MANAGEMENT OF HIGH GRADE GLIOMA

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GLIOMA

- Gliomas as proportion of all primary brain tumours: 45% in adults and 50% in adults and children combined
- In children (0-14 years) in Sweden- 47% of all CNS tumours astrocytoma/ glioma with 70% low grade.
- Class of Neuroepithelial tumours that includes multiple histological subtypes.
- Histological subtypes that comprise glioma- changed over time- may vary among investigators
- Early classification schemes- astrocytic, oligodendroglial & ependymal tumors as well as medulloblastoma, ganglioneuroma, pinealoma & neuroepithelioma
- Later classification-this broad group renamed as tumours of neuroepithelial tissue and expanded to include additional histological types

GLIOMA

- **ICD-O-3**: Giloma includes malignant glioma NOS ependymoma, subependymoma, oligodendroglial tumours, astrocytic tumours, mixed glioma, choroid plexus tumours, medulloblastoma, PNET, dysembryoplastic neuroectodermal tumours- each of these includes more specific histological subtypes
- **Histological Group for Comparative studies**: Astrocytic, Oligodendroglial, Ependymal, and mixed tumours as well as gliomas of uncertain origin. Choroid plexus tumours and medulloblastoma are excluded from “glioma”
- **CBTRUS**: Astrocytic, Oligodendroglial, Ependymal, and Mixed tumours and three histologies mentioned earlier

HIGH GRADE GLIOMA

Malignant or High-grade glioma:

- Any age group- most often late adulthood.
- Appr. half of primary adult brain tumours
- Much less common in children
- Rapidly growing tumors
- Directly invade brain parenchyma
- Rarely metastasize outside CNS.
- Correspond to: Anaplastic gliomas (WHO grade III) and GBM (WHO grade IV).
- Molecular genetics and results from clinical series: two distinct diseases with unique behaviour, response to treatment, and prognosis.

GLIOBLASTOMA MULTIFORME

- 75% of all high grade gliomas.
- HP features- nuclear atypia, mitotic activity, vascular proliferation and necrosis – any 3 of these.
  Psuedopallisading necrosis a histologic hallmark
- Typically diffusely infiltrative.
- Prognosis poor – median survival appr. 1 year.
- Predictors of Survival: Pre T/t patient & tumour character .
  - Age at diagnosis,
  - Tumor histology,
  - KPS
  - Tumor location- frontal lobe tumors improved surv.
  - Extent of surgical resection,
  - Duration of neurologic symptoms,
  - Radiographic response to treatment

GLIOBLASTOMA MULTIFORME

- Most common & most aggressive subtype of Glioma
- Typical symptoms: Headache
  Cognitive changes
  Seizures
  Focal neurological deficits-weakness
- MRI- ring-enhancing lesion surrounding central area of necrosis on T1 weighted imaging- significant FLAIR hyperintensity surrounding the lesion
- Most cases- grow inexorably- finally refractory to all T/t
- Recent data- 5-yr survival of almost 30% in patients with favourable prognostic factors(age< 50 7 high PS)

GLIOBLASTOMA MULTIFORME

Surgery

- A critical component of T/t
- Survival: exten. resection> partial resection>exter. decomp
- Devaux et al (1993)- Resection & RT- med Surv,-50.6 Wks
- Laws et al (2003)- Biopsy & RT- med. Surv.-33.0 Wks
- Lacroix et al(2001)- Resection of at least 98% tumour tissue increased med. Surv. (13 Vs 8.8 months)
- Maximal surgical resection- currently accepted standard of care esp. for patients <65 yrs.
- Larger resection-increased diagnostic accuracy and tissue for molecular profiling- may prognosticate and guide T/t
- Gliomas- “ïnfiltrating propensities” without clear demarcation from normal tissues
- Include T/t with potential to target focal disease and microscopic tumour cells throughout brain.

