Role of Prophylactic Cranial Irradiation in Small Cell Lung Cancer

Kazi S. Manir

MD,DNB,ECMO,PDCR

Clinical Tutor

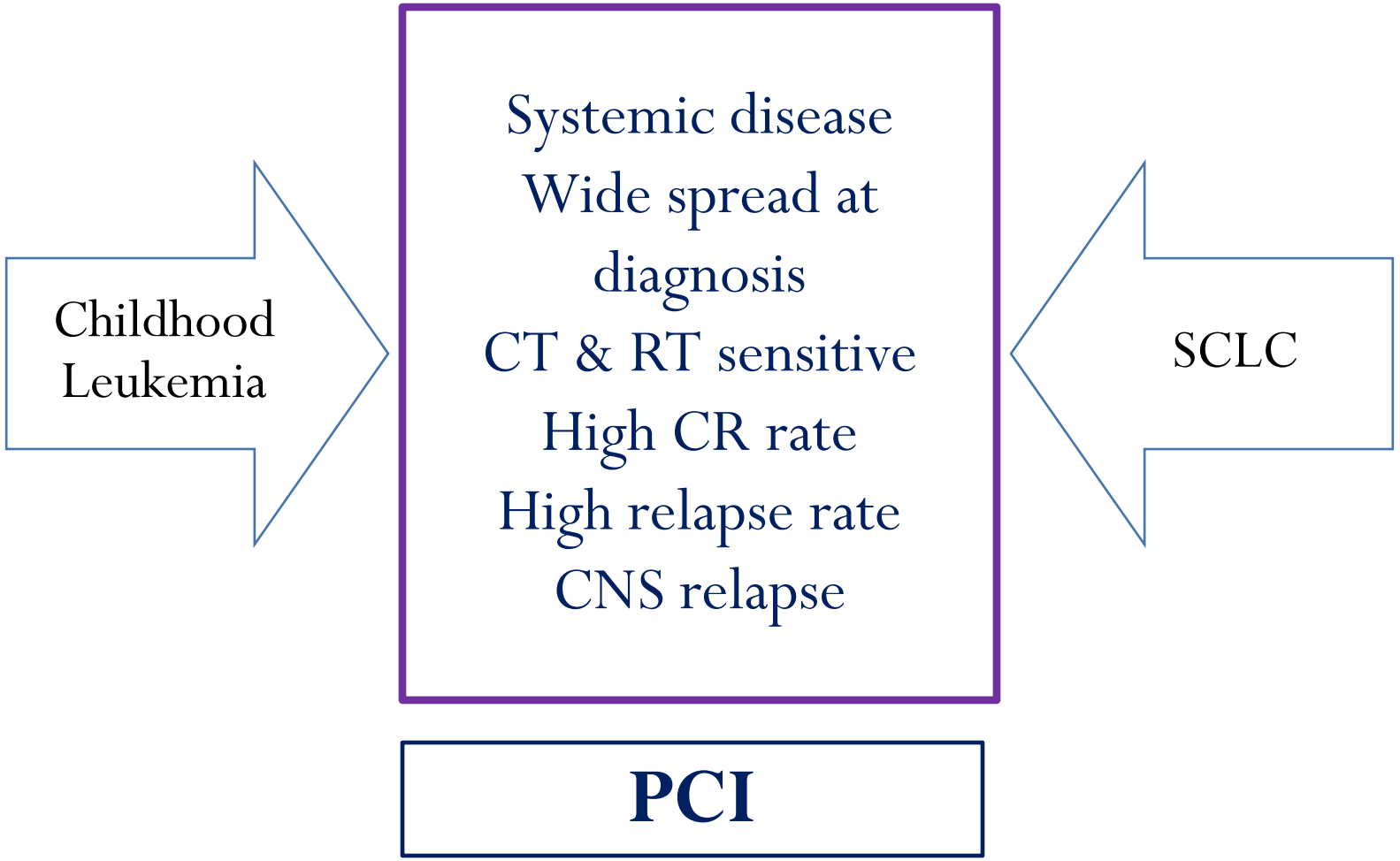
Department of Radiotherapy

R. G. Kar Medical College and Hospital, Kolkata

SCLC

- 15% of lung cancer
- 60% Extensive Stage Disease (ED)
- MS 23m for Limited Stage Disease (LD)
- MS 7-8m for ED
- 20% Brain mets at diagnosis
- 50-80% brain relapse after 2years of CTRT

The background...



Cancer Chemother Rep

Volume 4, Issue 4, Pages 239-241

Should initial treatment of small cell carcinoma include systemic chemotherapy and brain irradiation?

Hansen, H.H.

CNS METASTASES IN SMALL CELL BRONCHOGENIC CARCINOMA

Increasing Frequency and Changing Pattern with Lengthening Survival

JOHN L. NUGENT, MD, PAUL A. BUNN, JR., MD, MARY J. MATTHEWS, MD, DANIEL C. IHDE, MD, MARTIN H. COHEN, MD, ADI GAZDAR, MD, AND JOHN D. MINNA, MD

The records of 209 patients with small cell bronchogenic carcinoma were reviewed to define the problem of CNS metastases. CNS metastases were documented in 102 of these patients (49%) and 55 of 85 autopsied patients had CNS metastases (65%). The probability of developing a CNS metastasis increased with lengthening patient survival to a level of 80% after 2 years. As in other series, the cerebrum was the most frequently involved site. In addition, leptomeningeal, spinal, pituitary, and cerebellar metastases, and multiple sites of involvement were far more common than in previously reported series. Patients with bone marrow and liver metastases at initial staging were more likely to develop CNS metastases than those without these metastases. Bone marrow involvement was strongly associated with the development of leptomeningitis. Systemic chemotherapeutic agents which cross the blood brain barrier did not prevent the high frequency of CNS metastases. Pathologic studies suggested cerebral and leptomeningeal metastases may arise via hematogenous spread or via penetrating vessels from bone marrow to the subarachnoid space. Therapy for CNS metastases provided adequate palliation, and the majority of deaths were due to systemic rather than neurologic disease. Nevertheless, prophylactic therapy appears necessary at present to prevent the morbidity associated with these metastases. As further improvements in systemic therapy evolve, CNS prophylaxis may also be required for "cure" of patients with small cell lung cancer.

