

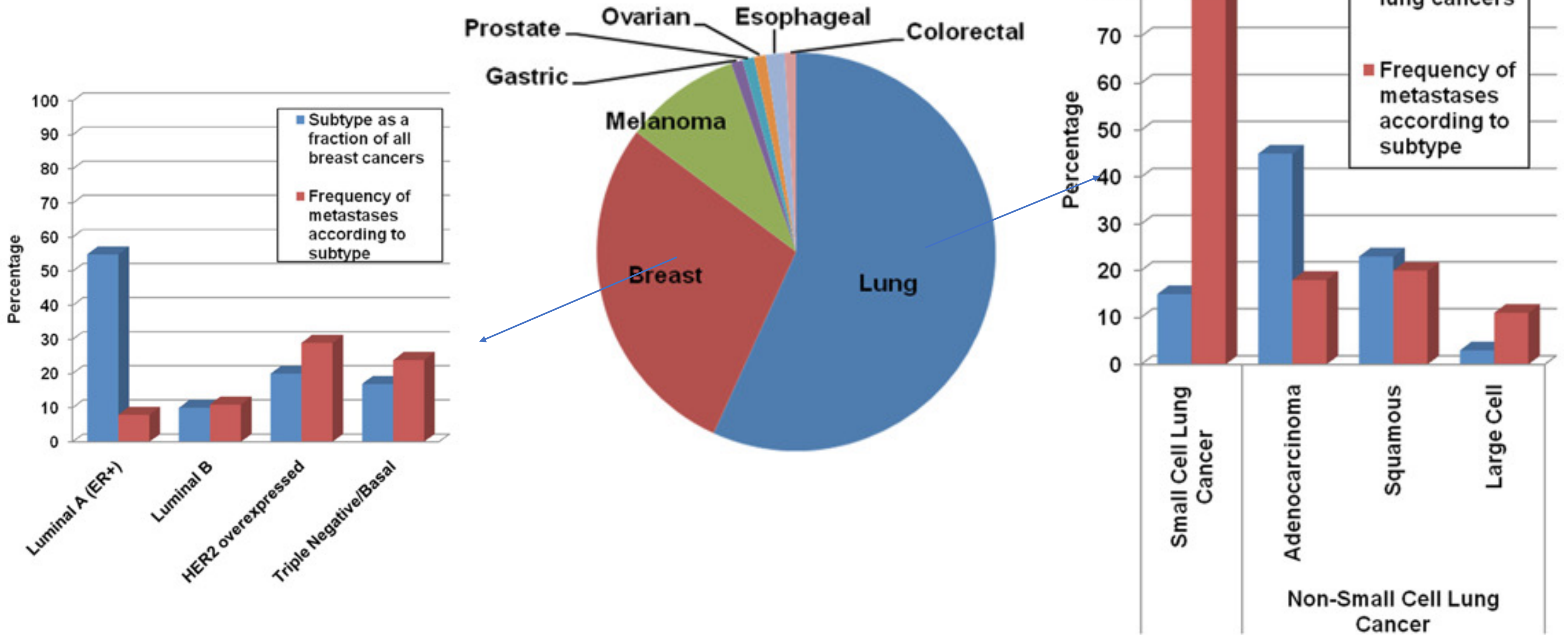
Brain Radiotherapy in Small Cell Lung Cancer: When?

Jeffrey Bradley, MD FACR FASTRO
Professor, Department of Radiation Oncology
University of Pennsylvania

Brain Radiotherapy in SCLC: When?

- **Management of SCLC Brain Metastases**
 - Prognosis
 - Local control vs toxicity
 - Treatment options
 - Whole Brain
 - Hippocampal-avoidance whole brain
 - Memantine
 - Stereotactic radiosurgery (SRS)
 - Fractionated SRS
 - Gamma knife vs linear accelerator comparison dosimetry
- **Prophylactic Cranial Irradiation**

Histology / Genetics of brain mets



brainmetgpa.com

GPA Index [Home](#)

From which of the following diagnoses does your patient have brain metastases?

- Lung Cancer**
Non-Small Cell and Small Cell >
- Melanoma** >
- Breast Cancer** >
- Renal Cell Carcinoma** >
- Gastro-intestinal Cancer**
Any site >

[Start over](#) **GPA Index** [Home](#)

The estimated MST (median survival time) from the time of initial treatment of the brain metastases is:

13 months
25th-75th percentile range: 7 - 23 months

Based on the following selected factors:

Diagnosis:	Lung Cancer Small Cell	
Age:	< 75 years	0.5
KPS:	90	1.5
Extra-cranial met.:	Yes	0
Number of met.:	4 - 7	0.5
	Total GPA:	2.5

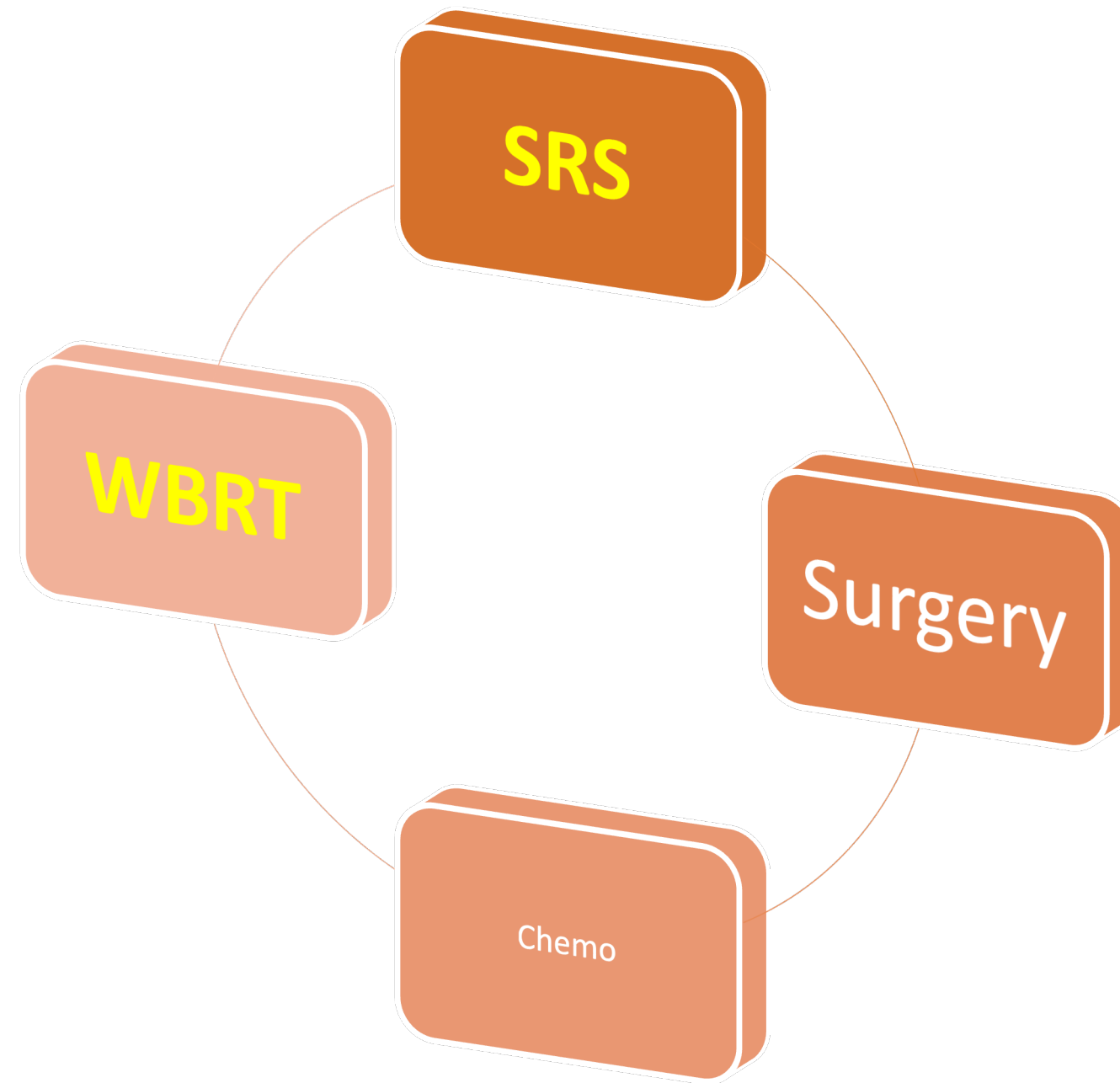
Based on the above, the EQ (Eligibility Quotient) is:

53%

The Eligibility Quotient (EQ) is the probability of surviving an additional 12 months from today. It is used by researchers to determine eligibility for clinical trials. We recommend patients with an EQ > 50% be enrolled in clinical trials.

All GPA factors (age, KPS, ECM, molecular profile, number of brain mets) should be entered based on the patient's status at the time of diagnosis of the brain metastasis(es), not the current status. If the EQ is reported as N/A, we do not have enough historical data to reliably compute the EQ for this combination of GPA and months since brain met diagnosis.

Treatment Options



50 years in 2 minutes - WBRT

- **WBRT** to 30-37.5 Gy @ 2.5-3 Gy/fx is a long held standard
- **Pro's**
 - Treats everything. 1y distant brain failure rates w/WBRT 15-30%.
 - Simple. Anyone can do it.
 - Inexpensive.
- **Con's**
 - Delays systemic therapy
 - LC w/WBRT not optimal. 1y LC w/WBRT alone ~50%.
 - *Neurocognitive effects*

50 years in 2 minutes - SRS

- **SRS** to 15-24 Gy in 1 fx may be used in lieu of or as an adjunct to WBRT
- **Pro's**
 - Higher rates of LC. 1y LC 70% w/SRS alone.
 - One day procedure. Minimizes delays in systemic therapy.
 - Less potential for neurocognitive effects.
- **Con's**
 - Doesn't treat everything. 1y distant brain failure w/SRS alone 40-70%.
 - ***LC can be better.*** For example, addition of WBRT improves 1y LC to 80-90%.
 - Not so simple. Special equipment / training required.
 - Expensive.

