Lancashire and South Cumbria Cancer Network

FINAL

Management Guidelines

for

Malignant Brain Tumours

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Section 1: Referral Pathway and General Guidelines

1.1. The Neuro-Oncology MDT Meeting

- Multi-disciplinary team case review is mandatory for all patients with a diagnosis of primary CNS malignancy.
- The Neuro-Oncology MDT meets weekly on Monday at 12 noon and Wednesday 11:30am in seminar room 8, Education Centre 1, at Royal Preston Hospital.
- Cases can be added to the list by contacting either the MDT coordinator or the Neuro-Oncology Specialist Nurse at Royal Preston Hospital on 01772 716565. A web form referral is available via LTHTR intranet and website.
- All cases of primary or secondary central nervous system tumours referred to the Neurosurgical Unit must be discussed at the Neuro-Oncology MDT meeting.
- All cases not requiring emergency neuro-surgical intervention should be discussed pre-operatively. This is recommended by the NICE Improving Outcomes Guidance to ensure:
  - That the optimum pre-operative imaging and investigations have been performed e.g. whether additional imaging would be helpful
  - That the planned resection is appropriate in light of proposed subsequent management i.e. that good-prognosis patients are offered maximal resection, but that poor prognosis patients are not subject to unnecessary surgery.
  - That if frozen section is planned, pathology are aware of this and surgery is scheduled for a suitable time e.g. not late on Friday afternoon
- All operated cases, benign or malignant, will be discussed post-operatively to confirm histology. Cases are identified and nominated by the Pathology department.
- The clinician in charge of the case, or their junior, should make an effort to attend the meeting to present the case and participate in the discussion.
- Minutes of the MDT meeting with management recommendations will be circulated to all involved parties.
- All patients who are to undergo surgery or require assessment prior to a definitive treatment decision are to be seen in the Neuro-Oncology Pre-operative Assessment Clinic within two weeks.

1.2 Surgical Guidelines

- A histological diagnosis should be sought in all patients, unless there is a specific reason not to do so. (Patient refusal, anaesthetic/surgical risk, for best supportive care). This is fundamental in planning patient management and ensuring that all patients are treated appropriately.
- All patients under age 70, with a good performance status should be considered for maximal safe cytoreductive surgery.
- Carmustine wafer implantation (Gliadel™) to be considered, if technically suitable and > 95% de-bulking achieved.
- All biopsies should be performed under image-guidance or stereotaxy
- Debulking or biopsy may be omitted in cases where:
  - The risks of biopsy outweigh the advantages of histological confirmation of diagnosis
The patient would not be a candidate for treatment, regardless of biopsy result, due to advanced age or poor performance status. Involve a neuro-oncologist for opinion on suitability for non-surgical treatments.

The patient declines the procedure.

1.3 Post-operative Imaging

Early (within 72 hours) post-operative MR imaging is required only in cases where the result will alter the patient’s initial post-operative management. Examples include:

- Patients where the distinction between complete and sub-total excision will determine whether or not post-operative radiotherapy will be offered e.g. low grade ependymomas
- Patients where if initial excision is incomplete, further surgery would be undertaken
- Patients with presumed low-grade gliomas, but with areas of concern for higher grade disease, to ensure that suspicious areas have been resected and that histology is representative

Immediate post-op imaging is not routinely indicated:

- Following resection of brain metastases – (I think we should, we do do this currently). Especially if not having immediate Whole Brain RT.
- In patients with high grade gliomas, who will undergo repeat MR imaging as part of their radiotherapy treatment planning? adequate debulk
- In patients with low grade tumours including meningiomas where management is anticipated to be follow-up alone – in this group, repeat imaging 3 months post-operatively is adequate

1.4 Neuro-Oncology Pre-operative Assessment Clinic

- The clinic is held weekly on Tuesday morning on Day Unit at Royal Preston Hospital.
- The clinic is run by a Consultant Neurosurgeon and a Neuro-Oncology Specialist Nurse.
- All patients recommended for surgery from the MDT meeting are reviewed in the clinic for a complete assessment, provided they are able to attend. Some patients who are not suitable for an outpatient visit will be assessed on admission to the neurosurgical ward. This group should be the exception, and form only a minority of the referrals.
- The treatment options, MDT meeting decision and aims, risks and rationale of surgery are discussed with the patient and their families. An informed consent for surgery is obtained at this stage.
- Patients are then assessed in the general Pre-operative clinic, which runs concurrently in an adjacent room on Ward 2B, to be optimised for surgery and a general anaesthetic.
- The date for surgery is scheduled at this stage.
1.5 Oncology Referrals

- Patients are referred directly to the Clinical Oncologist at the Neuro-Oncology MDT following discussion of the histopathology. New patients are then seen in the Neuro-Oncologist clinic at the earliest available opportunity to discuss further treatment such as radiotherapy and/or chemotherapy. The clinic is on Monday mornings, in the day unit. This clinic led by the consultant oncologists.

- **Patients requiring neuro-oncology review should be referred as soon as their histology result is available.** In general, the neurosurgical team will convey the histology result to the patient before their appointment with the oncologist. However, this is not always possible and should not serve to delay their oncology referral.

- **The patient and their carers must have the full support and necessary preparation from the specialist neuro-oncology nurses during this period.**

- Patients with uncomplicated post-operative recovery should be seen within 1-2 weeks of surgery so that any radiotherapy treatment required can be commenced within 6 weeks of surgery

- Three Clinical Oncologists – Dr Kennedy, Dr Kumar and Dr Reid – provide the service at LTHTR. Patients will potentially be seen by any of the three oncologists, except when it has been decided by the MDT to be referred to a specific oncologist.

### Stereotactic Radiosurgery and Stereotactic Fractionated Radiotherapy Clinic

Patients with 1-3 brain metastases, good performance status, with controlled/controllable extra-cranial disease are suitable for SRS/SFRT. These patients are discussed in the Neuro Oncology MDT, for suitability for SRS/SFRT and referred directly to the SRS clinic. This clinic is led by Dr Kumar and Dr Kennedy. The clinic occurs on Tuesday mornings in the day treatment centre. Ideally all patients are discussed with the primary disease site oncologist (e.g. breast, lung) to ascertain likely prognosis and further treatment options, prior to commencing SRS.

### Psychological and Social Needs

With all primary brain and spinal patients, especially high grade gliomas, consider the following:

1. Ongoing Neuro – rehabilitation. Options include referring for community physiotherapy, occupational therapy, local outpatient neuro-rehab centres or referral to a specialist neuro-rehabilitation physician. (Dr Shakespeare)
2. Counselling referrals for patient and/or carers.
3. Consider depression and psychosis in all patients. Discuss with the patients general practitioners and refer to local mental health services.
4. Formal Neuro-cognitive assessments and therapy for patients with a cognitive deficit or behavioural concerns, who are able to engage with this therapy and likely to achieve some benefit.

5. Consider referral to Rosemere Centre palliative care team, community palliative care team and local hospice services. If felt appropriate to refer, discuss with patient and family first.

6. All patients under age of 26 years should be referred to the Teenage and Young adult specialist nurse team and be offered treatment at the Young Oncology Unit at The Christie Hospital, Manchester.

7. Inform all patients about the Macmillan Information centre at The Rosemere Centre and offer to arrange a meeting with one of their advisors.

8. There is a monthly Network MDT held on Wednesday lunchtimes together with physiotherapy, speech and language and occupational therapy to discuss patients with complex needs.

Follow up

Follow up of all high grade glioma patients is in the Mon afternoon oncology clinics.
Follow up of low grade glioma patients is in the monthly low grade glioma clinic.
Follow up of meningioma’s and ependymomas is in the surgical clinics depending on specific consultant.
Pituitary patients after radiotherapy are followed up in the dedicated pituitary clinic led by the endocrinologists and base of skull surgeons.

Endocrine Referral
In patients who have received radiotherapy dose to the pituitary gland of >24Gy (non pituitary directed radiotherapy) refer for an endocrine assessment at 2 years post radiotherapy if remains well and no evidence of progressive disease.

Steroids
In general the lowest dose of steroids should be used, none if possible. If patients are on steroids for more than 1 week, the dose should be tapered slowly, titrated according to the patients symptoms.
A prophylactic proton pump inhibitor of H2 antagonist should be used.
Specific situations when steroid dose must be maintained (as directed by neurosurgeon or neuro oncologist) are: a. with gliadel insertion, b. the first week of radiotherapy (if still on steroids), c. during SRS treatment. Discuss with specialist consultant or registrar.
Whilst on steroids be vigilant for steroid related complications, such as candidiasis, risk of infections, type 2 diabetes, proximal myopathy, mood change, psychosis, insomnia, weight gain, avascular necrosis and osteoporosis.
Steroid side effects can be debilitating, serious and distressing for patients.
Section 2: Management Policies for Primary Tumours

2.1 High grade gliomas

2.1.1 First line treatment

Surgery to be considered as the first option in all patients. Refer to Section 1.2: Surgical Guidelines

2.1.1.i Glioblastoma Multiforme WHO grade IV

Management is dependent on patient age and performance status, and on patient choice. Definitions of WHO Performance Scores 0 – 4 are given in section 8.1. The criteria below represent broad guidance; each case needs to be considered on an individual basis.