Cancer 44:1885–1893, 1979.

Heine Hoi Hansen, MD 1938-2011

Cancer Treat Rep. 1981 Sep-Oct;65(9-10):811-4.

Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation.

Komaki R, Cox JD, Whitson W.

Abstract

The problem of brain metastasis from small cell carcinoma (SCC) of the lung has been appreciated for many years, but the magnitude of the problem has been underestimated. Recent studies have shown that the risk of brain metastasis increase as survival is prolonged. Although prophylactic cranial irradiation (PCI) has reduced the frequency of brain metastases, the effect on risk estimates of differences in the periods of observation was not evaluated. From 1974 through 1979, 131 patients with SCC of the lung who had no evidence of brain metastasis by radionuclide or computerized tomographic scan were treated in the Division of Therapeutic Radiology at the Medical College of Wisconsin Affiliated Hospitals. PCI was started in 1977; 57 patients received it and 74 did not. To correct for the differing periods of observation for the two groups, an actuarial calculation of the probability of brain metastasis was used. The calculated rate of clinical failure in the brain for patients who did not receive PCI was 28% at 12 months and 58% at 24 months. The calculated failure rate of the brain for patients who received PCI was 11% at 12 and 24 months. The difference in the probability of brain metastasis between the patients who did or did not receive PCI is highly significant (P less than 0.01). The true benefit of PCI becomes apparent only when the risk of intracranial metastasis is evaluated by methods that correct for incomplete followup. PCI eliminates the progressive increase in the risk of brain metastasis that accompanies increased survival and is important to maximize the probability for cure of patients with SCC.

To be discussed..

- **Historical evaluation**
- **Benefits**
- **Regimen**
- **Long term neurological toxicities**
- **Timing**
- **Candidates**

The goal for PCI

- Decreased Brain Relapse
- Improved Survival
- Improved QoL
- Least toxicity

Earlier studies

Study	Design	Criteria	Brain relapse	Survival	Neurological function	Remarks
PCI 85 trial Arriagada et al. (1995)	RCT PCI vs Obs (N= 300)	All stage After CR	2years 19% Vs 40%	2yr OS 29% Vs 21% (NS)	No difference	41% baseline neurological dysfunction
UK 02 trial Gregor A et al. (1997)	RCT PCI 36Gy/18# 24Gy/12# Obs (N =314)	Limited stage After CR	HR 0.44	OS HR 0.86 (NS) MFS HR 0.75	No difference (1yr F/U)	40% baseline neurological dysfunction

Earlier studies

CNS relapse rates in untreated controls and treated patients categorized according to the extent that brain imaging was performed at diagnosis or prior to randomization to exclude early metastatic disease in the brain.

Proportion with brain imaging	Modality	CNS relapses without PCI	Percent	CNS relapses with PCI	Percent	Timing of relapse
Not stated						
Slotman([†]E)		59/143	41%	24/143	17%	Initial and late
Wagner([†]E+[‡]L)		8/15	53%	3/16	19%	Initial and late
˙The minority						
Gregor([‡]L)	CT (13%)	65/120	54%	74/194	38%	Initial and late
Hansen([†]E+[‡]L)	None if asymptomatic	Not stated		Not stated		
Laplanche([†]E+[‡]L)	None	57/111	51%	44/100	44%	Initial and late
		Total 122/231	53%	Total 118/294	40%	
˙The majority						
Aroney([†]E+[‡]L)	CT	57/139	41%	6/30	20%	Initial and late
Arriagada([†]E+[‡]L)	CT	67/149	45%	28/145	19%	Initial
Beiler([†]E+[‡]L)	Nuclear medicine	5/31	16%	0/23	0%	Initial
Cao([‡]L)	CT	8/25	32%	1/26	3.8%	Initial and late
Eagen([‡]L)	CT	11/15	73%	2/15	13%	Initial and late
Jackson([†]E+[‡]L)	Nuclear medicine	4/15	27%	0/14	0%	Initial and late
Maurer([†]E+[‡]L)	CT/nuclear medicine	15/84	18%	3/79	4%	Initial and late
Niranen([‡]L)	Nuclear medicine	7/26	27%	0/25	0%	Initial and late
Ohonoshi([†]E+[‡]L)	CT	12/23	52%	5/23	22%	Initial and late
Seydell([‡]L)	CT	22/122	18%	5/107	5%	Initial and late
		Total 208/629	33%	50/487	10%	