Balancing the scales

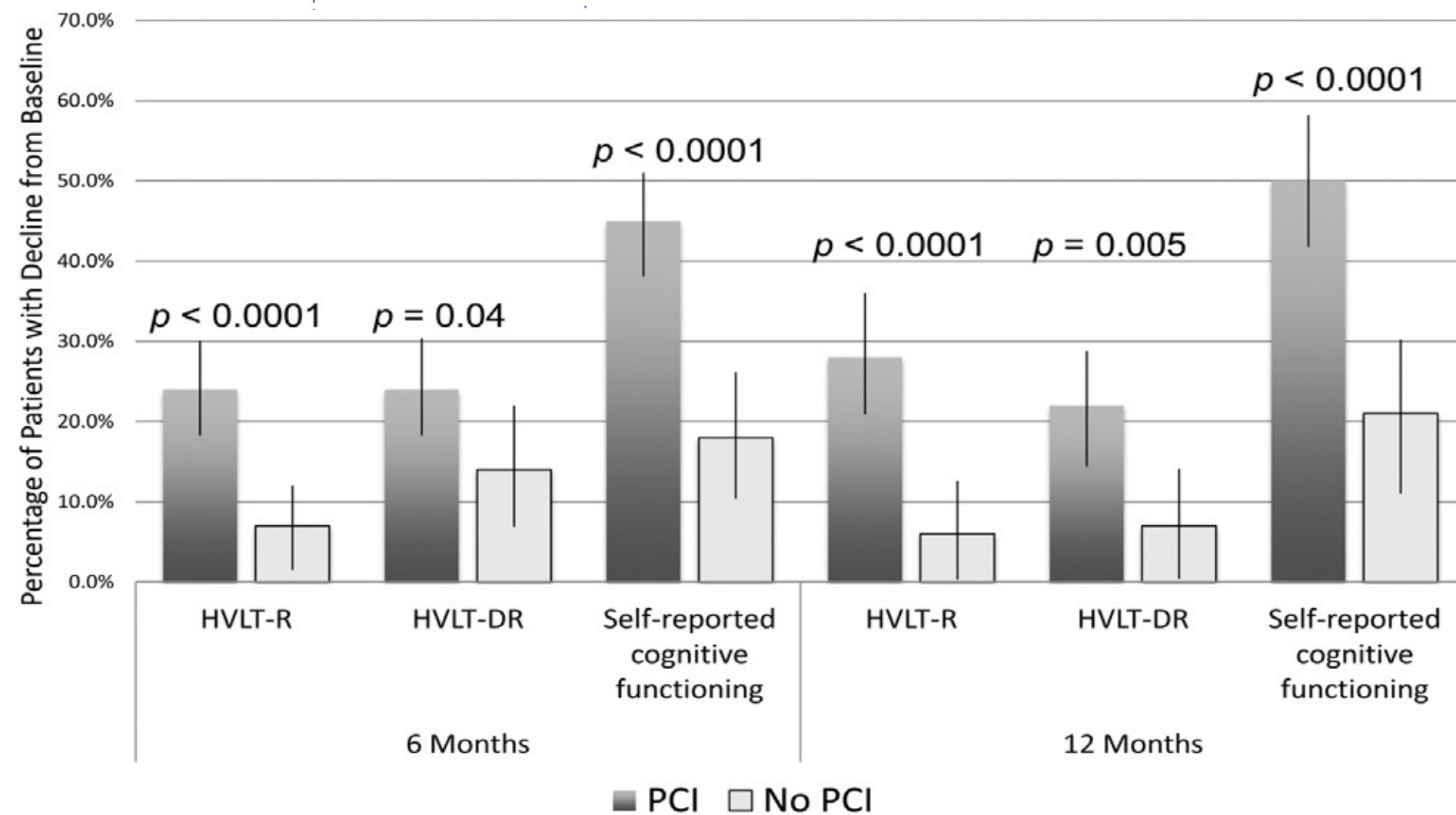
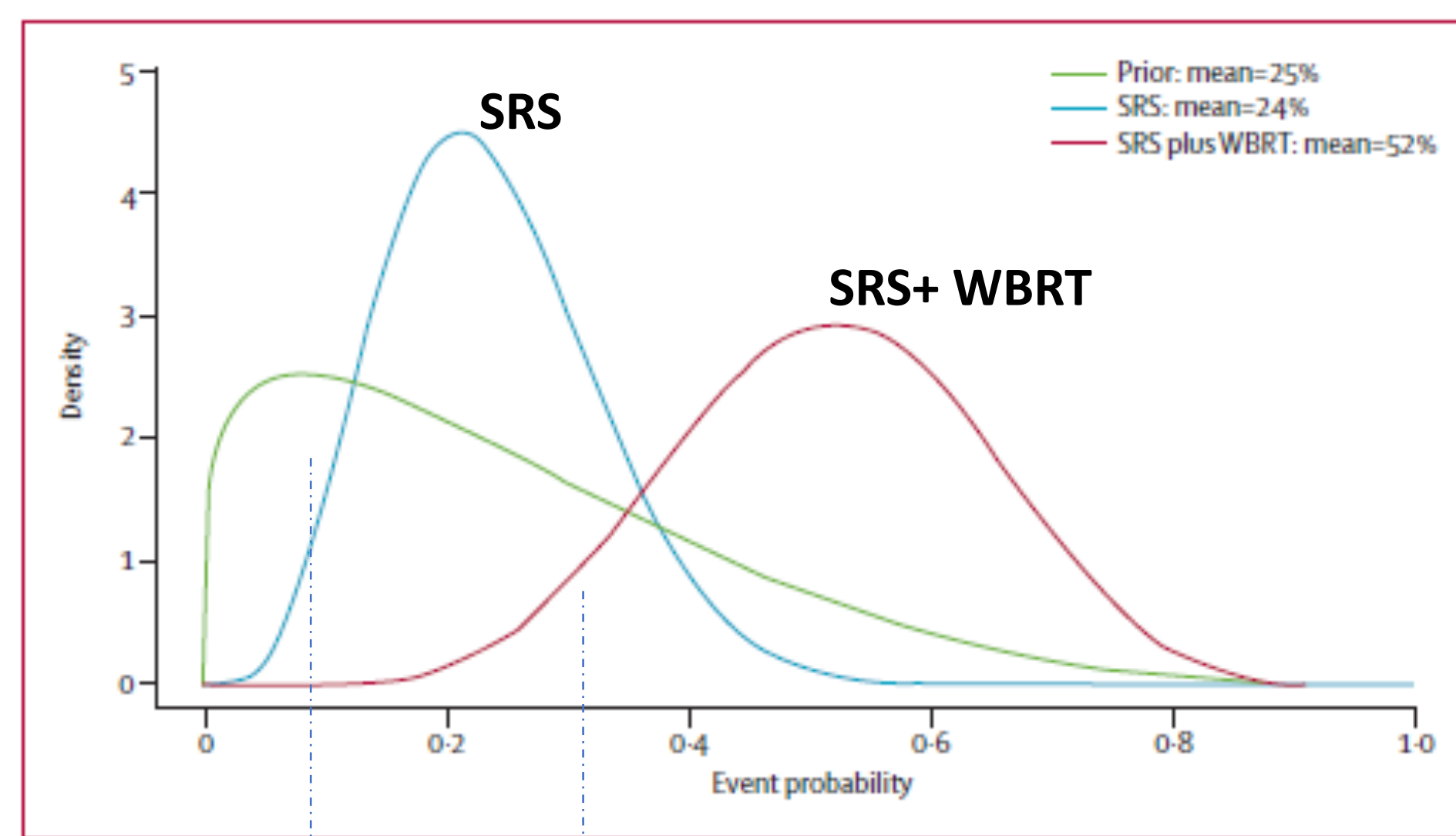
- **Reduce neurotoxicity with WBRT**
 - Drugs (memantine)
 - Technology (Hippocampal-avoidance)
- **Optimize local control with SRS**
 - Dosimetry
 - Fractionation



WBI / PCI and Cognitive Decline

- **Chang, et al (Lancet 2009)**
 - Phase III trial 58 pts w/ 1-3 mets tx'd w/ SRS vs. SRS+WBRT. Primary endpoint = decline in 4 mo HVLT-R
 - **WBRT + SRS had 53% vs. 24% decline in HVLT-R at 4 mo**

- **Gondi, et al (IJROBP 2013)**
 - Combined analysis of RTOG 0212 (PCI for NSCLC) and 0214 (PCI for SCLC)
 - Age, baseline neurocog impairment, and **use of PCI associated w/neurocognitive decline.**



So, now what?



**Let's not throw the baby out
with the bath water.**

RTOG 0614 – WBRT + memantine vs. placebo

- *Primary endpoint: Median decline HVLT-R DR of 0 vs. -0.90 @ 6 mo, $p=0.059$*

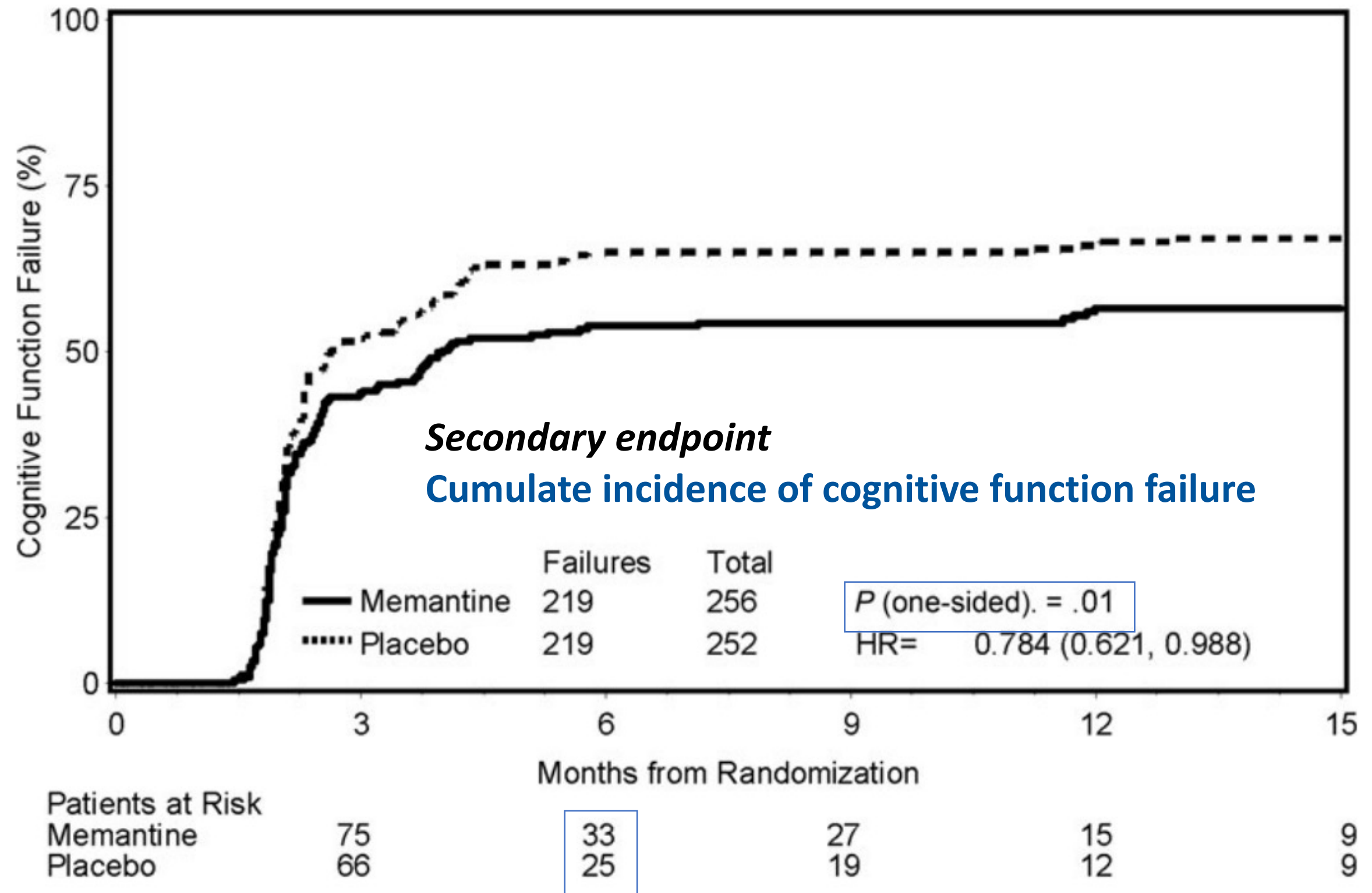
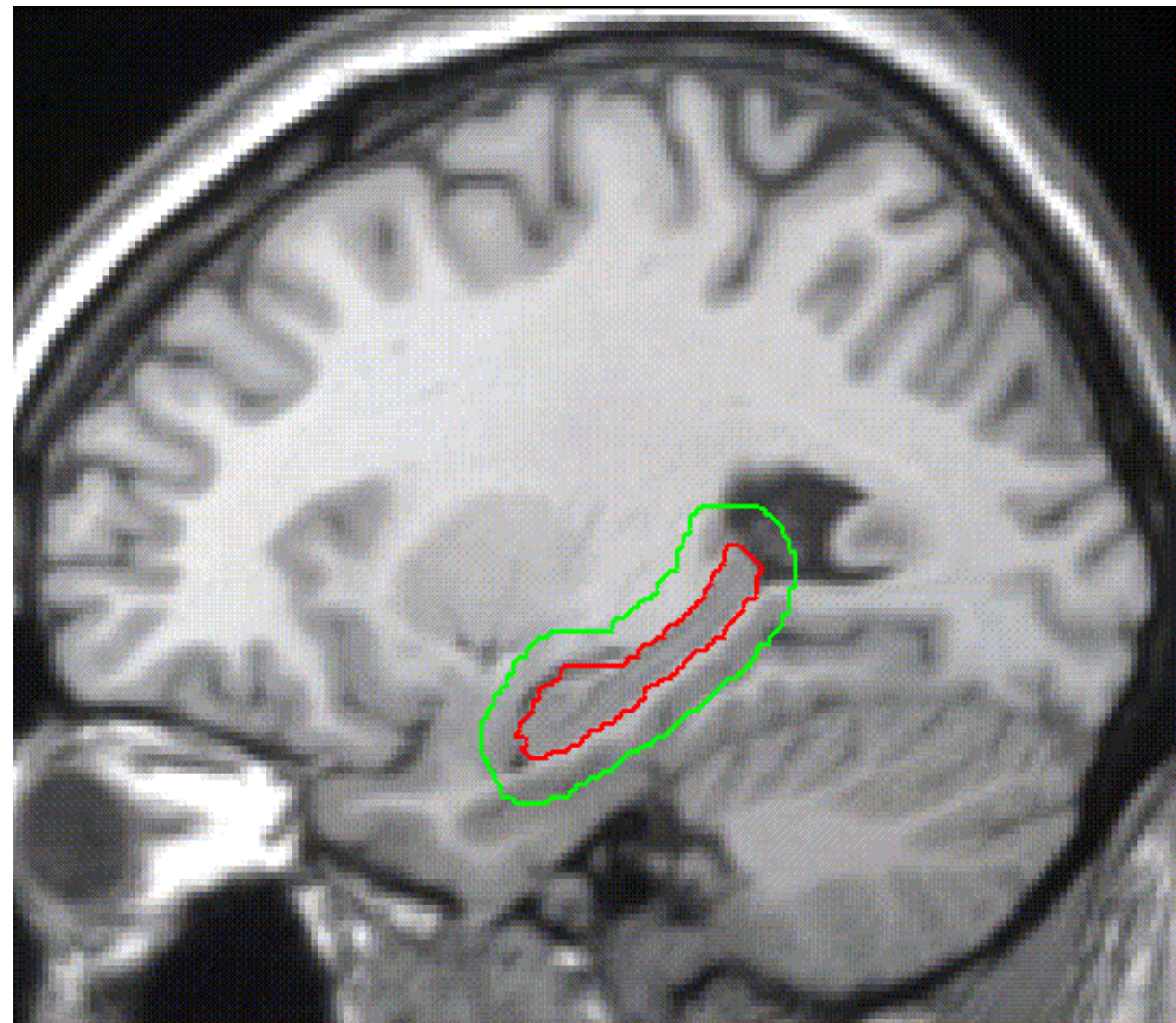


