Pan-Birmingham NHS
Cancer Network

Coversheet for Network Site Specific Group Agreed Documentation

This sheet is to accompany all documentation agreed by Pan Birmingham Cancer Network Site Specific Groups. This will assist the Network Governance Committee to endorse the documentation and request implementation.

Document Title	Guideline for the Management of Glioma	
Document Date	December 2009	
Document Purpose	The document provides information on the diagnois, referral and management of patients with primary glioma (high grade and low grade)	
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References	See document	
Consultation Process	Members of the West Midlands Neuro Oncology Supra Network Group	
Review Date (must be within three years)	December 2012	
Approval Signatures: Network Site Specific Group Clinical Chair	*To be added by Network Administrator when guideline goes to Review Group*	
Date Approved by Network Governance Committee	/ /	

ENDORSED BY THE CLINICAL GOVERNANCE COMMITTEE

Pan-Birmingham NHS
Cancer Network

Guideline for the Management of Glioma

Version History

Version	Date Issued	Brief Summary of Change / Process
0.1	27.09.07	Protocol produced by Prof Garth Cruickshank, Dr D Spooner, Prof B Jones, Dr I Geh and presented at the Supra Network Group on 27.09.07.
0.2	06.12.07	Reformatted following discussion with Prof Garth Cruickshank.
0.3	02.07.08	Following meeting with Claire Goddard and Fred Berki.
0.4	22.07.08	With amendments / clarification from Fred Berki. For consultation with Prof Garth Cruickshank.
0.5	08.09.08	Following review by Prof Garth Cruickshank.
0.6	06.10.09	Edited by Dr Paul Sanghera.
1.0	07.12.09	Approved following discussion and amendments.

1 Scope of the Guideline

This guidance has been produced to support the following:

a. The diagnosis and referral of patients with a suspected brain tumour
b. The management of patients with High Grade Glioma (HGG) including WHO classification grade 3 or 4 tumours, anaplastic tumours, Glioblastomas and Gliosarcomas
c. The management of patients with Low Grade Glioma.

2 Guideline Background

These guidelines are based on the 'Referral Guidelines for Suspected Cancer'[1] (www.dh.gov.uk) and 'Improving Outcomes for People with Brain and Other Central Nervous System (CNS) Tumours'[2] (www.nice.org.uk). They have been written by the West Midlands Neuro Oncology Supra Network Group which consists of brain / Central Nervous System (CNS) teams based at University Hospital Birmingham NHS Foundation Trust (UHBFT), University Hospitals Coventry and Warwickshire NHS Trust (UHCWT) and University Hospital of North Staffordshire NHS Trust (UHNST).

3 Organisation of Care for the Management of Brain Tumours

3.1 Specialist Multi Disciplinary Team (MDT) meetings are based at University Hospital Birmingham NHS Foundation Trust (UHBFT; QEH site), University Hospitals Coventry and Warwickshire NHS Trust (UHCWT) and University Hospital of North Staffordshire NHS Trust (UHNST).

3.2 All patients with suspected brain and other CNS tumours should be referred to a specialist MDT at UHBFT, UHCWT or UHNST for discussion of their management and treatment options, according to the 'Guideline for Referral to the Specialist Neuro Oncology Multi Disciplinary Team': www.birminghamcancer.nhs.uk

3.3 In some cases it may be appropriate for patients with advanced disease requiring palliative care only, to be treated locally after discussion with a specialist MDT.

3.4 In the event of a patient refusing to travel to UHBFT, UHNST or UHCWT, treatment may need to be arranged locally. The specialist MDT should be informed and the case discussed as normal. The patient should be informed as part of the consent process that they have elected to have treatment which is not in accordance with current guidelines.

Guideline Statements

4 Referral

4.1 Patients with the following should be referred to a specialst MDT urgently:

- Subacute neurological deficit developing over days to weeks (e.g. weakness, sensory loss, dysphagia, ataxia)
- New onset seizures characterised by one or more of the following:
  - Focal seizures
  - Prolonged post-ictal focal deficit
  - Status epilepticus
  - Associated inter-ictal focal deficit
- Patients with headache, vomiting and papilloedema
- Cranial nerve palsy (e.g. diplopia, visual failure including optician defined visual field loss, unilateral sensorineural deafness).

