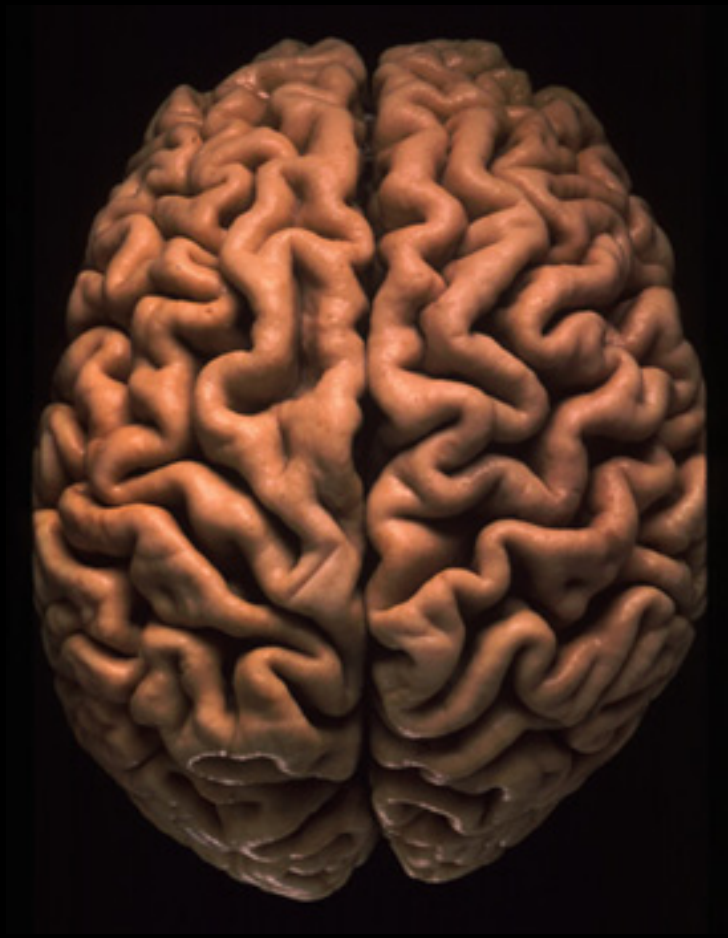
Neurocognition in Patients with Brain Metastases



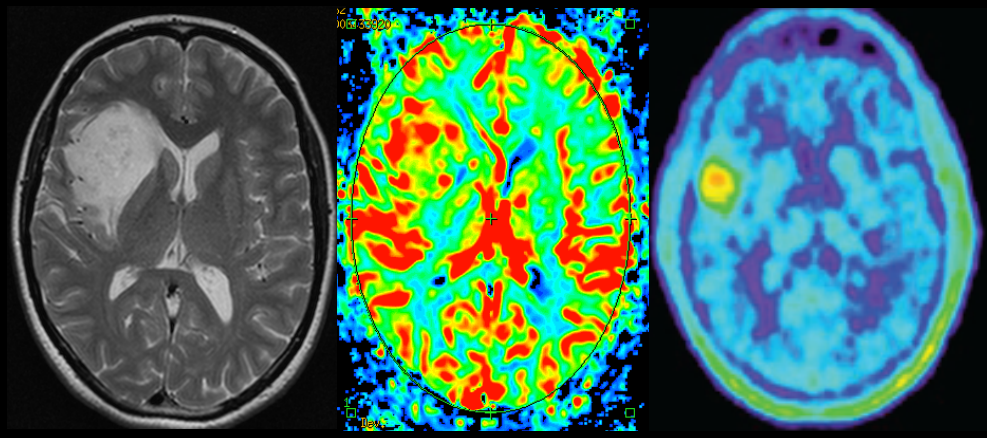
Martin Klein
VU University Medical Center
Amsterdam, The Netherlands

2nd Annual Brain Metastases Research and Emerging Therapy Conference
Rencontres Cancérologie Pacca
VU university medical center

Treatment Outcomes I

Traditional endpoints of efficacy:

- Physician's point of view:
  - Primary: OS
  - Secondary: PFS
  - Parameters of disease like MRI, rCBV, PET
  - Karnofsky, Barthel



MRI T2 rCBV FET PET

Treatment Outcomes II

Secondary/tertiary endpoints of efficacy:

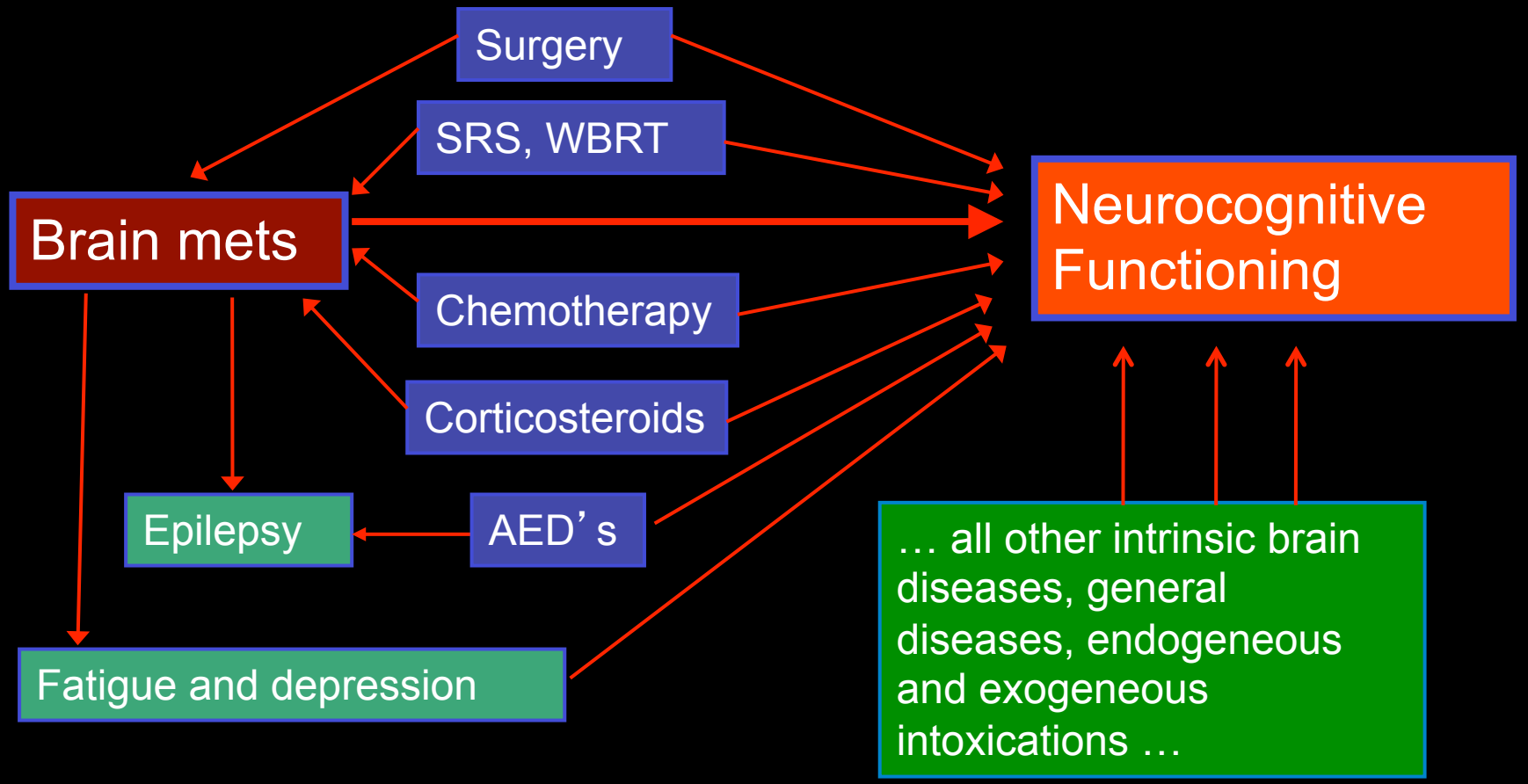
- Patient's point of view (patient reported outcomes)
- Largely ignored earlier due to dismal outcome
  - Health-related quality of life (HRQOL)
  - Depression
  - Fatigue
  - Neurocognitive functioning

Relevance of Neurocognitive Deficits

- Subtle cognitive impairment: ↓ HRQOL
- Recognizing effects of disease & therapy on neurocognitive outcomes important:
  - formulating treatment modifications
  - formulating strategies for rehabilitation

↳ maxime functional ability

Neurocognitive Functioning in Patients with Brain Metastases



Incidence of Neurocognitive Deficits

- Majority significant neurocognitive deficits
  - more common than physical disability
- Range: subtle problems with concentration, memory, affect, and personality to severe dementia
- Early report(1989): dementia in 11% patients who survived 1 year after WBRT
  - HOWEVER, none of patients treated with conventional schedules and doses developed serious long-term dementia!

