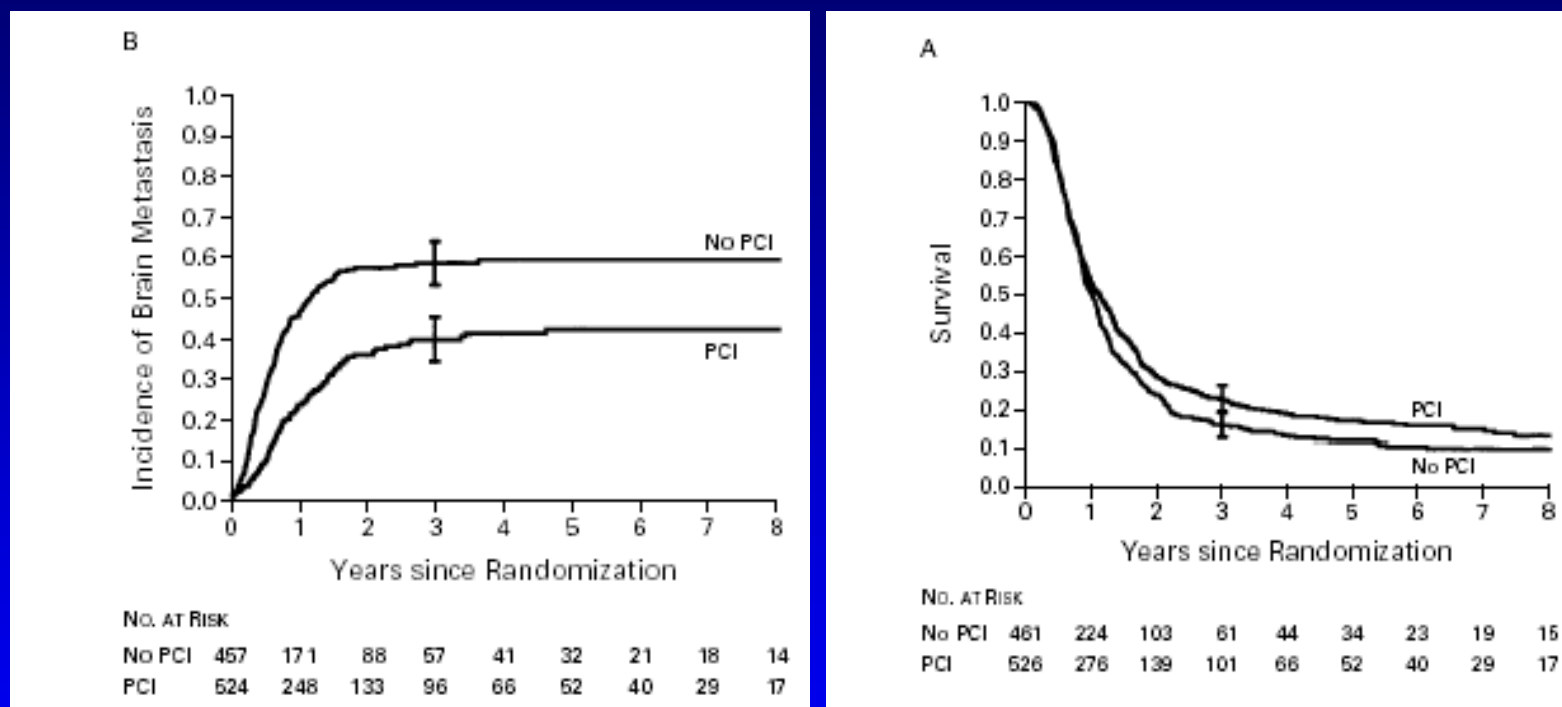
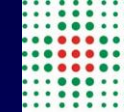


Figure 2. Kaplan-Meier Estimates of Survival (Panel A) and the Cumulative Incidence of Brain Metastasis (Panel B) in Patients with Small-Cell Lung Cancer in Complete Remission, According to Whether They Were Assigned to Treatment with Prophylactic Cranial Irradiation (PCI).

