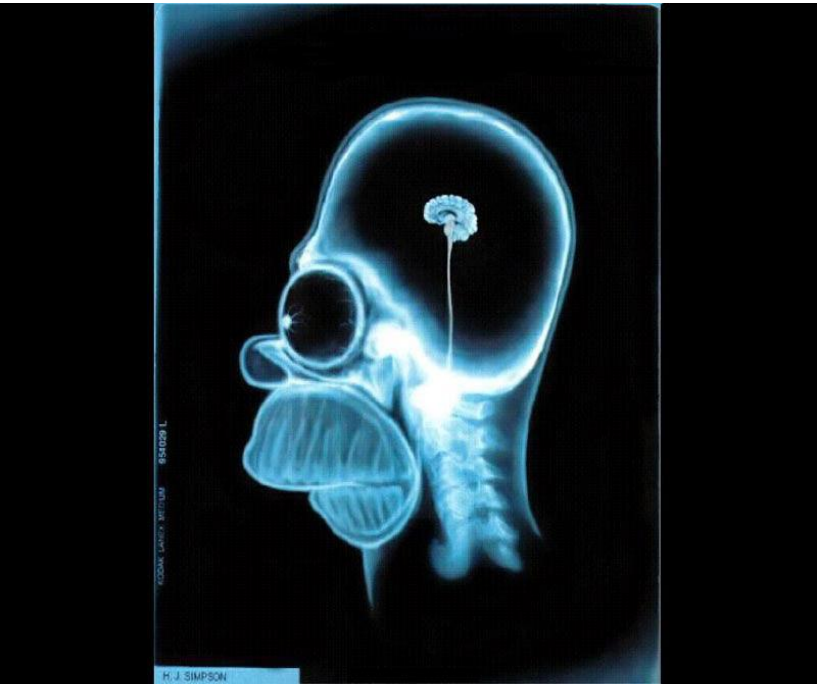
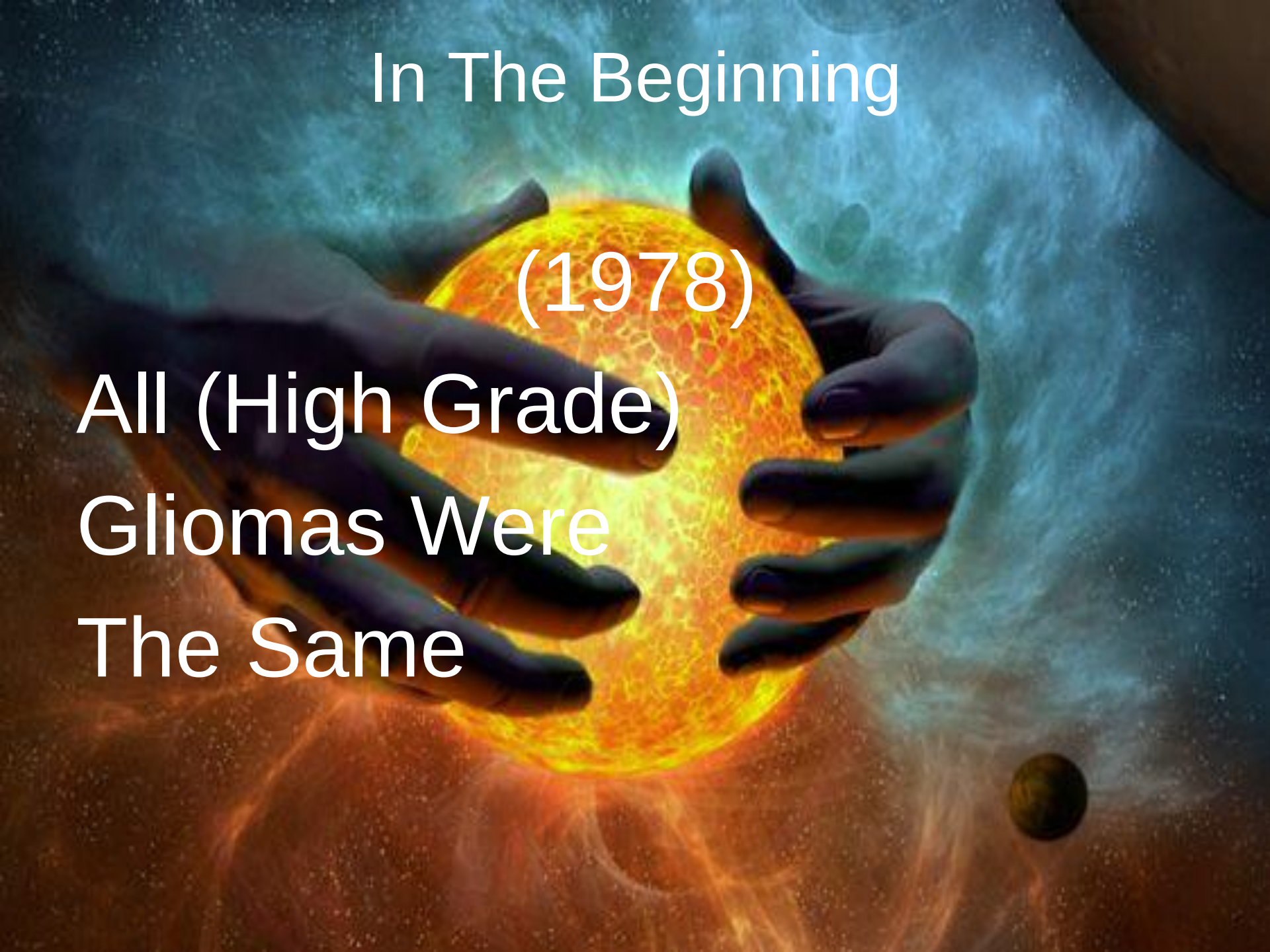


What's new in Management of Gliomas

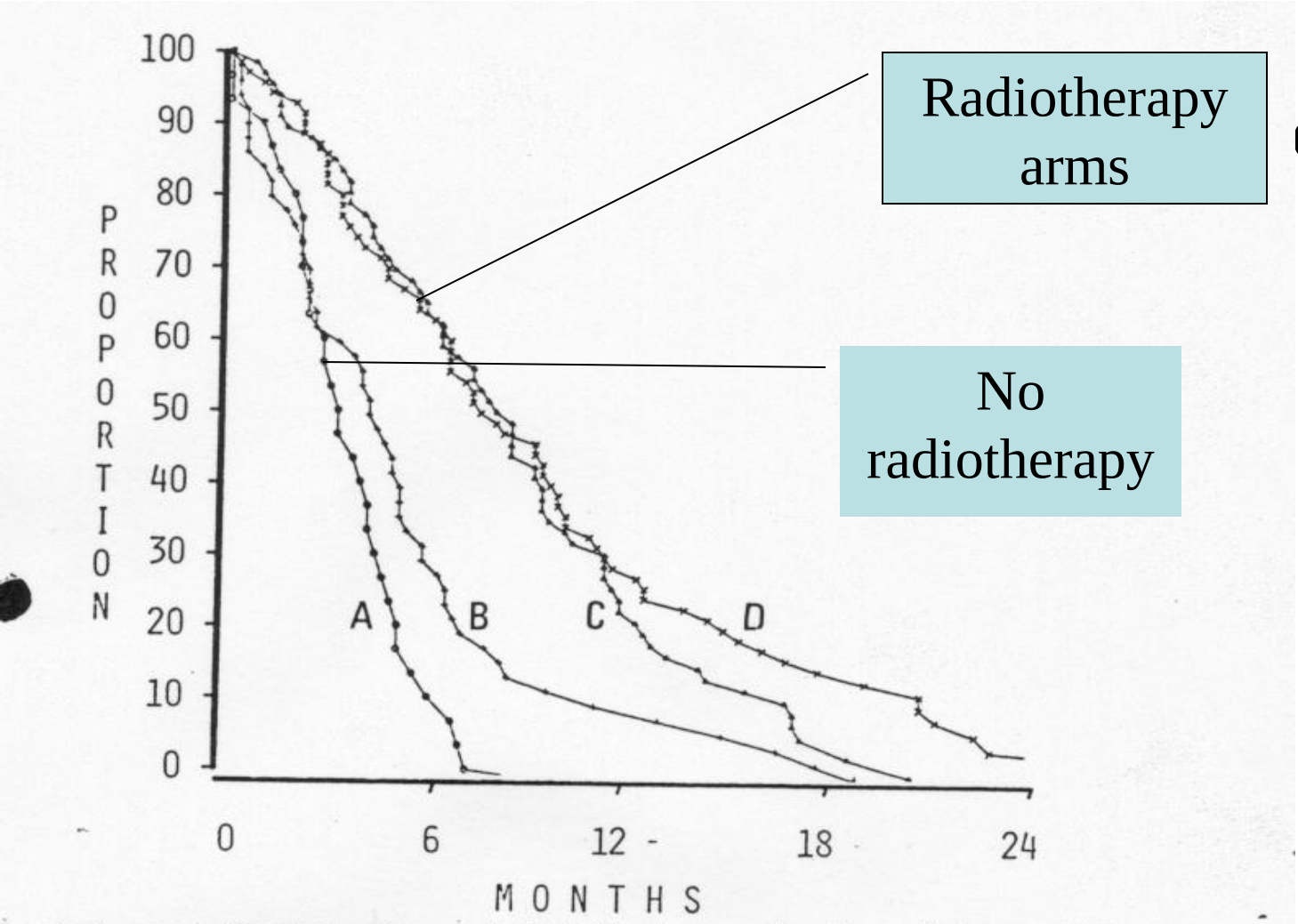
Allan James

Consultant Clinical Oncologist
Beatson West of Scotland Cancer Centre
Glasgow


In The Beginning
(1978)
All (High Grade)
Gliomas Were
The Same

- Background :
- Intrinsic CNS tumours = gliomas
- Grades 1-4: Low grade 1-2 (younger patients); High grade 3-4 (older patients)
- Most common disease in adults easily GBM (grade 4)
- Median survivals – G2 (10-15 yrs); G3 (2-5 years); G4 (1 year)

Radiotherapy for malignant glioma - Walker 1978



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

This and other studies at the time showed conclusively that radiotherapy improves survival in patients with malignant glioma

- Chemo (alkylating agents – CCNU, procarbazine, later Temozolomide) – low RR in general (20-30%), response times short
- Thus historically gliomas received up-front radical XRT, offered chemo at relapse but short survival anticipated
- Some exceptions were noted, seemed to respond well to chemo

- So what's changed
- Categorising and biomarkers
- Increasing role for chemo
- Improvements in XRT delivery
- Improvements in surgical technique and after-care
- Novel therapies…(?)

WHO Classification of Tumours of the Nervous System

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours

Diffuse astrocytoma	9400/3[1]
Fibrillary astrocytoma	9420/3
Protoplasmic astrocytoma	9410/3
Gemistocytic astrocytoma	9411/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytoma	9421/1
Pleomorphic xanthoastrocytoma	9424/3
Subependymal giant cell astrocytoma	9384/1

Oligodendroglial tumours

Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3

Mixed gliomas

Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	*9382/3*[2]

Ependymal tumours

Ependymoma	9391/3
Cellular	*9391/3*
Papillary	9393/3
Clear cell	*9391/3*
Tanycytic	*9391/3*
Anaplastic ependymoma	9392/3
Myxopapillary ependymoma	9394/1
Subependymoma	9383/1

Choroid plexus tumours

Choroid plexus papilloma	9390/0
Choroid plexus carcinoma	9390/3

Glial tumours of uncertain origin

Astroblastoma	9430/3
Gliomatosis cerebri	9381/3
Chordoid glioma of the 3rd ventricle	*9444/1*

Neuronal and mixed neuronal-glial tumours

Gangliocytoma	9492/0
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	*9493/0*
Desmoplastic infantile astrocytoma / ganglioglioma	*9412/1*
Dysembryoplastic neuroepithelial tumour	*9413/0*
Ganglioglioma	9505/1
Anaplastic ganglioglioma	*9505/3*
Central neurocytoma	*9506/1*
Cerebellar liponeurocytoma	*9506/1*
Paraganglioma of the filum terminale	8680/1

Neuroblastic tumours

Olfactory neuroblastoma (Aesthesioneuroblastoma)	9522/3
Olfactory neuroepithelioma	9523/3
Neuroblastomas of the adrenal gland and sympathetic nervous system	9500/3

Pineal parenchymal tumours

Pineocytoma	9361/1
Pineoblastoma	9362/3
Pineal parenchymal tumour of intermediate differentiation	*9362/3*

Embryonal tumours

Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Medulloblastoma	9470/3
Desmoplastic medulloblastoma	9471/3
Large cell medulloblastoma	*9474/3*
Medullomyoblastoma	9472/3
Melanotic medulloblastoma	*9470/3*
Supratentorial primitive neuroectodermal tumour (PNET)	9473/3
Neuroblastoma	9500/3
Ganglioneuroblastoma	9490/3
Atypical teratoid/rhabdoid tumour	9508/3

TUMOURS OF PERIPHERAL NERVES

Schwannoma

(Neurilemmoma,Neurinoma)	9560/0
Cellular	*9560/0*
Plexiform	*9560/0*
Melanotic	*9560/0*

Neurofibroma

	9540/0
Plexiform	9550/0

Perineurioma

	9571/0
Intraneural perineurioma	*9571/0*
Soft tissue perineurioma	*9571/0*

Malignant peripheral nerve sheath tumour (MPNST)

