

Adjuvant therapies for brain tumours

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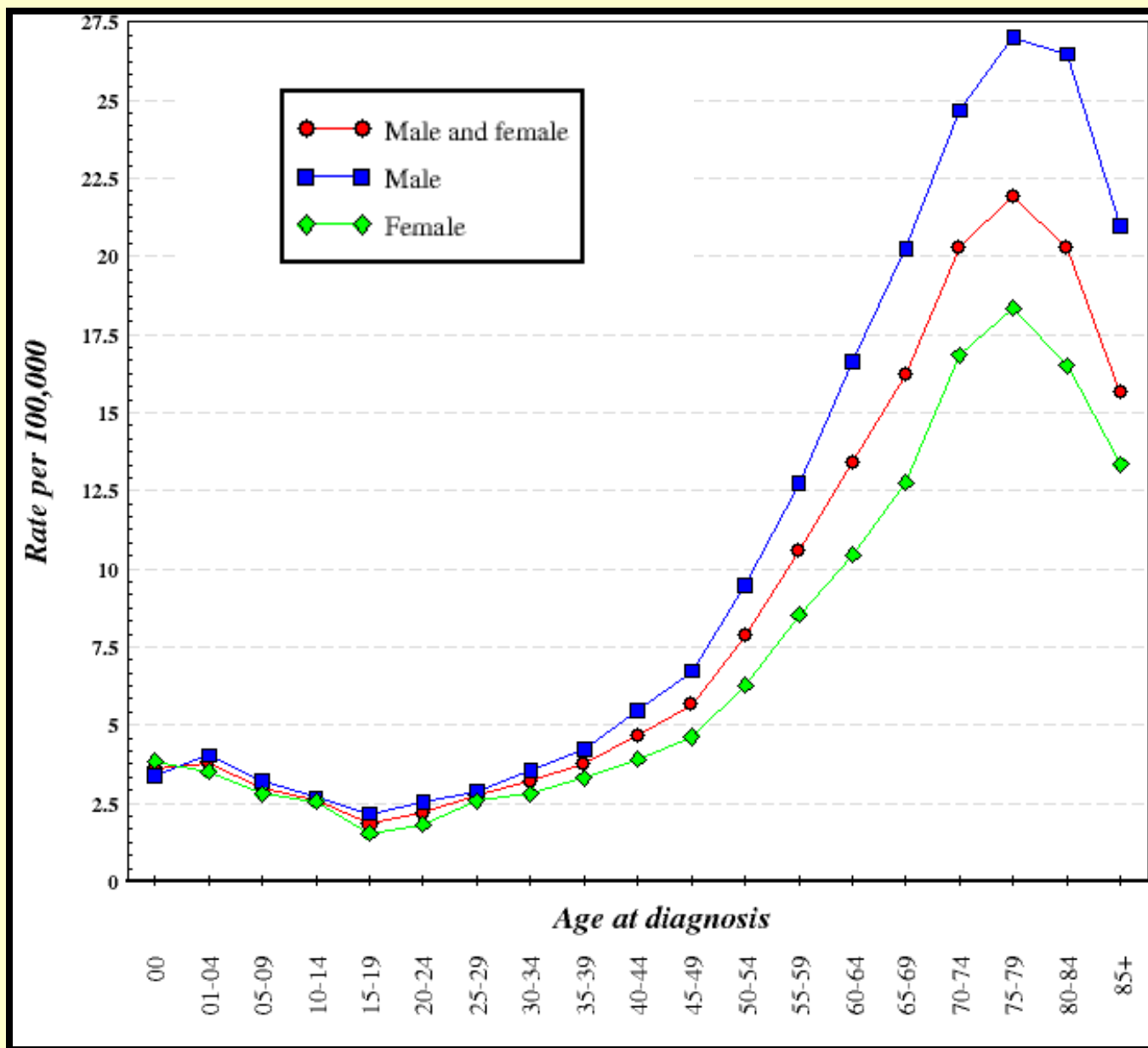
Primary brain tumours

- arise within the brain
- do not metastasise
- distinct from brain metastases
- rare but important...

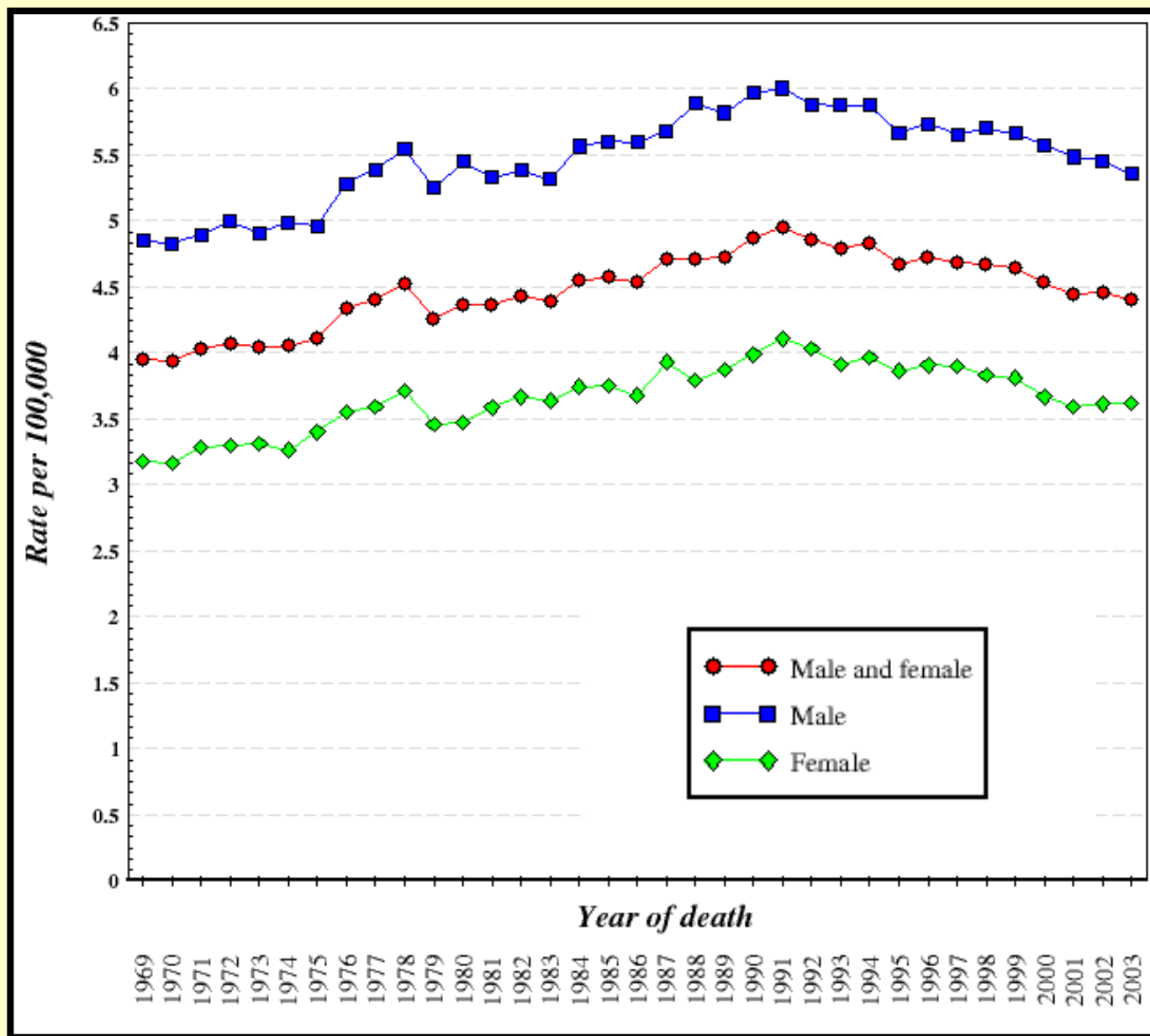
Primary brain tumours

- 8,600 new cases in UK per year
- incidence 7:100,000
- incidence and mortality increasing until recently
- 32% will live for 1 year or longer
- 15% will live for 5 years or longer
- severe physical, psychological and emotional symptoms
- breast cancer: 12.1 years life lost on average
- brain tumours: 20.4 years life lost on average

USA incidence rates for primary brain tumours



USA mortality rates for primary brain tumours



Primary brain tumours

- gliomas: arise from brain connective tissue (glial cells)
- meningiomas: arise from the meninges, usually benign
- primary CNS lymphoma: v. rare
- other types: v. v. v. rare

Primary brain tumours

- grade 1:

low grade

- grade 2:

pilocytic astrocytoma
children only

low grade (diffuse) astrocytoma
very slowly growing
may transform to high grade

- grade 3

high grade

- grade 4:

anaplastic astrocytoma
anaplastic oligodendroglioma

glioblastoma



Juvenile pilocytic astrocytoma



low grade
astrocytoma



glioblastoma

What does 'adjuvant' mean?