Davey P et al. Lung Cancer 2015

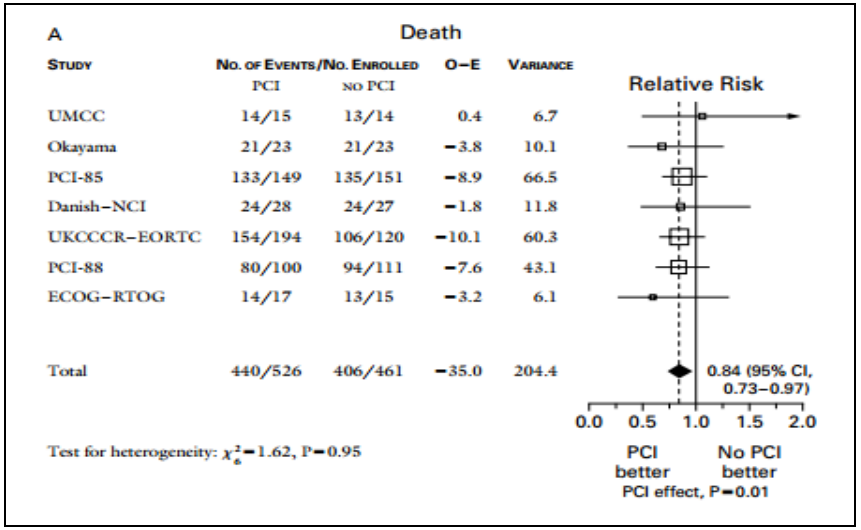
PCI in LD

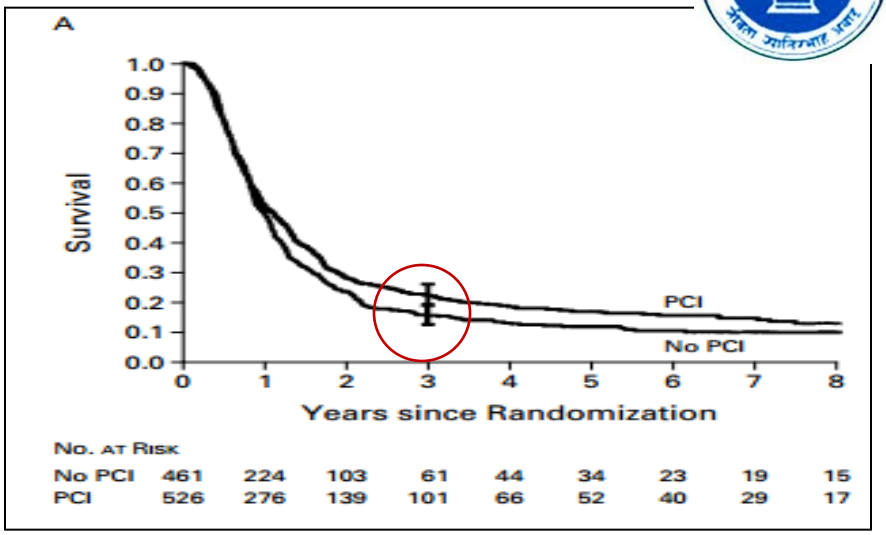
PCI OCG Meta-analysis (1977-1995)

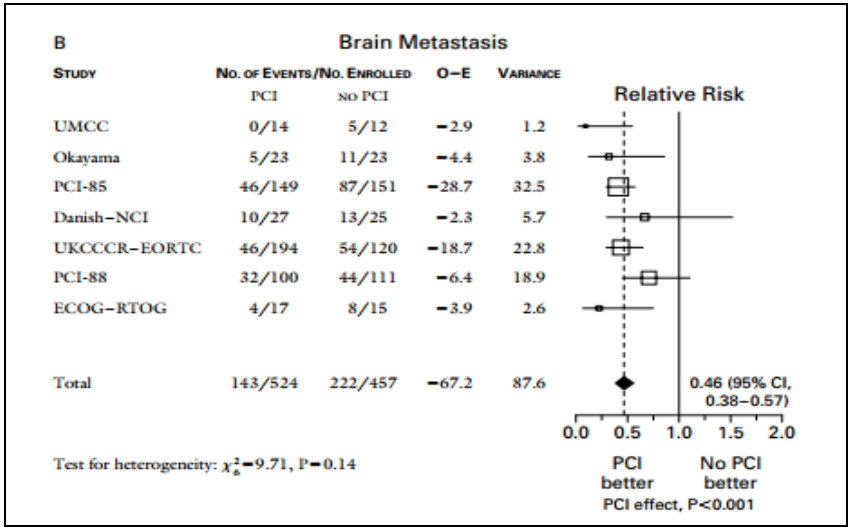
7 RCTs (n= 987) [LD 85%] PCI vs Obs (CR on X Ray)

- **30% absolute decrease in brain relapse at 3years.**
- **9% absolute increase in DFS in 3 year DFS**
- **OS benefit 6 % in 3years (21 % vs 15%).**
- Consistent benefit among subgroups (Age, PS, LD vs ED, and type of induction therapy).
- Trend of improved OS Brain Control in earlier PCI and higher dose.

Auperin A et al. NEJM 1999







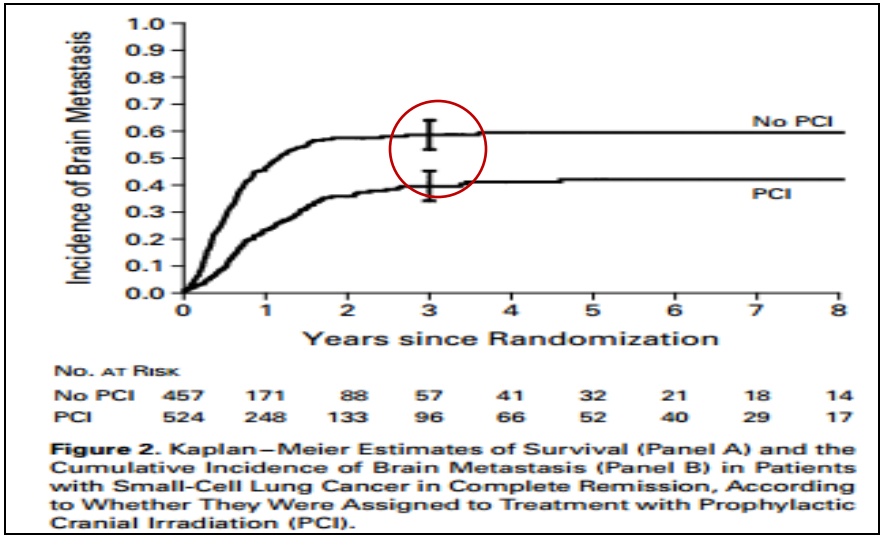


Figure 2. Kaplan−Meier Estimates of Survival (Panel A) and the Cumulative Incidence of Brain Metastasis (Panel B) in Patients with Small-Cell Lung Cancer in Complete Remission, According to Whether They Were Assigned to Treatment with Prophylactic Cranial Irradiation (PCI).

