Radiation-induced changes in brain function after cranial irradiation: Radiobiology and clinical review

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Disclosures

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• I have no conflicts of interest to disclose
Background and Overview

• RT has a pivotal role in the treatment of many CNS pathologies
  – both primary infiltrative brain tumors and metastatic disease
  – non-neoplastic disease processes
• Cranial irradiation has adverse effects on the normal CNS
  – acute changes associated with CNS edema – **vascular hypothesis**
  – glial precursors and resultant demyelinative necrosis – **glial hypothesis**
  – neither hypothesis adequately accounts for the fact that most patients with significant
cognitive deterioration exhibit no signs of overt vasculopathy or demyelination
• Molecular mechanisms culminating in the adverse effects not fully known
  – pre-clinical experiments provide some evidence
• Recent research focus direct toward functional assessments of injury
  – and the reparative and therapeutic role that BMDCs
Radiation-induced brain injury: Radiobiology

- Prior to 1970, brain considered to be radioresistant
  - central nervous system syndrome single doses >30 Gy
  - white matter necrosis occurring at fractionated doses >60 Gy
  - rodents studies determined dose dependent changes

- During the 1980s–1990s, late radiation-induced brain injury >6 months recognized as dose limiting toxicity
  - functional assessments of injury
  - characterized by vascular abnormalities, demyelination, and white matter necrosis morbidity and cognitive impairment
  - reduction in the proliferative capacity of glial or vascular endothelial cells; progressive and irreversible

1 Greene-Schloesser et al. (2012) Front Oncol 2: 73, 1–17
Radiation injury in brain

• Classical view: Late radiation-induced brain injury solely attributable to a reduction in the proliferative capacity of glial\(^1\) or vascular endothelial cells\(^2\)
  – viewed as progressive and irreversible

• Contemporary view: In recent years, appreciation that patients can develop significant cognitive impairment at >6 months even in the absence of detectable anatomic abnormalities
  – focus on function consequences\(^3\)

Radiation-induced brain injury

- Includes both anatomic and functional deficits
- Based on the time of clinical expression

Dose Dependent: Produces vascular damage

normally reversible and resolve spontaneously

1Greene-Schloesser et al. (2012) Front Oncol 2: 73, 1–17
Classic radiation injury in brain: Pathophysiology\textsuperscript{1,2}

- **Acute:** Direct effects on proliferating oligodendrocytes resulting in transient demyelination and breakdown of blood-brain barrier
  - Increase in size of the endothelial-glial junctions
  - Loss of microvasculature 2-4 wks, confirmed by MRI
  - Vascular insufficiency and infarction
  - Fatigue, nausea, cerebral edema, headache

- **Sub-acute:** somnolence syndrome, early onset leukoencephalopathy
  - Transient demyelination of cerebral white matter, 1–6 months

- **Chronic/Late:** Focal coagulative necrosis in white matter
  - Atypical endothelial cells and fibrinoid necrosis of small arterial vessels
  - Vascular occlusion, 6 months to 2 years post-therapy → dementia

Cognitive decline and irradiation: Overview

• Cognitive decline, 40–50% >1 year after irradiation\textsuperscript{1} in long-term brain tumor survivors
  – working memory\textsuperscript{2}, verbal memory\textsuperscript{3} and general IQ\textsuperscript{4}
  – single and fractionated doses

• Rats in Barnes water maze
  – Dose and time dependent, increased latency\textsuperscript{5}

\textsuperscript{1}Johannesen et al. Radiother Oncol (2003); \textbf{69}: 169–176
\textsuperscript{2}Welzel et al. Strahlenther Onkol (2008); \textbf{184}: 647–654
\textsuperscript{3}Welzel et al. IJROBP (2008); \textbf{72}: 1311–1318
\textsuperscript{5}Warrington et al. PloS One (2012); 7:e30444.
Radiobiology modeling parameters for the brain

- **α/β ratio**$^{1,2}$ = 2, Quantec$^{3,4}$ α/β ratio = 3
  - 60 Gy/30F: BED$_{2Gy}$ = 120 vs BED$_{3Gy}$ = 100