	9540/3
Epithelioid	*9540/3*
MPNST with divergent mesenchymal and / or epithelial differentiation	*9540/3*
Melanotic	*9540/3*
Melanotic psammomatous	*9540/3*

TUMOURS OF THE MENINGES

Tumours of meningothelial cells

Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	*9530/0*
Secretory	*9530/0*
Lymphoplasmacyte-rich	*9530/0*
Metaplastic	*9530/0*
Clear cell	*9538/1*
Chordoid	*9538/1*
Atypical	*9539/1*
Papillary	*9538/3*
Rhabdoid	*9538/3*
Anaplastic meningioma	9530/3

Mesenchymal, non-meningothelial tumours

Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma (intracranial)	8850/3
Solitary fibrous tumour	*8815/0*
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteosarcoma	9180/3
Osteochondroma	9210/0
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/1
Haemangiopericytoma	9150/1
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3

Primary melanocytic lesions

Diffuse melanocytosis	*8728/0*
Melanocytoma	*8728/1*
Malignant melanoma	8720/3
Meningeal melanomatosis	*8728/3*

Tumours of uncertain histogenesis

Haemangioblastoma	9161/1

LYMPHOMAS AND HAEMOPOIETIC NEOPLASMS

Malignant lymphomas	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3

GERM CELL TUMOURS

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumours	9085/3

TUMOURS OF THE SELLAR REGION

Craniopharyngioma	9350/1
Adamantinomatous	*9351/1*
Papillary	*9352/1*
Granular cell tumour	*9582/0*

METASTATIC TUMOURS

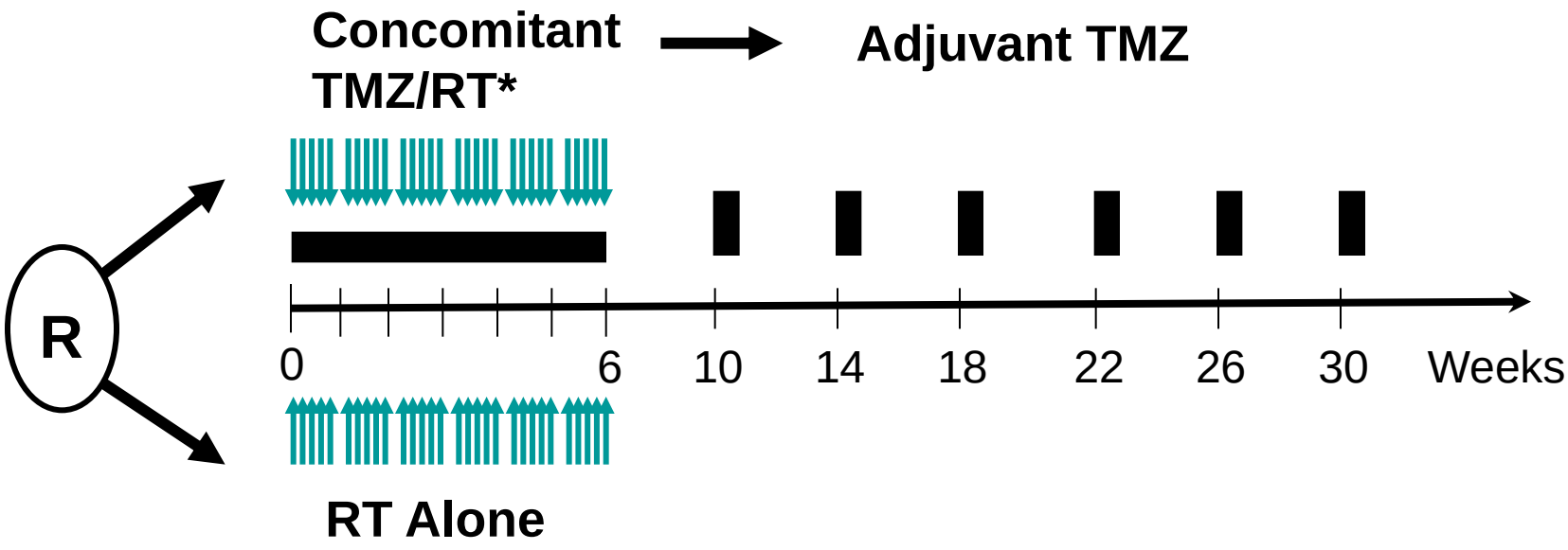
[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behaviour is coded /0 for benign tumours, /1 for low or uncertain malignant potential or borderline malignancy, (/2 for in *situ lesions*) and /3 for malignant tumours.

[2] The italicised numbers are provisional codes proposed for the third edition of ICD-O. They should,for the most part,be incorporated into the next edition of ICD-O, but they are subject to change.

What's New in GBM

- So what changed in March 2005
- Seminal paper presented ASCO 7/2004, then published NEJM 3/05
- EORTC concomitant and adjuvant TMZ with XRT
- Stupp et al
- Became standard of care overnight

What's New in GBM



Temozolomide 75 mg/m^2 po qd for 6 weeks,
then 150–200 mg/m^2 po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

***PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.**

Stupp trial in GBM

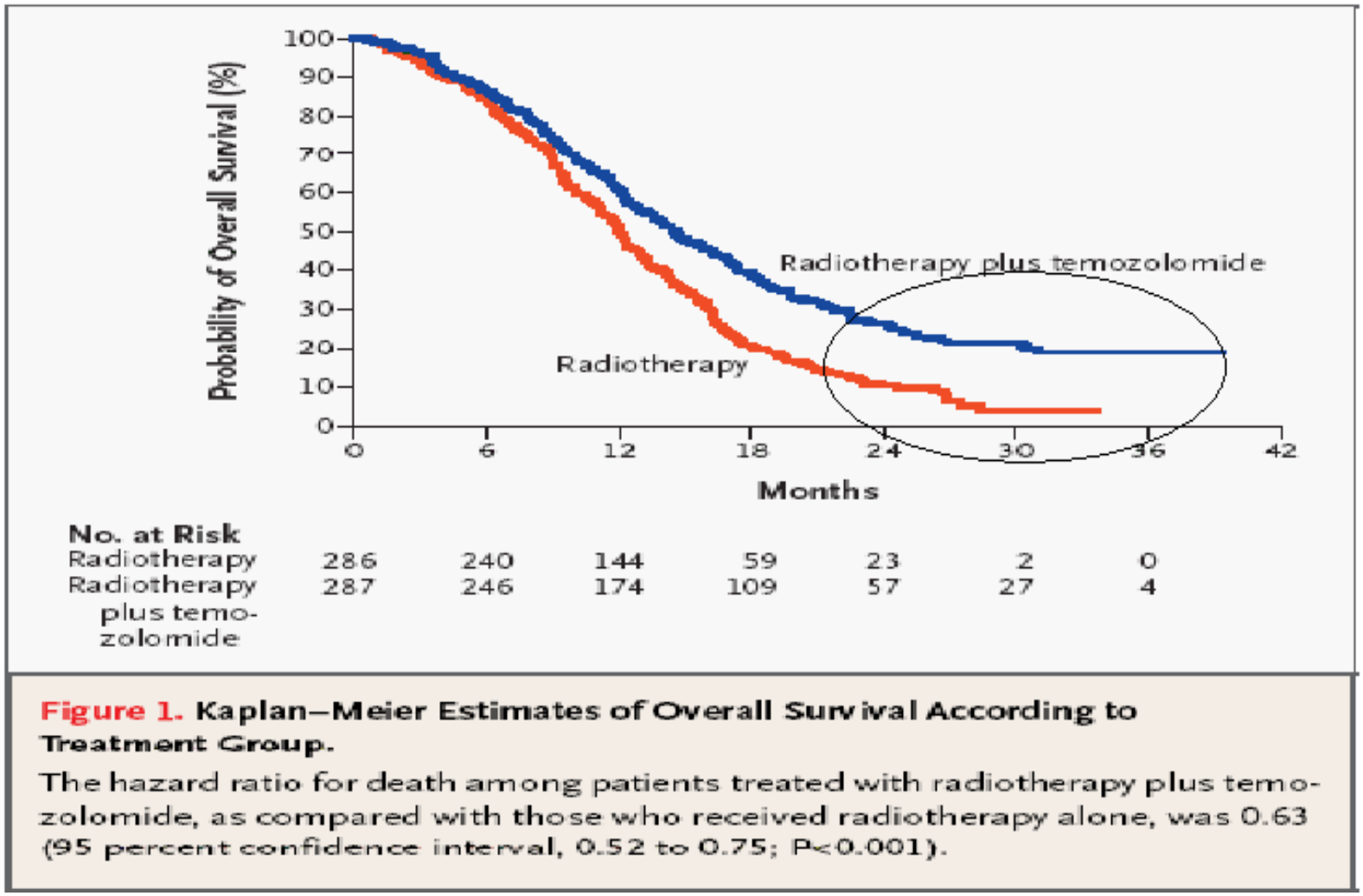


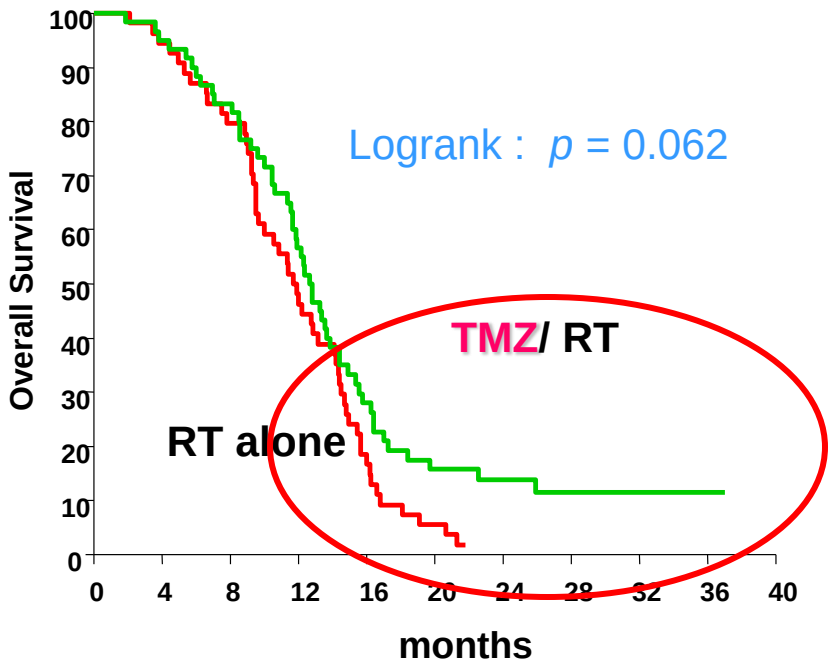
Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

MGMT Promoter Methylation Predicts Benefit from TMZ Treatment?

Unmethylated *MGMT*

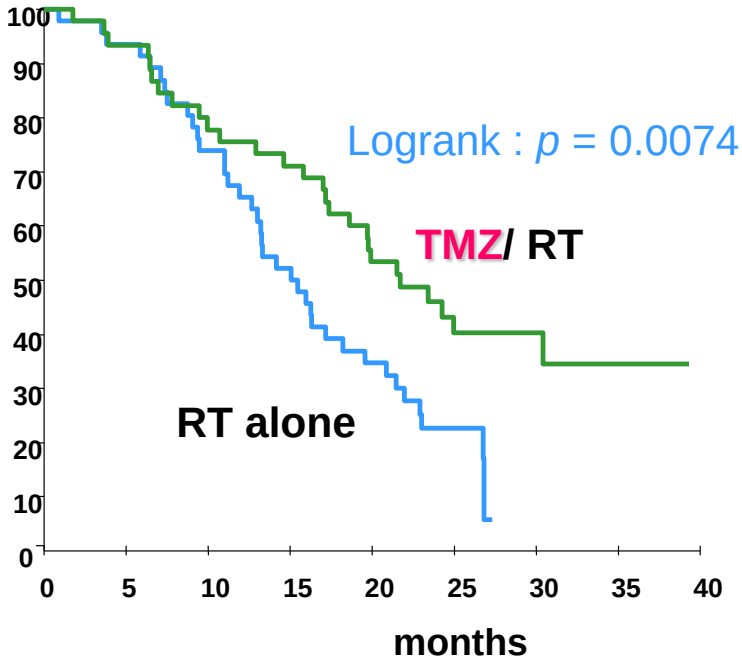
Randomization:	RT	TMZ/RT
Median OS, mo:	11.8	12.7
2-yr survival:	1.9%	13.8%