Unifocal disease

Age < 70, WHO PS 0-1
Radical radiotherapy 60Gy in 30 # with concurrent and adjuvant temozolamide

Age < 70, WHO PS 2
Radical radiotherapy; reserve chemotherapy for disease recurrence.

Age < 70, WHO PS 3-4
Palliative radiotherapy 40Gy in 15# or best supportive care. If PS improves after radiotherapy offer 6 cycles of adjuvant temozolamide.

Age > 70, WHO PS 0-2
Options include 40Gy in 15# alone, or Temozolamide alone if MGMT methylation positive (or low Allred score based on immunohistochemistry tests).
Some very fit patients age 70-80 with WHO PS 0, with small tumours may be suitable for radical radiotherapy and chemotherapy.
Also option of 30Gy in 6# over 2 weeks if difficulty with travel and patient not keen on hospital stay or numerous visits for radiotherapy.

Age > 70, WHO PS 3-4
Best supportive care.
Palliative radiotherapy may occasionally be considered for patients who achieve a good steroid response.
In this situation offer Palliative radiotherapy 30Gy in 6# over 2 weeks

Multifocal disease

Patients with glioblastosis cerebri or multiple GBM deposits require whole brain palliative radiotherapy. Prognosis is worse than for unifocal disease and dose and treatment regime will depend upon patient age and WHO PS.

Chemotherapy can be considered if patients remain well after XRT, or reserved for disease progression.

2.1.1.ii Anaplastic Astrocytoma, WHO grade III
Age < 70, WHO PS 0-2
Radical radiotherapy.
BR14 study investigating role of concurrent and adjuvant temozolamide. Consider entry.
Off trial, small additional survival benefit in young age group and PS0-1 with adjuvant temozolamide.

Age < 70, WHO PS 3-4 or age > 70
Palliative radiotherapy 40Gy in 15# or 30gy in 6 # (over 2 weeks)

2.1.1.iii Anaplastic Oligodendroglioma or Oligoastrocytoma, WHO grade III

Radical radiotherapy in all patients.
Patients with co-deletion of 1p and 19q: radical radiotherapy, plus adjuvant PCV x 6 chemotherapy. If unsuitable for PCV or not tolerated use concurrent and adjuvant temozolamide as per grade 4.

Patients with non co-deletion of 1p/19q: Radical radiotherapy.
BR14 study investigating role of concurrent and adjuvant temozolamide. Consider entry.
Off trial, small additional survival benefit in young age group and PS0-1 with adjuvant temozolamide

2.1.2 Follow-up Policy

2.1.2.i Appointments and scans
• Patients are reviewed 4 – 6 weeks after completion of radiotherapy. 4 weeks if plan to receive adjuvant temozolamide.
• Repeat MR imaging should be requested at this visit, to be performed 2 – 3 months after treatment completion.
• Patients who would be fit for further treatment and where treatment options exist should undergo repeat MR imaging 3 - 4 monthly for the first 2 years then 6 monthly to annually.
• Otherwise, further MR imaging should only be performed if clinically indicated by development of new symptoms or signs or to reassess response to subsequent treatment e.g. post chemotherapy.

2.1.2.ii Endocrinology assessment
• Patients should be referred for endocrinological assessment 2 years after treatment completion if:
  o Dose to the pituitary gland was > 24Gy
  o They remain well with no evidence of recurrent / progressive disease
  o Life expectancy is > 2 years

2.1.3 Management of Recurrent Disease

First Relapse
• Management of disease recurrence depends on previous treatment, nature of recurrence, performance status and disease-free interval.
• Options include:
  o Further surgery +/- carmustine (Gliadel™) wafers
  o Chemotherapy (Temozolamide / PCV)
  o Clinical trial entry
Second Relapse

- A minority of patients may go on to experience second disease relapse, while remaining in good general condition. Management will again depend on previous treatment, nature of recurrence and disease-free interval.

- Options include:
  - Further surgery
  - Re-challenge of initial chemotherapy regime if well tolerated and >6 month interval.
  - Further chemotherapy: continuous Temozolamide in a 21/28 day cycle
  - Re-irradiation, if > 2 years after initial irradiation
2.2 Low Grade Gliomas
Includes: WHO grade II astrocytomas (diffuse, fibrillary, gemistocytic), oligodendrogliomas, oligoastrocytomas.

2.2.1 General Guidelines
- Patients to be seen in the Neuro-Oncology Pre-operative Assessment Clinic initially to discuss treatment options.
- Histological confirmation (biopsy), maximal surgical resection or conservative/observation option may be offered in each individual case.
- Maximal resection to utilise surgical modalities such as awake craniotomies and cortical stimulation.
- Patients under observation to be followed up in the Low Grade Glioma Clinic. This is a multi-speciality clinic with input from a Consultant Neurosurgeon, a Clinical Oncologist, Neuro-Oncology Specialist Nurse and a specialist epilepsy nurse.
- Early post-operative MR imaging (within 72 hours) should be considered for patients where the aim of surgery was complete resection, or with any enhancing tumour component.
- In general, radiotherapy or chemotherapy should be deferred until there is evidence of disease progression or high risk features, especially if 3 or more factors.
- Early radiotherapy/chemotherapy is indicated if there are clinical, histological or radiological high risk features:
  1. Inoperable tumours causing intractable seizures
  2. Deep-seated inoperable tumour close to eloquent areas
  3. Patients with neurological deficits or progressive symptoms, especially if aged > 40
  4. Tumours with histological features of concern e.g. high proliferation index, gemistocytic histology
  5. Tumours with radiological features of concern e.g. contrast enhancement despite biopsy showing low grade histology
  6. Age over 40 years is a poor prognostic indicator
  7. >6cm size
  8. Tumour crossing midline
- The RTOG 9802 study has shown considerable survival gain if treated with early post operative radiotherapy and 6xPCV chemotherapy in patients >40 or <40 with partial debulking plus high risk feature.
- Patients should be followed up with MR imaging (+/- MR spectroscopy) repeated 3 months after initial surgery, 6 monthly for 2 years and then annually or on development of new clinical symptoms.
- Radiotherapy or further surgery should be considered at the earliest sign of disease progression.
- Pilocytic astrocytomas behave in a benign fashion. Complete surgical excision is usually possible and curative. Management is follow-up; additional treatment with chemotherapy or radiotherapy is rarely indicated. Midline tumours e.g. thalamic or pineal lesions are unlikely to be resectable and early XRT should be considered for local control.
- Early post-operative radiotherapy, rather than follow-up, is indicated for some groups of patients.

2.2.1.i Indications for early post-operative radiotherapy
- Inoperable tumours causing intractable seizures
• Deep-seated inoperable tumour close to eloquent areas which progress
• patients with neurological deficits or progressive symptoms, especially if aged > 40
• tumours with histological features of concern e.g. high proliferation index, gemistocytic histology
• tumours with radiological features of concern e.g. contrast enhancement despite biopsy showing low grade histology

2.2.1.ii Features suggesting disease progression
• increase in tumour size
• alteration of imaging characteristics e.g. development of contrast enhancement
• increase in symptoms or development of new symptoms

2.2.2 Treatment
• Standard treatment is generally with radical conformal radiotherapy; patients with 1p19q deleted oligodendrogliomas are sometimes offered chemotherapy alone.
• Extensive, diffuse low grade gliomas can be difficult to irradiate and be managed with first line chemotherapy instead.

2.2.3 Follow-up

2.2.3.i Appointments and scans
• First follow-up MR scan 2 – 3 months after treatment completion.
• Subsequent MR imaging should be performed 6 monthly for 2 years, then annually, or on development of new clinical symptoms.

2.2.3.ii Endocrinology assessment
• Patients should be referred for endocrinological assessment 6 months after treatment completion if:
  o dose to the pituitary gland was > 24Gy and
  o they remain well with no evidence of recurrent / progressive disease.

