Prophylactic Cranial Irradiation

Perspectives, and Lessons Learned

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Conflicts of Interest

- Consultant: BMS, Cavion, Elekta, Novartis, Novocure
- DSMB: Monteris
- Research Funding: Novocure, Cellectar
- Board of Directors of Pharmacyclics
- NRG Brain Tumor Committee Chair

Lessons from SCLC

- PCI improves intracranial control.
  - BOTH limited and extensive stage (well-selected)
- Increased intracranial control improves OS
- In the 1999 NEJM metaanalysis, 3 year intracranial control improved by 25% and OS3 improved by 5%
- NCF is relatively well preserved with conventional doses and schedules
  - BUT starts declining when 36 Gy or more is used (RTOG 0212)

All PCI NSCLC Trials Show Benefit

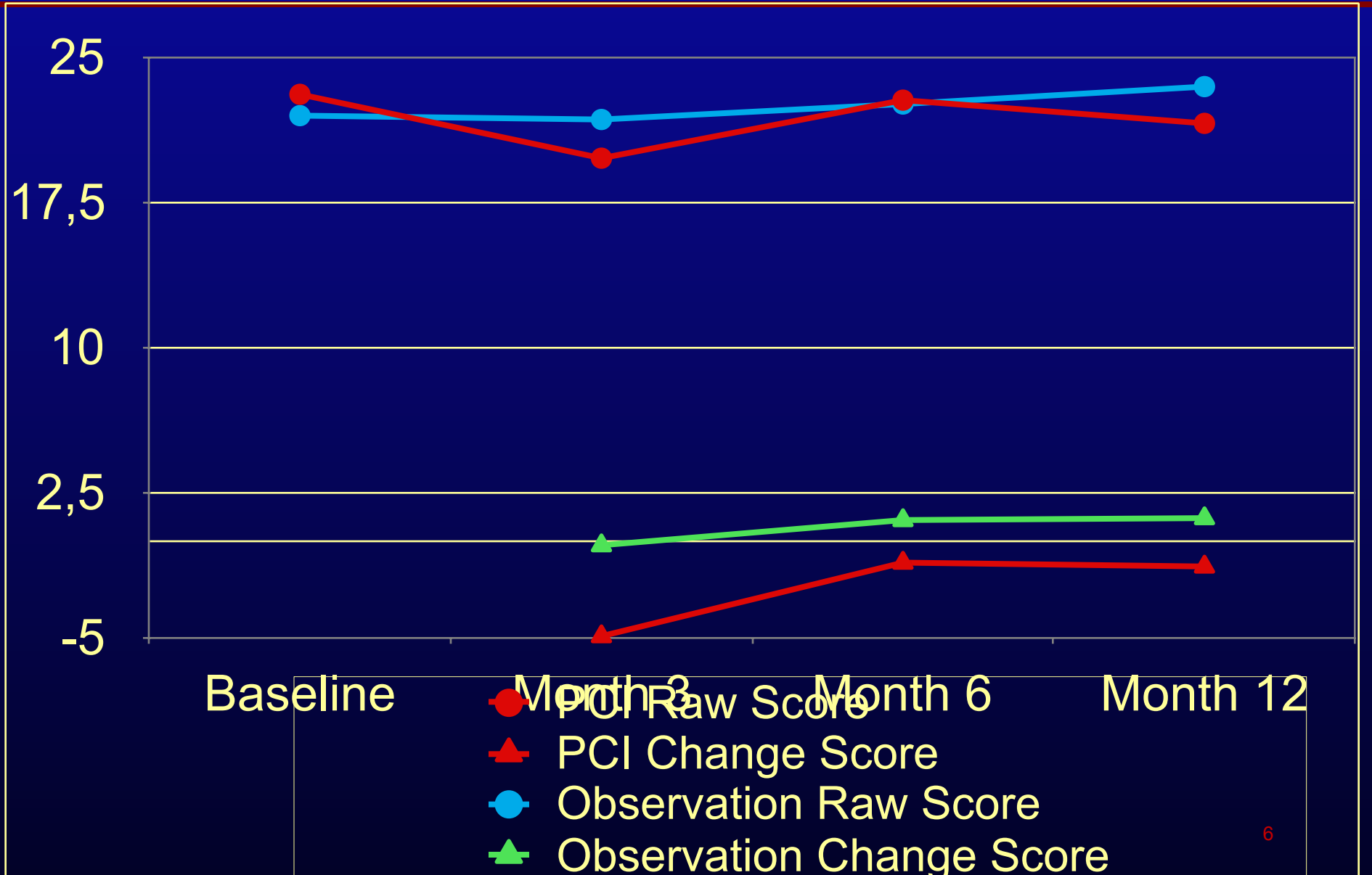
Study		CNS Failures		
	N	No PCI	PCI	p value
VALG, JAMA 1981	281	13%	6%	0.04
MDACC, J Neuro-Onc 1984	97	27%	4%	0.002
RTOG 8403, IJROBP 1991	187	19%	9%	0.1
Pottgen et.al, JCO 2007	112	24%	9%	0.02
Movsas et.al, ASTRO 2009	340	18%	8%	0.004
Cumulative Experience	1017	13-27%	4-9%	