Fig. 2. Cumulative incidence of cognitive function failure according to treatment arm.

Hippocampal damage from radiotherapy

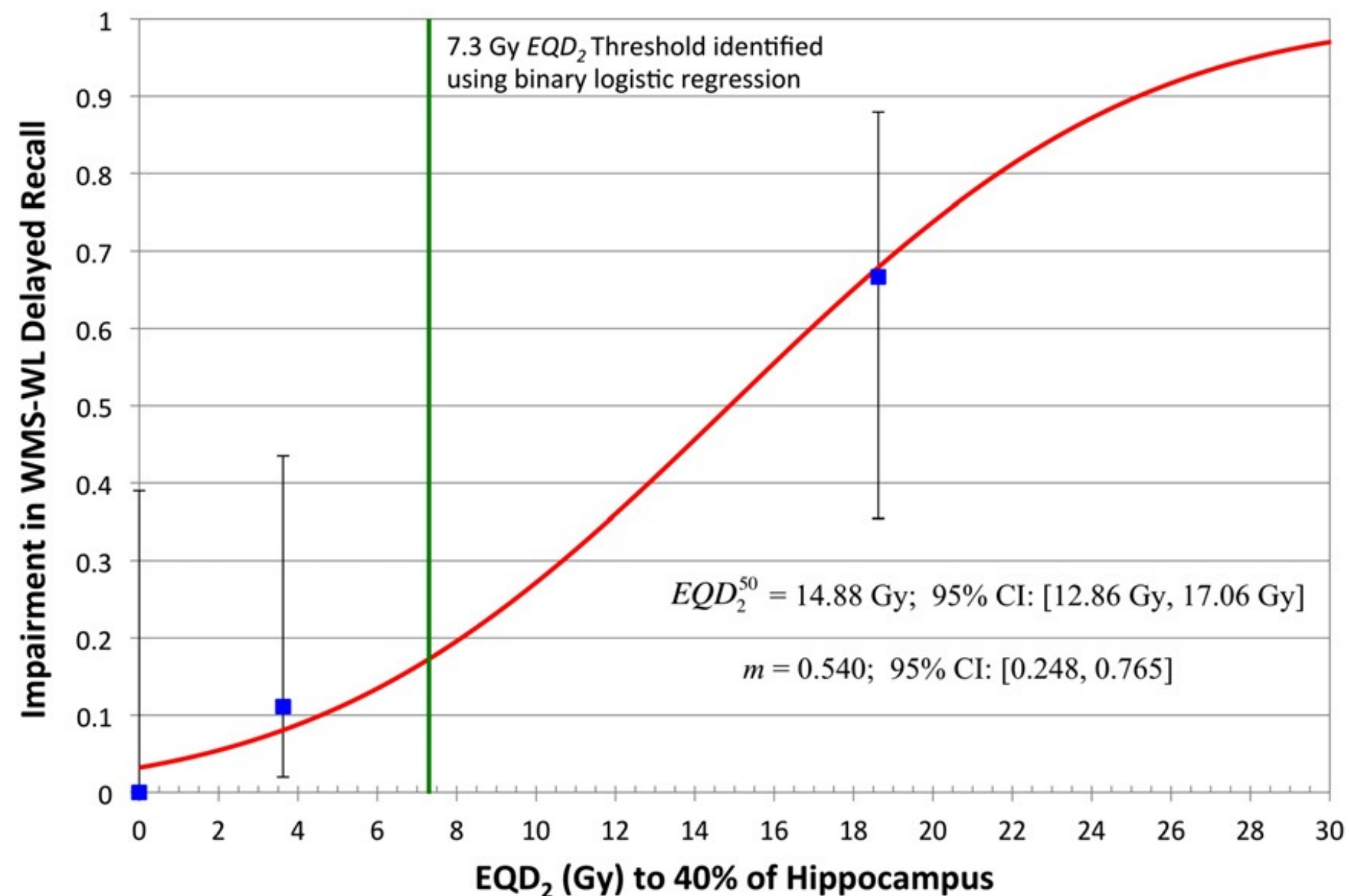
- Exquisite radiosensitivity of neuronal progenitor cells in subgranular zone of the hippocampus
- Injury to this “stem cell niche” has downstream effects on neurogenesis within and outside the hippocampus as well



Hippocampal damage from radiotherapy

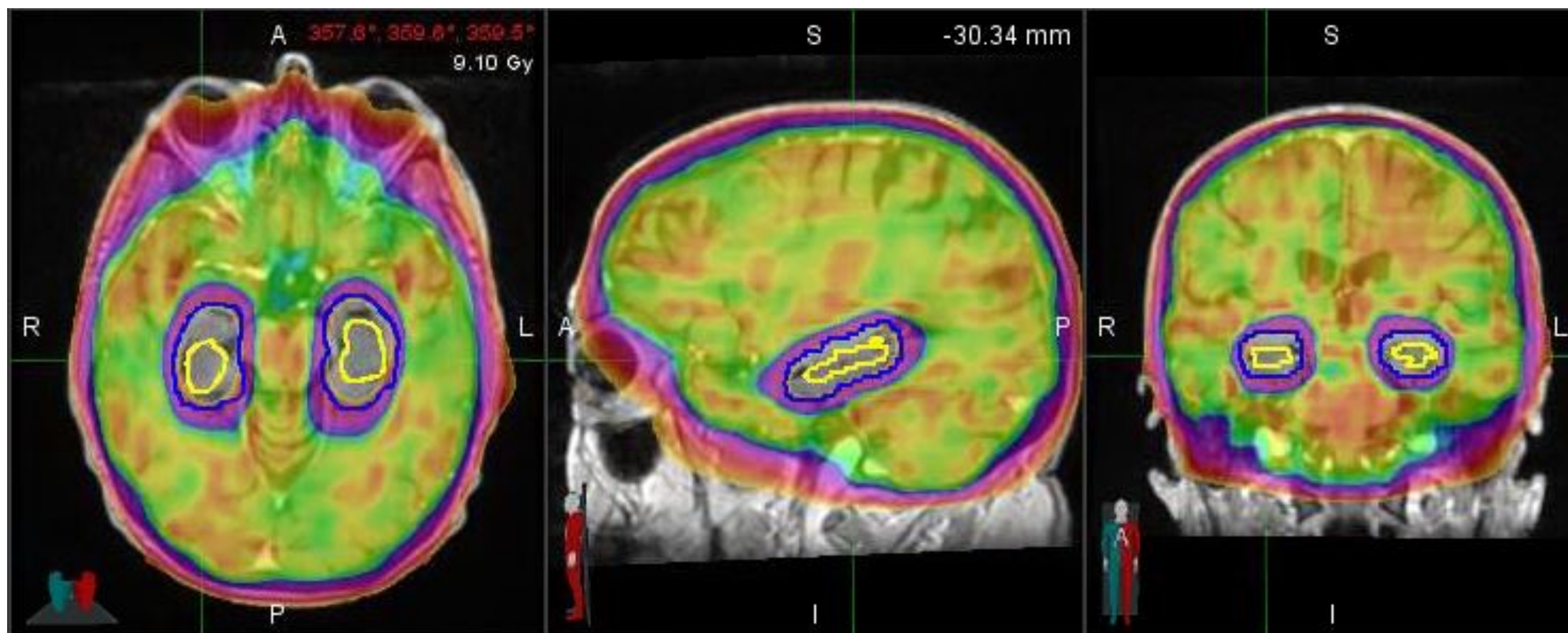
- **Gondi, *et al* (IJROBP 2011)**

- 29 pts tx'd w/ partial brain RT for benign/low-grade brain tumors
- Increasing dose to hippocampus associated with increasing impairment on Weschler Memory Scale-III Word List.



Hippocampal avoidance WBRT (HA-WBRT)

- IMRT technique, give whole brain 30 Gy/10 fx, keep hippocampus < 9 Gy



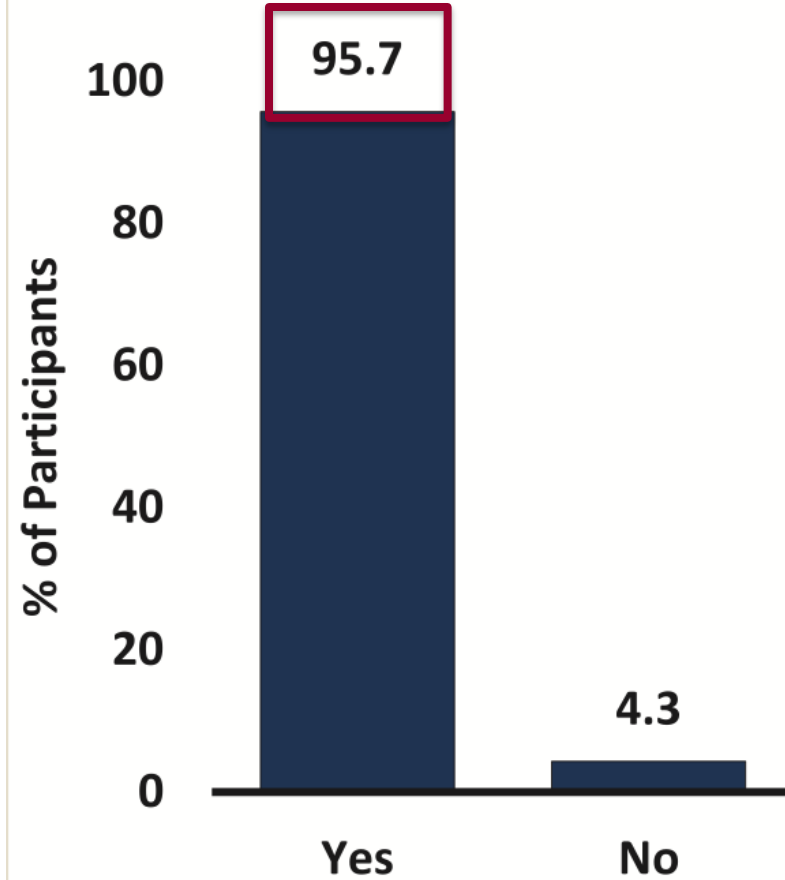
Background for SRS in SCLC

- Emerging evidence re: SRS for SCLC brain mets
 - Rusthoven et al.¹: SRS without prior PCI or WBRT, N=710
Retrospective across 28 centers (Asia, N. America, Europe)
Propensity score matched analyses:
 - WBRT a/w superior time to CNS progression, no OS benefit
 - Leptomeningeal progression 10.9%, neurological mortality 12.4%
 - Gaebe et al.²: SRS with/without prior PCI, N=1100
Systematic review, study-level meta-analysis
No OS difference between SRS and WBRT

