# Role of PCI in Small Cell Lung Cancer

Dr. Litan Naha Biswas
Apollo Gleanagles Hospital, Kolkata

# PCI in SCLC

Prophylactic application of cranial irradiation in Small cell lung cancer, after obtaining complete response with chemotherapy or chemo-radiation

Rationale?

- 10-14% pts have detectable brain metastasis at presentation
- at the time of death at least one third (35-40%) have brain mets.
- Approximately 50 % have brain metastasis when sent for post-mortem
- Frequency of brain metastasis increases, as survival time increases
- With improvements in survival after chemotherapy or chemo-radiation, recurrence in the CNS an increasing problem affecting 50% of pts at 2 yrs
- Pts with ESSCLC more likely to develop brain mets than LSSCLC (69% vs 47%)

# PCI in SCLC

## Objectives

- To prevent the clinical manifestations of previously present but occult CNS disease, as SCLC pts are at high risk of developing brain metastasis

- To prevent the morbidity associated with clinically evident brain metastasis, and conferring the patients a better quality of life

- Now known to improve survival to a significant degree, in addition to it's established role in preventing the morbidity associated with brain metastasis

# History of PCI in SCLC

- Success of PCI in ALL led to it's initiation in the late seventies
- Early clinical trials initiated in the eighties , showed significant decrease in incidence of brain metastasis
- But remained inconclusive with regard to the benefit in terms of overall survival.
- Safety of PCI was also a concern; largely on the basis of possible side effects on neuro-cognitive functions
- Retrospective reviews in the early nineties, uniformly showed decrease in incidence of brain metastasis, but survival in a few studies only
- Methodological shortcomings a big problem

# PCI in SCLC

New wave of Randomized Trials initiated in the late eighties and early Nineties, embarking on the following issues related to PCI

- Does it increase survival ?
- Is it applicable in only limited stage or in extensive stage as well ?
- Optimum dose of PCI
- late neurotoxicity
- benefit in older age (> 70 yrs)

# Does it increase survival ?

Randomized trials in late 1980s and early 1990s:

(3 large European studies including > 1000 patients)

Suggestion of improved survival in the PCI group in each case, but difference not statistically significant

None of the studies large enough (about 300 pts in each group) to provide sufficient power to detect meaningful difference in survival

# PCI in SCLC: Survival Issues

Meta-analysis of 7 randomized trials (1977-95):

- 987 pts (85% limited stage and 15% extensive)
- Randomized to PCI or Observation following complete response to chemotherapy or chemo-radiation
- PCI regimens varied from 24 Gy/ 12 fractions to 40 Gy/ 20 fractions
- At 3 yrs: significant reduction of Brain metastasis with PCI
  (33% vs 59% with observation)
  significantly improved Overall survival (20.7% vs 15.3%)
  (35% increase in 3 yr survival)
- Supporting data from Patel et al (8000 pts) : 5 yr survival 19% with PCI vs 11% without PCI
- Benefits consistent irrespective of age, P.S, stage and type of induction therapy, but no relation found with timing of PCI and survival
- **Publication of this study established role of PCI in limited stage SCLC**

# PCI in SCLC

**Is the benefit of PCI same in extensive stage as well ?**

- EORTC Randomized trial: 286 pts. with extensive stage
- randomized to PCI or Observation after any response to 4 or 6 cycles of chemotherapy
- PCI administered at 4-6 wks after chemotherapy
- 1 yr cumulative incidence of brain metastasis significantly decreased (15% with PCI vs 40% after observation)
- 1 yr overall survival significantly increased ( 27% vs 13%)
- 6 different PCI regimes permitted (BED varying from 25 to 39 Gy)
- With this study, PCI established in extensive stage SCLC also