PCI OCG Meta-analysis : Auperin A et al. NEJM 1999

BMC Meta-analysis (2001)

- 12 RTCs (N= 1547)
- PCI in post Chemotherapy CR.
- **Decrease of brain metastases incidence (HR: 0.48 for all the studies.**
- **Improvement of survival (HR: 0.82) in patients in CR.**
- **Long-term neurotoxicity was not adequately described.**

Meert AP et al. BMC Cancer (2001) 1:5

SEER database: Retrospective revie

- 1988-1997
- 7995 patients
- Retrospective series
- Median F/U 13month (1-180m)

Arm	2years (%)		5years (%)		10years (%)	
	CSS	OS	CSS	OS	CSS	OS
PCI	45	42	24	19	17	9
Control	28	23	15	11	11	6

- Consistent results irrespective of age and stage

Patel S et al. 2009 Cancer

Zhang et al. BMC Cancer 2014, 14:793
http://www.biomedcentral.com/1471-2407/14/793

BMC Cancer

RESEARCH ARTICLE Open Access

Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis

Wenwen Zhang[1], Wenjing Jiang[1], Linlin Luan[1], Lili Wang[2], Xiangrong Zheng[2] and Gongchao Wang[1*]

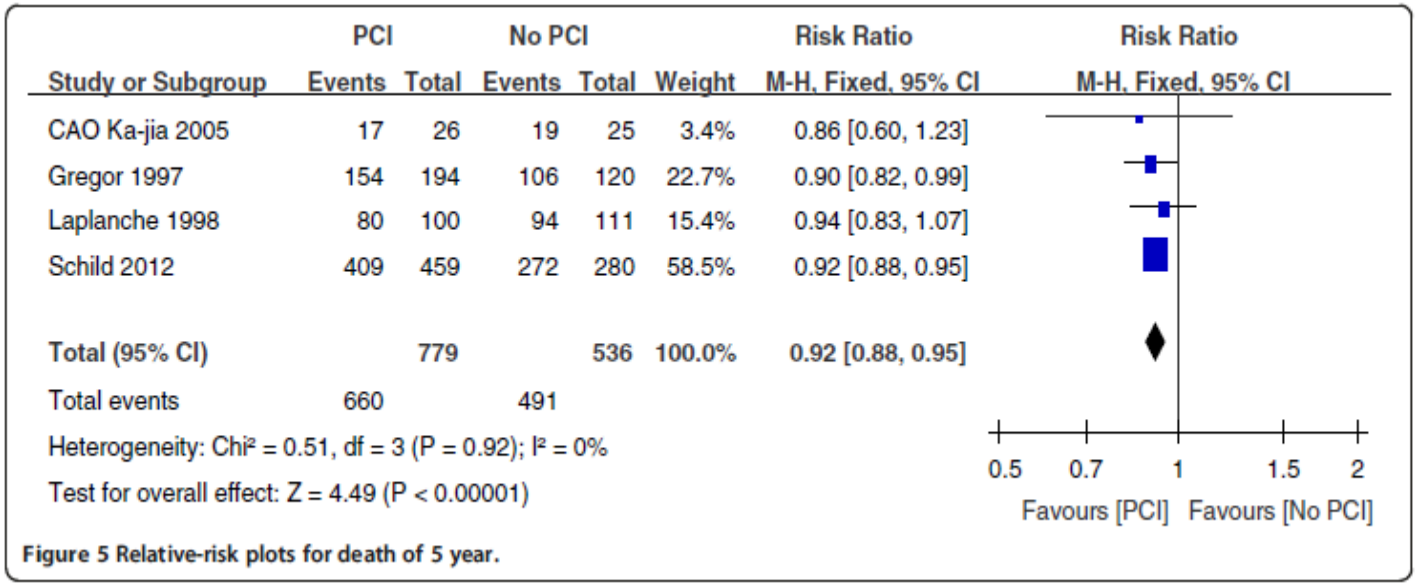


Figure 5 Relative-risk plots for death of 5 year.

PCI in Limited Stage disease

- **PCI after response to initial therapy is strongly recommended.**

- **Robust data**
- **PCI improves Brain Control**
- **PCI improves survival**
- **No Major neurocognitive dysfunction**

PCI in Extensive Disease

EORTC 08993-22993 (2007) RCT (n = 143)

- **PCI vs Obs (after ANY response to 4/6c CT)**
- **No baseline /repeated neuroimaging**
- **6 fractionation regimens used (BED 25-39Gy)**
- Lower risk of symptomatic brain metastases (hazard ratio, 0.27
- Risk of brain metastases within 1 year was 15 % vs 40 %
- Median DFS 14.7 wks vs 12 wks.
- Median OS from 6.7 m vs 5.4 m (after randomization).
- The 1-year survival rate was 27 vs 13 %.

Slotman B. et al. N Engl J Med 2007;357:664-72.