Normal levels of MGMT

Methylated *MGMT*

Randomization:	RT	TMZ/RT
Median OS, mo:	15.3	21.7
2-yr survival:	22.7%	46.0%

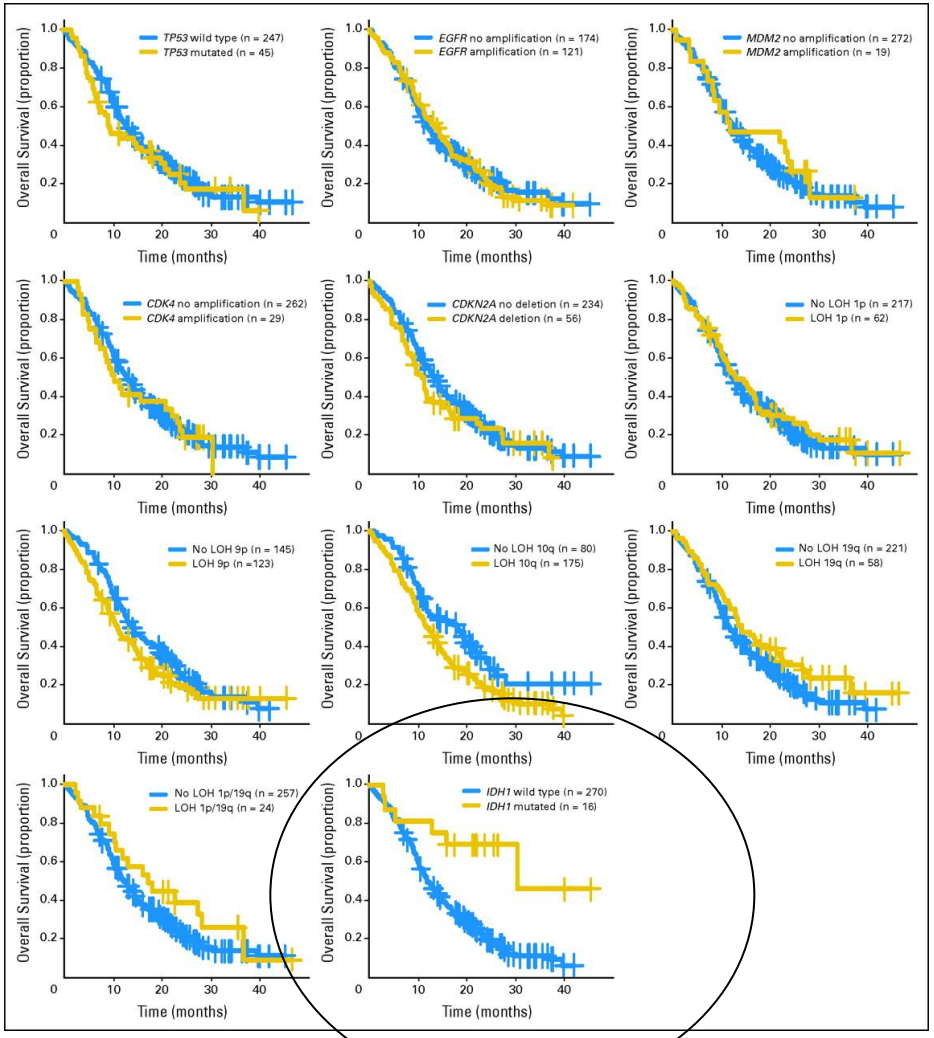


Low levels of MGMT

Retrospective data, but now confirmed in prospective trials

- This one paper confirmed the increasing role of chemotherapy in management of gliomas up-front
- Also confirmed the importance of biomarkers in defining better prognostic groups and predictive of chemo response

Fig 2. Overall survival by molecular markers: no significant association with TP53 mutation, EGFR amplification, CDK4 amplification, MDM2 amplification, CDKN2A homozygous deletion, loss of heterozygosity (LOH) 1p, LOH 9p, LOH 10q, LOH 19q or 1p/19q codeletion, but major prognostic role for IDH1 mutations

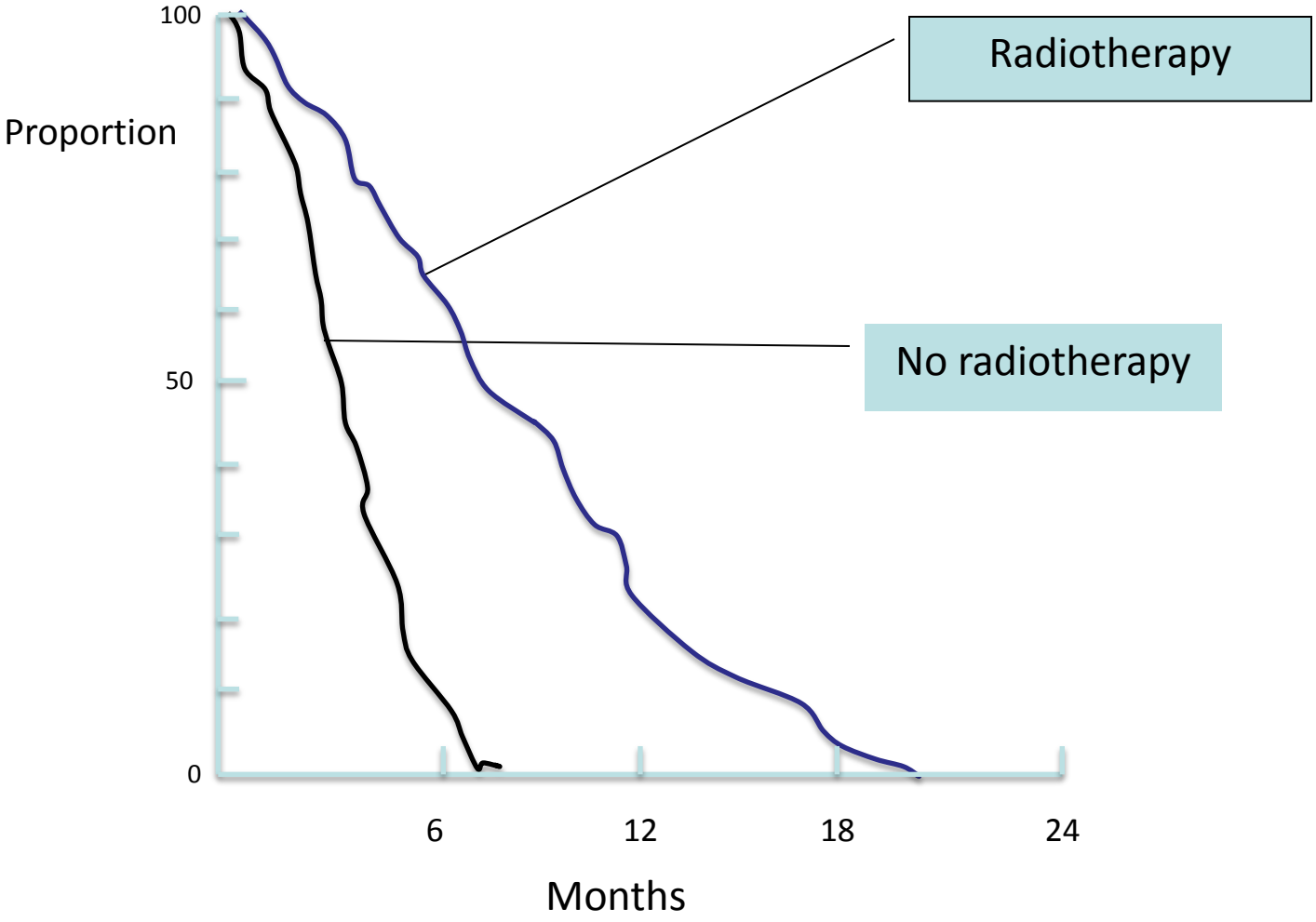


Weller, M. et al. J Clin Oncol; 27:5743-5750 2009

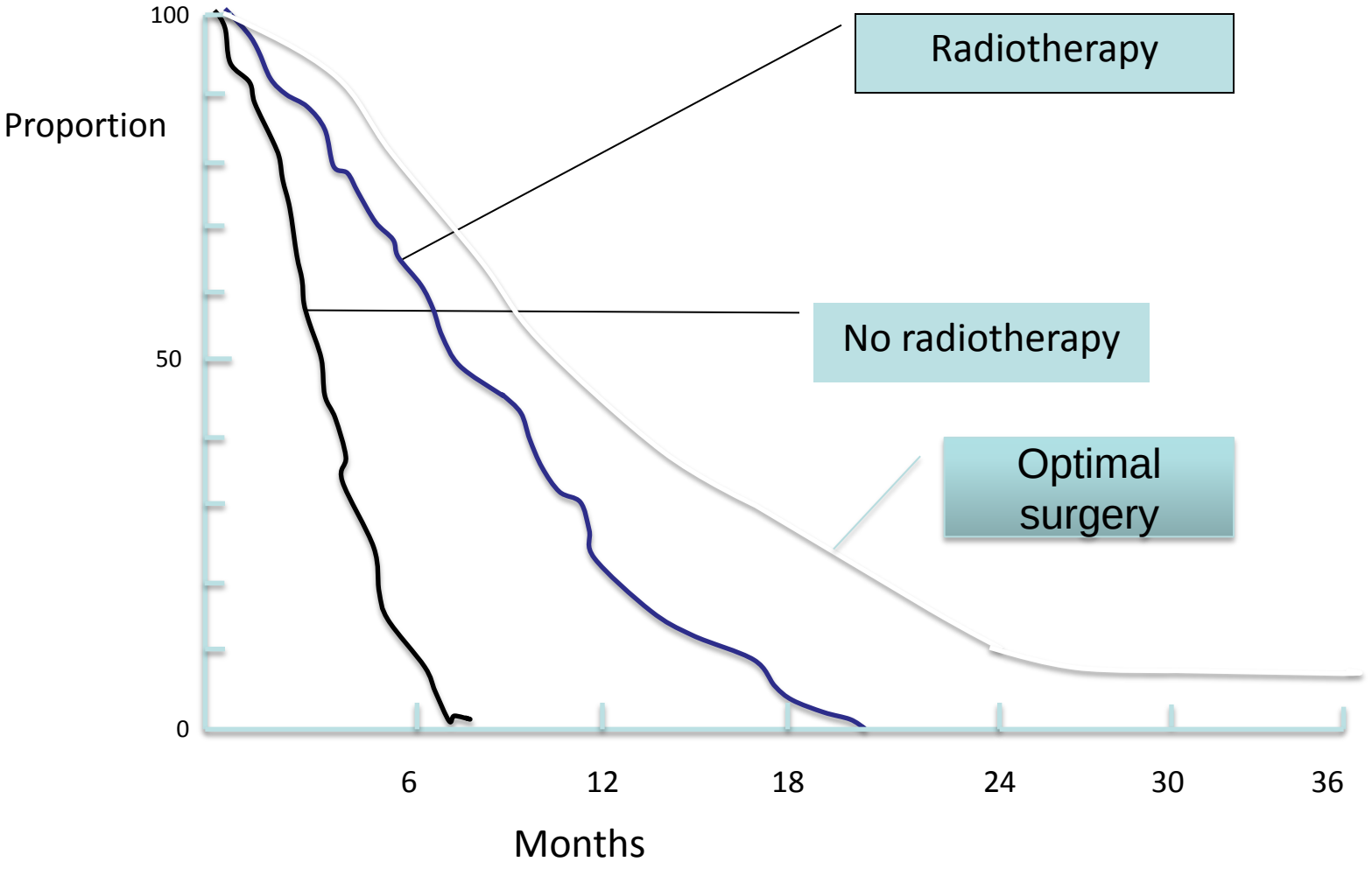
IDH-1

- Isocitrate Dehydrogenase is a ubiquitous enzyme which has the highest level of somatic mutation in astrocytomas. Particularly a heterozygous point mutation in codon 132, mostly R132H.
- The mutation is extremely common (near universal) in LGG, appears to be very early mutation in tumorigenesis.
- Rare in more malignant / high grade tumours, so in GBM only ~ 6% incidence – defines the GBM as secondary (started life as low-grade and transformed) the rest are primary GBM – different molecular profile.
- Its presence is strongly correlated with good outcome.
- Kreb's cycle enzyme – α-keto-glutarate product, impaired in mutated form.
- Products of the altered phosphorylation pathway of the IDH-1 mutation drive a series of enzymatic phosphorylations leading to hypermethylation of DNA, G-CIMP (glioma CpG island hypermethylation) - methylated MGMT already seen as positive biomarker.

