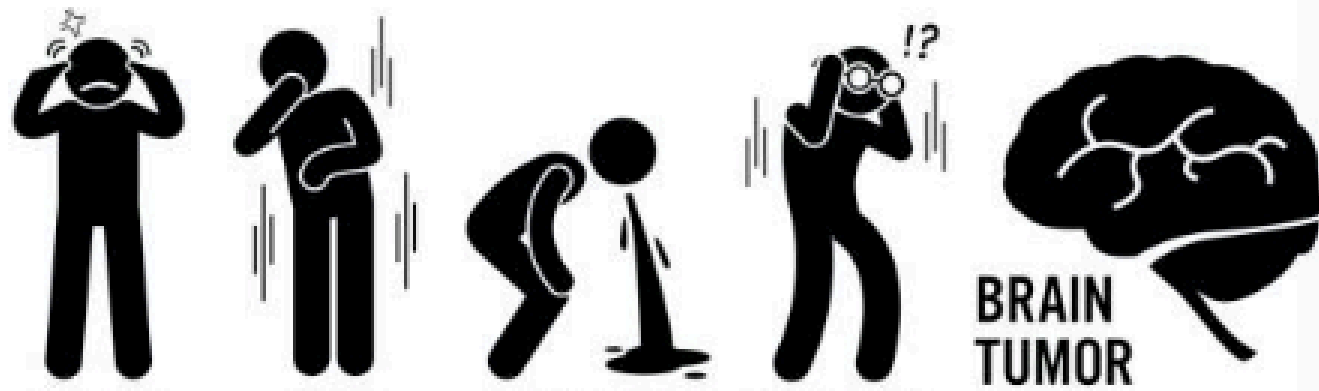


High Grade Glioma

A Medical Oncologist
Perspective



“The brain tumor’s incurable, but let me give you something for that dandruff.”