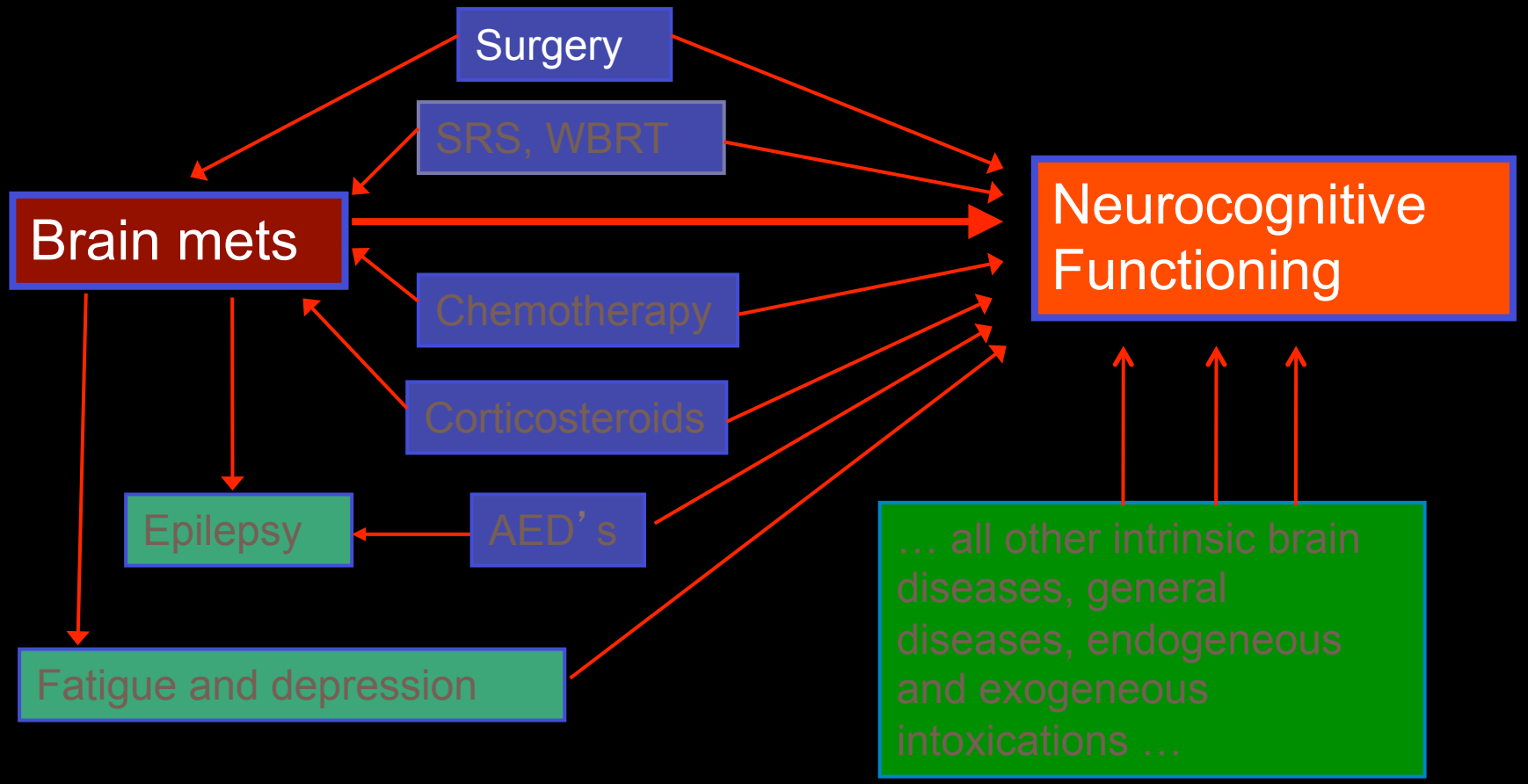
Incidence of Neurocognitive Deficits

- Prospective studies in SCLC with PCI: cognitive deficits prior to RT
  - 97% impaired at baseline(Komaki, 1995)
  - 40%–60% at randomization(Arriagada 1995; Gregor, 1997)
- Deficits unrelated to age, gender, previous therapy(Gregor,1997)
- Treatment and subsequent reduction in brain tumor load may even lead to improved neurocognitive function(Li, 2006)

Cognitive Assessment in Routine Clinical Context Feasible

- Extensive neurocognitive assessments in 55 brain metastases patients →
  - Excellent compliance rates prior to (95%), upon completion of (84%), and 1 month after (70%) WBRT (Regine, 2004)
- 100% compliance in single institution study in 30 patients (Herman, 2003)
- Large phase III trial (401 brain mets + WBRT + Motexafin Gadolinium)
  - 90.5% of patients baseline cognitive impairment (Meyers, 2004)

Neurocognitive Functioning in Patients with Brain Metastases



Aims Neurosurgery

- Local control, prolonging survival

- Reduce symptoms
  - improve neurological outcome
  - improve epilepsy control
  - improve cognitive outcome

Balance

- maximum tumor resection
- minimal functional damage

Local Therapy: Neurosurgery (Chargari, 2010)

- Surgical resection of single operable metastases indicated in patients with good control of extra cerebral metastatic disease & good prognostic group (KPS, age)

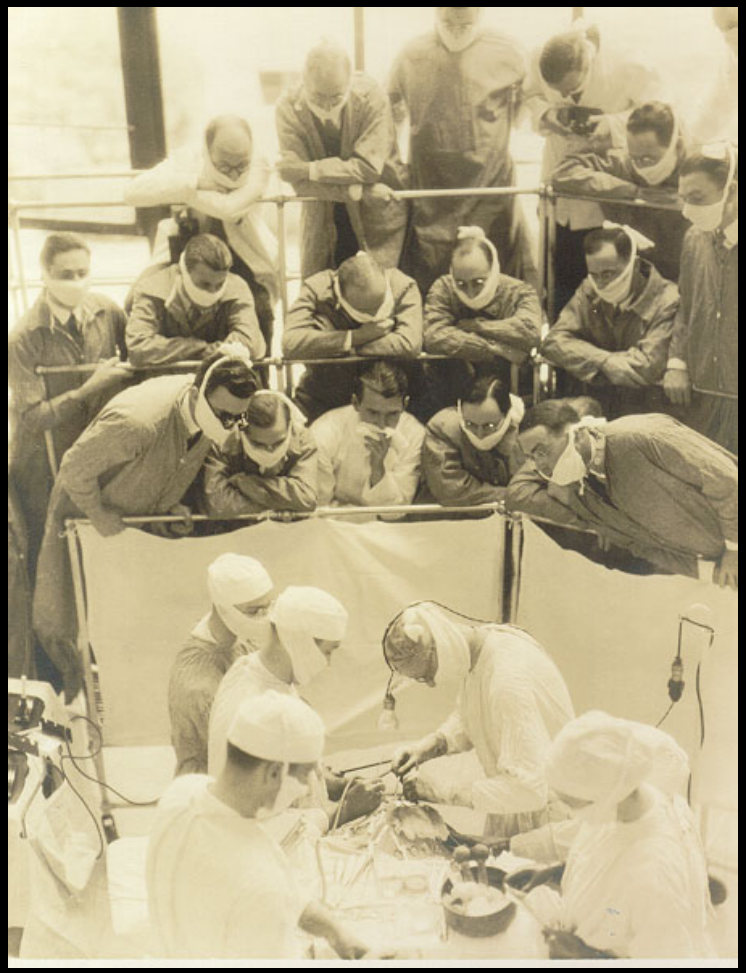
Table 1 | Randomized phase III clinical trials of WBRT alone versus WBRT plus focal treatment

Study	Total number of patients/patients with breast cancer	Number of metastases	Focal treatment	Brain relapse (%)*, WBRT alone vs combined treatment	Median overall survival (months), WBRT alone vs combined treatment
Patchell *et al.* (1990)[7]	48/3 (6.3%)	Single	Surgery	52 vs 20 ($P<0.02$)	3.5 vs 9.2 ($P<0.05$)
Noordijk *et al.* (1994)[8]	63/12 (19%)	Single	Surgery	NA	6 vs 10 ($P<0.05$)
Mintz *et al.* (1996)[9]	84/8 (11.9%)	Single	Surgery	NA	6.3 vs 5.6 (NS)

WBRT + resection associated with fewer recurrence and better HRQOL when compared to WBRT alone

Two studies also demonstrated survival benefit

Surgery Effects on Cognition



NO data on brain metastases!