PCI evidence: Subset analysis on ED

Study	Design	Brain control	Survival
Arriagada et al. 1997	RCT (n= 294,19% ED)	Improved	Improved (NS)
PCI Meta-analysis 1999 Auperin et al.	7 RCTs (n= 987,16%ED)	Improved (HR 0.44)	Improved (HR 0.87)
BMC Meta-analysis 2001 Meert AP et al.	7 out of 11 RCTs (n= 821 all stage)	Improved (HR 0.50)	Subset analysis absent
SEER database 2009 Patel S et al.	Retrospective (n= 7995)	Improved	CSS,DFS and OS improved

ASCO American Society of Clinical Oncology
Making a world of difference in cancer care

2014 ASCO Annual Meeting

Prophylactic cranial irradiation has a detrimental effect on the overall survival of patients with extensive disease small cell lung cancer: Results of a Japanese randomized phase III trial

Takashi Seto, Toshiaki Takahashi, Takeharu Yamanaka, Hideyuki Harada, Hiroshi Nokihara, Hideo Saka, Makoto Nishio, Kazuhiko Nakagawa, Koichi Takayama, Osamu Ishimoto, Koji Takeda, Hiroshige Yoshioka, Motoko Tachihara, Hiroshi Sakai, Koichi Goto, and Nobuyuki Yamamoto

- ED SCLC patient (n = 163) Post Chemo CR (MRI)
- RCT: 25Gy/10# PCI vs Obs
- Primary end point OS
- Secondary end point BM, PFS, A/E
- **Interim analysis 9.4 months study stopped**
- **Risk of Brain Metastasis reduced in PCI.**
- **Poorer Median OS in PCI arm 10.1 vs 15.1months**
- But PFS similar
- A/E similar

Seto T et al. JCO 32 5s 2014

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline

Charles M. Rudin, Nofisat Ismaila, Christine L. Hann, Narinder Malhotra, Benjamin Movsas, Kim Norris, M. Catherine Pietanza, Suresh S. Ramalingam, Andrew T. Turrisi III, and Giuseppe Giaccone

In patients with LS or ES SCLC who achieve a complete or partial response to initial therapy, prophylactic cranial irradiation [PCI] is recommended (grade 1B). *Remark: The regimen of 25 Gy in 10 daily fractions has the greatest supporting data for safety and efficacy. The panel notes that a recent Japanese study failed to demonstrate survival advantage with PCI in patients with ES SCLC. On publication of the mature data from this study, the recommendation for PCI in ES SCLC might be subject to revision.*

PCI in Extensive Stage

- **Consistent outcome data similar to Limited stage disease.**
- **Improved Brain Relapse rate.**
- **Improve Survival in some trials.**
- **Matured data from Japanese trial is pending.**

- **PCI after good response to initial treatment is still beneficial .**

PCI after CR/PR

Study	Design	Inclusion	Mode	Brain control	Survival
Arriagada et al. 1995	RCT N=300	All stage CR	CXR , Bronchoscopy	Improved	NS
Auperin et al. 1995	Meta analysis N = 987	All stage CR	CXR, CT, Bronchoscopy	HR 0.46	HR 0.84
BMC 2001 Meert AP et al.	Meta-analysis N= 1547	All stage CR/PR	CT Scan	All : HR 0.49 CR: HR 0.48	All: HR 0.94 CR: HR 0.84
Slotman et al. 2007	RCT N =145	ED Any response	Not mentioned	HR 0.24	OS DFS improved

- Non uniform response evaluation criteria.
- No study separately addressed the issue.
- Few studies included Partial Responses after initial treatment.
- Benefits in both Complete and Partial response after initial treatment.

Age

Table 2. Estimates of Cause-specific and Overall Survival by Age Grouping With or Without PCI

Age Group	CSS		*P*	OS		*P*
	5-year	10-year		5-year	10-year	
<60 y						
With PCI	30%	21%	<.0001	25%	16%	.0001
Without PCI	21%	16%		17%	12%	
60-66 y						
With PCI	21%	15%	.007	16%	7%	.004
Without PCI	17%	12%		13%	7%	
67-72 y						
With PCI	22%	15%	.002	16%	5%	.0005
Without PCI	15%	12%		10%	5%	
≥73 y						
With PCI	18%	7%	.0001	10%	2%	<.0001
Without PCI	9%	6%		5%	1%	

PCI indicates prophylactic cranial irradiation; CSS, cause-specific survival; OS, overall survival.

SEER database Patel S et al. 2009

Age >60 years significant predictor for long term neurotoxicity after PCI.

Glanz MJ et al. 1997

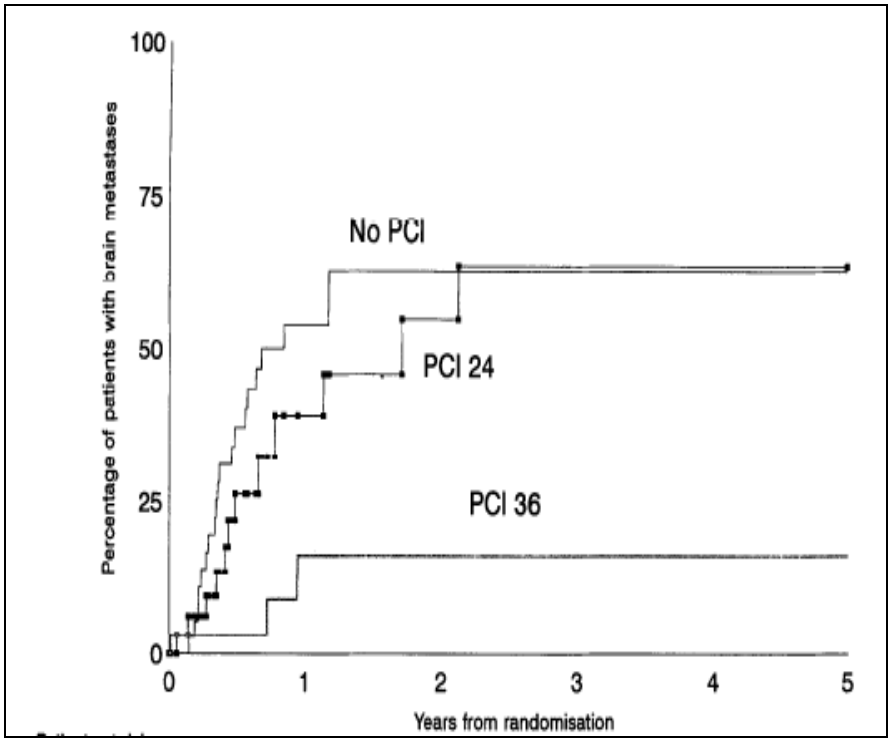
RTOG 0212 Wolfson AH et al. 2012

Regimen

Total Dose (Gy)	#	# size (Gy)	HR
36	18	2	0.16
20	5	4	0.23
30	10	3	0.28
8	1	8	0.44
24	8	3	0.45
30	15	10	0.49
24	12	2	0.71