2.3 Brainstem Gliomas

• May be high or low grade
• Due to location, surgery, even stereotactic biopsy, is almost always impossible
• Diagnosis made from MR imaging characteristics.
• Prognosis is dependent on the site and grade of tumour; exophytic tumours should be considered for debulking

2.3.1 Management
• Radical radiotherapy
• Chemotherapy reserved for recurrence

2.3.2 Follow-up
• Imaging 3 months post XRT, then 6 monthly for 2 years, then annually
2.4 Meningiomas

2.4.1 Initial management

2.4.1.i Benign Meningiomas, WHO grade I
• Management is complete surgical resection, with MR imaging repeated after 3 months and then annually
• Recurrence should be treated with further surgery. Stereotactic radiosurgery may be considered as an option
• Radiotherapy can be offered for:
  o Gross residual, inoperable disease causing, or likely to cause, significant symptoms
  o Inoperable recurrence
  o 2 or more recurrences at the same site
  o patients declining further surgery

2.4.1.ii Atypical Meningiomas, WHO grade II
• Adjuvant post-operative radiotherapy should be considered in all patients following resection of an atypical meningioma. However, the evidence base is controversial and post-operative radiotherapy may be omitted if:
  o Patients have undergone a Simpsons grade 1 resection
  o The risks of post-operative radiotherapy are deemed to outweigh the risk of disease recurrence e.g. patients with base of skull meningiomas already demonstrating signs of optic nerve damage with visual loss.
• Patients not receiving immediate post-op radiotherapy should be closely followed with MR imaging 3 months post-operatively and then annually, and radiotherapy offered at the earliest sign of disease recurrence.
• Following radiotherapy, MR imaging should be repeated annually or on development of new symptoms

WHO grade 3 meningiomas
All should receive post operative radiotherapy, regardless of extent of resection

2.4.2 Management of recurrent / progressive disease after radiotherapy
• All recurrences should be considered for further surgery
• There is little evidence to suggest that drug treatment is effective there is no possibility of further surgery.
• Stereotactic radiosurgery can be considered for small volume, localised recurrences of grade 1or 2 meningiomas following surgery and conventional radiotherapy

2.5 Primary Cerebral Lymphoma
2.5.1 Management Policy

- Steroids should only be commenced if absolutely necessary e.g reduced GCS and lowest dose possible. Steroids reduce diagnostic yield and cause needless delays to diagnosis and repeat biopsy. The patient needs an urgent biopsy. Cannot treat without histological confirmation. Start steroids post biopsy based on symptoms only. Urgent referral to Dr Kennedy or Kumar
- All patients must have GFR measured pre-treatment; this must be >60mls/min for patient to receive methotrexate
- If fit and <75 potential for radical management. In these patients must also have staging CT scan (PET CT ideal) of neck, thorax, abdomen and pelvis to exclude extra-cranial disease. Baseline FBC, U&E, LFTs and LDH also required. Lumbar Puncture for CSF analysis provides useful prognostic information (Cytology and Protein level)

2.5.1.i Patients of good performance status (WHO PS 0-2), good physiological reserve and Creatinine clearance >/>= 60mls/min

- High dose methotrexate and cytosine arabinoside x 4 cycles (See protocol section IV). Consider MATRIX regime as per IELSG 32 regime: Methotrexate, cytarabine, thiotepa and rituximab x4 cycles. Considerable survival benefit, but considerable toxicity possible.
- Post chemotherapy requires consolidation therapy. Whole brain and meninges radiotherapy or autologous stem cell transplantation are standard options.
- If consolidation autologous stem cell transplantation considered will require stem cell harvest after 2 cycles of chemotherapy and early liaison with transplant haematologist.
- MR scan 2 weeks after 4th cycle
- If complete response to chemotherapy requires consolidation therapy. Options include radiotherapy to whole brain and meninges 36Gy in 18# or autologous stem cell transplantation.
- If PR/SD after chemotherapy options include autologous stem cell transplantation or 36Gy in 18# to whole brain and meninges and a conformal boost to residual enhancing disease to 9Gy in 5#
- If Progressive disease post chemotherapy give radiotherapy to whole brain and meninges 36Gy - 40Gy plus a boost of 9Gy in 5#

Consider radical therapy above if young, previously fit, PS 3, but due to acute presentation of disease. Can still achieve remission.

2.5.1.ii Elderly Patients or those unfit for HDMTX (age >75 or WHO PS 3-4)

- Continue steroids, Proceed straight to radiotherapy. Options are 40Gy in 20# or 36Gy in 18# with 9Gy in 5# boost (if possible, depending on volume of disease and patients tolerance).
- If PS4, multiple comorbidities, >80 and frail consider Best supportive care alone or 20gy in 5# radiotherapy.

2.5.2 Follow-up

- Repeat MR scan 2-3 months post XRT, then annually or on development of new symptoms.

2.5.3 Management of disease relapse

- Options include PCV chemotherapy, Temozolamide or CCNU

2.6 Ependymomas

2.6.1 General remarks
• Ependymomas can occur infratentorially, supratentorially or in the spinal cord.
• Maximal safe resection should be performed, followed by early (within 72 hours) post-operative MR imaging to assess the extent of residual disease
• All patients with grade II and III ependymomas should be offered post-operative radiotherapy.
• Radiotherapy can be omitted in patients with grade I subependymomal tumours or occasionally in those with completely resected grade II tumours. These patients should be followed with repeat MR imaging at 3 months, then 6 monthly and XRT offered at the earliest sign of disease relapse
• Grade I Myxopapillary ependymomas tend to occur in the conus region of the spinal cord; complete resection is not usually possible and post-operative XRT may be considered.

2.6.2 Pre-radiotherapy investigations
• MR imaging of the brain and whole spine.
• CSF cytology, either pre-op or >14 days post-operatively

2.6.3 Management of Supratentorial Ependymomas
• Risk of CSF spread is low
• Provided MRI spine is normal and CSF is clear, cranio-spinal irradiation is not indicated.
• Treatment is with local field XRT

2.6.4 Management of Infratentorial Ependymomas
• If MR spine normal and CSF clear, local field irradiation is sufficient
• The place of spinal irradiation in high-grade infratentorial ependymomas is controversial. Patients are at higher risk of spinal spread, but there is little evidence that CSI has any definite impact
• If a good resection has been achieved, local field radiation is adequate. However, whole spinal irradiation should be considered in some circumstances e.g. high grade disease extending into cervical spinal cord.

2.6.5 Management of Spinal Cord Ependymomas

2.6.5.i Low grade, WHO Grade II
• If there is no evidence of disease elsewhere in the spinal cord or brain, treatment volume is confined to the affected region of the spinal cord.
• If there is evidence of tumour deposits at other sites, the whole spine +/- brain should be treated with boosts to sites of gross disease.

2.6.5.ii High grade, WHO grade III
• Intramedullary disease in the thoracic spine can be treated with irradiation of primary site alone
• Disease in the lower thoracic spine / cauda equina seems to confer a greater risk of drop metastases and whole spine XRT is recommended
• If CSF cytology is positive or there are radiologically apparent metastases, radiotherapy should be delivered to the whole spine +/- brain with boosts to the site of primary disease and any other spinal deposits

2.6.6 Follow-up
• Patients should have repeat MR imaging performed 3 months post XRT, 6 monthly for 2 years, then annually or on development of new symptoms
• Patients should be referred for endocrinological assessment 2 years after treatment completion if they fulfil the criteria listed in section 2.1.2.ii, above.

2.6.7 Treatment of recurrent / progressive disease
• Imaging +/- biopsy should be undertaken to try to differentiate progression from radionecrosis
• If patient remains fit, options include:
  1) Re-resection
  2) Stereotactic radiotherapy (to very small recurrences < 3cm)
  3) Chemotherapy – although little evidence to support benefit. Platinum and etoposide may be tried

2.7 PNET (Primitive Neuro-ectodermal tumour)
• Patients should have whole neuraxis imaging and CSF cytology

2.7.1 Supra-tentorial PNET
• Primary treatment: Chemotherapy with PNET 3 paediatric protocol (cyclo/etop/carbo/etop) or PACKER regime (former as effective but less toxic)
  • Followed by: Craniospinal irradiation

2.7.2 Posterior fossa PNET
• Treat as medulloblastoma

2.7.3 Spinal PNET
• Radiotherapy should be delivered to the whole spine with boosts to the site of primary disease and any other spinal deposits
• Chemotherapy reserved for recurrence

2.8. Pituitary Adenoma
• Radiotherapy given for residual or recurrent disease post-operatively, or for patients unsuitable for or refusing surgery
• Follow-up via specialist endocrinology clinics and Pituitary MDT Clinics

2.9 Craniopharyngioma
• Usually arise in the pituitary stalk in the suprasellar region from embryological remnants of Rathkes pouch
• Present with pituitary hypofunction, visual problems and headaches
• High risk of local recurrence
• Surgical guidelines are to perform a less aggressive resection to spare the hypothalamus. This should be followed by routine post-operative radiotherapy. If a complete resection has been performed, patients may be followed up and radiotherapy delivered on relapse.
2.10 Germ Cell Tumours

2.10.1 General Comments
- Management depends on whether they are HCG and AFP secreting or non-secreting
- CSF sampling required pre-treatment for cytology and AFP and HCG levels
- Risk of meningeval spread – need whole neuraxis imaging
- Aim of initial surgery is to obtain histological diagnosis and relieve any hydrocephalus; attempt at complete resection not required
- Following treatment of secreting germ cell tumours, surgery should be reconsidered if residual abnormalities are seen on post-treatment MR, due to the risk of residual teratoma

2.10.2 Pure Germ Cell Tumours (Germinomas)
- Non-secreting: HCG < 100, AFP –ve
- Primary treatment does not include chemotherapy
- Treatment is with low dose Craniospinal XRT with boost to primary tumour
- Move to omit spinal XRT. Ongoing clinical trial of whole cranium XRT with boost to whole ventricles and to tumour