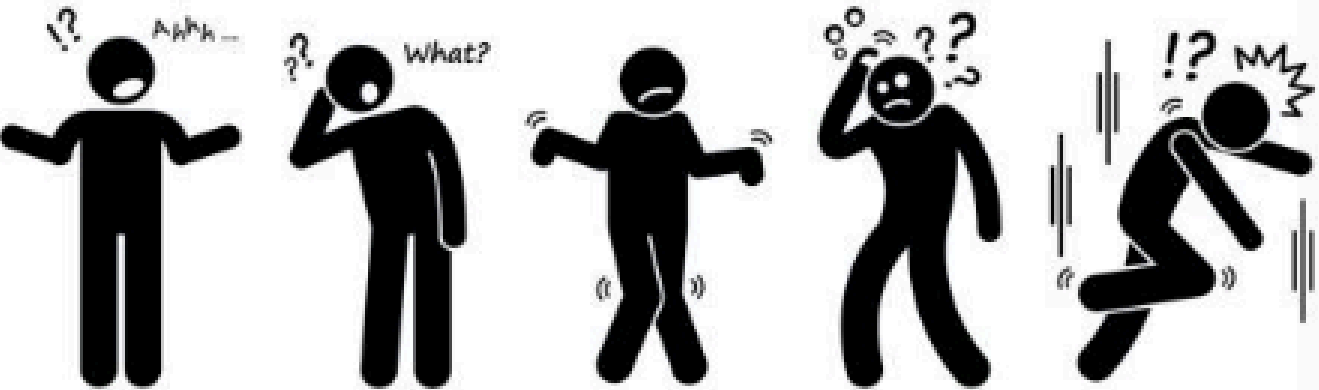
Headache

Nausea

Vomiting

Vision Problems

BRAIN TUMOR



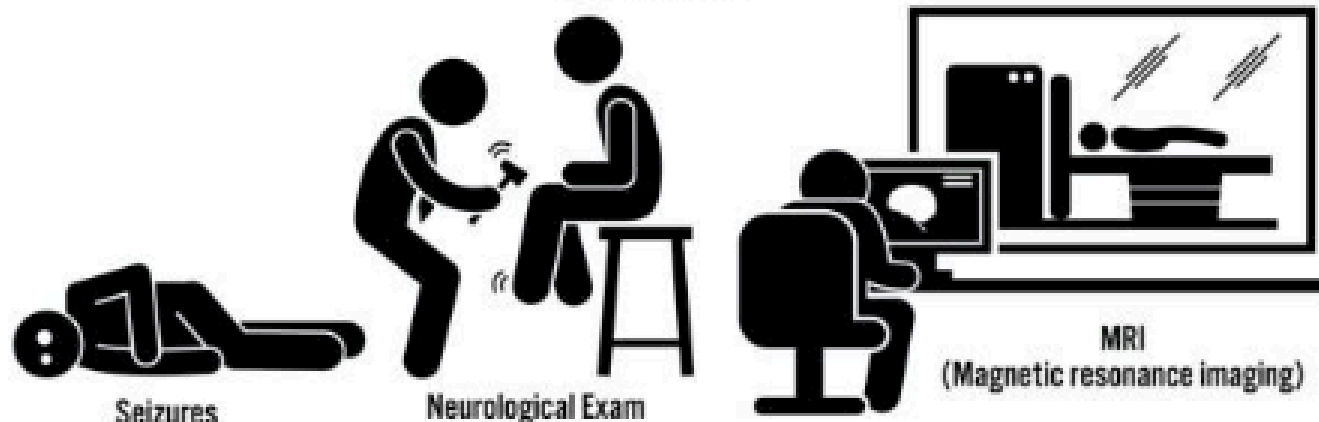
Speech Difficulty

Hearing Difficulty

Weakness in Arms and Legs

Confusion

Balance Difficulty



Seizures

Neurological Exam

MRI
(Magnetic resonance imaging)

Aim

- Overview of the medical oncologist perspective