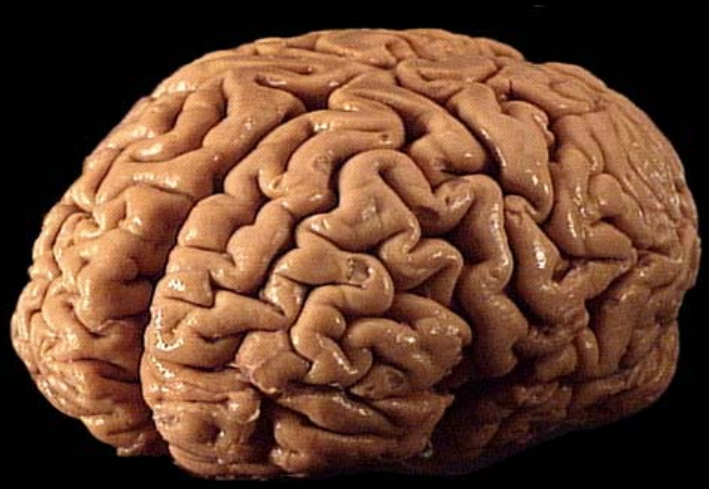
- EOR decisive?
- Focal cognitive deficits related to tumor location
- Differentiation difficult
  - Intracranial pressure
  - Corticosteroids
  - AEDs
  - Psychological effects

Impact of Resection on Cognition

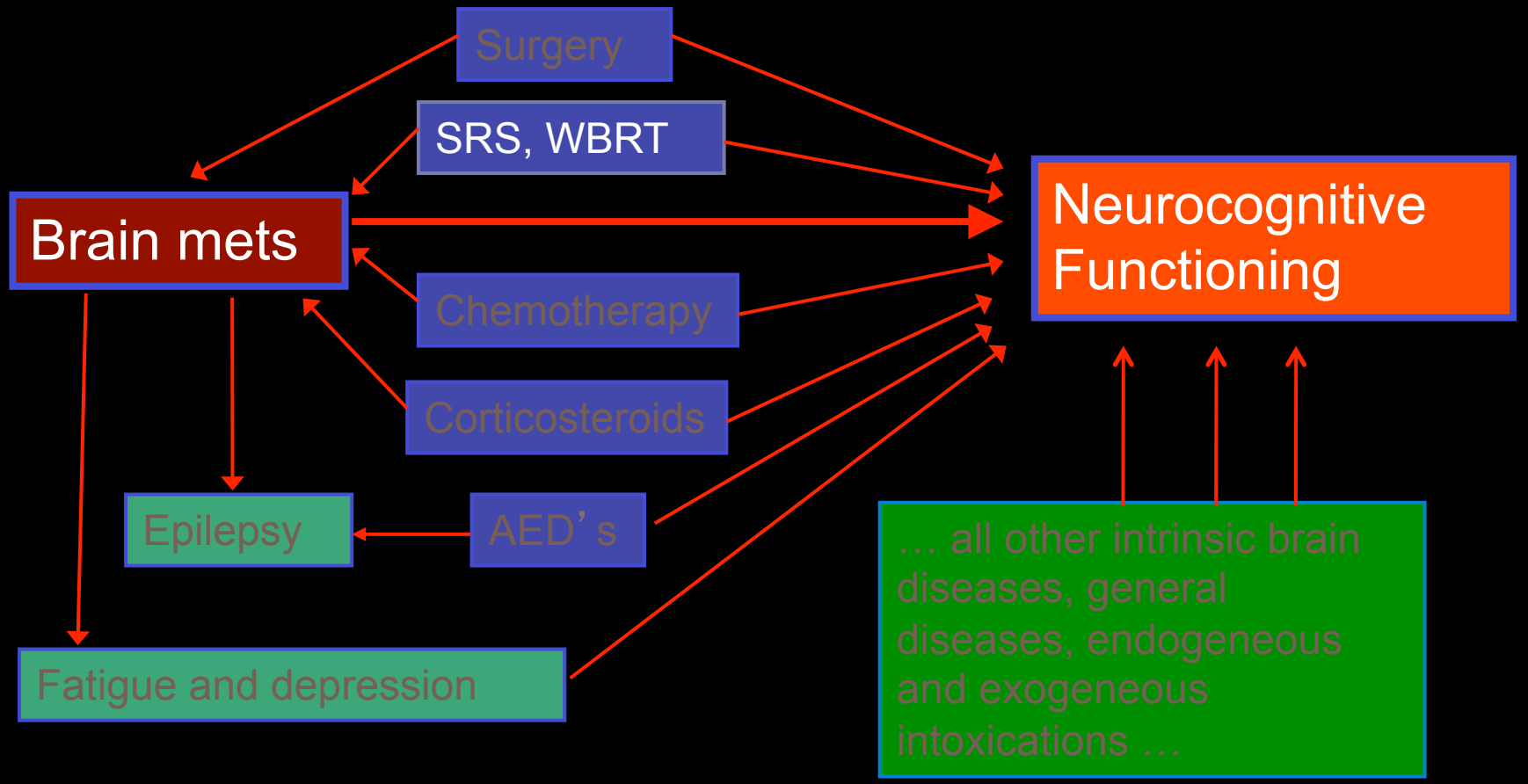
- Beneficial because of reduction of tumor mass
- Tumors in right hemisphere less risk
- Mainly (transient) neurological deficits owing to damage of normal surrounding tissue and/or edema

Tumor Location & Mood

- Ventromedial Prefrontal & Parietal Cortex:
  - anxiety
  - irritability
  - fatigue
- Dorsolateral Prefrontal & Somatosensory Cortex:
  - indifference
  - euphoria

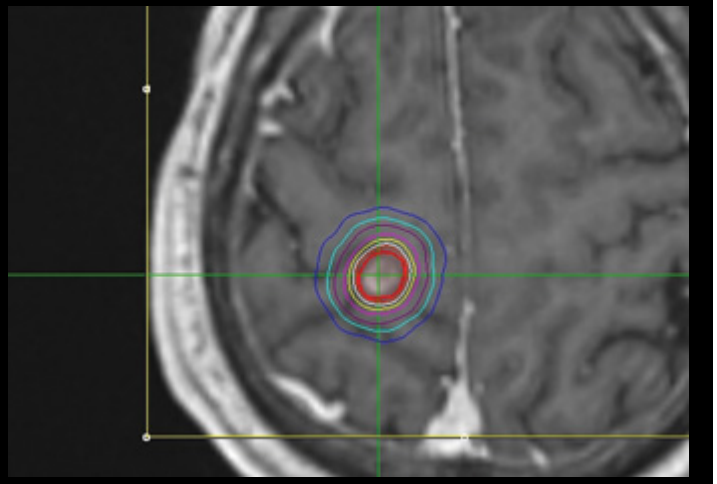


Neurocognitive Functioning in Patients with Brain Metastases



Local Therapy: SRS

- Single metastasis, but, resection not possible due to site of metastases or patient' s poor medical condition
- Highly conformational irradiation approaches such as Gamma Knife or Cyber knife radiation
- 3 or fewer brain metastases <4 cm in greatest dimension
- Low toxicity, high local control, cost effective
- 5 – 10% radiation necrosis, depending on follow-up



Local Therapy: WBRT & SRS(Chargari, 2010)

Table 2 | Randomized phase III trials of focal treatment alone versus focal treatment plus WBRT

Study	Total number of patients/patients with breast cancer	Number of metastases	Focal treatment	Brain relapse (%)*, focal treatment alone vs combined treatment	Median overall survival (months), focal treatment alone vs combined treatment
Patchell *et al.* (1998)[10]	95/9 (9.5%)	Single	Surgery	70 vs 18 (P<0.001)	9.8 vs 11 (NS)
Aoyama *et al.* (2006)[16]	132/9 (6.9%)	1–4	SRS	76.4 vs 46.8 (P<0.001)	8 vs 7.5 (NS)
Mueller *et al.* (2009)[17]	359/42 (11.7%)	1–3	SRS or surgery	54 vs 31.4 (P<0.001)	10.9 vs 10.9 (NS)
Chougule *et al.* (2000)[15]	73/NA	1–3	Gamma Knife®	LR: 13 vs 9 New BM: 43 vs 19	7 vs 5 (NS)

Local Control improved with combined therapy, reduced frequency of intracranial relapse
BUT: Lack of benefit in overall survival
WBRT + SRS results in greater risk of significant decline in neurocognitive function

"Dose-Limiting Toxicity" for the Brain

- Necrosis rates of ~5% starting at 60 Gy
  - 72 Gy with altered fractionation
- Visual damage of ~1-3% starting at >54 Gy
- Endocrine damage starts at ~45 Gy
- Cochlear dysfunction starts at >50 Gy