2.10.3 Teratomas and Non-germinomatous germ cell tumours
- Secreting: HCG > 100 & AFP secretors
- All patients should receive primary chemotherapy, followed by XRT
- Chemotherapy comprises Cisplatin / etoposide / ifosfamide x 4 (Paediatric germ cell protocol)
- Non-metastatic tumours: Local radiotherapy
- Metastatic disease: Craniospinal radiotherapy with boost to primary tumour

2.11 Medulloblastoma
- Cranio-spinal irradiation with concurrent vincristine 2mg / week
- Adjuvant chemotherapy with PACKER regime
- Recurrent disease: chemotherapy with temozolamide / cisplatin

2.12 Haemangiopericytoma
2.12.1 Initial management
- Primary resection
- High risk of local recurrence, so all patients should be offered post-operative radiotherapy
- Risk of systemic metastases, esp bones and liver

2.12.2 Treatment of recurrent / progressive disease
- Restaging, with consideration of further surgery / radiotherapy
- These tumours are not chemosensitive. There is no role for chemotherapy, even in the presence of metastatic disease

2.13 Pineal Tumours
2.13.1 General comments
- These include:
  Germ cell tumours (see section 2.10)
Pineal parenchymal tumours – pineocytoma, pineoblastoma, PPT of intermediate differentiation, mixed PPT
Astrocytomas (see above)

- Surgical management of PPT should be to obtain histological diagnosis and treat hydrocephalus

2.13.2 Pineocytoma
- Complete resection may be adequate, but is not usually possible
- Post-operative XRT should be offered for un-resectable / residual disease
- Radiotherapy dose and planning as per LGG guidelines

2.13.3 Pineoblastoma
- WHO grade IV; high risk of dissemination
- Behaves as medulloblastoma or PNET
- Treatment is with Craniospinal irradiation
- Chemotherapy on recurrence

2.14 Choroid plexus leions
Choroid plexus papilloma: resection alone
Choroid plexus carcinoma: Resection + post-op XRT

2.15 Haemangioblastoma
- 25% of cases are associated with VHL (von Hippel Lindau Syndrome)
- Primary management is complete surgical resection
- Post-op XRT is not routinely indicated
- XRT may be used for recurrent or unresectable disease
- Patients should have follow-up MR scan at 3 months, then annually

2.16 Chordoma
- Commonest sites: Clivus (Base of skull) or sacrococcygeal region
- Management: Surgical resection
- XRT for residual or recurrent disease
- Proton therapy may improve dose distributions; clinical oncologist to refer via NHS Proton panel for approval and funding.

2.17 Arterio-venous malformations
- Should be referred for stereotactic radiosurgery / gamma knife at a Tier 4 Stereotactic centre.

Schwannomas

- Vestibular schwannomas are common, but schwannomas arising from the base of skull, but also other cranial nerve roots occur, especially trigeminal.
• Bilateral VS is associated with Neuro-fibromatosis type 2
• Patients with suspected NF2 should have genetic testing and counselling.
• All patients are managed by the Base of Skull MDT
• Non NF2 patients can be offered surgery or stereotactic radiotherapy
• Conventional fractionated radiotherapy can be used for larger lesions in patients unsuitable for surgery/further surgery or declining surgery.
• NF2 patients should not generally be treated with radiotherapy due to the risk of secondary malignancies. Their options should be discussed by an NF2 MDT.
• If SRS is recommended for NF2 patients, this should be delivered via the Gamma Knife Centre in Sheffield
• NF2 patients with progressive disease who fulfil pre-designated criteria may be treated with iv bevacizumab, which can arrest and reverse VS growth.
Section 3: Management of Brain Metastases

3.1 General Comments

- Single or multiples lesions suggestive of metastases identified on imaging
- Resection of a solitary brain metastasis followed by whole brain radiotherapy can confer a survival advantage over whole brain XRT
- However, the morbidity of neurosurgery must be considered with reference the patient’s overall prognosis and diagnosis.
- Patients acutely unwell with brain metastases causing oedema, raised intracranial pressure and midline shift may require urgent surgery, which can be immediately lifesaving. Efforts will be made to consider the patient’s pre-morbid condition, history of malignancy, extra cranial disease extent, prognosis and to discuss with the patient’s primary oncologist. The patient’s wishes should also be considered (do they have an advanced directive or power of attorney?). Ultimately, in an emergency, it is at the discretion of the on call neuro surgical consultant to decide if urgent surgery is required.

3.2 Multiple lesions in patients with a known diagnosis of cancer

- Neurosurgical intervention may be indicated in certain cases up to 3 lesions.
- Stereotactic radiosurgery can be considered in suitable cases measuring up to 3cm.
- Palliative whole brain radiotherapy may be offered. In such cases, patients should be re-referred to their treating oncologist

3.3 Multiple lesions in patients with no previous diagnosis of cancer

- CT scan thorax / abdo / pelvis to look for a primary tumour and other sites of metastases
- If CT scan shows primary tumour or metastases elsewhere, it is reasonable to accept a diagnosis of disseminated malignancy without neurosurgical intervention
- If CT thorax / abdo / pelvis is clear, neuro-surgical biopsy should be undertaken to confirm the diagnosis of metastatic cancer and possibly point towards a primary site
- Other routine investigations searching for the primary e.g. GI Endoscopy, mammograms are not indicated unless the patient has specific symptoms suggesting disease at that site
- Identification of the primary site will in most cases not alter initial management.
- Neurosurgical intervention may be indicated in certain cases up to 3 lesions.
- Stereotactic radiosurgery can be considered in suitable cases measuring up to 3cm and <3 metastases.
- Palliative whole brain radiotherapy may be offered. In such cases, patients should be re-referred to their treating oncologist

3.4 Solitary lesions in patients with a known diagnosis of cancer

- CT scan thorax / abdo / pelvis to exclude metastases at other sites
- MR brain to ensure that lesion is solitary
- If clear, resection of metastasis can be considered
- The surgical intent should be to completely resect the metastasis
- Stereotactic radiosurgery to be considered for suitable lesions measuring less than 3 cm and <3 metastases
- Patients, particularly those with a short disease free interval i.e. whose disease has spread to the brain soon after their initial diagnosis, should be discussed with their treating oncologist pre-operatively
3.5 Solitary lesions in patients with no known diagnosis of cancer

• If radiologically lesion appears to be a metastasis, patients should have CT thorax / abdo / pelvis and MR brain to identify disease at any other sites
• If lesion is confirmed as solitary, patients should undergo maximum safe surgical resection. The aim is for total excision.
• Stereotactic radiosurgery to be considered for suitable lesions measuring less than 3 cm and < 3 metastases
• If other sites of disease are identified, case should be reviewed by MDT to identify appropriateness of neurosurgical intervention or alternative methods of obtaining histological diagnosis
• If a primary tumour is apparent e.g. lung, patients should be referred to e.g. lung team
• If a primary tumour site is not apparent, patients can be referred to the neuro-oncology team

Post-operative Options. Observation versus Radiotherapy

If a complete resection (as per post op MRI scan) options include:

1. Observation alone with 3-4 monthly MRI scans ordered and checked by primary site oncologist. Re-referred to Neuro MDT if concerns for scan review and discussion. If recurrence options include re-resect, whole brain radiotherapy or SRS.
2. Immediate post operative whole brain radiotherapy 30gy in 10#.

Whole brain radiotherapy immediately post op has been demonstrated to reduce surgical cavity and distant brain recurrence as well as reduce death due to neurological progression. Not demonstrated to improve overall survival. Side effects include fatigue and cognitive decline. Primary oncologist to discuss pros and cons with patient. To discuss with neuro-oncologist if clarification required.

If residual disease in surgical cavity (as per post op MRI) options include:

1. Re-do surgery
2. Observation, especially if uncertainty that the MRI appearances are definite tumour residual. Early repeat MRI scan. e.g 2 months
3. Whole brain radiotherapy 30Gy in 10#.
4. SRS or SRFT to cavity and site of residual disease. Can also use conformal conventional radiotherapy if cavity too large for SRS/SFRT.

If other small brain metastases identified on Brainlab scan or early post op scan can - offer SRS to these lesions or use whole brain radiotherapy if multiple >3 lesions.

Posterior Fossa Metastases

Metastases in the posterior fossa, even if relatively small can cause significant morbidity, due to compression of 4th ventricle and hydrocephalus. Deterioration can be rapid if untreated. Often these patients require urgent debulking of cerebellar metastasis or a VP shunt to relieve intra-cranial pressure.

Low threshold to offering post-operative radiotherapy to reduce the risk of progression and early return of symptoms. Even if thought to be a complete resection.

If posterior fossa metastases only and pressure surgically relieved, offer:
1. If well, GCS 15, no signs of raised ICP → 20Gy in 5# to posterior fossa alone. Use 30gy in 10# if future potential use of SRS (ie. Good PS and treatment options).

2. If still has some intra-cranial symptoms and GCS 13-14 → 30Gy in 10# to posterior fossa alone, with close observations and continue steroids 4-8mg dexamethasone.

