SWOG S1827: Randomized Trial of MRI Surveillance with and without PCI for Small-Cell Lung Cancer

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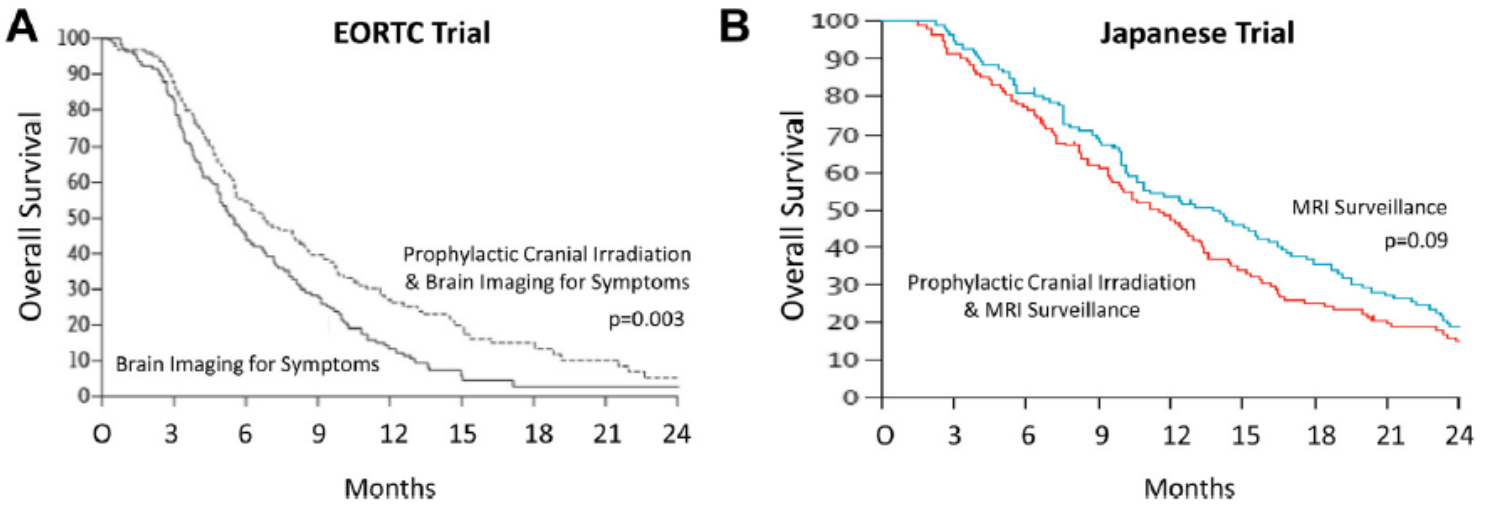
PCI Background

- PCI has consistently been associated with ↓brain mets ↑neurologic toxicity

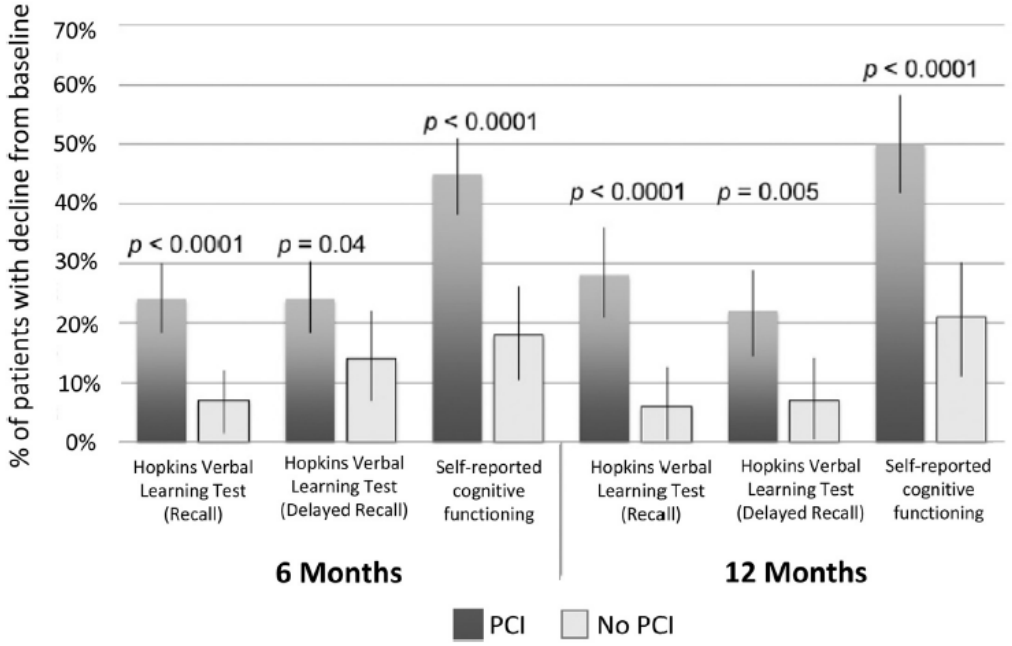
- PCI became standard for SCLC after 2 landmark studies demonstrating ↑OS
  - Meta-analysis of primarily LS-SCLC (Auperin, NEJM 1999) and an EORTC RCT in ES-SCLC (Slotman, NEJM 1999)
  - Both studies were limited by heterogeneous or absent brain staging and surveillance imaging

