Manchester Cancer

Clinical Guidelines for the Management of Primary Brain and Spinal Tumours

Including:

Referral and contact details for the Salford Neuro-oncology MDT

Management and follow-up policies for primary CNS tumours

Indications for referral of patients with Brain Metastases

Radiotherapy planning guidelines

Chemotherapy protocols

Epilepsy management policy

DVLA Driving regulations

These guidelines pertain to patients managed via the:

- *Greater Manchester and Cheshire Neuroscience MDT (SRFT)*
- *Greater Manchester and Cheshire Network (Supportive Care) MDT (The Christie NHS FT)*
- *Greater Manchester and Cheshire Neuroscience Disease Specific Supgroup (NDSG / Clinical Subgroup)*

and have been approved by these groups.

Contents

Section 1: Referral Pathway and General Guidelines

1.1. The Neuro-science MDT Meeting

- Multi-disciplinary team case review is mandatory for ***all*** patients with a diagnosis of primary CNS malignancy and is also appropriate for a selected subgroup of patients with brain metastases who may be candidates more aggressive management.
- The neurosciences MDT meeting meets weekly on Tuesday mornings at 9.30am in Seminar Room 8, Mayo Building, Salford Royal NHS FT (Hope Hospital).
- Cases can be added to the list by contacting Diane Jones or Diane Horrocks, MDT coordinators at SRFT. Tel: 0161 206 1378 or 0161 206 0080; Fax: 0161 206 1303; Email srftneurooncologymdt@nhs.net, or diane.c.jones@srft.nhs.uk or diane.horrocks@srft.nhs.uk
- Referral should be made via a faxed or emailed letter (from and to nhs.net email addresses only), detailing the precise question to the MDT, or via a referral form, available on request.
- The deadline for adding cases is 3pm on Friday, to allow adequate time to collate all information and review imaging before the Tuesday meeting.
- All cases of primary or secondary central nervous system tumours referred to the Neurosurgical On-call during the preceding week will also be discussed.
- All cases are discussed pre and post-operatively, unless emergency neuro-surgical intervention was required and pre-op discussion was not possible. Such cases are discussed post-operatively.
- Post-operative 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 within 24 hours of the meeting.

NB: There are separate Base of Skull and Pituitary MDTs which also meet at SRFT; the MDT co-ordinators (as above) can provide meeting, referral and pathway details.

1.2 Guidelines for surgical intervention

- *A histological diagnosis should be sought in all patients, unless there is a specific reason not to do so.* This is fundamental in planning patient management and ensuring that all patients are treated appropriately.
- All patients should be considered for maximal safe cytoreductive surgery.
- All biopsies should be ideally be performed under stereotactic guidance to increase the diagnostic yield.
- or biopsy may be omitted in cases where:
    - The risks of surgery 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
    - The patient declines the procedure
- Full surgical clinical guidelines are available from SRFT
- There are 5 sub-specialised neuro-oncology neuro-surgeons: Miss Konstantina Karabatsou (MDT Lead Clinician), Mr James Leggate, Mr John Leach, Mr Ajit Sofat, Mr Kanna Gnanalingham. All can be contacted via their secretaries at SRFT.

1.3 Post-operative Imaging

Early (within 72hours) post-operative MR imaging indicated as standard in the majority of cases where the intention has been to remove all or the majority of the tumour, to assess the extent of resection and form a baseline for future comparison. 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
- High grade gliomas prior to further treatment

Immediate post-op imaging is not routinely performed:

- Following resection of brain metastases
- In patients with benign tumours including meningiomas where management is anticipated to be follow-up alone – in this group, baseline imaging 3 months post-operatively is adequate
- Patients who have undergone biopsy only

The need for early post-operative imaging should be identified pre-operatively, and imaging booked electively.