- What do you need to know to care for a patient with high grade glioma and their families

Patient journey - HGG

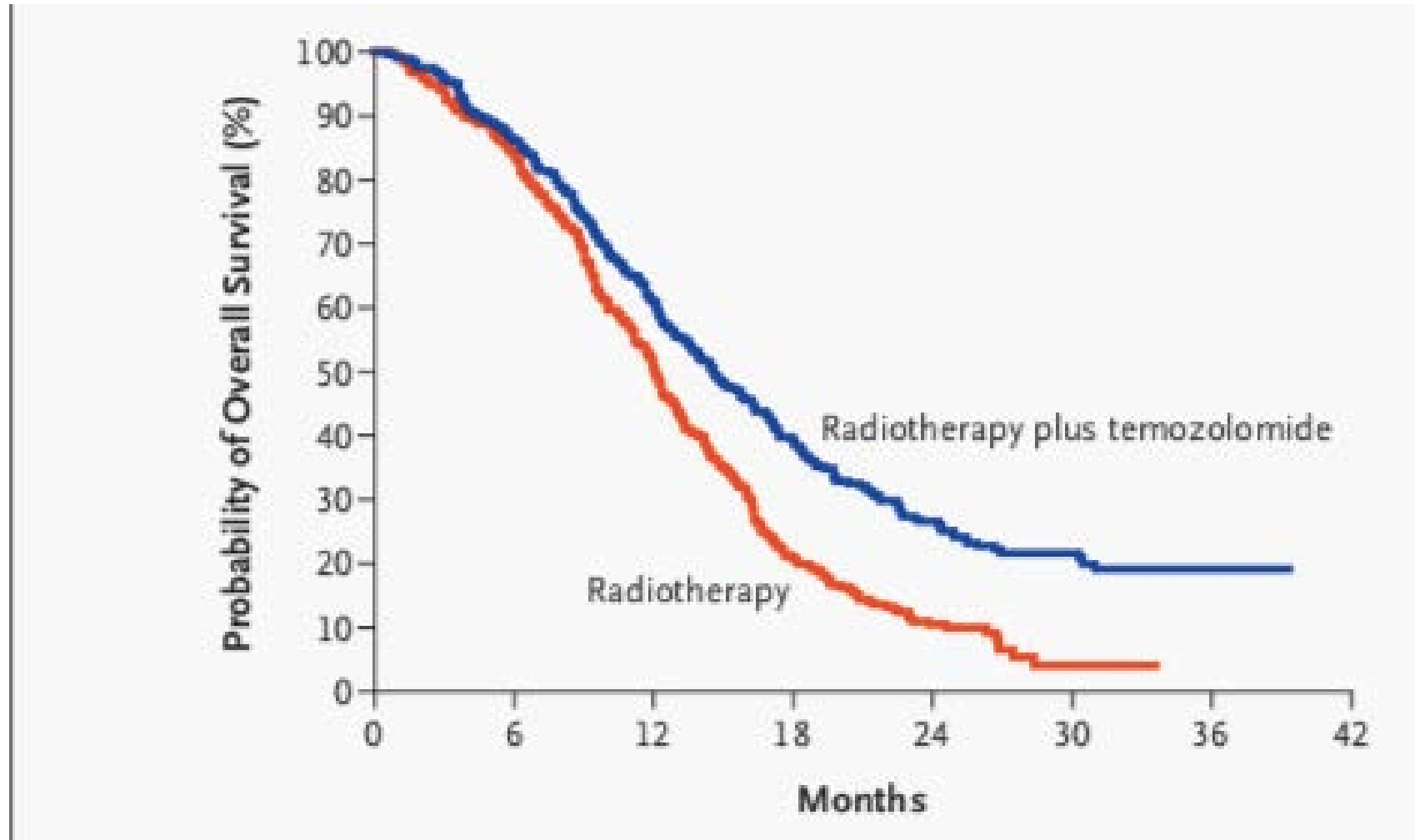
First meeting in clinic - (need to assess performance status)

- Post resection
- Review pathology
- Discuss treatment plan
 - Radonc first
- Outline rationale for treatment choice
- Review symptoms and concurrent medications
- Issues that may arise during treatment.