Background for NRG CC009

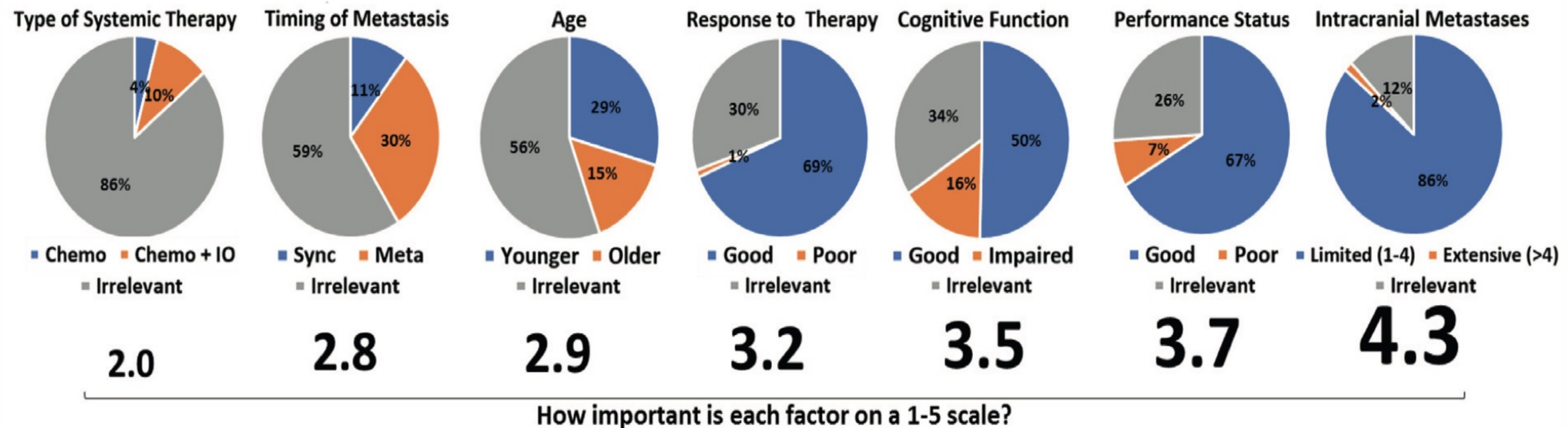
- Why not treat all SCLC brain metastasis patients with SRS?
 - Gjyshi et al.¹: Survey of 309 US Radiation Oncologists, 58% PP, 39% Acad, 3% other

A Would you ever consider SRS for SCLC?



A

You're more likely to offer SRS over WBRT to patients with which of the following factors?



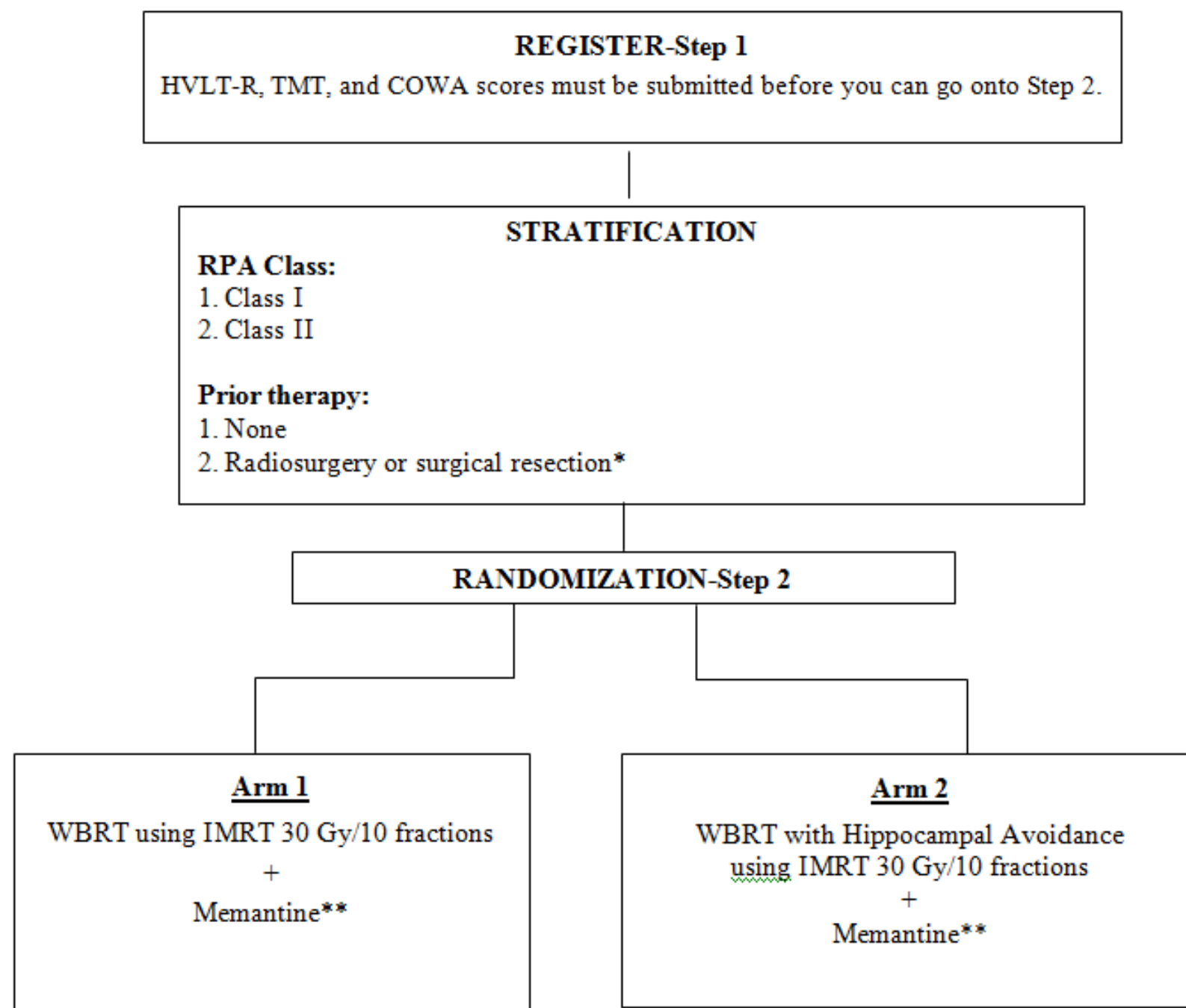
Background

- Why not treat all SCLC brain metastasis patients with SRS?

- Cross-Fire study¹: Retrospective (N=892-SCLC/N=4,785-NSCLC) + Prospective (JLGK0901, N=98-SCLC/N=794-NSCLC)
Inferior OS and time to CNS progression after SRS for patients with SCLC versus SRS for NSCLC
→ Reinforcing the unique biology of SCLC
- Safer Delivery of WBRT:
RTOG 0614²: Memantine confers **22%** relative risk reduction in neurocognitive toxicity
NRG CC001³: Hippocampal avoidance confers **additional 26%** relative risk reduction in neurocognitive toxicity
→ Sustained neurocog preservation with median f/u > 1 year⁴
→ Continued prevention of neuro symptoms with f/u > 1 year⁴

NRG CC001 – WBRT +/- Memantine in solid tumors

SCHEMA



*Radiosurgery or surgical resection within 8 weeks of randomization; otherwise stratify to *None*.

