ICRO Lecture 09 July 2021:
LOW GRADE GLIOMAS- A COMPLETE GUIDE

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Outline

- Clinical presentation
- Classification
- Radiology
- Surgery
- Prognostic factors
- Radiotherapy
- Chemotherapy
- Future research

Introduction

- Annual incidence of gliomas: six cases per 100,000 individuals worldwide
- Men 1.6-fold more likely to be diagnosed with gliomas than women
- Majority sporadic
- Familial tumour syndromes associated with gliomagenesis: Neurofibromatosis type I, Tuberous sclerosis, Turcot syndrome, Li–Fraumeni syndrome and

Clinical Presentation

- New-onset epilepsy
- Focal deficits (such as pareses or sensory disturbances)
- Neurocognitive impairment
- Symptoms and signs of increased intracranial pressure

Clinical Examination

- The Neurological Assessment in Neuro-Oncology (NANO) scale can be used to document some of the results of the neurological examination
- Neurocognitive assessment using a standardized test battery, beyond documenting performance status and performing a Mini Mental State Examination (MMSE)

WHO Grading of Brain Tumors

Based on four morphologic criteria: **cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation), and necrosis**

- Grade I: **Do not meet any** of the criteria. Slow growing, nonmalignant, long-term survival
- Grade II: Meet only one criterion, i.e., **only cytological atypia**. Slow growing but recur as higher-grade tumors. They can be malignant or nonmalignant
- Grade III: Meet two criteria, i.e., **anaplasia and mitotic activity**. Malignant and often recur as higher-grade tumors
- Grade IV: Meet three or four of the criteria, i.e., **anaplasia, mitotic activity with microvascular proliferation, and/or necrosis**. These tumors reproduce rapidly and are very aggressive malignant tumors

Histological Diagnosis

- LGG are separated into astrocytomas (those with nuclear irregularities with fibrillary processes) and oligodendrogliomas (Those with uniformly rounded nuclei and perinuclear halo (“fried egg”)
- A variant of diffuse astrocytic tumor is gemistocytic astrocytoma, characterized by abundant eccentrically placed cytoplasm. —rapid malignant progression

Incorporation of Molecular Markers

- The 2016 World Health Organization (WHO) classification integrates molecular markers in the routine histological diagnosis of CNS tumors. If molecular testing cannot be performed, the term “not otherwise specified (NOS)” is added
- Treatment startegies changed drastically
- Recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumour Taxonomy — Not Officially WHO (cIMPACT-NOW)
- Various practice-changing clinical trials
- Different Guidelines including the latest EANO 2020

Molecular markers-Gliomas

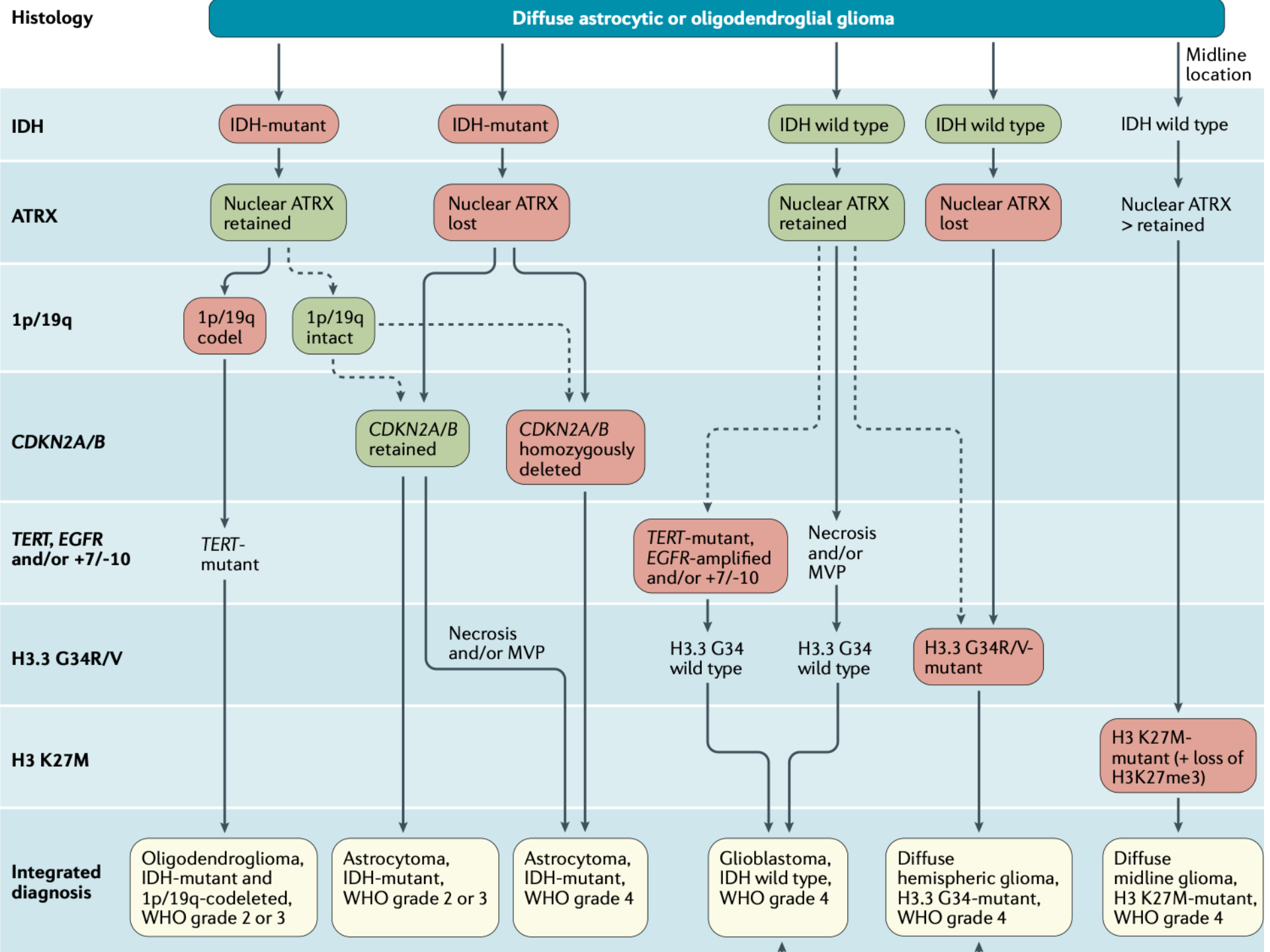
Molecular marker	Biological function of affected genes	Diagnostic roles
IDH1 R132 or IDH2 R172 mutation	Gain-of-function mutation	Distinguishes diffuse gliomas with IDH mutation from IDH-wild-type glioblastomas and other IDH-wild-type gliomas
1p/19q codeletion	Inactivation of putative tumour suppressor genes on 1p (such as *FUBP1*) and 19q (such as *CIC*)	Distinguishes oligodendroglioma, IDH-mutant and 1p/19q-codeleted from astrocytoma, IDH-mutant
Loss of nuclear ATRX	Cell proliferation and promotion of cellular longevity by alternative lengthening of telomeres	Loss of nuclear ATRX in an IDH-mutant glioma is diagnostic for astrocytic lineage tumours
Histone H3 K27M mutation	Histone H3.3 (*H3F3A*) or histone H3.1 (*HIST1H3B/C*) missense mutation affecting epigenetic regulation of gene expression	Defining molecular feature of diffuse midline glioma, H3 K27M-mutant
Histone H3.3 G34R/V mutation	Histone mutation affecting epigenetic regulation of gene expression	Defining molecular feature of diffuse hemispheric glioma, H3.3 G34-mutant
MGMT promoter methylation	DNA repair	None, but is a predictive biomarker of benefit from alkylating chemotherapy in patients with IDH-wild-type glioblastoma
Homozygous deletion of *CDKN2A/CDKN2B*	Encode cyclin-dependent kinase inhibitors 2A and 2B and tumour suppressor ARF, which function as regulators of Rb1 and p53-dependent signalling	A marker of poor outcome and WHO grade 4 disease in IDH-mutant astrocytomas

Weller M et al. Nat Rev Clin Oncol. 2021 Mar;18(3):170-186

Molecular markers-Gliomas

Molecular marker	Biological function of affected genes	Diagnostic roles
EGFR amplification	Cell proliferation, invasion and resistance to induction of apoptosis	*EGFR* amplification occurs in ~40–50% of glioblastoma, IDH wild type Molecular marker of glioblastoma, IDH wild type, WHO grade 4 (REF.[3])
TERT promotor mutation	Cell proliferation; promotes cellular longevity by increasing TERT expression	*TERT* promoter mutation occurs in ~70% of glioblastoma, IDH wild type and >95% of oligodendroglioma, IDH-mutant and 1p/19q-codeleted Molecular marker of glioblastoma, IDH wild type, WHO grade 4 (REF.[3])
+7/–10 cytogenetic signature	Gain of chromosome 7 (harbouring genes encoding, among others, PDGFA and EGFR) combined with loss of chromosome 10 (harbouring genes including *PTEN* and *MGMT*)	Molecular marker of glioblastoma, IDH wild type, WHO grade 4 (REF.[3])
BRAF^{V600E} mutation	Oncogenic driver mutation leading to MAPK pathway activation	Rare in adult diffuse gliomas but amenable to pharmacological intervention

Weller M et al. Nat Rev Clin Oncol. 2021 Mar;18(3):170-186


Histology
Diffuse astrocytic or oligodendroglial glioma
Midline location
IDH
IDH-mutant
IDH-mutant
IDH wild type
IDH wild type
IDH wild type
ATRX
Nuclear ATRX retained
Nuclear ATRX lost
Nuclear ATRX retained
Nuclear ATRX lost
Nuclear ATRX > retained
1p/19q
1p/19q codel
1p/19q intact
CDKN2A/B
CDKN2A/B retained
CDKN2A/B homozygously deleted
TERT, EGFR and/or +7/-10
TERT-mutant
TERT-mutant, EGFR-amplified and/or +7/-10
Necrosis and/or MVP
H3.3 G34R/V
Necrosis and/or MVP
H3.3 G34 wild type
H3.3 G34 wild type
H3.3 G34R/V-mutant
H3 K27M
H3 K27M-mutant (+ loss of H3K27me3)
Integrated diagnosis
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2 or 3
Astrocytoma, IDH-mutant, WHO grade 2 or 3
Astrocytoma, IDH-mutant, WHO grade 4
Glioblastoma, IDH wild type, WHO grade 4
Diffuse hemispheric glioma, H3.3 G34-mutant, WHO grade 4
Diffuse midline glioma, H3 K27M-mutant, WHO grade 4

Role of Molecular markers

- Diagnostic- for proper classification
- Prognostic Marker-Predicting biological behaviour
- Predictive marker-Predicting response to a particular therapy
- Therapeutic target-for treatment

Typical Genetic Signature in Gliomas

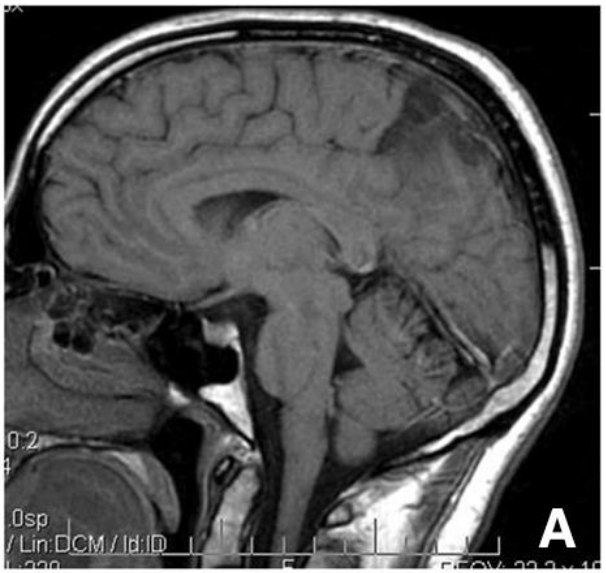
- ODG: 1p/19q codeletion, *IDH Mutation*, and mutation in *TERTp*
- Grade 2 & 3 Astrocytic tumors: *ATRX mutations(loss)* and *TP53* mutations
- IDH-wildtype GBMs: are characterized by the CNV of *EGFR*, *PTEN*, *CDKN2A/B*, *PDGFRA*, and *MET* genes, in addition to a lack of mutations in *IDH* and a codeletion in

Radiology

- **CT:** LGG appear as iso or low attenuation, poorly deliniated, often without contrast enhancement or perilesional edema.
- Calcifications (10–20% of cases) and may be related to oligodendroglial components.
- **Conventional MRI (cMRI)**
- LGG are often homogeneous with low signal intensity on T1-weighted images and have high signal intensity on T2-weighted sequences. The high T2 signal is not related to cellularity or cellular atypia, but rather oedema, demyelination and other degenerative changes
- Cystic components are also encountered
- FluidAttenuated Inversion Recovery (FLAIR) sequence shows the best contrast between presumed infiltrating tumor margins and normal brain