# PCI in SCLC

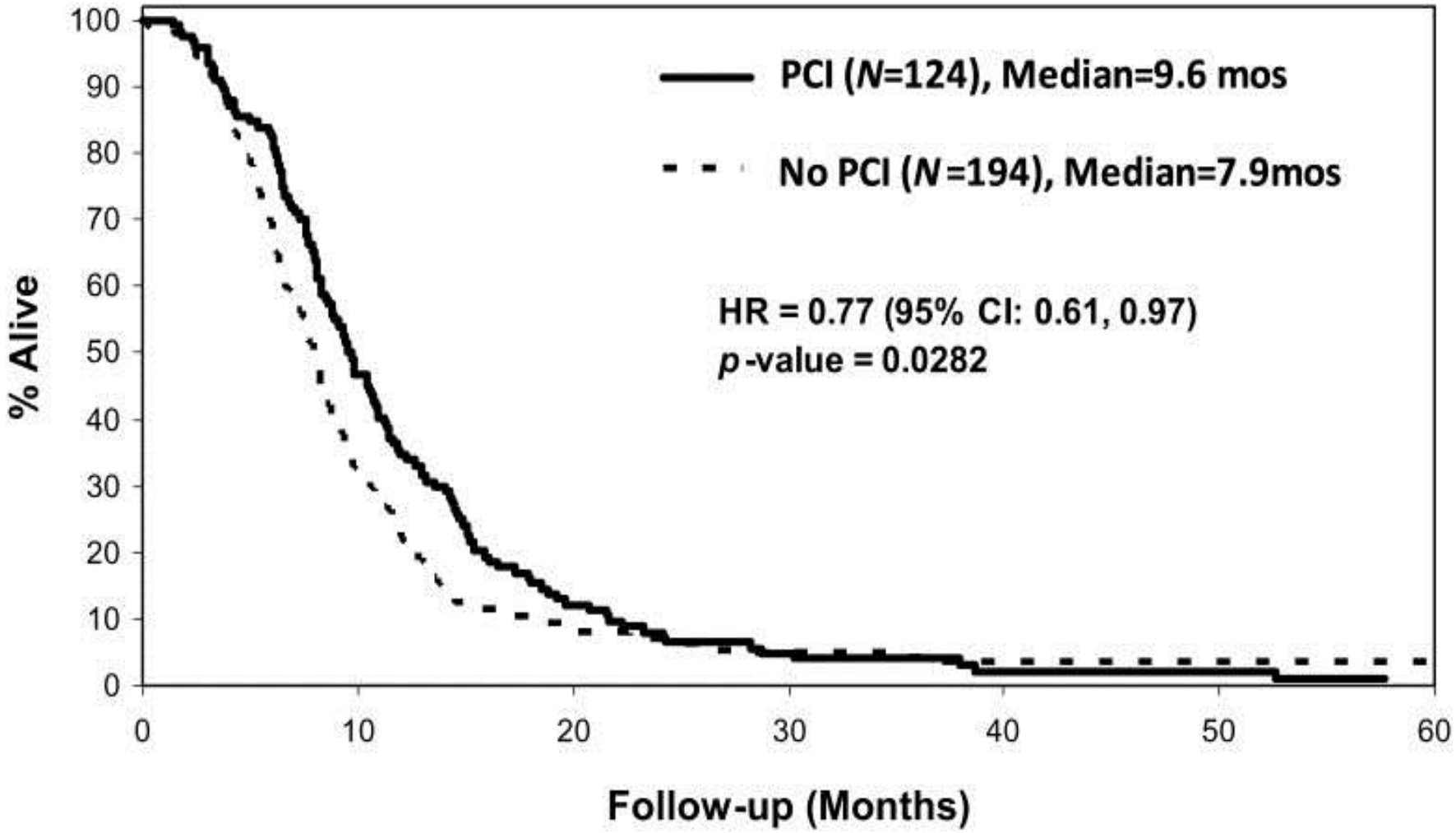
**Dose fractionation issues in PCI in Small cell lung cancer:**