- 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 it's associated toxicities
  - The NCCN now categorizes PCI as 'optional' in ES-SCLC and recommends MRI surveillance for all patients regardless of PCI delivery

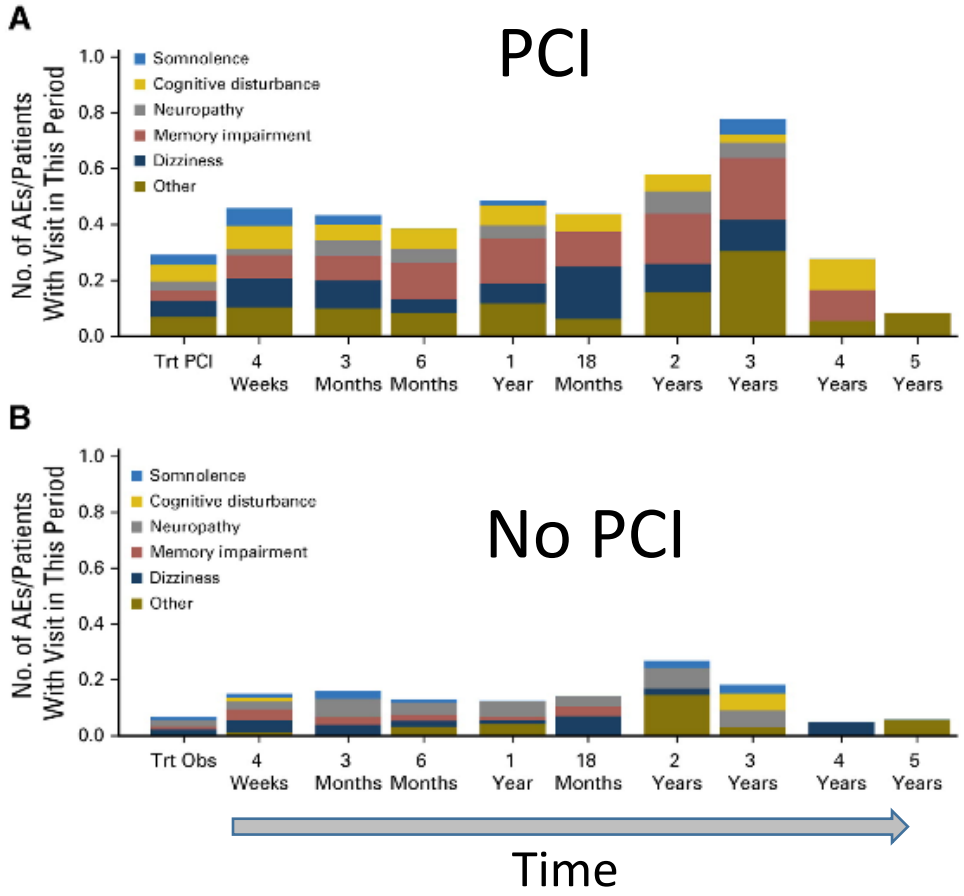


Why does it matter? PCI is associated with neurocognitive toxicity



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 (Guliani 2010, Lok 2015).

- Following the Japanese trial, routine PCI recommendations in ES-SCLC dropped from 72% to 44% (Gjyshi 2019).