- For fractionated RT with a fraction size of <2.5 Gy$^4$
  - Incidence of radiation necrosis
  - 5% at BED$_{3Gy}$ = 120 Gy (range, 100–140) and 10% at BED$_{3Gy}$ = 150 Gy (range, 140–170)

- Twice-daily fractionation, steep toxicity curve when BED$_{3Gy}$ dose is >80 Gy$^4$

- >2.5 Gy Fx, the incidence and severity of toxicity is unpredictable$^4$
  - The brain is sensitive to fraction sizes >2 Gy

- Emami: 5% risk of radionecrosis at 5 yrs, 60 Gy (by Standard Fractionation) to 1/3 of the brain$^5$
  - <3% for <60 Gy, 5% for dose of 72 Gy, 10% for 90 Gy$^4,6$

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$^2$Mayer and Sminia *IJROBP* (2008) 70, 1350–1360

$^3$Mayo et al. (2010) *IJROBP* 76(S3), S36–S41

$^4$Lawrence et al. (2010) *IJROBP* 76(S3), S20–S27


$^6$Marks et al. (2010) *IJROBP* 76(S3), S10–S19
Lawrence et al. (2010) IJROBP 76(S3), S20–S27

Relationship between biologically effective dose (BED) and radiation necrosis

- **Standard fractions**
- **Large dose fractions**
- **Twice daily**
For radiosurgery, the incidence of necrosis depends on the dose, volume, and region irradiated. Studies differ in their completeness of follow-up. For radiosurgery, the incidence of necrosis depends on the dose, volume, and region irradiated.

Neuroanatomical target theory: Predictive model

• Models of radiation brain injury predict the likelihood of radionecrosis (NCTP-based models)$^{1,2}$
  – function of the dose delivered and volume of brain irradiated
  – radiation-induced cognitive decline occurs at lower doses

• Progenitor cell depletion, disruption of brain connectivity, parallel processing reduction

• 3 dose levels related to particular mechanistic features important to cognition$^3$
  – At 10 Gy NSC reduction, 40 Gy prominent white matter disease, and 60 Gy risk of necrosis

$^3$Peiffer et al. (2013) *Neurology* **80**: 747–753
Neuroanatomical target theory: Predictive model


The $\%v_{10}$ (percent of ROI receiving 10 Gy), $\%v_{40}$, and $\%v_{60}$ were calculated for each ROI predicted performance on individual neurocognitive tests for each ROI. Regions that predicted global cognitive outcomes at doses $<$60 Gy included the CC, left frontal white matter, right temporal lobe, bilateral hippocampi, SVZ, and cerebellum.
In order to develop strategies to decrease the risks of brain RT, the risks must be **identified, defined & understood**
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**Brain metastases**
WBRT + SRS boost for brain metastases: RTOG 95-08

- RTOG 95-08 showed a survival advantage for patients with single (but not 2 or 3) BM treated with WBRT+ boost SRS\textsuperscript{1}, RPA class 1
  - multi-institutional
  - WBRT 2.5 Gy/F, 37.5 Gy, 3 wks, \textbf{SRS boost} with 1 wk
  - 331 pts; 167 WBRT and 164 WBRT+SRS
  - SRS boost not associated with toxicity

- \textbf{Secondary analysis of lung pts}\textsuperscript{2}
  - consistent with original analysis
  - Also for good prognosis (GPA 3.5-4.0) with 1, 2, 3 BM
  - WBRT has a role; WBRT neurocognitive effects can be mitigated

\textsuperscript{1}Andrews et al. (2004) Lancet \textbf{363}: 1665–1672
\textsuperscript{2}Sperduto et al. (2014) IJROBP \textbf{90}: 526–531
WBRT + SRS boost for Brain metastases: RTOG 95-08


2 Sperduto et al. (2014) IJROBP 90: 526–531
Phase 3 Trial of SRS ± WBRT for 1 to 4 BM\textsuperscript{1}

- Practice evolved from WBRT, SRS, SRS+WBRT
- Clinical decision: SRS alone or SRS+WBRT

1\textsuperscript{Sahgal et al. (2015) IJROBP 91: 710–717}
Brain metastases (BM) and memory decline

• Chang et al.: SRS+WBRT worse than SRS at 4 months\(^1\)

• Earlier analysis of prognostic factors in patients with brain metastases (RTOG 79-16, 85-28, 89-05)\(^2\)
  – only performance status, patient age, and primary tumor status were significant for survival