- 'furnishing added support'
- 'serving to help or assist; auxiliary'
- 'anything that aids in removing or preventing a disease, especially a substance added to a prescription to aid the effect of the main ingredient'
- '*Medicine/Medical*: utilizing drugs, radiation therapy, or other means of supplemental treatment following cancer surgery'

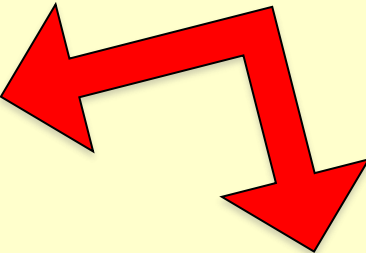
Oncological management

- Optimise quality of life / performance status
 - steroids to reduce cerebral oedema
 - reduce dose / discontinue as rapidly as possible
 - anticonvulsants
 - refer to other specialists as appropriate
- Assess patient and discuss non-surgical treatments
 - 'primary therapy' if tumour not resected or debulked
 - 'adjuvant therapy' following tumour resection or debulking

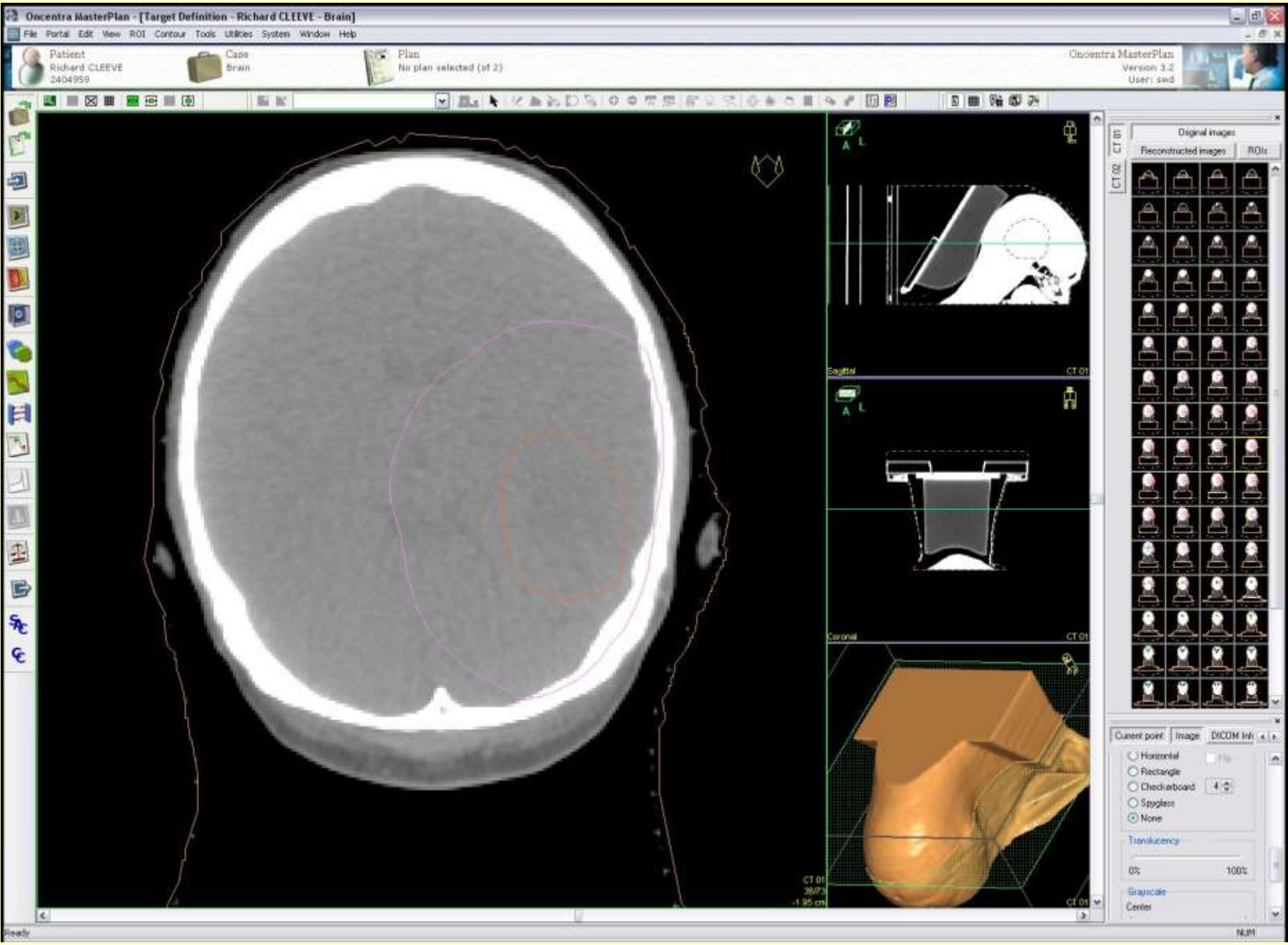
Oncological management

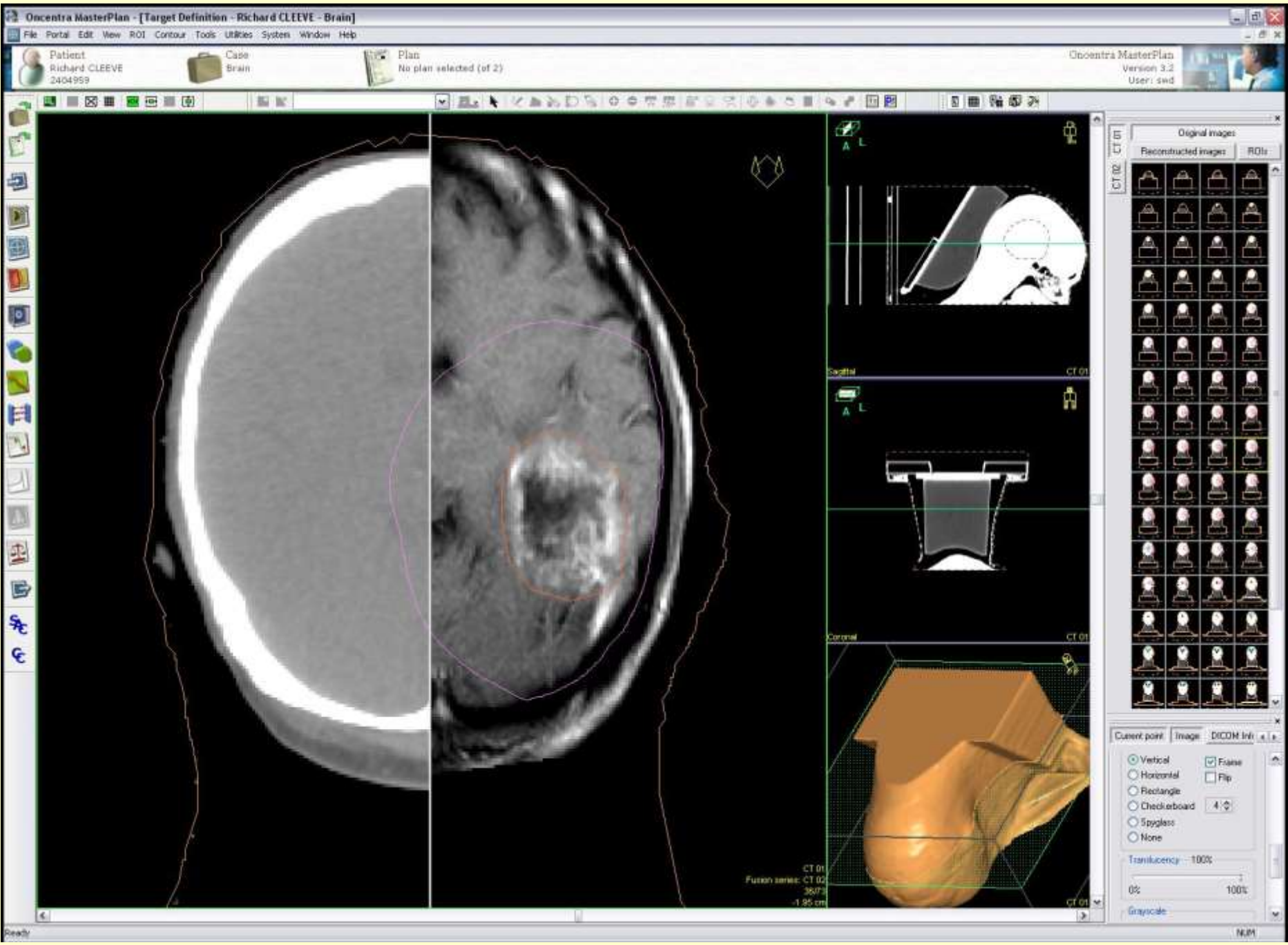


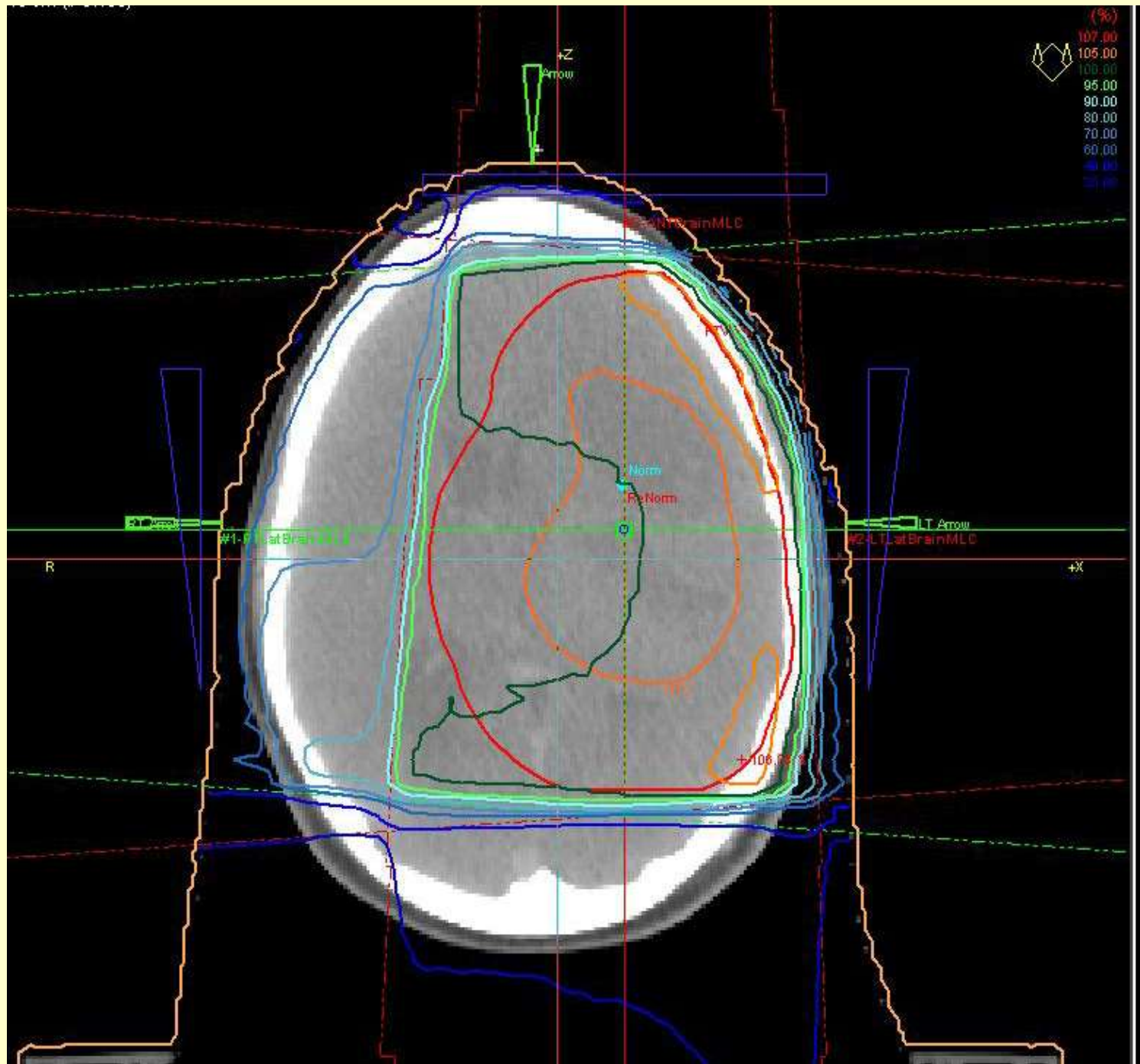
Principles of oncological treatment

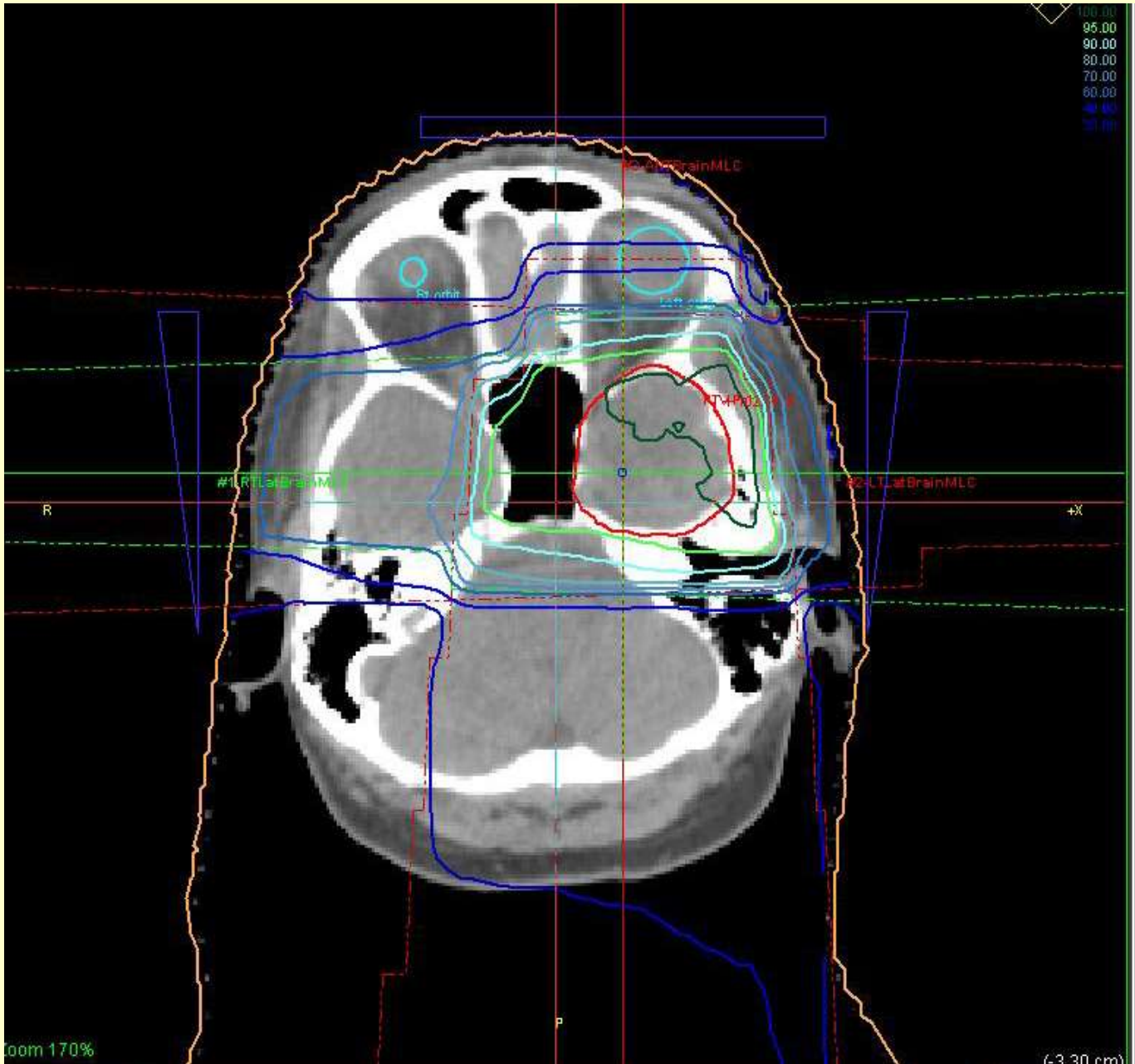
- Extend life
 - Improve or maintain quality of life
 - Minimise risks of side-effects
 - Acute (temporary)
 - Late (permanent)
 - Use evidence-based treatment(s) wherever possible
 - Enable patients to participate in clinical trials
- 