If patient have posterior fossa metastases that have been surgically managed and also other brain metastases evident on scan
   - Offer whole brain radiotherapy, doses as above

If posterior fossa metastases alone that have not been managed with surgery, options include:
   1. SRS (if meets SRS criteria)
   2. Posterior fossa radiotherapy alone 30Gy in 10# if well, GCS 15 and future potential use of SRS (ie. Good PS and treatment options)
   3. 20Gy in 10# over 2 weeks to posterior fossa alone if concern that radiotherapy could cause oedema and compression of 4th ventricle, patient is GCS13-14 or has raised ICP symptoms. Give dexamethasone 8-16mg per day and keep under close observation. For first 4 fractions, be an inpatient under neuro-oncology/surgery care.

If posterior fossa metastases, with other brain metastases, non surgically managed, options 1-3 above, but using whole brain radiotherapy instead of posterior fossa alone.
Section 4: Radiotherapy Planning Guidelines

4.1 Immobilisation and Positioning for radical treatments

Immobilisation: Thermoplastic shell
or headfix frame in younger patients with no dental problems and target volume near critical structures.
Use Vac Bag and prone position for radically treated spinal tumours.
Discuss with planning radiographers before.

Position: Mostly supine.
Cerebellar tumours may be treated prone.
Occipital / posterior parietal tumours can be treated either supine or prone, but supine is easier for MR fusion and for the patient; cases should be discussed with planning staff.

Planning scans: Post-op MR scan slice thickness 3mm or less, fused with CT scan
T1W MRI with contrast to fuse with planning CT scan for: High grade gliomas / meningiomas / cerebral lymphomas / ependymomas
T2W MRI to fuse with planning CT scan to define low-grade tumours gliomas.

4.2 High grade gliomas

4.2.1 General comments
- Treatment may be delivered in 1 or 2 phases
- Total radical dose: 60Gy in 30 fractions. 59.4Gy in 33# also acceptable for grade 3 gliomas, as per recent randomised controlled trials.
- Complexity of treatment planning and risk to critical structures need to be weighed against the poor prognosis of this disease

Indications for 2 phase treatment:
1) To hasten start of XRT – start with a simple parallel pair planned on simulator, then continue with CT planned boost
2) To reduce dose to critical structures – deliver tolerance dose to critical structure included in PTV or CTV, then introduce shielding and continue to treat GTV to full dose.
3) To reduce volume of irradiated brain – see below

4.2.2 Single phase treatment: Target Volumes
GTV = area of contrast enhancement and surgical cavity on T1w + contrast scan
CTV = GTV + 2.0-2.5cm, trimmed to areas not at risk of disease spread e.g. enclosed by bone, falx, tentorium, contra-lateral hemisphere (above corpus callosum), organs at risk. Include corpus callosum in CTV if within 2-2.5cm expansion volume.
PTV = CTV + 0.3cm, use 0.5cm if patient less tolerant of immobilisation

4.2.3 Two phase treatment: Target volumes
4.2.3.i To hasten start of XRT:
Phase I: Parallel opposed pair, planned on simulator to whole brain or to tumour with generous margins
Phase II: As for single phase treatment above
Dose: Phase I: 40Gy in 20 fractions, or lower.
    Phase II: 20 Gy in 10 fractions, or 60Gy minus phase I dose.
Can deliver parallel pair in 2Gy fractions and convert to conformal CT plan when planning complete, to continue to 60Gy in 30 fractions in total.

4.2.3.ii To shield organs at risk or reduce treated volume: See below

4.2.4 Management of Organs at Risk

- Contour optic chiasm and brain stem (there is no need to expand this volume).
  Optic chiasm appears on 3-4 (3mm) MR slices and extends 0.5cm superior to posterior clinoid.
- Treatment should be planned in 2Gy fractions to meet the following constraints:
  - Optic chiasm:
    Planned dose ≤ 54Gy.
    Maximum dose of up to 54Gy acceptable within beam penumbra.
  - Brainstem:
    Whole organ tolerance = 50Gy;
    If treating < 1/3 and only one side, accept doses up to 57Gy
    If treating < 1/3 but across midline, keep dose < 54Gy
    If treating > 1/3 or brainstem tumours, reduce fraction size to 1.8Gy
    and reduce dose to 54Gy in 30 fractions
    For grade 4 gliomas accept dose of 60Gy to brainstem

Treatment should be planned using the simplest possible field arrangement. Beams must not enter or exit through the eyes.

If it is impossible to generate a treatment plan which keeps within the tolerance doses above, consider the following:

- If overlap with critical structures is small, compromise PTV and CTV to limit dose to chiasm and brain stem as above and deliver 60Gy to GTV
- If it is impossible to limit dose to target organs without compromising dose to GTV, plan treatment in 2 phases, coming off optic chiasm after 50Gy:
  PTV = GTV + 3cm
  Phase I: 50Gy in 25 fractions to whole PTV
  Phase II: 10Gy in 5 fractions to PTV avoiding / shielding optic chiasm
- If the GTV lies in close proximity to critical structures e.g. temporal lobe tumours, such that shielding critical structures is unavoidable without significantly compromising the GTV, dose to whole PTV should reduced to 54Gy in 30 fractions

The dose (in 2Gy/fraction) to other normal tissues should, wherever possible, be kept below the following limits:

- Optic nerve < 60Gy
- Retina < 50Gy (though a small proportion, other than the macula, can receive up to 70Gy)
- Lacrimal gland < 40Gy
- Pituitary < 45Gy
Lens < 6Gy

4.2.5 Volume Constraints
- 60Gy in 30 fractions can be safely prescribed to volumes of up to 600cm$^3$ in a single phase.
  - If PTV volume > 600cm$^3$ but < 1000cm$^3$, treat in 2 phases.
    - Phase I: 40Gy in 20# to GTV + 3cm
    - Phase II: 20Gy in 10# to GTV + 1-2cm, to keep volume receiving 60Gy to < 600cm$^3$
- If PTV volume > 1000cm$^3$, convert to parallel pair

4.3 Low grade gliomas

4.3.1 Target Volumes
GTV = area of radiologically apparent tumour (T2W or FLAIR)
CTV = GTV + 1.5cm, trimmed to areas not at risk of disease spread e.g. enclosed by bone, contra-lateral hemisphere (above corpus callosum)
PTV = CTV + 0.5cm

4.3.2 Dose
- 50.4Gy in 28 fractions or 54Gy in 30 fractions.
- 45Gy in 25 fractions if large volume.

4.4 Brainstem gliomas (low or high grade)

4.4.1 Target volumes
GTV = area of radiologically apparent tumour (T1W + contrast or T2W)
CTV = GTV + 2cm above and below
PTV = CTV + 0.5cm

4.4.2 Dose
- 54Gy in 30 fractions high grade gliomas
- 50.4Gy in 28 fractions or 45Gy in 25 fractions if low grade glioma.

4.5 Meningiomas (Both grades I and II)

4.5.1 Target Volumes
GTV = area of radiologically apparent tumour (T1W + contrast)
CTV = GTV + 1cm. Edit to anatomical boundaries. Ensure dural tail is included with a margin of at least 1cm
PTV = CTV + 0.5cm

4.5.2 Dose
- Grade I meningioma: 50.4Gy in 28 or 54Gy in 30 fractions

- Grade II (Atypical meningioma):
  - Away from critical structures: 54-60Gy in 30#
  - Skull base or close to critical structures: 54Gy in 30#
  - or 50.4Gy in 28 fractions.

- Grade 3 meningioma: 60Gy in 30 fractions
4.6 Ependymomas
The regions to be treated are defined in section 2.6

4.6.1 Supratentorial
Target volume:
- GTV = pre-op MR volume
- CTV = GTV + 2cm (2.5 – 3cm along ventricular system)
- PTV = CTV + 0.5cm
Dose: 54Gy in 30 fractions

4.6.2 Infratentorial, no CSF spread
Single phase treatment, to primary tumour alone.
CT/MR planned; target volumes as per boost field above
Dose: 54Gy in 30 fractions

4.6.3 Spinal ependymomas
- Treatment position: Prone
- Immobilisation: Posicast (D/W mould room)
- Beam arrangement: 2-3 wedged posterior fields. For whole spine irradiation, 2-3 fields junctioned as per CSI techniques, junctions moved weekly

4.6.3.i Treatment of primary disease only
Indications: Low grade Ependymomas

Target volumes
- GTV = area of radiologically apparent tumour (T1W + contrast or T2W)
- CTV = GTV + 2cm above and below
- PTV = CTV + 0.5cm

Dose: depends on length of cord being treated
- < 10cm: 50Gy in 25 fractions.
- 10 - 15cm: 45Gy in 25 fractions (or 50Gy in 28 fractions)
- > 15cm: 40Gy in 20 fractions

4.6.3.ii Whole spine irradiation with boosts to primary tumour +/- sites of gross metastases
Indications: High grade ependymomas

Target volumes
Phase 1: Whole spine: CTV = spinal canal
- PTV = CTV + 0.5cm in all directions