# Meta-Analysis of 7 trials of PCI vs No-PCI in SCLC

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**Patients 987**

**Reduction of Risk  
Of Brain Mets by  
Radiotherapy Dose:**

<b>- 8 Gy x 1</b>	<b>24%</b>
<b>- 24-25 Gy x 8-12</b>	<b>48%</b>
<b>- 30 Gy x 10-15</b>	<b>66%</b>
<b>- 36-40 Gy x 18-20</b>	<b>73%</b>



# EULINT1 (EORTC 22003-08004, RTOG 0212, PCI99-01, IFCT 99-01)

	<b>PCI 25 GY (10 daily fr.)</b>	<b>PCI 36 GY (18 daily fr. or 24 fr. in 16 days)</b>
<b>N° Patients</b>	<b>360</b>	<b>360</b>
<b>Compliance dose %</b>	<b>95</b>	<b>93</b>
<b>Brain relapse</b>	<b>29</b>	<b>23</b>
<b>2YS %</b>	<b>42</b>	<b>37*</b>
<b>Chest relapse %</b>	<b>40</b>	<b>48</b>
<b>Extracranial relapse %</b>	<b>40</b>	<b>42</b>

**\* P = 0.05**

# Failed maintenance strategies

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- ◆ **High dose chemotherapy**
  - 3-fold dose-intensity ICE and PBPCs (Leyvraz, JNCI '08)
- ◆ **Anti-angiogenetic strategies**
  - Thalidomide (Lee, JNCI '09)
  - Vandetanib (Arnold, JCO '07)
- ◆ **Immunotherapy**
  - BEC2/BCG vaccination (Giaccone, JCO'05)

# Role of surgery in SCLC

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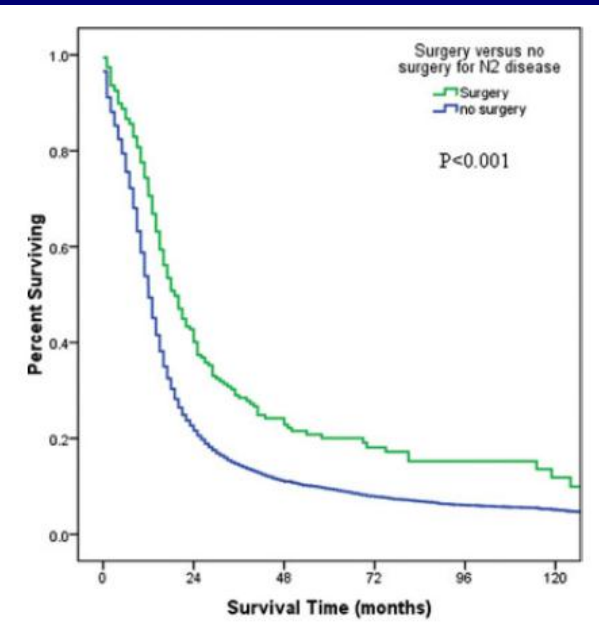
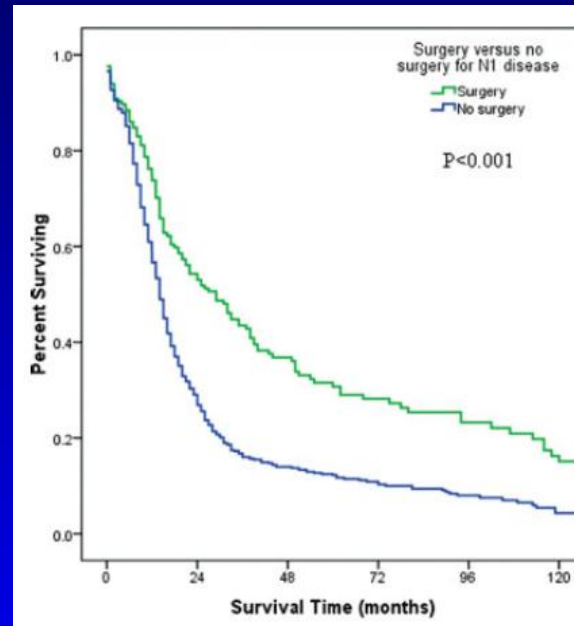
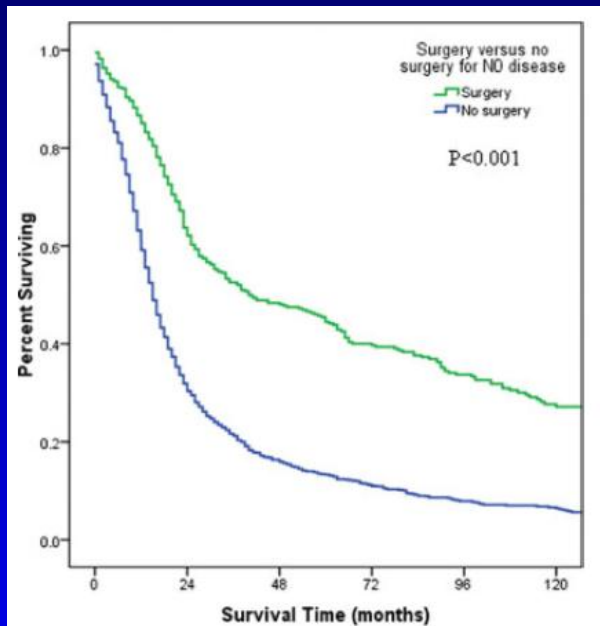
## NCCN guidelines '09:

**Pts with T1-T2N0 SCLC after standard staging evaluation (CT, PET, Brain Imaging, Mediastinoscopy or Endoscopic Mediastinal Staging) may undergo surgical resection (preferably lobectomy with mediastinal nodal dissection or sampling).**

**Pts who undergo complete resection should receive postop. CT +/- PCI.**

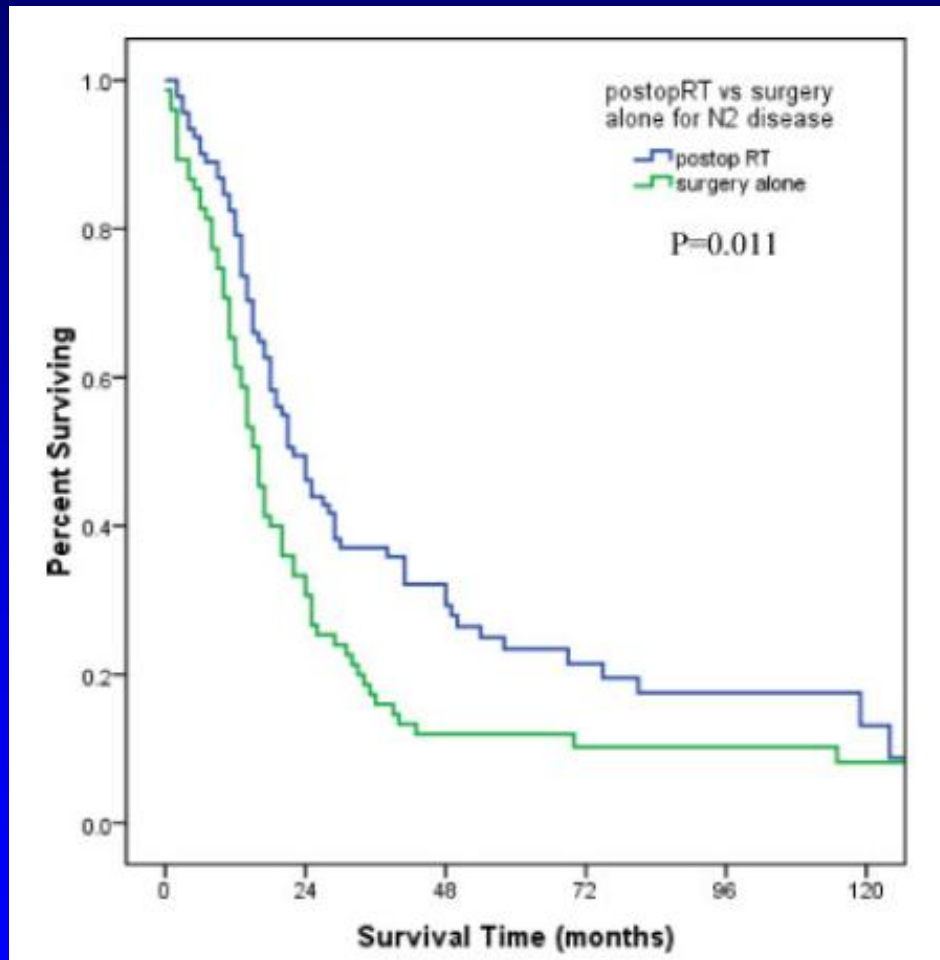
**Pts with N+ should also receive PORT**