4.2 Consider urgent referral to a specialist MDT for the following:

- Patients with non migrainous headaches of recent onset, accompanied by features suggestive of raised intra cranial pressure (e.g. woken by headache; vomiting; drowsiness)
- Patients who have a history of headaches who present complaining of an altered pattern or severity of headaches
- Patients aged 45 years onwards, who do not normally complain of headaches, now presenting with headache.

4.3 Any patient with a CT or MRI scan that indicates a tumour should be referred directly to their specialist MDT (at UHBFT, UHCWT or UHNST), a copy of the information should be sent to the patients consultant and GP.

5 Diagnosis and Staging

5.1 Histological confirmation of diagnosis by biopsy or surgical decompression should be attempted for all patients.

5.2 All patients should have MRI-based imaging with contrast.

5.3 All patients whose treatment plan includes Image Directed Surgery must have had an MRI with gadolinium.

5.4 Image directed surgery facilities should be available for all patients where this is the recommended treatment.

5.5 The following investigations should be available to patients and will be ordered according to the results of the MRI, following discussion with the patient:

a. Magnetic Resonance Spectroscopy and Perfusion
b. fMRI functional mapping prior to surgery
c. Diffuse Weighted Imaging (DWI) to identify fibre tracts prior to surgery (Tractography)
d. PET – FDG or preferably FET
e. Thallium SPECT.

6 Initial Management of all Tumours

6.1 All patients should be allocated a key worker / access to a clinical nurse specialist[2].

6.2 All patients should be offered Holistic Needs Assessment in accordance with the National Cancer Action Team Guidance[3].

6.3 Anti-convulsants and steroids (especially Dexamethasone from 2mg twice daily to 16mg per day) should be considered to improve symptoms due to local and global swelling, and control these symptoms until definitive treatment can be commenced.

6.4 All patients should be discussed at the specialist MDT meeting with their imaging prior to surgery. Where clinically indicated, discussions should include possible management with Gliadel wafers.

6.5 Where it is considered possible by the MDT that the patient may be suitable for Gliadel wafers, facilities should be made available for frozen section histology during surgery.

6.6 Attempts at histological diagnosis should be made for all patients either through biopsy or decompression surgery.

6.7 Surgical excision of tumours can control symptoms but carries a risk of morbidity and mortality defined by the tumour location and co-morbidity of the patients. Most patients will have resections; all should have a biopsy procedure unless there is a specific contraindication. Radical surgery has been shown to improve the response to chemoradiation with Temozolomide [4,5]. Radical maximal surgery is only possible in 20-40% of High Grade Glioma patients. Partial resection can be useful at controlling

mass effects and can help the patient to complete radiotherapy. Stereotactic biopsy likely to be 90-95% capable of returning a diagnosis can be further improved by using PET combined with MRI. 60% of the originating tumour will recur in 6/52, hence RT and RT with additional chemotherapy should be instigated within four weeks of surgery. Delay in commencing RT reduces survival [6,7].

6.8 Early postoperative MRI (within 48 hours) is recommended for patients suitable for radical chemoradiotherapy. This serves as a baseline, confirms the degree of resection and can help with radiotherapy planning.

6.9 Patients should be re-discussed at the specialist MDT with histology and general performance status details available.

6.10 Patients should be staged using the WHO system and classified as low grade or high grade (see appendix one).

6.11 All patients should have access to a full range of Allied Health Professionals as required, including Occupational Therapy, Physiotherapy, Endocrinology Teams and Neuro and Clinical Psychology.

6.12 All patients should receive a permanent record of their consultation where treatment options are discussed, and a full range of written information including that about their disease, tests, treatment, support groups and how to get help with finances.

6.13 All patients should have access to psychosocial and psychological support through the Clinical Nurse Specialist / designated key worker and via the dedicated Glioma Clinics, using Holistic Needs Assessment. Dedicated psychologist and psychiatric doctors with an interest in brain and other CNS tumours exist within University Hospital Birmingham NHS Foundation Trust and these will form part of the service development for the IOG.

7 Management of Primary Low Grade Glioma Disease

The optimal management of cerebral low grade glioma remains debated. The EORTC developed a prognostic score based on two large, randomized, multicentre trials (EORTC 22844 and 22845)[8]. In multivariate analysis, age ≥ 40 years, astrocytic tumour type, tumour size > 6cm, tumour crossing the midline, and neurologic deficit at diagnosis (before surgery) were significant adverse factors. A favourable prognostic score was defined as the presence of no more than two of these adverse factors and was associated with a median survival of 7.7 years (95% CI = 6.6, 9.3). The presence of 3-5 factors was associated with a median survival of 3.2 years (95% CI = 3.0, 4.0).

