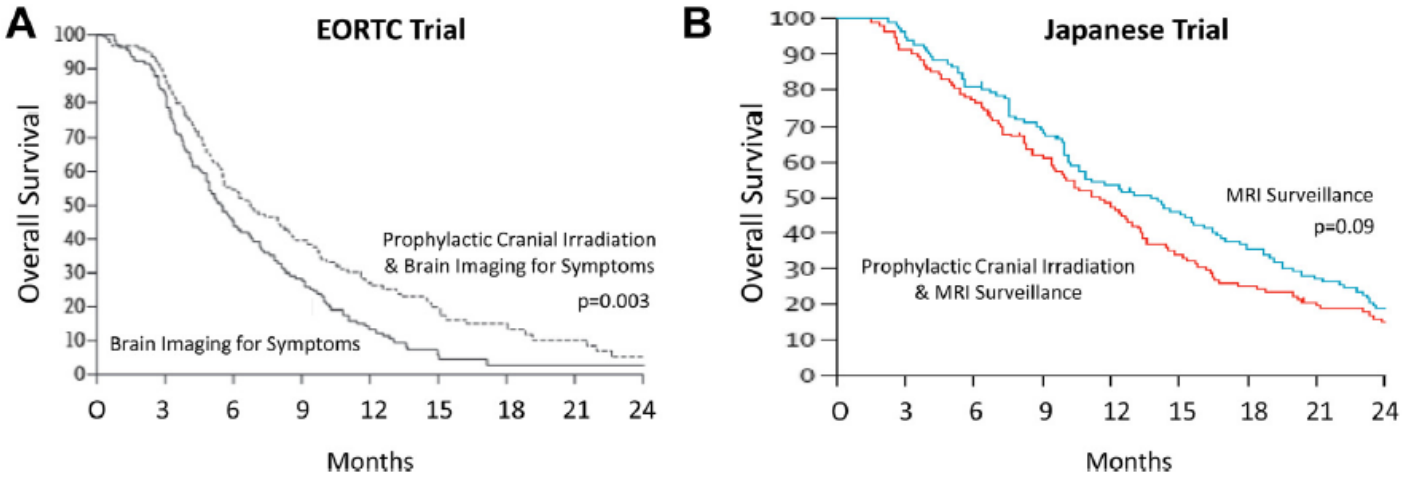
MAVERICK (SWOG S1827)

MRI Brain Surveillance Alone versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer

PI: Chad Rusthoven, Radiation Oncology Chair: Paul Brown,
Cognitive Chair: Jeffrey Wefel, Statistics: Mary Redman,
Translational Medicine Chair: Abhijit Patel, Radiology Chair: Justin Honce,
NRG Champion: Daphna Gelblum, Alliance Champion: Jyoti Patel,
ECOG Champion: Jyoti Malhotra, CCTG Champion: Jonathan Greenland,
VA Champion: Drew Moghanaki.