Phase II: Boosts to primary disease and secondary deposits:
- GTV = area of radiologically apparent tumour (T1W + contrast or T2W)
- CTV = GTV + 2cm above and below
- PTV = CTV + 0.5cm

These phases may be reversed, so that the boosts are given first, if this facilitates easier treatment planning

Dose:
Phase I: Whole spine: 35Gy in 20 fractions
Phase II: Boost fields: <10cm: 10Gy in 5 fractions (Total dose = 45Gy in 25 fractions)
- > 10cm: 15Gy in 8 fractions (Total dose = 50Gy in 28 fractions)
Whole spine with no other boost: 40Gy in 20 fractions
4.7 Other spinal tumours

4.7.1 Gliomas
Planning and doses as per low-grade ependymomas. Increase margins for high grade gliomas to 3cm if possible, depending on cord length

4.7.2 PNET
Planning as per high grade ependymomas, whole spine + boost to primary disease site

4.8 Primary CNS Lymphoma
Timing: 4 weeks after last dose of HDMTX
Treatment planned on simulator for phase 1, Conformal for boost phase 2
Immobilisation: Thermoplastic shell
Phase 1 Beam arrangement:
Parallel opposed pair, extending down to C2.
MLC shaping to ensure adequate meningeal coverage with leaves brought in to cover posterior half of orbit and nasopharynx.
Phase 2 boost: GTV contour residual enhancing tumour on T1w +contrast MRI. CTV=GTV plus 2cm margin. PTV = CTV plus 3-5mm
Dose: 2 phase, Phase 1: 36Gy in 18#, Phase 2: 9Gy in 5#. As per IELSG32 protocol

Single phase: 36Gy in 18# or 40Gy in20#

4.9 Pituitary adenoma
Immobilisation: Head-fix frame
Target volume: GTV = Tumour / post-operative residuum on MR imaging
CTV = GTV + 0.5cm
PTV = CTV + 0.5cm
Dose: 45Gy in 25 fractions for non functioning adenoma or 50.4Gy in 28 fractions if functioning adenoma.
Beam arrangement: 4 fields

4.10 Craniopharyngioma
Immobilisation: Head-fix frame
Target volume: GTV = MR post-op tumour residual
CTV = GTV + 1cm
PTV = CTV + 0.5cm
Dose: 54Gy in 30 fractions
Beam arrangement: 4 fields

4.11 Germ cell tumours

4.11.1 Pure germ cell tumours (germinomas, non-secreting tumours)
GTV = Gross tumour on fused CT / MR images
CTV = GTV + 1.5cm along ventricular walls / 1cm into brain substance
PTV = CTV + 0.5cm
Dose: 40Gy in 25 fractions
Disease at > 1 site / leptomeningeal spread

Low-dose Craniospinal irradiation: 25Gy in 15 fractions
Boost to primary tumour: 15Gy in 10 fractions

Boost GTV: Visible tumour on fused CT/MR images
CTV = GTV + 1.5cm along ventricular walls / 1cm into brain
substance (since prone to intra-ventricular spread)
PTV = CTV + 0.5cm

4.11.2 Teratomas and non-germinomatous germ cell tumours (Secreting tumours)

Non-metastatic:
Single phase treatment to primary tumour alone
Target volume and margins as above
Dose: 54Gy in 30

Metastatic
Craniospinal irradiation: 35Gy in 20 fractions
Cranial boost: 20Gy in 10 fractions

4.12 Medulloblastoma

Off-trial
- Cranio-spinal irradiation: 35Gy in 20 fractions to whole cranium and spine
- Boost to posterior fossa: 20Gy in 10 fractions
- Boost to metastases: 10Gy in 5 fractions

4.13 Haemangioblastoma

- Indication: Incompletely resected or recurrent disease
- Usually posterior fossa; treat prone
- Planned as per low grade glioma guidelines
- 54Gy in 30 fractions

4.14 Haemangiopericytoma

- Indication: All patients post-operatively
- Planned as per low grade glioma guidelines
- 60Gy in 30 fractions

4.15 Chordoma

4.15.1 Clivus
Immobilisation: Headfix
CT / MR planned
GTV = post-op volume
CTV = GTV + 0.5 – 1cm
PTV = CTV + 0.5cm
Dose: 54Gy in 30 fractions
Aim for highest possible dose with IMRT up to 70Gy in 35#. There is a strong dose response relationship with local control. Refer for proton panel to consider proton therapy.
4.15.2 Sacrococcygeal
Dose: Depends on volume
   Aim for 60Gy in 30 fractions, but may need to limit it to 50Gy in 25 fractions if volume large. If possible 70Gy in 35# with IMRT

4.16 Choroid plexus carcinoma

Planned as per LGG guidelines, 54Gy in 30 fractions
5 Chemotherapy Protocols

5.1 Temozolamide

5.1.1 Concurrent and Adjuvant Temozolamide

Indication: Histologically conformed glioblastoma multiforme WHO grade IV

And Age < 70 and WHO PS 0 - 1

Treatment algorithm for Concomitant and Adjuvant Temozolamide for Glioblastoma Multiforme

Histologically proven glioblastoma (WHO grade IV)
Age < 70
WHO PS 0-1
Absolute neutrophil count ≥ 1.5 x 10⁹/l
Platelet count ≥ 100 x 10⁹/l
Adequate hepatic and renal function

Focal conformal radiotherapy: 60Gy in 30 fractions to tumour + 2-3cm margins
With Concomitant temozolamide 75mg/m² once daily for 42 days. If misses dose, do not take extra.

4 weeks after completion of radiotherapy

Adjuvant temozolamide x 6 cycles
Cycle 1: 150mg/m² po od D1-5, q28
Cycles 2-6: 200mg/m² po od D1-5, q28
Treatment guidelines for Concomitant and Adjuvant Temozolamide for Glioblastoma Multiforme

1) Concomitant Phase
Patients should have a full blood count performed prior to commencing treatment, and then once weekly during radiotherapy.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TMZ interruption&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TMZ discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count</td>
<td>≥ 0.5 and &lt; 1.5 x 10&lt;sup&gt;9&lt;/sup&gt;/l</td>
<td>&lt; 0.5 x 10&lt;sup&gt;9&lt;/sup&gt;/l</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥ 10 and &lt; 100 x 10&lt;sup&gt;9&lt;/sup&gt;/l</td>
<td>&lt; 10 x 10&lt;sup&gt;9&lt;/sup&gt;/l</td>
</tr>
<tr>
<td>CTC non-heamatological toxicity (except for alopecia, nausea and vomiting).</td>
<td>CTC Grade 2</td>
<td>CTC Grade 3 or 4</td>
</tr>
<tr>
<td>Liver function tests including AST</td>
<td>If AST/ALT or ALP greater than 5 times the upper limit of normal</td>
<td>Severely deranged LFTS or liver failure.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Concomitant temozolamide can be continued at full dose when all of the following conditions are met: Absolute neutrophil count ≥ 1.5 x 10<sup>9</sup>/l, Platelet count ≥ 100 x 10<sup>9</sup>/l, CTC non-heamatological toxicity ≤ 1 (except for alopecia, nausea and vomiting).

Patients should receive prophylaxis against pneumocystis carinii pneumonia during this phase of treatment (Septrin 960mg od Mon, Wed, Friday). This should be continued until lymphocyte count >0.5, though in general can be discontinued at the end of the concurrent phase.

Tablets should be taken 1 hour before daily radiotherapy treatment and on an empty stomach, at least 2 hours since last food.

Emesis during concomitant phase is usually mild. Ondansetron 8mg po od can be given for the first 3 days, but thereafter, metoclopramide 10mg PRN is usually adequate.
2) Adjuvant monotherapy phase
If there has been no dose reduction during the concomitant phase, cycle 1 should be given at 150mg/m² po od D1-5 q28, 4 weeks after competing chemoradiotherapy. If all of the following criteria are met (absolute neutrophil count ≥ 1.5 x 10⁹/l, Platelet count ≥ 100 x 10⁹/l, CTC non-heamatological toxicity ≤ 1 (except for alopecia, nausea and vomiting), dose should be increased to 200mg/m² po od D1-5 q28 for cycles 2 – 6.

<table>
<thead>
<tr>
<th>TMZ dose levels for monotherapy treatment</th>
<th>Dose level</th>
<th>Dose (mg/m²/day)</th>
<th>Remarks</th>
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<tbody>
<tr>
<td></td>
<td>-1</td>
<td>100</td>
<td>Reduction for prior toxicity</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>150</td>
<td>Dose during cycle 1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>200</td>
<td>Doses during cycles 2-6 in the absence of toxicity</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Temozolamide dose reduction or discontinuation during monotherapy treatment</th>
<th>Toxicity</th>
<th>Reduce TMZ by 1 dose level</th>
<th>Discontinue TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count &lt; 1.0 x 10⁹/l</td>
<td></td>
<td></td>
<td>See footnote b</td>
</tr>
<tr>
<td>Platelet count &lt; 50 x 10⁹/l</td>
<td></td>
<td></td>
<td>See footnote b</td>
</tr>
<tr>
<td>CTC non-heamatological toxicity (except for alopecia, nausea and vomiting).</td>
<td>CTC Grade 3</td>
<td></td>
<td>CTC Grade 4b</td>
</tr>
<tr>
<td>Liver function tests including AST</td>
<td>If AST/ALT or ALP greater than 5 times the upper limit of normal</td>
<td></td>
<td>Severely deranged LFTS or liver failure.</td>
</tr>
</tbody>
</table>

b Temozolamide to be discontinued if:
Dose level –1 (100mg/m2/day) still results in unacceptable toxicity
The same grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction

5.1.2 Relapsed Disease
Temozolamide 150mg/m2 cycle 1, 200mg/m² cycle 2 and subsequent, days 1-5 q 28. Dose reductions as above.
Timing: To be taken on an empty stomach, at least 2 hours from last food.