1.4 Oncology Referrals

- Patients are seen in the Neuro-oncology new patients' clinic at SRFT on Thursday mornings.
- This clinic is staffed by a multi-disciplinary team comprising a Consultant Clinical Oncologist, Neuro-oncology specialist nurses and a specialist social worker.
- Patients requiring neuro-oncology review should be referred as soon as their ***final*** histology result is available. In general, the neuro-surgeon should 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, provided the patient is adequately informed and supported by the Clinical Nurse Specialists.
- The decision to list the patient for the neuro-oncology new patient clinic is made at the Tuesday am MDT and the specialist nurses contact the patient.
- Patients should be listed only on the basis of final histology only (not provisional histology or where supplementary reports, other than 1p19q status, are awaited).
- 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
- The four neuro-oncology consultant clinical oncologists alternate the new patient clinic and provide cross-cover. The clinic is never cancelled due to staff absence. In general: Dr Rao runs the clinic on the 1st Thursday, Dr McBain: 2nd Thursday, Dr Tran: 3rd Thursday, Dr Whitfield: 4th Thursday (5th Thursdays by rotation).
- Referred patients will be seen in the earliest available appointment slot, and may therefore come under the care of any consultant (regardless of who a referral letter is addressed to)
- If referral to a particular consultant is desired, this should be indicated in the referral letter, but clinicians should understand that this might delay their patient's appointment.

Section 2: Management Policies

2.1 High grade gliomas

2.1.1 First line treatment

2.1.1.i Glioblastoma Multiforme WHO grade IV

Management is dependent on patient age and performance status, and on patient choice. WHO PS refers to WHO Performance Scores 0 – 4. 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 with concurrent and adjuvant temozolamide chemotherapy

Age < 70, WHO PS 2
Radical or palliative radiotherapy; chemotherapy at recurrence. However, concurrent and adjuvant temozolomide is of benefit in younger patients of PS 2 and can be discussed on a case-by-case basis.

Age < 70, WHO PS 3-4 or age > 70, WHO PS 0-2
Palliative radiotherapy or best supportive care.

Some very fit patients age 70-80 of WHO PS 0-1 with small tumours may be suitable for radical radiotherapy +/- chemotherapy

Age > 70, WHO PS 3-4
Best supportive care. Palliative radiotherapy may occasionally be considered for patients who achieve a good steroid response.

Multifocal disease

Patients with gliomatosis cerebri or multifocal GBM require whole brain 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.

All potentially eligible patients should be considered for entry into the BR14 study investigating the role of concurrent and / or adjuvant temozolomide chemotherapy.

Off trial, adjuvant chemotherapy may confer a small additional survival benefit in the younger age groups and may be considered in patients of WHO PS 0-1 not suitable for trial entry. The first cycle may be given prior to radiotherapy, with subsequent treatment continued after radiotherapy.

Age < 70, WHO PS 3-4 or age > 70
As for grade IV gliomas above

2.1.1.iii Anaplastic Oligodendroglioma or Oligoastrocytoma, WHO grade III

Deletion of one or both 1p19q alleles is very important in predicting prognosis and chemosensitivity in this disease, and is useful in guiding management decisions.

Patients with intact 1p19q or loss of heterogeneity (loss of either 1p or 19q only):
May be eligible for the BR14 study as above and should be considered for study entry.

Off trial: Radical radiotherapy; the addition of adjuvant chemotherapy may be considered as above.

Patients with co-deletion of 1p and 19q:
Radical radiotherapy and adjuvant chemotherapy.

The established trial evidence is for radiotherapy followed by adjuvant PCV. This will be compared to radiotherapy with concurrent and adjuvant temozolomide and to chemotherapy alone (temozolomide) in a forthcoming study. Until this study opens or reports, off trial, the use of any of the 3 arms, or the use of PCV, can be justified in selected cases.

2.1.2 Follow-up Policy

2.1.2.i Appointments and scans

- Patients are reviewed 4 – 6 weeks after completion of radiotherapy, with chemotherapy commenced at that time as appropriate.
- 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 3-6 monthly (for GBMs) or 6 monthly (other histologies). Imaging frequency may be reduced after the first 2 years if clinically appropriate.
- 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:
    - Dose to the pituitary gland was > 24Gy
    - They remain well with no evidence of recurrent / progressive disease
    - 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:
    - Further surgery
    - Chemotherapy
    - Clinical trial entry

Second Relapse

- Only a minority of patients who experience second disease relapse remain well enough for consideration of third-line treatment. Management will again depend on previous treatment, nature of recurrence and disease-free interval.

- Options include:
    - Further chemotherapy including re-challenge with initial regime
    - Re-irradiation, if > 2 years after initial irradiation
    - Further surgery

2.2 Low Grade Gliomas

Includes: WHO grade II astrocytomas (diffuse, fibrillary, gemistocytic), oligodendrogliomas, oligoastrocytomas.