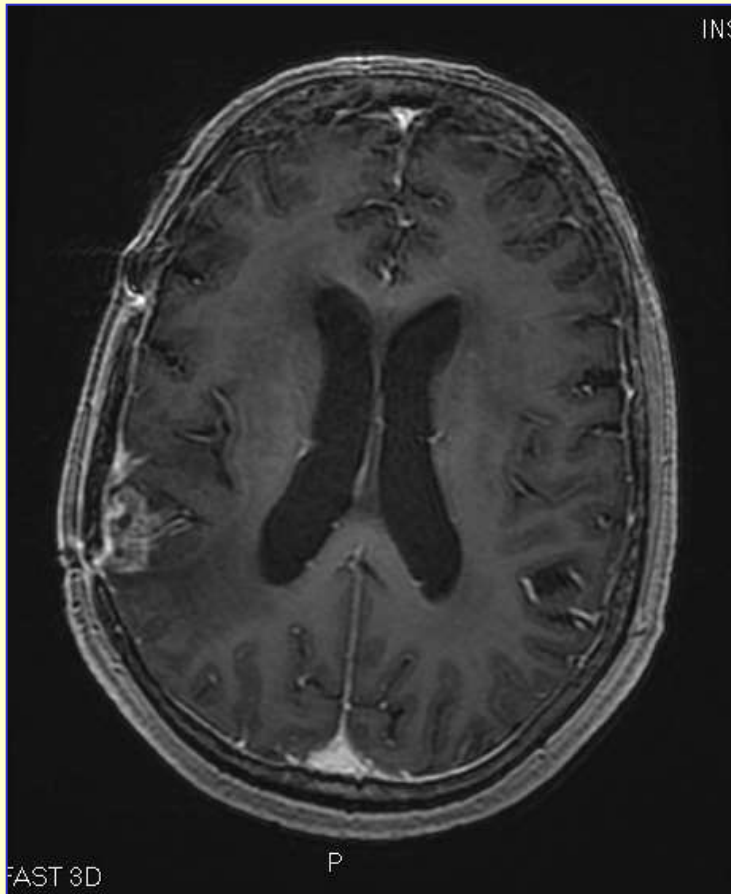




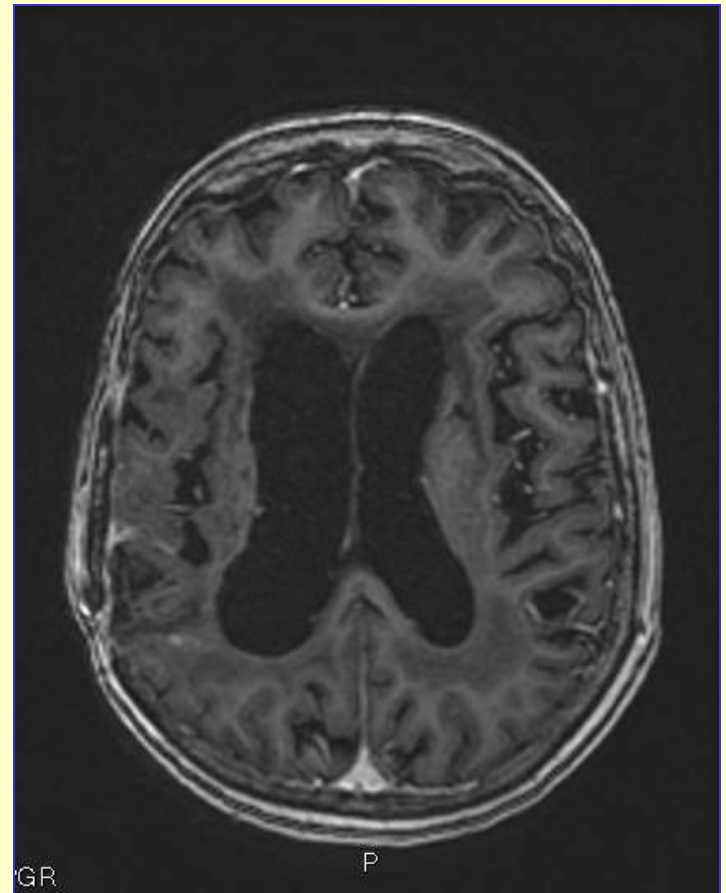








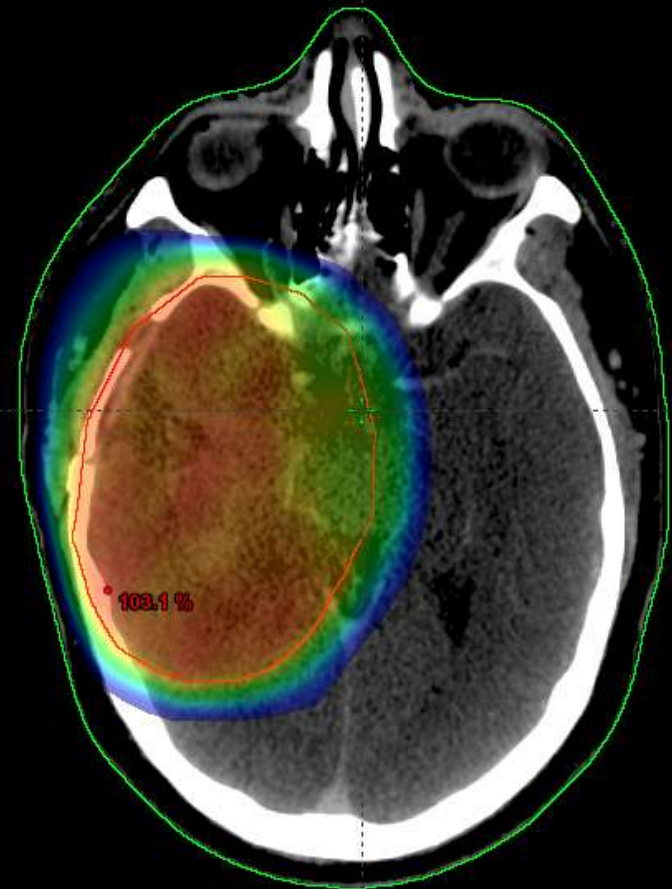
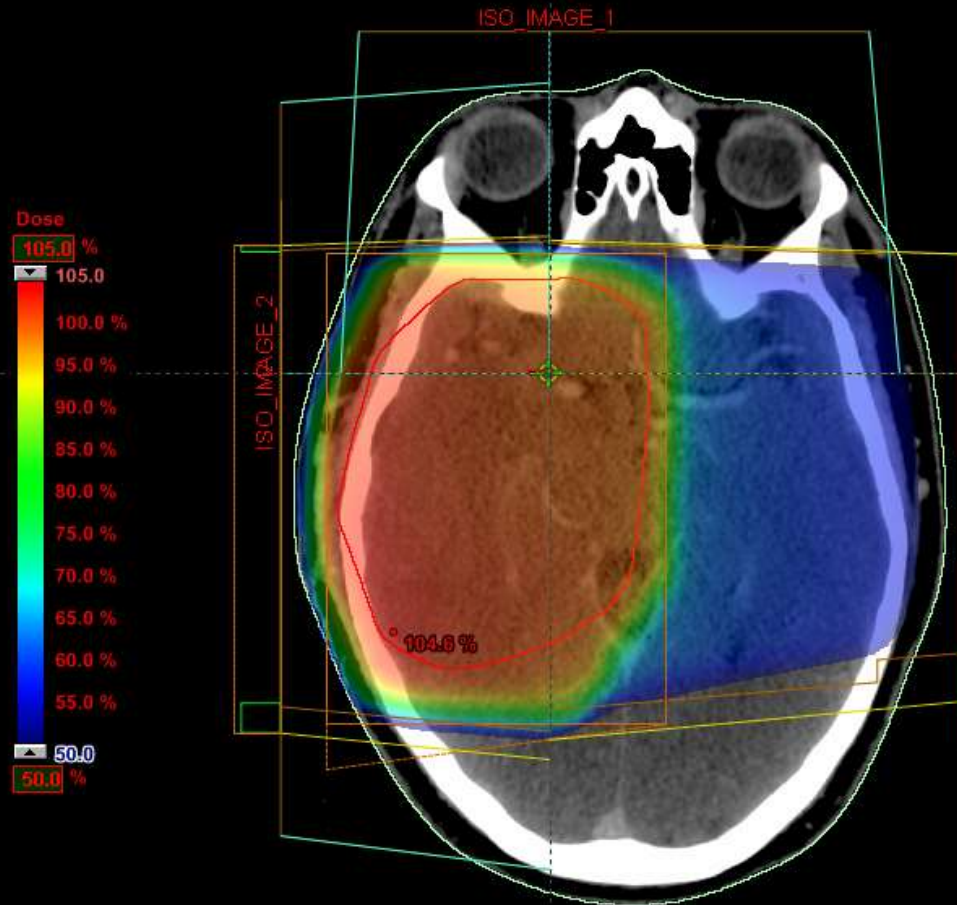
Pre-radiation