- Multi-institutional Intergroup trial: (720 patients)
- Standard dose PCI (25 Gy in 10 daily fractions) vs High dose PCI (36 Gy in 18 daily fractions or 24 twice daily fractions)
- At 2 yrs. No significant difference in incidence of brain mets. (29% in standard arm vs 23% with high dose)
- No significant diff. In survival between the 2 groups (42% in standard dose arm vs 36 % with high dose)
- Increased incidence of chronic neurotoxicity at 1 yr. after PCI in the 36 Gy cohort (p=0.02)
- These results established 25 Gy in 10 daily fractions (2.5 Gy/fraction) as standard dose of PCI in small cell lung cancer

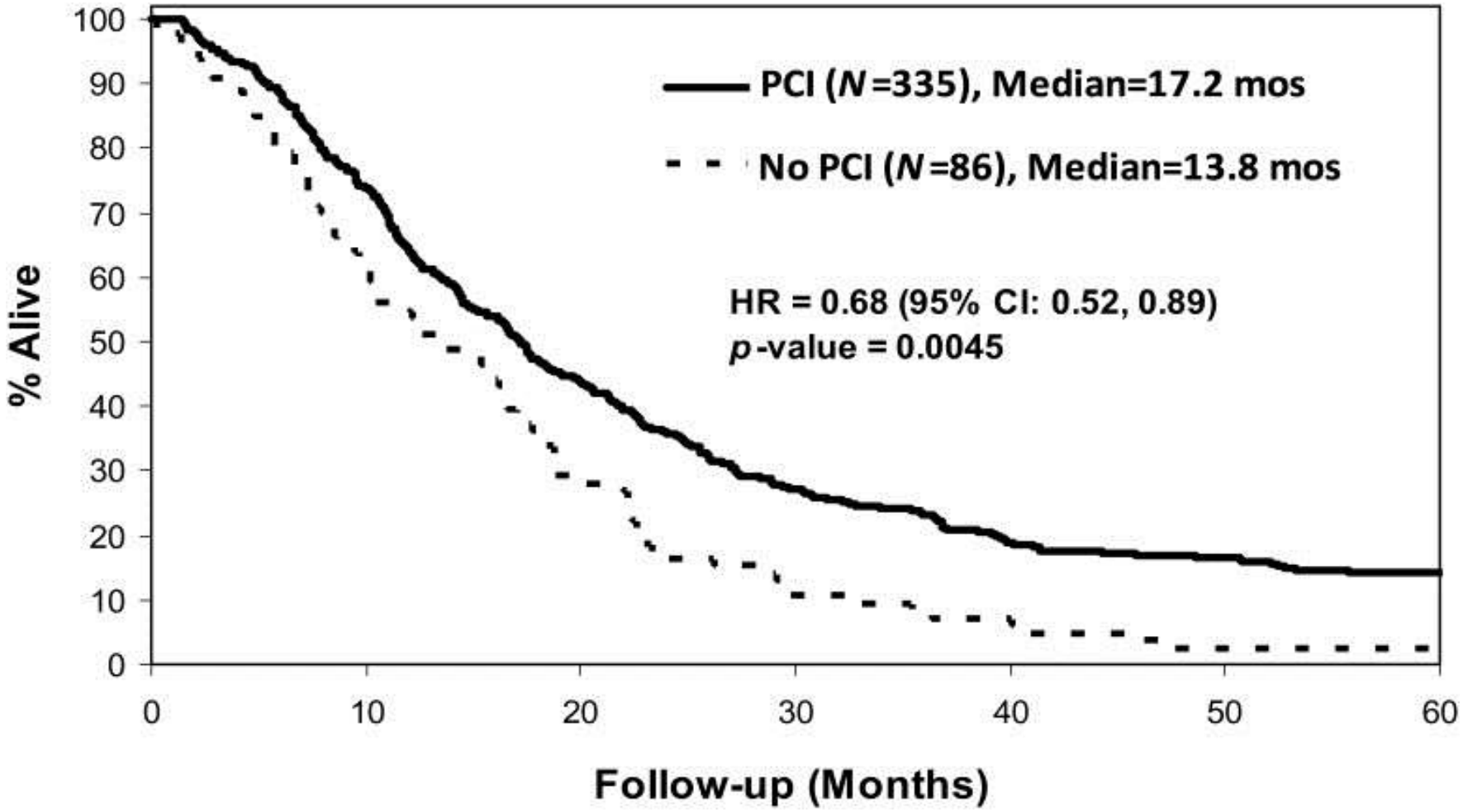
# Recent observations from NCCTG Pooled analysis