Radiology Contd…

- **Advanced MRI (aMRI):** Diffusion weighted imaging (DWI), MR Spectroscopy and Perfusion MRI:- complements, the anatomic information obtained from cMRI
- DWI quantifies tumor cellularity (Water diffusivity within the extracellular compartment is inversely related to the content of the intracellular space). LGGs present low cellularity and non-restricted diffusion.
- DTI and further application using fiber-tracking techniques (tractography) can reveal relationship between the tumor and adjacent white matter tracts: LGG tend to deviate, rather than destruct or infiltrate the adjacent white matter
- MRS noninvasively measure the brain metabolites in vivo. LGG present decreased N-Acetyl-Aspartate (NAA) peak, medium choline peaks, absence of lactate peak and increased myo-inositol.
- Perfusion-weighted MRI generates a series of parameters, including relative cerebral blood volume (rCBV), referring to volume of blood in a given region of brain tissue…estimation of tumor microvascular density. LGGs usually show no increase in tumor rCBV: LGG have rCBV values of range between 1.11 and 2.14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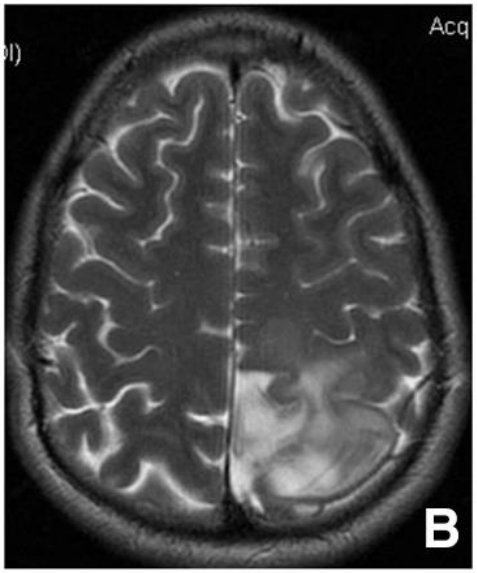
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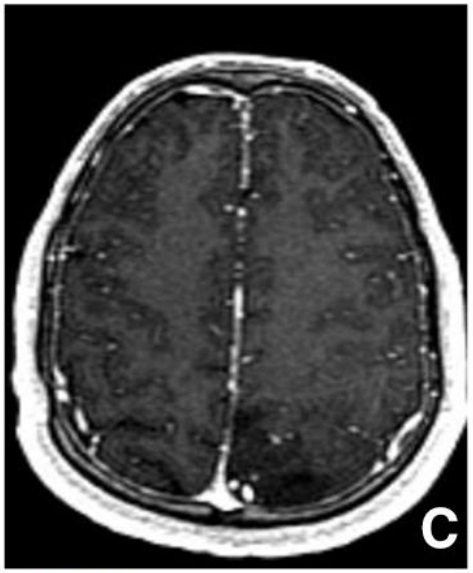
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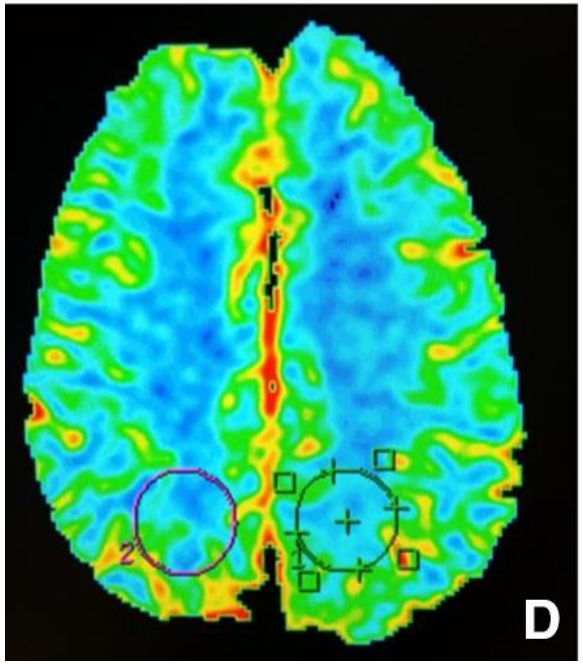
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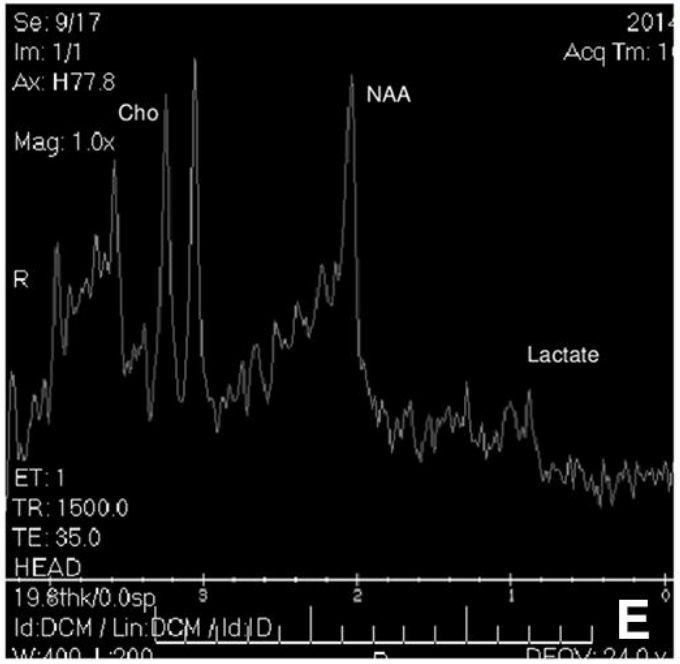
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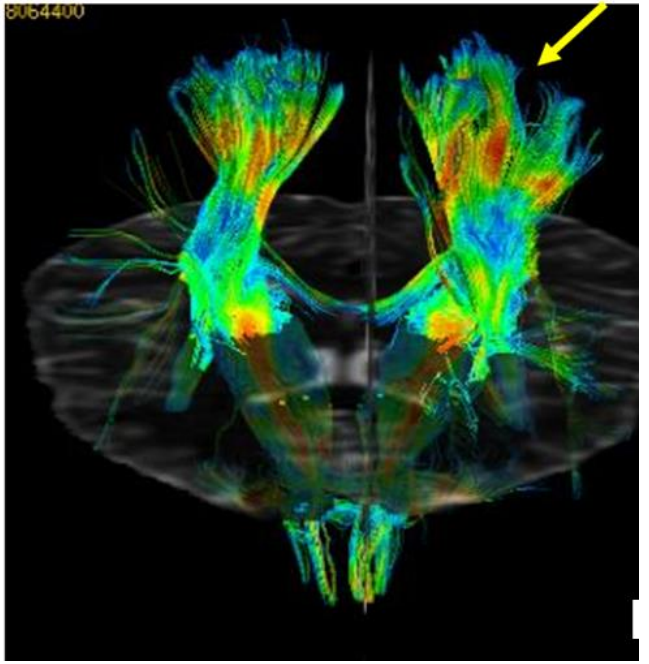
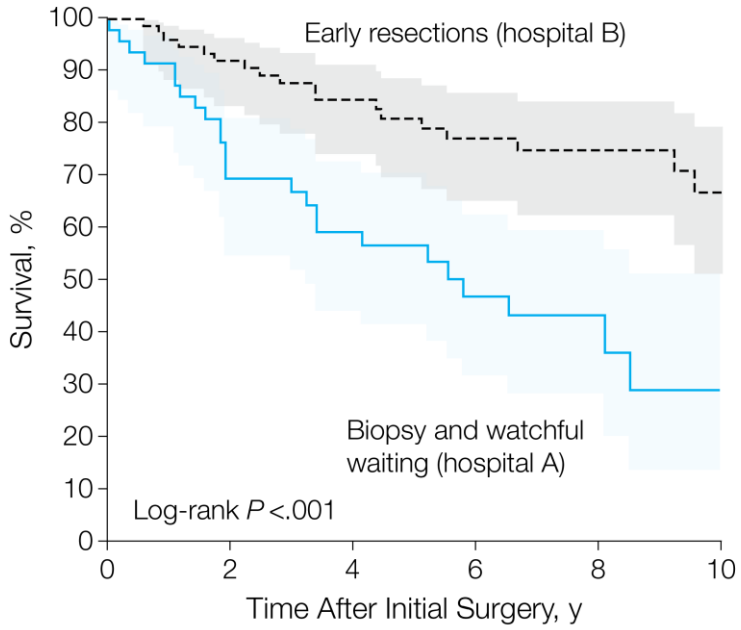


Surgery in LGG

- LGG predilection for eloquent regions, the risk of inducing new neurological deficits had tempered enthusiasm for radical resection
- However resection of low-grade glioma improves overall survival and importantly delays the time to malignant progression.
- Early surgery and the widespread adoption of awake craniotomy with intra-operative functional mapping have revolutionised low-grade glioma management.
- Permanent Neurological deficit in experienced centres:1.4%–3.4%; Temporary deficit: 17%–26%. most patients improve within 3 months
- Duffau et al found that neurological deficit reduced from 17% to 6.5% using

Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas



No. of patients at risk

Biopsy	47	30	23	14	6	3
Resection	75	67	48	39	22	13

Jakola AS et al. JAMA 2012; 308(18):1881-8

Median survival of 5.8 years (95% CI, 3.0-8.7) at hospital A, while median survival was not reached at hospital B ($P < .001$).

Outcome	Hospital A (n = 66)	Hospital B (n = 87)	*P* Value
Surgical complications	6 (9)	7 (8)	.82
New or worsened neurological deficits[a]	12 (18)	18 (21)	.70
Perioperative death, 30-d mortality	1 (2)	0	.25
Malignant transformation[b]	37 (56)	31 (37)	.02

Preoperative management

- Corticosteroids to decrease mass effect and vasogenic edema
- Anti convulsants for those having seizures
- Baseline motor, language and neurocognitive assessment
- cMRI and aMRI:-Perfussion, Tactography, MRS, fMRI—Neuronavigation and functional Neuronavigation

Why surgery in LGG?

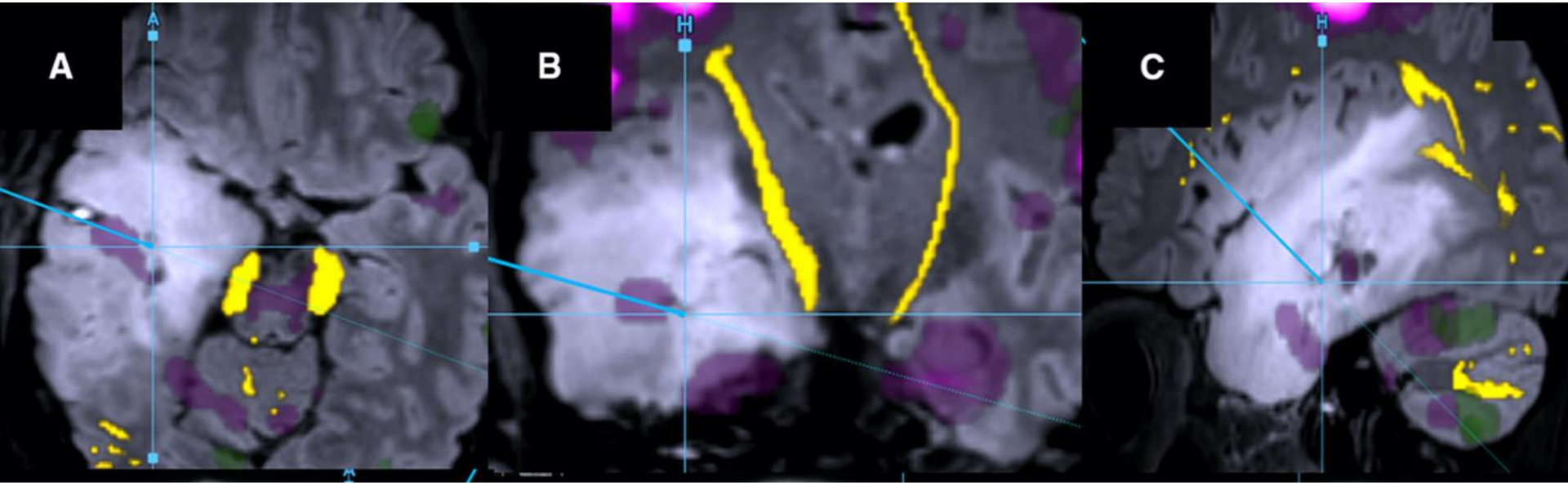
- Better survival with more EOR.
- Histological diagnosis and molecular analysis.
- Ameliorated mass effect and intracranial tension.
- Ease control of seizures (LGG with seizures would have seizure-free in 67–70% and improvement in another 20–25%).

Surgery

- GTR/NTR
- STR
- Decompression
- Biopsy only (deep lesions including brainstem, diffuse and/or multicentric tumor. Stereotactic/open)

Tactography, Functional MRI

Preoperative Neuronavigation and functional Neuronavigation



fMRI and DTI tractography of axial (A), coronal (B), and sagittal (C) FLAIR sequences in a patient with a WHO grade II infiltrative astrocytoma. Note displacement of corticospinal tract (yellow) in addition to language (green) and motor (purple).