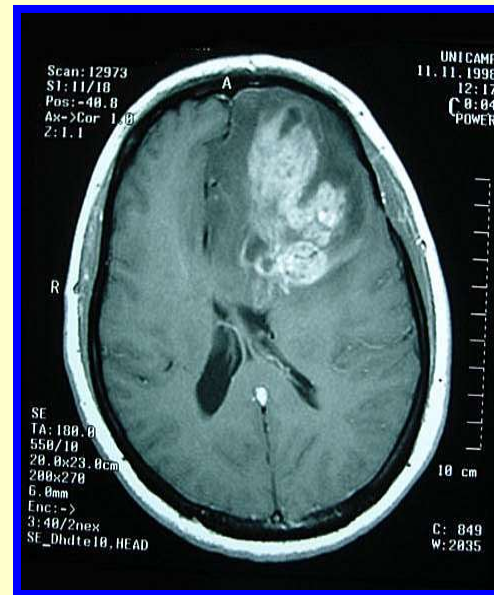


18 months
post-radiation

Conformal RT

IMRT

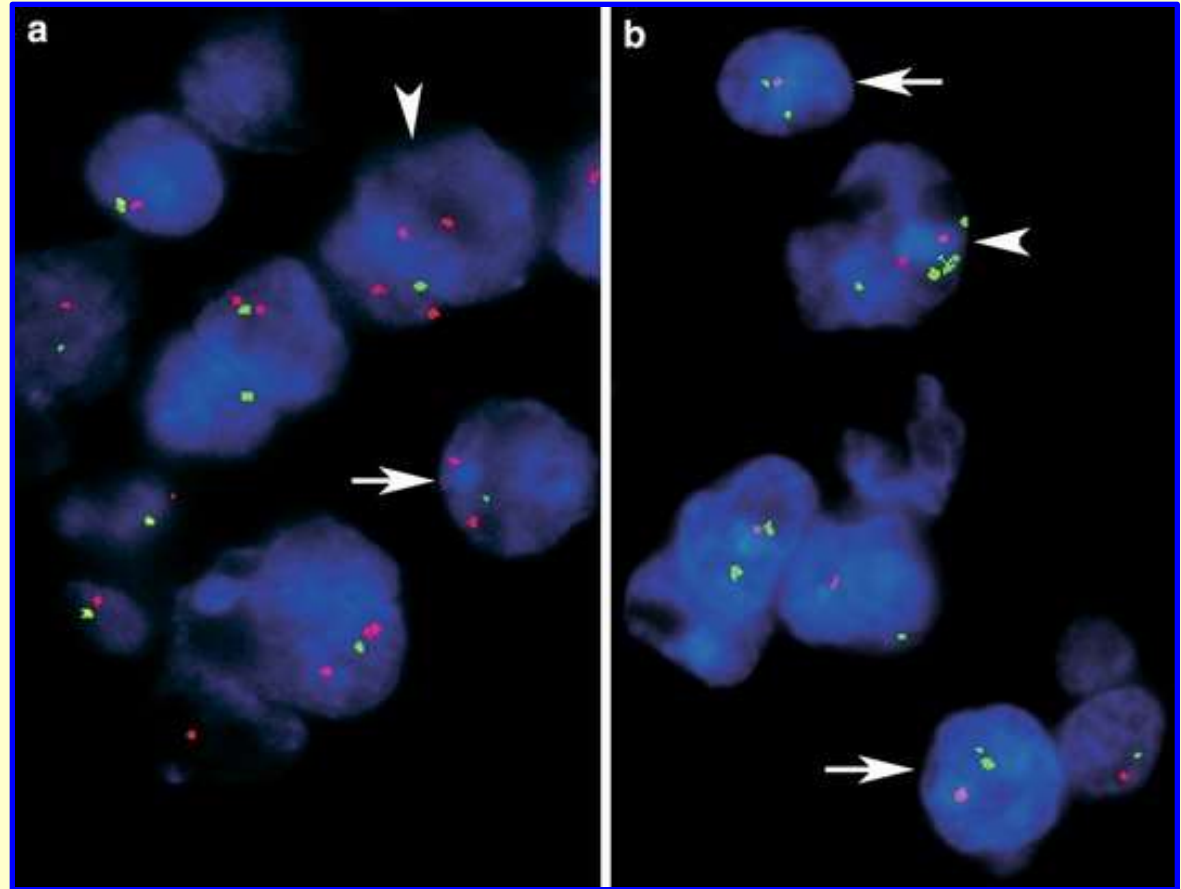
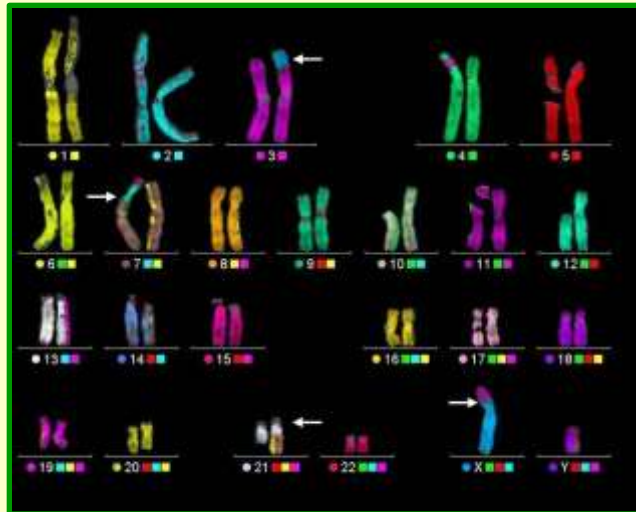
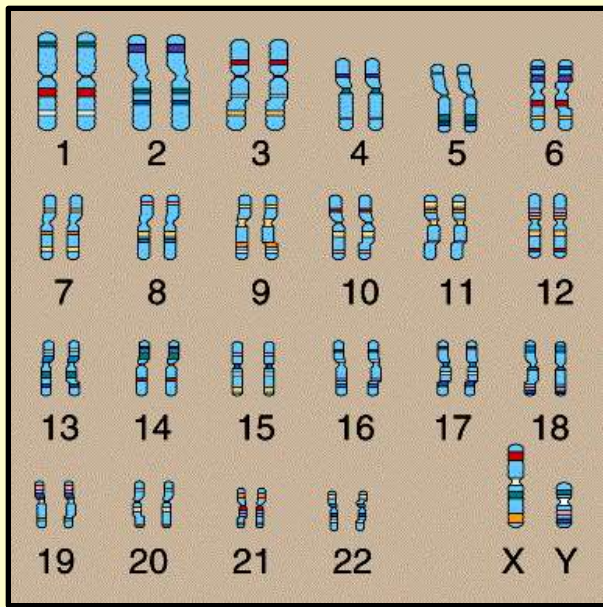




- efficacy of many drugs limited by blood-brain barrier
- fat soluble agents more effective
- most chemotherapy drugs used for brain tumours act by damaging DNA
- some tumours highly resistant but others very sensitive...

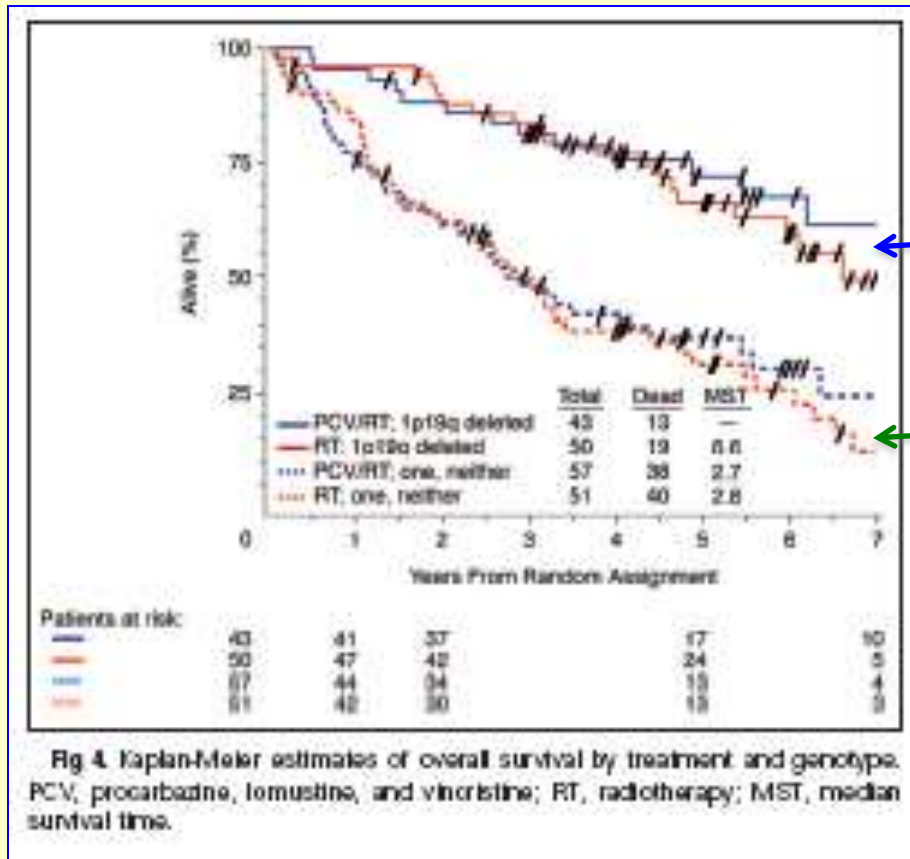
Chemotherapy regimes

- **PCV:**
 - Procarbazine 100 mg/m², oral, days 1 - 10
 - CCNU 100 mg/m², oral, day 1
 - vincristine 2 mg, iv, day 1
 - rash, prolonged myelosuppression, nausea
 - 6 – 8 week cycle
- **Temozolomide:**
 - single agent
 - 200 mg/m², oral, days 1 - 5
 - nausea, mild myelosuppression
 - 28 day cycle



Co-deletion of chromosome sections 1p and 19q is associated with better prognosis and more benefit from chemotherapy