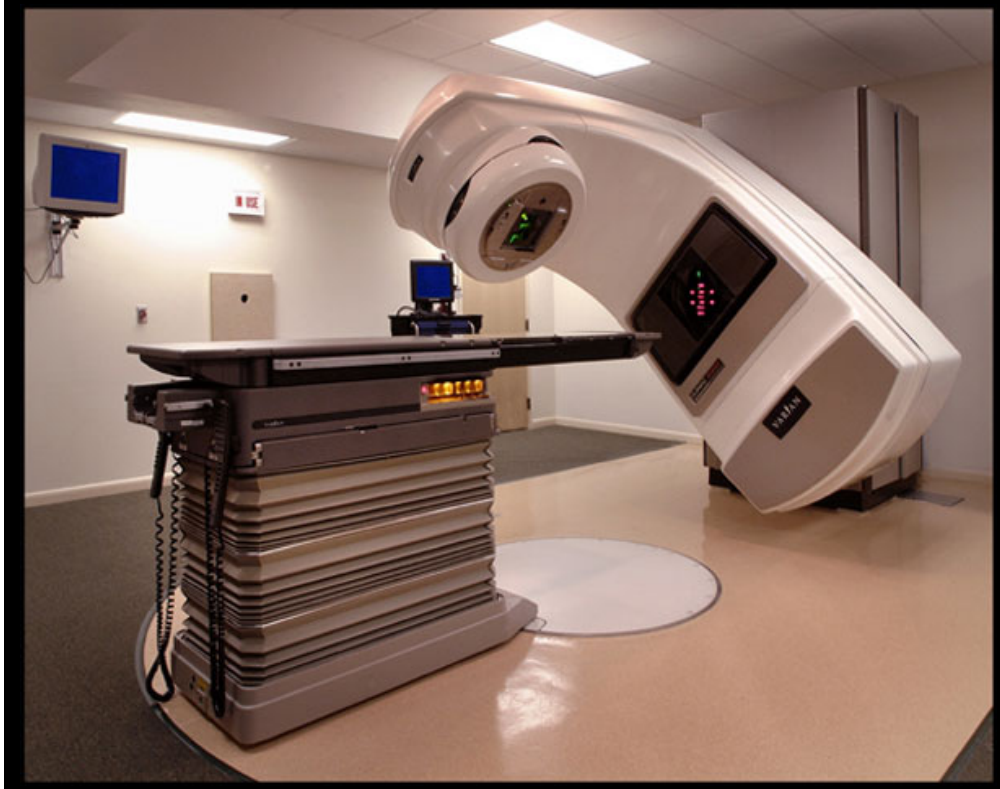
- Neurocognitive damage
  - Depends on what you measure, when, & age

Determinants of Radiation-Induced Injury

- Fraction size
- Advanced age (>60 years)
- Higher total dose
- Volume of brain irradiated
- Chemotherapy
- Co-morbid vascular risk factors
  - E.g., diabetes mellitus

Effects Radiotherapy on Cognition

Late Delayed Radiation Injury

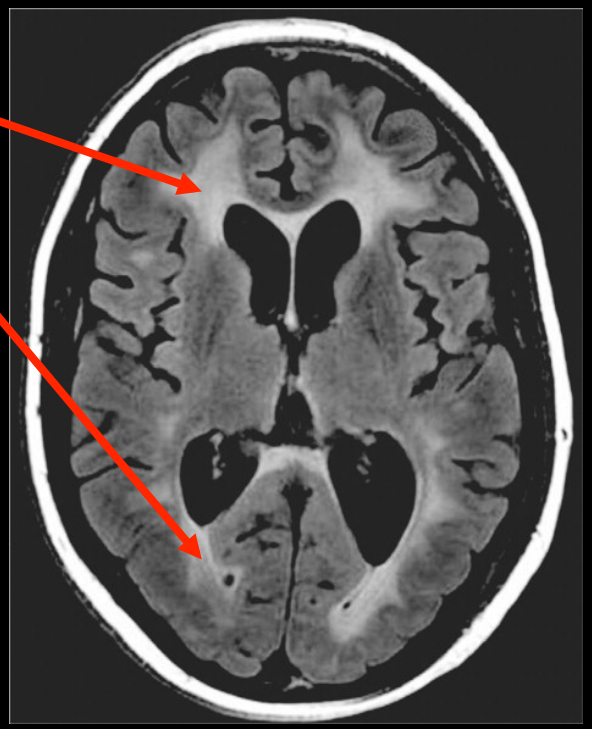


- 3 months to 3 years (or longer) after RT
- Necrosis subcortical white matter
- Cortical atrophy
- Demyelination
- Vascular changes

Radiation-Induced Injury

Subcortical white matter changes

- Neurobehavioral slowing
- Apathy
- Fine motor control
- Executive functions (mental flexibility)
- Memory (retrieval)

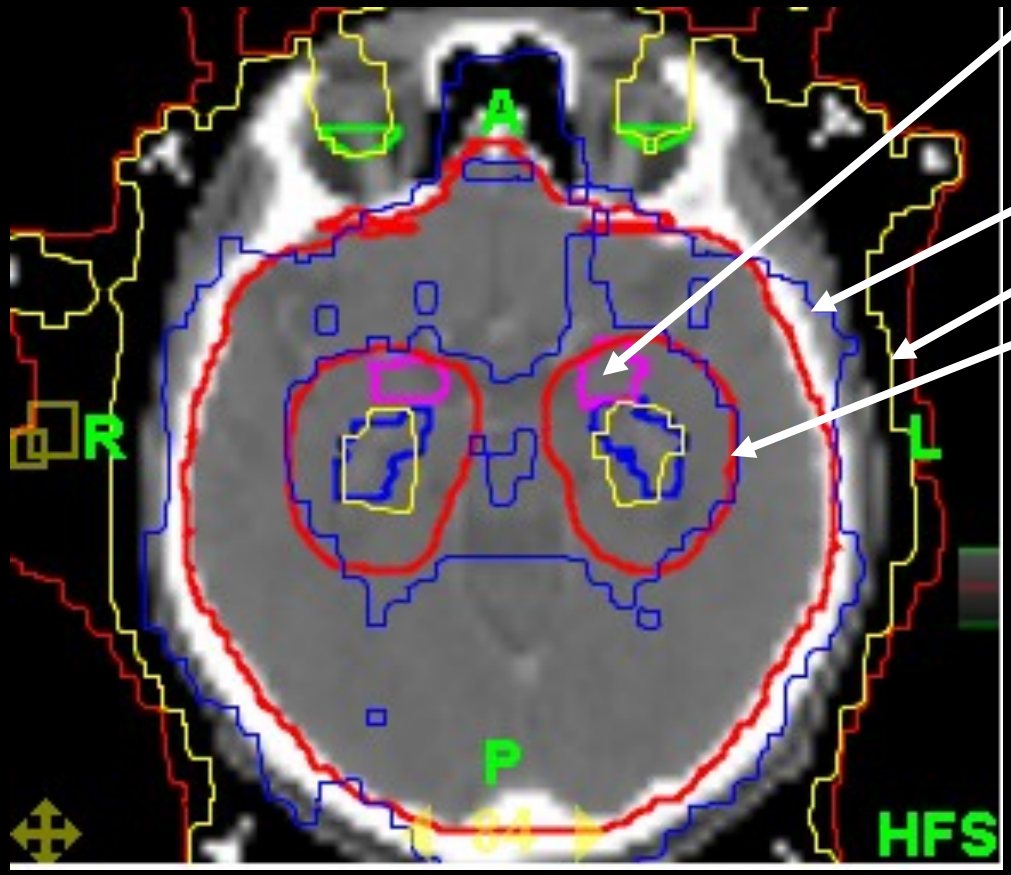


FLAIR MRI, 6 mo after WBRT (30 Gy) for lung metastasis

Hippocampus Avoidance Hypothesis - Memory

- The hippocampus plays a significant role in RT induced dementia
- Doses as low as 2 Gy cause significant toxicity to the hippocampus
- Conformal avoidance of the hippocampus may help reduce neurocognitive deficits

Hippocampus Avoidance with IMRT



Avoidance Region

30 Gy
6 Gy
3 GY

IMRT with tomotherapy achieves significant dose reduction (hippocampus), while delivering 30 Gy to the rest of the brain

6 years following RT+ (50%) or RT- (50%) (*N*=195)

Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study

M Klein, J J Heimans, N K Aaronson, H M van der Ploeg, J Grit, M Muller, T J Postma, J J Mooij, R H Boerman, G N Beute, G J Ossenkoppele, G W van Imhoff, A W Dekker, J Jolles, B J Slotman, H Struikmans, M J B Taphoorn

Summary

Background Because survival benefits of treatment with radiotherapy are questionable and such treatment can cause substantial damage to the brain over time, the optimum management strategy for low-grade gliomas remains controversial. We aimed to identify the specific effects of radiotherapy on objective and self-reported cognitive function, and on cognitive deterioration over time, in patients with low-grade gliomas treated with early radiotherapy.