• Later, multi-institutional database analysis to define the prognostic assessment for BM\(^3\)
  – brain and breast pts; primary endpoint determined behavior
  – Hippocampal sparing and/or memantine use for longer survivors

\(^1\)Chang et al. (2009) Lancet Oncol 10: 1037–1044
\(^2\)Gaspar et al. (1997) IJROBP 37: 745–751
\(^3\)Sperduto et al. (2012) J Clin Oncol 30: 419–425
\(^3\)Slade and Stanic (2016) Contemporary Clinical Trials 47: 74–77
SRS+WBRT for brain metastases: Chang et al. (2009)

• 1 to 3 newly-diagnosed brain metastases
• 58 pts; n=30 SRS [RTOG 90-05], n=28 in SRS+WBRT (30 Gy in 12F of 2.5 Gy)
• SRS first, followed by WBRT within 3 weeks
• 24% (SRS) v 52% (SRS+WBRT) decline in verbal learning and memory at 4 months
• The 1-year freedom from CNS recurrence was 27% (95% CI=14–51) for SRS and 73% (46–100) for SRS+WBRT (p=0.0003)

Chang et al. (2009) Lancet Oncol 10: 1037–1044
The 1-year local tumor control rate was 67% for patients in the SRS group and 100% for patients in the SRS plus WBRT group (p=0.012).

The 1-year distant brain tumor control rate was 45% for patients in the SRS group and 73% for patients in the SRS plus WBRT group (p=0.02).

SRS+WBRT showed a significant drop in HVLT–R at 4 months compared with SRS alone (52% vs 24%); despite higher overall brain tumor recurrence. Persisted at 6-month follow-up.

Mechanism: Proposed adverse neurogenesis in hippocampus.
Risk of WBRT used for BM: Lung and Breast

Incidence of Leukoencephalopathy After Whole-Brain Radiation Therapy for Brain Metastases
Junko Ebi, PhD, Hisashi Sato, MD, Masaru Nakajima, MD, and Fumio Shishido, PhD

Department of Radiology, Fukushima Medical University, Fukushima, Japan

- Retrospective -111 patients who underwent WBRT for brain metastases: 30 Gy in 10Fx or 11Fx + SRS boost
- Incidence increased with longer follow-up:
  - 34.4% (6 mo), 42.9% (21 mo), 66.7% (24 mo), 100% (36 mo)
- Single institution study. Selected patients shown be considered focal SRS not WBRT. How to select those patients?

Ebi et al. IJROBP (2013), 85(5):1212-1217
In order to develop strategies to decrease the risks of brain RT, the risks must be identified, defined & understood

Prophylactic cranial irradiation (PCI)
Prophylactic cranial irradiation, WBRT & memory

- Multi-center randomized phase III evaluating PCI in 536 pts with non-small-cell lung cancer, 30 Gy in 15F once daily\(^1\)
- PCI significantly decreased the risk of BM without improving 1-year OS
- WBRT led to a decline in memory function (HVLT) despite reducing incidence of new BM; no change in QoL/MMSE at 1 yr

\(^1\)Sun et al. (2011) J Clin Oncol 29: 279–286
Prophylactic cranial irradiation, WBRT & memory

- Randomized study, RTOG 0212 (PCI in SCLC)\(^1\)
  - 265 pts, 131 in Arm 1, 67 in Arm 2, and 66 in Arm 3
  - PCI arms (36 Gy 18F 2 Gy (3\(^{rd}\) arm, 12 days BID 1.5 Gy)) compared to the PCI arm (25 Gy, 10F)
  - significant increase at 1 year of neurocognitive function (HVLT) decline in the higher-dose arm
  - increasing age to be the most significant predictor of chronic neurotoxicity (p = 0.005)

\(^1\)Wolfson et al. (2011) *IJROBP* **81**: 77–84
PCI in patients with limited-stage SCLC

- Meta-analysis of 720 patients with limited-stage SCLC: PCI as
  - standard 25 Gy in 10 daily Fx of 2.5 Gy (n=360)
  - higher dose 36 Gy, 18x2Gy or 16 days BID 1.5 Gy
  - endpoint BM; secondary neurological function and QoL: acute responses
- No significant reduction in incidence of BM was observed after higher-dose PCI (29% v 23%); a significant increase in mortality