- Separate surveys of SWOG (n=115) and Alliance (n=78) members indicated equipoise regarding PCI
  - 85-87% indicated they would enroll patients on a randomized trial of MRI surveillance +/- PCI
  - 68-75% wanted the study to include both limited and extensive-stage patients
  - Respondents also strongly preferred hippocampal avoidance PCI (76-90%) and memantine (83-92%) to be allowed but not required

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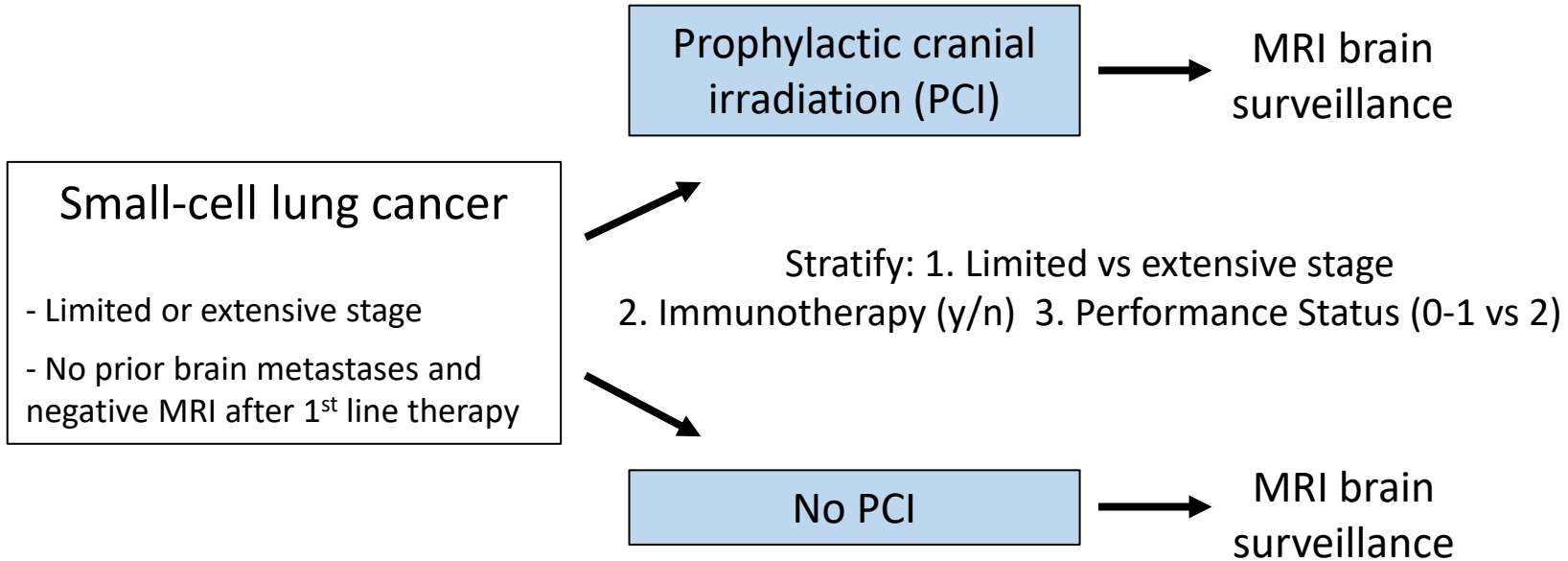

Primary Endpoint
- Overall survival (non-inferiority)

Secondary Endpoints
- Cognition
- 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 and cognitive testing scheduled at 3, 6, 9, 12, 18, 24 months
- Radiation therapy is recommended at the time of brain metastases
- Hippocampal-avoidance PCI is allowed
- Patients who underwent surgical resection or SBRT for early-stage disease are allowed

Notes

- **NRG CC003**: PCI w/wo hippocampal avoidance.
  - CC003's primary endpoint = 6 month cognitive preservation rates (not OS) and as now closed to accrual
  - In S1827, hippocampal avoidance is permitted based on physician's discretion [tracked prospectively for planned analyses]
  - If CC003 is positive, S1827 will be amended to make HA "recommended". This is not be expected effect the primary endpoint of S1827 (OS).

- **NRG LU005**: LS-SCLC treated with chemoRT +/- atezolizumab – now closed to accrual in the US

- **S1827's pragmatic design**
  - Given the importance of the PCI question and large accrual goal, S1827 was designed to be maximally inclusive of the varying and evolving patterns of care delivery in SCLC (eg, hippocampal avoidance, memantine, immunotherapy, salvage WBRT and SRS) and to prioritize low barriers to enrollment.
  - PCI is the historic standard of care, and thus S1827 is a therapeutic de-escalation trial testing whether MRI surveillance alone can maintain similar OS and demonstrate improved cognitive preservation and QOL.

  - Note - S1827 incorporates the **same cognitive** testing battery as **NRG CC001 and CC003 (HVLT-R, TMT A & B, COWA)** and has the same cognitive chair (Dr Jeff Wefel). Sites that have participated in these NRG trials are already equipped to enroll on S1827. For sites that have not, the certification process created by Dr Wefel is designed to be straightforward.

Open at 283 sites
Accrual is 104/668 as of 7/13/22