Treatment depends on pathology

- Grade
- IDH (isocitrate dehydrogenase) genes (oncogenic mutation)
- 1p/19q deletion -- > code1 = oligodendroglioma
- MGMT (O(6)-methylguanine-DNA methyltransferase) methylation

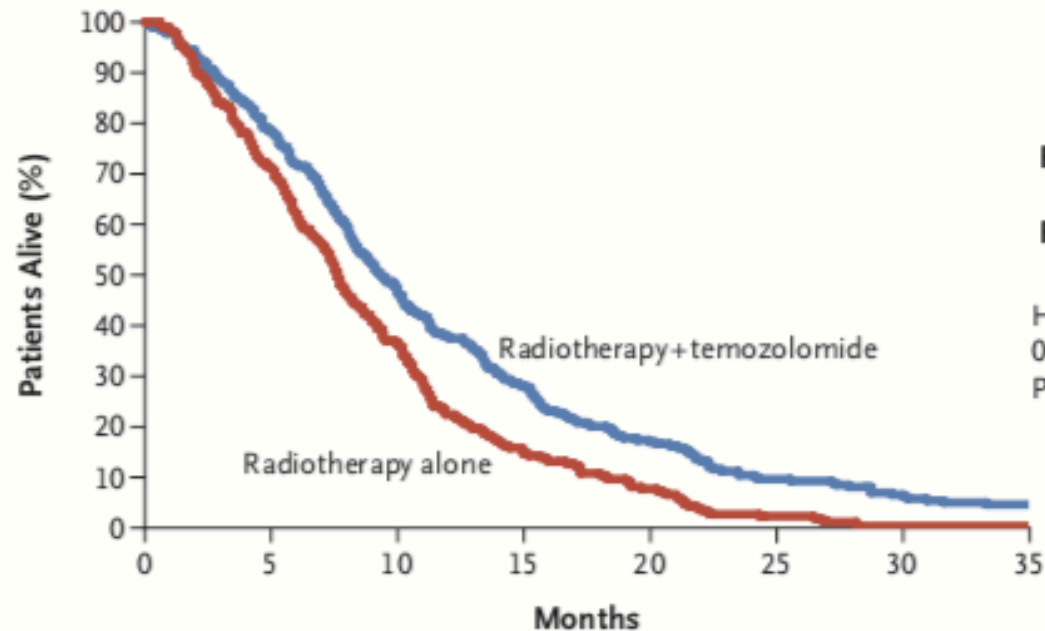
OS in GBM w Chemorads



Chemorads
60Gy 30Days
Followed by 6mo of
maintenance chemo

Elderly study – short course rads vs chemorads for elderly (40Gy in 15F)

A Overall Survival



Median Overall Survival

mo (95% CI)

Radiotherapy+
Temozolomide
Radiotherapy Alone

9.3 (8.3–10.3)

7.6 (7.0–8.4)

Hazard ratio for death,
0.67 (95% CI, 0.56–0.80)
P<0.001

No. at Risk

Radiotherapy+ temozolomide	281	217	129	77	43	23	15
Radiotherapy alone	281	196	100	40	19	5	1