**Memantine to be administered during and after WBRT for a total of 24 weeks.

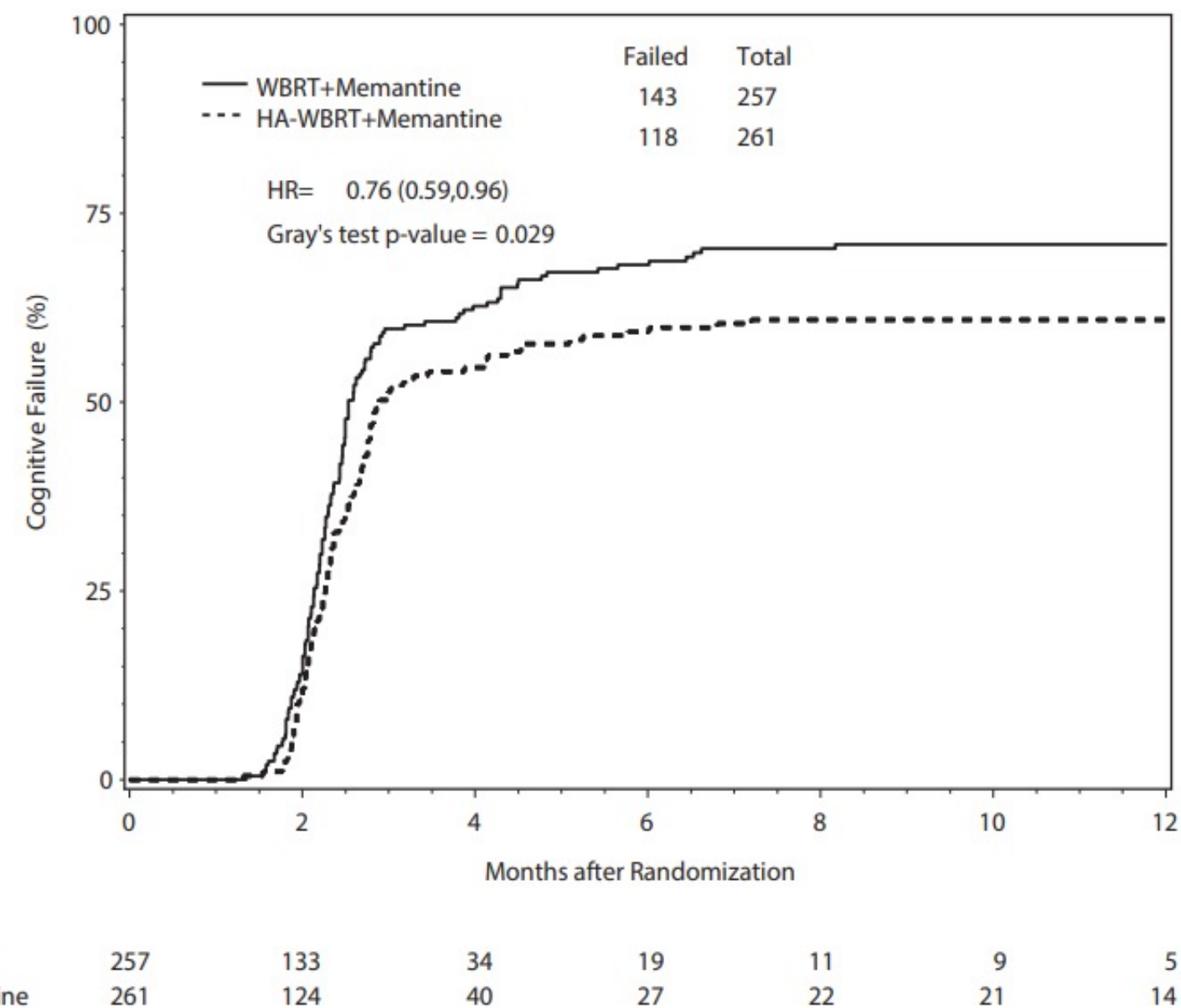
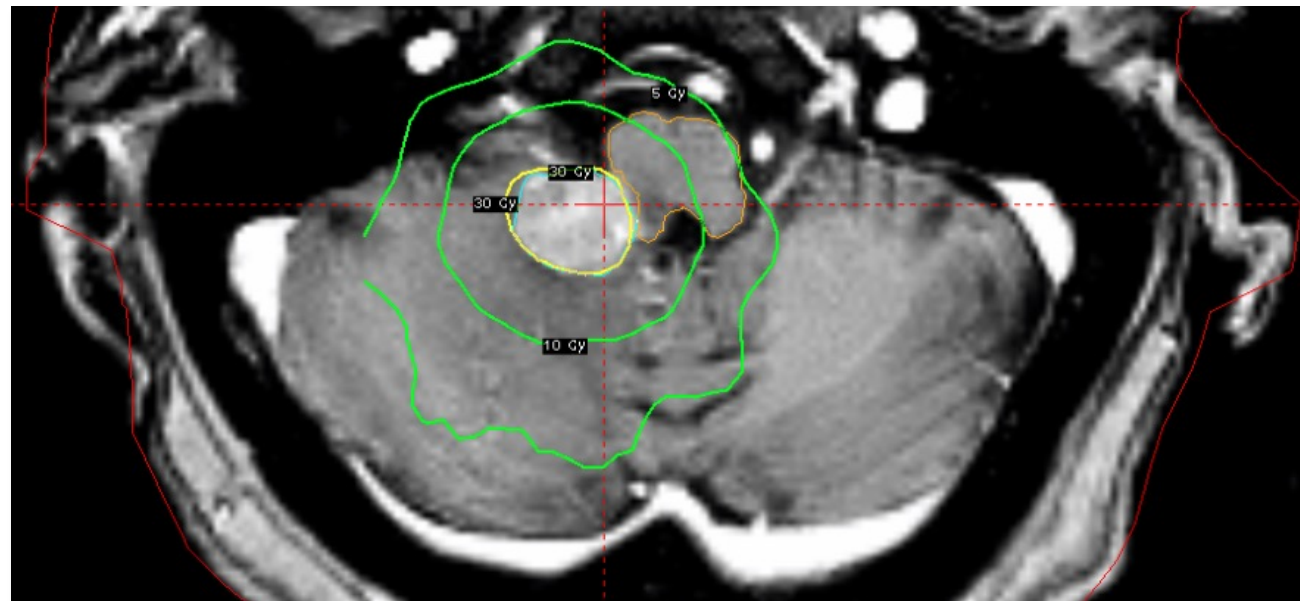
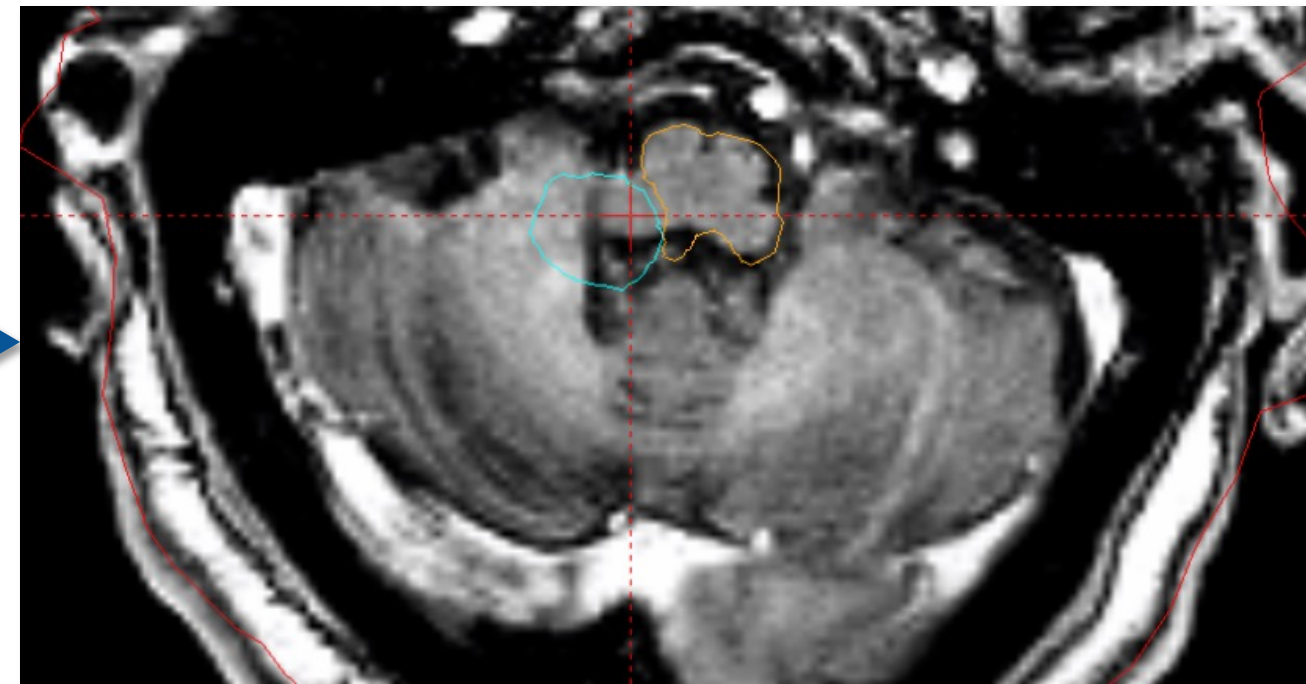


Fig. 2. Time to cognitive failure. Abbreviations: HA-WBRT = hippocampal avoidant whole-brain radiation therapy; HR = hazard ratio; WBRT, whole-brain radiation therapy.

Fractionated SRS – Location, location, location



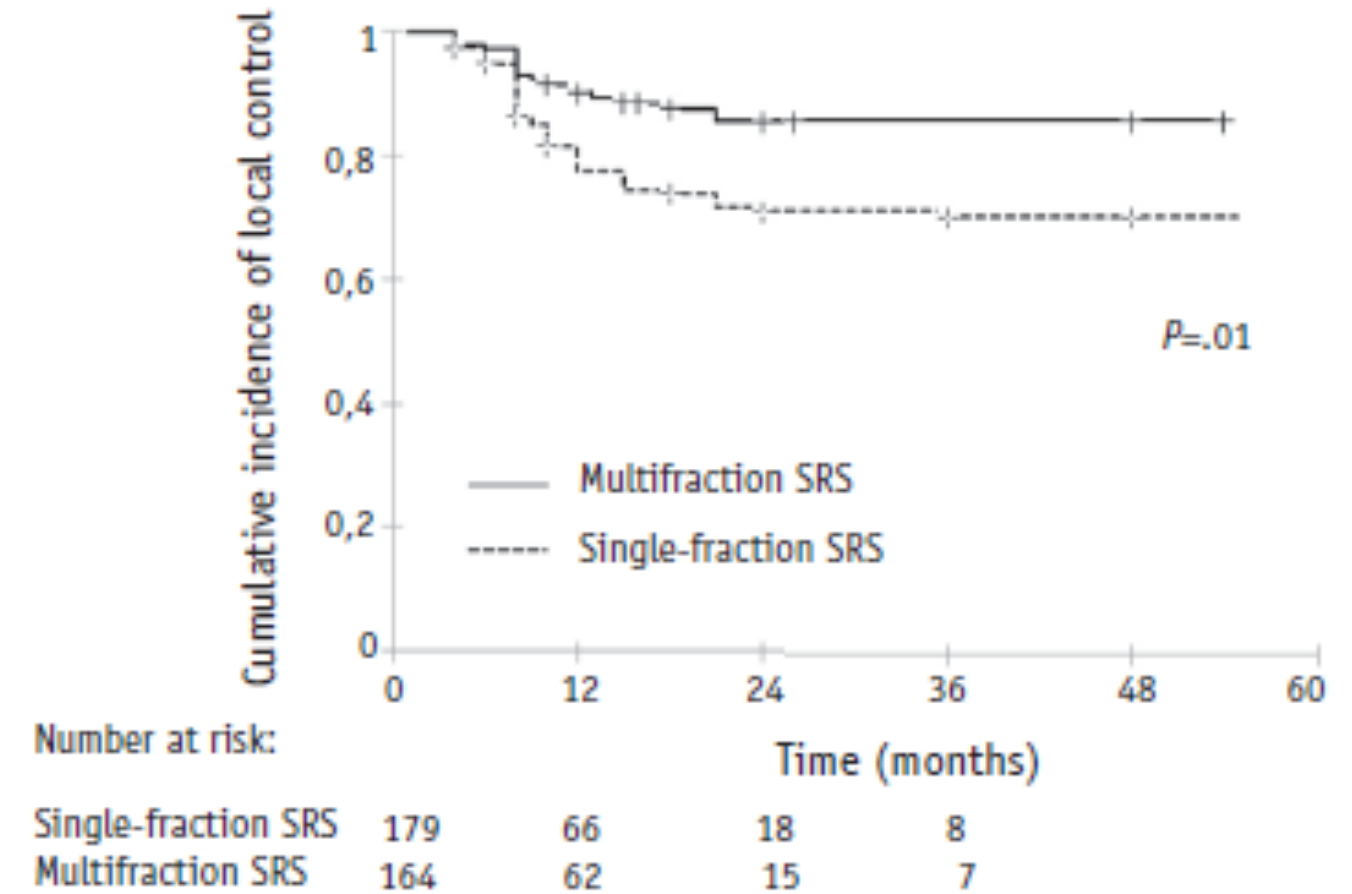
30 Gy/5 fx @ 50% IDL



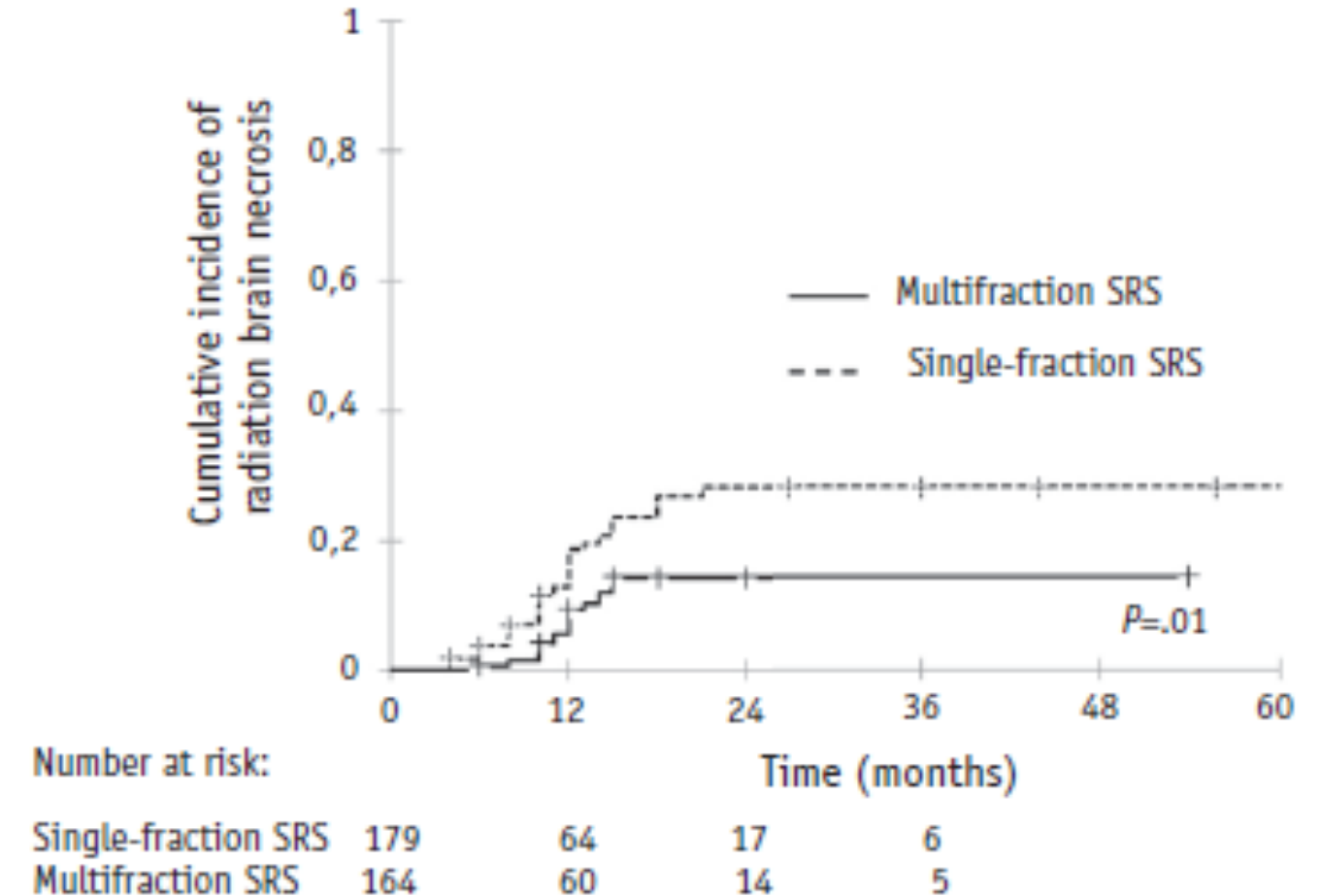
Fractionated SRS

- **289 pts w/brain mets > 2 cm tx'd w/ 1 (15-18 Gy) vs 3 fx (27Gy/3) linac SRS**
- Well balanced, except median tumor volume ***larger for 3 fx SRS*** (12.5 vs. 8.8 cc, p=0.005)
- Propensity score matching on age, sex, histology, size, irradiated volume
 - ***LC: HR 0.35 (0.13-0.76)***
 - ***RN: HR 0.22 (0.14-0.73)***

