Radiotherapy, systemic treatment and combined modality treatment of CNS tumors 'from past to present'

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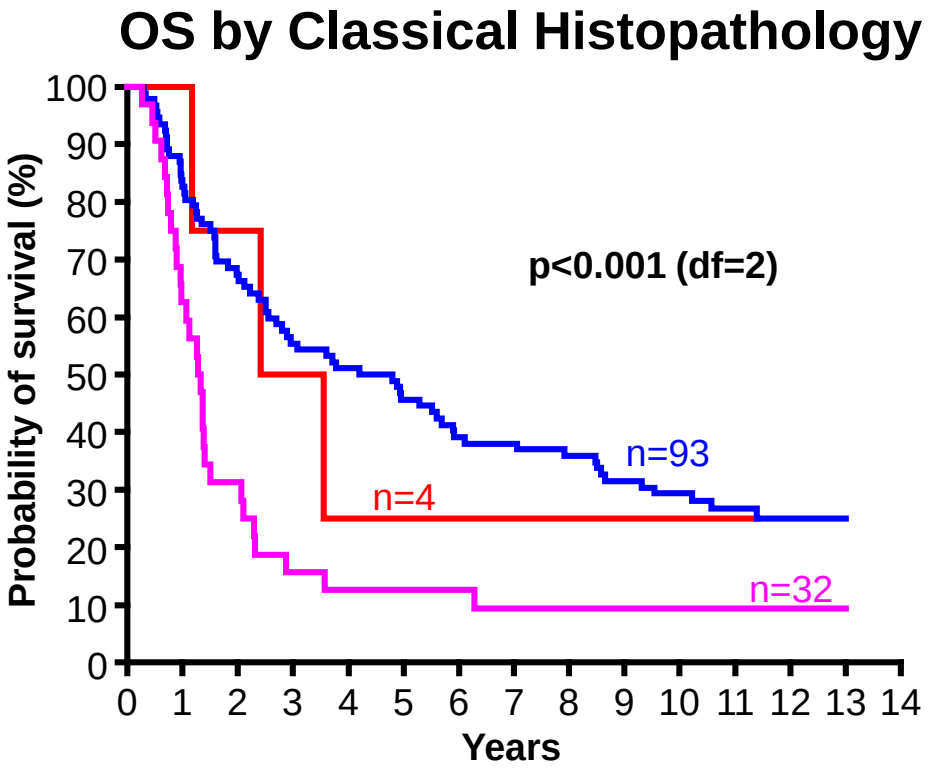
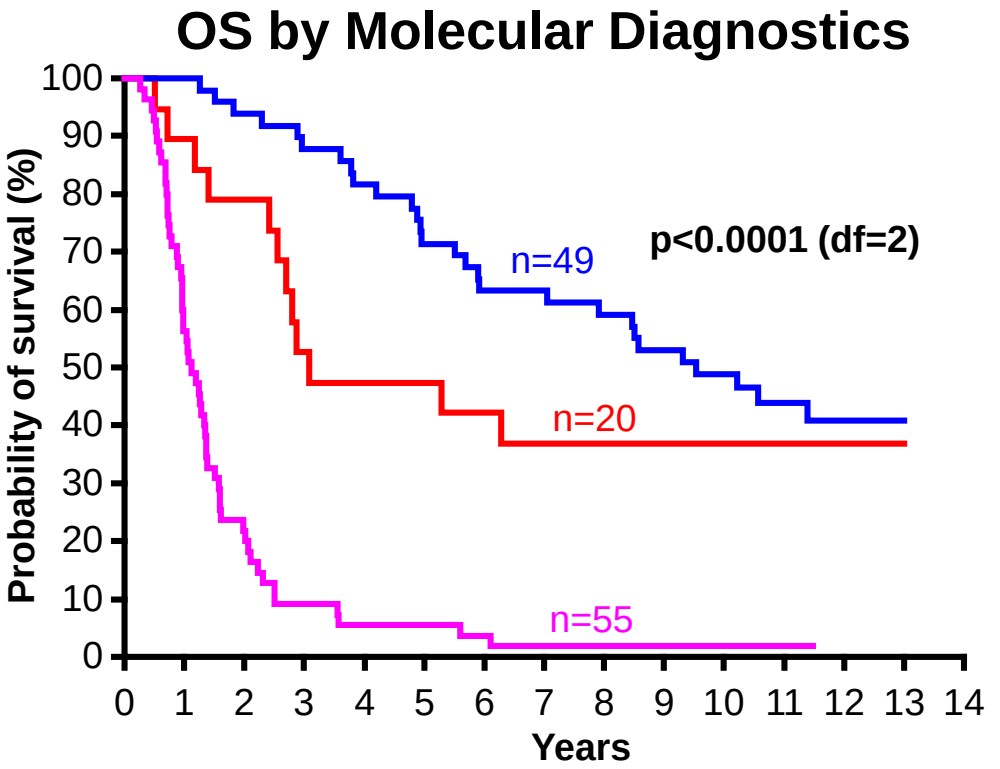
photons

Glioma in 2019: combining treatments?

- The major change: WHO 2016 requires the reclassification of knowledge
- Old trials were done on histology, with only a few trials allowing analyses in molecular groups
- And: old trials enrolled based on histology
  - Which include remarks on grade
- The latest shift: the understanding somne low grade glioma are more like gliobkastoma

Next Generation Sequencing Allows For More Precise Prognostic Classification

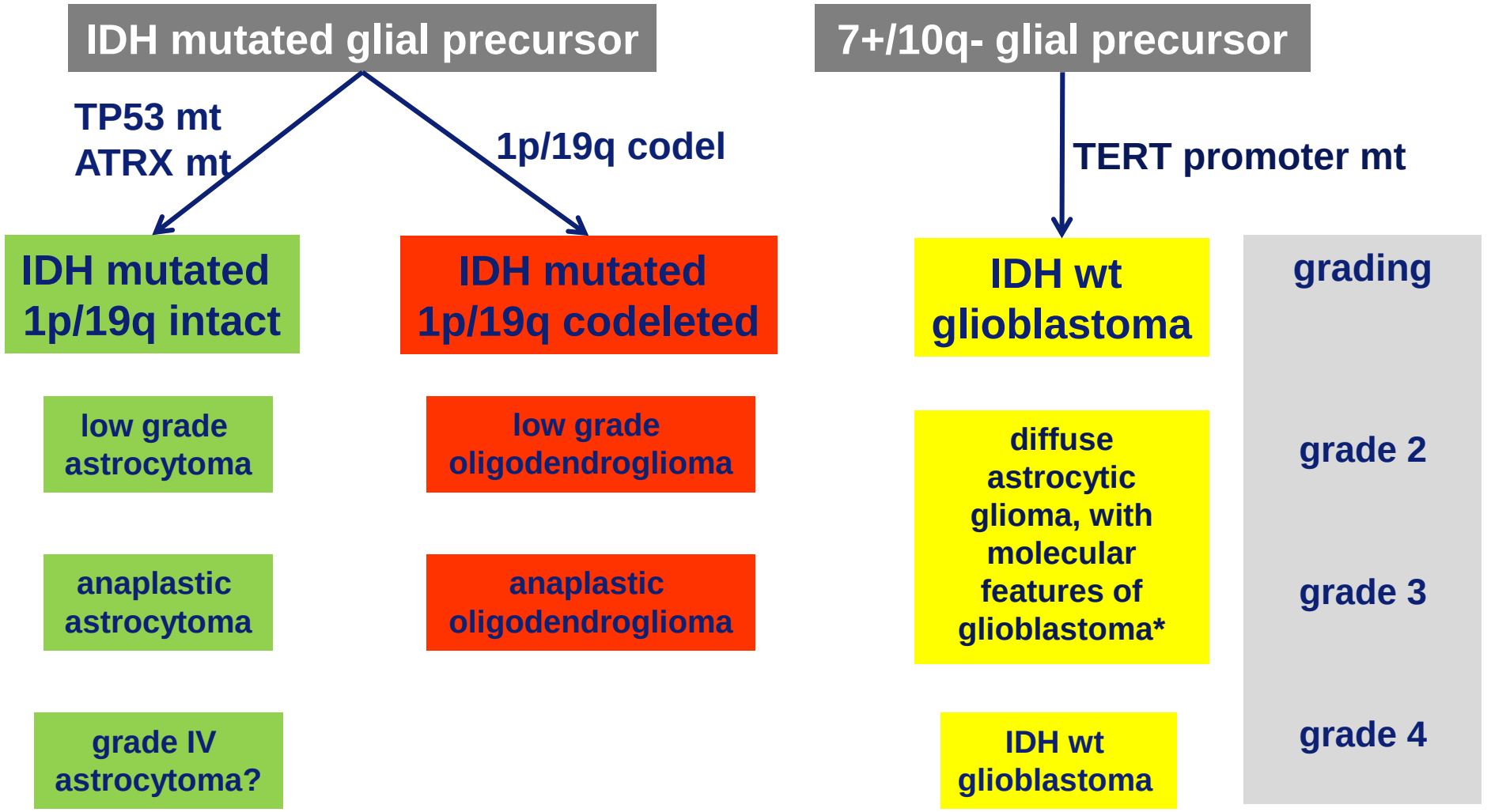




Tumor	Molecular Characteristics
oligodendroglioma	IDH mutated (mt), 1p/19q loss
astrocytoma	IDH mt
glioblastoma	Trisomy 7 & 10qLOH (7+/10q LOH), 10q LOH with EGFR amplification, or *TERT* mt without 1p/19q co-deletion

Dubbink HJ, *et al. Neuro Oncol* 2016; **18:**388–400.

A modified WHO 2016 classification for diffuse glioma



*Either 7+/10-, or EGFR ampl, or TERT promoter mt

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Louis et al, Acta Neuropathol 2016, 131:803820, Brat et al, Acta Neuropathol 2018 (c-IMPACT-NOW

OS in molecularly defined anaplastic glioma as reported in large phase III trials

study	histology	Molecular subtype	treatment	n	Median OS	Median PFS
RTOG 9802	Low grade glioma	IDH mutated (all) IDHwt	RT/PCV or RT RT/PCV or RT	71 42	13.1 yrs 5.1 years	
EORTC 26951	Anaplastic oligodendroglioma	1p/19q codeleted IDHmt 1p/19q intact 7+/10q-/TERTpmt	RT/PCV RT/PCV RT or RT/PCV	43 23 55	NR (>14 yrs) 8.3 yrs 1.13 yrs	147 4.2 yrs NS
RTOG 9402	Anaplastic oligodendroglioma	1p/19q IDHmt (all)	RT/PCV	59	14.7 yrs	8.4 yrs
RTOG 9804	Anaplastic astrocytoma	IDH mt (IHC) IDHwt	RT/chemo	49 54	7.9 yrs 2.8 yrs	
NOA4	Grade III	1p/19q codeleted IDHmt 1p/19q intact IDHwt	RT or chemo	66 83 58	NR 7.0-7.3 yrs 3.1 – 4.7 yrs	

Anaplastic glioma	Reported survival after RT/chemo
Oligodendroglioma, IDHmut & 1p/19q codeleted	> 14 years
Astrocytoma, IDH mutated	7 - 8 years
Astrocytoma IDH wt	1 – 4.7 yrs

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Some historical facts

- Early trials on radiotherapy combined grade 3 and 4 glioma
- Used whole brain radiotherapy
- CT scan introduced in the late seventies
- Switch to partial brain radiotherapy in the early eighties

RCT's exploring radiotherapy in high grade glioma

RT

No RT

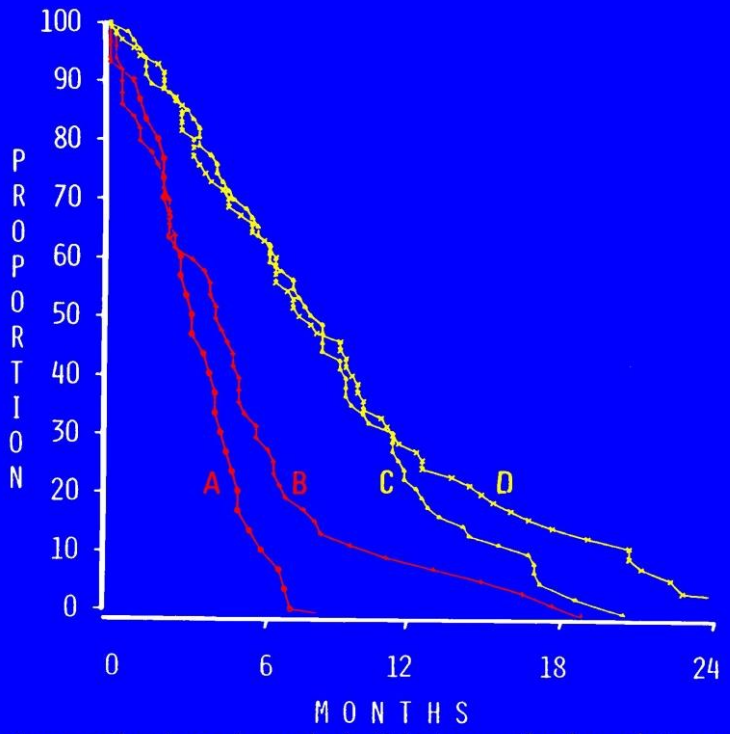


FIG. 1. Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

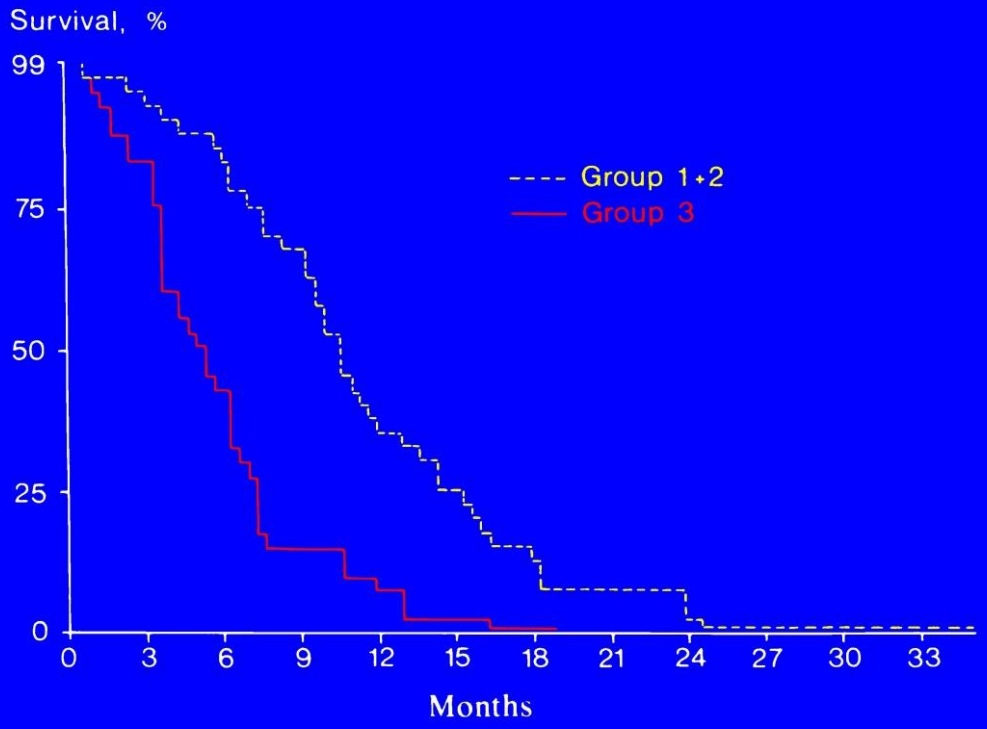
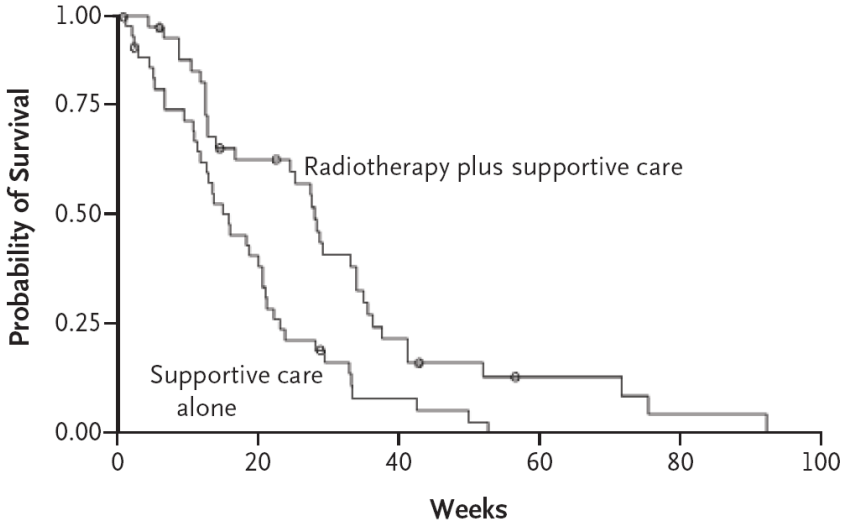


FIG. 1. Survival of the three groups in the trial.
Group 1: Surgery + radiotherapy + bleomycin;
Group 2: Surgery + radiotherapy + placebo;
Group 3: Surgery alone.