<table>
<thead>
<tr>
<th>Reported transitory acute toxicity‡</th>
<th>Low dose</th>
<th>High dose</th>
<th>Not significantly difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate toxicity grade 1 or 2</td>
<td>178 (50%)</td>
<td>191 (54%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Headache</td>
<td>85 (24%)</td>
<td>99 (28%)</td>
<td>0.24</td>
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<tr>
<td>Fatigue</td>
<td>106 (30%)</td>
<td>121 (34%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14 (4%)</td>
<td>13 (4%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>80 (23%)</td>
<td>101 (28%)</td>
<td>0.07</td>
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</table>

In order to develop strategies to decrease the risks of brain RT, the risks must be identified, defined & understood

GBM
Cognitive and radiological effects: Low-grade glioma

• LGG have a good prognosis
  – substantial risk of late or delayed radiation injuries
  – 195 pts; LGG + cognitive testing, 6 year follow-up
  – LGG most deleterious effect on cognition, more than RT

• Later 12 year follow-up\(^1\)
  – long-term cognitive loss associated with RT as primary treatment
  – regardless of fraction dose

\(^1\)Douw (2009) *Lancet Neurol* 8: 810–818
Cognitive and radiological effects: **Low-grade glioma**

Effect of the Addition of Chemotherapy to Radiotherapy on Cognitive Function in Patients With Low-Grade Glioma: Secondary Analysis of RTOG 98-02

Roshan S. Prabhu, Minhee Won, Edward G. Shaw, Chen Hu, David G. Brachman, Jan C. Buckner, Keith J. Stelzer, Geoffrey R. Barger, Paul D. Brown, Mark R. Gilbert, and Minesh P. Mehta

- **Folstein Mini–Mental State Examination (MMSE)** — screening test for dementia and cognitive impairment

- **PCV to RT for LGGs did not result in significantly higher rates of MMSE score decline than RT alone through 5 years post RT; although PCV improves PFS**

Cognitive and radiological effects: High-grade glioma

EpiBrainRad: an epidemiologic study of the neurotoxicity induced by radiotherapy in high grade glioma patients

Thomas Durand1,2, Sophie Jacob3, Laura Lebouil2, Hassen Douzane2, Philippe Lestaevel3, Amithys Rahimian4, Dimitri Pismaras2, Loïc Feuvret2, Delphine Leclercq5, Bruno Brochet6, Radia Tamarat3, Fabien Milliat2, Marc Benderitter1, Nicolas Vayatis7, Georges Noël8, Khê Hoang-Xuan2, Jean-Yves Delattre2, Damien Ricard1,2,9 and Marie-Odile Bernier3*

- Newly-diagnosed HGG treated by RT and concomitant-adjuvant TMZ
- Prospective study
- Main objective is to assess cognitive impairment
  — Runs 2015-2017; first analysis end of 2016

In order to develop strategies to decrease the risks of brain RT, the risks must be identified, defined & understood

Retreatment of GBM
Re-irradiation of GBM

• Malignant GBMs relapse in up to 90% of cases
  – close proximity to the initially irradiated volume

• The recovery capacity (brain low repair capacity)
  – initial BED, and the time interval between the initial exposure
    and re-irradiation $\alpha/\beta=2\text{Gy}$; EQD2 formulation

• Increases from conventional reirradiation (81.6–101.9 Gy) to FSRT (90–133.9 Gy) and SRS (111.6–137.2 Gy)
  – increase in dose from conventional to conformal techniques but
    without increasing probably of brain necrosis

• Radiation-induced normal brain tissue necrosis was found to occur at NTDcumulative $>100$ Gy.