Maximal safe resection at presentation should be considered if deemed safe. Histological confirmation of diagnosis should be achieved prior to radiotherapy or chemotherapy. It may also provide important prognostic information.

Early radiotherapy can delay time to progression and control symptoms but does not impact overall survival (EORTC 22845)[9]. Due to potential radiotherapy toxicity (in particular neurocognitive decline which is associated with reduction in quality of life)[10],

asymptomatic patients predicted to have a favourable outcome should undergo active surveillance rather than immediate radiotherapy.

Radiotherapy should be considered in the following patients if not suitable for resection alone (adapted from EORTC criteria):

1. Age ≥ 40 years
2. Radiologically proven progressive lesion
3. Neurological symptoms others than seizures only (focal deficits, signs of raised intracranial pressure, mental deficits)
4. Intractable seizures
5. Large un-resectable infiltrating tumours (> 6cm) and those crossing midline.

See appendix two for radiotherapy guidelines.

Primary chemotherapy remains under investigation but may be an option for patients unsuitable for surgery or radiotherapy.

Active surveillance should initially include 3-6 monthly reviews with MRI and may be nurse or consultant led. More extended interval reviews (6-12 monthly) may be appropriate in stable clinical situations. Patients undergoing active surveillance should be offered treatment in response to their clinical condition and MRI results as the need arises *and after Specialist MDT discussion*. Decisions are made on a case by case basis.

8 Management of Primary High Grade Glioma Disease

8.1 Patients with Grade 3 Disease

- Where possible, these patients should be identified at the initial MDT discussion and the option of Gliadel Wafers be considered prior to surgery.

- Patients receiving radiotherapy should be commenced within 2 weeks of biopsy or 4 weeks of decompression surgery.

- Molecular markers (1p19q and MGMT promoter methylation) may be helpful in selected cases.

8.2 Patients with Grade 4 Disease

- Patients suitable for active treatment should be offered radiotherapy alone or combination therapy (radiotherapy and Temozolomide; RT/TMZ). See appendix three and four for details. NICE approval has been given for concomitant Temozolomide with radiotherapy, followed by adjuvant treatment for newly diagnosed Glioblastoma in patients who are WHO performance 0 or 1. This follows the Stupp trial[5]. The benefit from combined modality treatment appears greatest for patients with favourable prognostic characteristics[11].

- Treatment should be commenced within 2 weeks of biopsy or 4 weeks of decompression surgery.

- Depending on performance status and patients' wishes, these patients should be managed in a defined pathway of care e.g. palliative care or active management.

9 Relapse or Disease Progression

- At time of relapse or disease progression, patients should be re-discussed at the Specialist MDT with their most recent MRI.

- Treatment decisions are made on a case by case basis and will depend on their previous treatment, in particular their previous doses of radiotherapy.

- All patients should have access to Gliadel and Temozolomide as per the NICE Guidance.

10 Palliative Care

All patients who do not fall within the recommended guidelines for follow-on treatment, or who decline such treatment, should be offered palliative support. This may initially take the form of in-hospital assessment by the Palliative Care Team; alternatively, approaching or following discharge, referral can be made to hospice / community palliative care teams. Patients who continue to attend clinic, but who have progressive symptoms are offered guidance and advice regarding management e.g. steroid or anti-convulsant therapy. Referral to the appropriate specialism can be made e.g. neurology for seizures. A Palliative Care referral may also be appropriate for patients receiving active treatment.

Monitoring of the Guideline

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Appendix One:

WHO Grading of Primary Brain Tumours

Astrocytic tumours	I	II	III	IV
Subependymal giant cell astrocytoma	•			
Pilocytic astrocytoma	•			
Pilomyxoid astrocytoma		•		
Diffuse astrocytoma		•		
Pleomorphic xanthoastrocytoma		•		
Anaplastic astrocytoma			•	
Glioblastoma				•
Giant cell glioblastoma				•
Gliosarcoma				•
Oligodendroglial tumours				
Oligodendroglioma		•		
Anaplastic oligodendroglioma			•	
Oligoastrocytic tumours				
Oligoastrocytoma		•		
Anaplastic oligoastrocytoma			•	
Ependymal tumours				
Subependymoma	•			
Myxopapillary ependymoma	•			
Ependymoma		•		
Anaplastic ependymoma			•	
Choroid plexus tumours				
Choroid plexus papilloma	•			
Atypical choroid plexus papilloma		•		
Choroid plexus carcinoma			•	
Other neuroepithelial tumours				
Angiocentric glioma	•			
Chorcoid glioma of the third ventricle		•		