Hervey-Jumper SL et ai. J Neurooncol 2016;DOI 10.1007/s11060-016-

Awake Craniotomy

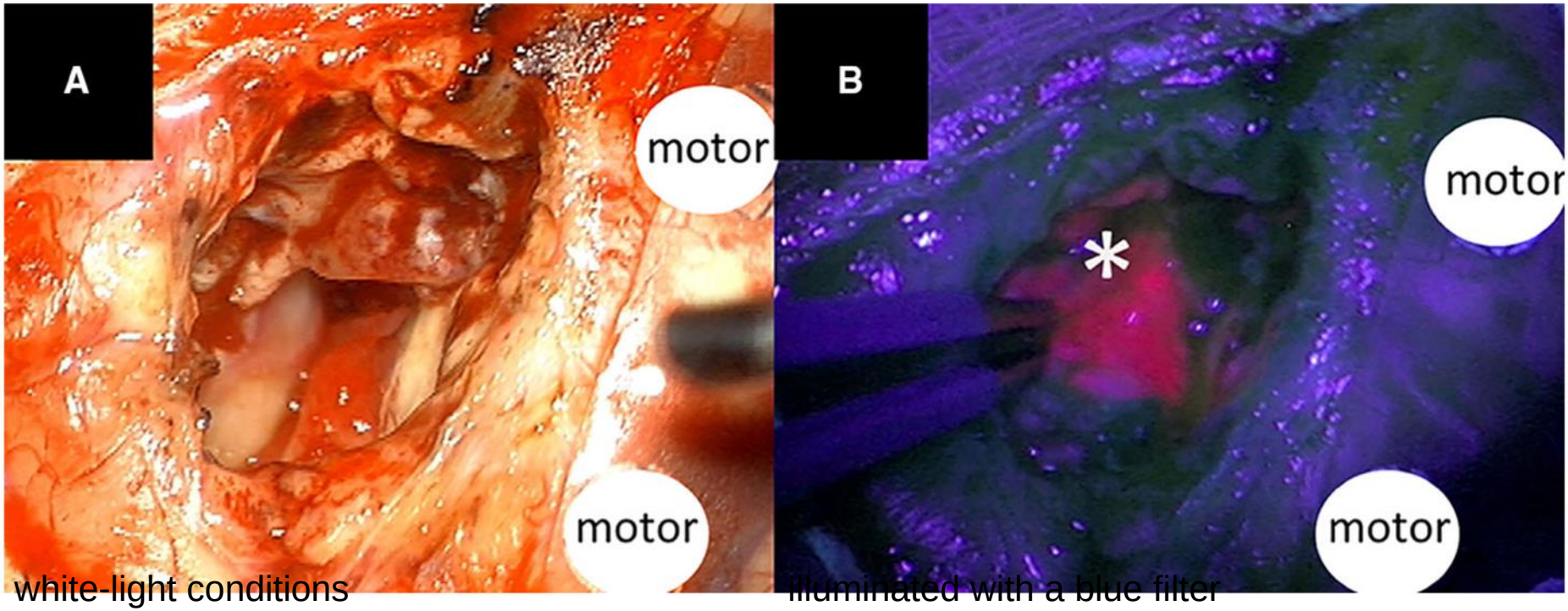
- Indication: a supratentorial intrinsic brain tumor located within or adjacent to regions presumed to have language or sensorimotor function on preoperative imaging
- Contraindications: uncontrolled persistent cough, hemiplegia with less than antigravity motor function, patients with severe dysphasia, greater than 25 % naming errors despite a trial of corticosteroids and diuresis, and large tumors with mass effect with >2 cm of midline shift
- Large tumors, obese patients, patients with a psychiatric history and/or severe anxiety, intraoperative seizures, chronic smokers, a chronic cough, reoperation with extensive dural scarring, and severely impaired preoperative function all potential risk factors
- Intraoperative mapping gold standard technique: Stimulation is delivered using a

Literature on EOR in LGG

Overall survival	Non-volumetric studies	No. patients	Volumetric studies	No. patients
Benefit	North et al. [16]	77	van Veelen et al. [25]	75
	Philippon et al. [18]	179	Claus et al. [9]	156
	Rajan et al. [19]	82	Smith et al. [23]	216
	Leighton et al. [15]	167	Sanai and Berger [20]	104
	Nakamura et al. [4]	88	Incekara et al. [11]	128
	Yeh et al. [27]	93	Hollon et al. [10]	109
	McGirt et al. [53]	170	Snyder et al. [24]	93
	Ahmadi et al. [155]	130		
	Chaichana et al. [156]	191		
	Jakola et al. [28]	153		
	Lote et al. [3]	379		
	Nicolato et al. [5]	76		
	Scerrati et al. [6]	131		
	Ito et al. [12]	89		
	Karim et al. [14]	311		
	Peraud et al. [17]	75		
	Shaw et al. [21]	203		
	Shibamoto et al. [22]	178		
No benefit	Whitton and Bloom [26]	88	None to date	
	Bauman et al. [8]	401		
	Johannesen et al. [13]	993		

Hervey-Jumper SL et ai. J Neurooncol 2016;DOI 10.1007/s11060-016-

5-ALA fluorescence



white-light conditions

illuminated with a blue filter

Orange fluorescence (Asterisk) is seen at the base of the resection cavity, indicating residual disease.

Hervey-Jumper SL et ai. J Neurooncol 2016;DOI 10.1007/s11060-016-

Adjuvant Treatment

- Surgery alone is not curative in patients with low-grade gliomas, and additional therapy (radiation and/or chemotherapy) is ultimately required.
- However, the optimal timing of additional therapy is uncertain and the decision to proceed with immediate versus delayed postoperative therapy must be individualized.

LGG Prognostic scores

Score (no/yes)	University of California San Francisco score (2008)	Pignatti score (2002)
0/1	Age >50 years	Age ≥40 years
0/1	Karnofsky Performance Status	Astrocytoma
0/1	≤80	Maximum diameter ≥6 cm
0/1	Eloquent location	Tumour crossing midline
0/1	Maximum diameter >4 cm	Neurological deficit

The Pignatti score: low risk (score 0–2) and high risk (score 3–5), with median survival of 7.8 years in the low-risk group and 3.7 years in the high-risk group

Hayhurst C. Pract Neurol 2017;0:1–8.

High risk factors in RTOG 9802

- >/=40 yrs; Subtotal resection or biopsy

Buckner JC et al. N Engl J Med 2016; 374:1344-55

- For <40 yrs and GTR (Low risk) (RTOG 111 pts)- Factors associated with a poorer prognosis for progression-free survival (PFS):

1. Preoperative tumor diameter ≥ 4 cm;
2. Astrocytoma/oligoastrocytoma histological type
3. Residual tumor ≥ 1 cm

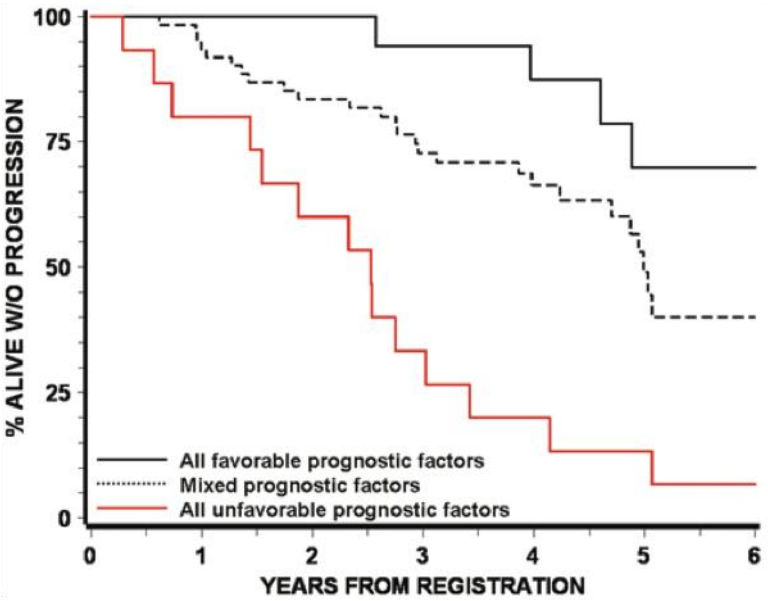
Shaw EG et al. J Neurosurg 109:800350–800401, 2008

Factors to decide adjuvant therapy

- > 40 years
- Large preoperative tumour size > 4 cm
- Incomplete resection
- Astrocytic histology
- Tumor crossing midline
- Neurological deficits
- Absence of 1p/19q-codeletion
- IDH mutation status

- It is important to recognize, however, that individual risk factors are relative (including the age cut-off of 40 years and exist on a biological continuum. In addition, there is no single agreed-upon definition of low versus high risk, and risk has been variably defined across trials.

‘Wait and see’ approach for low risk



111 patients

Overall survival rates at 2 and 5 years were 99 and 93%, respectively.

PFS rates at 2 and 5 years were 82 and 48%, respectively

Shaw EG et al. J Neurosurg 2008;109:800350–

- A “wait and see” approach following initial surgery may be followed in young patients < 40 years) with a favorable prognosis who have undergone an extensive resection for an IDH-mutant low-grade glioma, especially if molecular studies show the presence of a 1p/ 19q-codeletion
- It is expected that these patients will eventually recur and require additional therapy at the time of progression

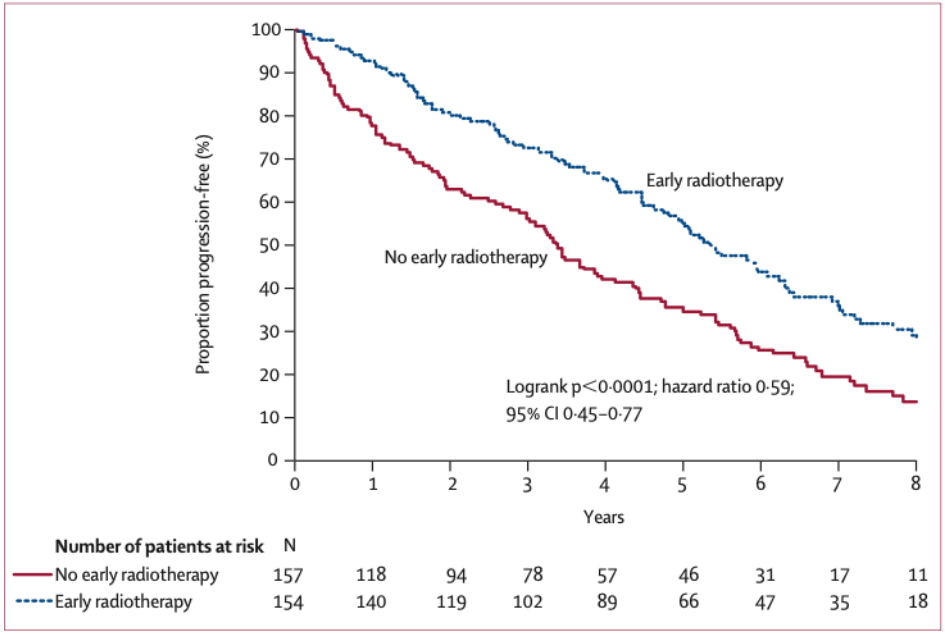
Leading studies of RT in LGG

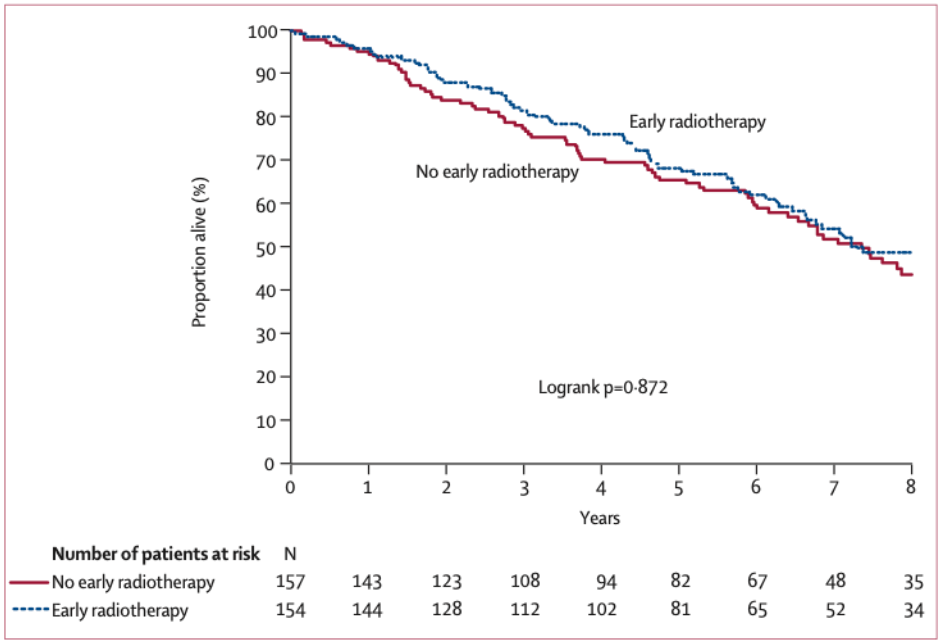
Trial	Treatments	Number of Patients	Median Overall Survival (Years)	Median PFS	5-Year OS (%)	5-Year PFS (%)
Karim et al. EORTC 22844 [101]	45 Gy in 25 ff	171	NA	NA	58	47
	59.4 Gy in 33 ff	172	NA	NA	59	50
Van den Bent et al. EORTC 22845 [102]	54 Gy in 30 ff	157	7.4	5.3	68	55
	Observation	157	7.2	3.4	66	35
Shaw et al. NCCT/ RTOG/ECOG [103]	50.4 Gy in 33 ff	101	NA	NA	72	55
	64.8 Gy in 36 ff	102	NA	NA	64	52
Buckner et al. RTOG 9802 [104]	54 Gy in 30 ff	126	7.8	4.0 Years	63	44
	54 Gy in 30 ff + PCV × 6	125	13.3	10.4 Years	72	61
Baumert et al. EORTC 22033-26033 [105]	TMZ × 12 cycles	237	NR	39 months	NA	29
	50.4 Gy in 28 ff	240	NR	46 months	NA	40

Lombardi G et al. *Cancers* **2020**, *12*, 3008; doi:10.3390/cancers12103

Timing of Radiotherapy?