GLIOBLASTOMA MULTIFORME

Radiotherapy

- Diffusely infiltrate brain beyond gross tumour & recur locally
- RT-a critical component – focus T/t to areas of highest risk
- In current form- GTV and margin of several cms.
- Benefit clearly seen since 1970s. Use dates back to 1925.
- Shapiro and Young (1976)- CT Vs CT+RT. RT 4.5Gy+1.5Gy
  RT+CT(BCNU+VCR)- med. Surv-44.5 wks
  CT-med. Surv-30 wks
- Coop. Gr. Trials: Improved surv. for RT ± nitrosurea- med surv.-9-12months vs. half of this when RT excluded.
- Radiosurgery- interest in past- abandoned after -ve trials
- Current standard- total of appr. 60Gy/30#
- Different total dose,fractionation and delivery method tried
- Ext. beam RT+Temozolamide & adjuvant Temozolamide

GLIOBLASTOMA MULTIFORME

Early Brain Tumour Study Group Studies

	Med. Surv.(weeks)	P-Value
BTSG 6901(Walker et al, 1978)		
Best supportive care	14	
BCNU	18.5	0.119
Radiation	35	0.001
Radiation+BCNU	34.5	0.001
BTSG 7201(Walker et al, (1980)		
MeCCNU	31	
Radiation	37	0.003
Radiaiton+BCNU	49	<0.001
Radiaiton+MeCCNU	43	<0.001

Dose Response to Radiation based on 3 BTSG studies (Walker et al 1979)

	No RT	≤45 Gy	50 Gy	55 Gy	60 Gy
Med. Surv (wks)	18	13.5	28	36	42
P-value		0.346	<0.001	<0.001	<0.001

GLIOBLASTOMA MULTIFORME

Brachytherapy for GBM

- Retrospective data- technique promising- I-125 improved med. Surv. From 17.9 months in RTOG Class III patients to 28 months. Improvement also in Class IV & V (Videtic et al. 1999)
- Prospective studies failed to support this

	Med. Surv.(weeks)	P-Value
Brain Tumour Cooperative Group (Selker 2002)		
60.2 Gy	58.5	
60.2 Gy+I-125 (60Gy)	68.1	0.101
Princess Margaret (Laperriere et al,1998)		
50 Gy	57.2	
50Gy+I-125 (60Gy)	59.8	0.49
UCSF (Sneed et al, 1998)		
59.4 Gy+I-125 (60Gy)	76	
59.4 Gy+ I-125(60Gy) + Hyperthermia	85	0.02

GLIOBLASTOMA MULTIFORME

Radiation Volumes:

- Historically margins to cover potential microscopic disease beyond visualised area of disease-typically 2cm around gross tumour
- Better imaging and sophisticated radiation delivery-variation in margin
- Partial brain RT is standard – no benefit of WBT in terms of survival and control (Shibamoto et al, 1990)
- 90% recurrence within 2cm of known primary tumour- 2-3cm margin typically
- Using oedema to delineate microscopic disease imperfect- imaging that is more specific to tumour better
- UCSF- MRI spectroscopy to define volume (Park et al, 2007)
- Univ. Michigan- 11C-methionine PET(Lee et al, 2007)
- IMRT as a means to hypofractionate /deliver more dose centrally in some centre
- Preliminaary studies- RT over 2-4 weeks without concurrent CT comparable to full 6 weeks T/t(Floyd et al, 2004; Sultanem et al 2004)

GLIOBLASTOMA MULTIFORME

Radiation Volumes:

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	RTOG (old)	RTOG (new)	EORTC	NABTT
Total Dose	46 Gy	46 Gy	60 Gy	46 Gy
Initial Margin	2 cm block	2cm dosimetric to PTV	2-3 cm dosimet. to PTV	1 cm dosimetric to PTV
Initial Vol. Def.	T2/FLAIR	T2/FLAIR	T1+ Contrast	T2/FLAIR
Boost	+	+	-	+
Boost Dose	14Gy	14 Gy		14Gy
Boost Margin	2.5cm block	2.5 cm dosimet. to PTV		1cm dosimetric to PTV
Boost Vol. Def.	T1 + Contrast	T1+ Contrast		T1+ Contrast
IMRT allowed	No	No	No	Yes
Final Dose	60Gy	60 Gy	60 Gy	60 Gy

GLIOBLASTOMA MULTIFORME

Radiation Volumes:

- IMRT as a means to hypofractionate /deliver more dose centrally in some centre
- Preliminary studies- RT over 2-4 weeks without concurrent CT comparable to full 6 weeks T/t(Floyd et al, 2004; Sultanem et al 2004)
- With this RT can be given safely and effectively in a shorter period of time
- IMRT using conventional fractionation- incorporated into current studies including studies by NABTT- uses 5mm margin for CTV and PTV both for initial and boost volume