Walker et al New Engl J Med 1980;303:1323-9

Kristiansen et al Cancer 1981;47:649-52

The value of RT in elderly glioblastoma patients: the ANOCEF trial



No. at Risk					
Supportive care alone	42	17	3	0	0
Radiotherapy plus supportive care	39	24	8	3	1

HR 0.47 (95% CI, 0.29 to 0.76; P = 0.002)
(confirmed glioblastoma only)

Randomization: best palliative care vs RT 50 Gy in fractions of 1.8 Gy

Eligible:

- Newly diagnosed glioblastoma or AA
- KPS ≥ 70
- ≥ 70 years of age

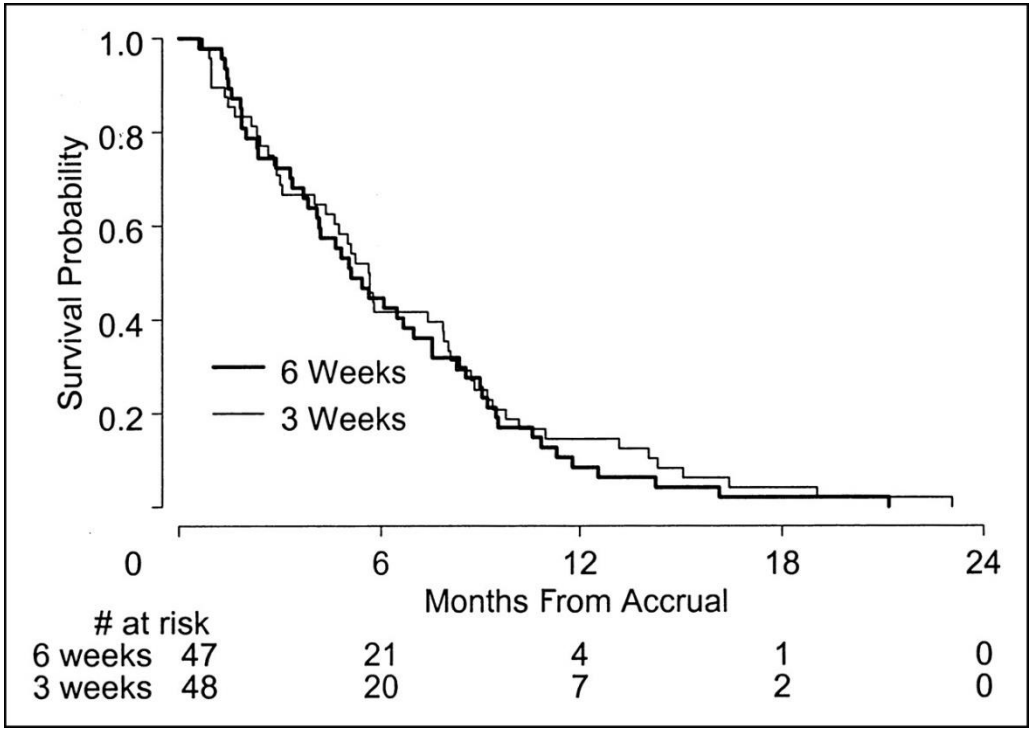
Entered: 85 patients (81 confirmed glioblastoma)

Treatment	Median OS	Median PFS
Best palliative care	16.9 wks	5.4 wks
RT	29.1 wks	14.9 wks

Keime-Guibert et al, NEJM 2007;356:1527-35

Short vs long RT in poor prognosis patients (60 Gy in 30 fractions vs 40 Gy in 15 fractions)

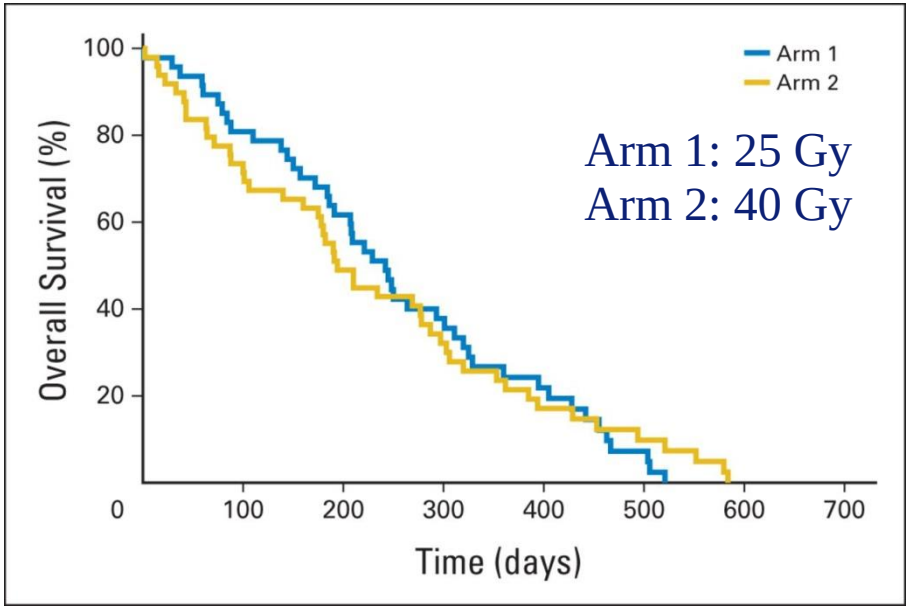
- eligibility criteria included age ≥ 60 years, histologically confirmed GBM, and KPS ≥ 50
- 100 patients randomized : 51 to standard RT and 49 to shorter-course treatment.
- Median OS similar : 5.1 months for the 6-week group and 5.6 months for the 3-week group (hazard ratio, 0.89; 95% CI, 0.59 to 1.36; *P* = .57;



(Roa et al, J Clin Oncol. 2004;22:1583-8)

Can we shorten RT further? 40 Gy vs 25 Gy in elderly and frial glioblastoma

- Phase III trial in elderly and frail patients, n = 98
  - ≥ 50 yrs, KPS 50-70 (frail)
  - ≥ 65 yrs KPS 80-100 (elderly)
- Randomized to either 40 Gy in 15 fractions or 25 Gy in 5 fractions
  - Age > 65: 70% in 40 Gy arm, 54% in 25 Gy arm
- Median OS not inferior
  - 40 Gy: 6.4 mo, 95% CI [5.1 – 7.6]
  - 25 Gy: 7.9 mo, 95% CI [6.3 – 9.6]



Roa et al, J Clin Oncol 2015;33:4145-4150

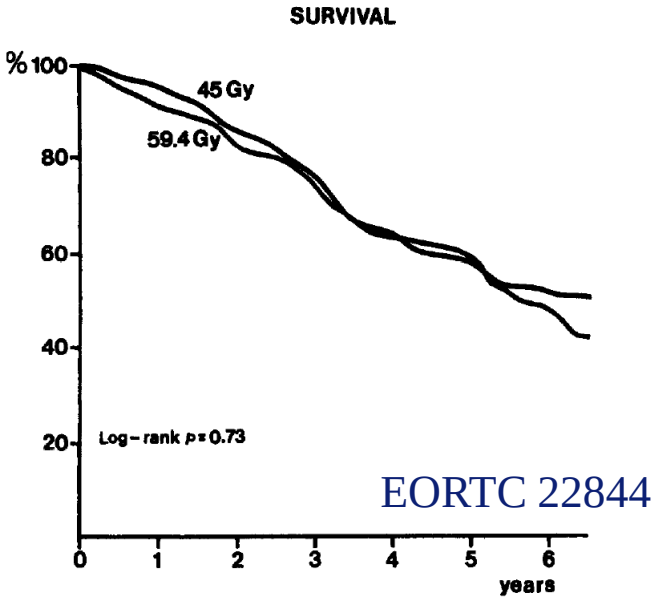
High dose boost trials to tumors with limited diameter

- No improvement of 15-24 Gy SRS boost prior to conventional 60 RT[1]
- No improvement of a 60 Gy I^{125} interstitial brachytherapy boost after 50-60 Gy conventional RT[2,3]
- Benefit after conventional 60 Gy followed by 60 Gy brachytherapy with hyperthermia?[4]
  - Small trial, highly selected patients

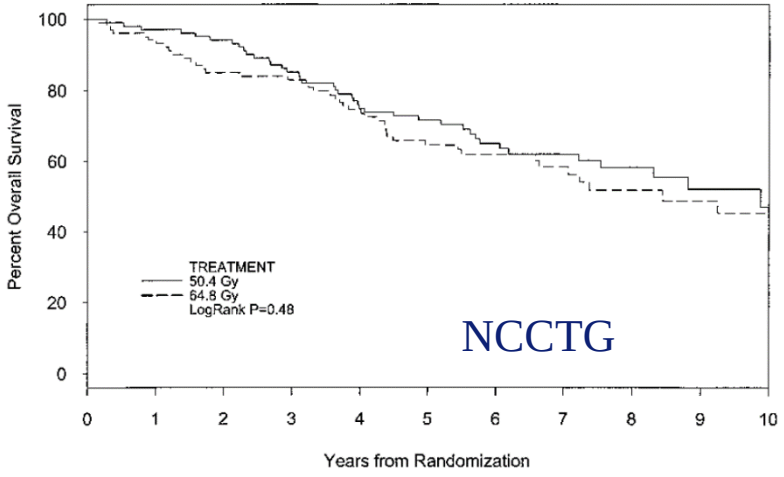
[1]Souhami et al, Int J Radiation Oncology Biol Phys 2004;60:853-860, [2]Selker et al, Neurosurg 2002;51:343-357, [3]Laperriere et al, Int J Radiation Oncoloy Biol Phys 1998;41:1005-1011, [4]Sneed et al, Int J Radiation Oncology Biol Phys 1998;40:287-295

The dose and low grade glioma

- Two dose finding trials
  - EORTC : 45 Gy vs 59.4 Gy
    - n = 379 pts
  - NCCTG: 50.4 Gy vs 64.8 Gy
    - n = 203 pts
- Neither trial improved outcome after higher dose RT
- Standard of care: conclusion
  - US: 54 Gy
  - Europe: 50.4 Gy



EORTC 22844



NCCTG

Shaw et al, J Clin Oncol 2002;20:2267-76, Karim et al, Intern J Radiation Oncol Biology Physics 1996;36:549-56

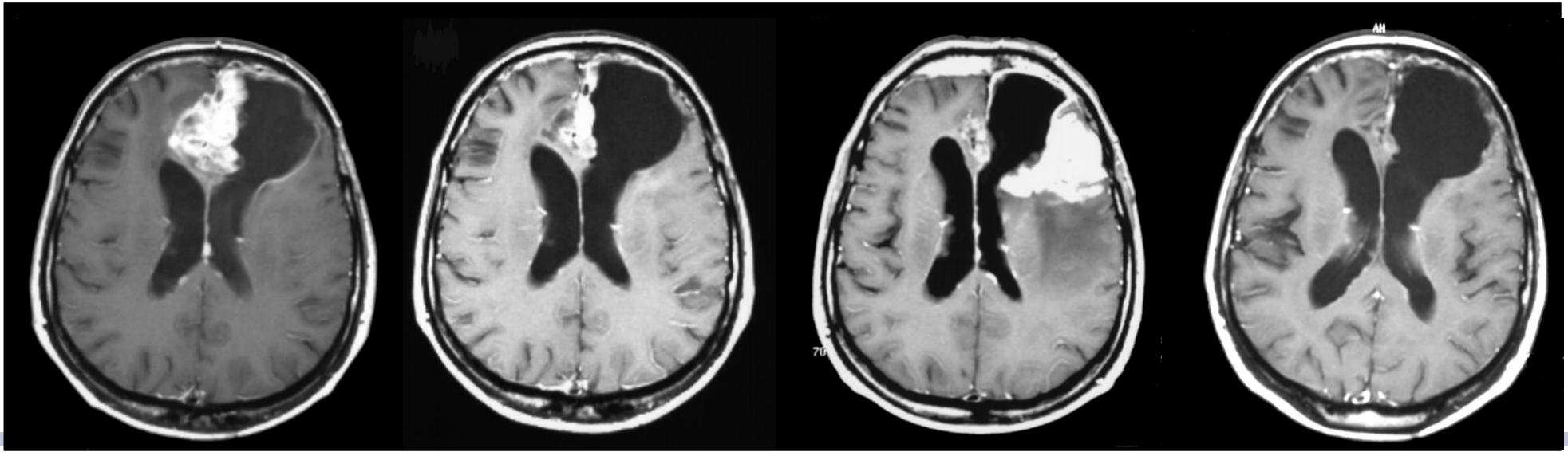
The dose of radiotherapy in glioma

- Well established
  - In glioblastoma:
    - No further benefit > 60 Gy
    - Hyperfractionated RT studies: no increased benefit
    - Hypofractionated RT indicated in frail and elderly
  - In low grade:
    - More is not better
- Not so well established
  - How does shorter RT schedules affect outcome of combined chemotherapy/radiotherapy
  - In those favorable IDHmt lower grade glioma: do we need 50.4 Gy?