IDH mutation and treatment

IDH Mutated

IDH WT

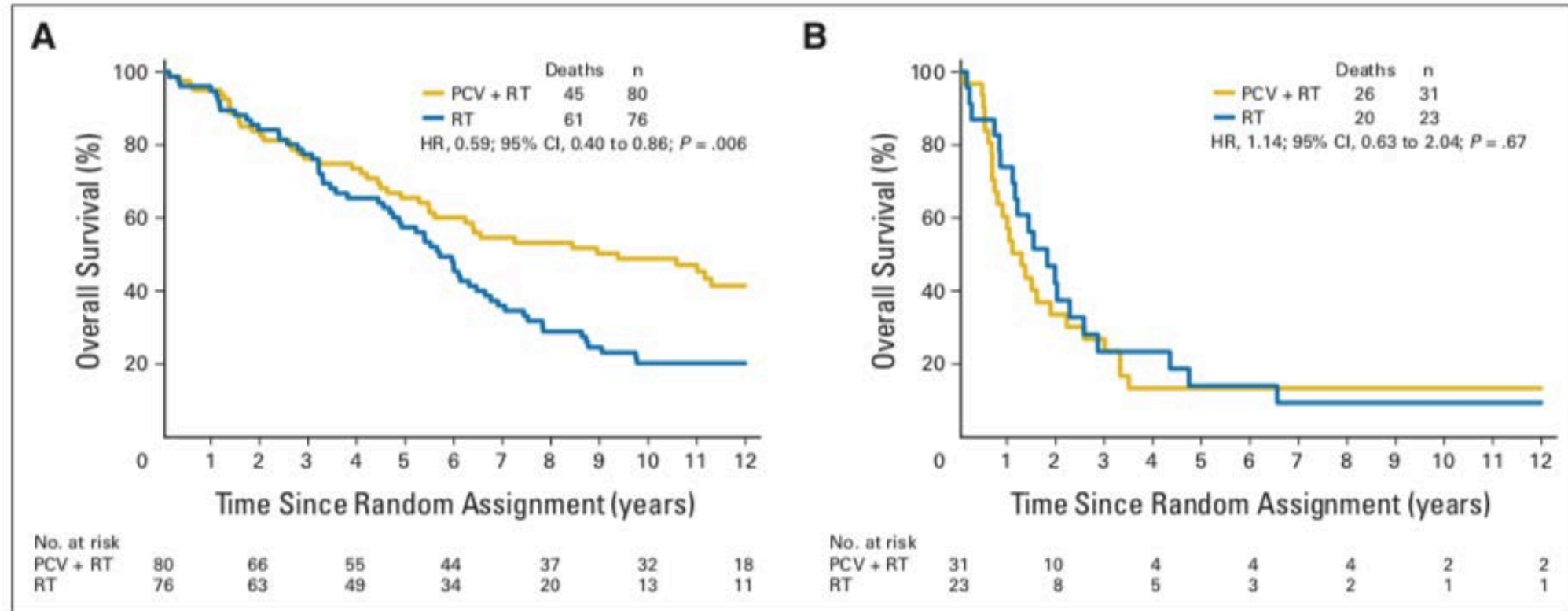
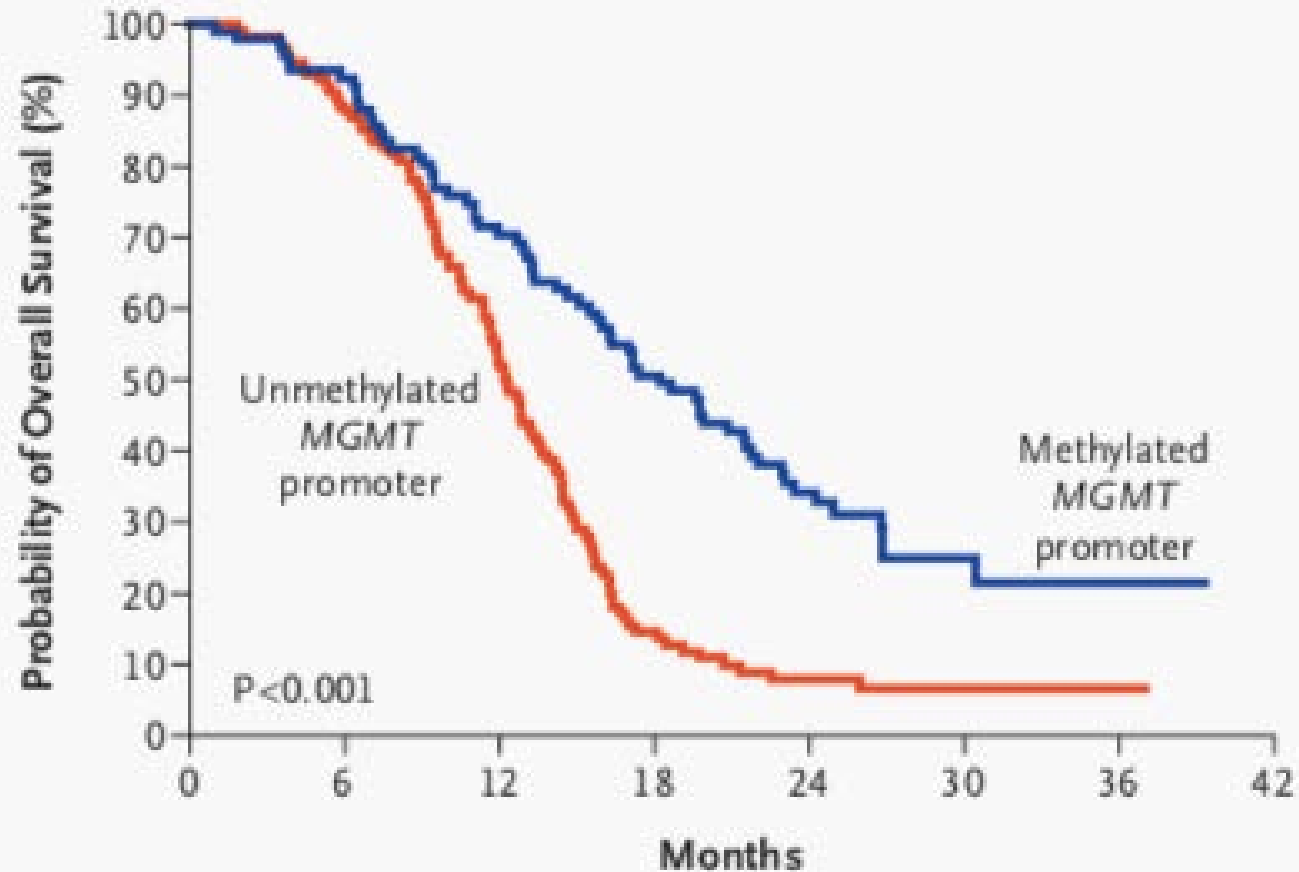