1p 19q deletion in anaplastic oligodendroglioma

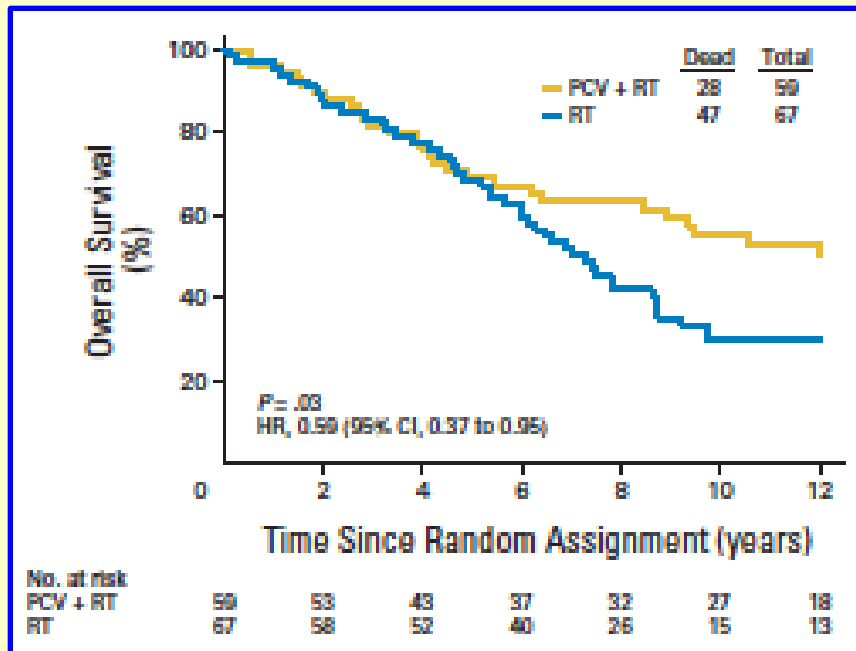


1p19q deleted

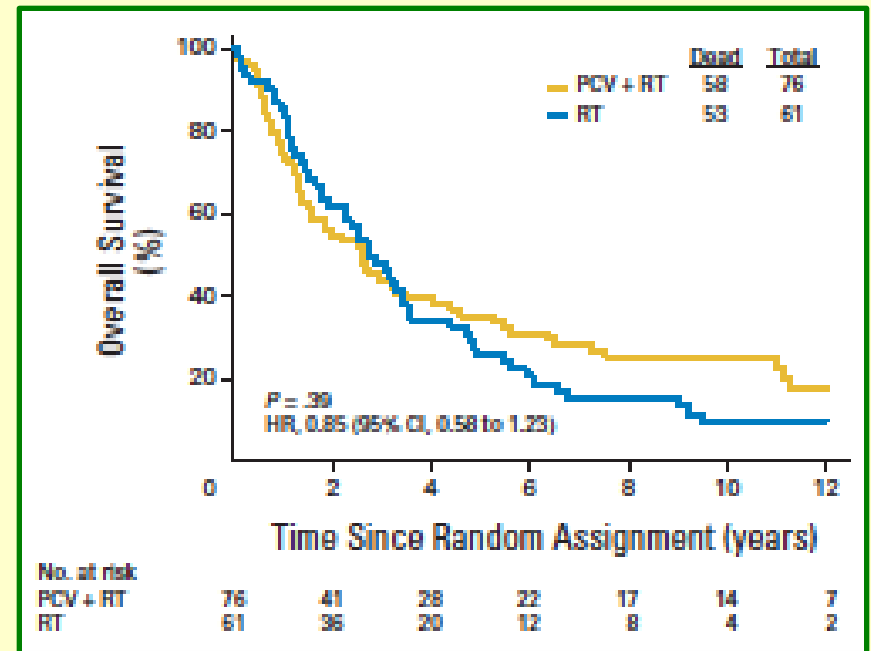
1p19q intact

- what are the responsible genes?
- how do they impact on survival?

1p 19q deletion in anaplastic oligodendroglioma

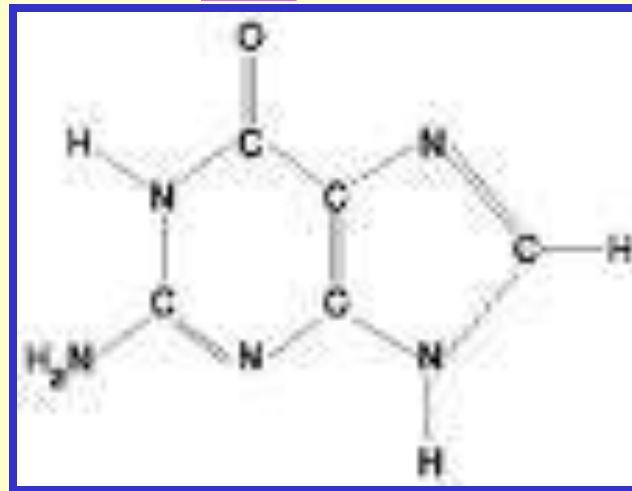
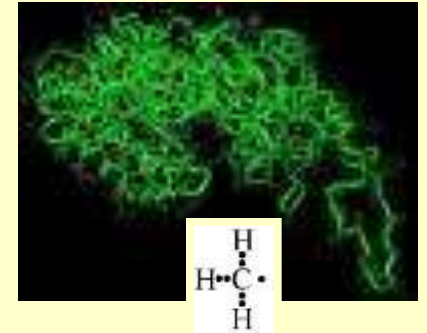
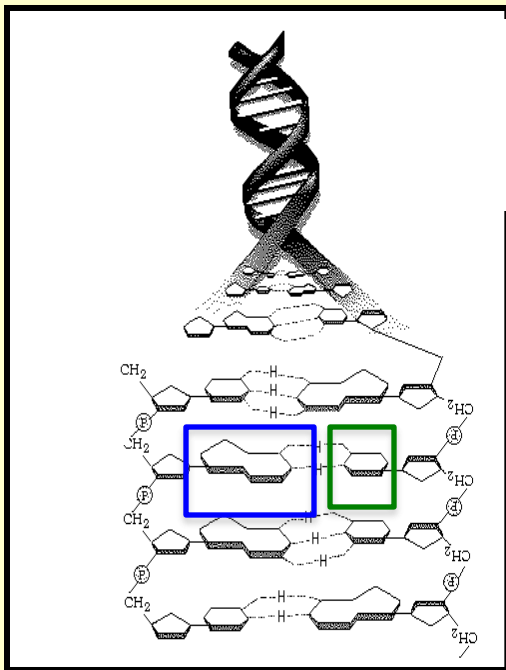


1p19q deleted

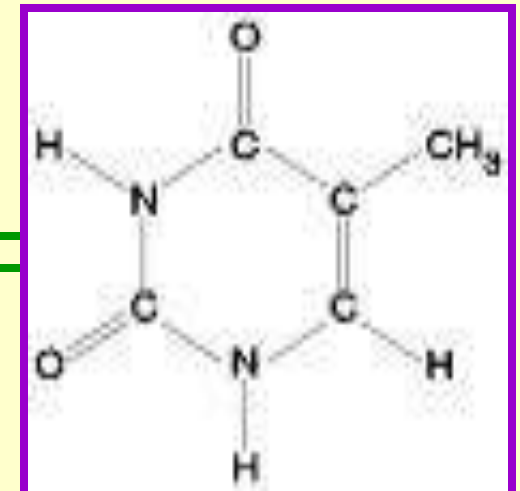


1p19q intact

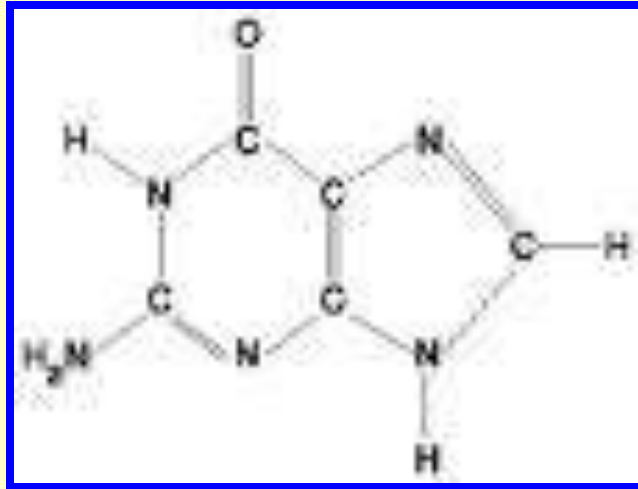
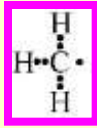
Temozolomide



guanine



thymine



O6-methylguanine



O6-methylguanine
methyltransferase

↓
MGMT

Benefit from temozolomide is increased in patients whose tumours have low levels of MGMT