Early Vs Delayed RT in LGG: EORTC 22845





	No early radiotheraphy (n=157)	Early radiotherapy (n=154)	Hazard ratio (95% CI)
Overall survival			
Median years (95% CI)	7·4 (6·1–8·9)	7·2 (6·4–8·6)	0·97 (0·71–1·34)
Proportion alive at 5 years	65·7% (57·8–73·5)	68·4% (60·7–76·2)	
Progression-free survival			
Median years (95% CI)	3·4 (2·9–4·4)	5·3 (4·6–6·3)	0·59 (0·45–0·77)
Proportion free from progression at 5 years	34·6% (26·7–42·5)	55·0% (46·7–63·3)	

RT Dose: 54 Gy in 1.8 Gy fr

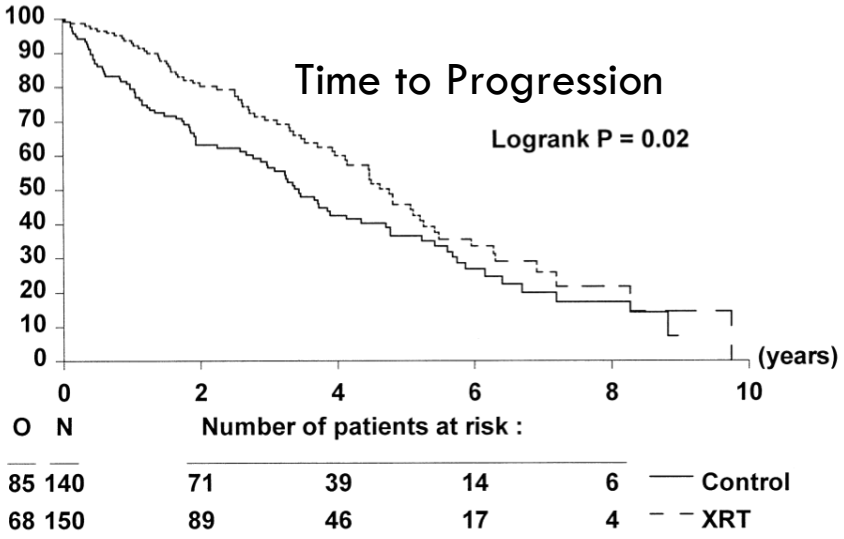
In the control, 65% received RT at progression.

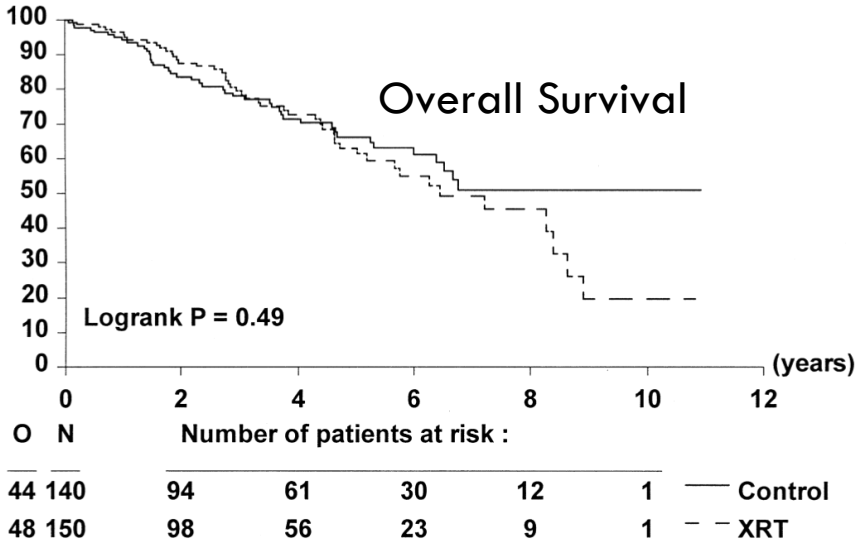
Seizures were better

vandenBent MJ et al. Lancet 2005; 366: 985–90

Early Vs Delayed: EORTC 22845/MRC BR04

- Phase III (n = 290)
- Early RT (54 Gy) versus No postoperative RT



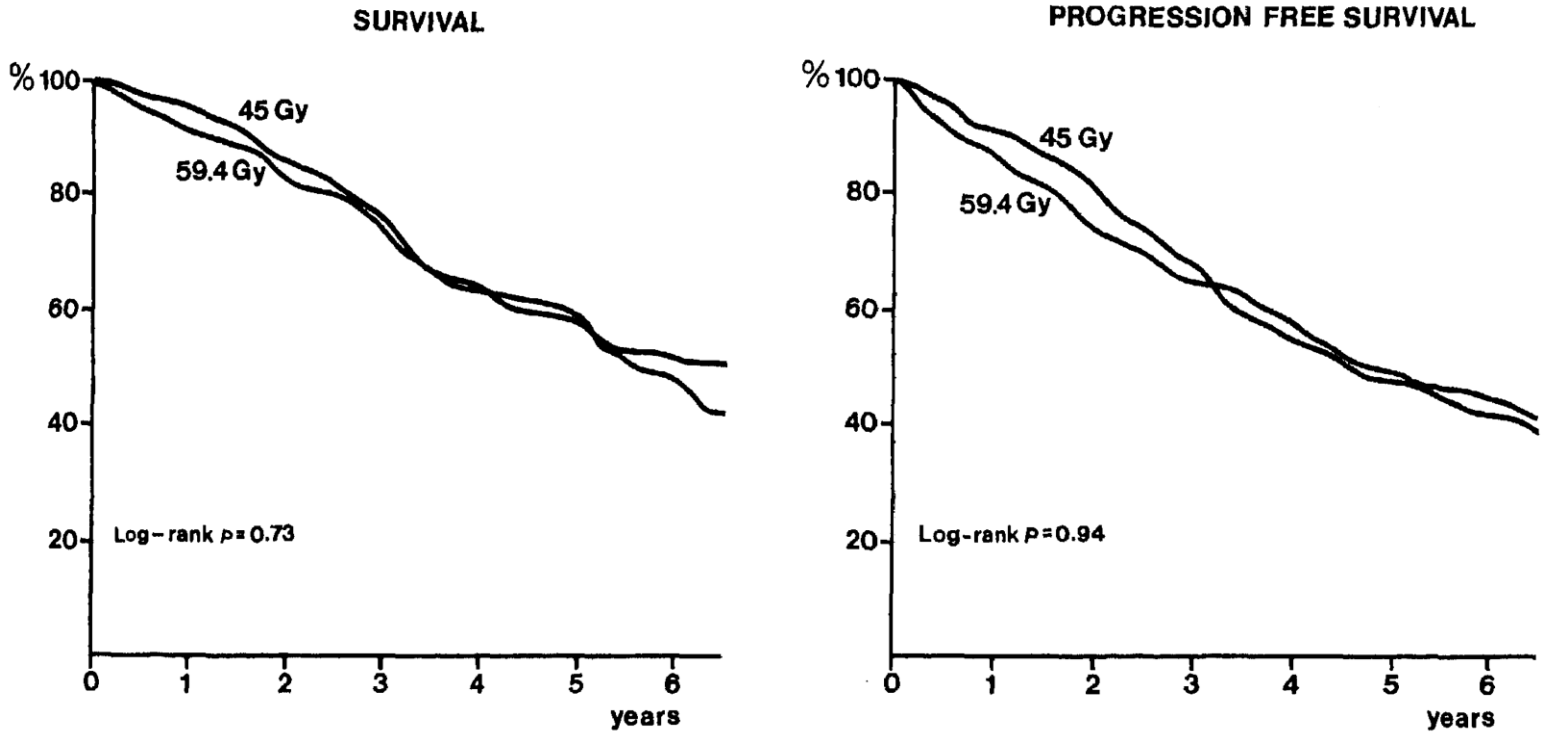


- Early RT showed an improvement in TTP (4.8 versus 3.4 years; p = 0.02). HR = 0.68 (95% CI 0.50–0.94).
- No differences in OS: HR = 1.15 (95% CI 0.67–1.74). The 5-year OS rate were: 63 versus 66% (p = 0.49).

Karim AB et al. Int. J. Radiation Oncology Biol. Phys., 2002; 52:316–324

Dose of RT?

RT Dose: EORTC 22844



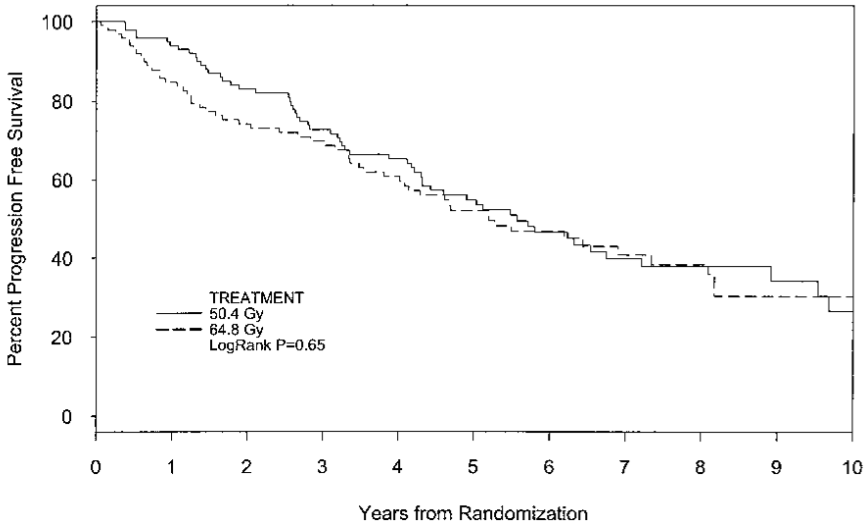
N=379.

At a median follow-up of six years, OS was 58% and 59% in the 45 Gy and the 59.4 Gy arms,

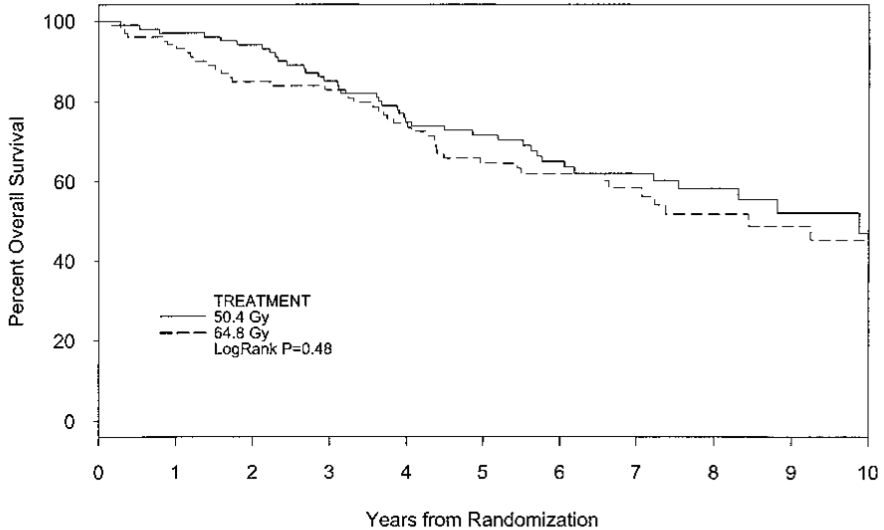
Karim AB et al. Int J Radiat Oncol Biol Phys.1996 Oct 1;36(3):549-56.

RT Dose: NCCTG/ RTOG/ECOG Study

N=203; 50.4 Gy/28 fr versus 64.8 Gy/36 fr



50.4 Gy	N(t)	101	82	44
	S(t)		83%	55%
	CI		76-91%	46-66%
64.8 Gy	N(t)	102	70	40
	S(t)		74%	52%
	CI		66-83%	43-64%



50.4 Gy	N(t)	101	94	60
	S(t)		94%	72%
	CI		90-99%	63-81%
64.8 Gy	N(t)	102	83	54
	S(t)		85%	65%
	CI		78-92%	56-75%

Survival at 2 and 5 years is nonsignificantly better with low-dose RT; survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64%, respectively, with high-dose RT (log rank *P* □ .48).