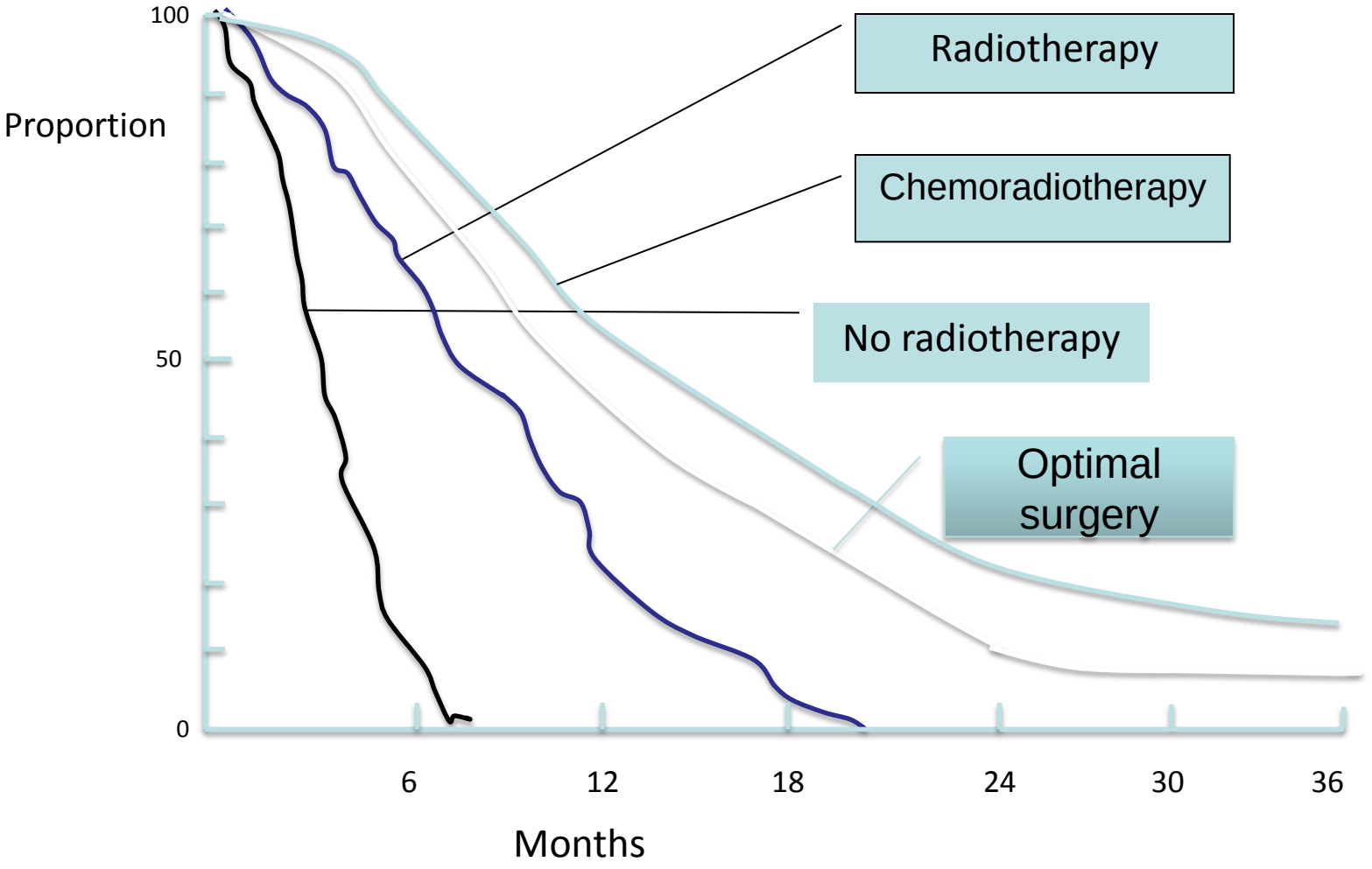
Biomarkers


100
Proportion
50
0
Radiotherapy
No radiotherapy
6
12
18
24
Months

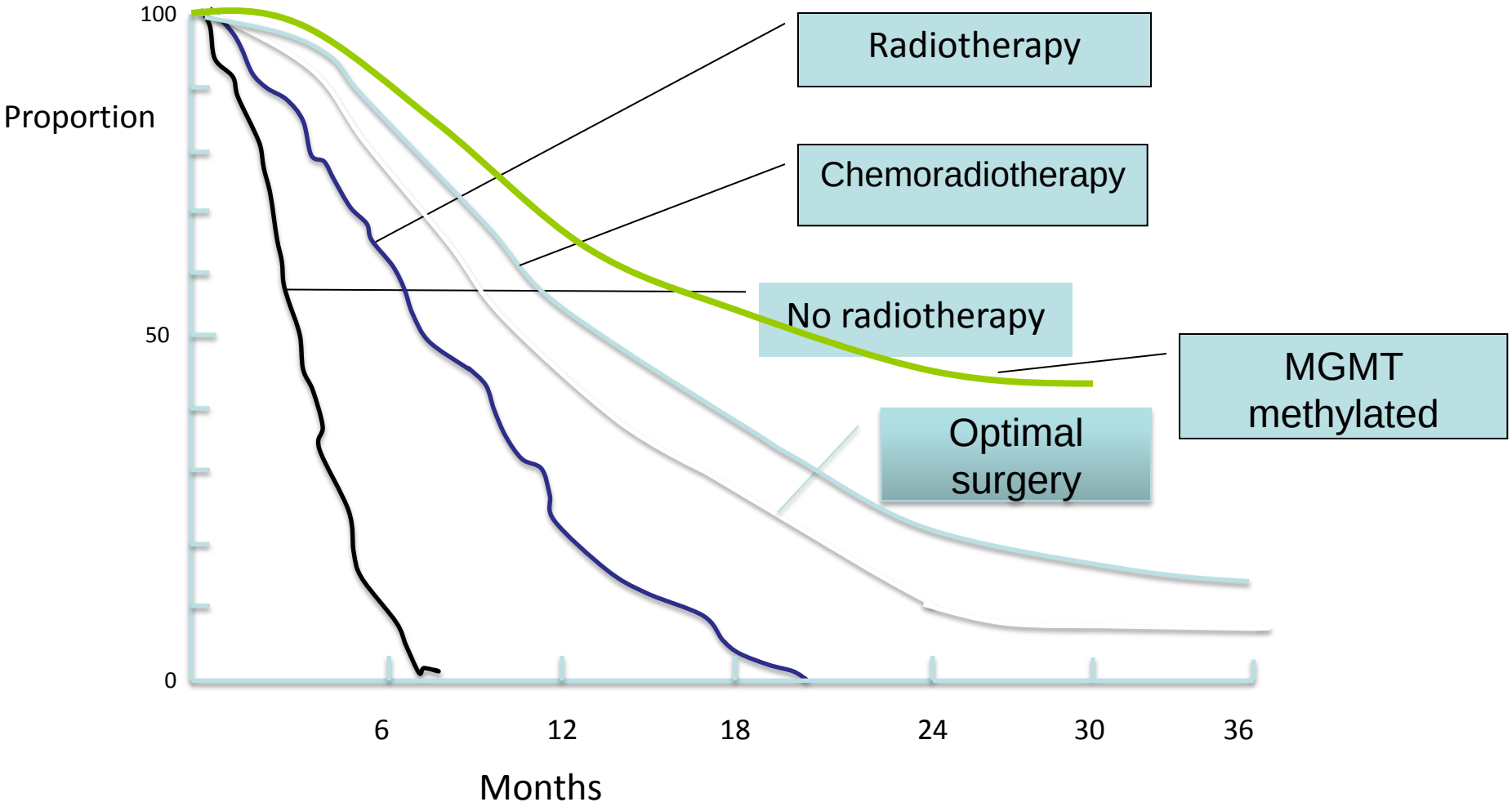
Biomarkers


100
Proportion
50
0
Radiotherapy
No radiotherapy
Optimal surgery
6
12
18
24
30
36
Months

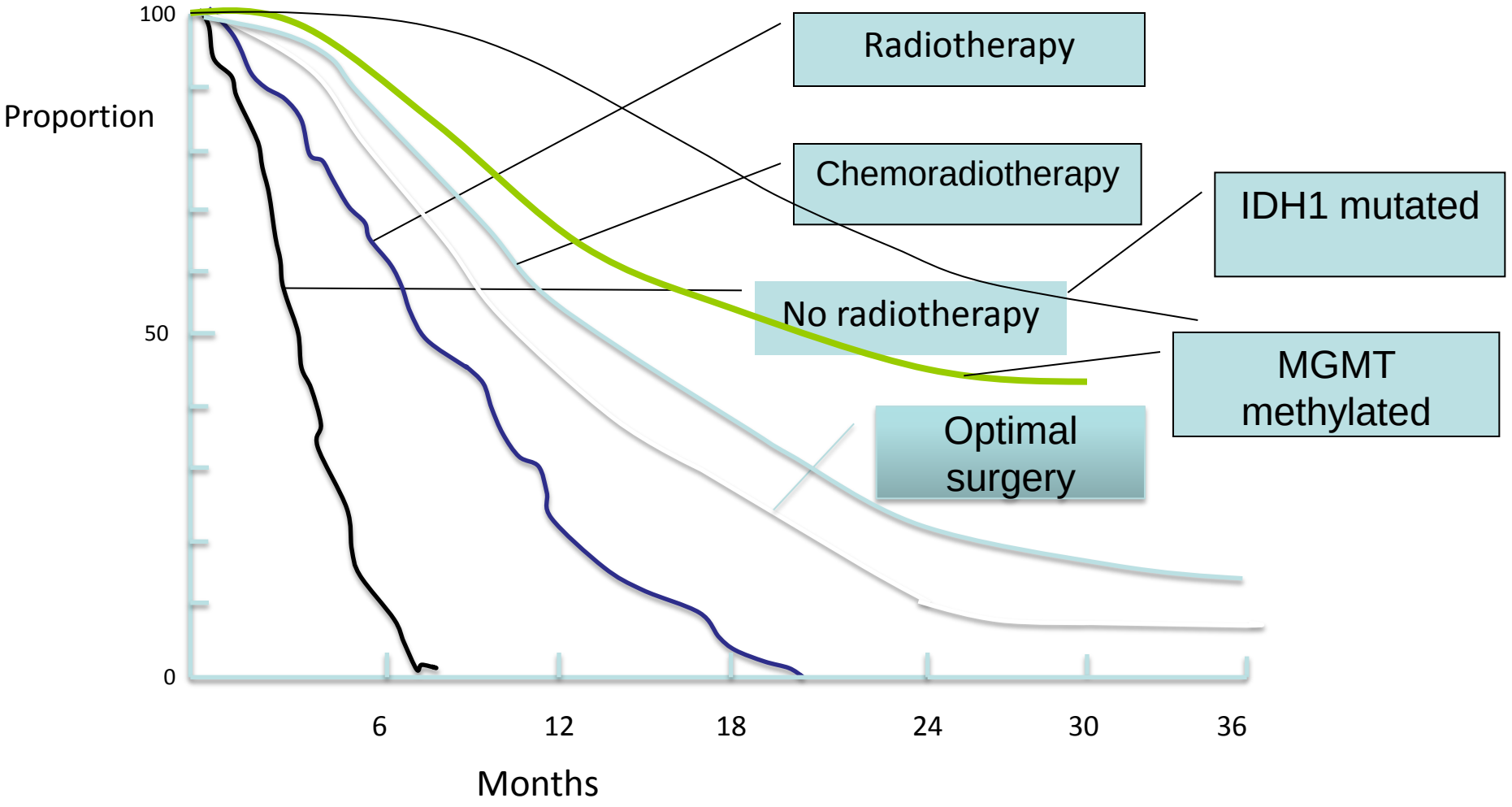
Biomarkers


100
Proportion
50
0
Radiotherapy
Chemoradiotherapy
No radiotherapy
Optimal surgery
6
12
18
24
30
36
Months

Biomarkers


100
Proportion
50
0
6
12
18
24
30
36
Months
Radiotherapy
Chemoradiotherapy
No radiotherapy
MGMT methylated
Optimal surgery

Biomarkers


100
Proportion
50
0
6
12
18
24
30
36
Months
Radiotherapy
Chemoradiotherapy
No radiotherapy
Optimal surgery
IDH1 mutated
MGMT methylated

Glioblastoma is not one disease

Classic

EGFR mutation/amplification/overexpression
PTEN loss/mutation
CDKN2A loss
NES overexpression
Notch & Shh pathways activation

Proneuronal

PDGFRA amplification
IDH1 mutation
PIK3A/PIK3R1 mutations
TP53, CDKN2A & PTEN loss/mutation
Proneural marker expression
(*SOX, DCX, DLL3, ASCL1, TCF4*)
Oligodendrocytic marker expression
(*PDGFRA, OLIG2*, *TCF3* and *NKX2-2*)

Mesenchymal

NF1 loss/mutation
TP53 loss/mutation
PTEN loss/mutation
MET, CHI3L1, CD44, MERTK overexpression
TNF family & NFκB pathways activation

Neuronal

EGFR amplification/overexpression
Gene signature of normal brain
Neuron marker expression
(*NEFL, GABRA1, SYT1, SLC12A5*)
Remains to be better defined

As more markers are discovered, aim is to sub-classify GBM into likely different disease entities, which may ultimately be treated in individual strategies (cf NSCLC)

- Back to chemo
- Known for years that some gliomas responded better to chemo when delivered in palliative setting

Grade 3 LOH 1p19q

- Cairncross et al observed in 1990s that patients with oligodendroglioma component had far higher chemoresponsiveness, up to 80% responding in different case series. Later tied in to codeletion (LOH) of 1p19q.
- So does adding chemo to standard of care (XRT) improves survival?
- EORTC 26951, RTOG 9402
- XRT with adjuvant chemo, or initial chemo followed by XRT, both vs XRT alone – chemo was old-fashioned PCV (procarbazine, CCNU, vincristine)
- Initially published 2006 with ~ 7 years follow-up
- Showed no difference OS between patients, regardless of LOH status

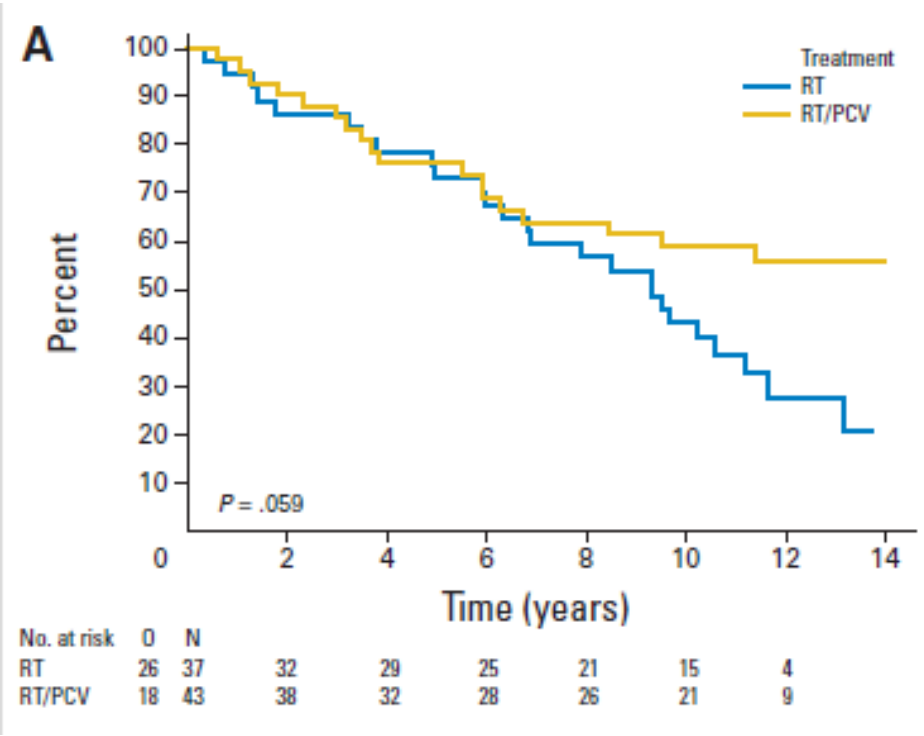
Revised after further follow-up

- 2013, after prolonged follow-up, re-analysed
- Clear late survival advantage for LOH patients only
- Prognostic value of LOH confirmed
- Sequencing of XRT and chemo did not seem to matter
- (No chemo alone arm)