Anti-emetics: Many patients find temozolamide significantly emetogenic; zofran 8mg od for 5/7 can be prescribed to be taken pre-treatment each day.

5.2 PCV Regime

Indications:
- Relapsed disease
- Adjuvant treatment for Grade III gliomas (anaplastic astrocytoma, anaplastic oligodendrogliomas) and Grade 2 oligodendrogliomas, oligoastrocytomas.
- Occasionally for Grade IV tumours not eligible / suitable for concurrent temozolamide.

Regime: Days 1 – 10, q42
NB 6 week treatment cycle; FBC nadir is late – approx 4 weeks post treatment

Drug doses (standardised, not /m2):
- Day 1: Vincristine 2mg iv (standard dose)
- Day 1: CCNU 160mg po od (200mg if BSA >1.9m²)
- Days 1-10: PCV 150mg po od (200mg if BSA > 1.9m²)

Toxicity: Main toxicities are nausea (dexamethasone and ondansetron 8mg po bd should be routinely prescribed with metoclopromide 10mg tds PRN), neutropaenia, lethargy. Patients can also experience constipation or rarely neuropathy due to vincristine.

If patients develop a rash, they should stop the procarbazine tablets immediately; these should be omitted from future cycles.

Dietary restrictions: Patients are advised to avoid foods containing tyramine due to possible interaction with procarbazine. Foods to be avoided for the 10 days of procarbazine treatment and 48 hours thereafter include cheese, gravy and red wine. This is detailed in the PCV chemo info sheet.

Dose reductions:
- Treatment can be at full dose if: WCC > 3, neutrophils > 1.5, platelets > 150.
- Thrombocytopenia or neutropaenia necessitating > 1 deferral of treatment: Reduce procarbazine duration from 10 to 7 days.

CCNU capsules are available only as 40mg; procarbazine only as 50mg, therefore dosing flexibility is limited.

3rd line options for high grade gliomas include: continuous temozolamide 21 days out of 28 days, 50mg per day, irinotecan, cisplatin and carboplatin iv and intra-arterial cisplatin
5.3 Administration of High Dose Methotrexate (MTX) and cytarabine

**Indication:** Primary CNS Lymphoma

**Regime:** Fortnightly for 4 cycles before XRT

**Most common side effects:**
- Nausea
- Mucositis
- Neutropaenia

**Pre-treatment investigations:**
- GFR – must be > 60mls/minute.
  - If GFR < 60 mls/min, do not give MTX and proceed directly to XRT

**Before commencing methotrexate**

1) Ensure urine pH ≥ 8
   - Give iv sodium bicarbonate as per chemo prescription sheet
   - If urine pH remains < 8, continue 1.4% sodium bicarbonate 500mls 2 hourly until urine pH ≥ 8
   - Failure to adequately alkalinise urine can lead to drug crystallising in renal tubules, risking renal damage

2) Ensure pt is not on NSAIDs or aspirin, as these inhibit drug excretion. Also avoid penicillins, cephalosporins, co-trimoxazole and proton pump inhibitors

3) Ensure pt has not developed ascites, pleural effusions or other oedema e.g. ankle oedema since previous treatment. (History and examination are adequate; other tests only if clinically indicated)
   - MTX is retained in these “third space fluid”, slowing excretion and risking increased toxicity.
   - If ascites or other oedema has developed, methotrexate should be deferred until it has been treated, or omitted completely.

4) Ensure WCC > 3, neutrophils > 1.5, calc. creatinine clearance or GFR > 60 mls/min

5) If serum creatinine is rising, repeat GFR. Otherwise, calculated creatinine clearance is adequate.

**Timing of treatment**

- MTX is “on hold” and **MUST be taken off hold** as soon as decision to treat and admission are confirmed
- Because MTX levels must be checked every 24 hours, and the lab runs the levels assay at 2pm daily, aim to start methotrexate as early in the day as possible, and not on Thursdays or Fridays.

**Treatment protocol**

- Sodium bicarbonate 1.4% 500mls iv over 1 hour
  - If urine pH < 8, continue 1.4% sodium bicarbonate 500mls 2 hourly until urine pH ≥ 8
  - Methotrexate 3g/m² iv over
  - Sodium bicarbonate 1.4% 500mls iv over 1 hour
  - Sodium bicarbonate 1.4% 500mls iv over 1 hour
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Checking Methotrexate Levels

- It is VITAL that methotrexate levels are taken **24 hours after the start of the MTX infusion**, and are **repeated at 36 and 48 hours**, and then every 24 hours until criteria below are fulfilled.
- If the timing of levels is not exactly as above, make sure the time that levels were taken is recorded on blood form.
- Levels are taken in a U&E tube and sent to biochemistry at Alder Hey Hospital, Liverpool.
- Runs are done at approx 2pm daily; results are available on labo or medway 1.5 to 2 hours later.
- If levels will be needed at weekends, please notify biochemistry on Friday and telephone the on-call biochemist before sending samples on Saturday and Sunday.

Rescue and criteria for discharge:

- Folinic acid rescue **MUST** be commenced 24 hours after the start of MTX infusion (i.e. without waiting for levels).
- Standard rescue: 30mg iv every 3 hours for the first 24 hours, then 30 mg po 6 hourly continued for 3 days.
- Continue to check urine pH and maintain pH ≥ 8 until methotrexate level < 150 i.e. evidence that patient is clearing the drug satisfactorily. This can be done with either iv Sodium bicarbonate (as above) or with oral Sodium Bicarbonate 1g tds. Also maintain fluid intake of 3 l/day (oral +/- ivi).
- If 48 hour level < 150, allow home with folinic acid 30mg qds for 3 days TTO.
- If 48 hour level > 150, increase folinic acid to 60mg qds and keep patient in hospital.
- Continue to check levels daily until < 150 before allowing home with folinic acid 30mg qds for 3 days TTO. Increase rescue to 60mg every 6 hours for 3 days for 2nd and subsequent cycles. If in doubt, always over-rescue.

Troubleshooting: No methotrexate levels available

- Every effort should be made to avoid this situation by compliance with the guidelines above, re timing of starting treatment and pre-warning lab to expect weekend levels.
- The initial 24, 36 and 48 hour levels are particularly critical.
- However, if levels are unavailable, continue at previous folinic acid dose (30mg po 3 hourly, or the level to which it had been reduced) without any further reductions until it is possible to obtain levels.
- Patient must not be discharged until levels have been obtained and comply with guidelines above.

Troubleshooting: Management of delayed excretion

If levels are failing to fall e.g. still > 150 after 4 days:

- Ensure urinary alkalinisation is maintained with either iv or oral Na bicarb (1g tds).
- Ensure fluid intake is at least 3l/day (e.g 2l iv + free oral fluids).
- Monitor creatinine daily. Continue to check levels every 24 hours.
- Increase folinic acid rescue to 60 mg qds and give i.v.
- Keep patient in hospital until 7 days post MTX to ensure mucositis is not developing.
- If well and creatinine stable, allow home when MTX < 30.
- If excretion has been delayed, review clinical indication for further doses of MTX.
- If further doses are given, increase initial rescue to e.g. 60mg po 3 hourly for 24 hours, then reduce according to levels.
  - If levels after 72 hours are still > 1000, contact consultant and pharmacist for higher rescue / alternative antidote.
6. Guidelines for the management of Epilepsy in Neuro-oncology patients

- Epilepsy is common in patients with brain tumours, especially those with primary low-grade tumours.
- Management is individualised, based on patient factors and toxicities; it is impossible to provide prescriptive treatment protocols.
- Additional advice can be sought from Drs Mohanraj or Clough (available via their secretaries at Salford), who are happy to see or discuss any neuro-oncology patients.