Shaw BE et al. J Clin Oncol 20:2267-2276.

RT dose contd..

- RTOG 9802
  - 54 Gy/28 Fractions
- RTOG 0424
  - 54 Gy in 30 fractions
- EORTC 22033-26033
  - 50.4Gy/28Fractions

Chemotherapy in LGG

Studies of Chemotherapy in LGG

Clinical Trial	Phase	Patients	Arm(s)	Results
RTOG 9802 [104]	III	≥40 years or subtotal resection or biopsy	RT versus RT-PCV	RT-PCV > RT for OS and PFS
EORTC 22033-26033 [105]	III	>40 years or progressive disease or tumor > 5cm or crossing midline or neurological symptoms	RT versus TMZ	No difference for PFS (all patients) Subgroup analyses: *IDHm*/non-codel: RT > TMZ for PFS *IDHm*/codel and *IDHwt*: no difference
RTOG 0424 [112]	II	3 or more: ≥40 years, astrocytoma, bihemispherical tumor, preoperative tumor size ≥ 6 cm, preoperative neurological function status > 1	RT-TMZ	5-year OS rate: 60.9% Median OS: 8.2 years (95%CI: 5.6–9.1)
Eyre et al. [115]	II	Incomplete surgical resection	RT versus RT-CCNU	No difference between treatment arms Median OS (all patients): 4.45 years
Ruda et al. [116]	II	Incomplete surgical resection or biopsy or progressive disease	TMZ alone	Median PFS: 3.4 years (95%CI: 2.2–4.3) Median OS: 9.2 years (95%CI: 8.2–11.9)
Wahl et al. [117]	II	Gross residual disease after resection	TMZ alone	Median PFS: 4.2 years (95%CI: 3.0–5.0)Median OS: 9.7 years (95%CI: 7.2–11.3)
Kaloshi et al. [118]	II	Progressive disease, refractory epilepsy, neurological deficit	CCNU alone	Median PFS: 27.8 months (95%CI: 21.2–59.6) 5-year OS rate: 71%
Kesari et al. [119]	II	Oligodendroglioma and oligoastrocytoma with a MIB-1 index > 5% or recurrent LGG	TMZ alone	5-year OS rate: 73% 5-year PFS rate: 34%

Lombardi G et al. *Cancers* **2020**, *12*, 3008; doi:10.3390/cancers12103

PCV X 6 Cycles

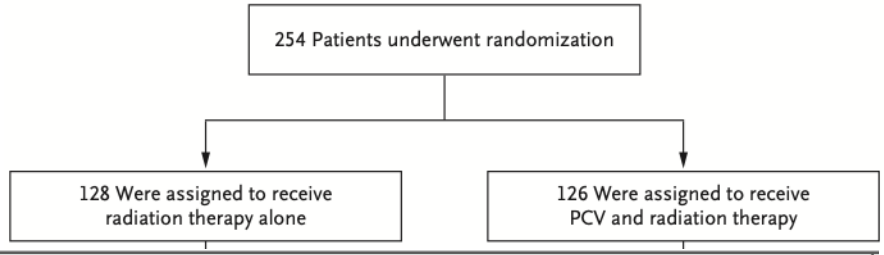
- Procarbazine 60 mg per square meter of body-surface area orally per day on days 8 through 21 of each cycle
- CCNU 110 mg per square meter orally on day 1 of each cycle
- Vincristine 1.4 mg per square meter [maximum dose, 2.0 mg] administered intravenously on days 8 and 29 of each cycle)

TMZ Chemoradiation

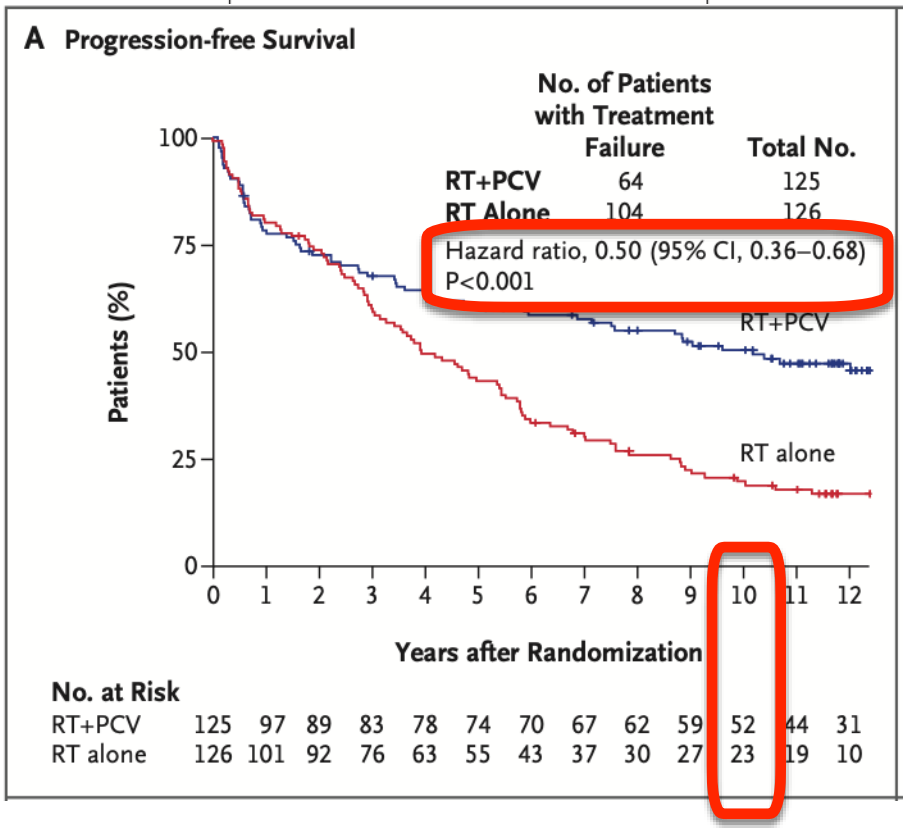
The cycle length was 8 weeks

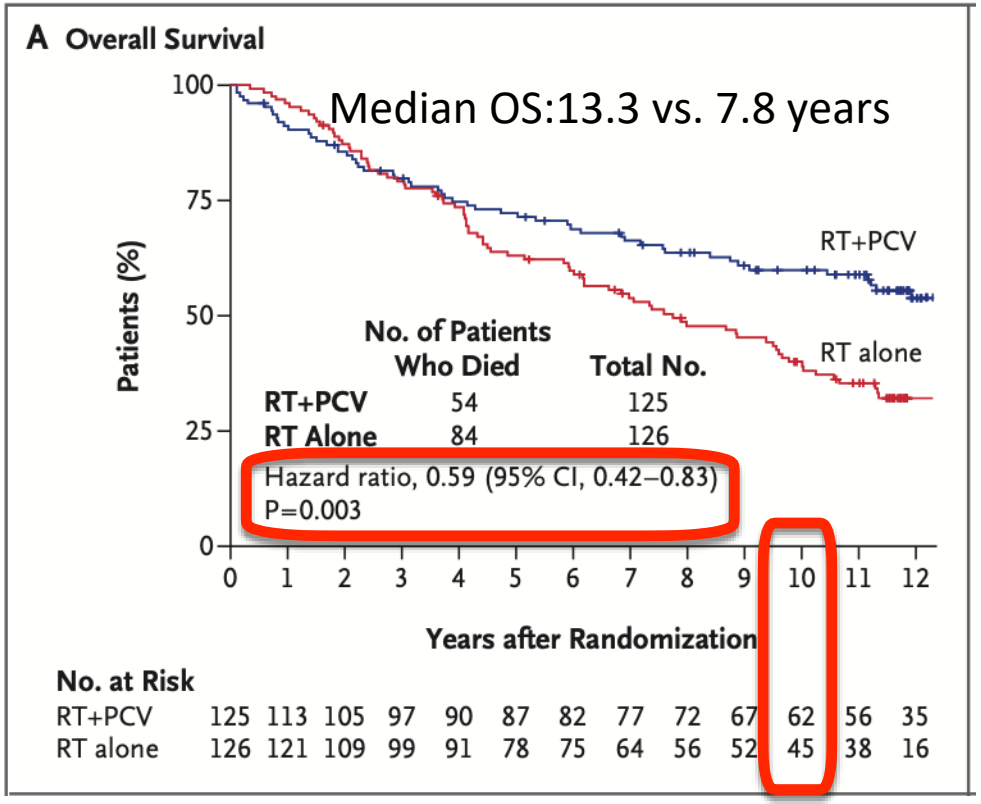
- Concurrent TMZ 75 mg/m2 daily with radiation
- Adjuvant TMZ 150-200 mg/m2 every 28 days x 6-12 cycles, starting one month after RT