EORTC

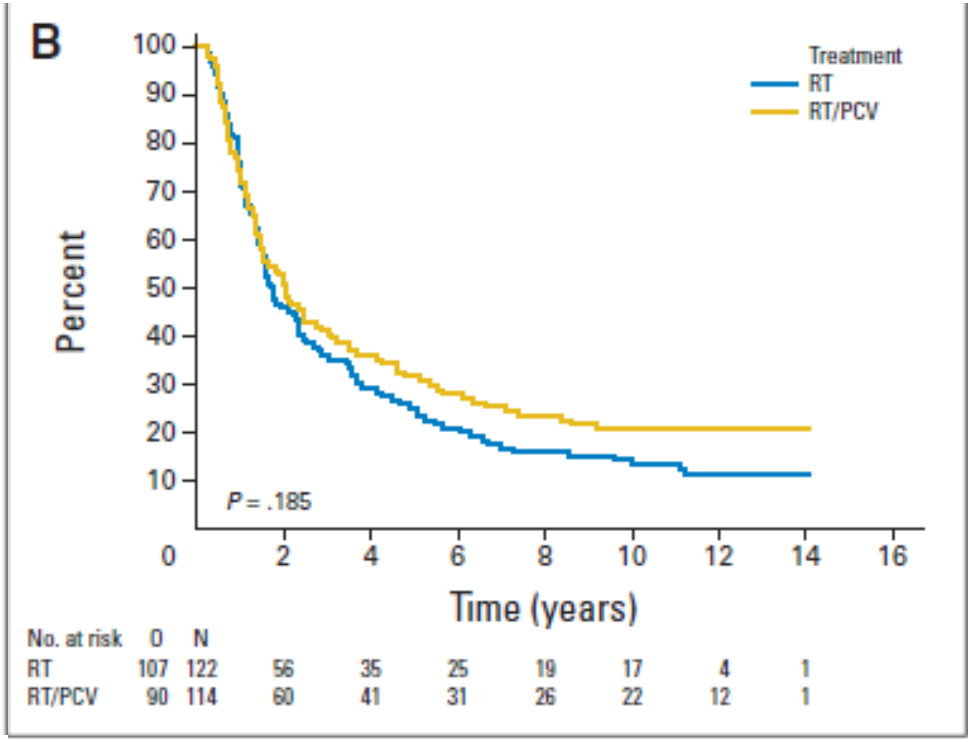
(Oligodendrogliomas)

LOH 1p19q tumours – OS better, late effect



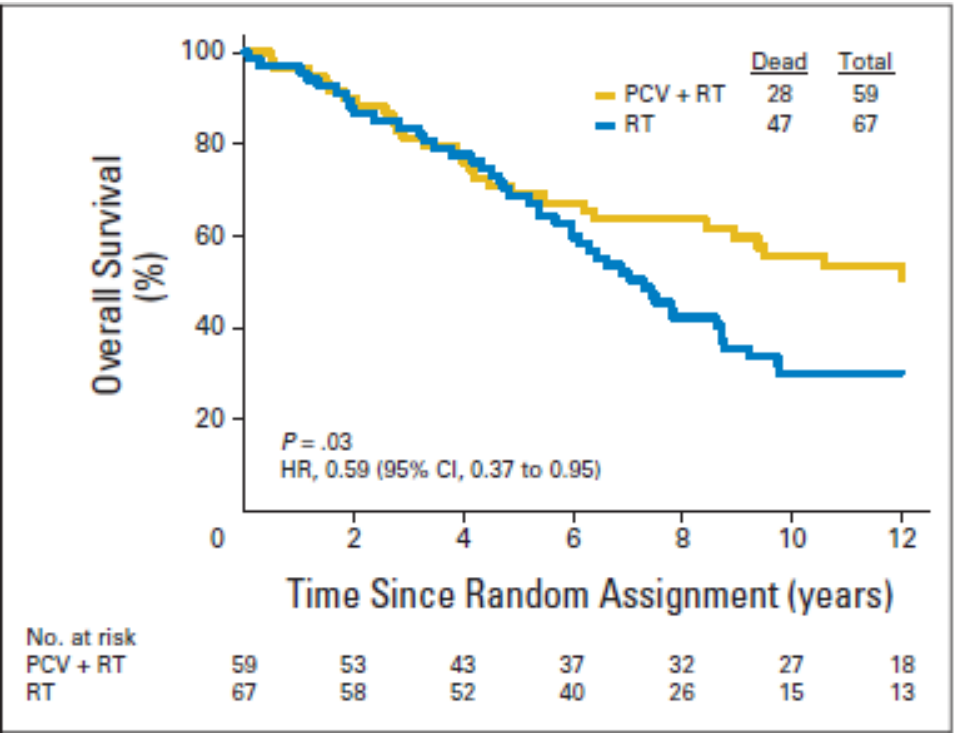
(Astrocytomas)

No LOH – no benefit, poor prognosis

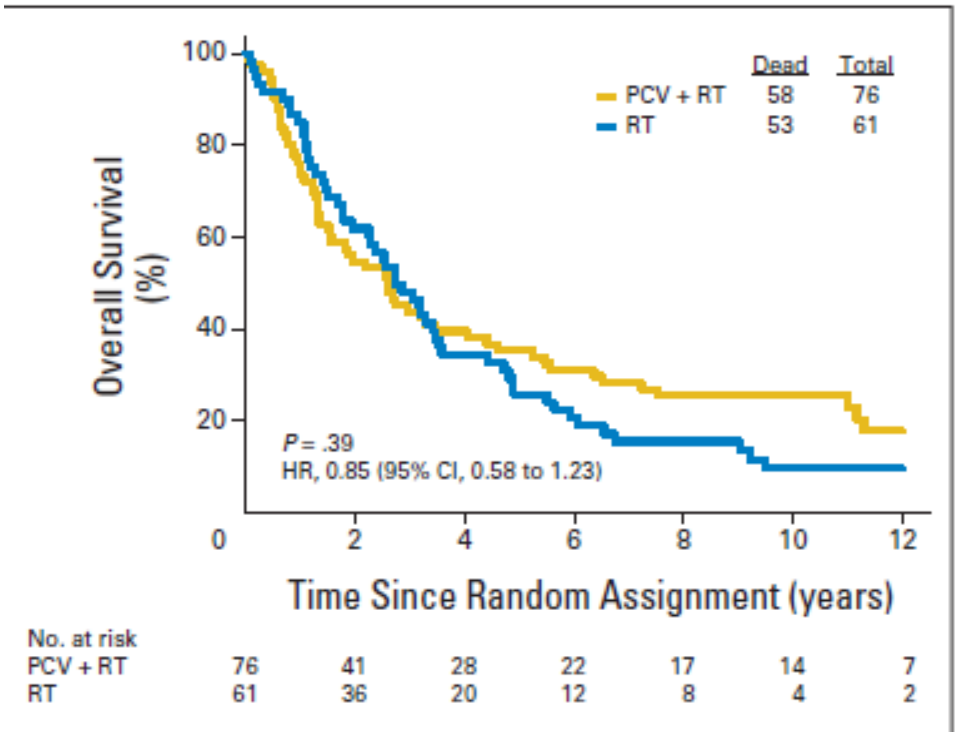


RTOG

LOH – OS better, late effect



No LOH – no benefit, poor prognosis



G3 Oligodendrogliomas, LOH 1p19q

- For co-deleted patients, combination therapy with XRT and chemo accepted as standard-of-care
- Sequencing not important
- ? Can TMZ substitute PCV
- No chemo only arm – is all this benefit conferred by chemo alone? Probably not
- CoDel study being designed (testing concomitant chemo and PCV vs TMZ)
- Shape of survival curves is very unusual

- So GBM –chemoXRT; G3 oligos (codeleted LOH 1p19q) – chemo + XRT
- What about G3 astrocytomas (non-codeleted) and low grade tumours?
- CATNON – XRT + concomitant and/or adjuvant chemo (temozolomide)
- Low grade – RTOG9802 study of XRT vs XRT + adjuvant chemo

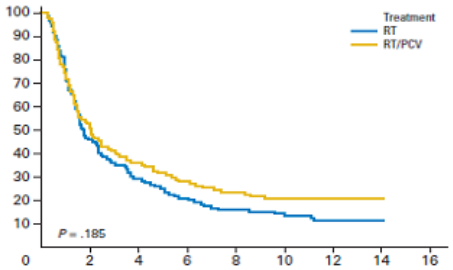
G3 astrocytoma – CATNON – interim analysis

- The IDMC felt that patients still undergoing radiotherapy as well as those patients who have finished radiotherapy treatment within the past three months still may benefit from adjuvant temozolomide. We therefore ask you to identify these patients in your own institution and discuss this recommendation with them.
- Postradiotherapy temozolomide significantly improved overall survival in patients with grade 3 anaplastic glioma without the 1p/19q codeletion.
- After a median follow-up of 27 months, median overall survival was 41.1 months in the radiotherapy-alone arm and had not been reached in the temozolomide arm; 5-year overall survival was 44% and 56%, respectively, representing a 33% reduction in risk (*P* = .003).

Adjuvant temozolomide	Overall survival		PFS
	Median	**% 5 year**	**Median**
No (n = 372)	41.1 months	44.1%	19.0 mo
Yes (n = 373)	Not reached	55.9%	42.8 mo

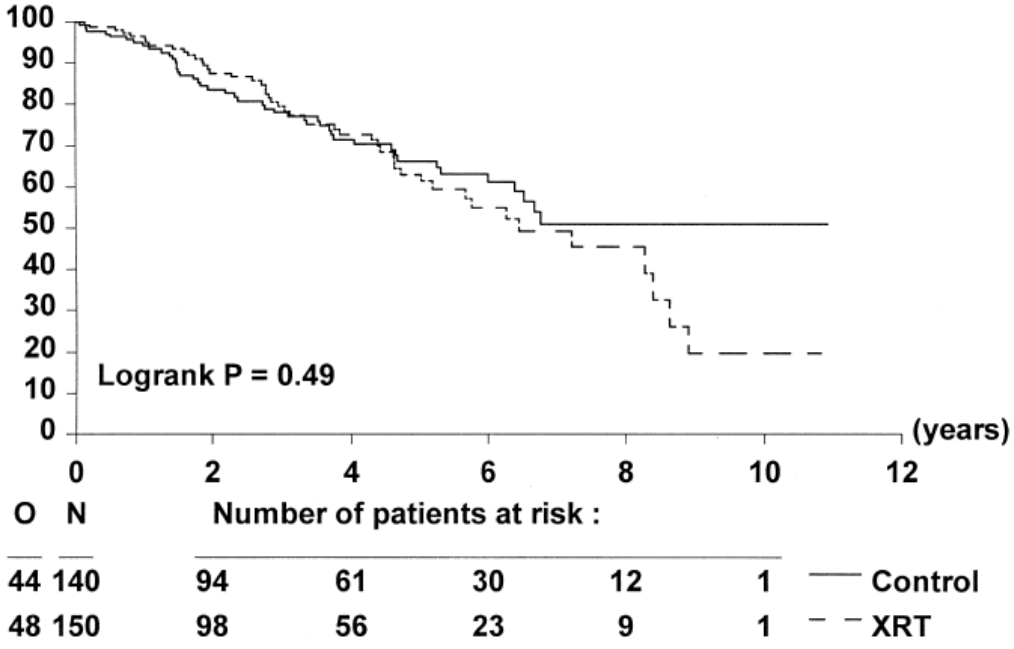
G3 astrocytomas (no LOH)

- So in the studies used to justify sequential XRT/chemo in codeleted patients, adding PCV to XRT had no additional benefit in non-codeleted (astrocytic) tumours

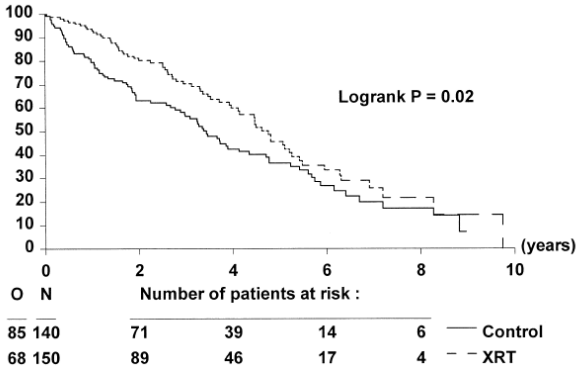


- Yet in CATNON, adjuvant chemo (temozolomide) seems to add benefit
- Are these chemos equivalent, is one better than another. Would TMZ substitution in co-deleted patients have bigger (or no) benefit.