Fig 1. Kaplan-Meier estimates of overall survival (OS) by treatment (procarbazine, lomustine, and vincristine [PCV] plus radiotherapy [RT] or RT) for patients with (A) *IDH*-mutated and (B) nonmutated tumors. Hazard ratio (HR) ratio for OS for those with mutated tumors was 0.59 (95% CI, 0.40 to 0.86; $P = .006$); HR for those with nonmutated tumors was 1.14 (95% CI, 0.63 to 2.04; $P = .67$).

MGMT Methylation



Median OS
18.2mo (methy) vs 12.2

Hazard Ratio
0.45 (95% CI, 0.32-0.61)

MGMT

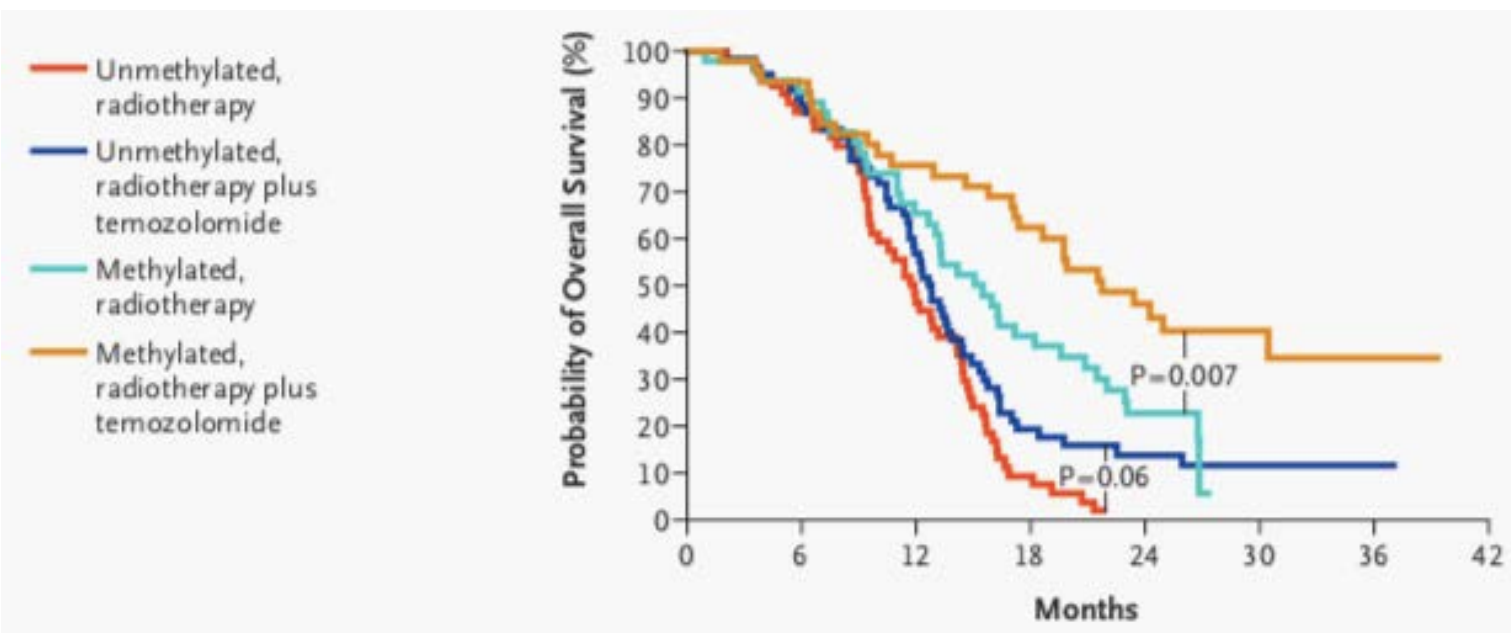
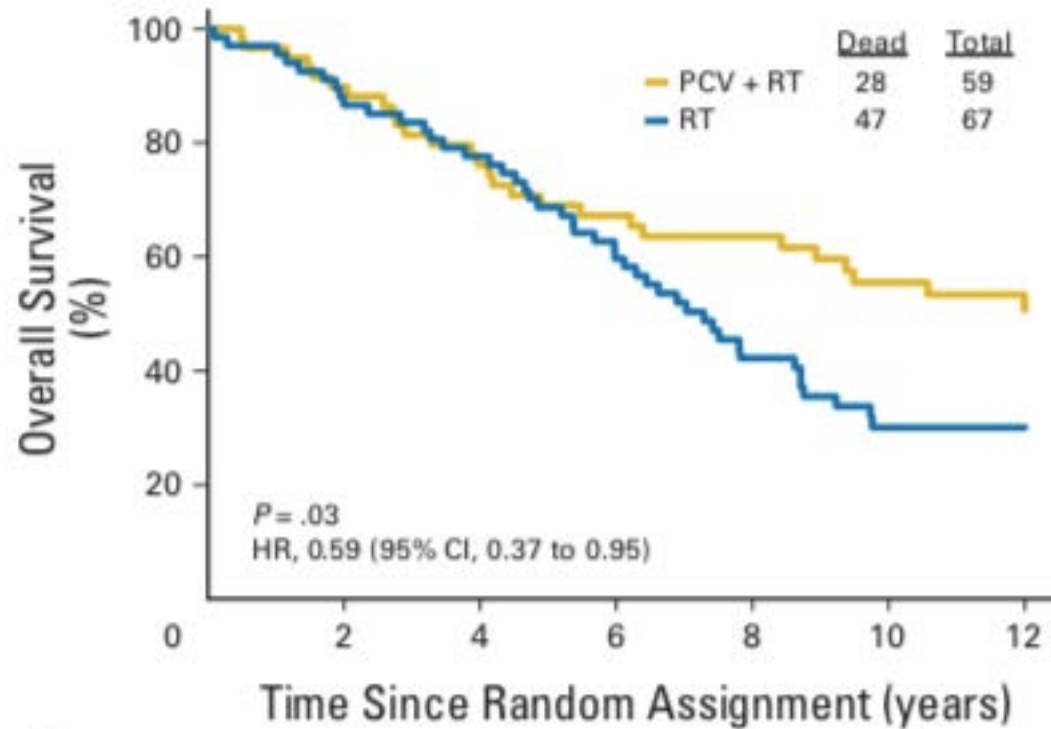