Methods 195 patients with low-grade glioma (of whom 104 had received radiotherapy 1–22 years previously) were compared with 100 low-grade haematological patients and 195 healthy controls. Our analyses aimed to differentiate between the effects of the tumour (eg, disease duration, lateralisation) and treatment effects (neurosurgery, radiotherapy, antiepileptic drugs) on cognitive function and on relative risk of cognitive disability.

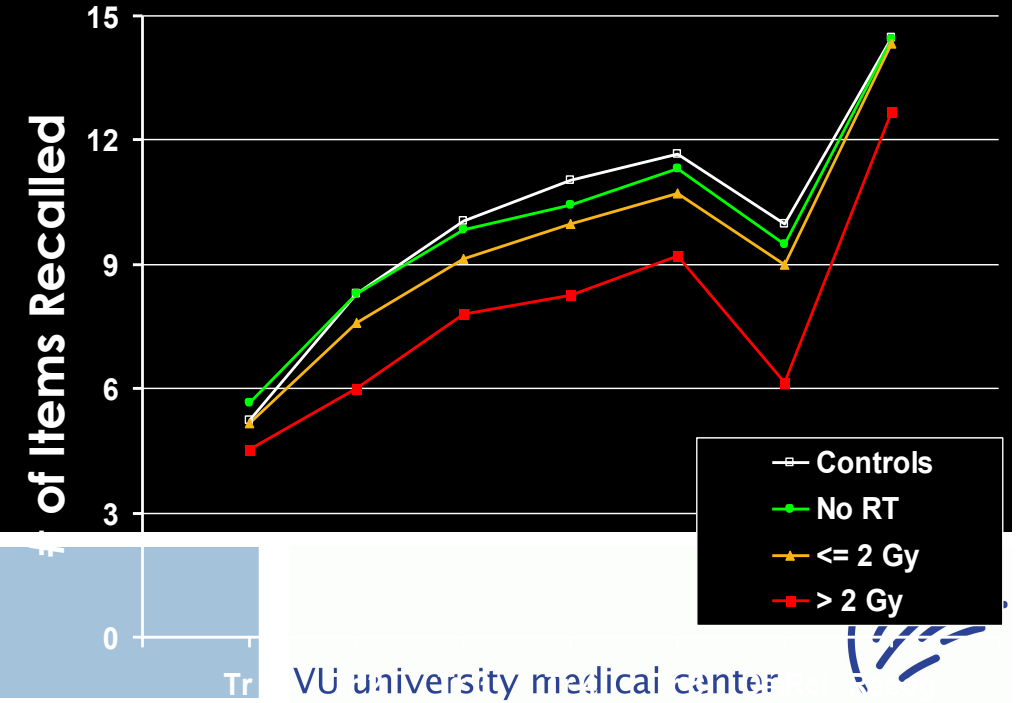
Additionally, the effects of other medical factors, especially antiepileptic drug use, on cognitive function in glioma patients deserve attention.

Lancet 2002; **360:** 1361–68

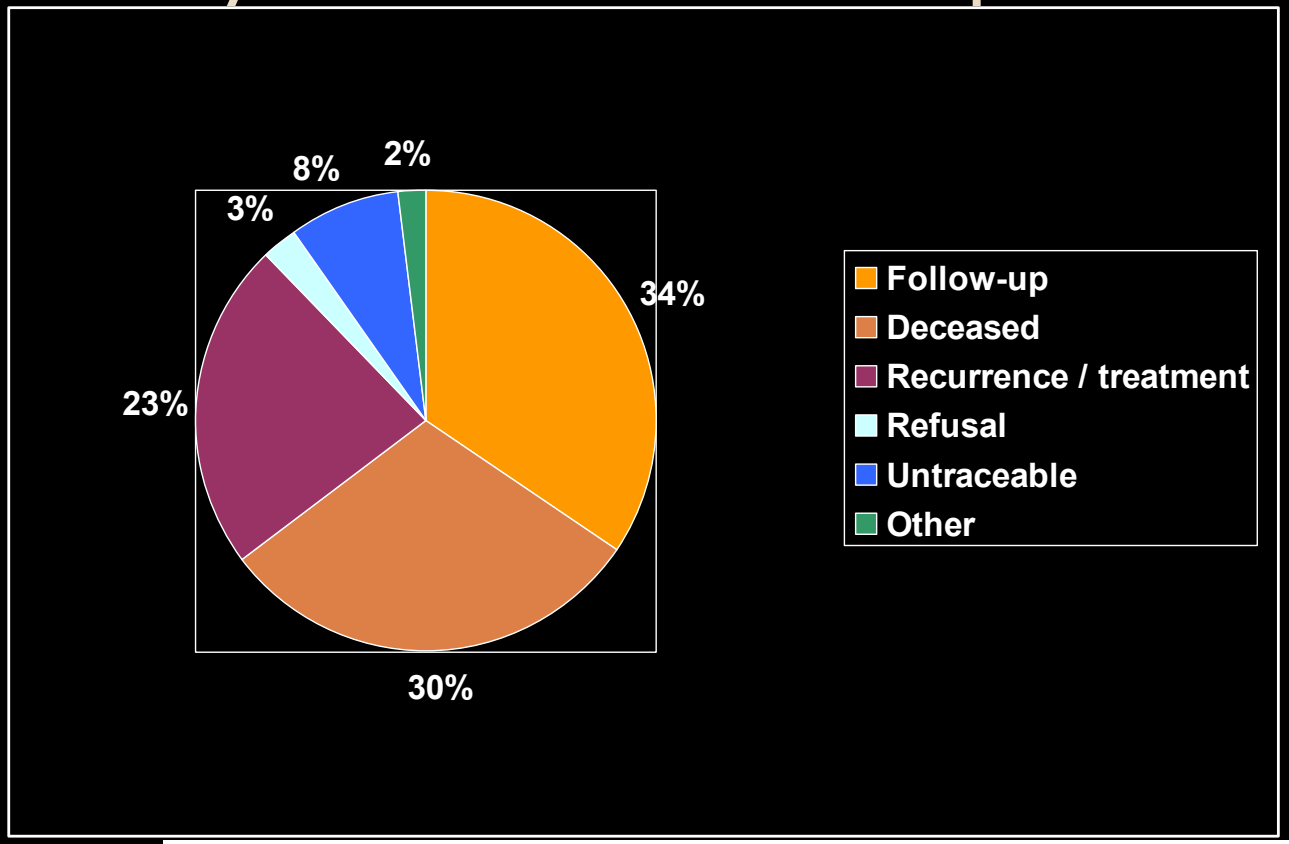
Introduction

Among adult cancer patients, patients with gliomas (ie, primary brain tumours arising from glial tissue) form a minority. Compared with lung and breast cancer, which have rates of about 60 per 100 000 in the Netherlands, the rate of gliomas is tenfold lower, with about 1000 new patients every year.[1] Nevertheless, these cancers have a serious effect on the health-care system in general, and especially on patients and their families. Not only do glioma patients have to cope with the diagnosis of incurable disease, they and their families are usually also confronted with the patient's decrease in cognitive and emotional function as a result of cerebral disease.

Although the median survival of adult glioma patients with low-grade tumours is much longer than that of



12 year Follow-up LGG (*N*=67)



Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up

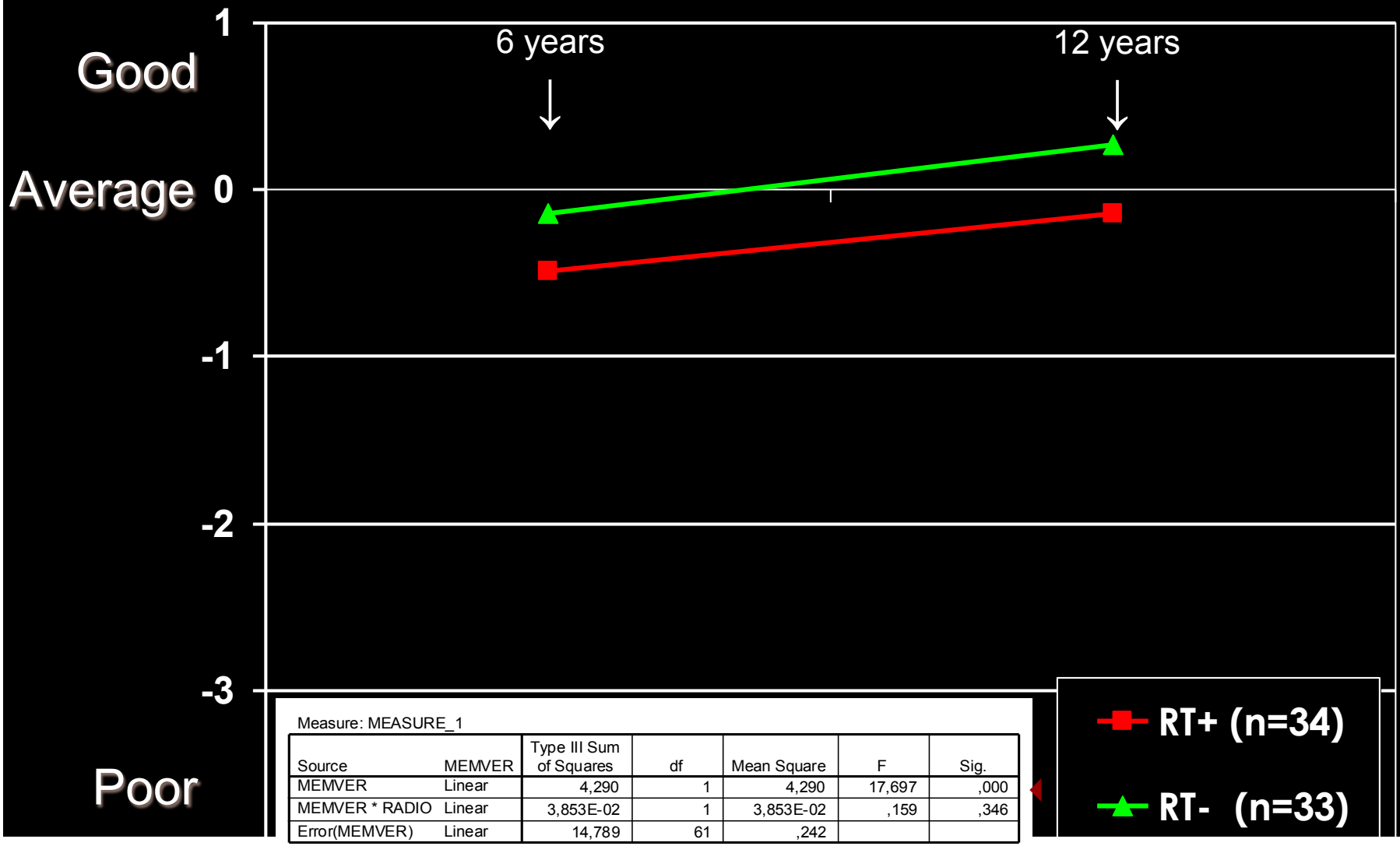
Linda Douw, Martin Klein, Selene S A A Fagel, Josje van den Heuvel, Martin J B Taphoorn, Neil K Aaronson, Tjeerd J Postma, W Peter Vandertop, Jacob J Mooij, Rudolf H Boerman, Guus N Beute, Jasper D Sluimer, Ben J Slotman, Jaap C Reijneveld, Jan J Heimans

Lancet Neurol 2009; 8: 810–18
Published Online

Summary

Background Our previous study on cognitive functioning among 195 patients with low-grade glioma (LGG) a mean of 6 years after diagnosis suggested that the tumour itself, rather than the radiotherapy used to treat it, has the most

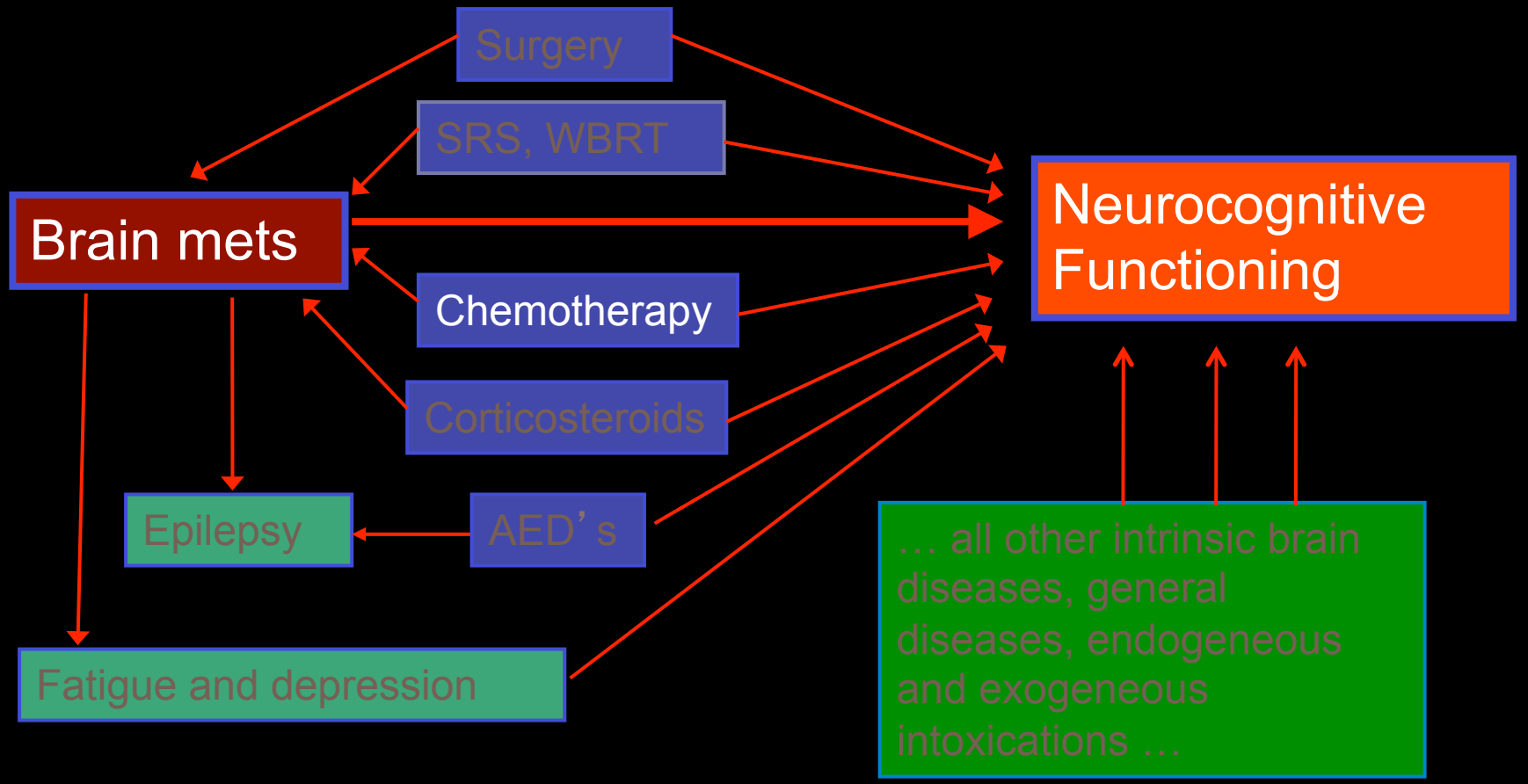
Verbal Memory



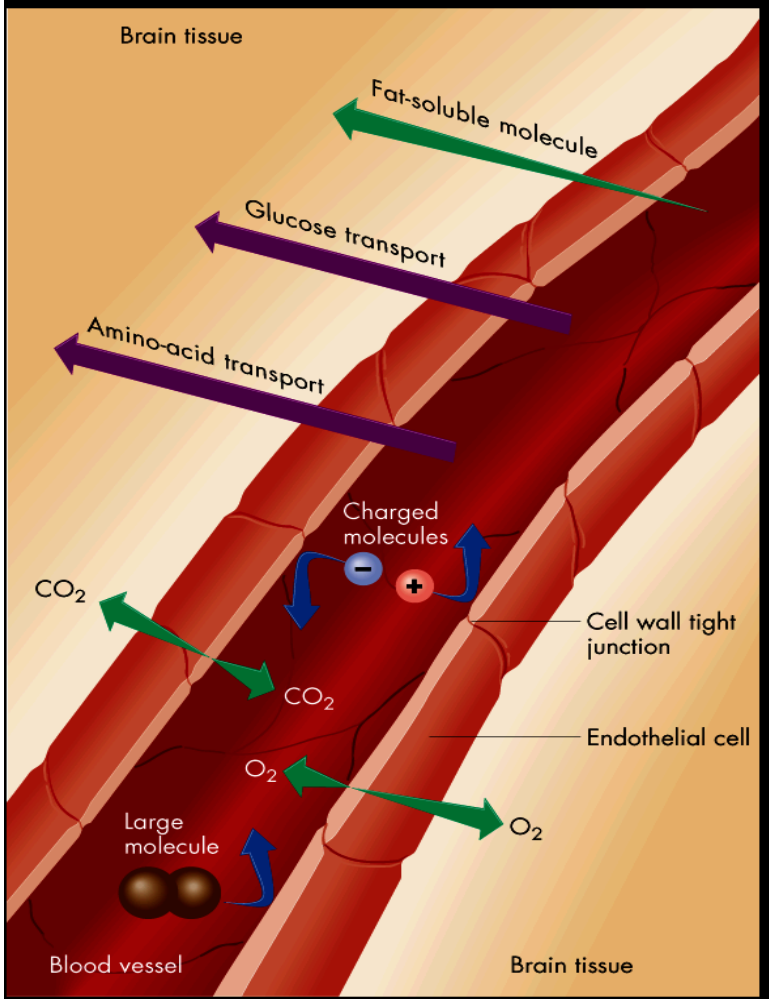
Measure: MEASURE_1

Source	MEMVER	Type III Sum of Squares	df	Mean Square	F	Sig.
MEMVER	Linear	4,290	1	4,290	17,697	,000
MEMVER * RADIO	Linear	3,853E-02	1	3,853E-02	,159	,346
Error(MEMVER)	Linear	14,789	61	,242		