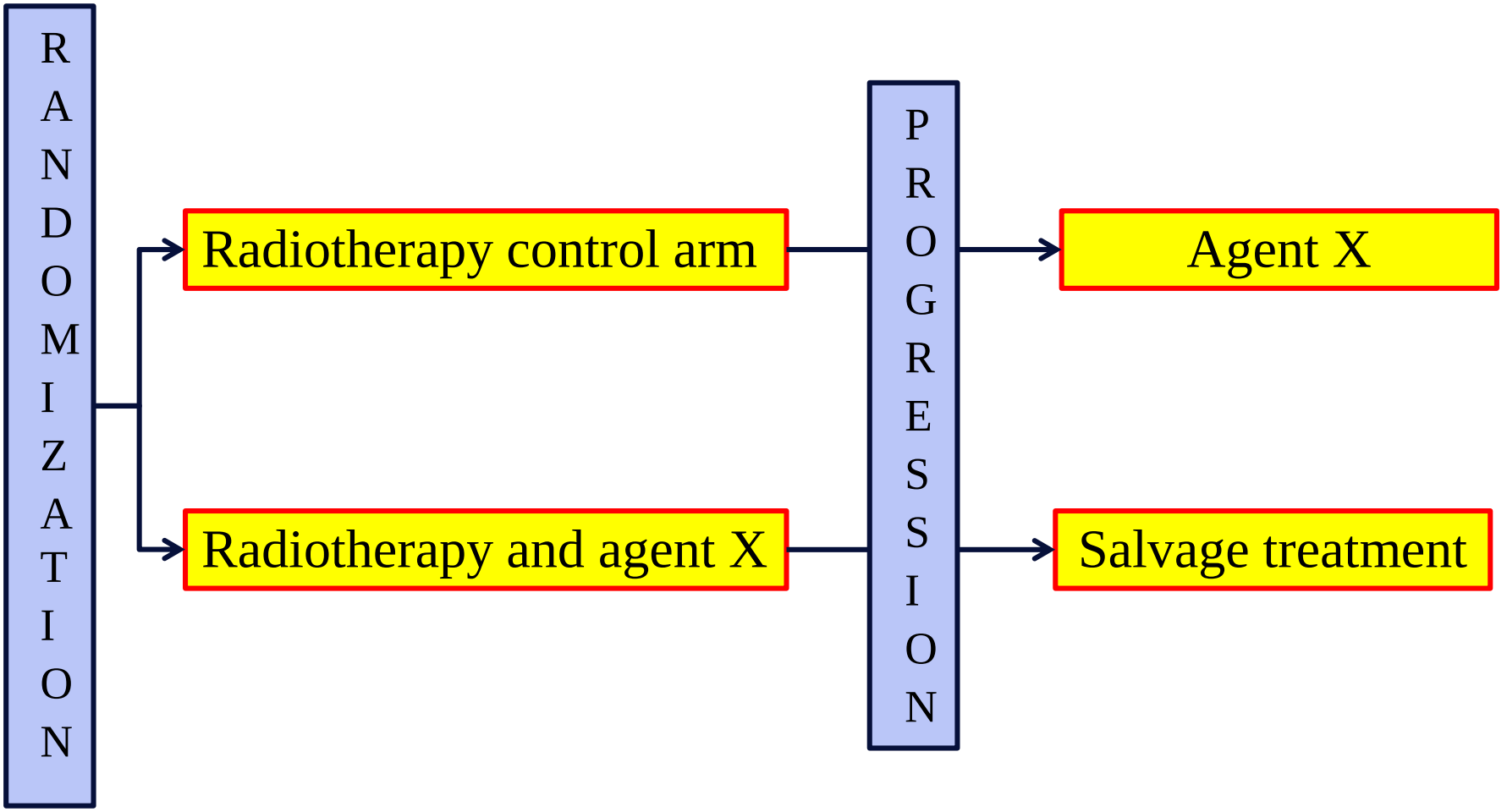
1994: a 46 year old patient with a recurrent anaplastic oligodendroglioma

Erasmus MC Kanker Instituut

- 1986 resection, RT for low grade oligodendroglioma
- 1992 re-resection for left frontal anaplastic recurrence
- April 1993 PD, start PCV chemotherapy
  - 6 cycles PCV: partial response
- October 1994 PD, retreatment with PCV chemotherapy
  - PR again, discontinuation PCV for hematological toxicity

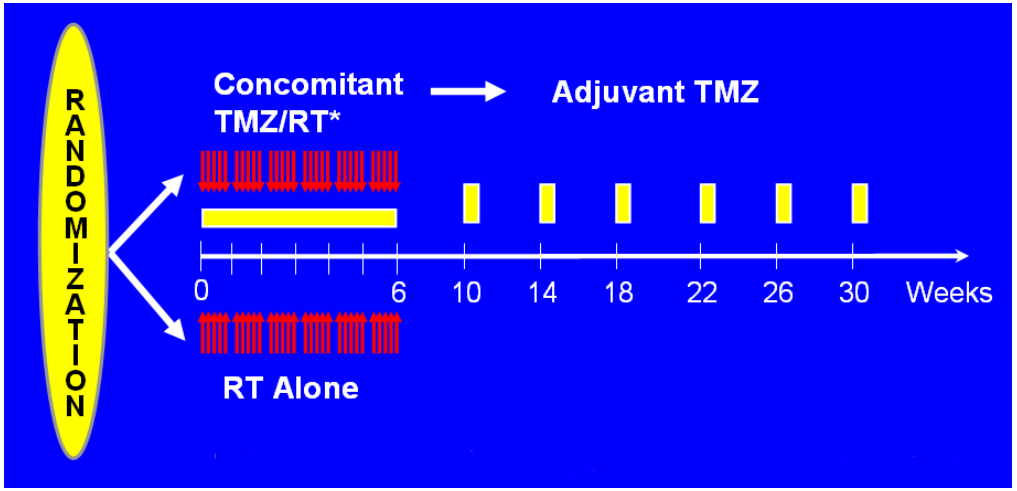


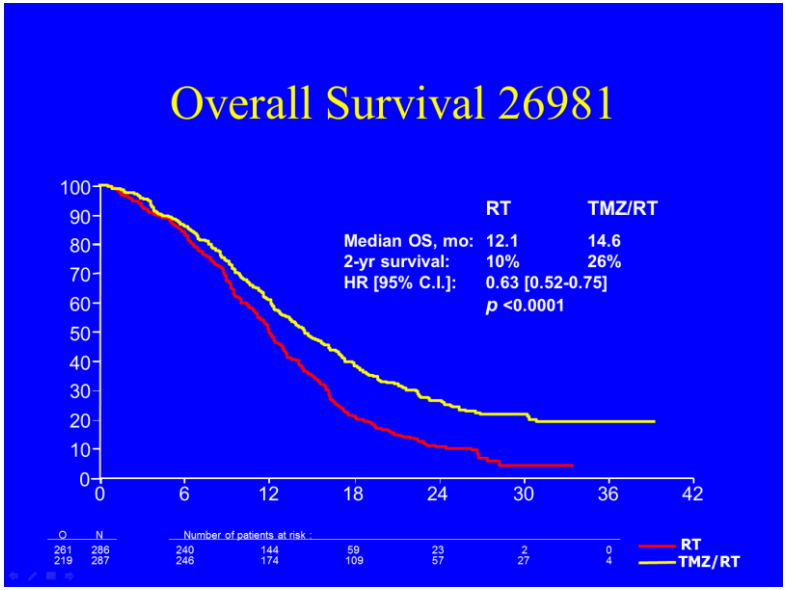
Trials on adding chemotherapy to radiotherapy in glioma: crossover at PD



- Studies with crossover design: typical endpoint PFS
- OS disturbed by treatment effects at progression
- Cross over is a major issue in trials on agents that are avialable on the market

Temozolomide chemo-irradiation in newly diagnosed glioblastoma: EORTC 1981



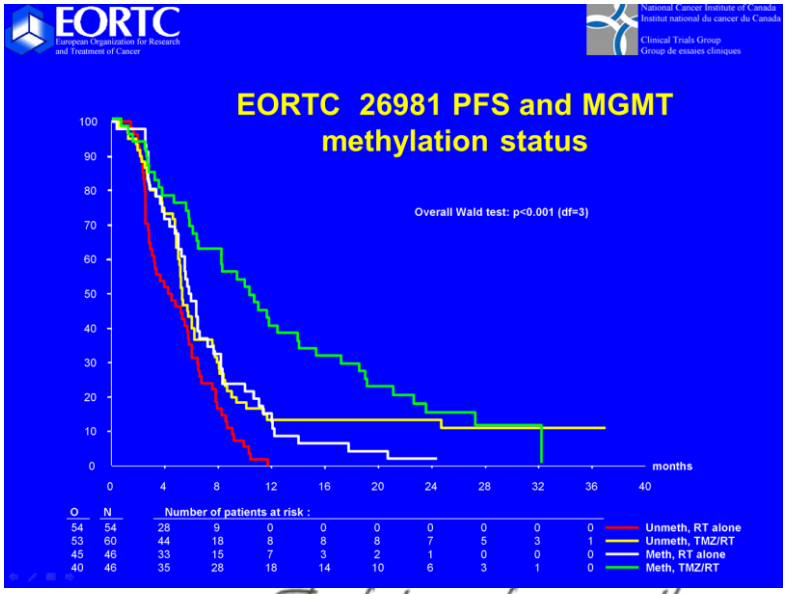


EORTC 26981:

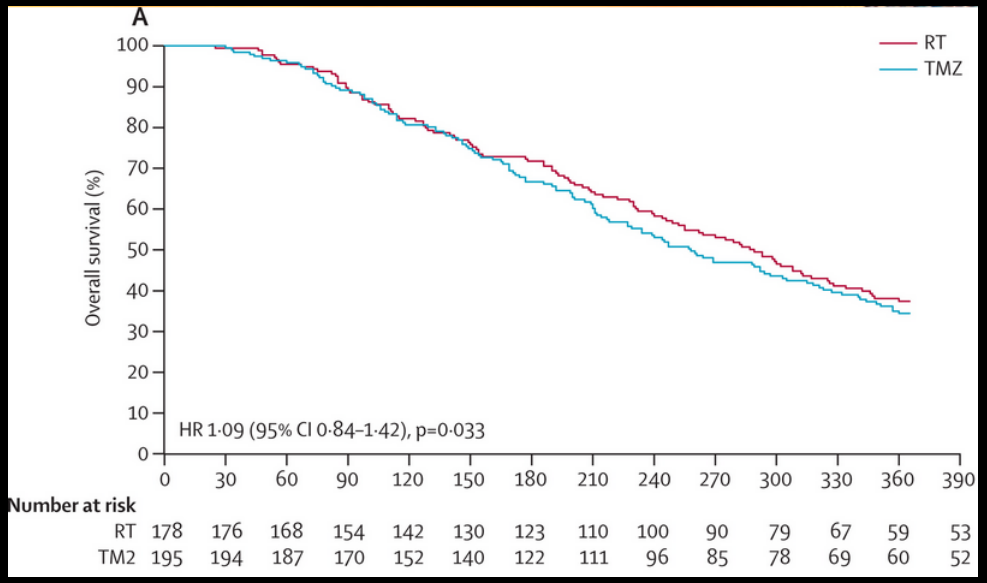
- glioblastoma: chemotherapy insensitive
- concurrent and adjuvant temozolomide

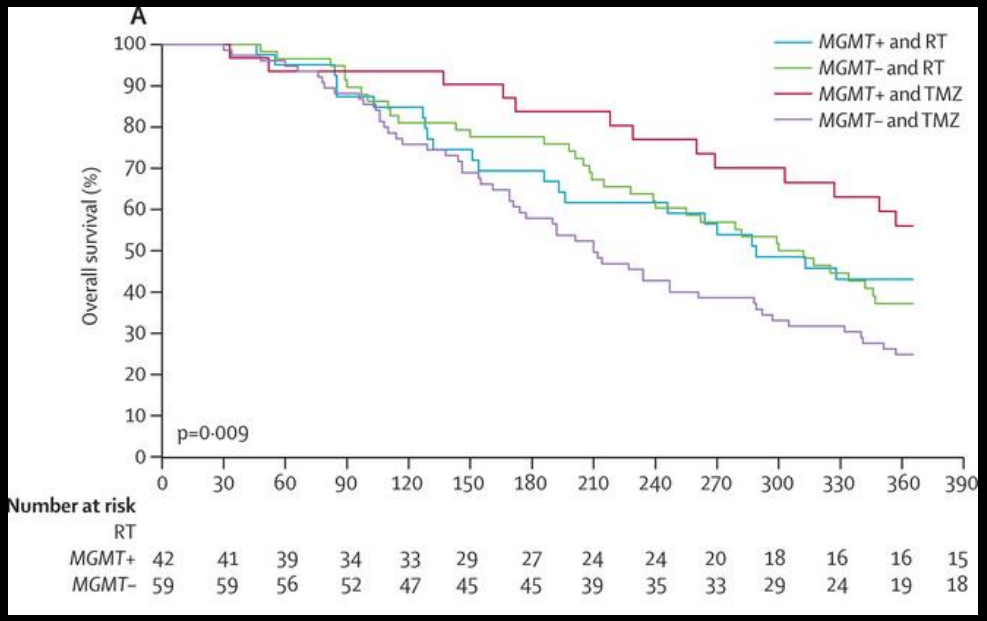
➢ Temozolomide improves outcome

➢ **Benefit of temozolomide in MGMT promoter methylated tumors**



NOA-8 trial: RT versus TMZ in elderly glioblastoma patients





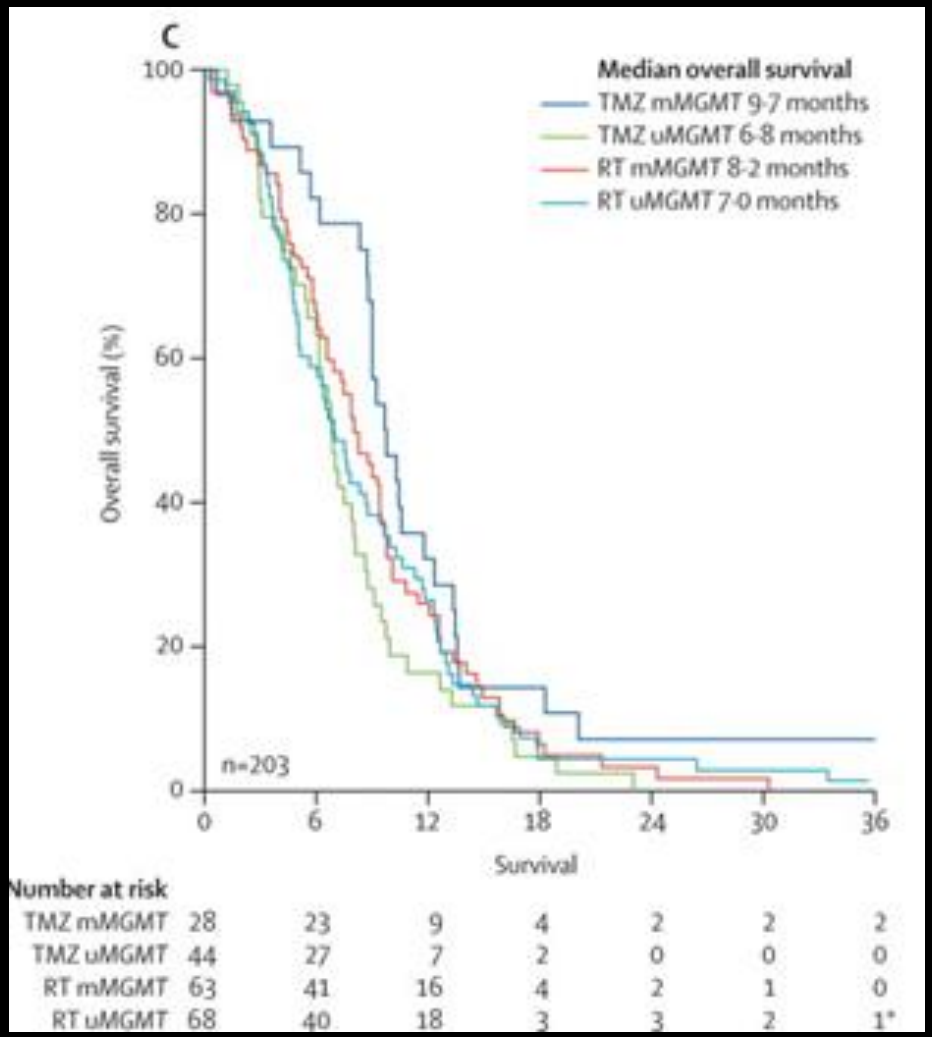
- 373 elderly patients randomized between RT and temozolomide (1 on week on/one week off schedule)
- No major difference in OS