Table 1. Effect of MGMT Promoter Methylation Status on Survival, According to Random Treatment Assignment.*

Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
Methylated MGMT promoter		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.48 (0.31–0.75)
Overall survival		
Median duration (mo)	15.3 (13.0–20.9)	21.7 (17.4–30.4)
Rate at 2 yr (%)	22.7 (10.3–35.1)	46.0 (31.2–60.8)
Hazard ratio for death	1.00	0.51 (0.31–0.84)
Unmethylated MGMT promoter		
No. of patients	54	60
Progression-free survival		
Median duration (mo)	4.4 (3.1–6.0)	5.3 (5.0–7.6)
Rate at 6 mo (%)	35.2 (22.5–47.9)	40.0 (27.6–52.4)
Hazard ratio for death	1.00	0.62 (0.42–0.92)
Overall survival		
Median duration (mo)	11.8 (9.7–14.1)	12.7 (11.6–14.4)
Rate at 2 yr (%)	<2†	13.8 (4.8–22.7)
Hazard ratio for death	1.00	0.69 (0.47–1.02)

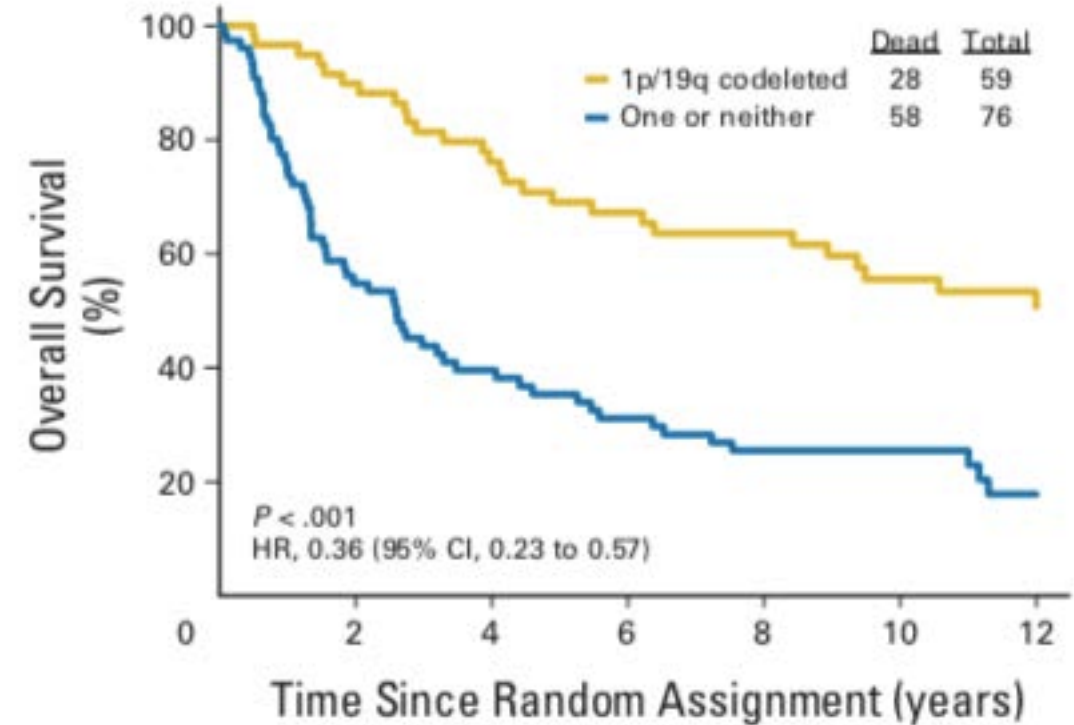
1p19q codelet.

Different Treatment



No. at risk	0	2	4	6	8	10	12
PCV + RT	59	53	43	37	32	27	18
RT	67	58	52	40	26	15	13

Codelet vs non-codelet



No. at risk	0	2	4	6	8	10	12
1p/19q codeleted	59	53	43	37	32	27	18
One or neither	76	41	28	22	17	14	7

Treatment depends on pathology ... part 2

- GBM – combined chemoradiotherapy followed by maintenance chemo
- Elderly GBM – short course chemorads. Particularly if MGMT methylated
- Grade 3 Astrocytoma with IDH WT – Treat like GBM
- Grade 3 A with IDH mutated - better prognosis treat with rads followed by PCV chemotherapy
- Grade 2 Oligo (1p/19q code) / IDH mutated – rads then PCV



Adverse Effects of treatment – GBM / G3 WT

- Lethargy
- Pancytopenia (weekly bloods, telephone clinic)
- Nausea
- Constipation
- Rash
- Pressure effects with radiotherapy

Adverse Effects - PCV

- Pancytopenia ~ week 4-6
- Rash
- Lethargy
- Nausea
- Constipation

Adjunctive therapies

- Cerebral edema
 - Dexamethasone (& PPI)
 - Acetazolomide (ACED Trial)
- Antiseizure medications
 - Levetiracetam
 - Sodium Valproate
 - Clobazam / lacosamide / phenytoin / carbamazepine
- Prophylactic antimicrobial therapy
 - Bactrim DS
 - Antivirals

Brain Tumour - Adverse effects

- Dependent on region involved
- Pressure effects (space occupying lesion / oedema)
 - Dexamethasone (& PPI)
 - Acetazolomide (ACED Trial)
- Seizures
 - Levetiracetam
 - Sodium Valproate
 - Clobazam / lacosamide / phenytoin / carbamazepine

Frontal lobe

Executive functions, thinking, planning, organising and problem solving, emotions and behavioural control, personality