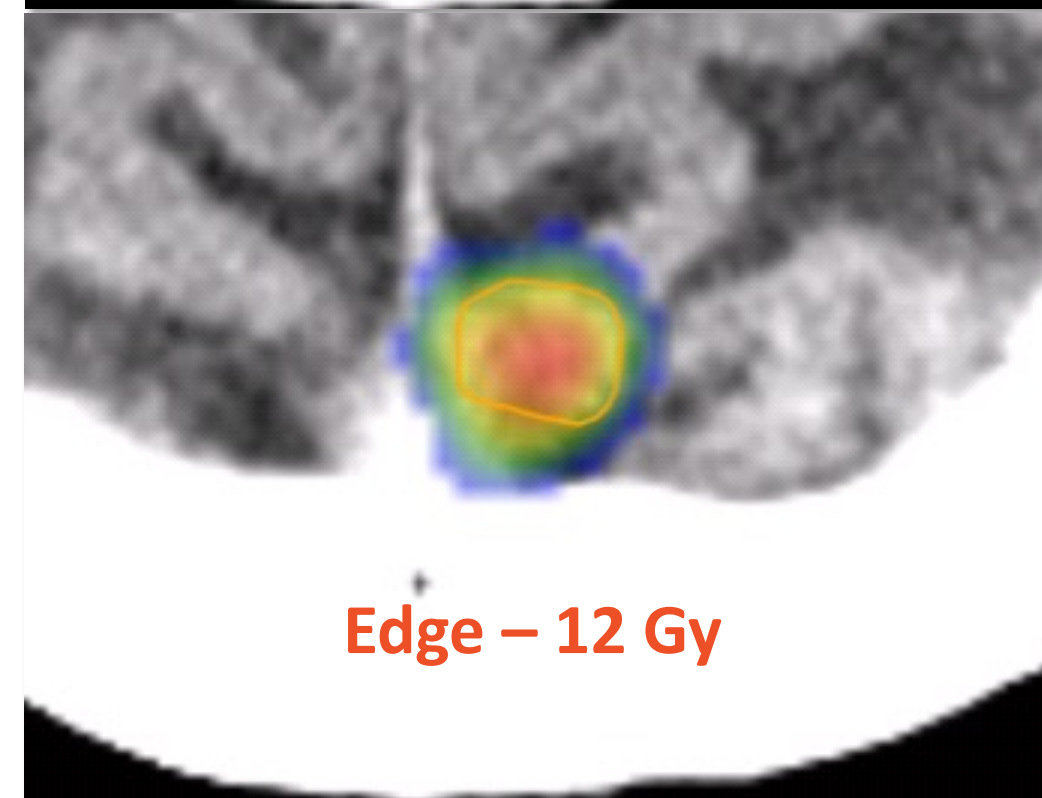
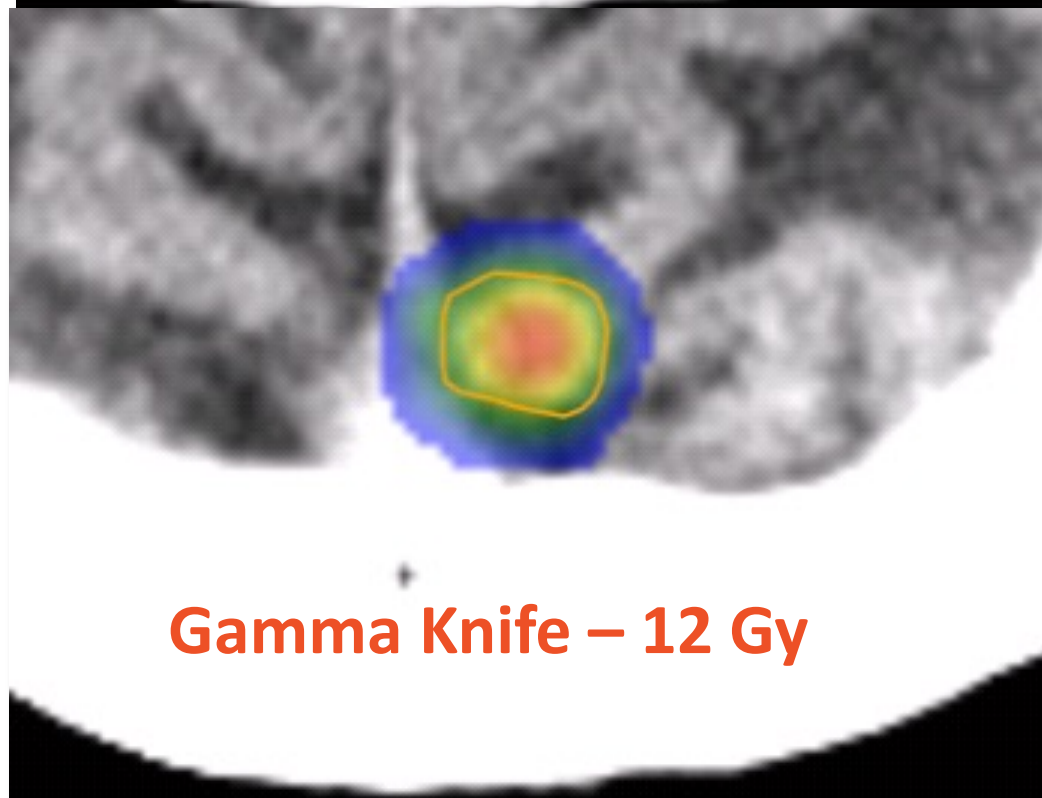
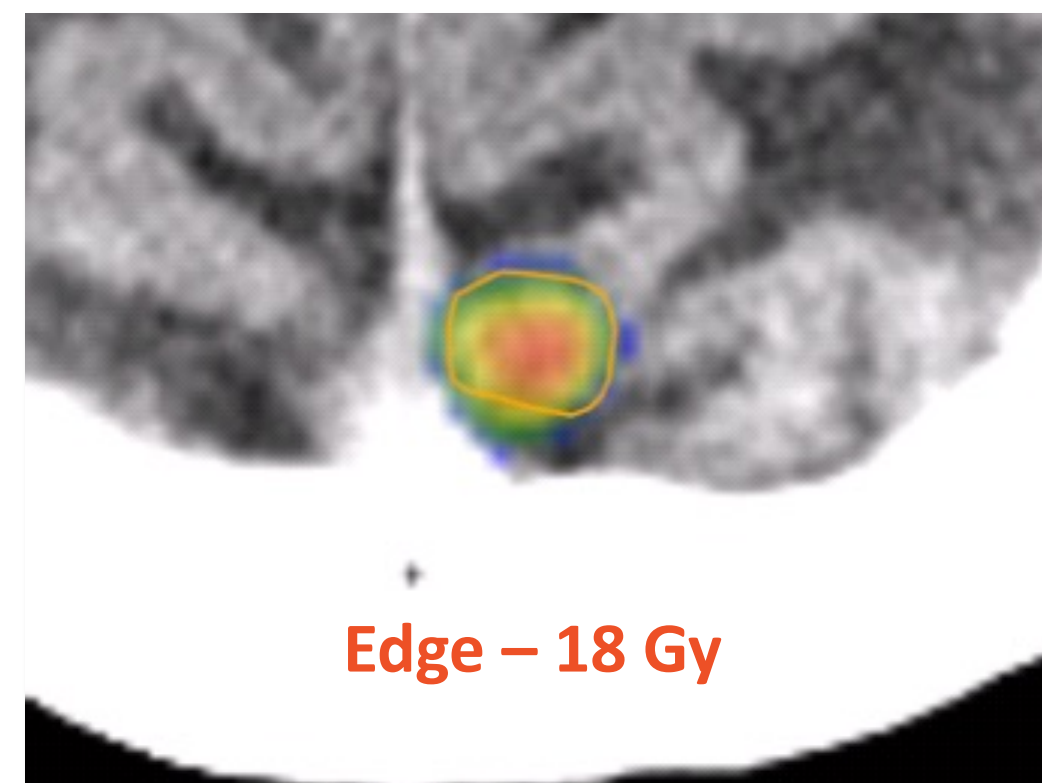
1y LC 54% vs. 73%