GLIOBLASTOMA MULTIFORME

Simulation:

- CT based simulation typically used
- Thermoplastic mask and contrast usually given.
- GBM may progress after postoperative images acquired- contrast used in simulation may help identify progression following surgery
- After CT simulation, fusion of MRI image if available
- Critical structures typically included-lenses, eyes, optic nerve, optic chiasm, pituitary, hypothalamus, cochleas, brainstem
- MRI simulators used in some institutions. Not currently common place- avoid some of the inaccuracies associated with MRI fusion, including interval tumour progression or brain shift, and poor fusion

GLIOBLASTOMA MULTIFORME

Dose Limiting Structures:

- Given poor outcome-tumour coverage often not sacrificed to limit dose to critical structures
- Improv. outcomes & subsets living ≥5yrs- reducing late tox. a concern
- Higher doses can be given to these- compromise of tumour coverage not allowed
- Clinical judgement used to exclude these sensitive structures from PTV
- May exclude regions where natural barriers precludes microscopic tumour extension- cerebellum, contralateral hemisphere, directly across from tentorium cerebri & ventricles

GLIOBLASTOMA MULTIFORME

Dose Limitation to Critical Structures (RTOG 0525 study)

Structure	Dose Limit
Optic Chiasm/Optic nerve	54 Gy
Retina	50 Gy
Brainstem	60 Gy
Lens	Shielded from direct beam
Cervical Spine	Shielded from direct beam

GLIOBLASTOMA MULTIFORME

Toxicity:

Structure	Dose Limit
Likely(>10%)	Redness and soreness, hair loss, fatigue, lethargy, temporary aggravation of symptoms- headaches, seizures, weakness
Less likely (<10%)	Mental slowing, Ear/ear canal reactions- short term hearing loss, cataracts, behavioural change, nausea, vomiting, pituitary related endocrine changes, severe damage to brain tissue, dizziness, seizures, dry mouth altered taste
Rare but serious(<1%)	Optic injury- possibility of blindness, permanent hearin g loss, depression

Incidence of radiation in GBM following 60Gy difficult to determine- estimated to be 5% by extrapolation data

GLIOBLASTOMA MULTIFORME

GBM in elderly/poor performance patients:

- RT beneficial in elderly-Keime-Guibert et al (2007) RT vs best supportive care- RT improves survival- 81 patients 70 or older, 50Gy or no RT- 29.1 wks med. surv. with RT vs. 16.9 wks with no RT.
- Roa et al (2004)- 100 patients ≥ 60yrs- 60Gy/30# vs 40Gy/15#- med. surv 5.1 mo vs 5.6 mo (p=0.57, NS)-no CT used
- RT 0525 allows elderly to enrol- presumption that elderly may benefit from aggressive T/t incorporating CT
- Other studies to see if CT can benefit this subset
- Chamberlain et al (2007)- TMZ without RT being investigated in elderly
- In poor PS patients, KPS <60- hypofractionated course of RT reasonable(Bauman GS et al ,1994; Chang EL et al, 2003) – 30Gy/10# or 37.5Gy/15# WBT or focal RT 40-45Gy/15#- these patients do poorly with med. Surv. 7 months

GLIOBLASTOMA MULTIFORME

Radiation sensitizers:

- Motexafin Gadolinium(Xcytrin) –previously known as Gadolinium Texaphyrin or Gd-Tex- redox mediator selectively targets tumour cells- generation of reactive oxygen species and fixation of damage by radiation
- Phase I study in GBM- max tolerated dose 5mg/kg/day daily for 2 wks, then 3 times per week till RT completion (Ford et al 2007)
- RTOG 0513, a Phase I/II study of Gd-Tex with concurrent TMZ completed

GLIOBLASTOMA MULTIFORME

FOLLOW-UP:

- MRI scan 4 weeks after completion of CT+RT, 2-3 months thereafter
- Pseudoprogression- one area of controversy- worsening FLAIR or T1 contrast soon after RT completion- may resolve if followed long enough rather than changing planned T/t course
- Controversial how to image psudoprogression and distinguish from tumour progression
- Cause unknown- seen more frequently with using aggressive upfront T/t-acute T/t related changes including blood-brain barrier disruption and edema
- While FU of GBM pseudoprogression a D/d

RE-IRRADIATION

GBM

- Studied both for local and distant recurrence-often stereotactically
- Often given stereotactically