- 739 patients in total (421 limited and 318 extensive SCLC)
- Included those with stable disease or better following Chemotherapy with or without Thoracic RT
- 1 yr survival 56% (with PCI) vs 32% (without PCI)
- 3 yr survival 18 % with PCI vs 5% without PCI
- Still significant after adjusting for age, P.S, stage, degree of response and number of metastatic sites(HR 0.82, P=0.0004)
- Significantly more grade 3 adverse events (64%) compared to non-PCI pts(50%)
  - Alopecia and lethargy commonly associated with PCI
  - Dose of 25 Gy/ 10 fractions better than 30 Gy/ 15 fractions (p=0.018)

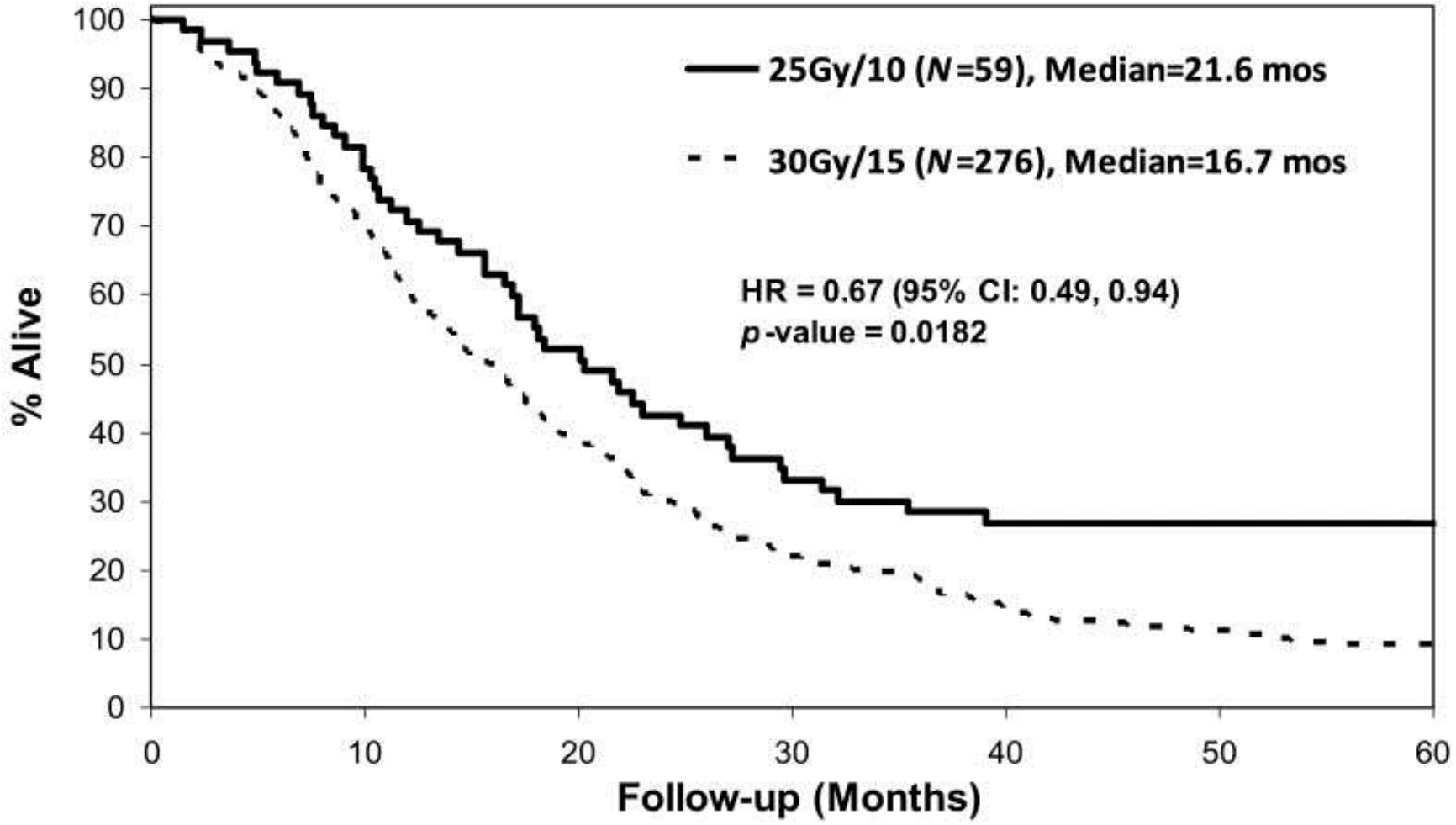
Survival impact of prophylactic cranial irradiation (PCI) (versus no PCI) across all extensive small-cell lung cancer patients.