# Surgery in SCLC: should its role be re-evaluated

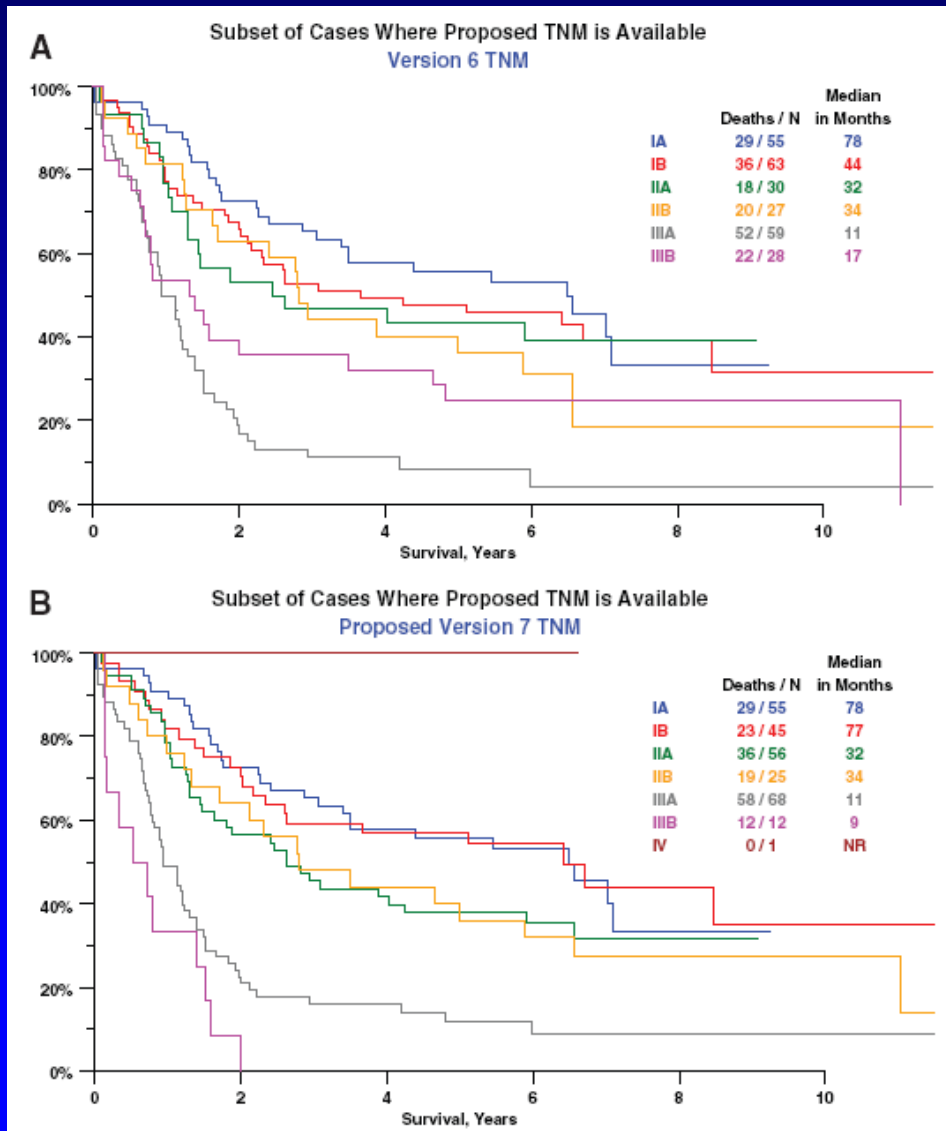


- Survival analysis of 14179 SCLC-LD pts (863 surgically resected) belonging to the SEER registry (years 1988-2002)
- Lobectomy had the best outcome