2.2.1 General Guidelines

- Histological confirmation should be sought in all patients at time of initial presentation, with maximal tumour resection performed where possible
- 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 recurrence unless there are clinical, histological or radiological features of concern (see below).
- If managed with initial active surveillance, patients should be followed up with MR imaging 3 months after initial surgery, 6 monthly for 2 years and then annually or on development of new clinical symptoms.
- Further surgery and / or treatment with radiotherapy or chemotherapy 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, although should be considered in adults with incomplete resection. Midline tumours e.g. thalamic or pineal lesions are unlikely to be resectable and early XRT should be considered for local control.

2.2.2.i Indications for early post-operative radiotherapy

- inoperable tumours causing symptoms including intractable seizures
- deep-seated tumour close to eloquent areas which is likely to be inoperable if it progresses
- 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

2.2.2.ii Features suggesting disease progression and that radiotherapy is indicated

- 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

- Radical conformal radiotherapy remains the first-line standard of care for most non-co-deleted, patients pending the outcome of the BR13 low grade glioma study
- Patients with 1p19q co-deleted oligodendrogliomas or oligoastrocytomas, or patients with very extensive, diffuse low grade gliomas which would be difficult to irradiate, may be managed with first-line chemotherapy.

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 2 years after treatment completion if:
    - dose to the pituitary gland was > 24Gy *and*
    - 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, can be prohibitive
- Diagnosis is, in most cases, 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 generally reserved for recurrence

2.3.2 Follow-up

- Imaging 3 months post XRT, then 6 monthly for 2 years, then 6-12 monthly

2.4 Meningiomas

2.4.1 Initial management

2.4.1.i Benign Menigiomas, WHO grade I

- Management is complete resection, with MR imaging repeated after 3 months and then annually
- Recurrence should be treated with further surgery
- Radiotherapy can be offered for:

    - Gross residual, inoperable disease causing, or likely to cause, significant symptoms
    - Inoperable recurrence
    - 2 or more recurrences at the same site
    - Patients declining further surgery
- Small volume recurrences may also be treated with stereotactic radiosurgery, although local control is inferior to conventional radiotherapy.

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:
    - Patients have undergone a Simpsons grade 1 resection
    - 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.

2.4.1.iii Malignant Meningiomas, WHO grade III

- All patients require post-operative radiotherapy to high-grade glioma doses, regardless of extent of resection
- Follow-up imaging should be undertaken after 3 months and then 6 monthly due to the high rate of relapse.

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 in grade 1 and 2 meningiomas.
- Stereotactic radiosurgery may be occasionally considered for small volume, localised recurrences of grade 1 or 2 meningiomas following surgery and conventional radiotherapy.
- Response rates in grade 3 meningiomas are not sufficiently high to justify SRS in the majority of cases.
- For inoperable recurrent grade 3 meningiomas, consideration can be given to chemotherapy with doxorubicin and cyclophosphamide. Although some initial responses may be seen, treatment is toxic, relapse inevitable and outlook poor.
- There is a small body of evidence reporting benefit of bevacizumab in recurrent meningiomas of any grade for whom no other treatment options exist, but this is not standard.

2.5 Primary Cerebral Lymphoma

2.5.1 Management Policy

- Surgical management requires only biopsy to confirm diagnosis; debulking / resection is not indicated
- Ideally, it is preferable if biopsy is performed prior to commencement of steroids, but this is not always feasible if the patient is deteriorating symptomatically.

- Staging and additional investigations should be undertaken in line with the British Neuro-Oncology Society Guidelines (www.bnos.org.uk)
- Outcomes are best when patients are managed with intensive combination chemotherapy
- Patients who are potentially fit for chemotherapy (age generally < 75, WHO PS 0-3 and GFR >60mls/min) are managed by the Lymphoma Disease Group (Dr Linton or Prof Radford) at The Christie NHS FT to whom they should be promptly referred post-biopsy.
- It is preferable to with-hold radiotherapy following chemotherapy if possible, particularly in older patients, due to the risk of neuro-cognitive decline
- Radiotherapy may be given post chemotherapy to patients who are intolerant of chemotherapy, who do not achieve complete remission or are treated within a clinical trial. These decisions should be made in conjunction with the lymphoma team.
- Patients unfit for chemotherapy may be offered palliative radiotherapy.

2.5.1.i Patients of good performance status (WHO PS 0-3, GFR > 60mls/min)

- Refer to Medical Oncology for consideration of combination chemotherapy (high dose methotrexate with cytarabine) or clinical trial entry.