<table>
<thead>
<tr>
<th>Indications for commencement of an antiepileptic drug (AED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 epileptiform seizure in a patient with a known SOL</td>
</tr>
</tbody>
</table>

Indications do not include:

- Seizures developing within the first week after neuro-surgery in patients with no pre-operative history of seizures.
- Routine prophylaxis

<table>
<thead>
<tr>
<th>General principles of AED treatment in patient with brain tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEDs can produce sedation, tiredness and mental slowing in a dose dependent manner.</td>
</tr>
<tr>
<td>Patients with brain tumours and epilepsy will almost universally need long-term (life long) anti-epileptic drug treatment. Tolerability is as important as efficacy</td>
</tr>
<tr>
<td>Low starting dose and slow titration improves tolerability. This has to be balanced against the need to gain seizure control quickly.</td>
</tr>
<tr>
<td>If the patient is unable to take the first AED at an adequate dose because of side effects, the drug should be withdrawn, and a second drug commenced. When the first AED does not result in control of seizures despite adequate dose, a second AED should be commenced at a low dose. Withdrawal of the first AED may be possible subsequently, but combination therapy with two drugs is sometimes necessary.</td>
</tr>
<tr>
<td>Except in the situation of severe allergic rash, withdrawal of AEDs, especially barbiturates and benzodiazepines, should be a gradual process.</td>
</tr>
<tr>
<td>Reliable and authoritative patient information can be found at <a href="http://www.epilepsy.org.uk">www.epilepsy.org.uk</a></td>
</tr>
</tbody>
</table>
Choice of AED

First line drugs (initial monotherapy)

*Lamotrigine (Lamictal):*

**Dose**
25mg OD, increasing by 25mg every two weeks till on 50mg BD. Further increases can be made in 50mg steps. Maintenance dose 150-400mg/day.

**Side effects**
Rash (3-4%, can be severe), sedation, sleep disturbance.

**Interactions**
Does not induce hepatic microsomal (P450) enzymes, not known to interact with chemotherapeutic agents. Major interaction with valproate (increases serum lamotrigine level) and the combined oral contraceptive pill (reduces serum lamotrigine level)

Maximum starting dose of lamotrigine in patients on valproate is 25 mg on alternate days (or 12.5 mg daily), and max maintenance is 200mg daily. If valproate added to lamotrigine, halve the dose of lamotrigine when dose of valproate ≥ 500 mg/day.

**Monitoring**
Serum level monitoring not routinely required, but may be useful in special situations (pregnancy, combination therapy with valproate)

*Levetiracetam (Keppra):*

**Dose**
250mg OD or BD, increase by 250mg weekly/biweekly. Maintenance dose 1000-4000 mg. Can be given intravenously. Perceived advantage of ‘rapid titration to effective dose’ hence preferred if rapid control desired.

**Side effects**
Behavioural (depression, anxiety and aggression)

**Interactions**
No known pharmacokinetic interactions.

**Monitoring**
No monitoring required

*Sodium Valproate (Epilim Chrono)*

**Dose**
300mg OD or BD, increased at weekly/biweekly to 300-500 mg and then 500mg BD. Maintenance dose 1000-3000 mg /day. Can be given intravenously, role in treatment of status epilepticus. Controlled release preparations result in smoother blood levels

**Side effects**
Weight gain, hair loss, tremor, thrombocytopenia, rarely idiosyncratic hepatic toxicity, hyperammonaemic encephalopathy.

**Interactions**
Inhibits the metabolism of nitrosoureas, and may enhance toxicity form these agents. Inhibits metabolism of lamotrigine (see above).

Worst drug to take in pregnancy (Valproate + lamotrigine is the worst combination in terms of major congenital malformation) hence avoid if
pregnancy possible. Because of this and cosmetic side effects, best avoided in young women.

Monitoring
FBC and LFT at baseline, 4 weeks and 6 monthly thereafter. Serum levels do not correlate with clinical efficacy, hence monitoring not indicated, except to check compliance.

Second line (seizures continuing despite adequate doses of first AED)
Any of the above 3 drugs can be used with the others, bearing in mind the pharmacokinetic interaction between lamotrigine and valproate.

Pregabalin (Lyrica)
Dose
75mg OD, increasing by 75 mg weekly/biweekly to maintenance dose of 150mg BD
Also licensed for generalised anxiety disorder and pain. No known pharmacokinetic interactions
Side effects
Sedation, weight gain, GI upset
Interactions
No known interactions
Monitoring
No monitoring required

Zonisamide (Zonegran)
Dose
Starting dose 25mg OD, increase by 25mg every two weeks, to 50mg BD thereafter by 50mg every two weeks, maintenance dose 100-400mg
Side effects
Sedation, weight loss, depression, risk of renal calculi – avoid in patients with h/o renal stones or surgery to the renal tract
Interactions
No clinically significant drug interactions reported
Monitoring
No monitoring required

Clobazam (Frisium)
Dose
10mg BD (3-5 day course, separated by 2-3 weeks). For short term control of seizures (those with established pattern of clustering of seizures, perimenstrual exacerbation). Tolerance develops with prolonged use, hence long term use not routinely recommended. Gradual withdrawal advisable for courses longer than 1 week.
Side effects
Sedation (5mg BD may be tried if excessive sedation)
Interactions
Exacerbation of sedative side effects with other drugs that have similar effects
Monitoring
No monitoring required
Other antiepileptic drugs including carbamazepine, oxcarbazepine and topiramate, are not included in this list owing to unfavourable pharmacokinetics (hepatic enzyme induction) and adverse effect profile. However, they may be useful in specific situations.

**Withdrawing / changing AEDs**

Complete withdrawal of AEDs should only be attempted only in patients who have been seizure free for a period of time, and only if the causative lesion has been adequately treated (eg: complete resection of DNET or ganglioglioma). This should be preceded by a full discussion of risk of seizure recurrence and consequences thereof (eg: for driving)

An AED which is failing to control seizures, or which is causing unacceptable toxicity, must be withdrawn slowly, decreasing the dose every 2 weeks, typically over 6-8 weeks, longer for barbiturates.

**Strategies for managing prolonged / serial seizures, impending status epilepticus**

Patients with structural brain lesions are at increased risk of experiencing status epilepticus or serial seizures.

*Serial seizures:*
Patients may experience increasing frequency of partial seizures before suffering a generalised convulsive seizure, which evolves into status epilepticus. If this pattern of seizures has occurred once, patients and their families should be given the option of using Clobazam 10mg BD for 3 days to abort the episode of status.

*Prolonged generalised seizure:*
If seizures persist for >5min, or 2 min more than the usual duration of seizures for the patient, intervention is required. In most cases this would require a 999 call. If one such episode has occurred, patient’s family / carers should be offered the use of buccal midazolam. This requires a test dose, and will need to be referred to epilepsy nurse specialists for training of family/ carer.

*In hospital management of status epilepticus:*
Generalised convulsive seizure lasting >5min should be treated with intravenous Lorazepam 4mg given over 2 minutes (or diazepam 10mg IV, if Lorazepam unavailable). If seizures continue 5 min after the injection, valproate 800mg (10mg/kg) should be administered as IV bolus over 3-5 minutes, followed by intravenous infusion of valproate 1.6 gram over 24 hours. If seizure continues for >5-10 minutes after administration of valproate bolus, the patient should be given general anaesthesia using midazolam, propofol or thiopentone, intubated and admitted to ITU.

**Palliative care**

Midazolam and phenobarbitone may be given subcutaneously by syringe driver (phenobarbitone should not be mixed with morphine in the same syringe). Doses vary and should be titrated to symptom control.
7. DVLA Driving Regulations for patients with CNS malignancies

All patients who have been found to have a brain tumour must contact the DVLA and inform them of their diagnosis. All are prohibited from driving for a period of time.

Patients with low grade tumours, WHO grade I or II, are not permitted to drive a car for a minimum of 1 year from their main initial treatment.

For patients with high grade tumours, WHO grade III or IV, or brain metastases, this is 2 years.

Supportive and Palliative Care

The prognosis for a number of high grade brain tumours is poor and despite best efforts with active anti-cancer therapies, the outcome can be fatal. Honesty with patients and their carers at all points is important, but to still maintain hope and provide encouragement.

Quality of Life is important. Treatments with limited success should be used judiciously and not jeopardise quality of life at the end of life.

Supportive care and the patient’s holistic needs should be considered at all stages of the patient’s illness, not just after treatment failure.

Consider:
1. Psychological needs and high incidence of depression in brain tumour patients
2. Practical needs – home situation, adaptations
3. Financial and Supportive needs
4. Encouraging social interaction and travel (if possible and desired).
5. Place of Care. Are the patient and family coping at home?

Consider the effect of the illness on the patient’s main carers and the significant impact the illness can also have on them.

End of Life Care

At later stages of the patient’s illness the smooth transition from active care to terminal care needs to be achieved. Prompt referrals to palliative care can provide useful local community support at the end stages of illness. Identifying disease progression is based on clinical and radiological signs. Reduced performance status, fatigue, confusion and altered cognition can be early clinical signs of progression.

Avoiding unnecessary hospitalisation in the last few weeks of life, with attendances to A&E/MAU is important. Early liaison with GP’s and local palliative care services can avoid this. Provide clear letters to GPs with clarity on where the patient is up to, the treatment aims and intent of care. GPs should adopt the Gold Standard Framework for cancer care. If patients are an inpatient at the end of life, focus on supportive needs, ward level care, allowing a natural death (DNAR) and be available to meet the family for support.