# Role of PORT in SCLC



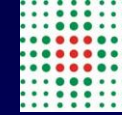
# TNM staging in SCLC



IASLC Staging Committee,  
JTO '09

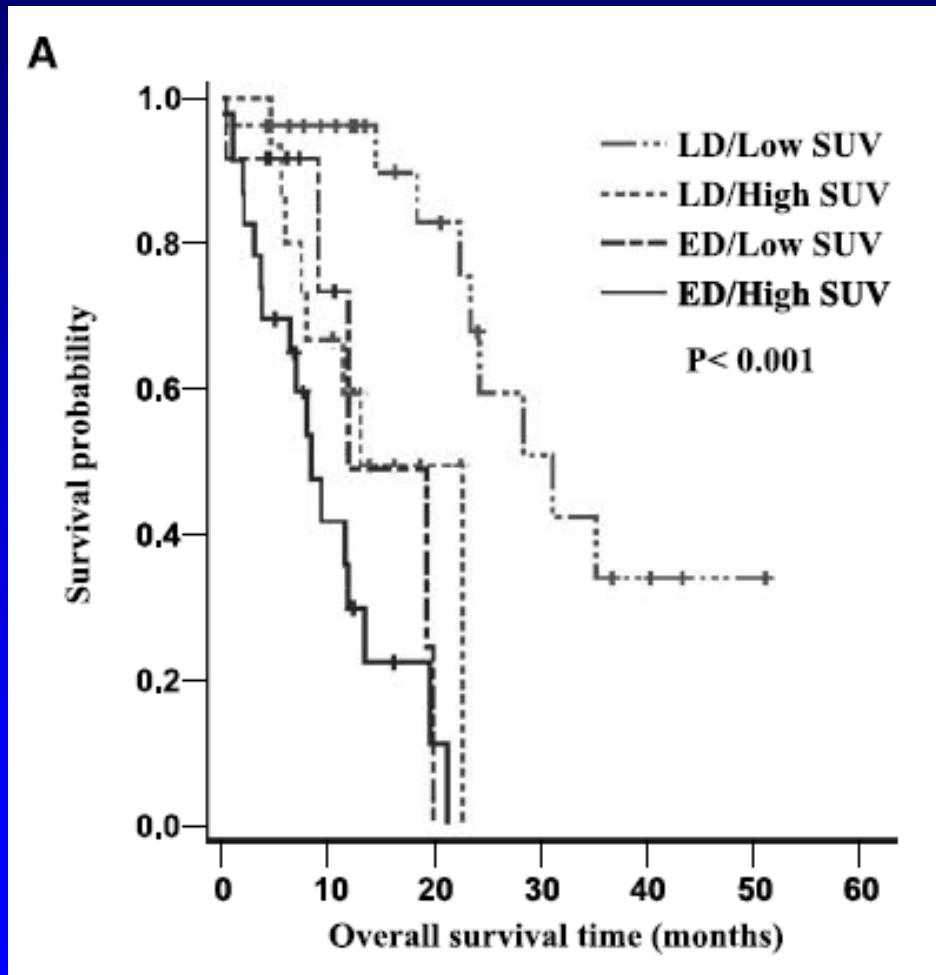
# Novel prognostic factors in SCLC-LD

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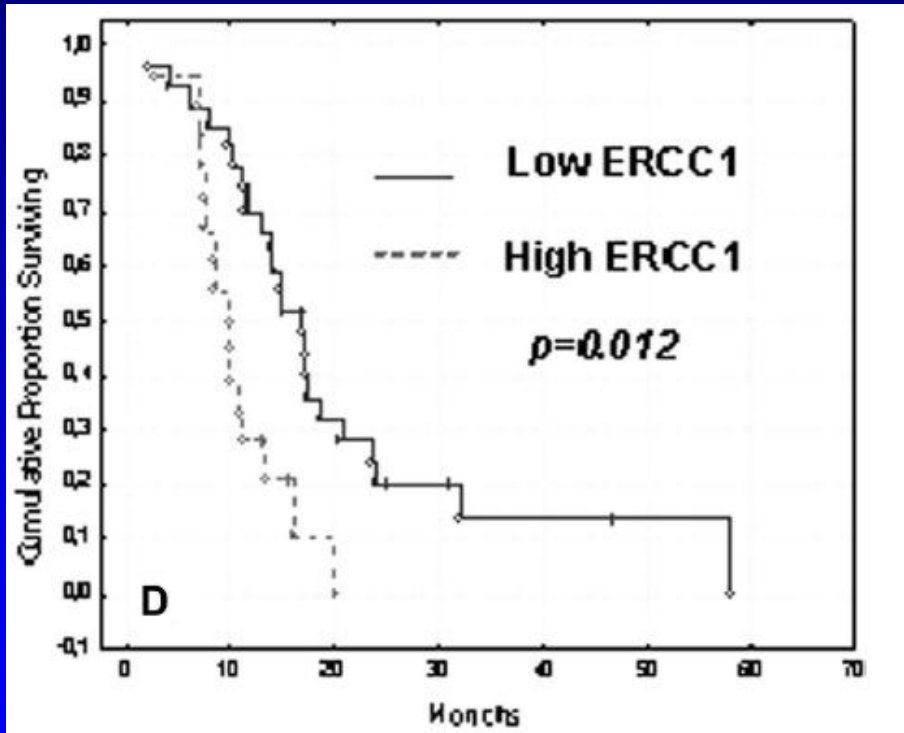
- ◆ **FDG PET Uptake**
- ◆ **ERCC1**

# FDG PET uptake and SCLC prognosis



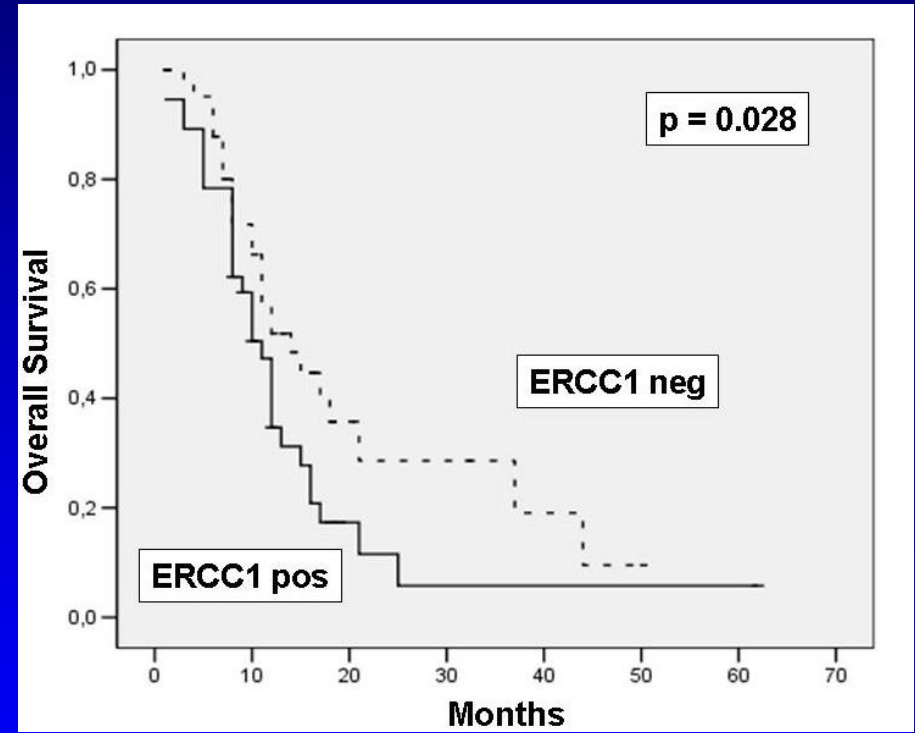
# Prognostic role of ERCC1 in SCLC-LD

Gene expression

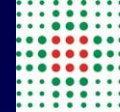


Ceppi, JTO '08

Immunohistochemistry



Rossi, JTO '10



## Conclusions

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- ◆ Addition of chest RT and brain RT improves outcome and timing/duration of chest RT appear crucial to obtain maximal benefit
- ◆ Optimal dose, fractionation and volume remain to be defined (ongoing studies)
- ◆ Only a minority of patients candidate to concurrent CT-RT due to advanced age, comorbidities, poor PS and tumor volume/location
- ◆ Surgery still plays a role for very selected cases
- ◆ Promising role of PET for staging, RT planning and prognosis