Neuronal and mixed neuronal-glial tumours				
Gangliocytoma	•			
Ganglioglioma	•			
Anaplastic ganglioglioma			•	
Desmoplastic infantile astrocytoma and ganglioglioma	•			
Dysembryoplastic neuroepithelial tumour	•			
Central neurocytoma		•		
Extraventricular neurocytoma		•		
Cerebellar liponeurocytoma		•		
Paraganglioma of the spinal cord	•			
Papillary glioneuronal tumour	•			
Rosette-forming glioneuronal tumour of the fourth ventricle	•			
Pineal tumours				
Pineocytoma	•			
Pineal parenchymal tumour of intermediate differentiation		•	•	
Pineoblastoma				•
Papillary tumour of the pineal region		•	•	
Embryonal tumours				
Medulloblastoma				•
CNS primitive neuroectodermal tumour (PNET)				•
Atypical teratoid / rhabdoid tumour				•
Tumours of the cranial and paraspinal nerves				
Schwannoma	•			
Neurofibroma	•			
Perineurioma	•	•	•	
Malignant peripheral nerve sheath tumour (MPNST)		•	•	•
Meningeal tumours				
Meningioma	•			
Atypical meningioma		•		
Anaplastic / malignant meningioma			•	
Haemangiopericytoma		•		
Anaplastic haemangiopericytoma			•	
Haemangioblastoma	•			

Tumours of the sellar region				
Craniopharyngioma	•			
Granular cell tumour of the neurohypophysis	•			
Pituicytoma	•			
Spindle cell oncocytoma of the adenohypophysis	•			

Appendix Two:

Radiotherapy for Low Grade Gliomas

Two randomized controlled trials showed no benefit to dose escalation for Low Grade Gliomas. The EORTC randomized patients to 45 Gy versus 59.4 Gy and found no difference in 5 year survival between the two arms[12]. The NCCTG / RTOG / ECOG compared 50.4 Gy versus 64.8 Gy and also found no difference in 2 or 5 year survival[13]. Since the dose prescription used in the first studies was based on previous ICRU guidelines (Report No. 29 of the International Commission on Radiological Units), and the dose prescription to different isodose levels may have resulted in slightly higher total doses than 45 Gy, a minimum dose of 50 Gy is used by most. In addition there is a risk of underestimation of the grade of tumour.

Immobilisation:	Supine / prone using beam directional shell / frame.
Localisation:	Contrast enhanced CT scan (unless contra-indication to contrast). MRI fusion: take into account full sequence MRI including T2 / Flair.
CTV:	Gross tumour volume (GTV) + 1.5 – 2cm geometric growth. Reduce margins according to anatomical barriers (e.g. tentorium) applying caution at midline structures.
PTV:	Margin to allow for day to day variation determined locally (e.g. 0.5cm).
Dose / Fractionation:	50 – 54 Gy using 1.8 – 2 Gy fractions (higher dose is recommended in presence of patchy enhancement / uncertainty of grade).
Technique:	Conformal plan to achieve minimum 95% isodose coverage.
Verification:	Imaging verification to confirm set up according to departmental policy.

Appendix Three:

Radiotherapy for High Grade Gliomas

The radiation high dose volume should encompass the gross tumour volume (GTV) defined using contrast enhanced imaging. The clinical tumour volume (CTV) will cover potential areas of microscopic spread around the GTV, except in regions of anatomic boundaries (such as bone, falx, tentorium) where the margin may be reduced.

Immobilisation:	Supine / prone using beam directional shell / frame.
Localisation:	Contrast enhanced CT scan (unless contra-indication to contrast). MRI fusion (T1 with Gadolinium).
CTV :	Tumour / tumour bed + 1.5 – 2cm.
PTV:	Margin to allow for day to day variation determined locally (e.g. 0.5cm).
Dose / Fractionation:	55 – 60 Gy using 1.8 – 2.0 Gy fractions (dependent upon volume and normal tissue constraints being met). 2 phase technique may be an alternative to achieve 60 Gy to GTV while maintaining constraints and reducing the volume of brain receiving a high dose (limit 60 Gy to 33%[14]).
Technique:	Conformal plan to achieve minimum 95% isodose coverage.
Verification:	Imaging verification to confirm set up according to departmental policy.