PCI Background

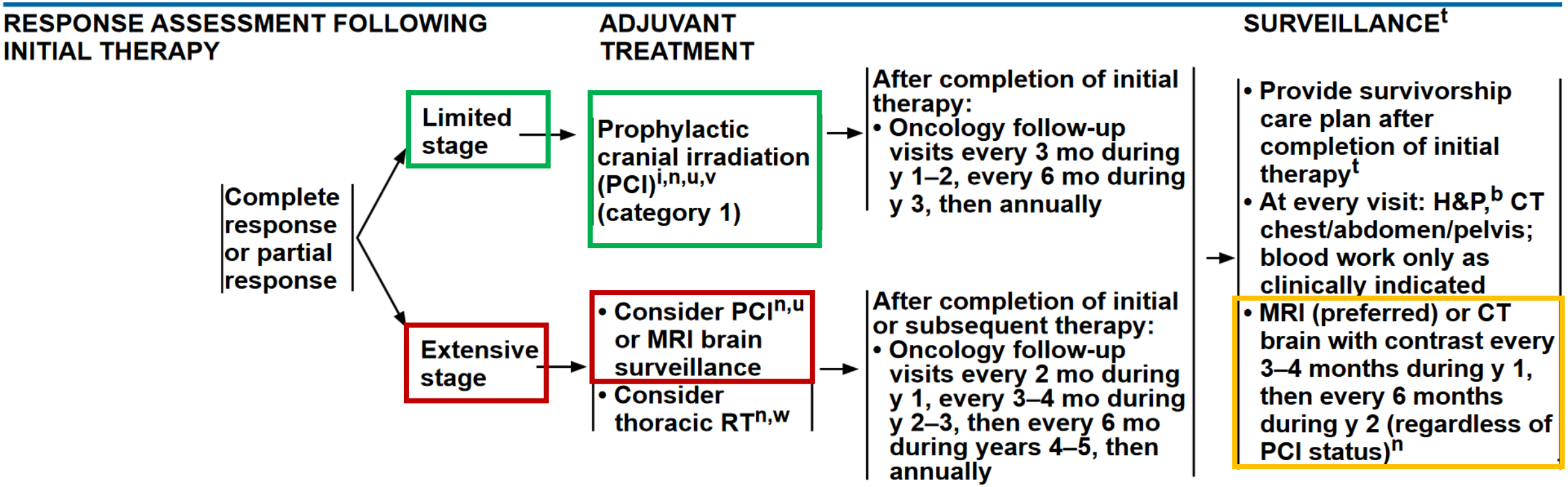
- PCI has historically been associated with ↓brain metastases and ↑neurologic toxicity
- PCI became the standard-of-care for SCLC following 2 landmark studies demonstrating ↑OS:
  - (1) Meta-analysis of primarily LS-SCLC (Auperin, *NEJM* 1999) and (2) an EORTC RCT in ES-SCLC (Slotman, *NEJM* 2007)
  - Both studies were limited by heterogeneous or absent brain staging and surveillance imaging
- In 2017, a Japanese RCT in ES-SCLC (Takahashi, *Lancet Oncol*) evaluated MRI surveillance +/- PCI
  - Reported no differences in PFS or OS with the addition of PCI (median OS 13.7 vs 11.6 mo, p=0.09, favoring no-PCI)
- Implications?
  - MRI surveillance (allowing for early salvage therapy for brain mets) may allow for the avoidance of PCI and its associated toxicities
  - The NCCN now categorizes PCI as 'optional' in ES-SCLC and recommends MRI surveillance for all patients regardless of PCI delivery



Auperin, *NEJM* 341.7 (1999): 476-484
Slotman, *NEJM* 357.7 (2007): 664-672
Takahashi, *Lancet Oncol* 18.5 (2017): 663-671

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Small Cell Lung Cancer



PCI is a NCCN category-1 recommendation for LS-SCLC and a standard option for ES-SCLC

MRI surveillance is now recommended for <u>all patients</u> (regardless of PCI delivery)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2020
Small Cell Lung Cancer

NCCN treatment options for SCLC brain metastases have also evolved to include SRS and HA-WBRT in carefully selected cases…

PRINCIPLES OF RADIATION THERAPY

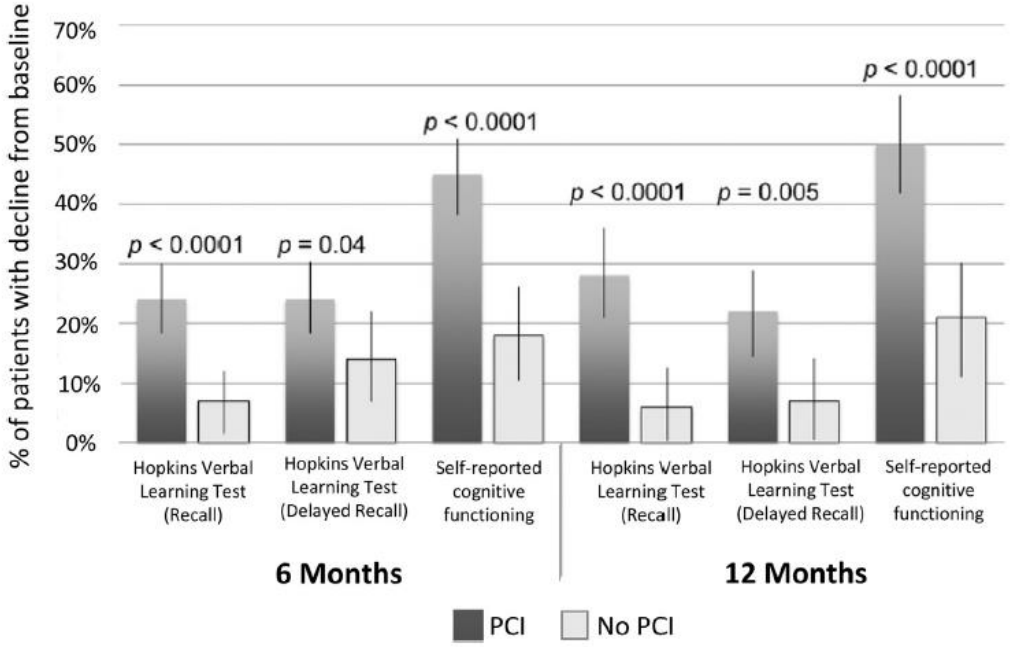
Brain Metastases:

- Brain metastases should typically be treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS)

- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[34,35] SRS is preferred, if feasible.[36,37]

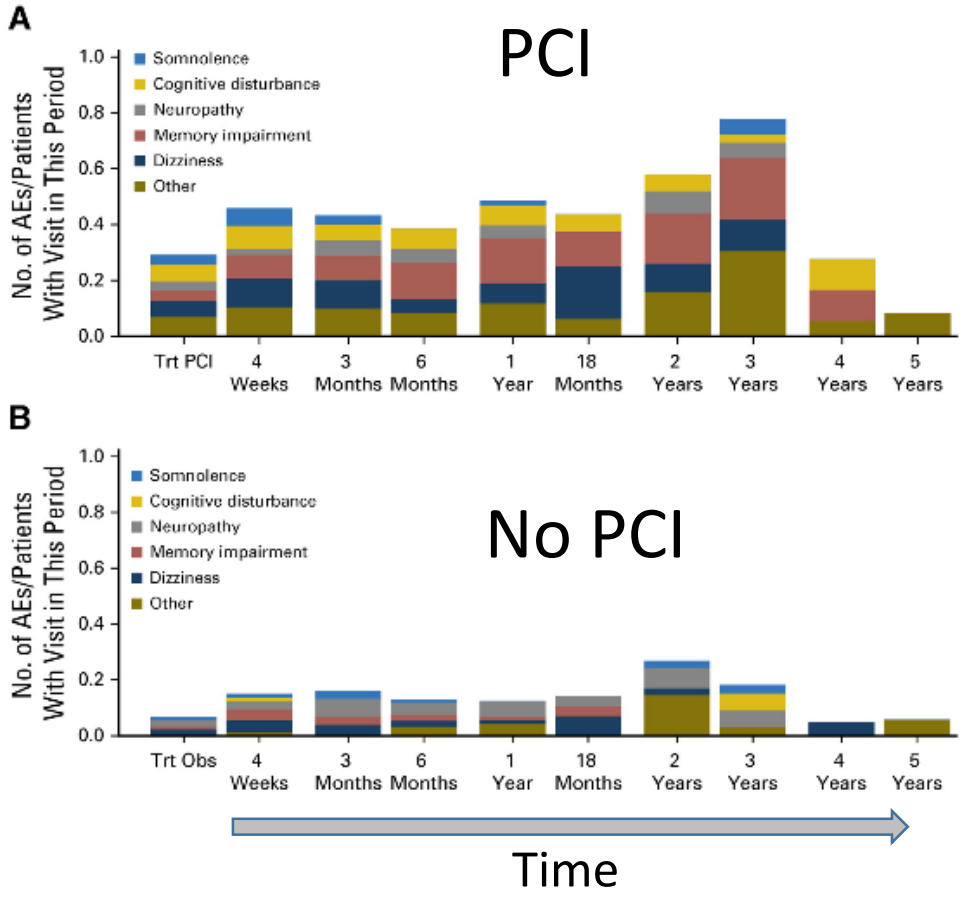
- For patients with a better prognosis (eg, ≥4 months), consider hippocampal-sparing WBRT using IMRT[38]

Why does it matter? PCI is associated with neurocognitive toxicity



Tested and self-reported cognitive function with/without PCI in RTOG 0212 and 0214

Gondi, Vinai, et al *International Journal of Radiation Oncology* Biology* Physics* 86.4 (2013): 656-664.