But: Event Free Survival

- In patients with MGMT promoter methylation: longer after TMZ
  - 8·4 months vs 4·6 mo after RT
- MGMT unmethylated: longer EFS after RT
  - 3·3 months vs 4·6 months after RT

Wick et al, NOA-8 trial, RT versus TMZ
Lancet Oncol 2012;13:707-15

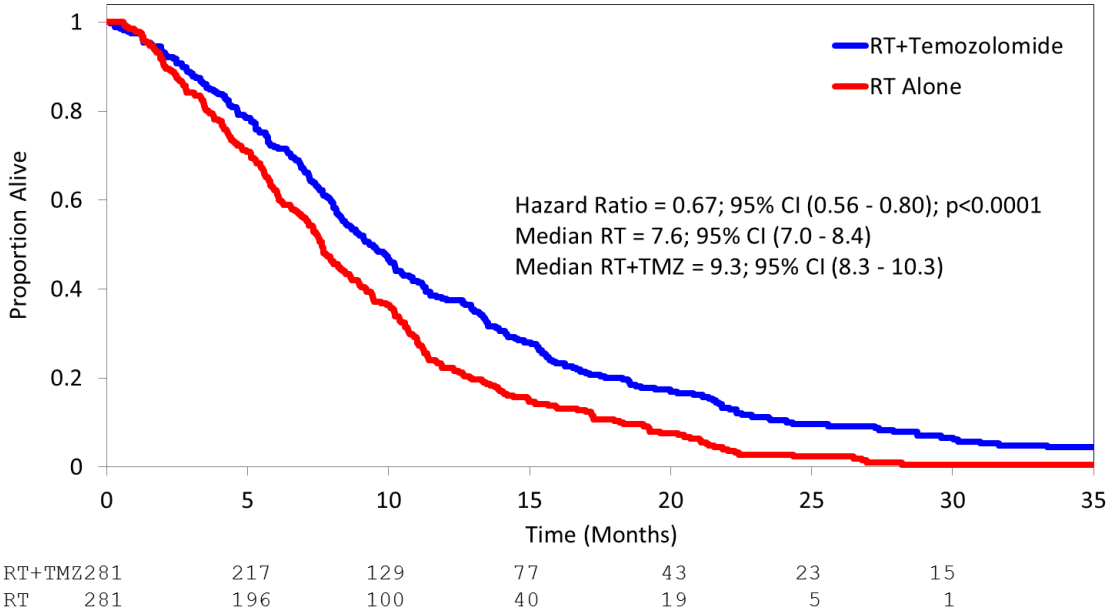
Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

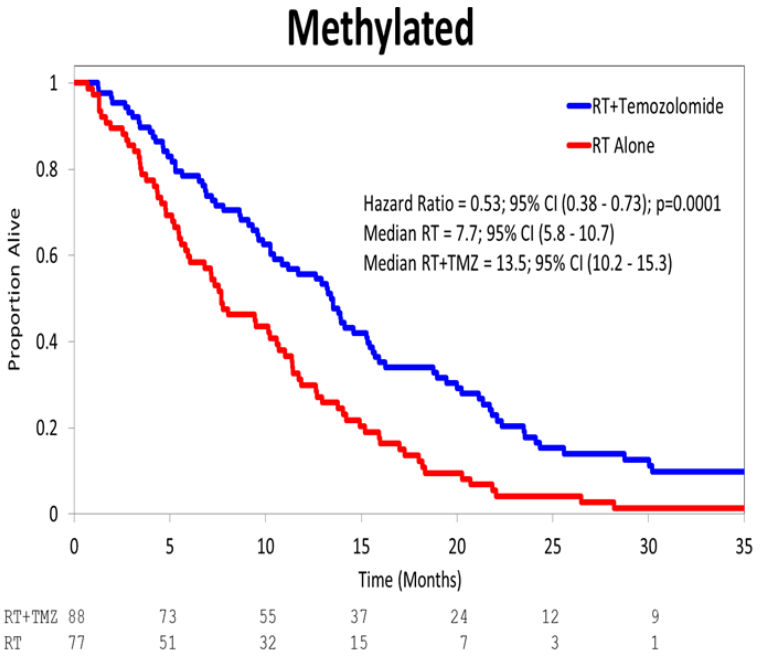


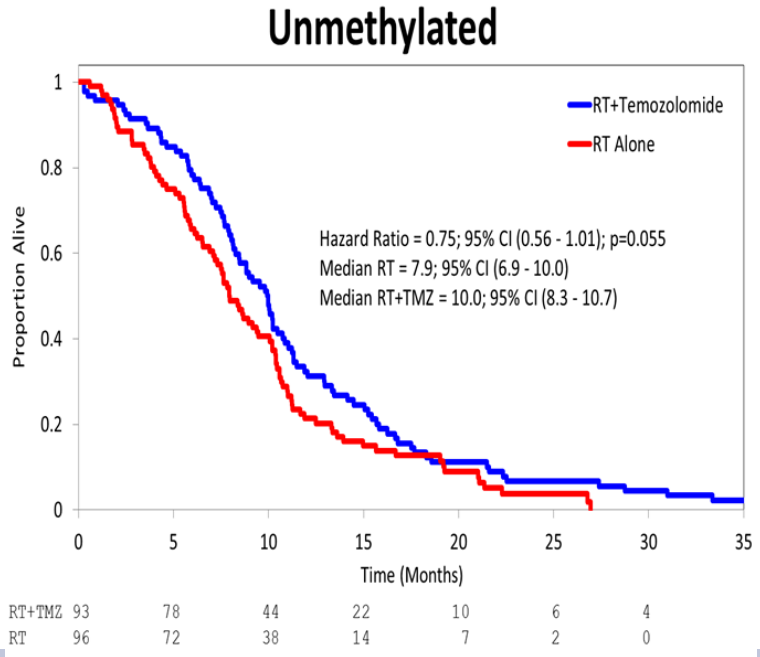
- For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy
  - HR for temozolomide vs standard radiotherapy: 0·35 [0·21-0·56], p<0·0001
  - HR for hypofractionated vs standard radiotherapy: 0·59 [95% CI 0·37-0·93], p=0·02
- OS after TMZ in MGMT methylated patients: 9·7 months [95% CI 8·0-11·4]

Malmström et al, Nordic trial
Lancet Oncol 2012;13:916-26

The elderly trial: a step back in glioblastoma targeted treatment?



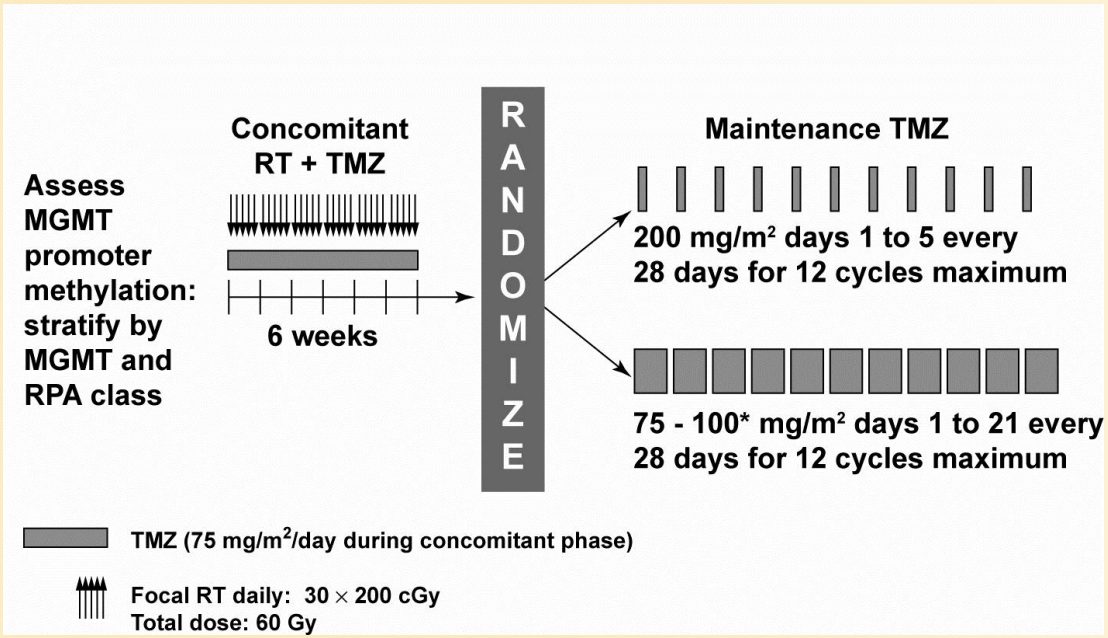




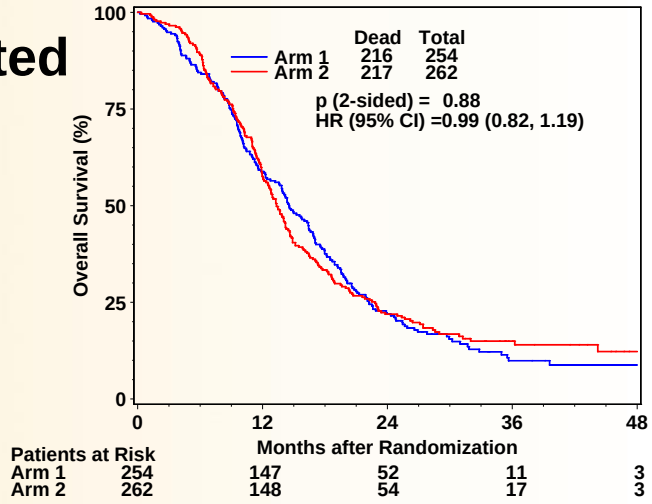
	12 mo OS	
	unmeth	meth
RT	29.9 (19.9-40.5)	21.3 (13.7-30.0)
RT + TMZ	55.7 (44.7-65.3)	32.3 (23.0-42.0)

The “elderly trial’’; Perry et al, NEJM March 2017

OS RTOG 0525 Standard TMZ (1-5/28 days) vs dose dense TMZ (3 wks on/1 wk off) Outcome by methylation status

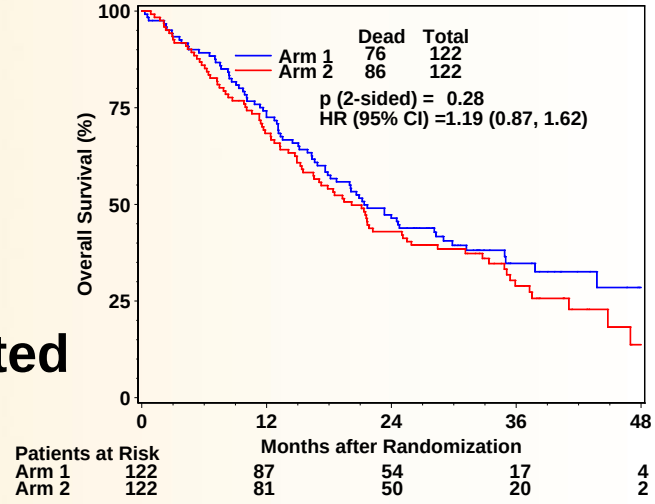


unmethylated



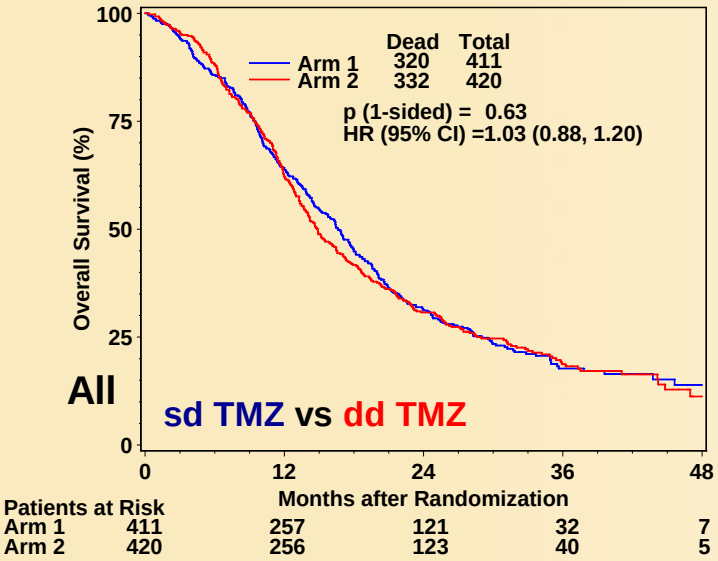
RTOG 0525: Will dose intense temozolomide deplete MGMT based resistance?