RTOG 9802: RT 54Gy/28Fr +/-PCV

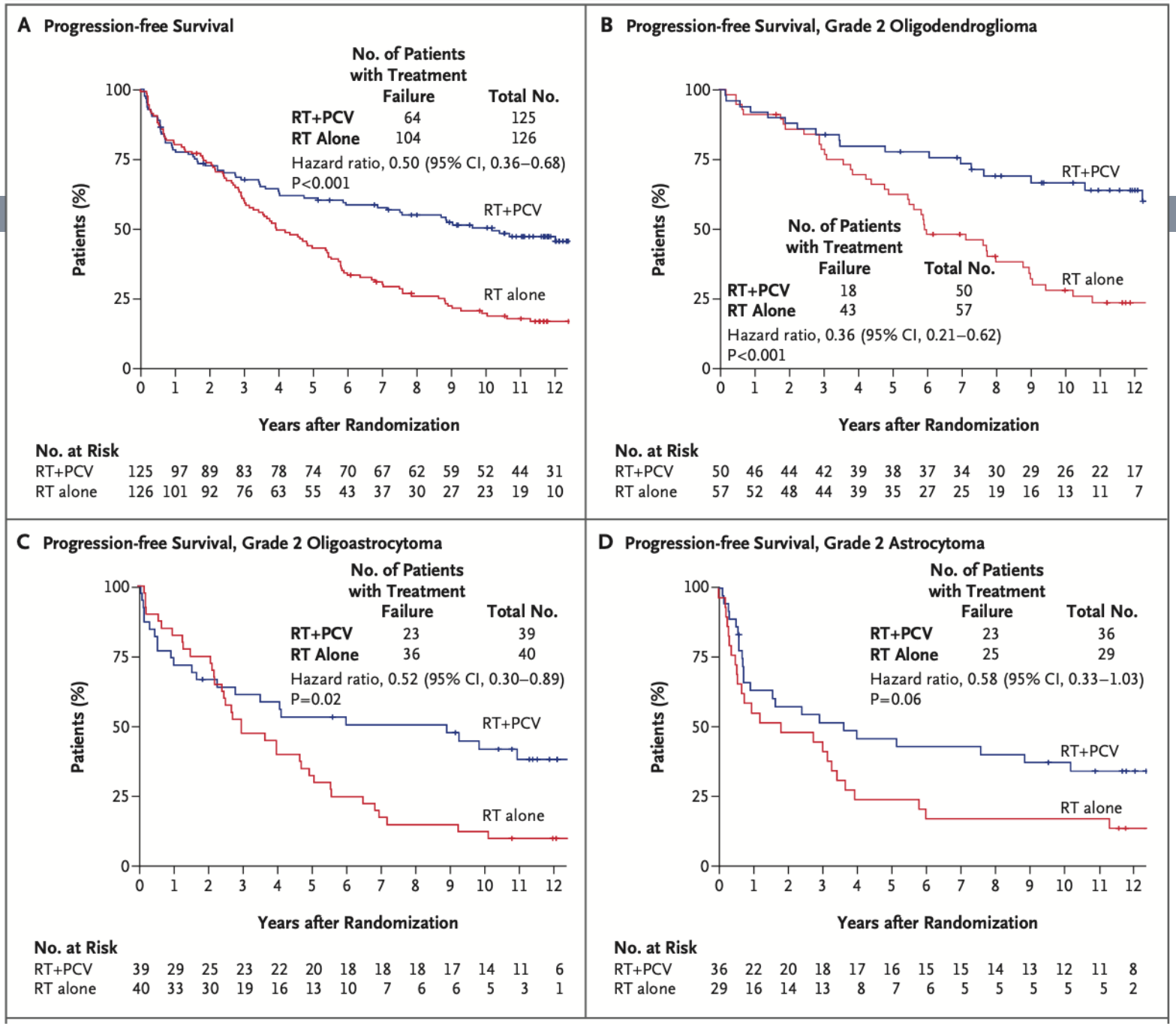


- High-risk LGG:
  - Age >/ 40 years and/or
  - Subtotal resection

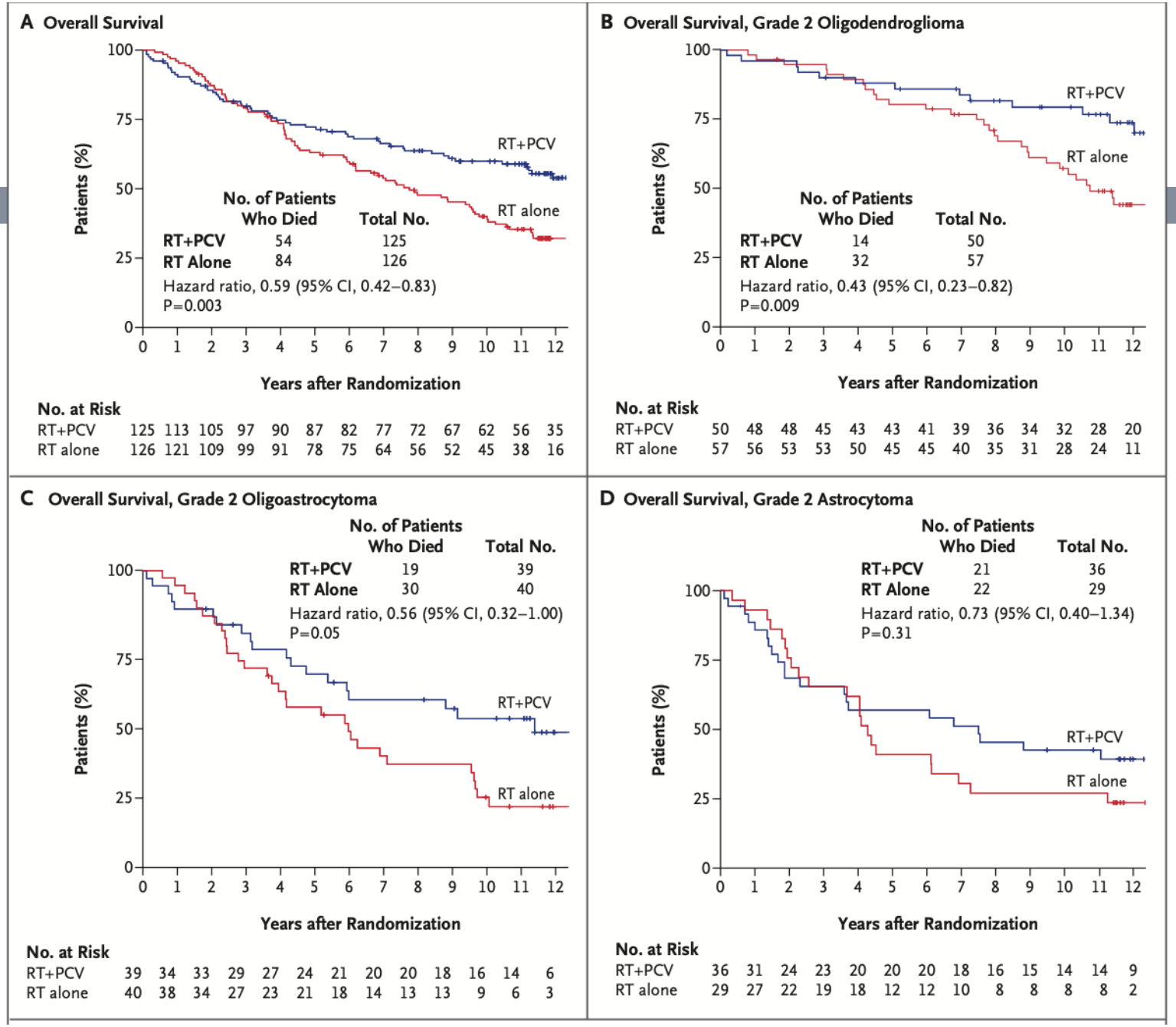




Buckner JC et al. N Engl J Med 2016; 374:1344-55

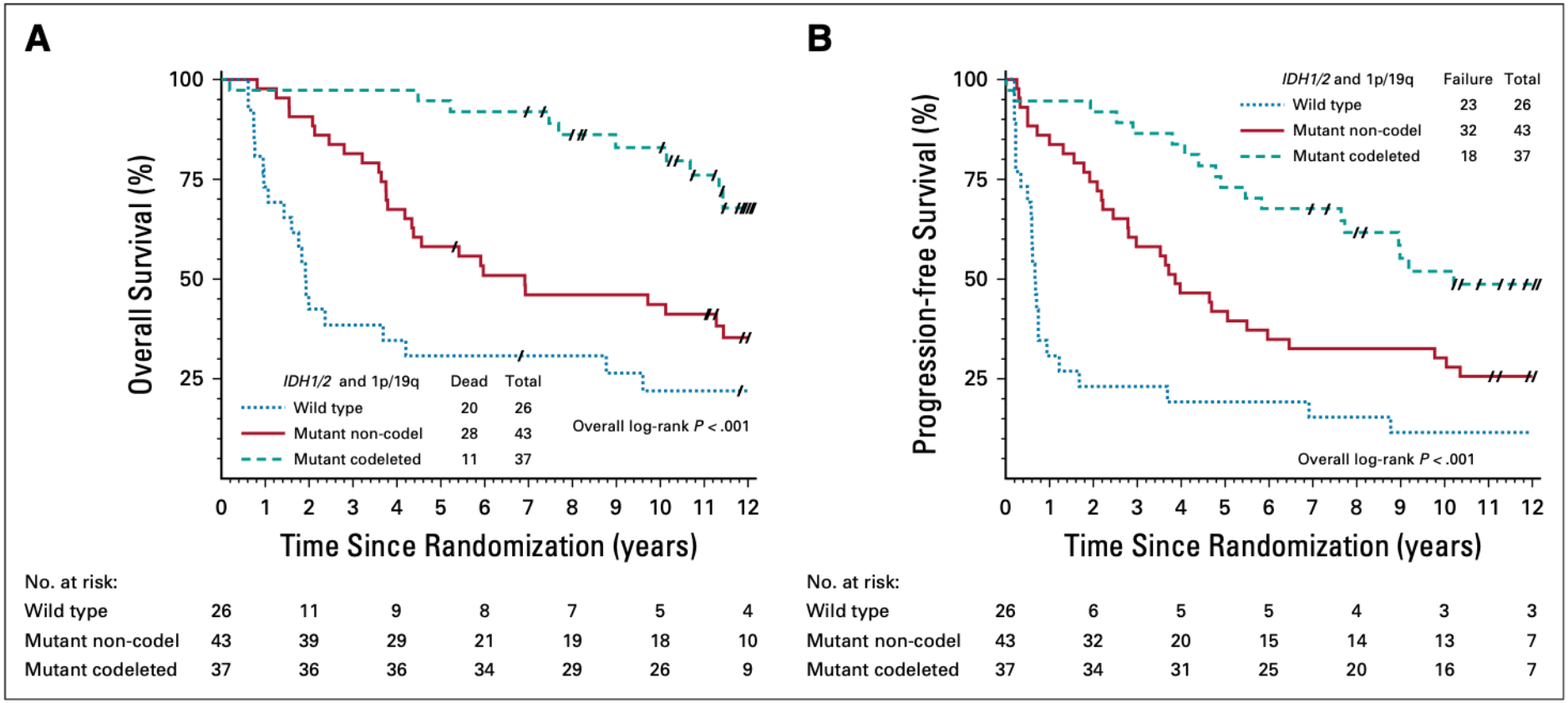


Buckner JC et al. N Engl J Med 2016;374:1344-55



Buckner JC et al. N Engl J Med 2016;374:1344-55

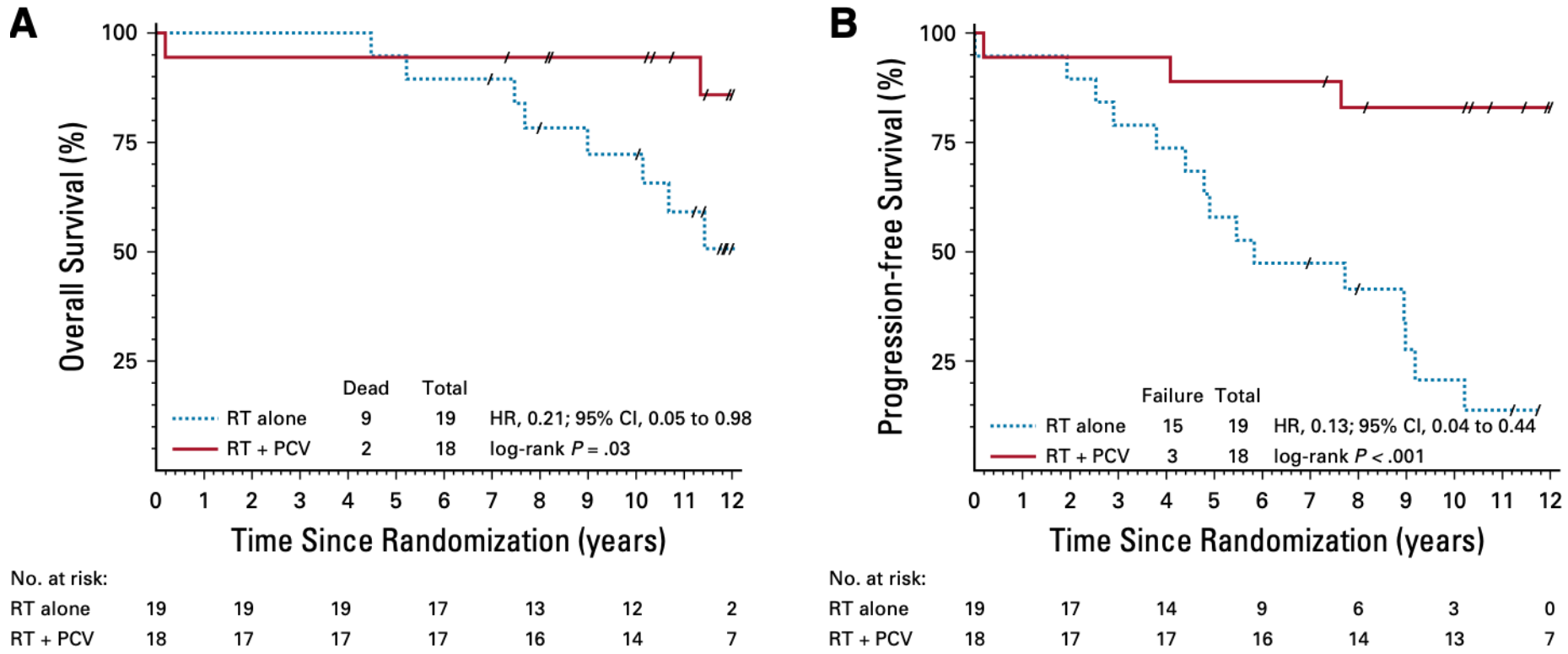
RTOG 9802 acc to IDHmut/wt/codel



IDHmut has longer survival than wt, regardless of treatment

Bell EH et al. J Clin Oncol 2020 Oct 10;38(29):3407-3417.