Study	Authors	Nos of Pts.	Med. Dose in Gy	Med. Surv
U. Michigan	Kim et al 1997	20	36 (30.6-50.4)	9 mo
Germany	Vordermark et al. 2005	14	30. Hypo. Stereo. Med 5Gy/#	7.9 mo
U Heidelberg	Combs et al. 2005	53	36. Med #-2Gy 1mm mar. stereo	8 mo
U Wisconsin	Tome et al. 2007	99	LDR radiation. 0.2 Gy pulses 3 min apart	6 mo 31% surv

GLIOBLASTOMA MULTIFORME

FUTURE DIRECTIONS:

- Better molecular imaging techniques to define and follow areas of disease and better understanding of biology of the disease
- Use of heavy particles- Carbon ions tried in Japan(Mizoe et al , 2007)
- Radioimmunotherapy with I-125-EGFR Mab 425- tried and promising- med surv 20.4 months added with RT+TMZ (Li et al 2007)
- Future studies to define role and role of other radioimmunotherapies

ANAPLASTIC GLIOMA

- 25% of high grade gliomas in adults
- Typically in patients during youth to middle adulthood.
- May be astrocytic, oligodendrocytic or mixed lineage
- Primarily or secondarily from low grade precursor.
- Aggressive, invasive- usually do not demonstrate necrosis or neovascularization
- Anaplastic Astrocytoma-med surv 3 yrs- age at diagnosis, KPS, extent of resection and mental status

Class	Features
I	Age <50,normal mental status
II	Age≥50, KPS 70 to 100, at least 3 mon from time of first symp to initiation of t/t
III	Age<50, abnormal mental status

ANAPLASTIC GLIOMA

- Anaplastic oligodendroglioma- better prognosis- med surv-5-7 yrs (Cairncross et al. 2007; van den Bent et al (2006)
- Loss of heterozygosity at 1p and 19q – separate subgroup with improved outcome
- Age at diagnosis, location, extent of resection, PS and extent of chromosomal deletions- predictive of survival
- Mixed histologies, anaplastic oligoastrocytoma-variable prognosis depending on predominant histology and other prognostic factors

ANAPLASTIC GLIOMA

IMPORTANCE OF MOLECULAR GENETICS

- 1p and 19q- loss of heterozygosity- early genetic alteration in the transformation and progression of oligodendroglioma.
- Combined codeletions of 1p 19q- 63% patients with oligodendroglioma and 52% patients with mixed oligoastrocytoma- rare in patients with astrocytomas (8-11%)
- Deletion in 1p and 19q- longer PFS and & chemo- and radiosensitivity
- O6 methylguanine-DNA methyltransferase (MGMT)- potentially important regulator in response to CT
- MGMT blunt therapeutic effects of alkylating agent and lead to resistance
- Epigenetic silencing of MGMT through promoter methylation- increased overall survival and better response to treatment with TMZ and BCNU
- MGMT promoter methylation- in 12-42% in anaplastic glioma vs 45% in GBM-not adequately studied in anaplastic glioma

ANAPLASTIC GLIOMA

TREATMENT APPROACH

- Majority of trials general series on malignant or high grade glioma that include GBM
- T/t of anaplastic glioma has been extrapolated from results of these trials
- Historical trial by Walker(1978)- patients with Anaplastic Glioma receiving adjuvant RT- improved survival compared to those receiving best supportive care, CT with BCNU alone and RT+BCNU
- Further rationale for this approach and established RT techniques based on trials including all patients with malignant glioma
- T/t with RT –volume and dose same as for GBM
- Several trials examined addition of CT- role remains controversial
- Use of T/t modifiers such as RT and CT sensitizers investigational

ANAPLASTIC GLIOMA

CHEMOTHERAPY

- Addition of CT to maximal surgical resection followed by RT- long controversial in patients with malignant glioma
- Stewart (2002)- metaanalysis- examined 12 randomized trials including patients with malignant glioma treated with RT+CT- small significant long term survival benefit with addition of CT
  - increase in 1 yr survival of 6% from 40% to 46% , 2 month increase in med surv
  - less than 30% patients had anaplastic glioma
  - marginal surv. advantage, given additional toxicity-not led to universal acceptance of this approach

ANAPLASTIC GLIOMA

CHEMOTHERAPY

- EORTC 22981/26981- Stupp et al (2005)- significant survival benefit in patients with GBM treated with concomitant and adj. TMZ after max. surgical resection and RT- use of CT in GBM standard.
- Result of this trial – a paradigm shift in favour of CT+RT for all malignant gliomas despite lack of evidence showing benefit in patients with anaplastic glioma.
- Subsequent trials- thrown light on role of CT in patients with anaplastic glioma
- Clear guidelines from results of RCT awaited.