A significant correlation ($p = 0.016$) was found: the higher the $\text{EQD2}_{\text{cumulative}}$, the shorter the time interval between the initial exposure and re-irradiation.
Conclusion: Pulsed reduced-dose-rate RT is a re-irradiation strategy that is well tolerated, allowing for safe retreatment of larger target volumes to high doses with palliative benefit. Cumulative doses >100 Gy were well tolerated.
In order to **develop strategies** to decrease the risks of brain RT, the risks must be identified, defined & understood.
Preservation of cognitive impairment: Avoidance

- **WBRT for Brain Metastases (RTOG 0933)**\(^1\)
  - a single-arm phase II study; 113 pts; 30 Gy in 10F
  - primary endpoint cognition via HVLT-R at 4 months, QoL
- **Conformally avoid the hippocampal neural stem-cell compartment**
- **Conformal avoidance associated with significant preservation of memory and QoL**
  - Compared with historical controls
- **Conformal avoidance of the hippocampus poses the risk of attenuating the benefit of WBRT for emergence of new brain metastases within the hippocampal avoidance region: 8.6%**\(^2\)

Preservation of cognitive impairment: neuroprotection

• WBRT for Brain Metastases + memantine (RTOG 0614)\(^1\)
  \- randomized to receive placebo or memantine (20 mg/d), within 3 days of initiating radiotherapy for 24 weeks; 554pts; 2.5 Gy in 15F
  \- primary endpoint delay recall cognition via HVLT-R at 24 weeks, QoL

• Less decline in the primary endpoint of delayed recall (n.s.)

• Memantine had better cognitive function over time
  \- delayed time to cognitive decline, reduced the rate of decline in memory, executive function, and processing speed brain

• The rate of cognitive decline over time slowed by 4 months in both arms, but more so in the memantine arm.
  \- benefit from memantine was due mainly to a difference between 3 and 6 months

\(^1\)Brown et al. (2013) *Neuro Oncol* **15**: 1429–1437
Mitigation of radiation-induced cognitive impairment

- Pathogenesis of radiation-induced cognitive impairment in animal models: Use of MW-151
  - Neuro-inflammation from activated microglial cytokines

Mechanisms of injury
Overview of neurogenesis

• The development and maturation of new neuronal populations from neural progenitor cells\(^1\)
  – neural stem cells (NSCs) because of multi-potent state

• Neurogenesis observed in subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus
  – direct evidence for adult neurogenesis in humans\(^2\)
  – nuclear-bomb-test-derived \(^{14}\)C in genomic DNA\(^3\)

• 700 new neurons per hippocampus per day; modest decline with age
  – hippocampal neurogenesis pivotal for normal cognitive function, memory formation and spatial processing

\(^1\)Gage Science (2000) 287, 1433–1438
\(^2\)Eriksson et al. (1998) Nat. Med. 4, 1313–1317
\(^3\)Spalding et al. (2013) Cell 153, 1219–1227
The hippocampal circuitry

- The hippocampus is located within the temporal lobe
- Extends longitudinally across the brain
- Distinct sub-regions — DG, CA1, and CA3 — trisynaptic circuit
- DG generates new functional neurons throughout adulthood — integrate into local pre-existing circuits

Dentate gyrus (DG)
Cornu ammonis (CA)

Pereira Dias, et al. (2014). Neuro Oncol. 16(4): 476–492
Mechanisms of injury

cell killing
Effects of radiation on hippocampal circuitry

• RT directed against proliferating tumor cells
  – aim is to restrict aberrant cell division
• RT ablates the neurogenetic process
  – increase in level of apoptosis in neural stem cells\(^1\)
  – postmortem tissue, reduced neurogenesis after radiotherapy\(^2\)
• Neural stem cells unchanged 4 wks post RT in rodents
  – not cell killing *per se* but microenvironmental
  – microvascular angiogenesis in the neurogenic niche
  – inflammatory response from the microglia

Neural stem/precursor cells in the dentate SGZ

• Extremely radiosensitive, apoptosis seen with relatively low doses, in C57/BL mice peaks 12 h after RT\(^1\)
  – dose dependent, activated microglia indicate that neurogenesis associated with a inflammatory response
  – response of precursor cells and altered neurogenesis indicate causative role in radiation-induced cognitive impairment\(^2\)
  – Newly-born BrdU-positive cells
    • effects on neuron production in the DG, less so on newly-born astrocytes and oligodendrocytes (2-4 months after RT)

Pathogenesis of white matter necrosis

• White matter necrosis is the dominant presentation

• Numerous studies identified two prominent changes
  – parenchymal cell loss that involves demyelination
  – vascular endothelial damage