Prospective Randomized Trials of PCI in NSCLC

Lessons from 0214

- 50% 6 month compliance with HVLT completion
  - 50% loss of data!
- The MMSE is an insensitive tool
- Memory declines early, and can exhibit some recovery! Is it biphasic?
  - Implicates an “early responding” cell population
- Memory decline does not translate to sustained QOL deterioration

HVLT-R: Early Decline Followed by Some Recovery



What Options Other than WBRT Exist?

- **Limit PCI to well-defined very high-risk subpopulations**
- **Modulate negative effects of WBRT**
  - Pharmacologic, e.g. Brown, et al, RTOG 0614, NeuroOnc, 2013, Rapp, et al, Donepezil, JCO 2015
  - Dosimetric, e.g. RTOG 0913, HAWBRT, Gondi, et al, JCO, 2014
- **Novo-TTF: *Investigational***
- **BBB-penetrating chemotherapy, e.g. temozolomide: *Off-label use***
- **BBB-penetrating targeted agents for tumors harboring driver mutations, e.g. erlotinib for EGFR+ NSCLC, etc. *Off-label use***
- **Non-BBB approaches such as Ipilimumab: *Hypothetical***

RTOG 0614: Time to Cognitive Decline

- **Time to cognitive decline**
  - **Longer for memantine arm (HR 0.78**; 95% CI, 0.62 to 0.99; p=0.02)

- **Memantine improved probability of cognitive preservation at 24wk**
  - 30.6 vs 19.7% for placebo

Investigational

Brown P, et al, Neuro Oncol, 2013, PMID: 23956241

0933: HVLT Results

- Probability of HVLT deterioration as ***defined by the Reliable Change Index***:

HVLT	2 mo	4 mo	6 mo
Total Recall	30.8%	**19.0%**	13.8%
Recognition	35.8%	11.9%	3.6%
Delayed Recall	30.2%	33.3%	17.2%