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Astrocytoma

- Adj, T/t with CT after RT- not universally adopted- conflicting data in literature
- Addition of CT, best agents and timing- still debated
- PCV regimen initially considered standard following results of Levin et al (1990)- RT with BCNU or PCV- improved survival with PCV compared to BCNU- statistically significant only for anaplastic glioma
- Opponents cited retrospective review of RTOG protocols by Prados et al(1999)- 432 patients of anaplastic astrocytoma- no significant difference in surv.
- UK MRC trial (2001)- prospective phase III – 674 patients – maximal surgical resection followed by RT alone or RT then PCV-17% anaplastic astrocytoma. Surv equivalent in both arms and all subgroups, including histology. Med. Surv in anaplastic astrocytoma, 13-15 months, lower than expected surv. of 2-3 yrs in previous trials- debate on applicability of these results

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Astrocytoma

- Hildebrand et al (1994)- phase III trial showing survival benefit with RT+ concurrent dibromodulcitol(DBD) and adj.DBD & BCNU compared to RT alone (13 vs 10.4 months, p=0.044). Further review- surv. in patients with anaplastic astrocytoma imrpoved to greater extent compared to GBM- nos. of anaplastic astrocytoma too small to reach significance
- Hildebrand et al (2008)- continuation of previous phase III trial- including solely patients with anaplastic astrocytoma- RT alone as control arm- 193 patients – RT alone or RT con. and adj. BCNU/DBD- closed early due to decreasing accrual. Trend towards increased surv. Not found to be sig. (23.9 vs. 27.3 months, p=0.111).
- Levin et al (2002)- phase II trial- safety & outcomes of patients on accl. # RT with Carboplatin foll. by PCV- 76.7% of 90 patients with ana. astrocytoma. Med. Surv. 28.1 mon. & 28.7 mon.for patients with ana. astrocytoma. Serious neurologic deficit/dementia in 10% patients

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Astrocytoma

- TMZ – shown activity in patients with recurrent ana. Astrocytoma
- Yung et al (1999)- 162 patients with ana. Astrocytoma- TMZ at first relapse- 6 mon PFS was 46% and overall surv. 13.6mon. Response rate- CR-8% and PR-27%- trial suggested TMZ has antitumour activity with acceptable safety profile
- Combs et al (2008)- retrospective ananlysis- RT alone vs. RT+TMZ- no difference in survival
- Neyns et al (2008)- TMZ in dose dense schedule- good activity
- Balmaceda et al(2008)- part of multi-institutional phase II trial - 28 patients with recurrent ana. Astrocytoma – twice daily TMZ- med. PFS 5.8 mon med. OS-14.6 mon- without increasing toxicity. Overall RR-46%
- Other agents examined in rec. ana. Astrocytoma- CXN and CPT-11- modest efficacy (Chamberlain et al. 2006, 2008)

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Astrocytoma

- No prospective randomized trial showing benefit of addition of CT to standard therapy of maximal surgical resection and then RT
- Some trials suggest benefit- improvement have been modest and not significant statistically
- PCV chemotherapy with or without other agents- the regimen most frequently examined
- TMZ has emerged as potentially promising treatment for anaplastic glioma- activity in early clinical trials
- Larger phase III trials examining patients with anaplastic astrocytoma alone needed to better define t/t guidelines

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Oligodendroglioma / Oligoastrocytoma

- Several early clinical studies- high rates of radiographic response to PCV- gained reputation of being highly chemosensitive. (Cairncross et al, 1988; Kim et al. 1996)
- Results prompted two large RCT, RTOG 9402 and EORTC 26951- if sequential RT and CT a therapeutic benefit over RT alone
- Results produced more controversy- significantly improved PFS without increase in OS in patients treated with seq. CTRT vs RT- CT reserved for salvage
- As median FU increases forthcoming data may resolve this impasse
- Presented update of RTOG 9402 suggests significant improvement in survival of patients treated with seq. CTRT- results have very small patient numbers at long FU and preliminary