Neurocognitive Functioning in Patients with Brain Metastases



Chemotherapeutic agents in brain metastasis



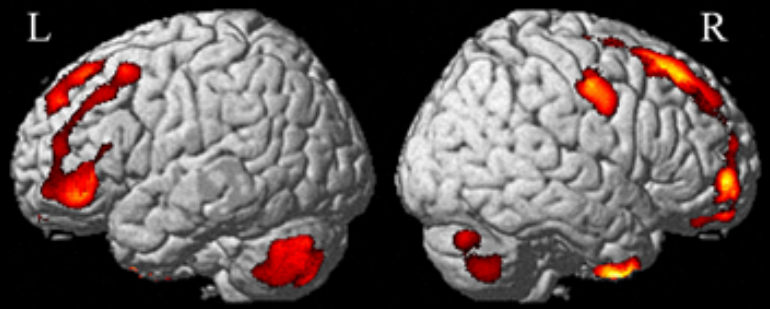
- Most large molecules and electrically charged molecules cannot cross the BBB
- Unfavorable characteristics of most anticancer agents, cytotoxics, and molecularly targeted agents

Chemotherapeutic agents

- Systemic anti-cancer therapies for control of primary or extracranial metastatic disease, before or after diagnosis of brain metastases
- Many agents have effects on brain function
- Chemotherapy-related cognitive impairment in 17% – 75% patients
  - subtle neurocognitive deficits more common than dementia

Chemotherapy-Induced Cognitive Dysfunction

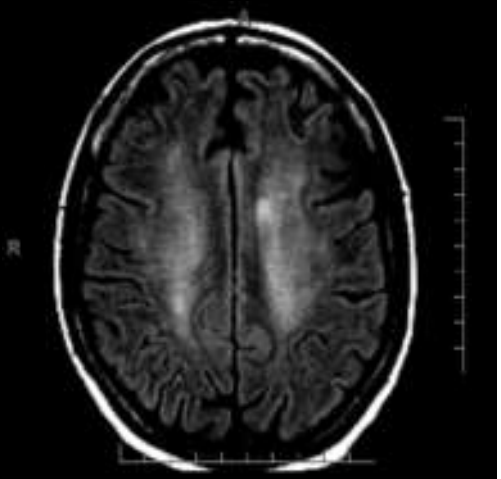
- Most commonly affected domains:
  - Attention, learning, and processing speed consistent with disruption of frontal network systems



- Etiology differs according to agents used

Chemotherapy-Induced Cognitive Dysfunction

- Methotrexate and 5FU are particularly neurotoxic
- Cisplatin, etoposide and vincristine:
  - White matter injury (Komaki, 1995)
- Reasons for brain damage
  - Direct injury to the gray and white matter
  - Microvascular injury
  - Secondary insults due to immune-mediated inflammatory responses



Candidate mechanisms

- Blood–Brain Barrier integrity
- DNA damage and telomere shortening
  - e.g., AD, MCI
- Cytokine deregulation
- Individual genetic susceptibility
  - blood–brain barrier transporters
  - DNA repair mechanisms
  - cytokine regulation
  - neuronal repair and plasticity
  - neurotransmission