• O-2A cells precursors of oligodendrocytes: most radiosensitive glial cell type; oligodendrocytes are target
  – change in architecture, arrival of astrocytes and microglia
  – data suggest oligodendrocytes as critical structure, albeit timeframe of death not consistent with white matter necrosis

• Targeting experiments indicate vascular damage involved
  – BNCT to deliver doses to vasculature, leads to white matter necrosis

1Kim et al. (2008) J Neurooncol 87: 279–286  
1Morris et al. (1996) Radiat Res. 146: 313–320
Mechanisms of injury

vascular mediated
Neuroinflammation & cell recruitment by cranial RT

• Neuroinflammation evident after acute and late effects\(^1\)
  – role in initiation and progression of damage unclear
  – post-RT steroid and NSAIDs have benefit
  – preclinical and patient studies

• Acute and persistent increases in number of CD3+ and CD11c+ cells in the CNS, increased expression of MHC II
  – endogenous microglia or from infiltrating leukocytes
  – time and dose dependent recruitment of BMD myeloid cells\(^2\)
  – CCR2 signaling vital for myeloid cell recruitment\(^3\)

\(^3\)Moravan et al. (2016) Journal of neuroinflammation 13: 30
WBRT: Vascular Cognitive Impairment

- Fractionated WBRT induces dose-dependent impairment in rat brain in 10 weeks\(^1\)
  - endothelial apoptosis suppresses endothelial cell proliferation
  - disruption of the BBB, thickening and vacuolation of the vascular basement membrane
  - breakdown and microvascular rarefaction in rat brain as early as 10 weeks following fractionated

- Single doses of 5–20 Gy 15% decrease in endothelial cells within 1 day, maintained for at least 1 month, but recovery evident with repopulation\(^2\)

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WBRT: Vascular Cognitive Impairment

- **Angiogenesis and neo-vascularogenesis**
  - HIF-1, VEGFR → EPCs, expressing surface markers such as VEGFR2 (KDR/Flk-1).
  - CD34 and CD133, are mobilized from the bone marrow and circulate in the blood → BMDCs locate to sites of RT damage
  - strong evidence to support the role of EPCs in re-endothelialization, neovascularization, and endothelial repair

Response of endothelial cells

• EC apoptosis following cranial irradiation
• EC apoptosis precedes BMDC recruitment
  – chemokines and cytokines continue to maintain memory of RT injury – at least 7 days
• BMDCs migrate outside of the vessel lumen, where a subpopulation remain intimately involved with the vasculature and encircle the vessel lumen

1Burrell, Hill and Zadeh. (2012) PLoS ONE 7(6) e38366
High-Resolution In-Vivo Analysis of Normal Brain Response to Cranial Irradiation

Kelly Burrell¹, Richard P. Hill²,³, Gelareh Zadeh³,⁴*

1 Brain Tumor Research Centre, SickKids Research Institute, Toronto, Canada, 2 Ontario Cancer Institute/Princess Margaret Hospital and Campbell Family Institute for Cancer Research, University Health Network, Toronto, Canada, 3 University of Toronto, Toronto, Ontario, Canada, 4 Toronto Western Hospital University Health Network, Toronto, Canada

Dose dependent

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Conclusions

• Brain RT characterized by vascular abnormalities, demyelination, white matter necrosis → cognitive impairment\(^1\)

• Reduction in the proliferative capacity of glial or vascular endothelial cells
  – progressive and irreversible

• Upfront WBRT to SRS for BM did not worsen neurocognitive function\(^2,3\)
  – caveat being these studies used less-robust MMSE

• Significant drop in HVLT–R total recall at 4 months SRS+WBRT v SRS alone (52% vs 24%)\(^4\): Stopped.

• WBRT has acute and late effects
  – Spurred the concepts of mitigation or stem cell avoidance
  – Promoting neurogenesis

• Future clinical trials to continue to use validated methods such as HVLT; and at multiple time points

\(^1\) Greene-Schloesser et al. (2012) Front Oncol 2: 73, 1–17
\(^2\) Aoyama et al. (2006) JAMA 295: 2483–2490
\(^3\) Roos et al. (2006) Radiotherapy and Oncology 80: 318–322
\(^4\) Chang et al. (2009) Lancet Oncol 10: 1037–1044