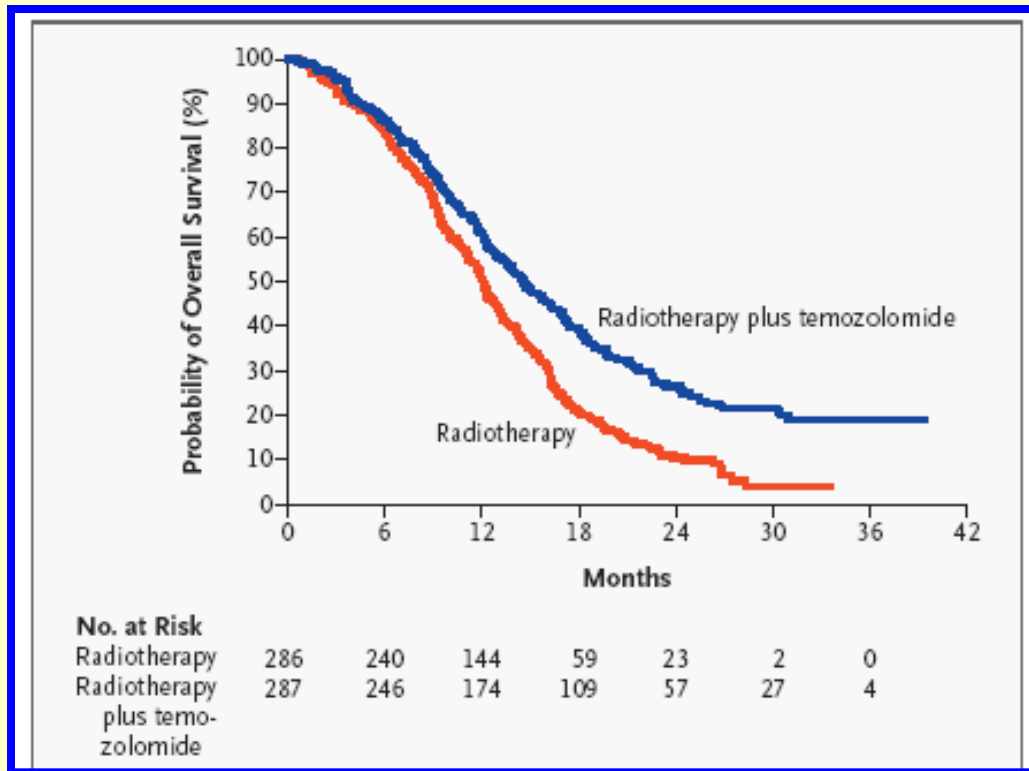
Treatment of glioblastoma



Temozolomide

Surgery

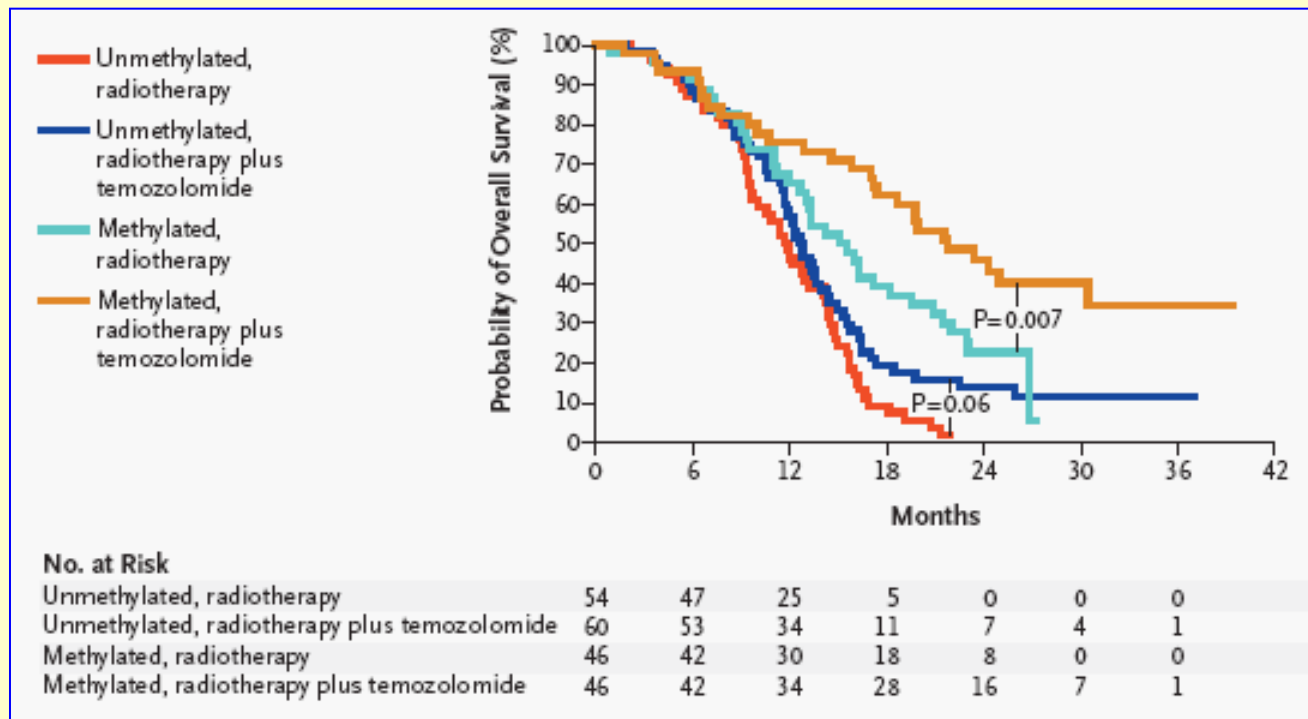
Radiotherapy



Patients aged less than 70

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc.,



- Patients with 'silenced' MGMT lived longer
- There is also more benefit from adding temozolomide to radiotherapy for these patients

Pseudoprogression after concomitant RT-TMZ

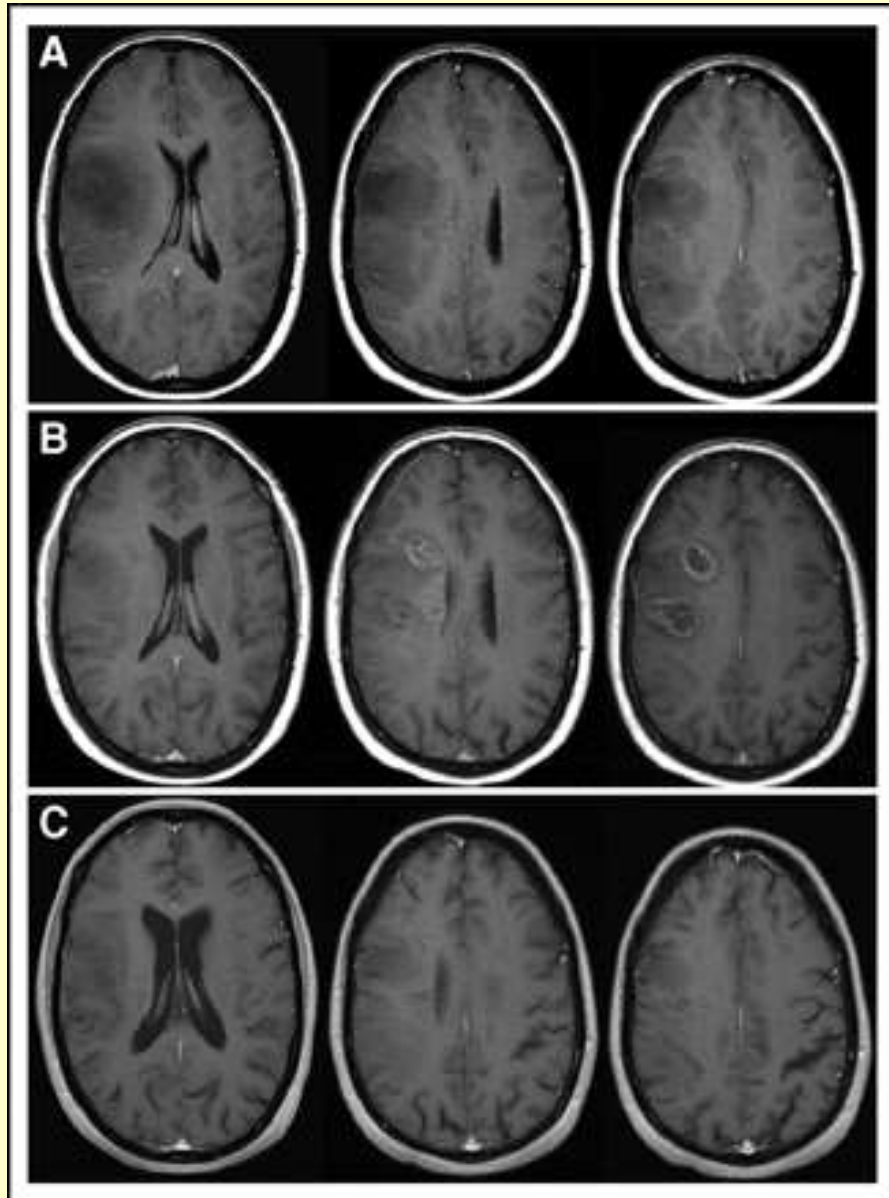
Conclusions: up to 50% of high grade glioma patients treated with chemo-irradiation who have a progressive MRI lesion immediately after RT suffer from pseudo-progression.