A short course of radiation is a reasonable option for patients who are elderly with poor performance status and for younger patients with poor performance status (KPS < 50) or large volume / multifocal disease not suitable for 60 Gy. Where practical, the above planning principles should be adopted. When using virtual simulation or opposed fields, diagnostic imaging should be taken into account with a minimum 2cm margin. Dose fractionation schedules for these patients are as follows:

- 30 Gy in 6 – 8 fractions[15]
- 36 Gy in 12 fractions[16]
- 40 Gy in 15 fractions (shown to be equivalent to 60 Gy in 30 fractions in elderly patients[17]).

Appendix Four:

Scheduling for Combination Radiotherapy with Temozolomide (RT/TMZ)

RT/TMZ: 6 weeks of radiation with daily concurrent Temozolomide at 75mg/m^2 prescribed for 42 days continuously (including weekends). This is followed by 6 cycles of monthly Temozolomide at 200mg/m^2 daily for the first 5 days of each cycle. Consider 150mg/m^2 for the first adjuvant cycle.

i. Commence RT/TMZ < 4/52 after surgery or ~2/52 post biopsy (NICE Improving Outcomes Guidance, Jun 2006).

ii. AT START: CXR, ECG, FBC, renal, hepatic, RB Sugar, AED levels (if appropriate) prior to starting Temozolomide.

iii. Optimum time for Temozolomide capsules is 1 hour prior to radiotherapy on an empty stomach. Anti-emetics to be taken at least 30 minutes prior to the Temozolomide.

iv. CONCOMITANT RT/CHEMOTHERAPY PHASE

Responsibilities of regular review may be shared between oncologist, specialist radiographer and Clinical Nurse Specialist (CNS).

CNS / Pharmacy / Oncologist: appropriate counselling is required prior to dispensing oral chemotherapy which should include information on neutropenic pathway (NCEPOD report on patients dying within 30 days of systemic anti-cancer). A dedicated oral chemotherapy clinic with allocated pharmacy support is recommended. Records should be kept of chemotherapy dose (based on body surface area) and any subsequent dose reductions or changes.

Weekly review of toxicity, medications (including dexamethasone dose) and bloods (FBC, urea and electrolytes, liver function tests) is required during radiotherapy.

Last week of radiotherapy: Medical Review: GP letter / summary of radiotherapy treatment / follow up arrangements / medication instructions / MRI scan request for 4-6 weeks post radiotherapy.

v. EMESIS CONTROL

Days 1-3: 5-HT3 antagonist.
Ensure patient has adequate anti-emetics to use if required thereafter (e.g. Domperidone).

vi. DEXAMETHASONE DOSE

The patient should be weaned down to the lowest dose of dexamethasone on which s/he remains stable. This will require regular review. Post operative volume of disease / extent of surgical resection should be considered prior to weaning.

vii. ADJUVANT PHASE

Start adjuvant Temozolomide 28 days following completion of radiotherapy for six months (6 cycles).

Visits 2-5 **Medical / CNS Review**: drug modification.
CNS / Pharmacy Review: chemotherapy prescription.

Visit 6 **Medical Review**: re-staging MRI scan.

viii. TOXICITY

All patients should be aware of the emergency admissions policy for patients on chemotherapy.

Haematological toxicity: Pancytopenia Common Toxicity Criteria (CTC) grade 4 is unusual – STOP TREATMENT. Provide emergency admission and bone marrow support as required. CTC grades 2 / 3 require delay in TMZ and dose reduction. Cumulative effect of Temozolomide may result in myelosuppression following the 6 weeks of radiotherapy and interim patient review should be considered if there are concerns.

Lymphopenia: Consider Co-Trimoxazole (Septrin) prophylaxis 480mg twice daily on Monday, Wednesday and Friday.

Risk of opportunistic infection: Lymphopenia Grade II <500 23% CD4<200, Grade III <200 35%. Increased risk with prolonged (>10 days) lymphopenia.

Non-haematological toxicity CTC grade 2 (except alopecia, nausea and vomiting): Delay TMZ and dose reduction.

Non-haematological toxicity CTC grade 3 and 4 (except alopecia, nausea and vomiting): Stop Temozolomide.

Skin Rash: Usually safe to treat through unless >Grade II CTC (Stupp EORTC no Stephens Johnson reported).

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