Gregor A et al. Eur J Cancer 1998
Arriagada R et al. J Natl Caner Inst 1995
Young GY et al. The Oncologist 2001

UK02 trial (Gregor A et al.), UK (1997)



RCT (n = 314) 3arm

PCI 36: 36Gy/18#

PCI 24: 24Gy/12#

No PCI

Hazard Ratio

PCI 36 vs No PCI : 0.16

PCI24 vs No PCI : 0.71

Non significant survival advantage : PCI vs NO PCI (HR 0.86)
No Major difference in neurotoxicity and QoL between two schedule

Intergroup study (PCI 99-01,EORTC 22003-08004, RTOG 0212, and IFCT 99-01)

- **RCT**
- LD-SCLC patients (n = 720) (PCI after CR to chemo- RT)
- Standard dose (25 Gy/2.5 Gy QD)
- Higher dose (36 Gy/2 Gy QD)
- High dose (36 Gy/1.5 Gy b.i.d.)
- Baseline and follow up Neuro QoL evaluation.
- **No significant difference in 2-year incidence of brains metastases (29% vs 24%)**
- **Poorer 2-year OS in higher dose group (37 vs. 42%) probably due to increased cancer-related mortality.**

Le Pechoux et al. Lancet Oncol 2009;10:467-474.

Intergroup study (PCI 99-01,EORTC 22003-08004, RTOG 0212, and IFCT 99-01)

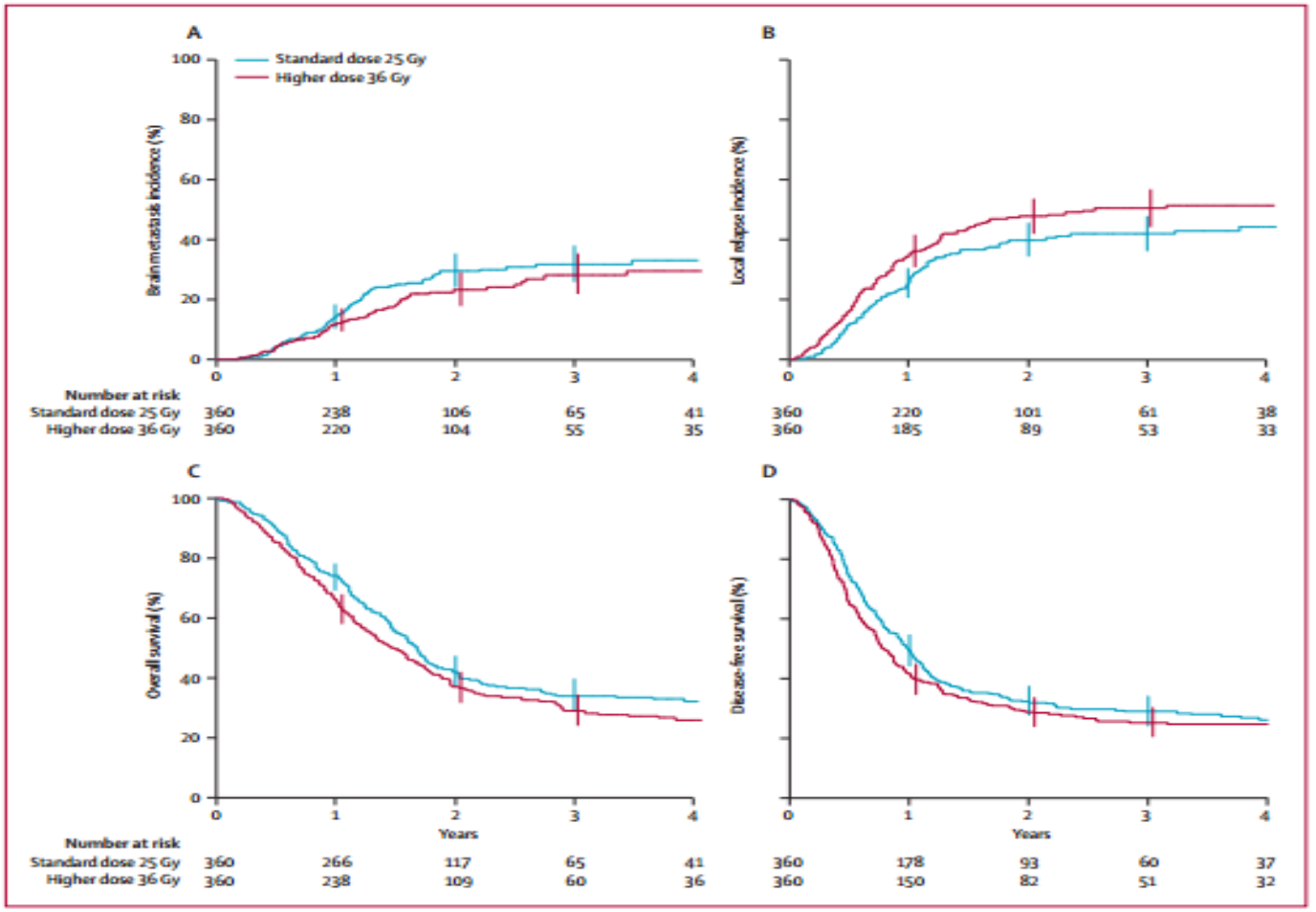
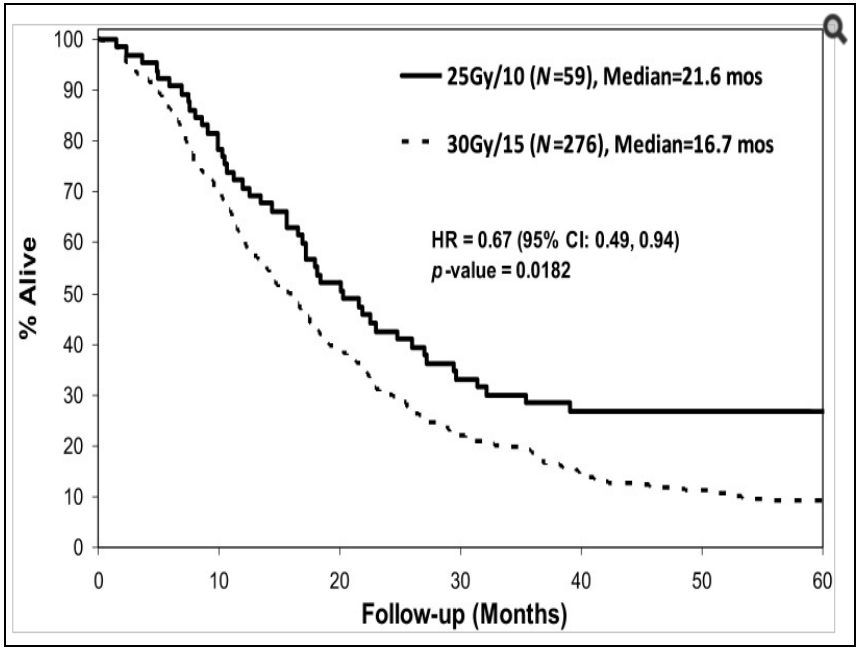