What about Low Grade Disease

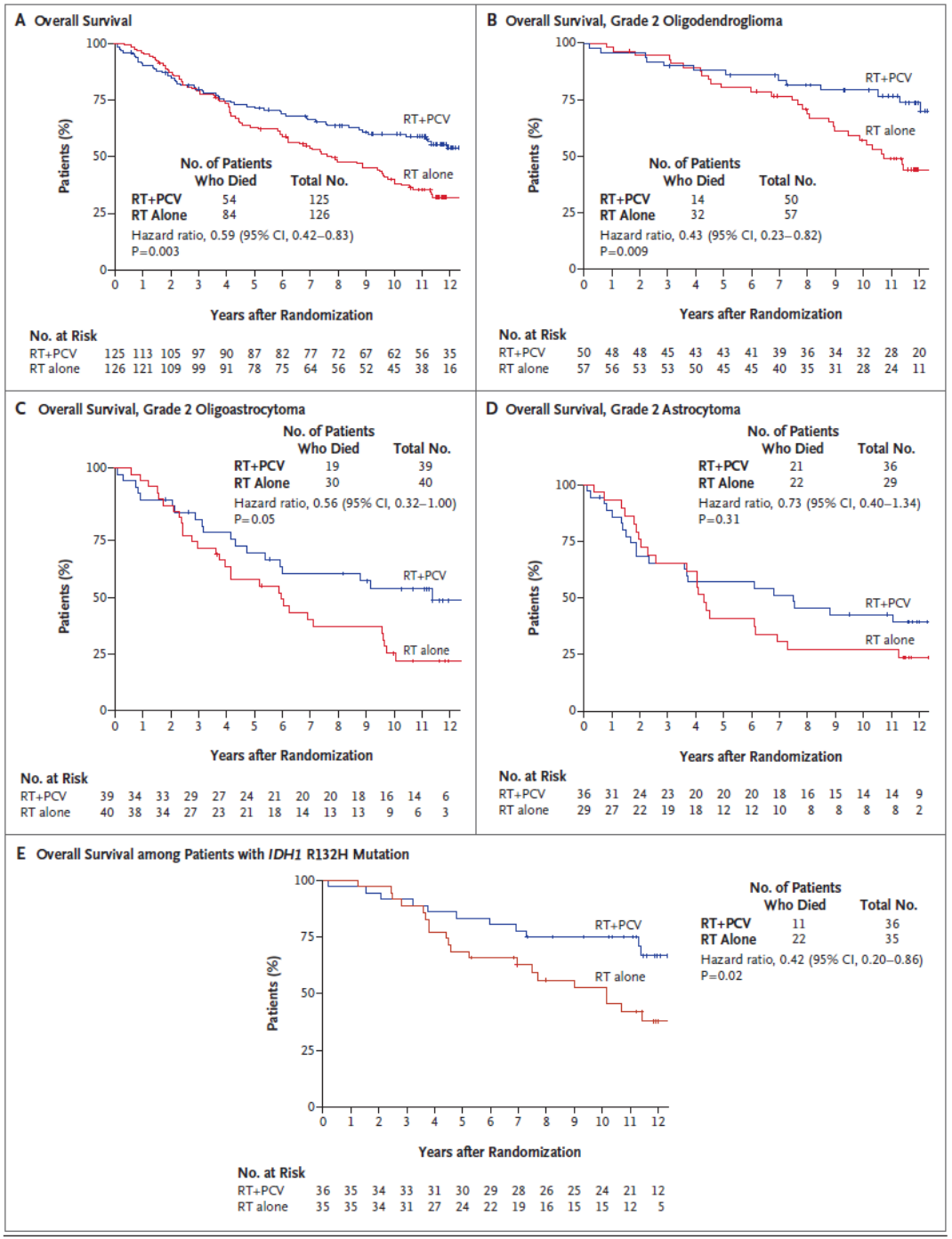


Historical study of immediate vs delayed XRT in newly diagnosed LGG – **<u>overall survival</u>**
How does this data fit with new studies? When to treat?



TTP – XRT does delay progression

"High Risk"
Low Grade Gliomas – RTOG 9802
High risk – anticipated survival <10 years
(Age, size, midline, neuro impairment, enhancement)



Low Grade disease, high risk

- Summary – XRT + chemo better, especially in oligos (cf G3 oligo patients); also benefit in IDH mutated patients (majority of G2 tumours); no statistical benefit in astrocytic tumours (few patients are G2, no LOH, IDH wild type – some might call this such bad prognostic score that should consider as G3 – so XRT + chemo as per CATNON…)
- Controversy - outmoded chemo, can TMZ be substituted?

- Concerns with this study – it is driving early intervention for low grade good prognostic tumours due to clear survival advantage
- But this was a study of what to use when treatment needed, not when to treat.
- Already (admittedly old) evidence saying initial surveillance policy is not detrimental.
- “nothing as damaging for the brain as progressive glioma”
- This is disingenuous – a tumour growing 1mm every 3 years will cause less harm than XRT initially

What's new in Management of Gliomas (LGG)

- XRT can be cognitively damaging – seems dose-dependent (dose/day, total dose), volume of brain, and time dependent (longer one waits, more damage revealed)
- These tend to be younger fitter patients contributing to society, using their brains to work
- Some of this has been demonstrated in studies, some is just observed
- Many will not progress for many years
- Would delaying the start of aggressive multi-modality treatment now be detrimental?
- Even if detrimental, maybe the benefit in terms of QoL / cognition outweighs any survival differences

Chemo Summary…..

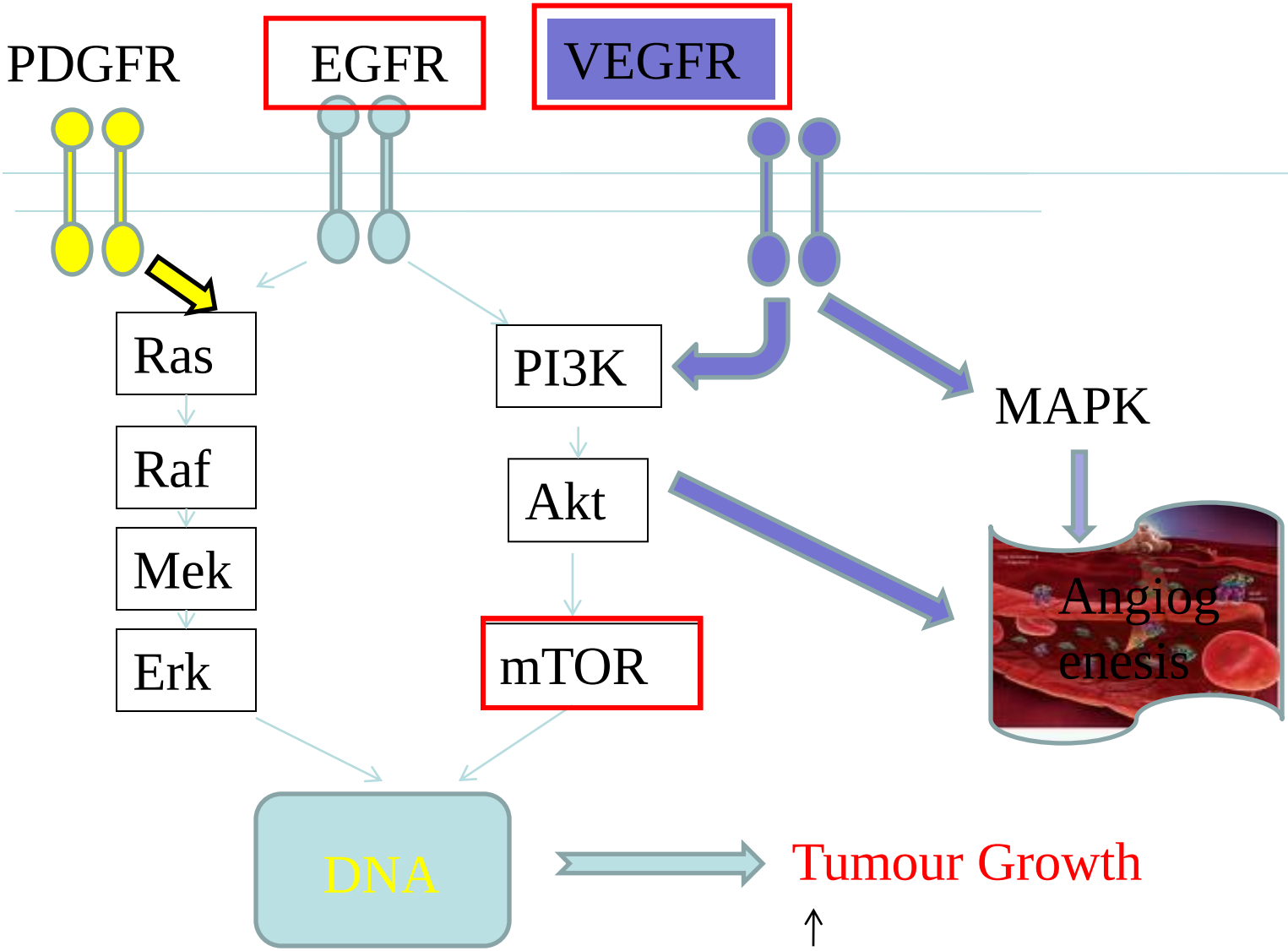
- 10 yrs ago – mainstay of all gliomas was XRT, with a bit of chemo at relapse
- Then added chemo to GBM (G4 disease)
- Then Oligo G3 – add chemo
- Then Astro G3 – add chemo
- Then (almost) all G2 – add chemo

- Difficult now to consider a patient who does not get combined modality therapy
- Probably gone as far as we can with conventional therapy (nearly)
- As treatment intensifies, so does morbidity, early and late
- **Improving survival – increasing risk of surviving long enough to get significant radiation damage**

What’s new in glioma 2018

- So much for conventional chemo, what about all those novel agents
- Biological therapy
- Immunotherapy
- Cannabis….?
- Care oncology cocktail

Targetted (biological) therapy

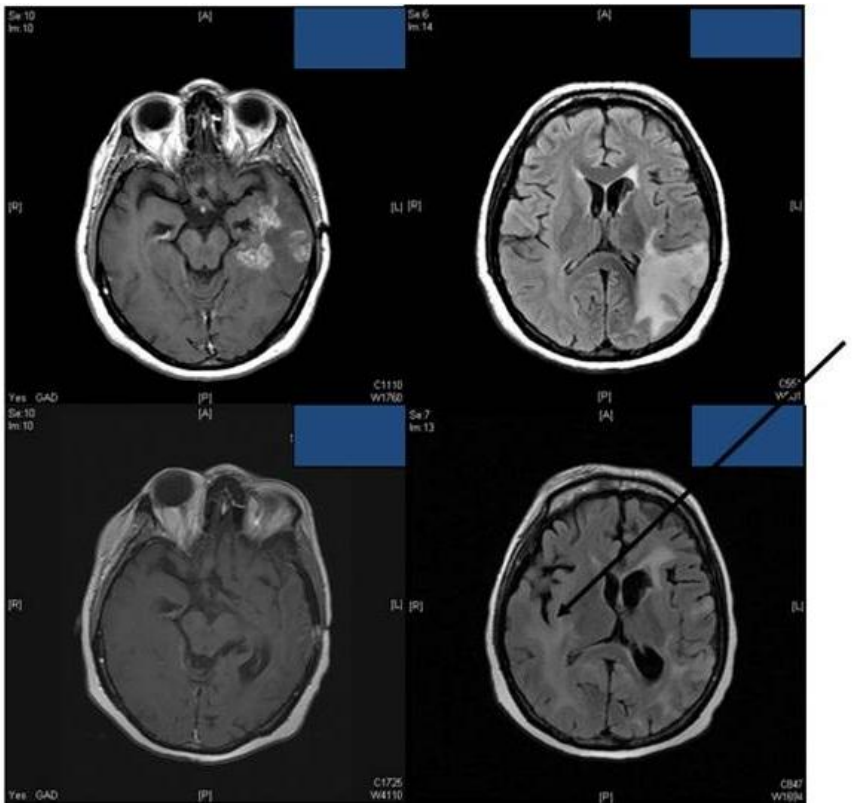


Avastin – bevacuzimab, VEGF

- GBM / HGG – rapid growth, neovascularisation
- VEGF expression high in Gliomas
- Obvious target, initial trials very encouraging response (radiological and symptomatic)

Before Rx.

4 weeks After Rx.