If it is decided that radiotherapy is to be given subsequently, this should be:

- Radiotherapy to whole brain and meninges, no sooner than 4 weeks after last cycle of methotrexate.
- POP planned on simulator: 40Gy in 20 fractions, or as per trial protocol

2.5.1.ii Elderly Patients or those unfit for HDMTX (age >70 or WHO PS 3-4)

- Continue steroids
- Omit chemotherapy; proceed straight to radiotherapy
- CCNU 160mg od q42 can be considered if initially unfit for HDMTX

2.5.2 Follow-up

- Repeat MR scan 2-3 months post XRT, then 6 monthly or on development of new symptoms.

2.5.3 Management of disease relapse

- Refer to medical oncology for consideration of chemotherapy.

2.6 Ependymomas

2.6.1 General remarks

- All patients with suspected ependymomas should undergo imaging of the entire craniospinal axis preoperatively
- 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 III ependymomas should be offered post-operative radiotherapy.
- All patients with grade II ependymomas should be considered for post-operative radiotherapy. Radiotherapy may occasionally be omitted in selected cases where macroscopically complete excision has been achieved.
- Radiotherapy can generally be omitted in patients with grade I subependymomal tumours.
- Patients not treated with post-op XRT should be followed with repeat MR imaging at 3 months, then 6 – 12 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; if complete resection is not possible then 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 inclusion of at least the distal 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
- PNET is included within the British Neuro-Oncology Society Guidelines (www.bnos.org.uk) on management of rare tumours which should be consulted

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 as above or reserved for recurrence

2.8. Pituitary Adenoma

- Managed via the Pituitary MDT
- Initial management usually surgical or medical
- Radiotherapy given for residual or recurrent disease post-operatively, or for patients unsuitable for or refusing surgery
- Follow-up via specialist endocrinology clinics

2.9 Craniopharyngioma

- Managed via the Pituitary MDT
- 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 occasionally 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 (levels checked in both blood and CSF, if possible)

- CSF sampling required pre-treatment for cytology and AFP and HCG levels (from blood and CSF, if possible)
- Risk of mengingeal 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 and sites of metastatic disease

2.11 Medulloblastoma

- Medulloblastoma is included within the PNET Guidelines of the British Neuro-Oncology Society (www.bnos.org.uk) ; these should be consulted
- Completeness of resection is prognostically important; if resection is initially incomplete, further surgery prior to craniospinal radiotherapy may be considered; close collaboration with the MDT is vital.
- Cranio-spinal irradiation with consideration of concurrent vincristine 2mg / week, following surgical resection, depending on patient fitness
- Adjuvant chemotherapy with PACKER regime
- Recurrent disease: consider 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 / metastatic disease

- Restaging, with consideration of further surgery / radiotherapy
- These tumours respond poorly to chemotherapy. Regimes containing doxorubicin / cyclophosphamide may have minor, short-lived activity.
- Recent reports have suggested more promising results for temozolomide combined with bevacizumab. Application for funding for this can be considered, but it remains non-standard.

2.13 Pineal Tumours

2.13.1 General comments

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

- Surgical management of PPT should be to obtain histological diagnosis and treat hydrocephalus
- There are British Neuro-Oncology Society Guidelines (www.bnos.org.uk) on management of pineal tumours which should be consulted

2.13.2 Pineocytoma

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

2.13.3 Pineal Parenchymal Tumour of Intermediate Differentiation

- Complete resection not usually possible
- Equivalent to WHO grade II-III
- Post-operative XRT is indicated and should be offered routinely
- Involved field radiotherapy is adequate; full cranio-spinal radiotherapy is not routinely indicted
- 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
- Role of chemotherapy is controversial; young, fit patients may be offered adjuvant chemotherapy (PACKER) accepting that this incurs significant toxicity
- Otherwise, chemotherapy on recurrence

2.14 Choroid plexus lesions

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

2.15 Haemangioblastoma

- 25% of cases are associated with VHL (von Hipplel 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
- Base of skull lesions managed via the Base of Skull MDT; Sacro-coccygeal via the Sarcoma MDT
- Management: Surgical resection
- Post-operative XRT unless clear indications to with-hold eg patient not fit, technically impossible
- Proton therapy may facilitate delivery of higher XRT doses and all cases should be referred to the Proton Panel for their assessment.
- If accepted for Proton Therapy, treatment is delivered in the USA or Europe
- If unfit for proton therapy, conventionally planned radiotherapy may be offered.