ANAPLASTIC GLIOMA

CHEMOTHERAPY

Anaplastic Oligodendroglioma / Oligoastrocytoma

- Studies have examined the role of TMZ
- Chinot et al (2001)- 48 patients who previously failed PCV CT-Response 43.8% (CR-16.7%, PR-27.1%), OS 10 months. Gr 3 thrombocytopenia in 6.3%
- Reputation as a chemosensitive tumour from dramatic response on imaging in early trials
- Prospective RCT have not shown improvement in survival by addition of CT
- PCV regimen was associated with substantial toxicity in these trials
- TMZ shown good activity with little toxicity- not evaluated in phase III trials
- Updated results of RTOG 9402 and EORTC 26951 and further prospective RCT needed to define standard treatment imaging

ANAPLASTIC GLIOMA

RADIOTHERAPY AND CHEMOTHERAPY MODIFIERS

- Have been investigated in trials with mixed results
- Prados et al (2004)- Phase III prospective RCT- addition of BUdR in patients with anaplastic astrocytoma randomized to receive conventional RT +PCV with or without BUdR as infusion during each week of RT. Interim analysis predicted no survival advantage for the BUdR arm. Study closed . In the 190 patients eligible for analysis no survival benefit with addition of BUdR
- Levin et al (2003)-Phase III trial-Difluoromethylornithine (DFMO) added to PCV. PCV alone vs. PCV+DFMO following RT. 288 patients Anaplastic astrocytoma (78.1%) and Oligodendroglioma/ Oligoastrocytoma (17.5%)

  Hazard function showed surv. Diff. over first 2 yrs , did not continue after 2 yrs. Diff. in OS and PFS not significant.
- Use of RT and chemical modifiers remains investigational

RE-IRRADIATION

Anaplastic Glioma

- Even after best available treatment majority develop local progression within or near site of initial disease within ≤ 5 yrs (Bauman et al , 1996).
- Re-iiradiation of recurrent anaplastic glioma after standard T/t historically contraindicated due to increased risk of radionecrosis.
- Newer techniques using CRT, Brachytherapy and SRS shown to be safe in carefully selected patients

RE-IRRADIATION

Anaplastic Glioma- Results of Re-iiradiation in Recurrent AG

Study	Modality	Nos. & Histology	Med. Surv
Bauman et al. 1996	Conv. EBRT	11 GBM & AG	2.8
Kim et al. 1997	3-D EBRT	7 GBM / 7AG	7.0
Voynov et al. 2002	IMRT	5 GBM / 5 AG	10.1
Sneed et al. 1997	Brachytherapy	45 AG	12.3
Gabayan et. al. 2006	Brachytherapy	15 AG	10.0
Tatter et al. 2003	Brachytherapy	21 GBM and AG	12.7
Sanghavi et al. 1999	Radiosurgery	30 GBM and AG	8.0
Cho et al. 1999	Radiosurgery	27 GBM / 19 AG	11.0
Kondziolka et al. 1997	Radiosurgery	23 AG	31.0
Cho et al. 1999	FRST	15 GBM / 10 AG	12.0
Vordemark et al. 2005	FRST	5 AG	15.4
Shepherd et al. 1997	FRST	29 GBM and AG	11.0
Combs et al. 2005	FRST	42 AG	16.0

ANAPLASTIC GLIOMA

- Aggressive, invasive, biologic heterogeneity depending on cell type, astrocytic, oligodendrocytic or mixed
- Molecular genetics important- co-deletions at 1p19q emerging an important prognostic and predictive factor for patients with anaplastic oligodendroglioma
- Standard T/t- maximal surgical resection followed by adjuvant RT
- Addition of CT – not been universally adopted – conflicting data regarding outcome and additional toxicity concern with regimens studied thus far.
- Some extrapolate results of EORTC 22981/26981 and favour CTRT
- Other trails have failed to show survival benefit in anaplastic glioma treated with CT (Cairncross et al. 2006; van den Bent et al. 2006; MRC trial 2001; Hildebrand et al 2008) failed to show survival benefit
- Radiation and CT modifiers not shown to improve outcomes in RCT.
- Future directions include T/t with TMZ but not Phase III trials completed
- Further studies needed before addition of CT as standard of care.