Avastin

- Given expedited FDA licence in gliomas based on response rates and delaying progression
- BUT – these are not true responses – the VEGF inhibitor is stabilising the endothelial lining, “sealing” the BBB, and preventing contrast leakage, improving oedema
- The underlying tumour could well be progressing “unseen”

Avaglio and ROG studies

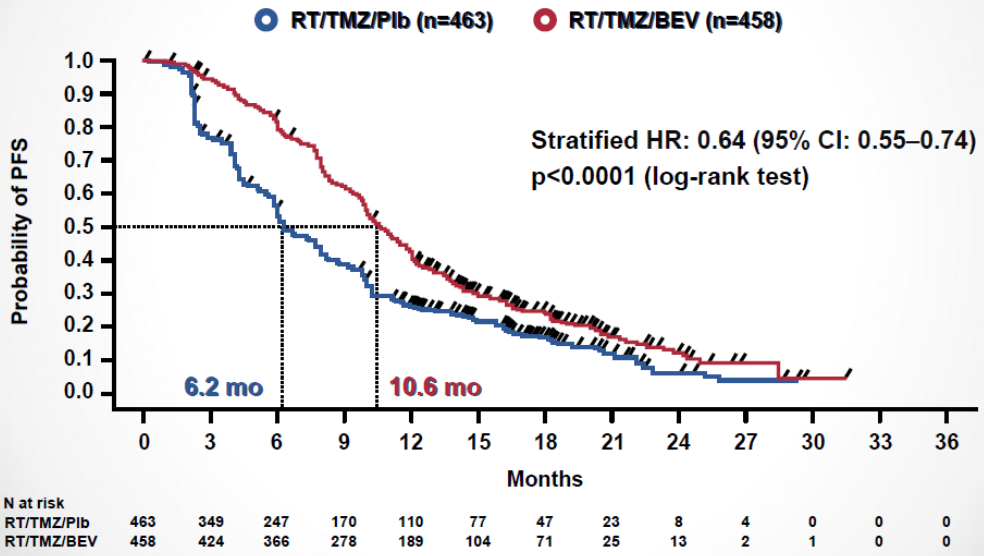
- Adopted as standard of care in many countries prior to any randomised data
- Added avastin to chemo XRT
- 2 large randomised multinational phase 3 trials
- No benefit in OS:

Table 3. Bevacizumab efficacy in newly diagnosed GBM.

	EORTC/NCI [3]	RTOG 0525 [98]	AVAGLIO		ROG 0825	
	XRT/TMZ + TMZ	XRT/TMZ + TMZ	Placebo	BEV	Placebo	BEV
n	287	189	463	458	317	320
Median PFS (months)	6.9	9	6.2	10.6 (HR: 0.64; p < 0.0001)	7.3	10.7 (p=0.004)
Median OS (months)	14.6	16	16.8	16.9	16.1	15.7

Randomized studies assessing the efficacy of standard of care or standard of care plus bevacizumab.

Investigator-Assessed PFS (Co-Primary Endpoint)



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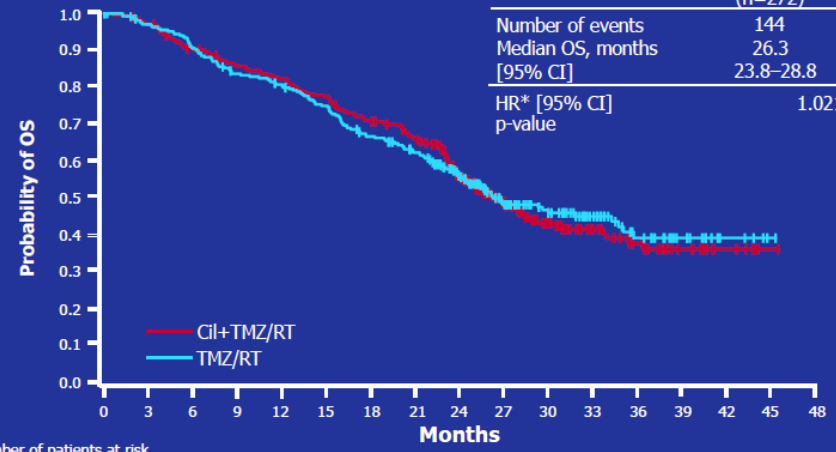
Avastin

- PFS significantly prolonged – patients reportedly stay stable for longer then rapidly deteriorate
- Off avastin, more steady deterioration, more prolonged disability before dying (studies don't demonstrate that actually, but it's the claim)
- Even then, although this is a clear benefit for patients, purely in terms of QoL
- Estimated mean cost/patient would be £18000
- Essentially very good, very expensive version of steroids
- How much are we (NHS) willing to pay for QoL?

New Agents update

- Centric study: integrin inhibitor, methylated MGMT only.
- Integrins – cell surface proteins interact with ECM, help in cell motility.
- Over-epressed in GBM, possible target for therapy
- Negative; no impact on OS

Overall survival (ITT)



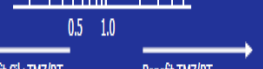
	Cil+TMZ/RT (n=272)	TMZ/RT (n=273)
Number of events	144	138
Median OS, months	26.3	26.3
[95% CI]	23.8–28.8	23.9–34.7
HR* [95% CI]	1.021 (0.808–1.291)	
p-value	0.8623	

Number of patients at risk

Cil+TMZ/RT	272	263	242	228	218	205	187	169	122	84	55	36	25	14	6	1	0
TMZ/RT	273	259	242	221	212	196	172	155	120	80	58	40	24	14	5	1	0

Subgroup analyses – overall survival

Subgroup	(number of patients)	Median (months) Cil+TMZ/RT vs TMZ/RT	HR* [95% CI]
Overall Survival	ITT population (n=545)	26.3 vs 26.3	1.01 [0.80 , 1.28]
MGMT ratio	<log2(8) (n=67)	24.3 vs 24.6	1.01 [0.52 , 1.96]
	>=log2(8) (n=477)	26.8 vs 26.9	1.02 [0.80 , 1.32]
Change of cut-off value for MGMT-status	Randomized before adaptation of cut-off (n=244)	28.0 vs 30.0	1.04 [0.74 , 1.47]
	Randomized after adaptation of cut-off (n=301)	25.0 vs 25.4	0.99 [0.72 , 1.37]
Age	<50 years (n=136)	NR vs NR	0.95 [0.54 , 1.67]
	>=50 years (n=409)	24.0 vs 24.5	1.04 [0.80 , 1.34]
Gender	Male (n=291)	25.3 vs 26.8	1.04 [0.75 , 1.43]
	Female (n=254)	27.2 vs 26.2	0.97 [0.69 , 1.36]
Ethnic origin	Caucasian/white (n=419)	25.0 vs 25.7	0.97 [0.75 , 1.27]
	Other (n=90)	28.4 vs NR	1.44 [0.76 , 2.73]
Region	North America (n=65)	23.2 vs 29.6	1.12 [0.56 , 2.26]
	Europe (n=368)	27.9 vs 24.6	0.89 [0.67 , 1.18]
	Rest of the world (n=112)	25.1 vs 34.7	1.46 [0.86 , 2.50]
RPA class	Class III (n=86)	NR vs 35.1	0.63 [0.31 , 1.31]
	Class IV-V (n=453)	25.0 vs 25.7	1.08 [0.84 , 1.39]
ECOG PS	ECOG PS 0 (n=307)	29.3 vs 26.9	0.86 [0.63 , 1.20]
	ECOG PS >= 1 (n=237)	23.3 vs 26.1	1.24 [0.88 , 1.74]
MMSE	MMSE <27 (n=106)	20.4 vs 18.3	1.35 [0.86 , 2.13]
	MMSE >=27 (n=432)	28.8 vs 31.9	0.99 [0.75 , 1.31]
Steroid use at baseline	Yes (n=216)	23.2 vs 25.4	1.05 [0.75 , 1.49]
	No (n=329)	28.4 vs 34.3	1.02 [0.74 , 1.40]
Extent of surgery	Total resection (n=269)	30.4 vs 34.3	0.95 [0.67 , 1.36]
	Non Total Resection (n=274)	23.8 vs 23.6	1.03 [0.75 , 1.40]
Antiepileptics at baseline	EIAED (n=111)	33.7 vs 24.4	0.79 [0.46 , 1.36]
	Non-EIAED (n=220)	26.2 vs 25.9	0.99 [0.68 , 1.43]
	No Anti-epileptics (n=213)	25.3 vs 26.9	1.17 [0.81 , 1.70]

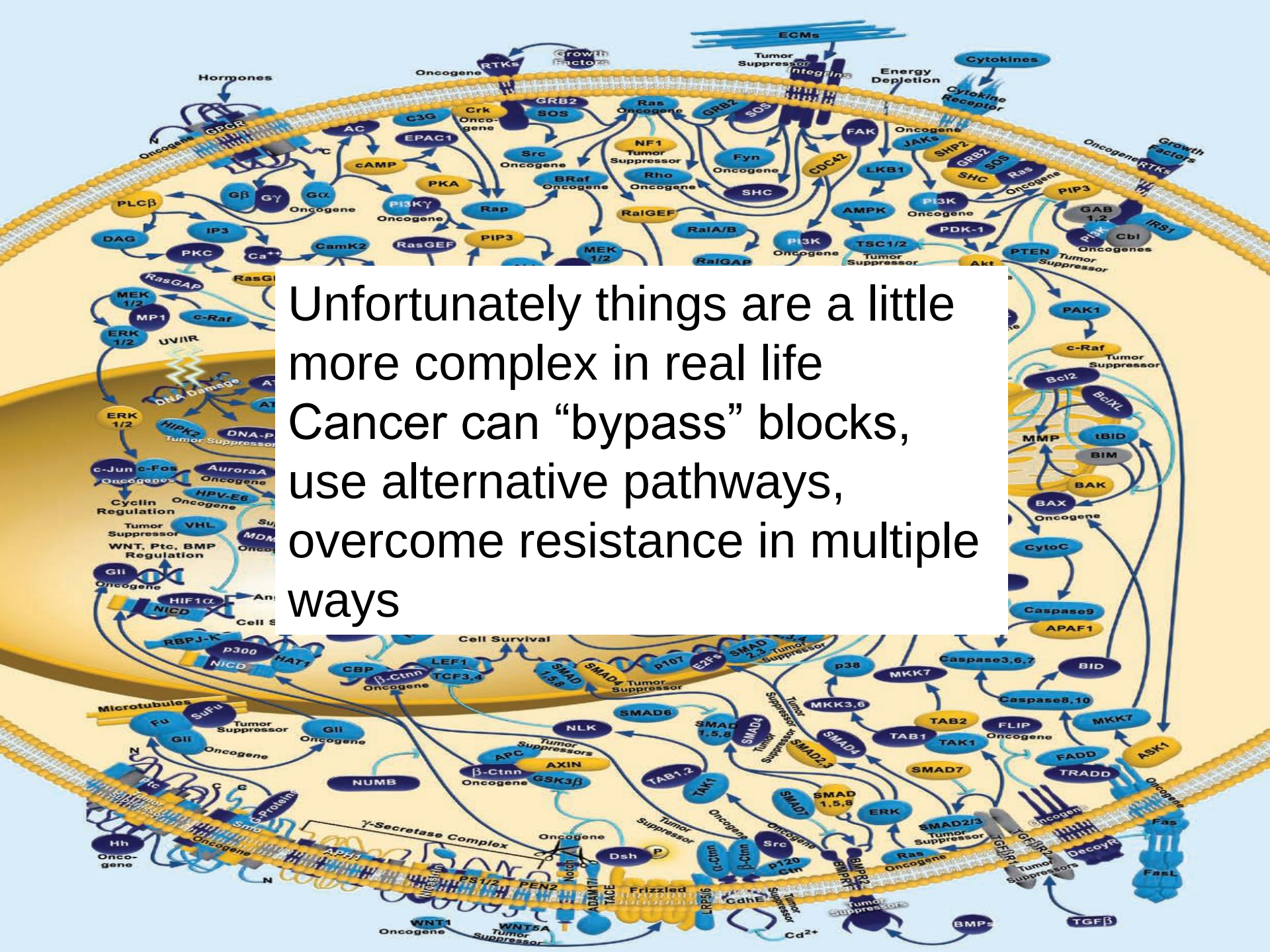


*Unstratified HR.
NR, median not yet reached.

CENTRIC - No difference in OS / PFS

New Agents update

- Centric study: integrin inhibitor, methylated MGMT only.
- Integrins – cell surface proteins interact with ECM, help in cell motility.
- Over-epressed in GBM, possible target for therapy
- Negative; no impact on OS
- Avastin in recurrence – again Phase 3 randomised studies have been presented demonstrating no survival benefit (despite phase 2 data)


Unfortunately things are a little more complex in real life
Cancer can “bypass” blocks, use alternative pathways, overcome resistance in multiple ways

Targetted Therapy

- Problem:
- Not as simple as this, cancers rarely reliant on one growth pathway, and can bypass any blocks
- Solution – “dirty drugs”
- Multiple agents? – cost!
- Combine with cytotoxic agents?
- Combine with radiotherapy?
- Individualised therapy? (genetic sequencing)

Novel agents

- Immunotherapy – too early to tell
- Intriguing results in other cancers
- Early phase trials ongoing in glioma – vaccines, checkpoints inhibitors, oncolytic viruses, et al
- One randomised trial so far in recurrence – Nivolumab vs avastin – no difference
- Survival in recurrent GBM (median 3-6 months0 may be too short to demonstrate a benefit to such agents
- Cause for concern – gliomas seem able to influence the local immune environment in their favour. Jury is out still.