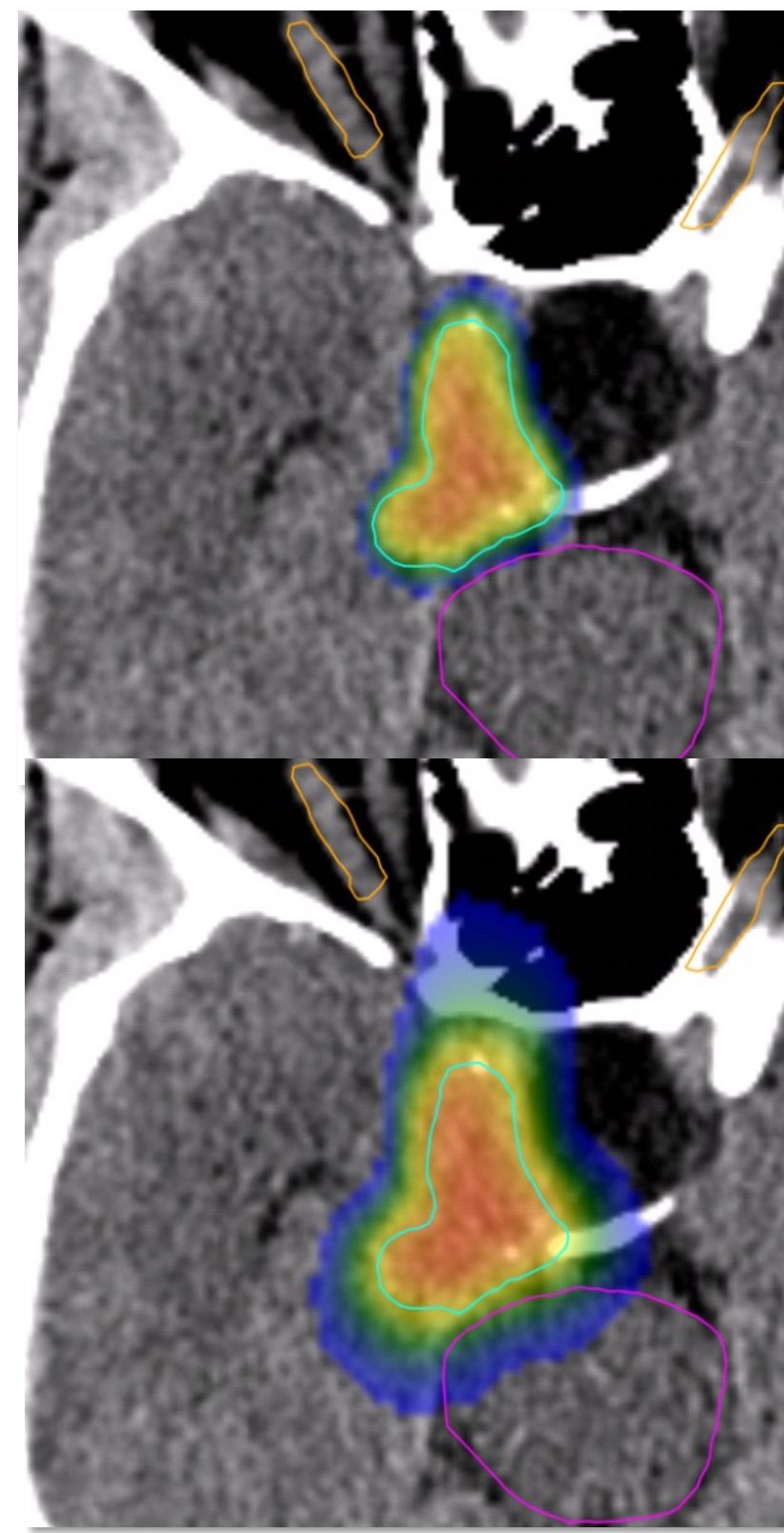
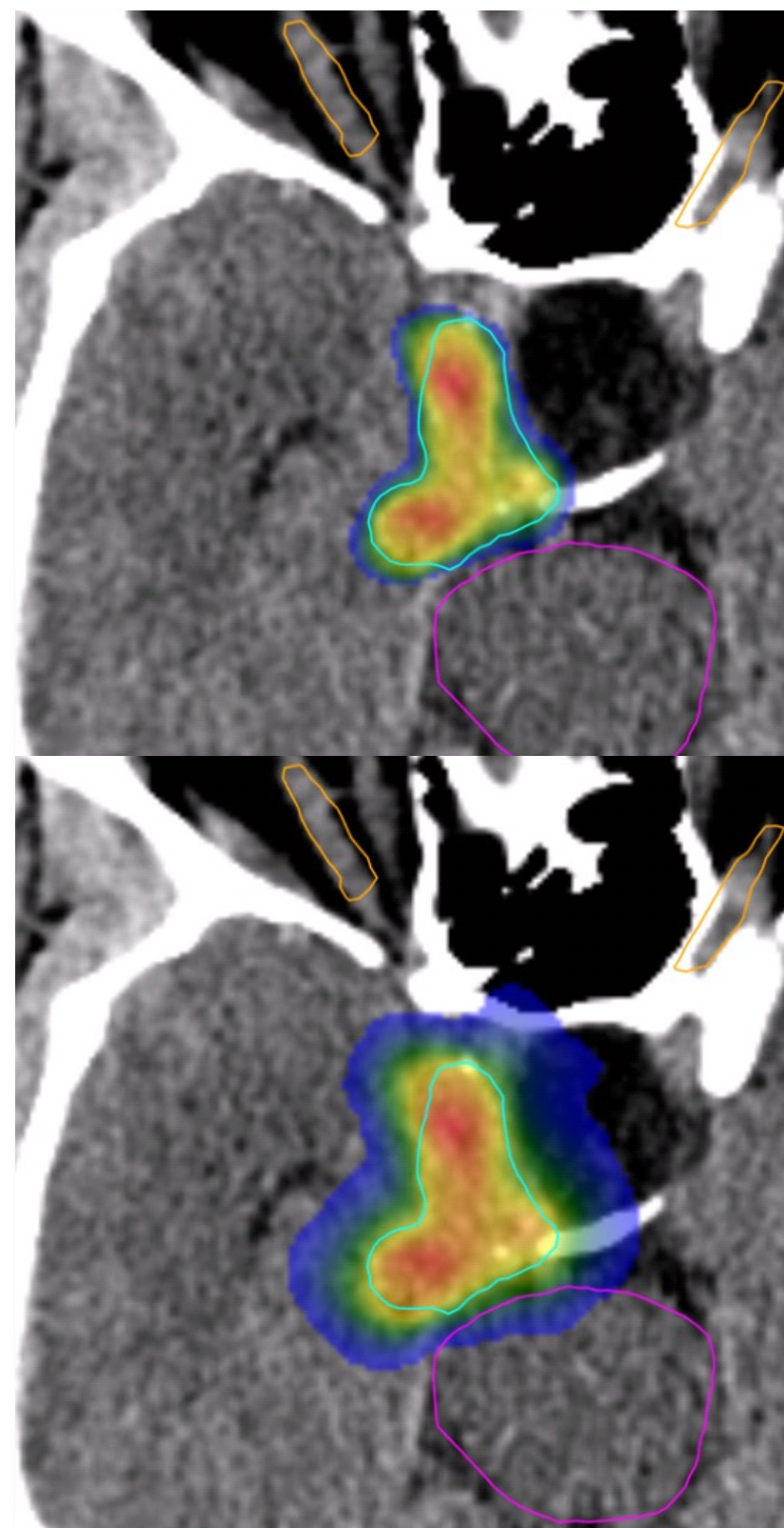
1y RN 18% vs. 9%



1fx SRS multiple mets – GK vs. Linac (Edge)



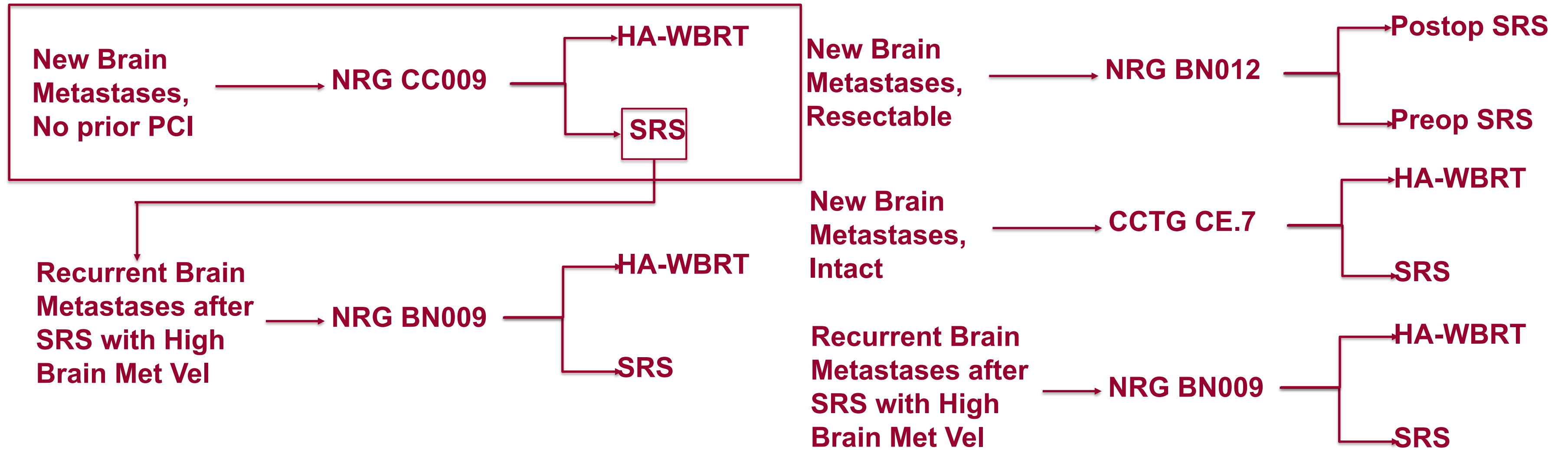
5 fx SRS – GK vs. Linac (Edge)