Survival impact of prophylactic cranial irradiation (PCI) (versus no PCI) across all limited small-cell lung cancer patients.



# Effect of dose level on survival after PCI



# Does it cause Neurotoxicity ?

- Study by Johnson & Co-workers (1985): Decline in neuro-cognitive function with some correlation with abnormalities in CT Scan in long term survivors
- **Problems more frequent when concurrent CT given, or fraction size more**
- 'Dangerous Liaison' between PCI and Chemotherapy the probable cause of increased neurotoxicity (PMH Study)
- Conclusions based however on clinical findings, not upon formal Psychometric testing
- Two large randomized trials (PCI 85 and UK 02) did incorporate Psychometric testing before and after PCI, but found no difference at 5 yrs of follow-up
- **Up to 40% of pts have significant abnormalities in neuro-cognitive functioning even before the PCI, and PCI adds very little to worsen the condition**
- One possible area of concern is an effect from the chemotherapy regimens used to improve survival- needs further exploration

# Novel ways to avoid neuro-toxicity

- Neurocognitive toxicity partly related to radiation induced injury to neural progenitor cells in the hippocampus (inverse relationship between radiation dose to the hippocampus and performance on neuropsychological testing)

- RTOG 0933 Study: **Hippocampus sparing cranial irradiation** to reduce the incidence of neurocognitive toxicity, as the hippocampus is rarely affected by BM but displays the major site of learning, memory and spatial information .

- Exploring IMRT for PCI, the mean doses to the hippocampus could be reduced by 81-87% to doses of 0.49-0.73 Gy with preserved target volume coverage and homogeneity.

- Neuroprotective drugs ? Under exploration

# Conclusions

- High propensity for SCLC to develop Brain Metastasis
- PCI significantly lowers the incidence of BM, in patients achieving good response to induction chemotherapy
- No evidence of serious morbidity associated with PCI, if given after completion of all chemotherapy and in moderate fraction size
- Meta-analysis confirmed the survival benefit in both limited and extensive SCLC pts in complete remission (5% improvement in 3 yr survival)
- Although different dose fractionation regimes are in practice, 25 Gy in 10 fractions and 36 Gy in 18 fractions are within the standard of care. Dose of 30 Gy in 15 fractions clearly suboptimal
- Optimal fraction size 2.5 to 3 Gy to avoid late neuro toxicity
- Timing of PCI: Should start as early as feasible after completing chemotherapy
- Objective psychometric testing should be done, if feasible before and after PCI to asses neuro-cognitive morbidity
- Little data on use of PCI in pts >70 yrs of age