2.17 Vestibular Schwannomas

- Vestibular schwannomas are most common, but schwannomas arising at the skull base from other cranial nerve roots, especially trigeminal, are managed similarly.
- Bilateral VS is associated with Neuro-fibromatosis type 2
- All patients are managed via the Base of Skull MDT or the NF2 MDT
- Non-NF2 patients may be offered surgery or stereotactic radiosurgery via the Base of Skull joint Oncology / Surgical clinic.
- Conventionally fractionated radiotherapy may be indicated for larger lesions in patients unsuitable for or declining surgery
- NF2 patients should generally NOT be treated with radiotherapy due to the risk of second malignancy; their options should be carefully discussed via the NF2 MDT.
- If SRS is recommended by the NF2 MDT, this is delivered at The National Gamma Knife Centre at Sheffield
- NF2 patients with progressive disease who fulfil pre-designated criteria may be treated with IV bevacizumab which has been shown to arrest or reverse VS growth

3. Secondary CNS Malignancies: Management of Brain Metastases

3.1 General Comments

- Single or multiple lesions suggestive of metastases identified on imaging
- Resection of a solitary metastasis or SRS for up to 4 small metastases (or a combination of both) can confer a survival advantage over whole brain XRT alone
- WBRT is generally indicated following surgical resection
- However, the role of more aggressive management with neurosurgery or SRS must be considered with reference the patient's overall prognosis and diagnosis

3.2 Multiple lesions in patients with a known diagnosis of cancer

- Patients should be re-referred to their treating oncologist
- Neuro-surgical intervention is rarely indicated, but patients with ≤4 small metastases, KP > 70 and controlled systemic disease may be referred to the Neuro-oncology MDT at SRFT (referral details as before) for consideration of SRS.
- In all other cases, management is with palliative whole brain radiotherapy or best supportive care under the supervision of 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 may be considered 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.
- Patients should be considered for initial treatment with palliative cranial radiotherapy and investigated further if new symptoms develop.
- Patients of good performance status with up to 4 metastases all measuring < 4cm may be considered for stereotactic radiosurgery.

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
- In patients with systemically controlled disease and good performance status, resection of metastasis or stereotactic radiosurgery can be considered
- The surgical intent should be to completely resect the metastasis
- 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
- Re-refer to treating oncologist for whole brain XRT post-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
- Discussion of these cases at the neuro-oncology MDT is vital because other differential diagnoses include GBM or cerebral abscess
- If lesion is confirmed as solitary and CT TAP is clear, patients should undergo maximum safe surgical resection

- If other sites of disease are identified, case should be reviewed by MDT to identify appropriateness of neuro-surgical intervention or alternative methods of obtaining histological diagnosis
- SRS should only be offered for solitary lesions with no previous cancer diagnosis if a primary site elsewhere in the body has been confirmed.
- Patients undergoing resection should be referred for post-op whole brain XRT
- 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 or their local carcinoma-of-unknown primary site (CUP) team

4. Radiotherapy Treatment Planning Guidelines

4.1 Immobilisation and Positioning for radical treatments

Immobilistion: Perspex shell
or headfix frame in younger patients with no dental problems and target volume near critical structures

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 (usually T1W with contrast, but sometimes need T2W or FLAIR to define low-grade tumours), slice thickness 3mm or less, fused with CT scan.

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
- 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
CTV = GTV + 2.5cm, trimmed to areas not at risk of disease spread e.g. enclosed by bone, contra-lateral hemisphere (above corpus callosum), organs at risk
PTV = CTV + 0.5cm

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 ≤ 50Gy.
        Maximum dose of up to 54Gy acceptable within beam penumbra.
    - Brainstem:
        Whole organ tolerance = 54Gy;
        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

Treatment should be planned using the simplest possible field arrangement. If at all possible, beams should 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 < 55Gy
Retina < 50Gy (though a small proportion, other than the macula, can receive up to 70Gy)
Lacrimal gland < 30Gy
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
54Gy in 30 fractions

4.4 Brainstem gliomas (low or high grade)

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

4.4.2 Dose
54Gy in 30 fractions.

4.5 Meningiomas (Both grades I and II)

4.5.1 Target Volumes
GTV = area of radiologically apparent tumour (T1W + contrast)
CTV = GTV + 0.5cm (1cm along dura)
PTV = CTV + 0.5cm