These data support the notion to continue TMZ in case of progressive lesions immediately after RT/TMZ.

Taal, ASCO abstract 2007

Pseudoprogression after/during treatment

Pre-treatment



1 month post
RT + TMZ

4 months post
RT + TMZ

Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme

James J. Vredenburgh, Annick Desjardins, James E. Herndon II, Jennifer Marcello, David A. Reardon, Jennifer A. Quinn, Jeremy N. Rich, Sith Sarthornsumetee, Sridharan Gururangan, John Sampson, Melissa Wagner, Leighann Bailey, Dorel D. Bigner, Allan H. Friedman, and Henry S. Friedman

- 35 patients with recurrent GBM after previous RT and chemo
- Median time from diagnosis 14 months
- 57% of tumours shrunk by 50% or more
- but 11 patients discontinued treatment because of toxicity

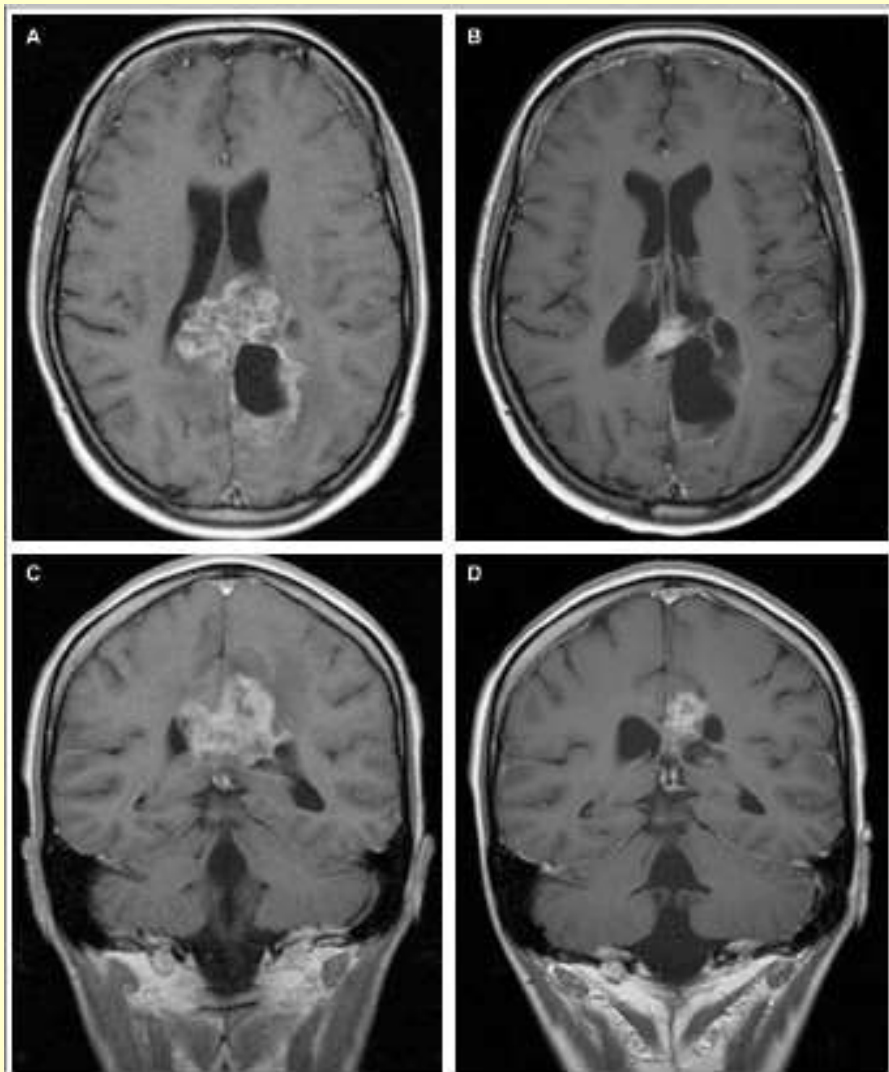


Fig 3. Baseline and post-treatment magnetic resonance imaging of a patient treated with temozolomide and radiation. Post-treatment axial and coronal T1-weighted magnetic resonance scans are shown with glioblastoma multiforme in A, B, baseline and C, D, after four cycles of temozolomide treatment.

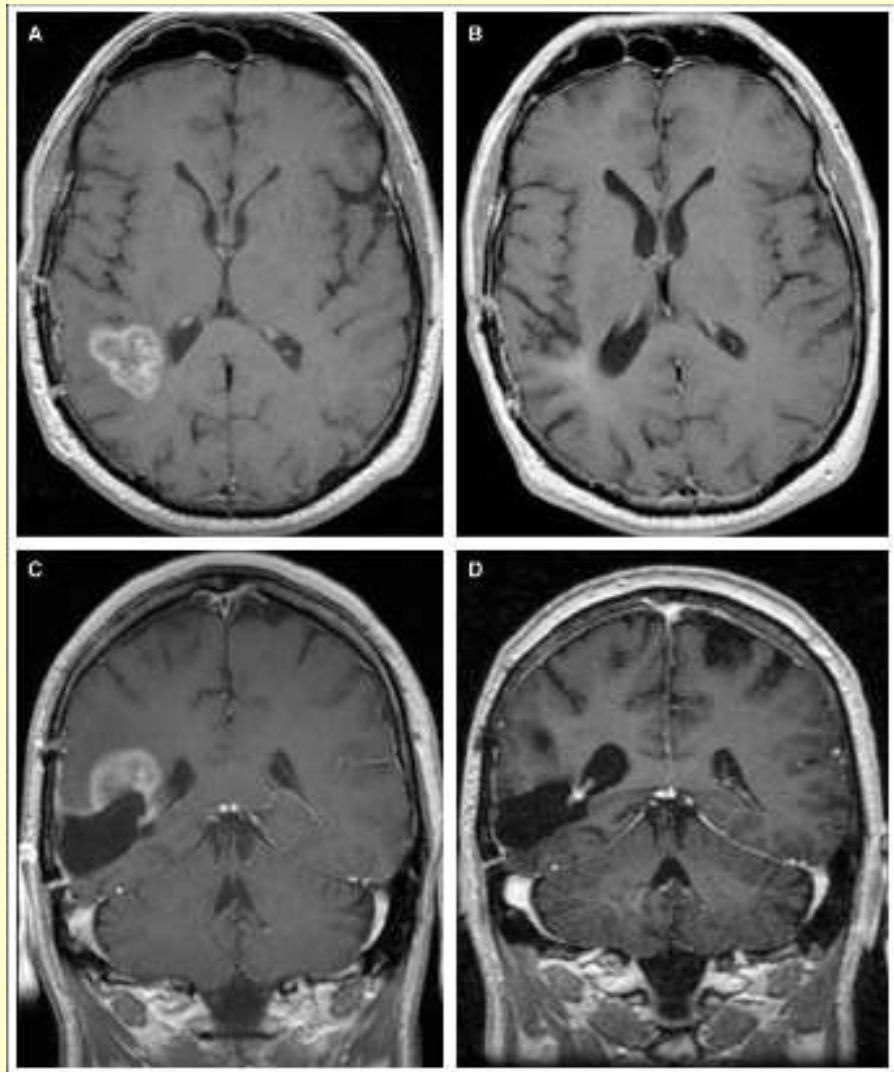


Fig 4. Baseline and post-treatment magnetic resonance imaging of a patient treated with temozolomide and radiation. Post-treatment axial and coronal T1-weighted magnetic resonance scans are shown with glioblastoma multiforme in A, B, baseline and C, D, after four cycles of temozolomide treatment.

Basel, 17 November 2012

Roche study showed that Avastin helped people with newly diagnosed glioblastoma live longer without their disease worsening when added to radiation and chemotherapy

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced results from the positive phase III AVAglio study. The study showed Avastin (bevacizumab) in combination with radiation and temozolomide chemotherapy reduced the risk of cancer worsening or death (progression-free survival; PFS) by 36 percent compared to radiation and temozolomide chemotherapy plus placebo (HR=0.64; $p < 0.0001$) in people with newly diagnosed glioblastoma, the most common and aggressive form of primary brain cancer. PFS assessed by trial investigators was a co-primary endpoint for the study. The interim results for overall survival (OS), the other co-primary endpoint, did not reach statistical significance (HR=0.89; $p = 0.2135$). Final data on overall survival are expected in 2013. The data were presented at the 17th Annual Meeting of the Society for Neuro-Oncology in Washington D.C., USA.

Principles of oncological treatment

- Extend life
 - Improve or maintain quality of life
 - Minimise risks of side-effects
 - Acute (temporary)
 - Late (permanent)
 - Use evidence-based treatment(s) wherever possible
 - Enable patients to participate in clinical trials
-
- Assess patients and tumours very carefully
 - Balance likely benefits of treatment with likely risks
 - Give patients and families as much information as they want
 - Indicate how reliable different sources of information are
 - Assist patient and family in making their decision