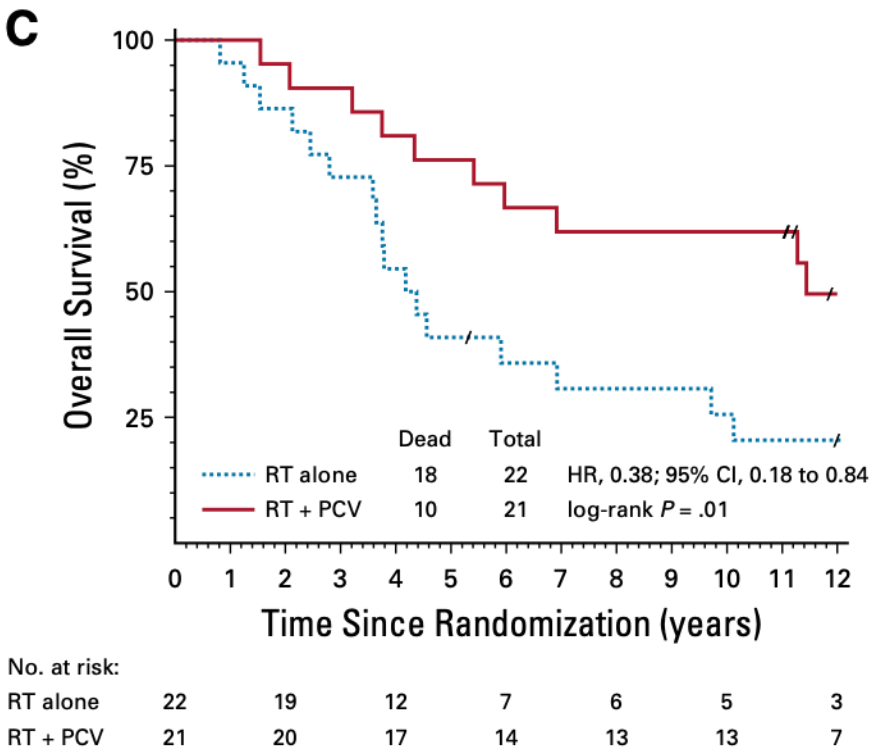
RTOG 9802; IDHmut/Codel

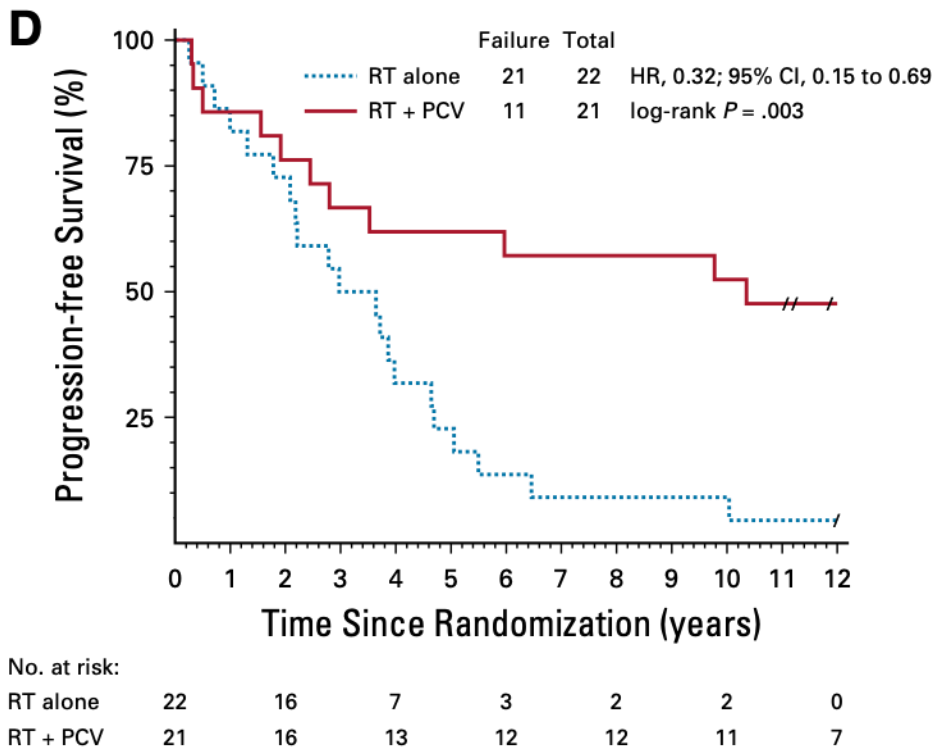


Significantly improved PFS & OS by adding PCV

Bell EH et al. J Clin Oncol 2020 Oct 10;38(29):3407-3417.

RTOG 9802; IDHmut/non-codel

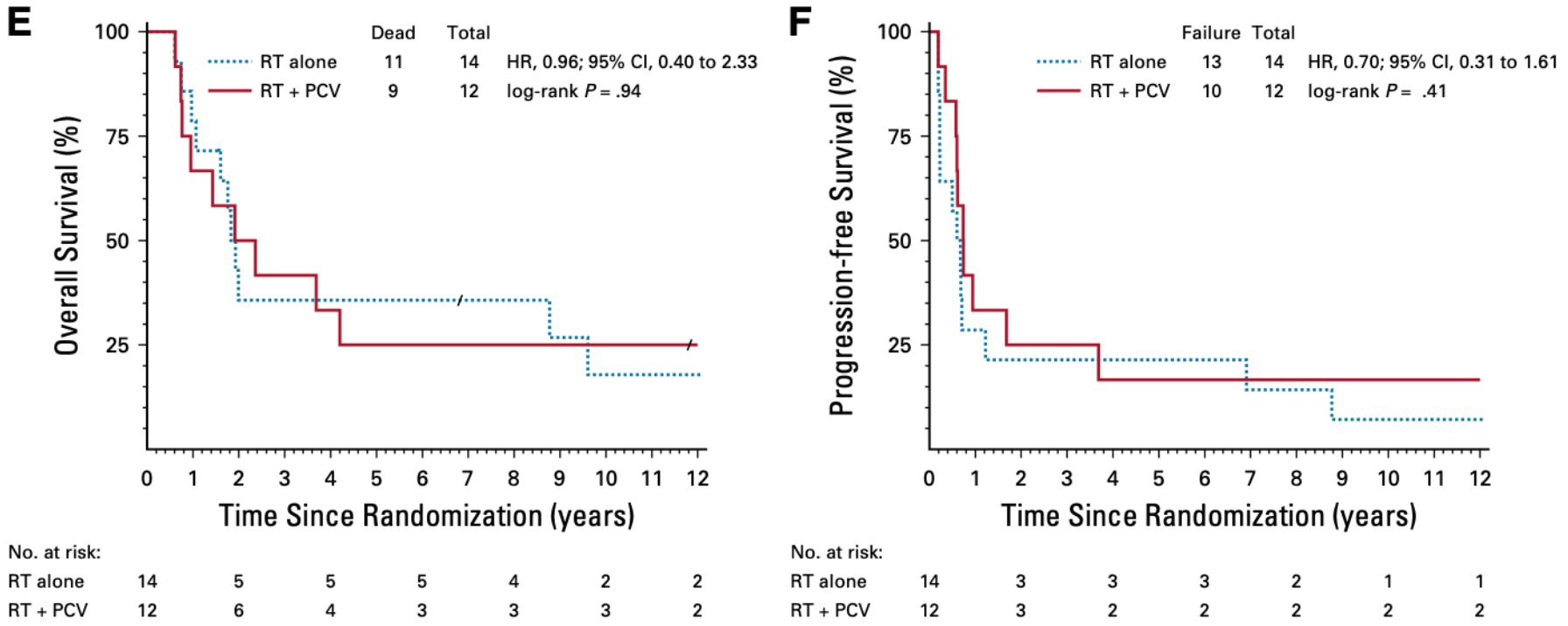




Significantly improved PFS & OS by adding PCV

Bell EH et al. J Clin Oncol 2020 Oct 10;38(29):3407-3417.

RTOG 9802; IDHwt



No Significant PFS / OS advantage by adding PCV

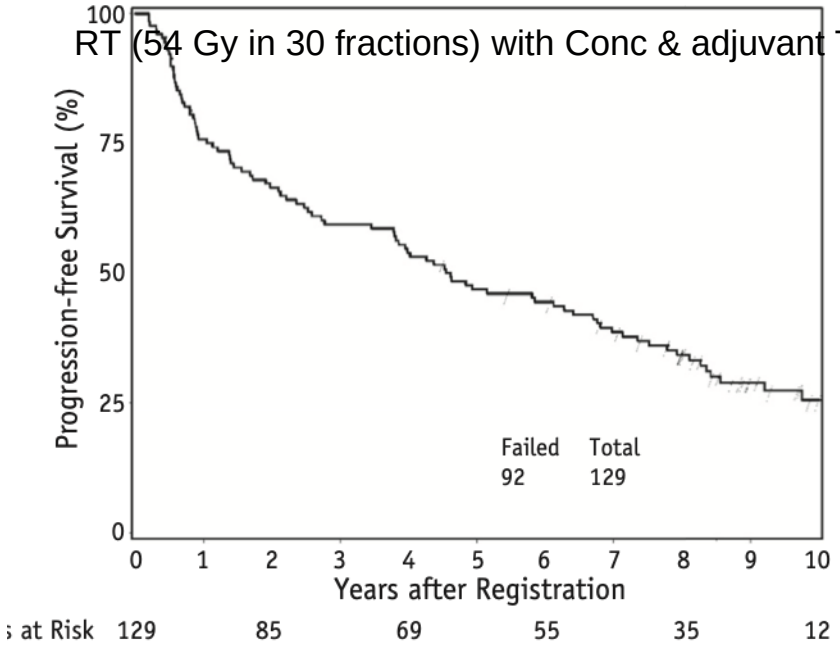
Bell EH et al. J Clin Oncol 2020 Oct 10;38(29):3407-3417.

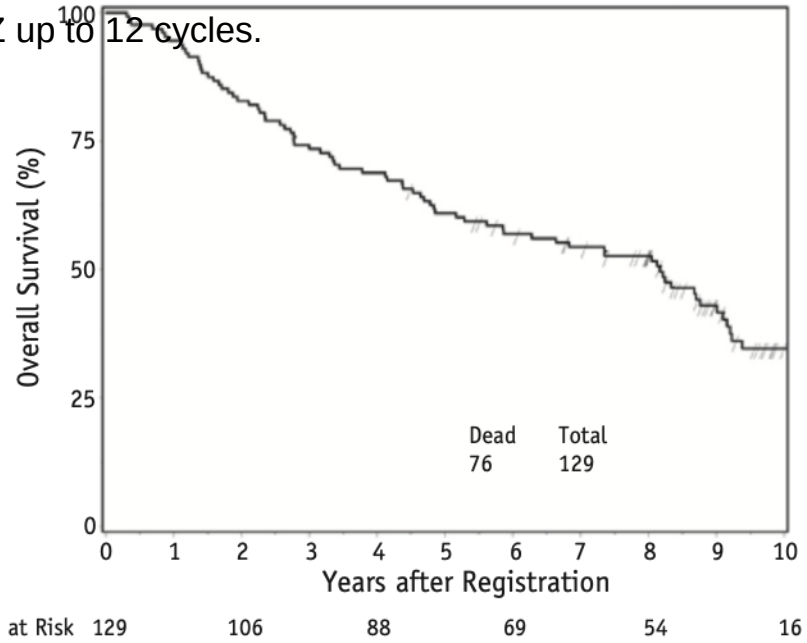
Can TMZ replace PCV?

RTOG 0424-single arm phase 2

High-risk LGG with >/=3 risk factors as defined by Pignatti

RT (54 Gy in 30 fractions) with Conc & adjuvant TMZ up to 12 cycles.





The MST was 8.2 years (95% CI, 5.6-9.1).

The 3-year OS rate was 73.5% (95% CI, 65.8%-81.1%). Five year OS rates were 60.9% (95% CI, 52.4-69.4). 10-year OS rates were 34.6% (95% CI, 25.1-44.1),

Fisher BJ etal. Int J Radiation Oncol Biol Phys, 2020; 107, 720-725

TMZ or PCV??

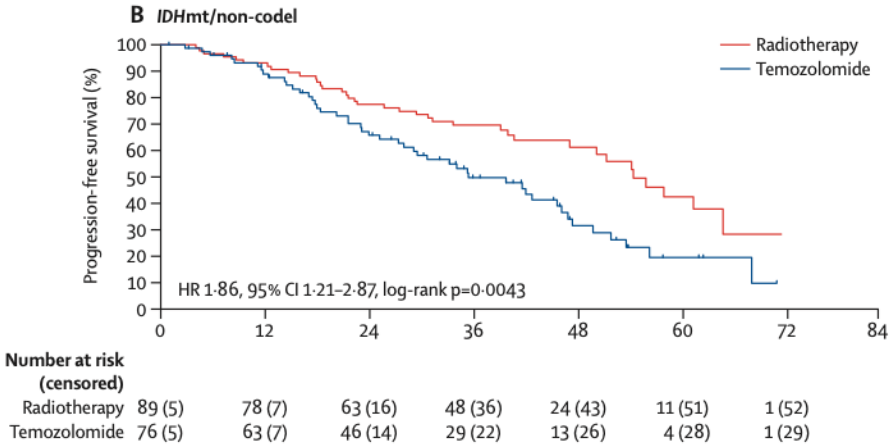
- Whether temozolomide should replace PCV is not clear.
- However, temozolomide may not be as efficacious as PCV in low-grade gliomas. For example, median survival in RTOG 0424 has not been reached, but early results demonstrated median PFS of 4.5 years and a 3-year PFS rate of 59%. These results with temozolomide appear inferior to those with PCV from RTOG 9802 in which median PFS was 10.4 years and the 3-year PFS rate was 75–80%, although cross-trial comparisons are fraught with difficulty because of differences in entry criteria and study populations.

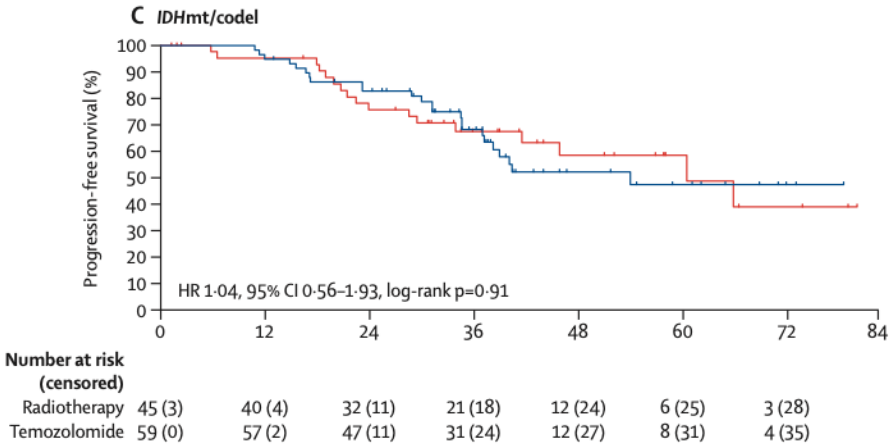
TMZ alone as initial adjuvant therapy?