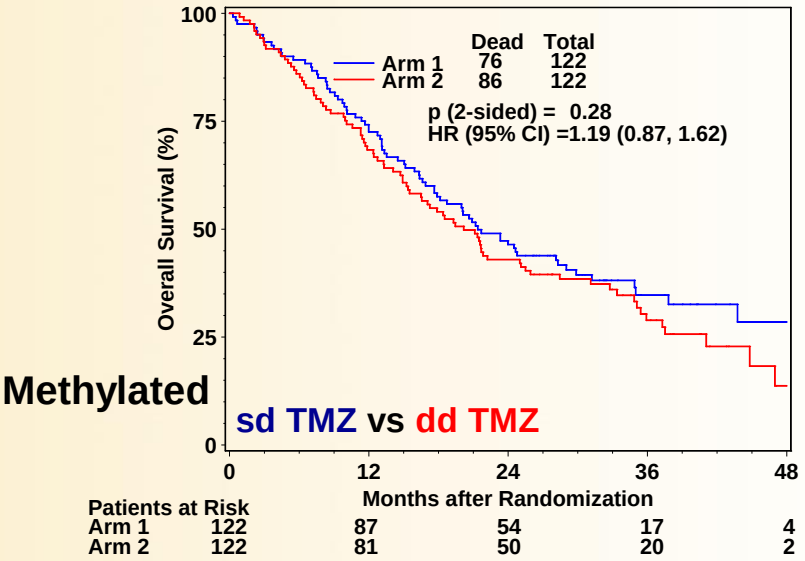
methylated

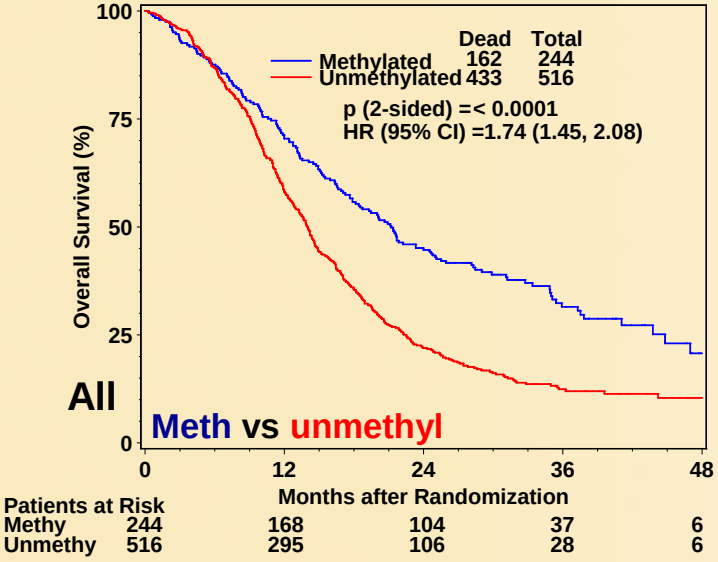


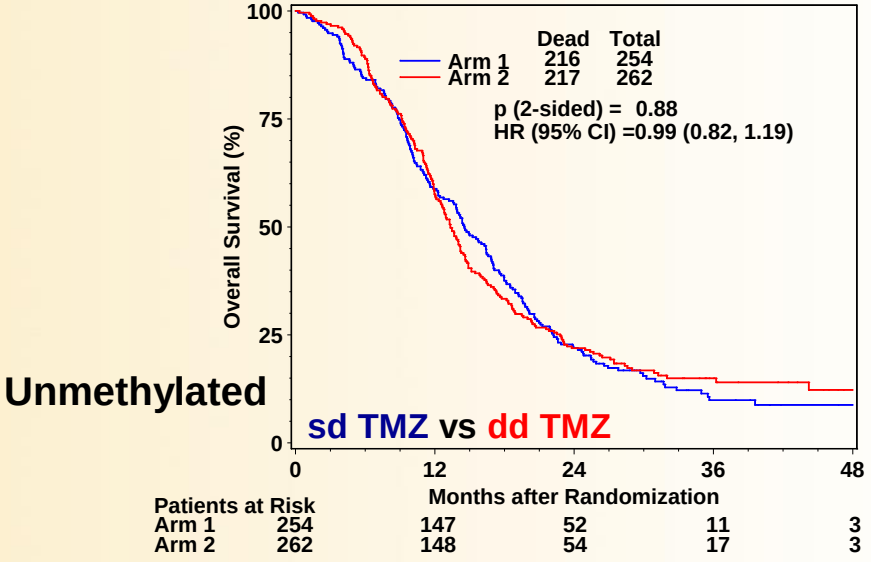
Overall survival standard dose TMZ vs dose dense TMZ

RTOG 0525: Overall Survvial by Treatment and MGMT status



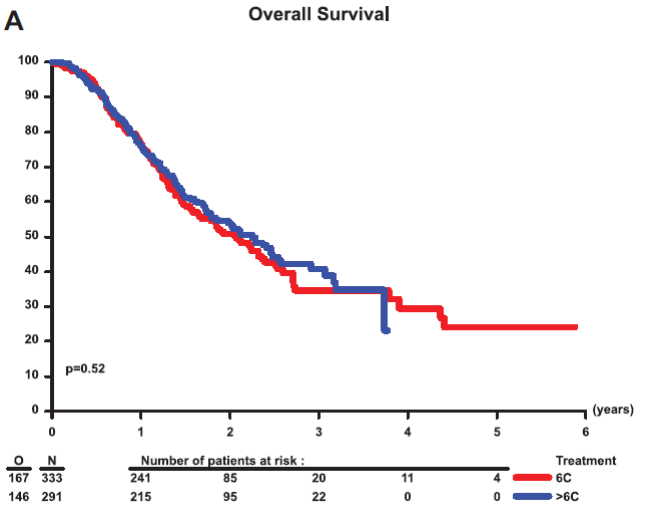


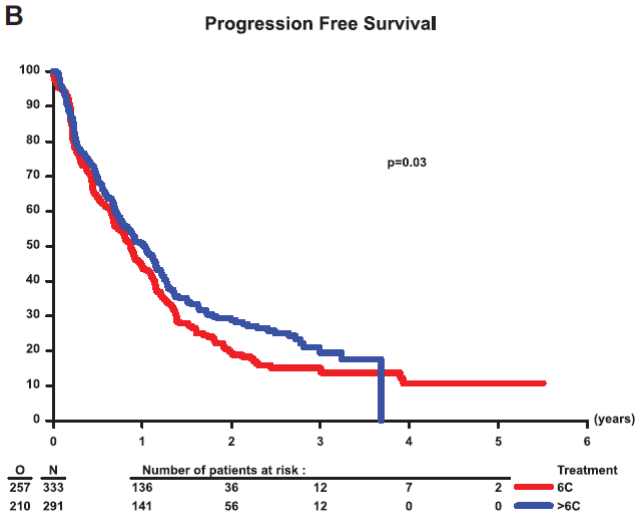


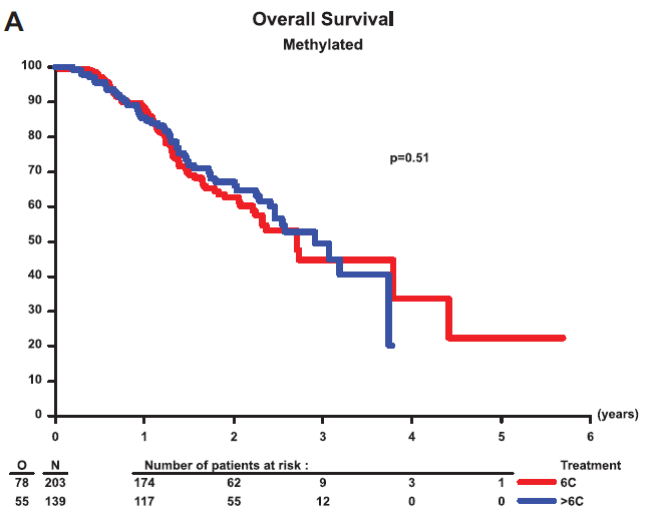


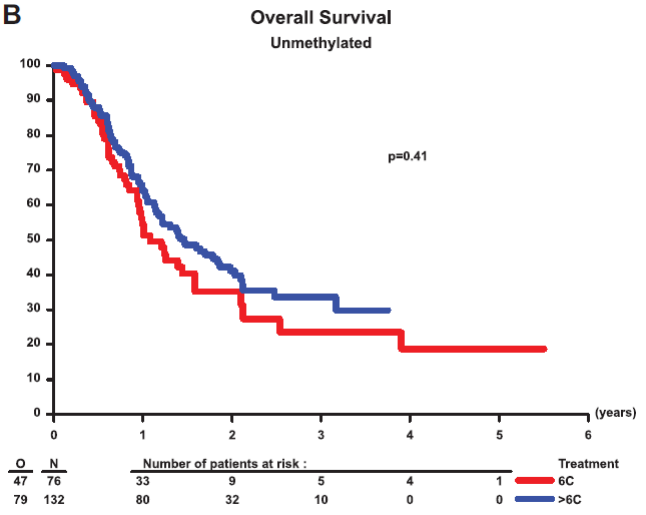
Duration of adjuvant temozolomide treatment

- Meta-analysis covering 2214 GBM patients treated within 4 trials.
- All patients who were progression free 28 days after cycle 6 were included.
- 624 qualified for analysis: 291 continued maintenance TMZ until progression or up to 12 cycles, while 333 discontinued TMZ after 6 cycles.
- Continuing TMZ beyond 6 cycles was not shown to increase overall survival for newly diagnosed GBM.









Blumenthal et al, neurooncology march 2017

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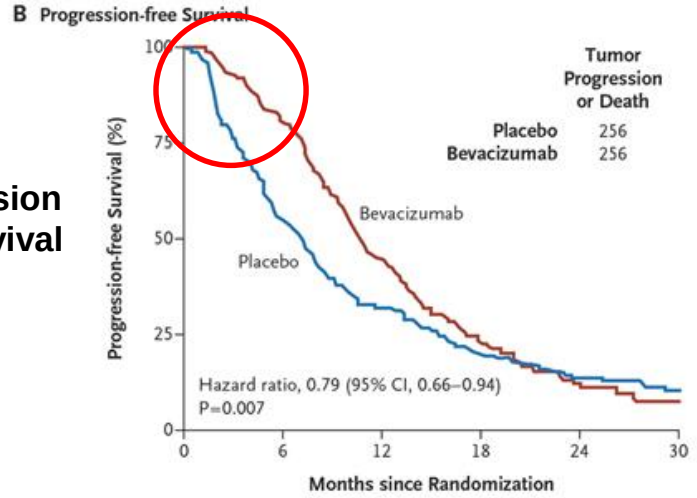
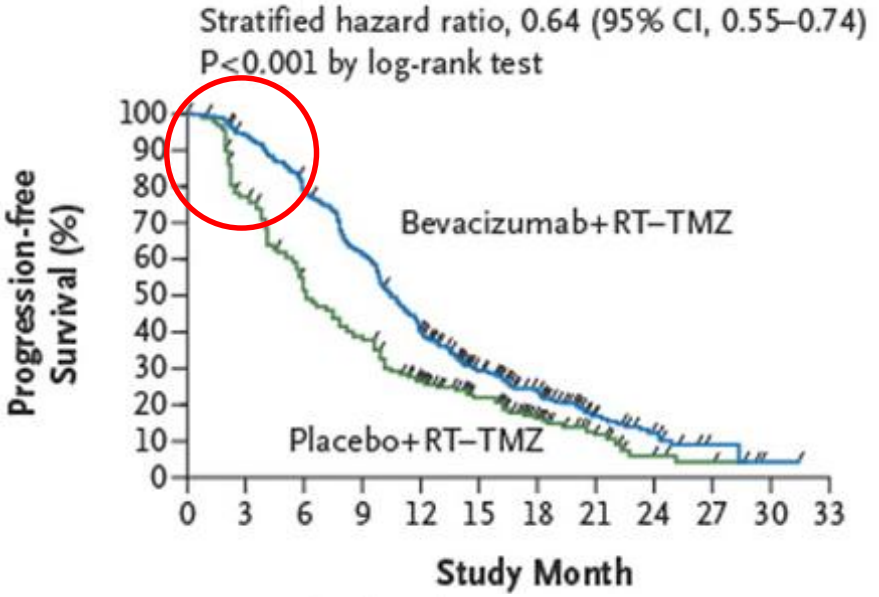
AVAGLIO and 0825: equal PFS and OS