Motor cortex

Movement

Sensory cortex

Sensations

Parietal lobe

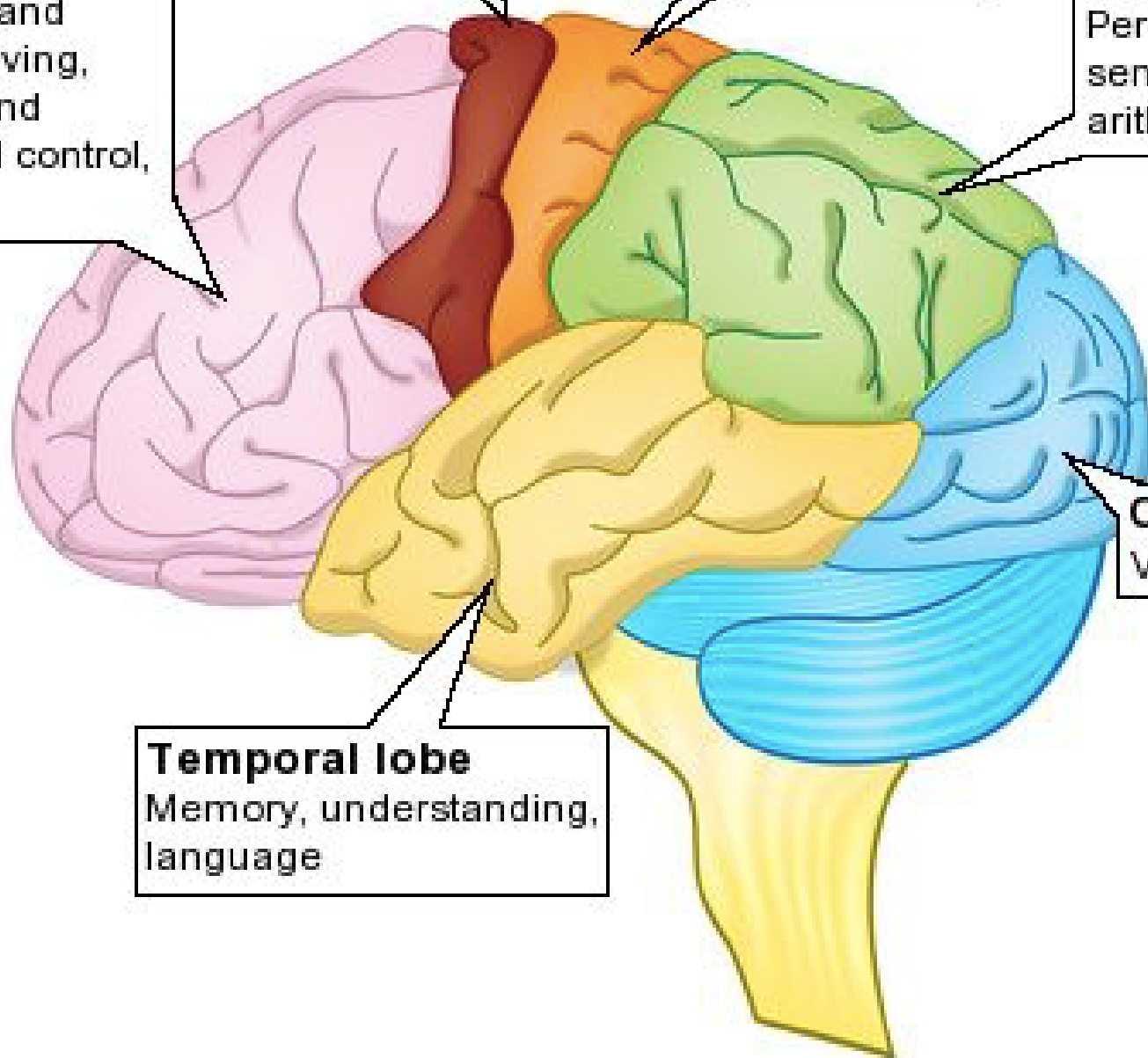
Perception, making sense of the world, arithmetic, spelling

Occipital lobe

Vision

Temporal lobe

Memory, understanding, language



Brain Tumour Adverse Effects

- Mood Disorders
 - bouts of intense anger, confusion, and unpredictable behaviour
 - Unpredictable emotional outbursts – tears / crying
 - agitation, volatile emotions, memory impairment, verbal attacks, physical aggression, and impaired impulse control.
- Memory Loss
 - Short or long term, loss of passage of time / sense of self
- Difficulty communicating
 - Aphasia, dysphasia (receptive and expressive)



**THE WORST WAY TO TELL A PATIENT
THEY HAVE A BRAIN TUMOR.**

It's ALL in your head

Brain Tumour Adverse Effects

- Executive Dysfunction
 - complex group of skills we use
 - to plan,
 - make decisions,
 - problem solve,
 - self-monitor,
 - make sound judgments,
 - multi-tasking,
 - social behaviours,
 - motivation,
 - concentration,
 - absorbing information,
 - controlling emotion

Characterised by

“No get up and go”

“no forward planning”

Rigid thought processes

Inability to anticipate consequences

Inability to make accurate judgements

or find solutions if things go wrong

Acting impulsively

Difficulty controlling emotions



**“I FEEL LIKE I JUST DON'T KNOW
YOU ANYMORE, RICHARD!”**

Issues

- Can't have a constructive conversation with a person who has a brain injury or memory loss ("hitting your head against a brick wall")
- Frustrated by loss of independence (loss of ability to drive), awareness of loss of function,
- Lack of insight.
- Loss of social niceties... displaying disinhibited behaviour
- Personality change impacts on relationships within and around the individual and family unit



Other issues

- Schooling
- Working
- Driving

- New therapies, immunotherapy, vaccine therapy, TTF fields.
 - Trial Phase
 - Animal vs human studies
 - NGS

- Alternative therapies

References

- <https://www.headway.org.uk>
- Stupp, NEJM 2005, Chemorads for GBM
- Wick, NEJM 2017, shortcourse chemorads in elderly
- Cairncross, JCO 2014, IDH mut and glioma
- Hegi NEJM 2005, MGMT