4.5.2 Dose

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

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. IMRT planned

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
50-50.4Gy in 25-28 fractions.
Occasionally, 54Gy in 30fractions for high grade glioma

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

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

Immobilisation: Posicast shell
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.
Dose: 40Gy in 20 fractions

4.9 Pituitary adenoma

Immobilisation: As per radical RT
Target volume: GTV = Tumour / post-operative residuum on MR imaging
CTV = GTV + 0.5cm
PTV = CTV + 0.5cm
Dose: 45Gy in 25 fractions
Beam arrangement: 4 fields

4.10 Craniopharyngioma

Immobilisation: As per radical RT
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

<u>Disease at > 1site / leptomeningeal spread</u>

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)

<u>Non-metastatic:</u>
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 and metastatic sites boost: 20Gy in 10 fractions

4.12 Medulloblastoma

Off-trial

- Cranio-spinal irradiation: 35Gy in 20 fractions to whole cranium and spine - IMRT
- 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: As per radical XRT
CT / MR planned
GTV = post-op volume
CTV = GTV + 0.5 – 1cm
PTV = CTV + 0.5cm
Dose: 54Gy in 30 fractions

NB: These cases should ideally receive proton therapy. If conventional XRT must be used, the highest achievable dose will be delivered using IMRT, with decisions made on a case-by-case basis, but this is a rare scenario.

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. It may be possible to deliver 70Gy in 35fractions with IMRT.
Usually managed by the sarcoma team