- MDACC: Probability of HVLT Total Recall deterioration at 4 mos

SRS alone **24%** **SRS+WBRT** **52%**

Gondi V. ASTRO 2013 Plenary

Gondi, et al, JCO, 2014, PMID: 25349290

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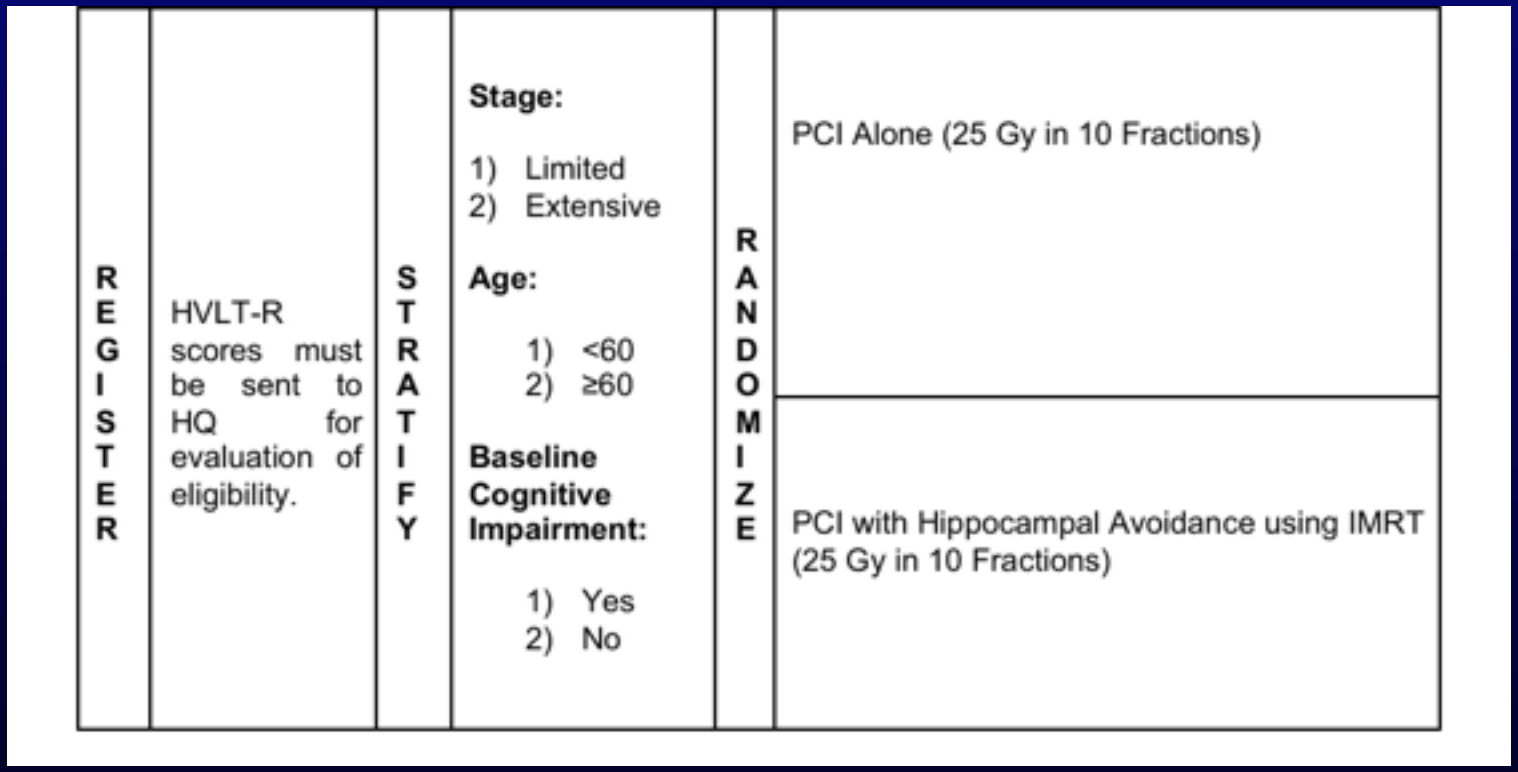
Phase II/III Trial of PCI with or without Hippocampal Avoidance for Small Cell Lung Cancer

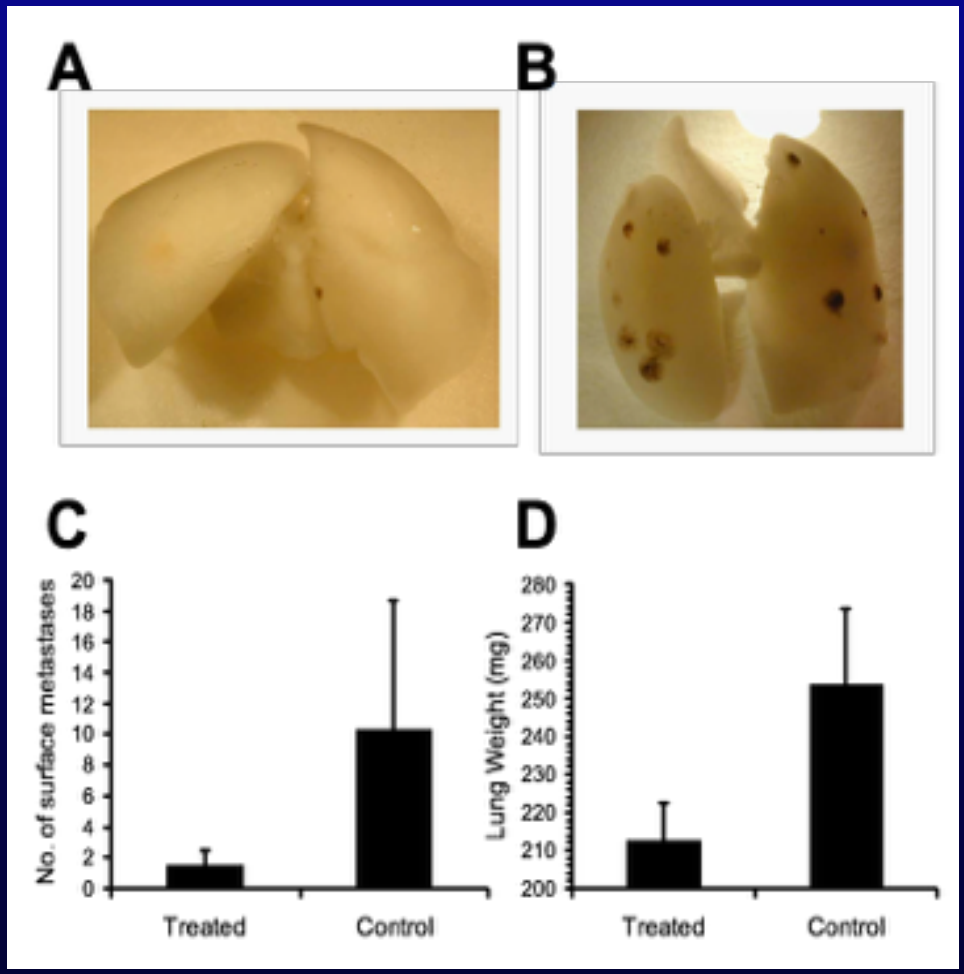
Primary Objective: Determine whether hippocampal avoidance during prophylactic cranial irradiation (HA-PCI) mitigates HVLT-R delayed recall decline from baseline to 6 months, as compared to PCI for patients with small cell lung cancer.