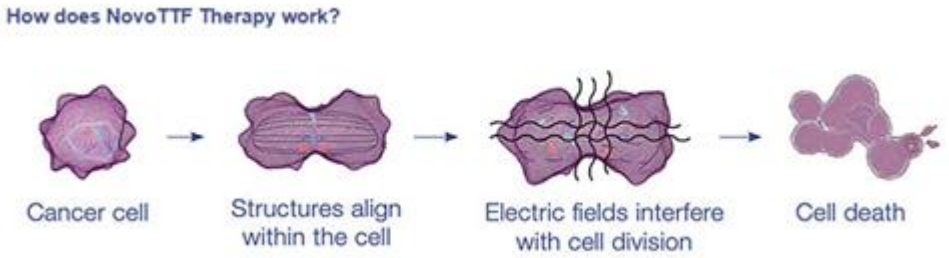
- What about one that does work….
- TTF

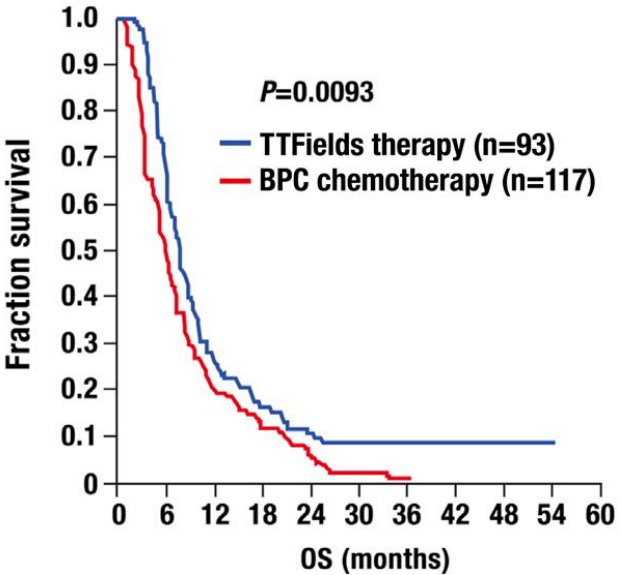
TTF

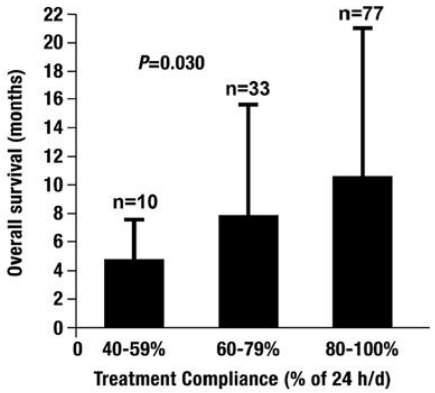
novocure™

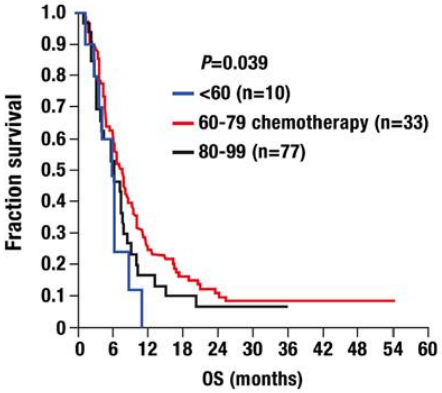
TTF

- The system delivers low-intensity (>0.7 V/cm), intermediate-frequency (200 kHz), alternating electric fields or Tumor Treating Fields (TTFields) to the brain via non-invasive transducer arrays attached to the shaved scalp of glioblastoma patients.









Of course, all this is saying is if you remain fit and use the machine you live longer. If you deteriorate, you die….

TTF

- Randomised study of standard CRT vs CRT + TTF – 542 pts
- Two-year survival rate among patients treated with TTFields, in combination with temozolomide, in the as-treated population, was 48% compared to 32% among patients treated with temozolomide alone (p=0.0058)
- Problems – trial was stopped early as “target achieved”; stats severely criticised; follow-up short, as lengthens, figures are apparently drawing together; no placebo; more chemo was administered to TTF group (reason unclear)
- Previous negative studies, but now this one. ?relevance
- $21000 per month. (my patient quoted £30,000)
- Per month.
- (name changed to “optune TTF”)
- Ethics of that cost are questionable

Other approaches

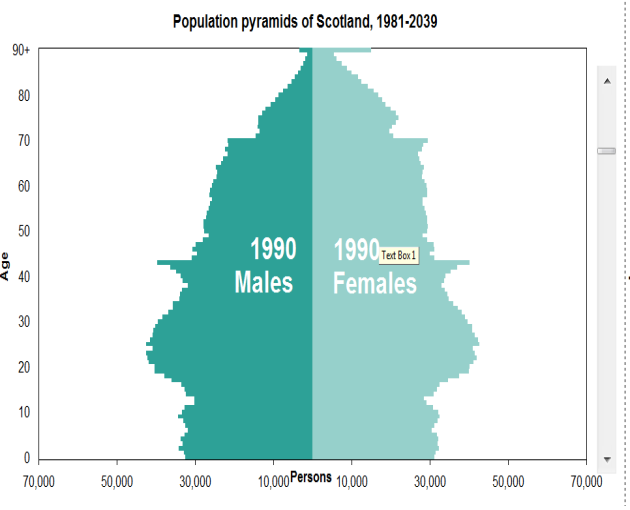
- Cannabis – how to take, what formulation, how much, how effective.
- Metformin, statins, anti-virals others (as recommended by Care Oncology)
- Ketogenic diet – “starve the cancer of glucose”
- Evidence for these:

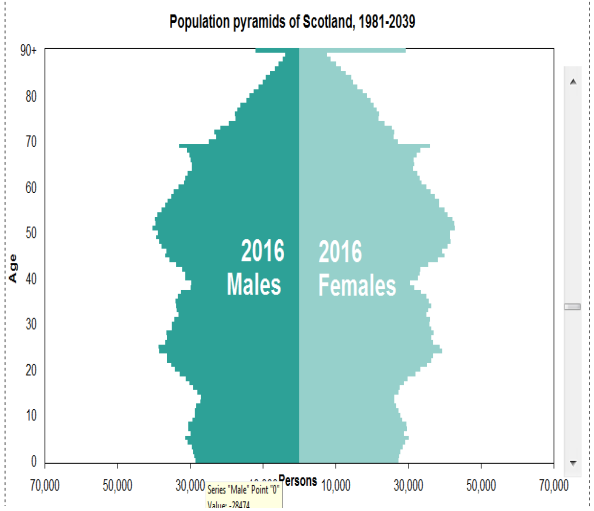
Other novel approaches

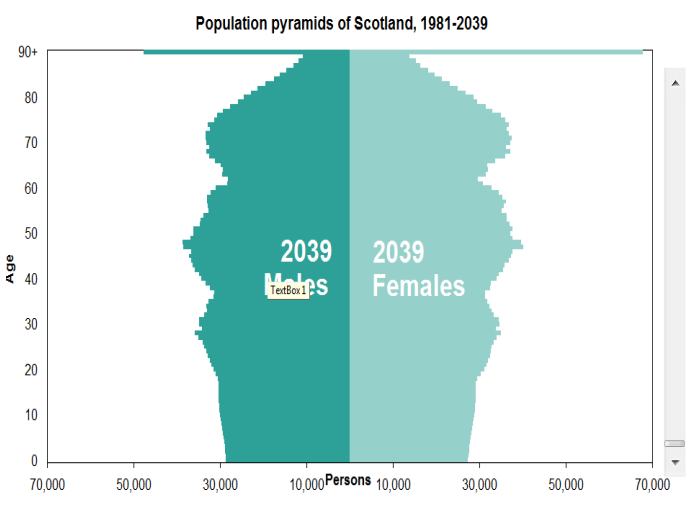
- More scientifically, a number of radio-sensitising strategies are being explored – PARP inhibitors, ATM inhibitors, wee-1 inhibitors.
- Theory is that glioma cells are the only real proliferating cell, so the normal tissue morbidity should not be increased while tumour kill is.
- Not quite true – late morbidity felt to be secondary to microvascular changes, and the blood vessel cells will be no different to elsewhere in body. Unclear if this argument will hold up.

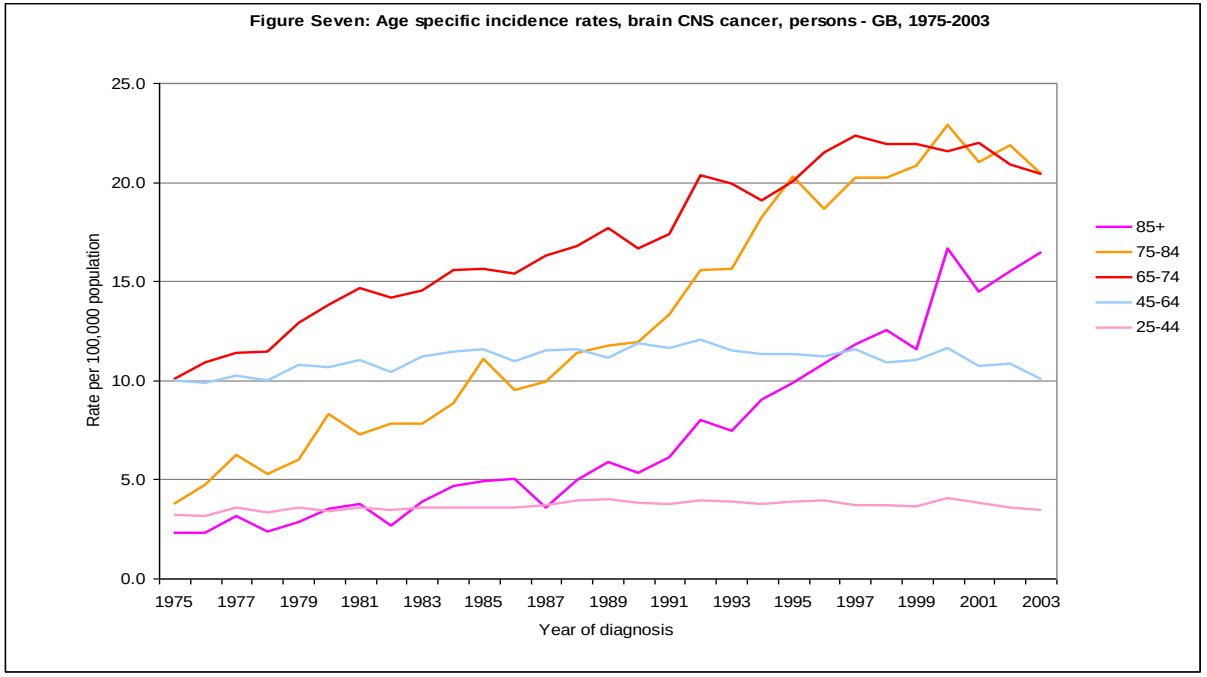
Finally…

- What's really new in gliomas?
- A massive upcoming challenge:
- Clinics are changing over next 20-30 years





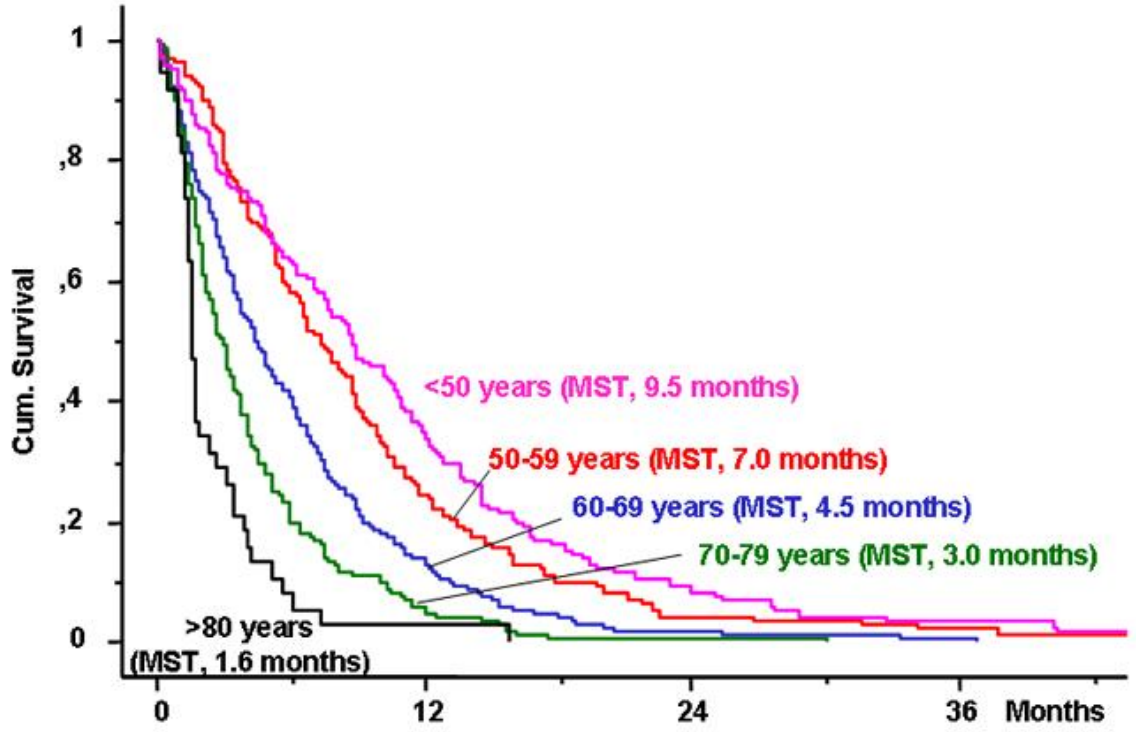




Double whammy – increasing age and glioma incidence increases with age

The elderly

Age is the single most powerful prognostic factor in glioma outcome



Ohgaki H et al. *Cancer Res* 64: 6892-6899 (2004)

The elderly

- Elderly in gliomas is >60
- We must get better at treating elderly patients, outcomes are grim and numbers increasing rapidly.
- No solutions above to this upcoming epidemic