AVAGlio

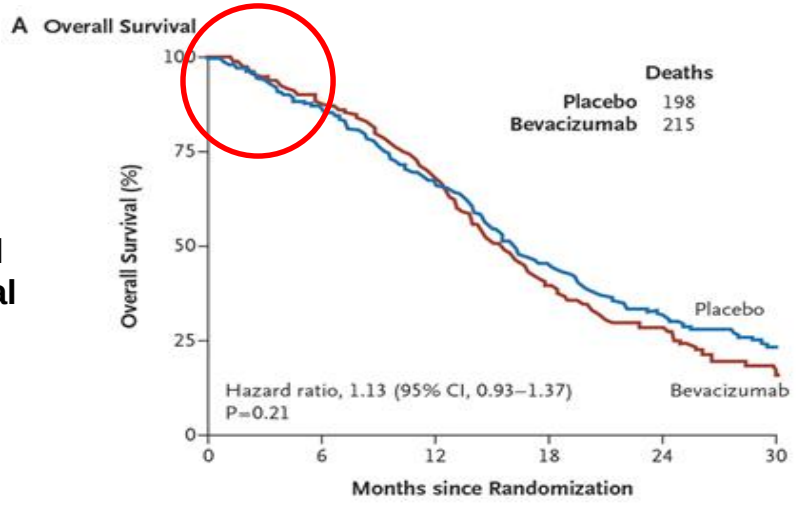
RTOG 0825

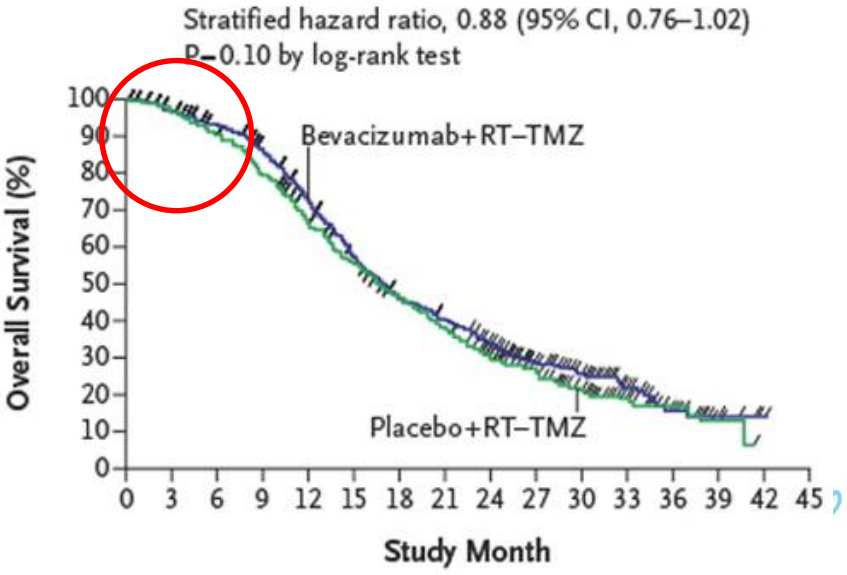
Progression free survival





Overall survival



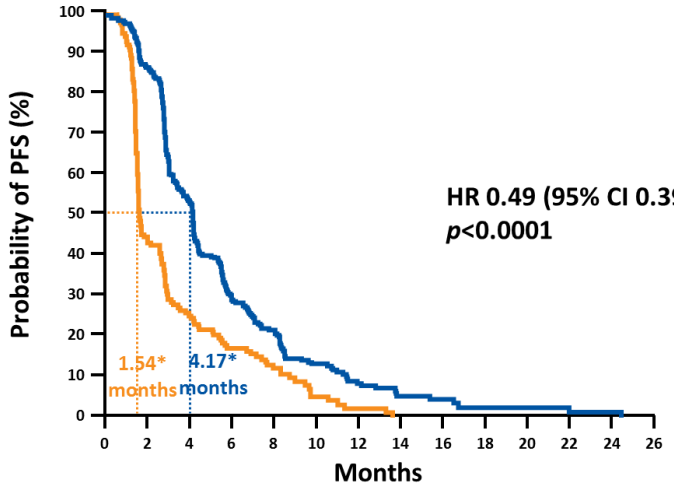


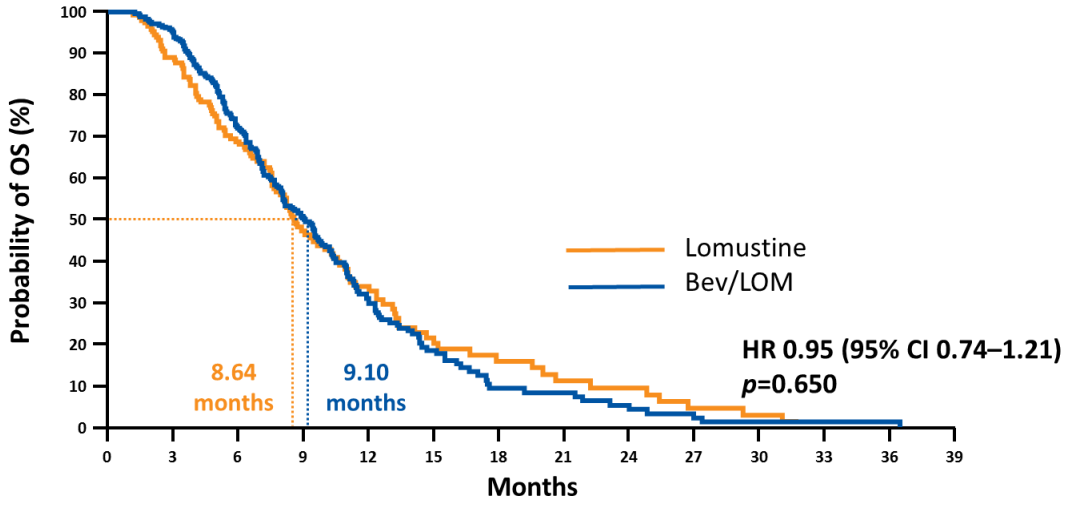
Cancer Institute brain tumor center

EORTC 26101: BEV/LOM versus lomustine only

Conclusion:

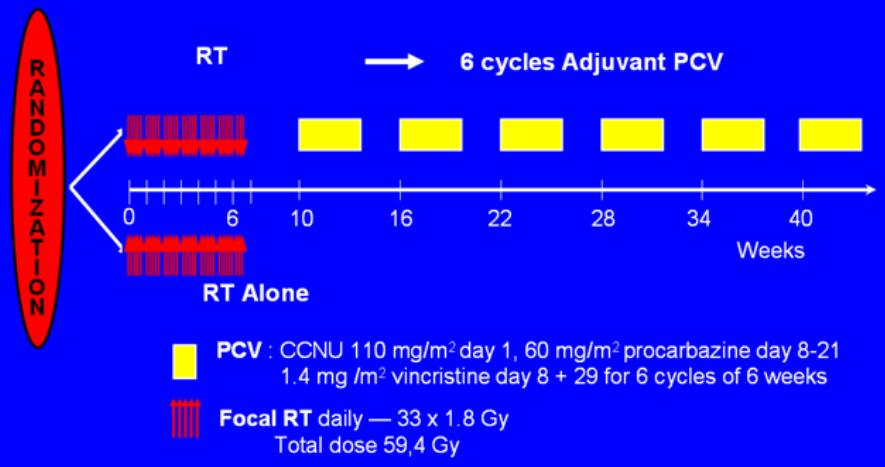
- Increased PFS, but no increase in OS
- No proven survival benefit of bevacizumab for either recurrent nor newly diagnosed glioblastoma
- No proven anti-tumor effect of bevacizumab on glioblastoma
- So far no subgroup that clearly benefits identified
- Use limited to (expensive) steroid function for patient without other options?





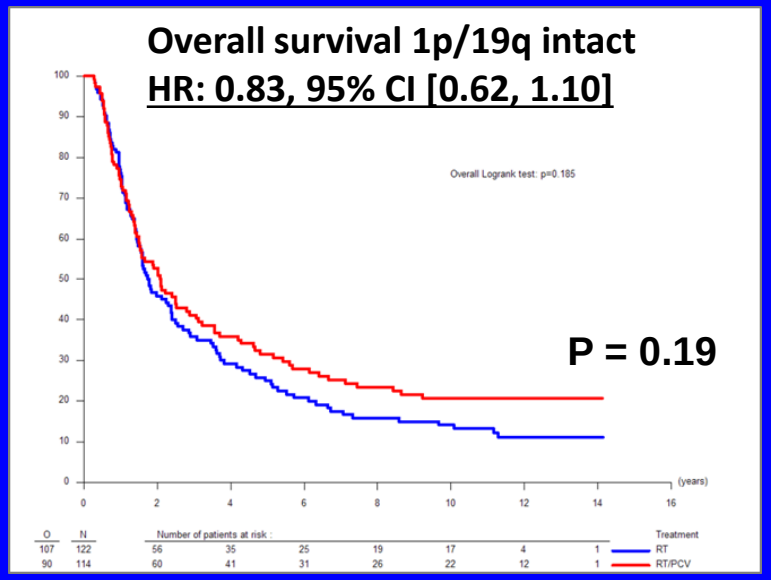
OS in 1p/19q co-deleted and intact patients

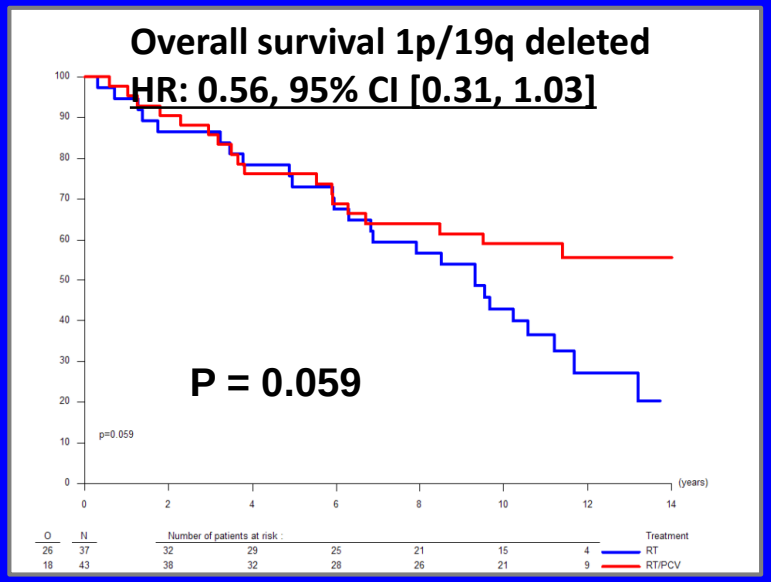
Treatment Schema EORTC 26951



Median	OS non-deleted (n = 236)	OS deleted (n = 80)
RT (37)	21 mo	112 mo
RT/PCV (43)	25 mo	Not Reached

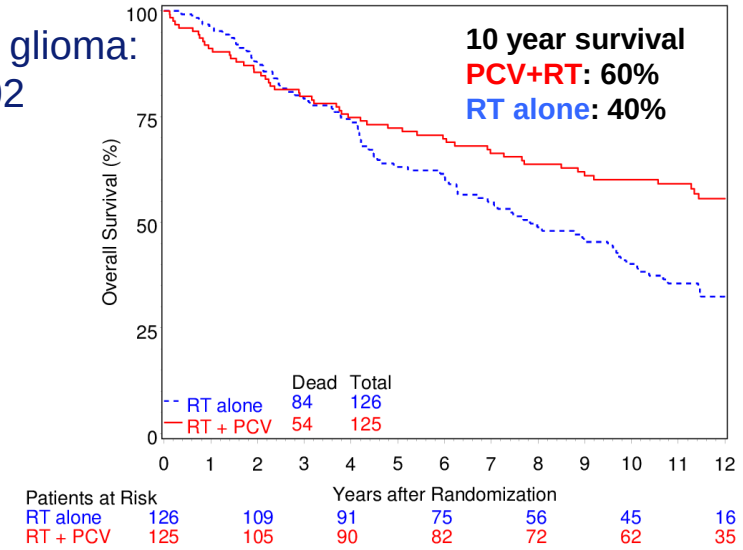
Conclusion: In 1p/19q co-deleted tumors clinically significant benefit of PCV



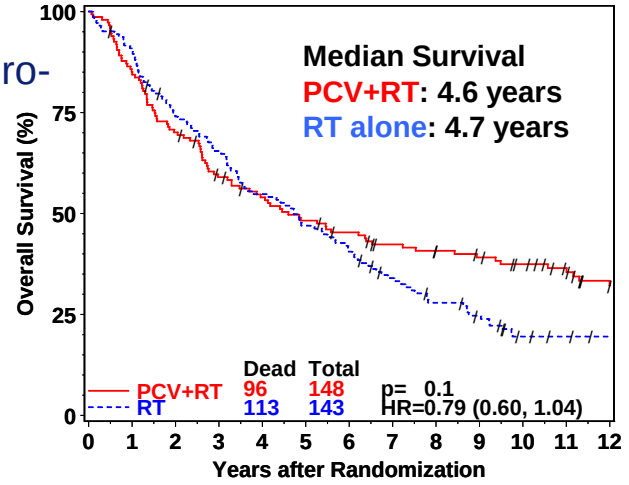


And chemo for all grade II and III!

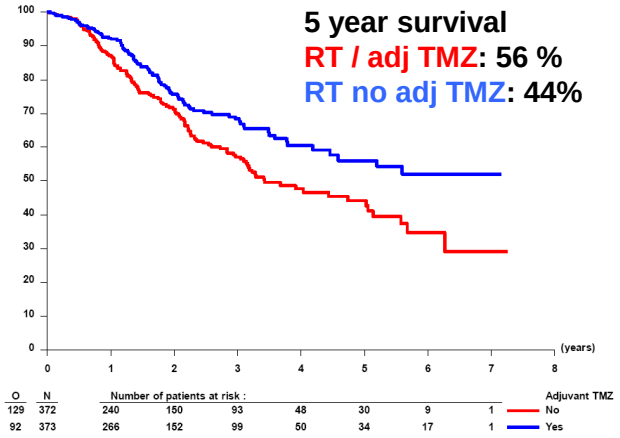
Low grade glioma: RTOG 9802



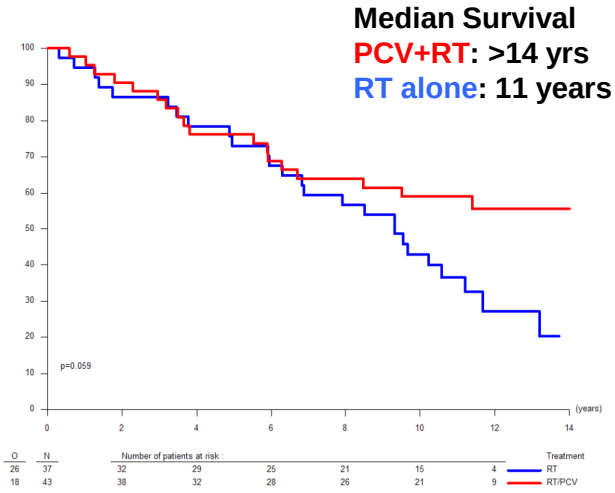
Anaplastic oligodendro-glioma: RTOG 9402



1p/19q intact anaplastic astrocytoma: the EORTC CATNON trial

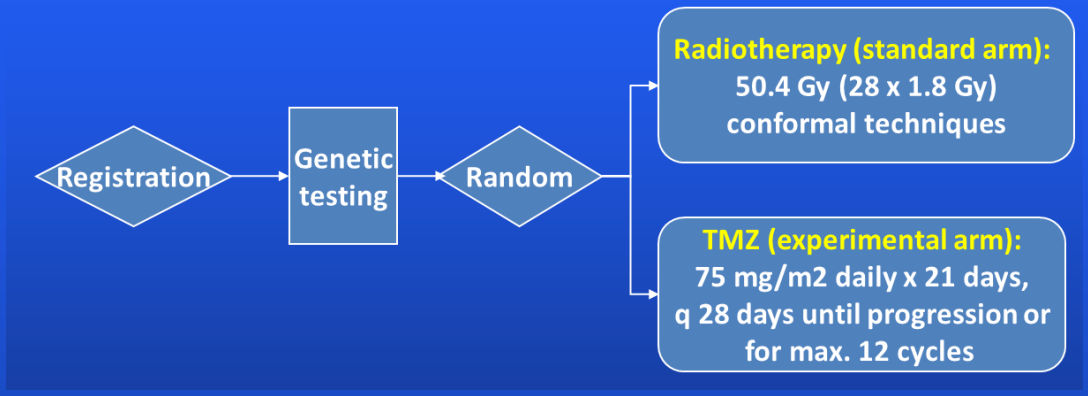


1p/19q codeleted anaplastic oligodendroglioma: EORTC 26951

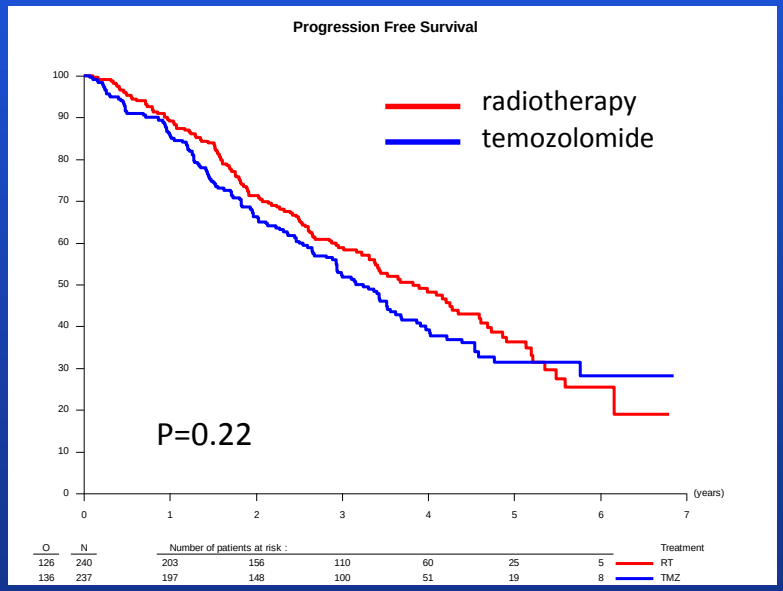


Erasmus MC Cancer Institute

EORTC 22033 TMZ vs RT in Low Grade Glioma PFS in Intent to Treat Population



Treatment	Hazard Ratio (95% CI)	Median (95% CI) (Months)
RT		46 (40, 55)
TMZ	1.2 (0.9, 1.5)	39 (34, 43)