Eligibility: Limited- or extensive-stage SCLC with no brain metastases status post chemotherapy +/- thoracic RT with no evidence of progression



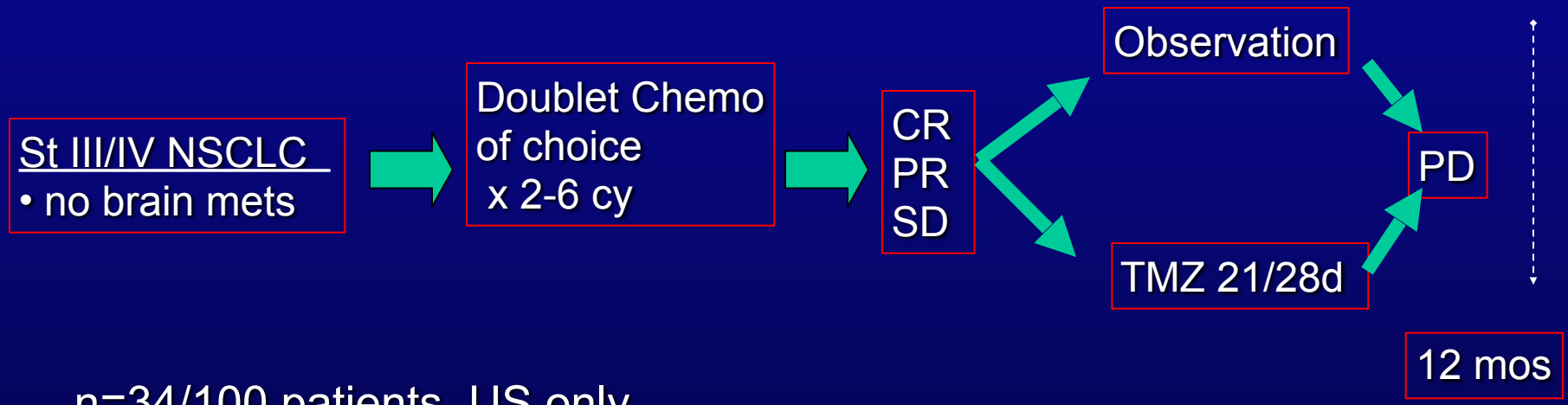
In Vivo TTFields Prevent Metastasis

- Mice tail veins injected with melanoma cells
- TTF to lungs for 7-14 d
- TTF lowered met count



Kirson et al., Clin Exp Metastasis 2009

Phase IIR Study of TMZ vs Observation in Stable or Responding Stage III/IV NSCLC PO5146



n=34/100 patients, US only
25/26 sites

Stratifications: Avastin, Yes or no; SD vs PR/CR; Stage III vs Stage IV

Endpoints:
Primary: incidence of brain mets at 12 mo post initiation of CTX
Secondary: Survival, toxicity, TT Brain mets, TTP, QOL

PMID 25069747. Boggs DH, et al: Clin Lung Ca, 15(6):433-40, November 2014.