Figure 2: **Kaplan-Meier curves showing total incidence of brain metastasis (A), local relapse (B), overall survival (C), and disease-free survival (D)**

Le Pechoux et al. Lancet Oncol 2009;10:467-474.

NCCTG pooled analysis

- N= 421 (LD)
- PCI 25Gy/10#
- PCI 30Gy/10#
- No PCI



Improved survival with 25Gy/10# (HR 0.67)

Schild SE et al. Ann Oncol 2012

RTOG 0212: Primary Analysis

Phase II RCT : 3arm (n = 265)

- Standard (25Gy/10#)
- Experimental High Dose (36Gy/18#)
- Experimental High Dose (36Gy/24#/1.5Gy BID)
- Neurotoxicity and QoL analysis

Initial results:

- Median F/U 25.3months
- **Increased chronic neuro toxicity (at 1year) in 36/18# arm.**
- **Brain relapse rates (at 1 year) are lower in higher doses (22% vs 10% vs 21%)**

Wolfson AH *Int J Radiat Oncol Biol Phys* 2011

Regimen

25Gy/10# in LD SCLC is Standard regimen till today.

- **Better Brain control**
- **Lesser Neurotoxicity**
- **? Better survival**

- **Improved survival with higher doses from initial RTOG 0122 data is encouraging.**

Timing

Auepeirn et al. 1999 (n = 633) Meta-analysis	Time interval between induction tt and Randomisation <4m 4-6m >6m	Risk of Brain mets HR 0.27 vs 0.50 vs 0.69	Greater effect in soon after randomisation
Suwinsky R et al. 1999 (n = ?)	Review Interval between tt initiation and PCI Early (<60days) Vs Late (>60days)	Better dose response for brain control	
Meert AP et al. 2001 (n = 1547) Meta-analysis	Initial vs Late PCI (Time frame not mentioned)	Brain relapse HR 0.29 (initial PCI)	Better Brain Control
Korczy´nska BS et al. 2010 (n = 129)	Early (during TRT) Late after TRT	Brain mets rate 7% vs 21%	Better brain control

Timing

- **Non-uniformity of definitions of "early" versus "late" PCI.**
- **Little evidences direct comparisons.**
- **Early initiation after completion of initial treatment (?< 6months of CTRT) is beneficial.**
- **Decreased brain relapse rate if initiated early.**
- **No impact on survival.**

Neurotoxicity: Older series

Study	Survivors	Study	Tool	Results
Catane et al. 1981 (n=71)	26m (18-42)	PCI PCI + IT MTX No PCI (Prospective)	Clinical EEG CT Scan	Only CT abnormality No Clinical /EEG change
Johnson BE et al. 1990 (n = 15)	>4 years	Observational (Prospective)	CECT MRI Clinical	Only CT/MRI changes No dramatic decline in clinical parameter
Lee JS et al. 1987 (n = 38)	>3yrs	PCI + Pal WBRT Vs No PCI (Retrospective)	CT Clinical	More clinical and CT changes
Lishner M et al. 1990 (n = 58)	>2years	PCI vs No PCI (Retrospective)	Clinical	19% vs 10% neurological problems
Frytak S et al. 1989 (n = 283)	>1.5 years	PCI vs No PCI (Retrospective)	Clinical	>25% more neuro toxicity

Neurotoxicity: Older series

van Oosterhout AG et al. (1995)

- Comparative with matched control (n=14)
- **No significant neurocognitive impairment during or after treatment**
- Disease related cognitive impairment may play a role.