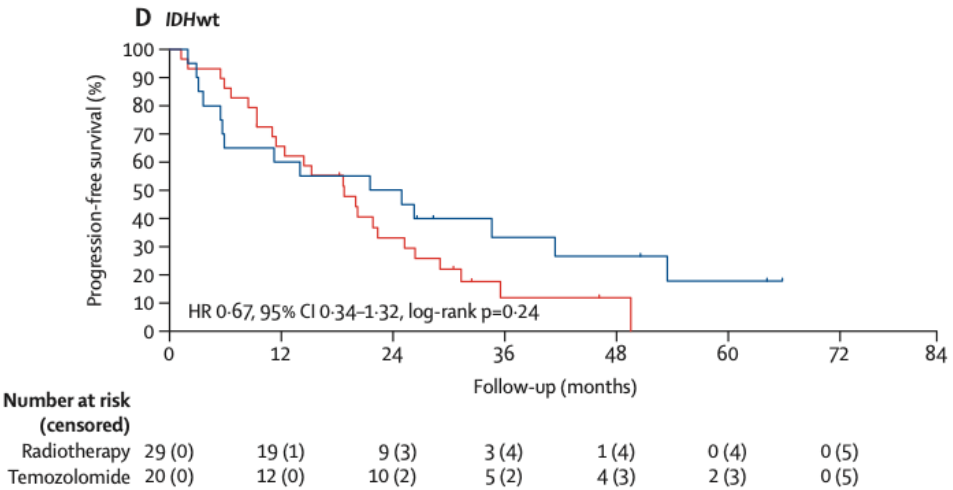
(deferring RT)

EORTC 22033-26033: TMZ Vs RT Phase 3 in High risk LGG

rological symptoms); 50.4Gy/28Fr Vs. TMZ 75 mg/m2/day, 21/28 x 12 cycles



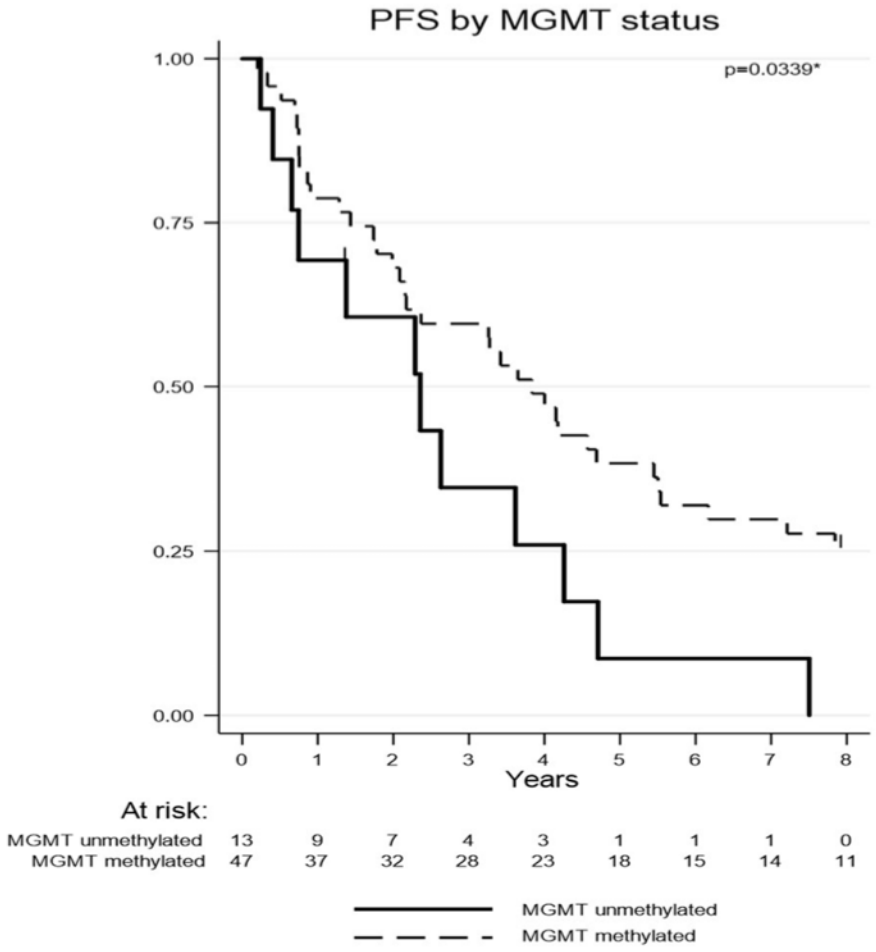


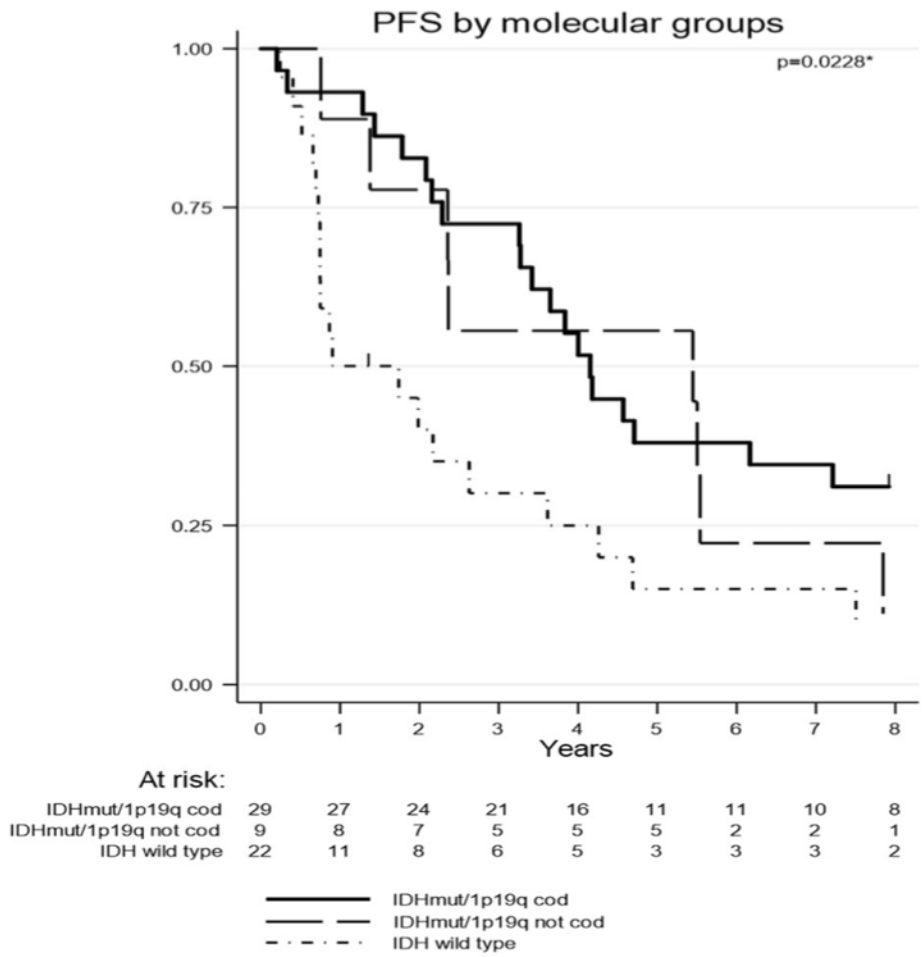


Baumert BG et al.
Lancet Oncol. 2016;17:1521-1532

Initial TMZ for LGG; AINO (Italian Association for Neuro-Oncology)

Phase 2





Ruda R et al. J Neurooncol 2019;145:115-123.

TMZ in LGG

Study	# Patients	Median F/U	Response Rate (CR + PR)	3y PFS	3y OS
Brada et al -	30	3 y	10%	66%	82%
Quinn et al -	46	<1 y	61%	NR	NR
Hoang-Xuan et al -	60	1.2 y	17%	NR	NR
Kesari et al -	44	3 y	20%	57%	81%
UCSF Wahl	120	7.5 y	6%	58%	81%

Table 4. Comparison to recent cooperative group studies utilizing adjuvant radiation

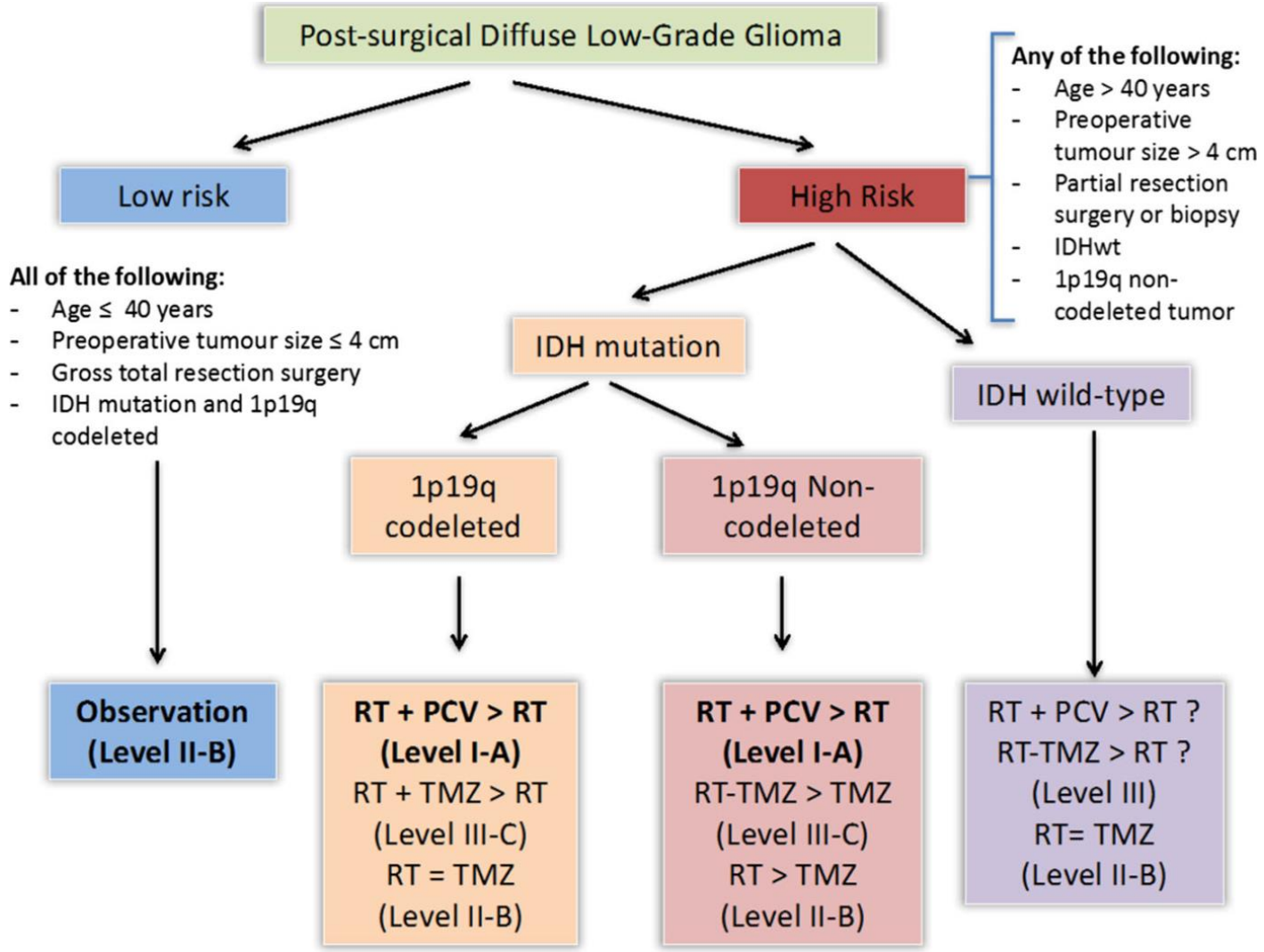
	RTOG 9802 RT[7]	RTOG 9802 RT+PCV[7]	RTOG 0424 RT+TMZ[23]	UCSF TMZ
Median age, y	40	41	49	39
Histology				
Oligodendroglioma	45%	40%	23%	48%
Oligoastrocytoma	31%	31%	22%	17%
Astrocytoma	23%	29%	55%	36%
Extent of resection				
GTR	9%	11%	19%	0%
STR	45%	41%	61%	77%
Biopsy only	47%	48%	16%	23%
Median PFS (y)	4.0	10.4	4.5	3.8
Median OS (y)	7.8	13.3	NR (>5 y)	9.7

Wahl M et al. Neuro Oncol 2017 Feb 1;19(2):242-251

IDHwt LGG

- Significantly worse prognosis compared with IDHmut
- Relatively small proportion and underrepresented in trials
- Some bear molecular similarity to glioblastoma (e.g., TERT mutations, loss of heterozygosity of chromosome 10). In such cases treat with immediate postoperative radiation and chemotherapy, regardless of extent of resection or other prognostic factors.
- The rational to use the same regimen as in glioblastoma, the Stupp regimen, is the fact that IDH-wt astrocytoma has the same biology and natural history is very similar to primary GBM

Diffuse LGG treatment algorithm



Thank You