Brain Metastases Tx for Lung Cancer

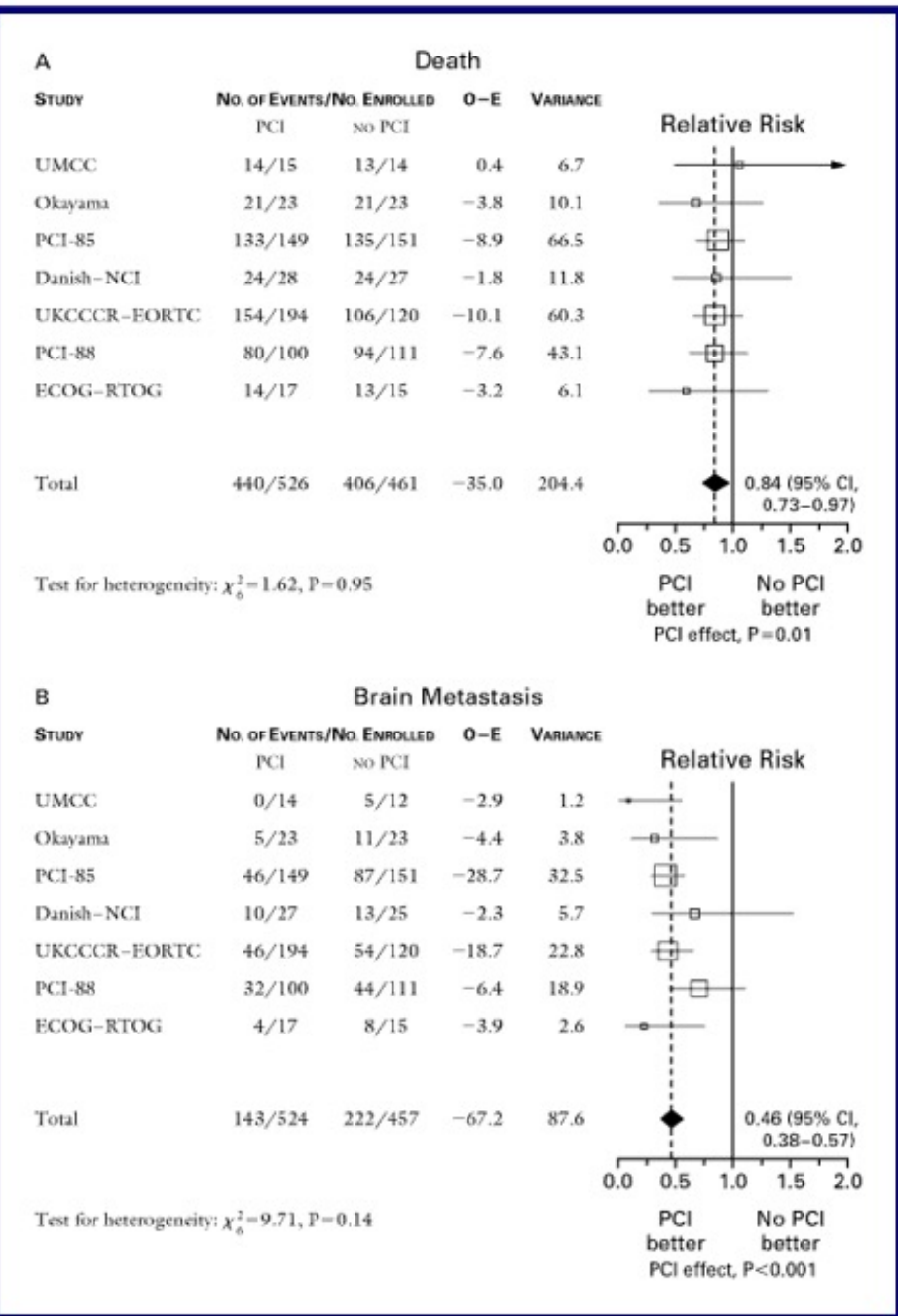
Small Cell Lung Cancer

Non-Small Cell Lung Cancer

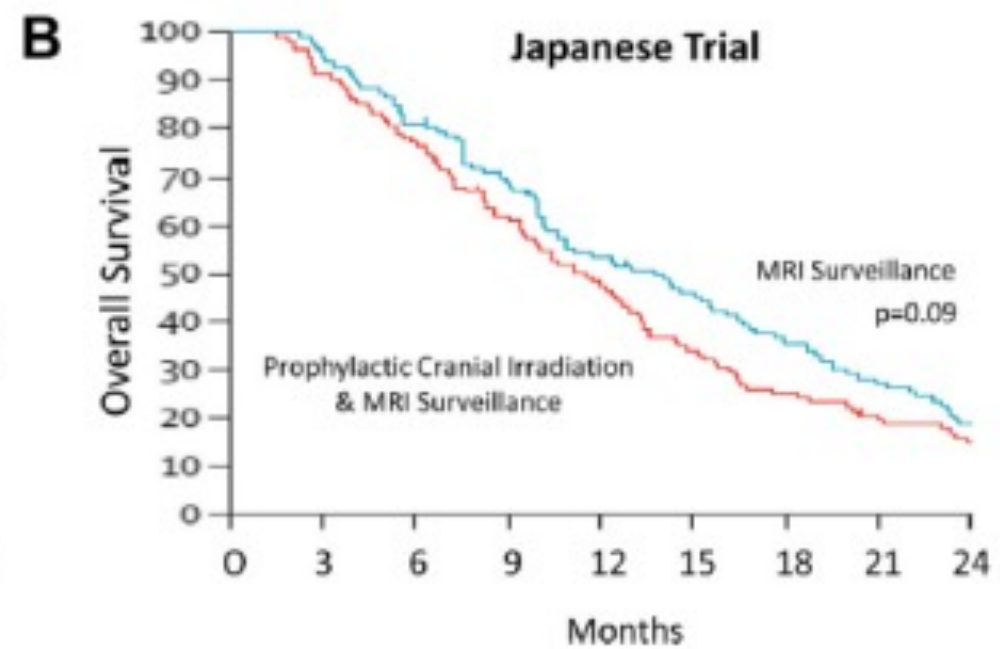
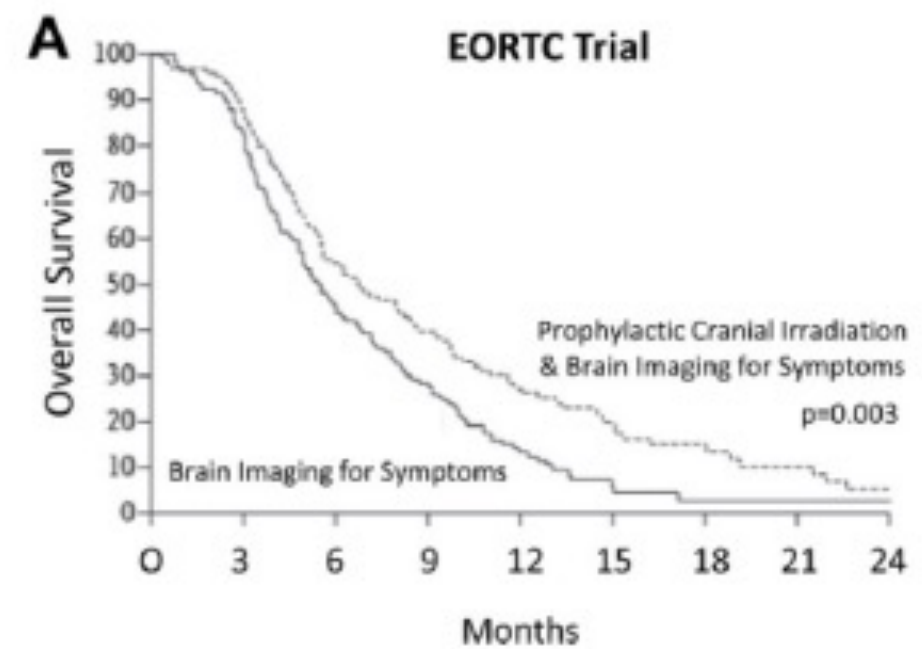
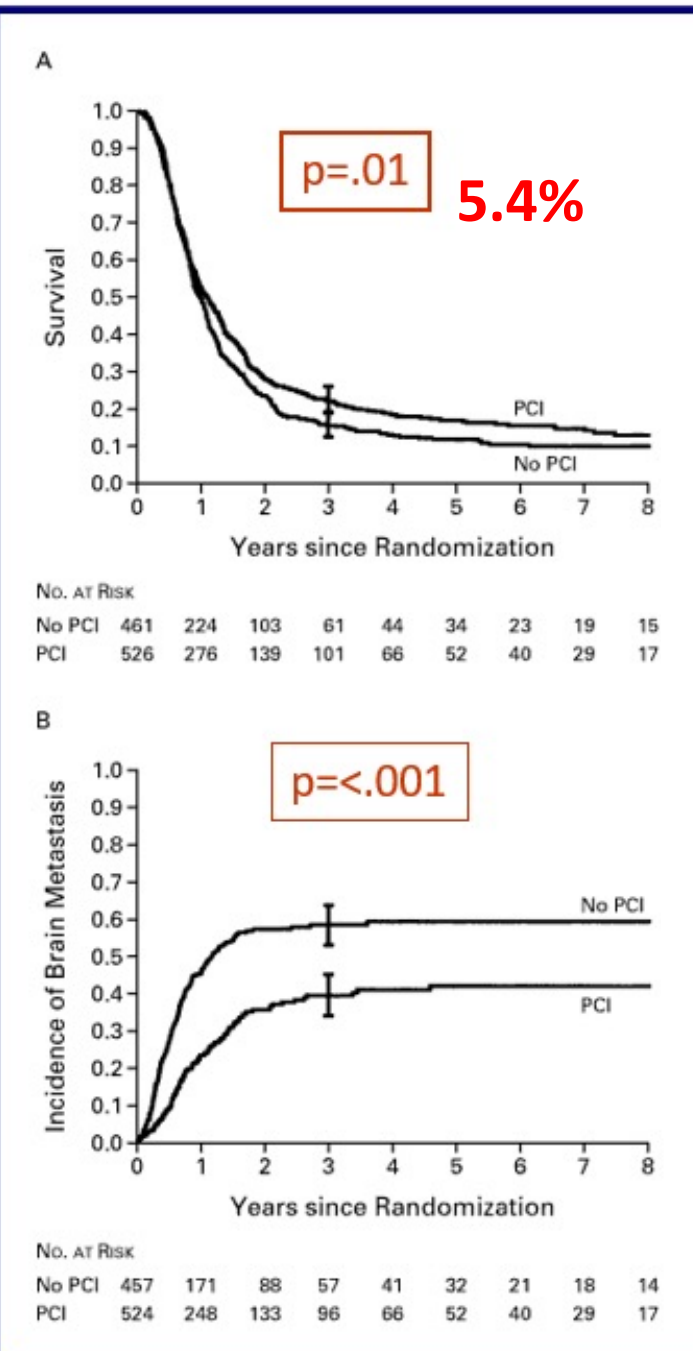


Prophylactic Cranial Irradiation in SCLC

- Reduction in brain metastases but increase neurologic toxicity
- Role of MRI Surveillance



Auperin 1999

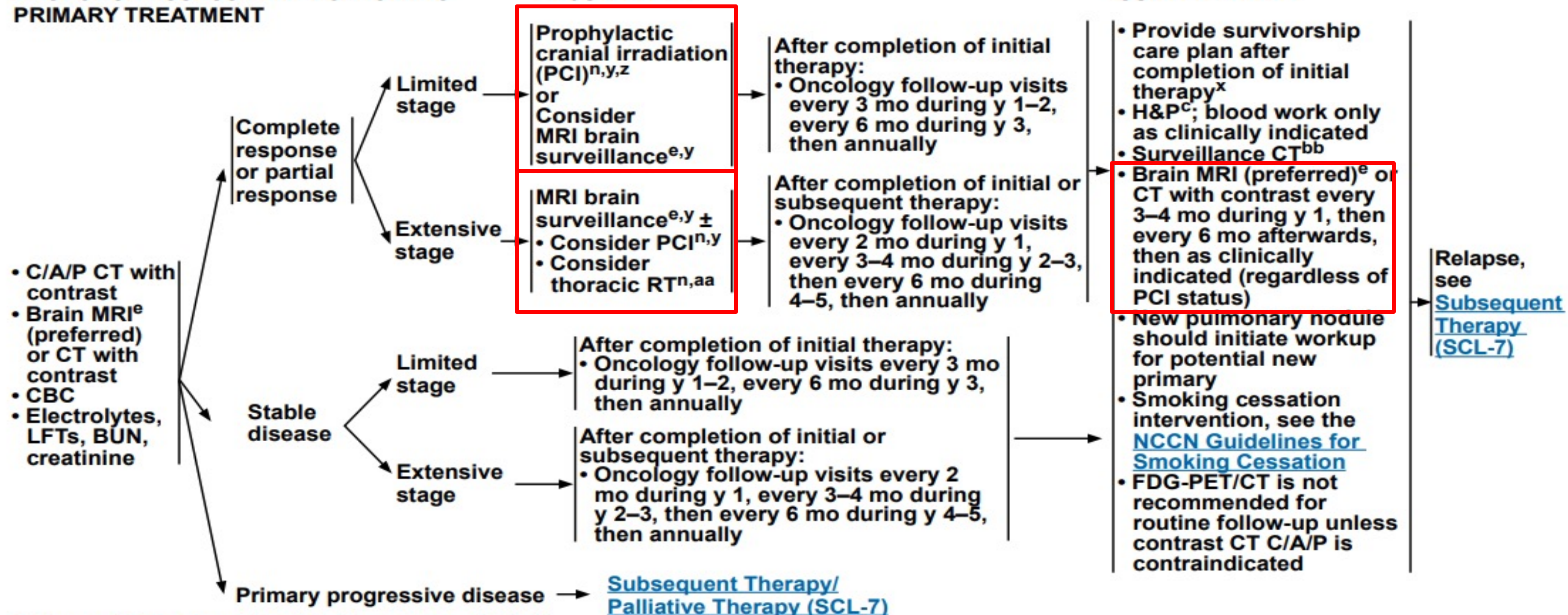


Slotman NEJM 2007 – Imaging for symptoms vs PCI
 Takahashi, Lancet Oncology 2017 – MRI surveillance +/- PCI

RESPONSE ASSESSMENT FOLLOWING
PRIMARY TREATMENT

ADJUVANT RT

SURVEILLANCE



^c [Signs and Symptoms of Small Cell Lung Cancer \(SCL-A\)](#).

^e Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

ⁿ [Principles of Radiation Therapy \(SCL-F\)](#).

^x [NCCN Guidelines for Survivorship](#).

^y PCI is not recommended in patients with poor PS or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close brain surveillance, MRI (preferred) or CT with contrast, should be carefully discussed with these patients.

^z The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0) SCLC. See [Principles of Radiation Therapy \(SCL-F\)](#).

^{aa} Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.

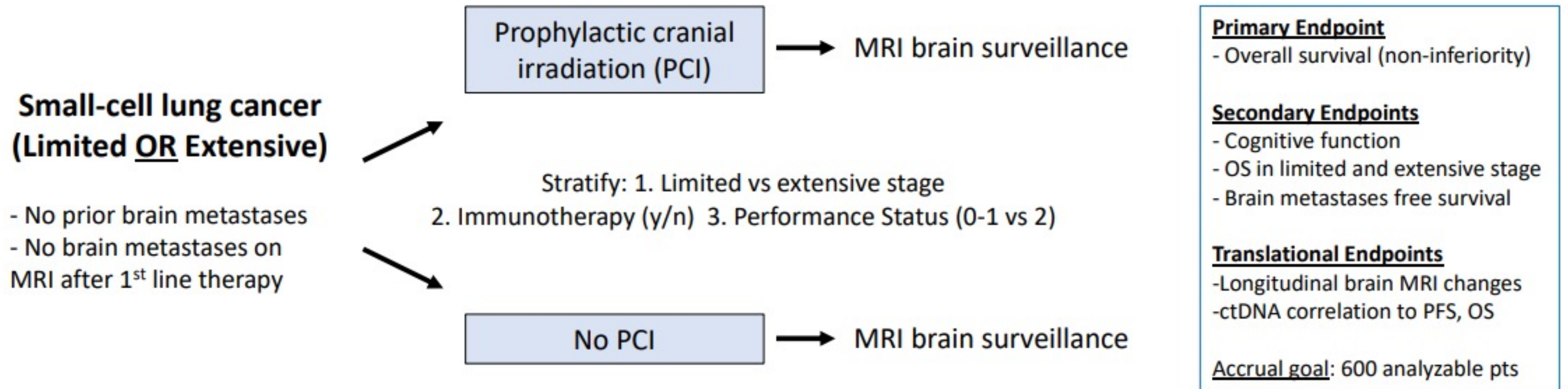
^{bb} Most NCCN Member Institutions use CT chest ± abdomen/pelvis every 2–6 months (more frequently in years 1–2 and less frequently thereafter).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MAVERICK (SWOG 1827)

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



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