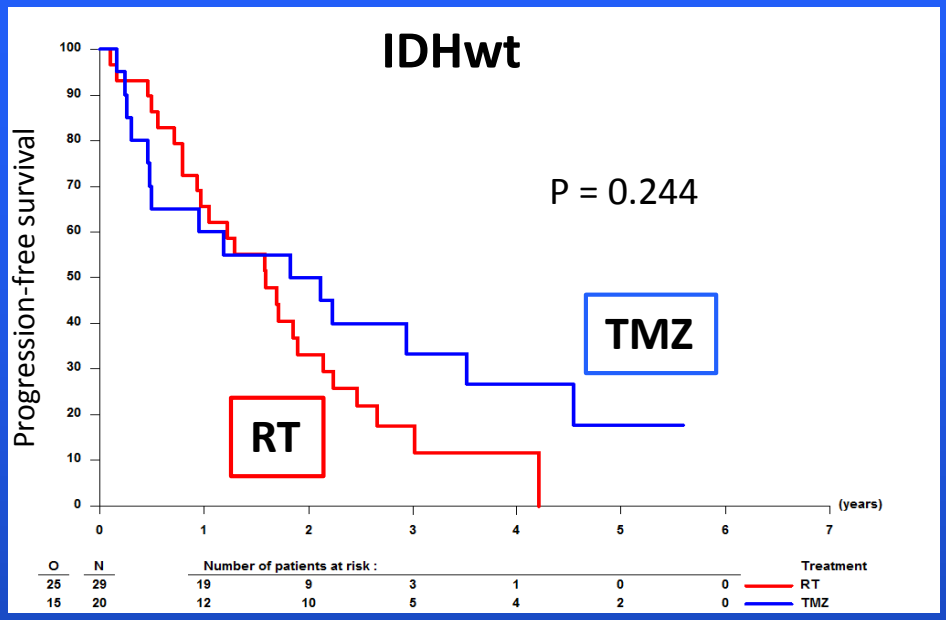


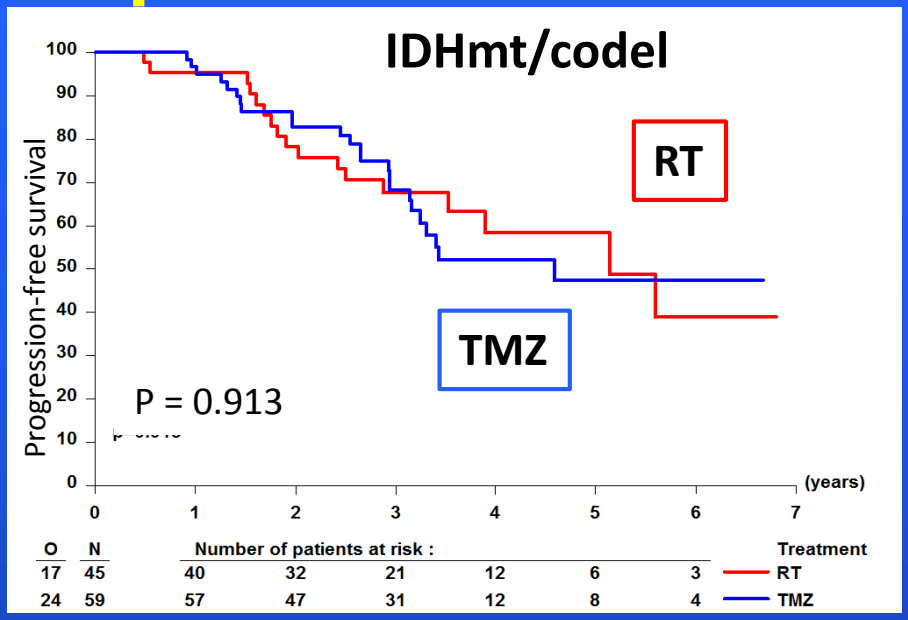
- Eligble: high risk low grade glioma patients
- Treated: 477 patients
- Primary endpoint: PFS
- Events: 126 RT, 136 TMZ
- Median OS not reached: immature

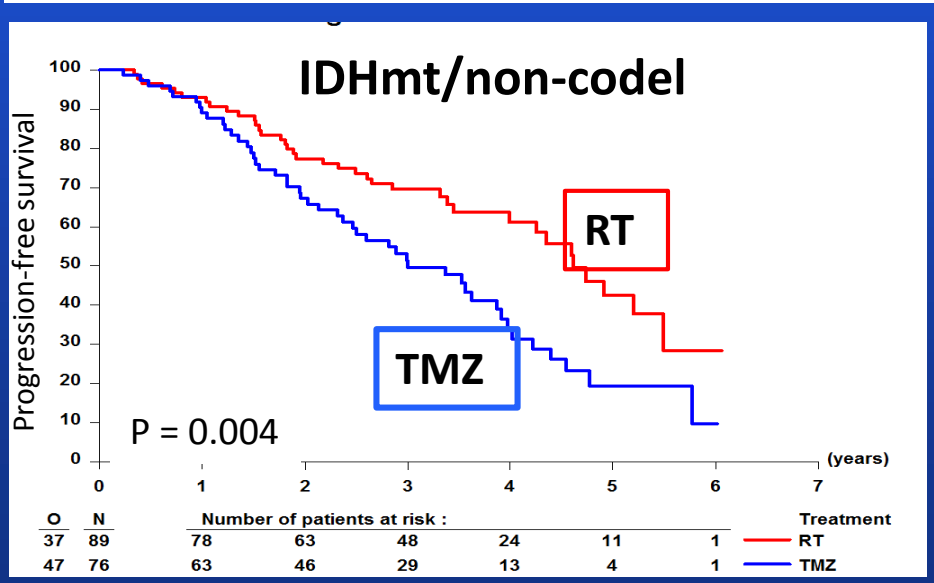
EORTC *The future of cancer therapy*

Baumert et all, Lancet Oncology 2016

EORTC 22033 on RT vs TMZ in low grade glioma: PFS in relation to 1p/19q and IDH status







Some safe conclusions:

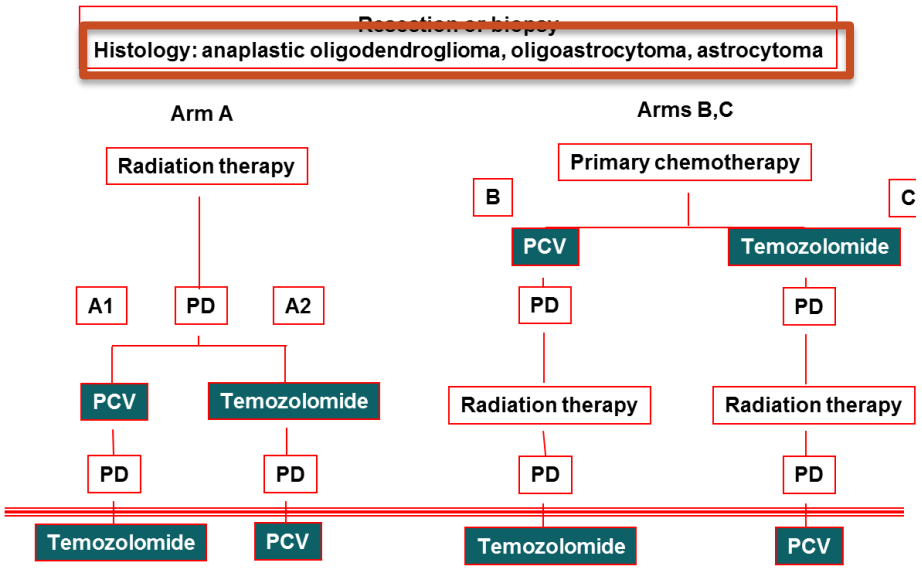
- **Initial chemotherapy does not improve outcome**
- **Intial chemotherapy in IDHmt astrocytoma may worsen PFS**

EORTC *The future of cancer therapy*

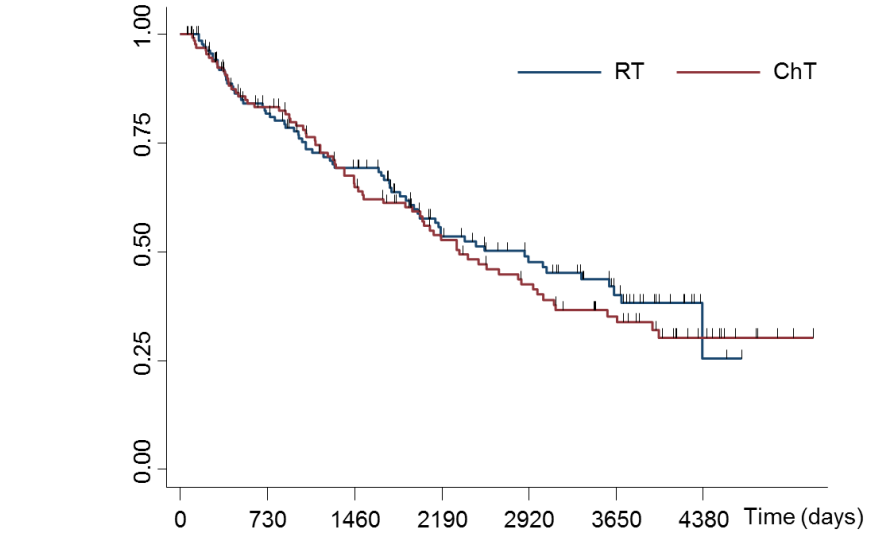
Slide courtesy dr Baumert
Lancet Oncology 2016

NOA-04: temozolomide vs RT in grade III glioma

NOA-04: Randomised phase-III-study of sequential radiochemotherapy oligoastrocytic tumors of WHO-grade III with PCV or temozolomide



NOA4: Overall survival – by therapy



Efficacy outcomes – by molecular diagnosis/therapy

Caveat: small numbers, many comparisons… but from a randomized trial

	IDH wt		IDHmut		Codel	
	RT (A) (n=28)	ChT (B/C) (n=30)	RT (A) (n=40)	ChT (B/C) (n=43)	RT (A) (n=35)	ChT (B/C) (n=31)
PFS	0.8	0.8	3.0	2.1	8.7	7.5
TTF	1.5	1.2	4.0	4.5	**10.1**	**8.1**
OS	**4.7**	**3.1**	**7.1**	**7.3**	NR (10.0-nr)	NR (6.6-nr)

- No indication chemotherapy first will improve PFS or OS in any of the molecular subgroups

What are currently the questions?

- Delayed cognitive effects of treatment: can we decrease treatment intensity or reduce side-effects of radiotherapy?
  - Leaving out RT in chemotherapy sensitive patients
    - Eg, Hata et al, Onco Targets 2016;9:7123-31: PAV in 1p/19q codeleted tumors
- Adjuvant chemotherapy given after radiotherapy improves survival
  - Is survival further improved by direct post-operative treatment, regardless of extent of resection?

- Novel approaches???

What distinguishes high risk from low risk low grade glioma?

RTOG: either

- **Age ≥40**

OR

- **Subtotal resection / biopsy**

EORTC: At least 1 criteria of the following (indication for initiating therapy):

- Radiographic progression
- New or worsening neurological deficit
- Intractable epilepsy = persistent seizures interfering with everyday life and failure of 3 lines of anti-epileptic drug regimen
- ≥ Age 40 years

Purpose: define which patients are eligible for trials on adjuvant treatment

Geurts , van den Bent Cancer 2018

Erasmus MC Cancer Institute brain tumor center

EORTC 26951: Quality of Surival in a cohort with long term follow-up

Evaluation of cognitive functioning:

- Progression-free patients (n=27): highly variable
  - 44% no cognitive impairments
  - 30% severe cognitive impairments
- Treatment (small subgroups): additional PCV not associated with worse cognition
- 41% were employed and 81% could live independently
- Progressive disease (n=5): more cognitive impairments

- **Does this warrant postponement of RT?**

Habets et al, J Neurooncol 2014;116:161-8

Up-front PCV in large oligodendroglial tumors. The Erasmus MC experience: long term follow-up.

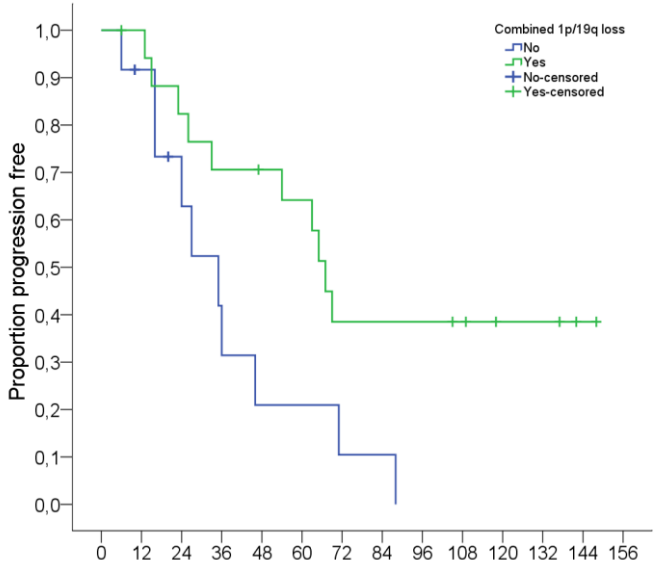
Median OS: 10 years

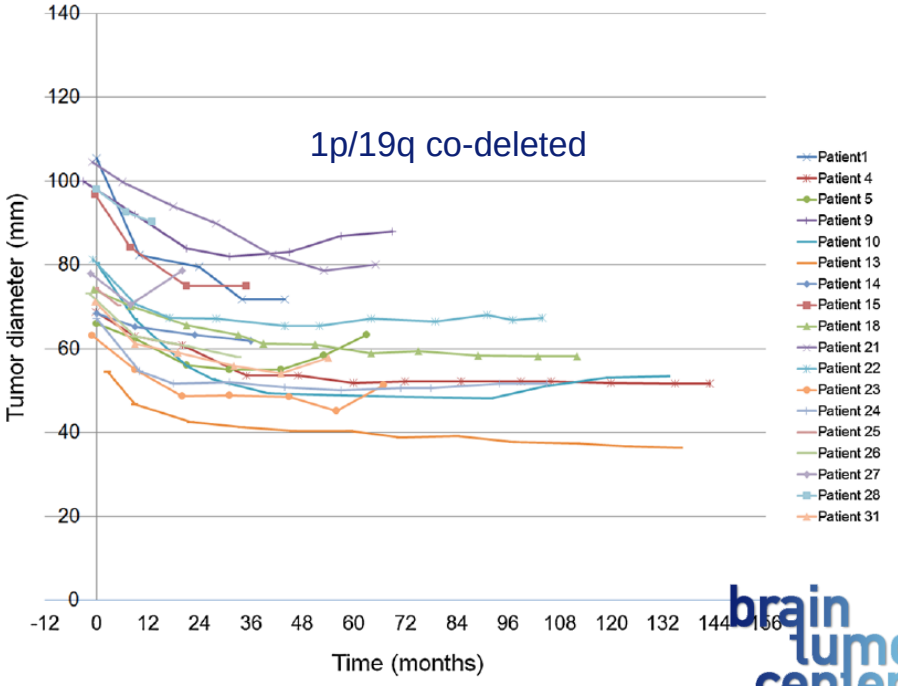
10 year-PFS 1p/19q co-deleted: 34%

Median delay RT:

- **1p/19q co-deletion: 6 year**
- **1p/19q intact: 2,5 year**

In general: until PD able to carry on normal activities incl work.