4.16 Choroid plexus carcinoma

Planned as per LGG guidelines, 54Gy in 30 fractions

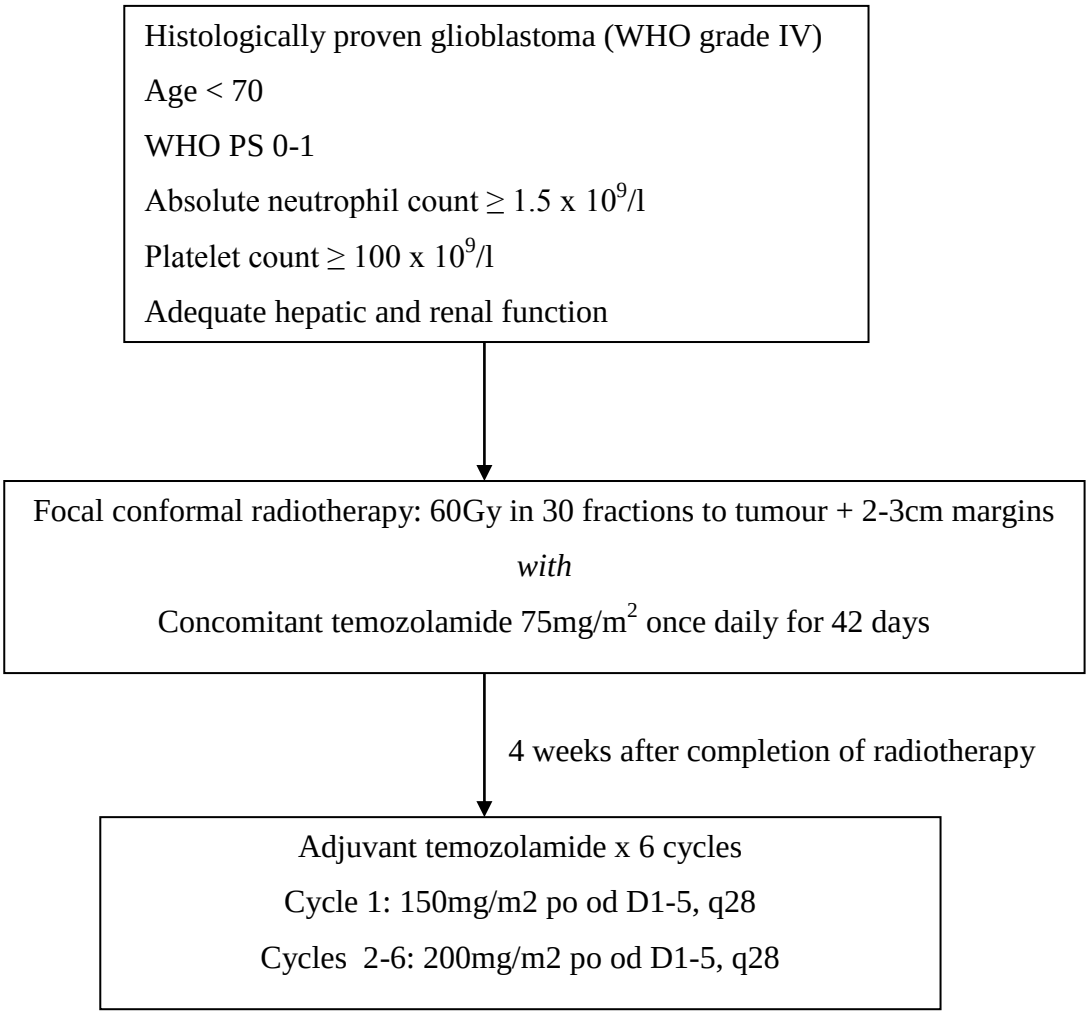
5 Chemotherapy Protocols

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



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.

Temozolamide dosing interruption or discontinuation during concomitant radiotherapy and temozolamide		
Toxicity	**TMZ interruption[a]**	**TMZ discontinuation**
Absolute neutrophil count	≥ 0.5 and $< 1.5 \times 10^9$/l	$< 0.5 \times 10^9$/l
Platelet count	≥ 10 and $< 100 \times 10^9$/l	$< 10 \times 10^9$/l
CTC non-heamatological toxicity (except for alopecia, nausea and vomiting).	CTC Grade 2	CTC Grade 3 or 4

[a]Concomitant temozolamide can be continued at full dose when all of the following conditions are met: Absolute neutrophil count $\geq 1.5 \times 10^9$/l, Platelet count $\geq 100 \times 10^9$/l, CTC non-heamatological toxicity ≤ 1 (except for alopecia, nausea and vomiting).

Patients should receive prophylaxis against pneumocystis carnii 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, metoclopromide 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/m^2 po od D1-5 q28, 4 weeks after competing chemoradiotherapy. If all of the following criteria are met (absolute neutrophil count $\geq 1.5 \times 10^9$/l, Platelet count $\geq 100 \times 10^9$/l, CTC non-

heamatological toxicity ≤ 1 (except for alopecia, nausea and vomiting), dose should be increased to 200mg/m^2 po od D1-5 q28 for cycles 2 – 6.

TMZ dose levels for monotherapy treatment		
Dose level	***Dose*** *(mg/m^2/day)*	***Remarks***
-1	*100*	*Reduction for prior toxicity*
0	*150*	*Dose during cycle 1*
1	*200*	*Doses during cycles 2-6 in the absence of toxicty*

Temozolamide dose reduction or discontinuation during monotherapy treatment		
Toxicity	**Reduce TMZ by 1 dose level**	**Discontinue TMZ**
Absolute neutrophil count	< 1.0 x 10^9/l	See footnote b
Platelet count	< 50 x 10^9/l	See footnote b
CTC non-haematological toxicity (except for alopecia, nausea and vomiting).	CTC Grade 3	CTC Grade 4[b]

[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/m^2 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; ondansetron 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, 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 >1.9m^2)
Days 1-10: PCV 150mg po od (200mg if BSA > 1.9m^2)

Toxicity: Main toxicities are nausea (dexamethasone and ondansetron 8mg po bd for two days 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.

Thrombocytopaenia 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.

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.

Indications for commencement of an antiepileptic drug (AED)

- ≥ 1 epileptiform seizure in a patient with a known SOL

Indications *do not* include:

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

- Routine prophylaxis

General principles of AED treatment in patient with brain tumours

- All AEDs can produce sedation, tiredness and mental slowing in a dose dependent manner.

- Patients with brain tumours and epilepsy will almost universally need long-tern (life long) anti-epileptic drug treatment. Tolerability is as important as efficacy

- Low starting dose and slow titration improves tolerability. This has to be balanced against the need to gain seizure control quickly.

- 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.

- Except in the situation of severe allergic rash, withdrawal of AEDs, especially barbiturates and benzodiazepines, should be a gradual process.

- Reliable and authoritative patient information can be found at www.epilepsy.org.uk

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 $\geq$ 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 1000-4000 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, peri-menstrual 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.**

Loss of licence is shorter for patients with grade 1 meningiomas. More specific information can be found in the DVLA website.