Komaki R et al. (1995)

- Observational Post PCI LD (n = 30)
- 97% patient had pretreatment neurocognitive impairment
- **No significant deterioration in short term follow up (6month-20months)**

Inter group Pooled analysis

Pooled data LD PCI: PCI 99-01, EORTC 22003- 08004, RTOG 0212 and IFCT 99-01

QoL and Neurocognitive analysis 25Gy and 36Gy

- N = 720
- >2years survivors
- CECT and MRI assessment
- Neurological assessments (subjective and objective)
- **Only 5% Grade II communication deficit, weakness of legs, intellectual deficit and memory abnormalities in PCI arms.**
- **Age > 60-65 yrs. a major co-factor.**
- **No difference between two fractionation schedule**

Le Pe′ choux C. Ann Oncol 2011

Long term neurotoxicity

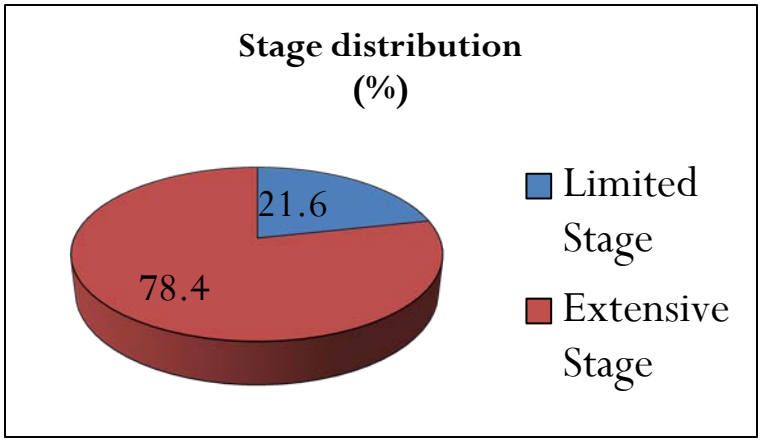
- **No direct prospective comparative evaluation in long term survivors.**
- **A significant population of cognitively impaired patients before PCI.**

Based on available evidences :

- **CECT /MRI changes do occur.**
- **Minor non-meaningful changes in Clinical Neuro QoL.**
- **> 60yrs of age/?ED major risk for ↓ Neuro QoL**

Institutional audit
R.G. Kar Medical College data

Time period	2013-2016
Total SCLC patients	97
Number of PCI cases	11 (11.3%)
PCI in LD	7(63.6%)
PCI in ED	4(36.3%)
Fractionation	
25Gy/10#	9(81.1%)
30Gy/10#	2(18.1%)
EBRT Fractionation	(PCI cases)
45Gy/25# BID	7(63.6%)
59.4Gy/33#	4(36.3%)



Median F/U	9.5 months (7-56)
Median survival	8 months
Median DFS	4 moths
Failure site	
Lung	8(72.7%)
Node	1(09.1%)
Bone	2(18.1%)

Acknowledgment : Dr. Sourav Ghosh & Dr. Satadru Biswas

Standard Treatment of SCLC

- **Limited Stage Disease:**

1-2cycles of EP

CTRT
With EP
(max 4cycle]

In CR/PR
PCI

In SD/PD
Subsequent Chemo

- **Extensive Stage Disease:**

4-6 cycles of EP

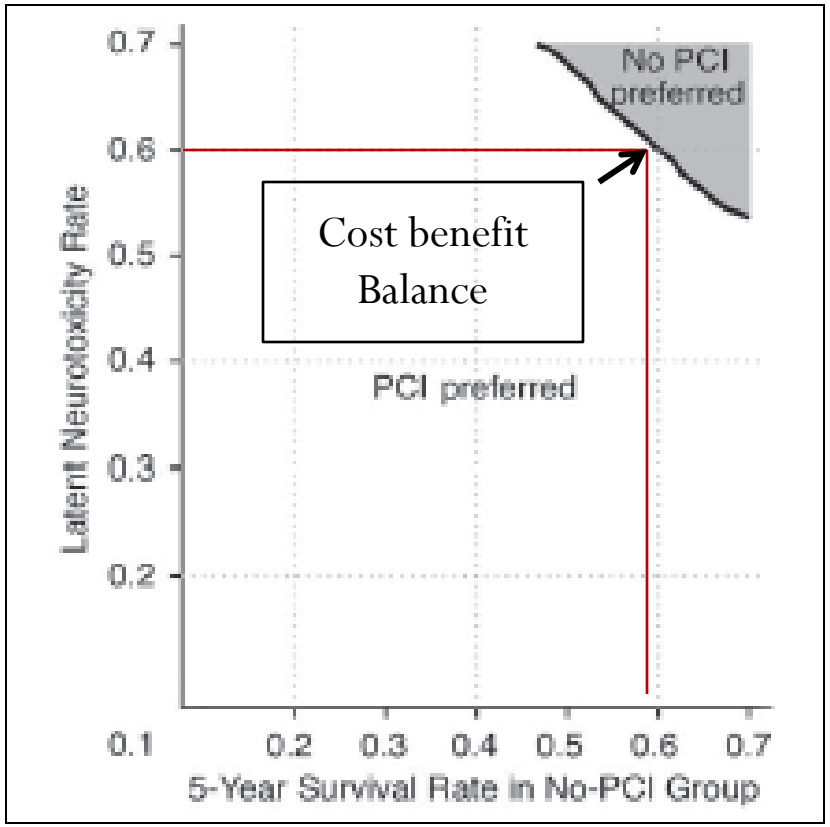
In CR/PR
PCI + Thoracic
RT

Not in
Poor PS
Neurocognitive
dysfunction

In SD/PD
Subsequent
Chemo

ASCO 2015
NCCN 2016
ESMO 2016

PCI or No PCI: The Future



Superiority of PCI over No PCI depends on

- **Low 5 year survival (<40-60%)**
- **Low/Moderate neurotoxicity rate**

Adopted from Lee JJ et al. JCO 2006

Take home message

- 50% reduction of isolated brain relapse in all stages.
- Translate survival advantages (5% increase in 5years).
- Prior MRI to exclude asymptomatic brain mets is needed.
- Only for patients who have responded to CT/CTRT.
- Only after planned induction treatment.
- Only with normal baseline neurological status, age <65Yrs and good PS.
- Long term neurocongnitive data still not robust.

Thank you