De Ruysscher, Dirk, et al. "Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non–Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study." *Journal of Clinical Oncology* (2018): JCO-2017.

Patterns of care and equipoise on PCI

- Although the NCCN considers PCI a category-1 recommendation for LS-SCLC, approx. 40% of LS-SCLC patients do not receive PCI primarily due to toxicity concerns (Giuliani 2010, Lok 2015).

- 2019 survey study of 487 radiation oncologists (Gjyishi 2019):
  - Following the Japanese PCI trial, routine recommendations for PCI dropped from 72% to 44% for ES-SCLC
  - 82% were willing to enroll patients on a trial of MRI surveillance +/- PCI for limited and/or extensive-stage

- Separate surveys of SWOG and Alliance members indicated equipoise regarding MRI surveillance +/- PCI for SCLC
  - 85% & 87% indicated they would enroll patients on a randomized trial of MRI surveillance +/- PCI
  - 68% & 75% wanted the study to include <u>both</u> limited and extensive-stage SCLC patients

Giuliani, Cancer 116.24 (2010): 5694-5699
Lok, *Advances in radiation oncology* 2.4 (2017): 548-554
Gjyishi, *JAMA network open* 2.8 (2019): e199135-e199135

MAVERICK (SWOG 1827): MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation: A Randomized Phase III Trial in Small-Cell Lung Cancer

Small-cell lung cancer

- Includes limited and extensive stage
- No prior brain metastases
- No brain metastases on MRI after 1st line therapy

Stratify: 1. Limited vs extensive stage
2. Immunotherapy (y/n) 3. Performance Status (0-1 vs 2)

Prophylactic cranial irradiation (PCI) → MRI brain surveillance

No PCI → MRI brain surveillance

Primary Endpoint
- Overall survival (non-inferiority)

Secondary Endpoints
- Cognitive function
- QOL
- OS in limited and extensive stage
- Brain metastases free survival
- Toxicity

Translational Endpoints
-Longitudinal brain MRI changes
-ctDNA correlation to PFS, OS

Accrual goal: 668 patients

- MRI brain surveillance scheduled at 3, 6, 9, 12, 18, 24 months
- Radiation therapy is recommended at the time of brain metastases (WBRT and SRS allowed)
- Hippocampal-avoidance PCI and WBRT are allowed
- Patients managed with any/all NCCN-acknowledged first-line treatment strategies are eligible

PIs Chad Rusthoven and Paul Brown

Notes

- **MAVERICK is open across the NCTN cooperative network (SWOG, Alliance, NRG, ECOG, and CCTG)**

- **VA partnership is a priority**
  - The VA has a track record of success with large randomizations that have been challenging in other settings, eg,
    - PIVOT: prostatectomy vs observation, 731 randomized (Wilt et al, NEJM 2012, 2017)
    - VALOR: surgery vs SBRT for early stage NSCLC, target accrual 670 (PI Moghanaki, ongoing)
  - We believe that the VA participation will be vital to the success of MAVERICK (target accrual 668)

- **The neurocognitive testing battery is identical to comparable NRG trials (eg, CC001, CC003)**
  - Dr. Jeff Wefel (cognitive chair) has led cognitive testing on numerous cooperative group trials and has successfully trained thousands of health care professionals (study coordinators, RNs, psychologists, MDs).
  - Straightforward, web/email based certification process.
  - Site provided for completion of baseline and follow up cognitive tests.

- **Pragmatic design**
  - MAVERICK was designed to be maximally inclusive of varying/evolving patterns of SCLC management (e.g., hippocampal avoidance, salvage WBRT and SRS, immunotherapy, thoracic RT in ES-SCLC, surgery and SBRT for early-stage) to capture the diversity of SCLC management and to prioritize low barriers to accrual.
  - Patients managed with any/all NCCN acknowledged treatment strategies are eligible for enrollment.
  - In patients receiving chemotherapy + immunotherapy followed by adjuvant immunotherapy, enrollment should take place after the chemotherapy component.