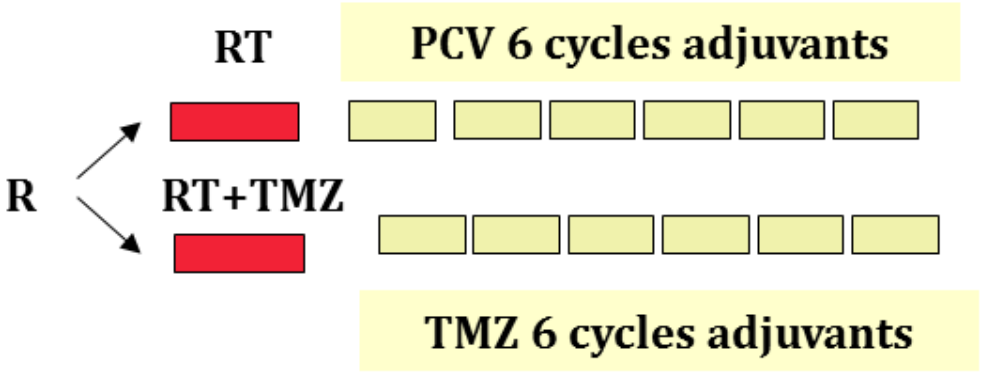


Taal et al, J Neuro-oncol 2015 Jan;121(2):365-72

brain tumor center

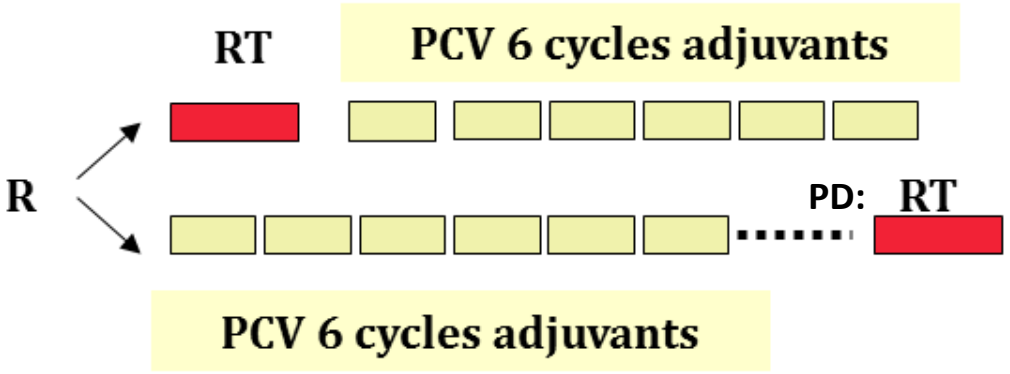
Oligodendrogliomas 1p/19q codel, IDH mut
Improving the standard of care

CODEL trial NCT00887146 **Choice of chemotherapy: PCV vs temozolomide**



- Is RT-TMZ equally effective as RT +PCV?
- Grade II and III
- Study duration: 11.5 years

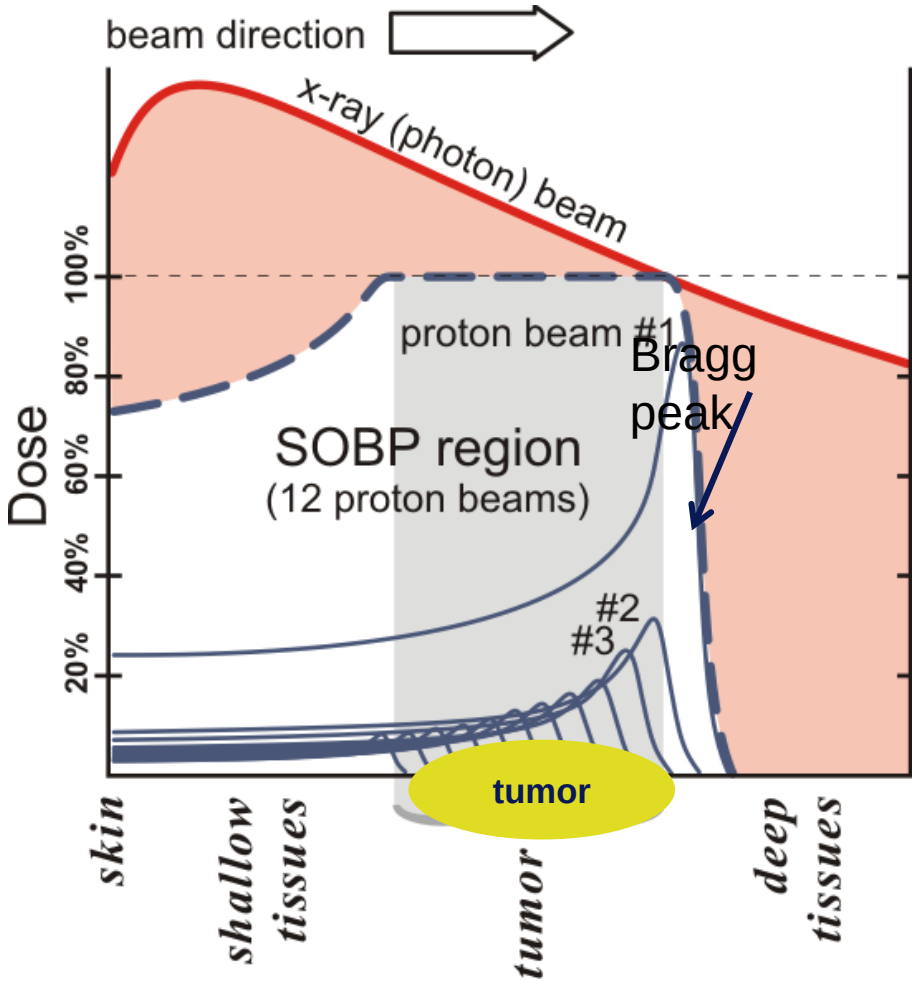
POLCA trial NCT02444000 **To reduce RT toxicity: PCV/RT vs PCV and RT at PD**



- Does delaying RT improve survival without neurocognitive deterioration?
- Grade III
- Study duration : 9 years

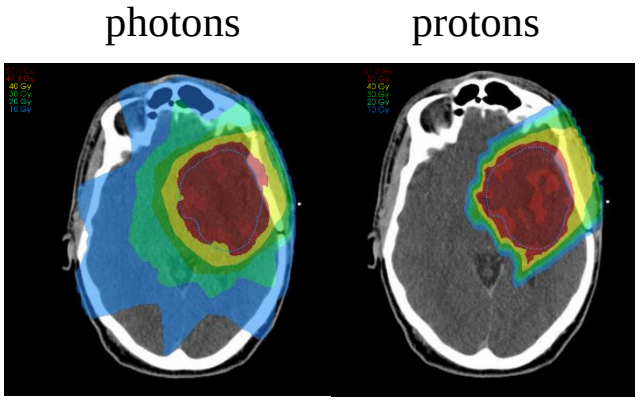
Protons

- Main advantage: less RT dosage behind the target
- ➢ Potential for sparing of normal brain
- However: increased risk to miss the target
- More expensive (like 2 months of TTF…)
- Standard of care for chordoma, preferred approach for eg, neuraxis RT in medulloblastoma



Role for proton therapy in lower grade glioma?

- Hippocampal sparing? Normal brain sparing?
- Endpoints of trials need to be:
  - Cognition
  - Site of relapse, OS



EORTC IDHmut grade II/III Study: Wait Or Treat?

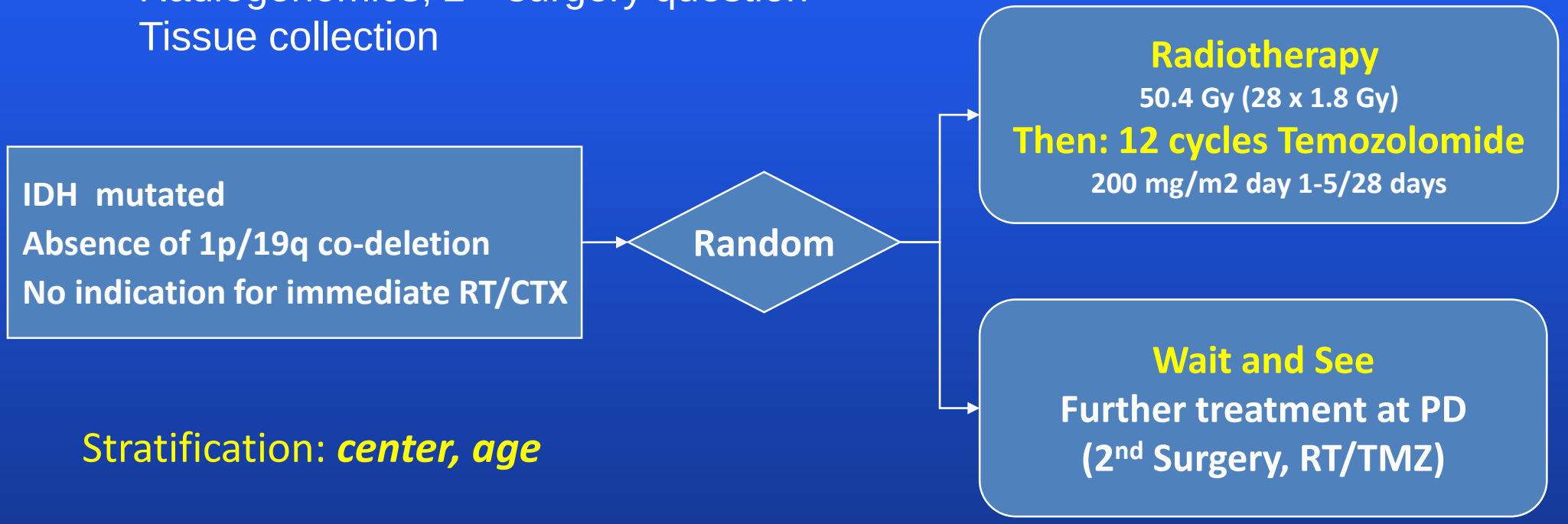
Primary endpoint: Next Intervention Free Survival

Secondary endpoints:

OS, QoL, Neurocognitive function

Radiogenomics, 2nd surgery question

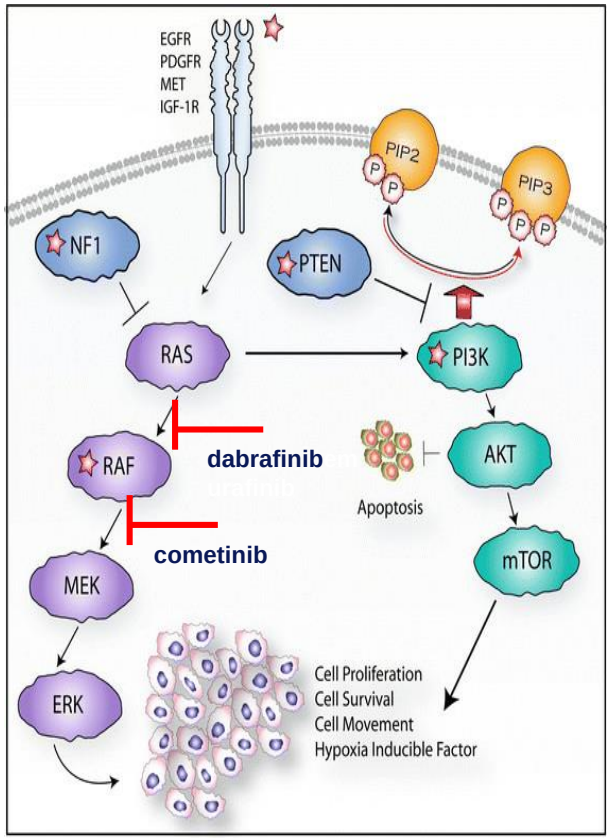
Tissue collection

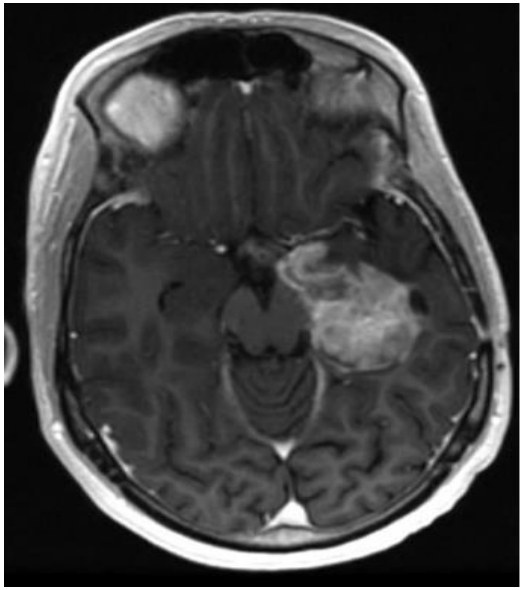


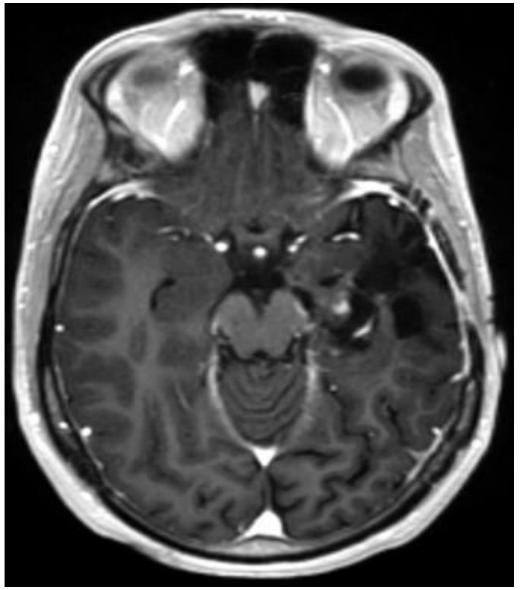
Stratification: ***center, age***

BRAF mutations: an actionable target

- BRAF mutations: frequent in (anaplastic) PXA (43-66%), ganglioglioma (18-43%), epitheloid glioblastoma and pilocytic astrocytoma (especially non-fossa posterior: 33%), papillary craniophayngioma
- Should be routinely investigated in any of these diagnosis







BRAF mutated glioblastoma before and after 4 cycles of combined RAF and MEK inhibition

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Some conclusions

- The data from phase III trials on all diffuse gliomas suggest improved outcome if radiotherapy is combined with chemotherapy
- Some RT questions remain unanswered
  - Impact of shortening treatment duration on concurrent part of RT/TMZ
  - Optimal RT dose in favorable prognosis IDHmt grade II, III glioma
- We have reached the limits of classical radio- and chemotherapy
- The challenge: combine QoL and OS

Theodore Kittelsen 1900

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See you there!