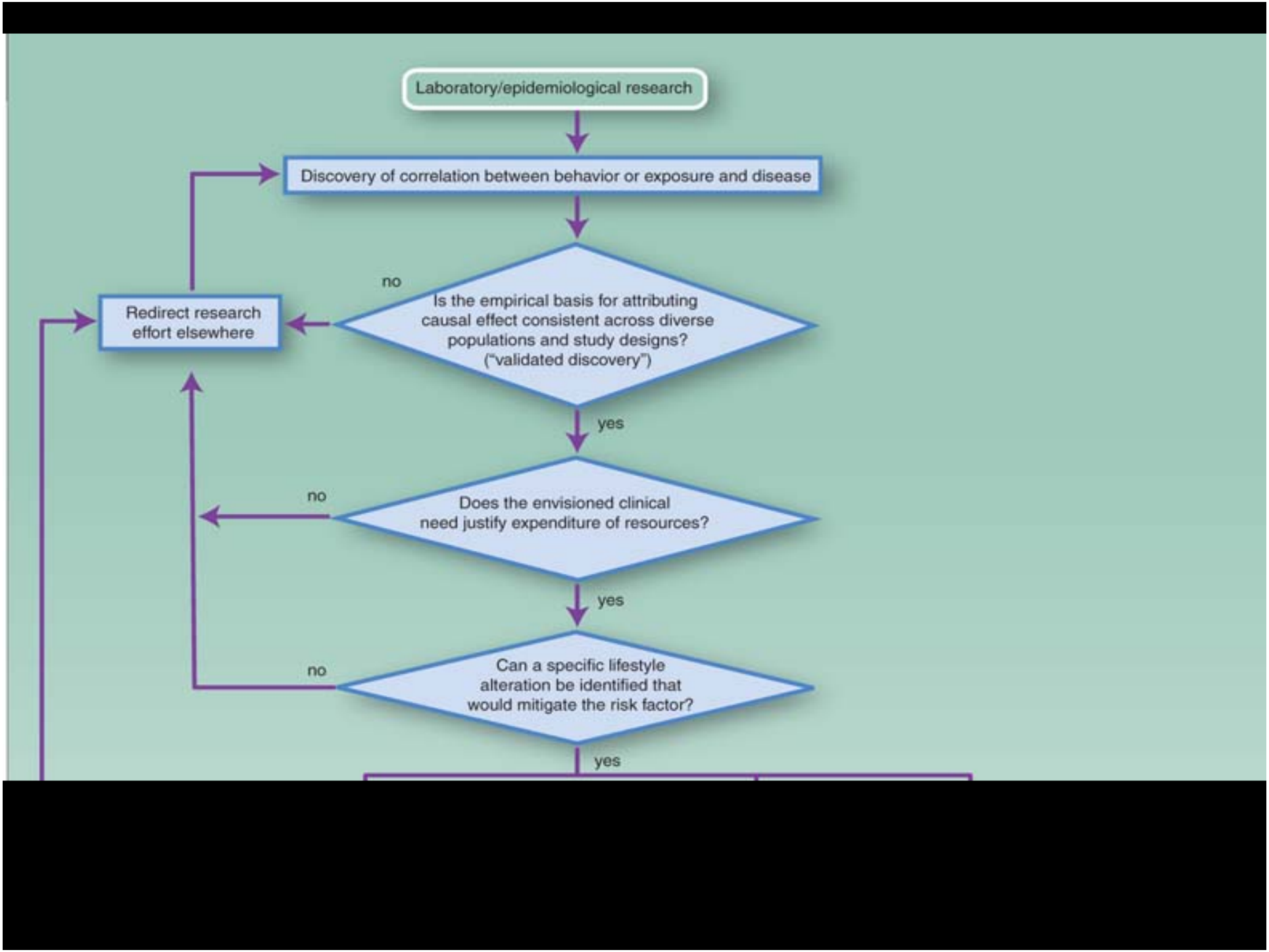
Conclusions

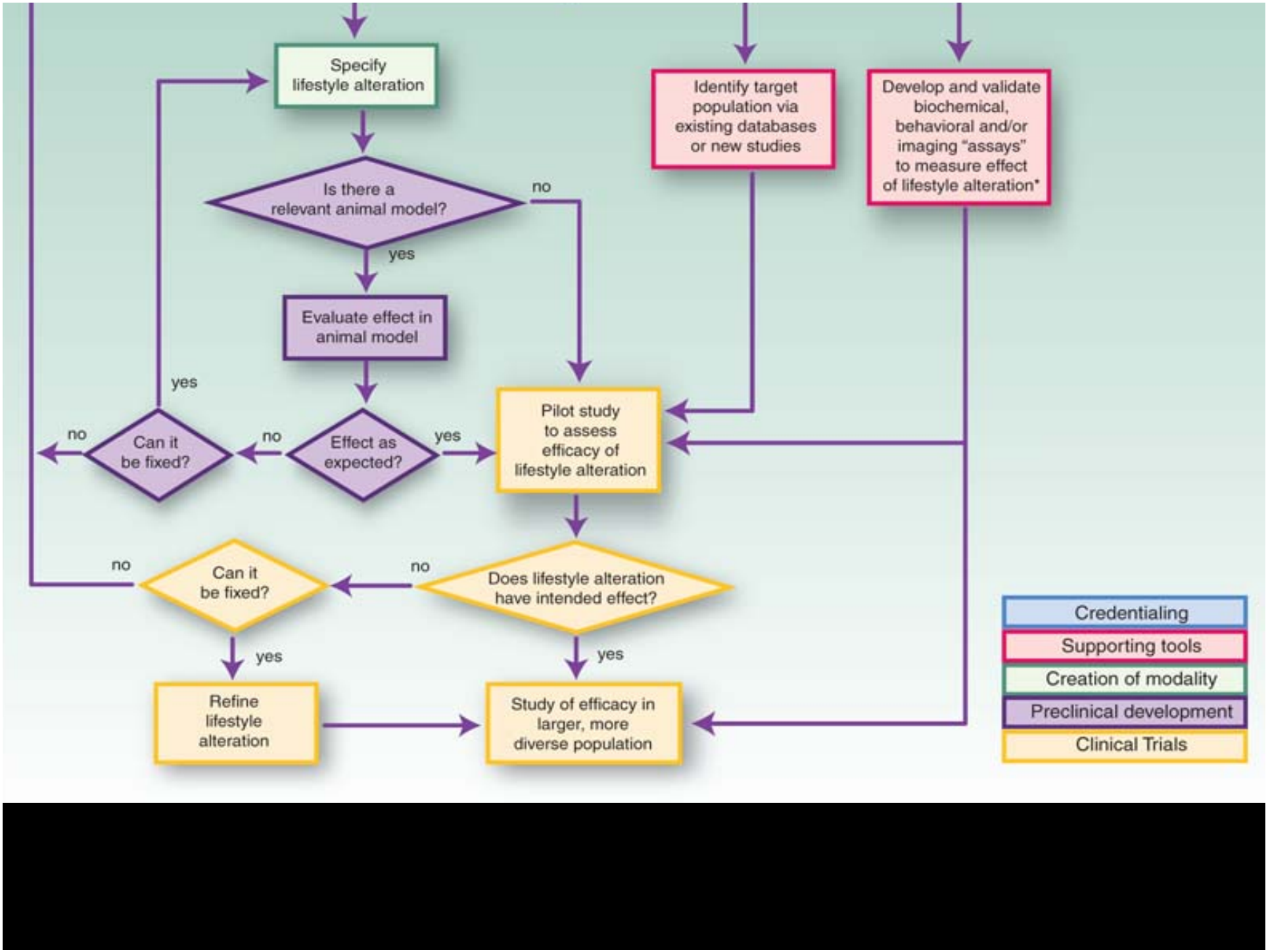
- Radiotherapy + chemotherapy plays a major role in the management of most brain metastases
- Newer technologies may allow an improved therapeutic index
- Except for SRS, unfavorable characteristics of most anticancer agents, cytotoxics, and molecularly targeted agents

Future Directions

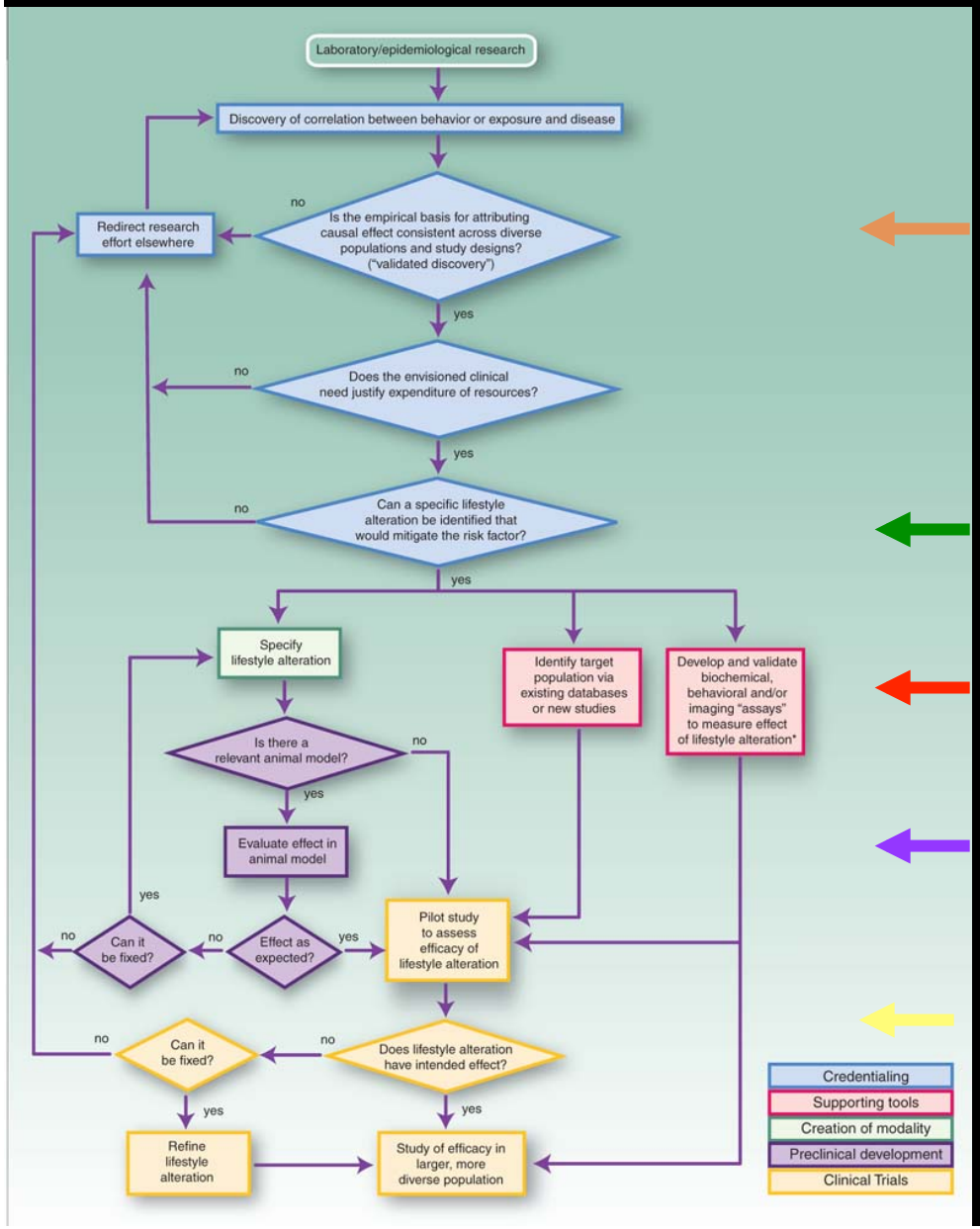
- Increase enrollment in early phase clinical trials to identify active agents for clinical use
- Strategies to avoid long term CNS complication of therapy
- Behavioral tools for anticipating/measuring long-term neurocognitive deficits
- HRQOL assessment of long term effect of systemic and CNS directed therapies

Thank you!


Laboratory/epidemiological research
Discovery of correlation between behavior or exposure and disease
Is the empirical basis for attributing causal effect consistent across diverse populations and study designs? ("validated discovery")
no
Redirect research effort elsewhere
yes
Does the envisioned clinical need justify expenditure of resources?
no
yes
Can a specific lifestyle alteration be identified that would mitigate the risk factor?
no
yes


Specify lifestyle alteration
Identify target population via existing databases or new studies
Develop and validate biochemical, behavioral and/or imaging "assays" to measure effect of lifestyle alteration*
Is there a relevant animal model?
no
yes
Evaluate effect in animal model
yes
Pilot study to assess efficacy of lifestyle alteration
no
Can it be fixed?
no
Effect as expected?
yes
no
Can it be fixed?
no
Does lifestyle alteration have intended effect?
yes
yes
Refine lifestyle alteration
Study of efficacy in larger, more diverse population
Credentialing
Supporting tools
Creation of modality
Preclinical development
Clinical Trials

RTOG: Memantine and Neurocog Training After Brain RT



RT to brain causes white matter damage and particularly affects hippocampal-dependent functions

of learning, memory, and spatial information processing

Medication plus memory training

Imaging, protein, inflammatory and genetic markers of neurocognitive function need further validation.

Animal models are relevant for assessing neurocognitive outcomes

Large scale multimodality study in primary or brain mets or PCI