Protocol for Planning and Treatment

The process to be followed when a course of chemotherapy is required to treat:

PRIMARY GLIOMA

(oligodendroglioma, astrocytoma, oligodendroglioma, oligoastrocytoma, including anaplastic, gliosarcoma and glioblastoma multiforme)

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

Definitive diagnosis of a malignant brain tumour is based on the results of biopsy, or occasionally a provisional radiological diagnosis is accepted.

2. STAGING

Since these are localised tumours the staging investigations are based upon T1, T2 and T-gadolinium-enhanced MRI scan of the brain.

3. HISTOPATHOLOGY

Definitive diagnosis rests upon the histology. Expert neuropathology diagnosis is provided by Professor Ironside and Dr C Smith in Edinburgh. Tayside neurosurgeons will refer tissue to Edinburgh for diagnosis.

4. RADIOTHERAPY / SURGERY

Surgery
Where possible maximal surgical excision will be performed or appropriate safe debulking. In eloquent areas of the brain, a biopsy only may be appropriate.
Subsequent treatment will depend upon the histological type and grade of tumour.

Radiotherapy

Glioma Grade	Fractionation
Grade 1	No adjuvant treatment
Grade 2	Treatment deferred until radiological or symptomatic progression [1]. Early radiotherapy to be considered if multiple poor prognostic factors – age >40, lesion >6cm, crosses midline, pre op neurological deficit) 50.4Gy in 28# over 5.5 weeks [2] 54 Gy in 30# over 6 weeks if high Ki 67 or contrast enhancing tumour on imaging
Grade 3	60Gy in 30# over 6 weeks If known to have 1p 19q deletion consider first line chemotherapy to delay XRT toxicity [3]
Grade 4 <60 years old , fit	60Gy in 30# over 6 weeks CT planned with concurrent temozolamide (TMZ) 75mg/m^2 daily during XRT. Then adjuvant TMZ 150mg/m^2 day 1-5 cycle1, TMZ 200mg/m^2 day 1-5 cycle 2-6 q28d [4]
Grade 4, >60 years old and fit, or < 60 years old and less fit	60Gy in 30# over 6 weeks
Grade 4 >60 years old or unfit any age	Consider 30Gy in 6 # over 2 weeks treating Mon, Wed and Fri [5] or Best Supportive Care.
Brain stem Glioma	54Gy in 30# over 6 weeks
Multifocal GBM or gliomatosis cerbri	Where whole brain needs to be treated use 54Gy in 30# or 30Gy in 6# depending on patient fitness.
In house study	Photodynamic therapy

Relapsed disease

Patients with low grade tumours which have progressed to a higher grade should be considered for radiotherapy in the first instance. These patients will be treated in a similar manner to that described for high grade gliomas.

5. CHEMOTHERAPY

Glioma Grade	Standard treatment	Trial
Grade 1	Nil	Nil
Grade 2	In patients with known 1p19q deletion consider PCV chemotherapy as 1st line if patient young and fit, to delay XRT toxicity.	BR13: – tumours with 1p19q loss randomised to 50.4Gy in 28# XRT or TMZ 75mg/m^2 daily for12 months or until progression (PD)
Grade 3	At time of surgery, if > 90% of tumour is thought to have been debulked, Carmustine wafers (Gliadel tradename) can be inserted. (6) Carmustine in this setting is associated with 29% decrease risk of death with an improved median survival of 2.3 months. See footnote	BR14: - tumours with no deletion of 1p19q randomised to 4 arm study: 54Gy in 33# vs 54Gy + concurrent TMZ vs 54Gy + adjuvant TMZ vs 54Gy +concurrent and adjuvant TMZ (Stupp protocol)
Grade 4 Fit and <60yo	At time of surgery, if > 90% of tumour is thought to have been debulked, Carmustine wafers (Gliadel tradename) can be inserted. (6) Associated with 29% decrease risk of death with an improved median survival of 2.3 months. See footnote Concurrent TMZ 75 mg/m^2 daily throughout XRT and adjuvant 150 - 200 mg/m^2 d1-5 q28d x 6	CENTRIC: ChemoXRT +/- Cilengitide (integrin inhibitor) in methylated MGMT tumours

Grade 4 > 60 yo or unfit	No chemo XRT alone	Elderly NCIC EORTC 26062 22061: > 65 yo and fit 40Gy in 15# +/- TMZ
Relapsed Glioma Chemo naive	If further surgery performed, Gliadel may be used as above. If fit for chemo, no evidence that PCV is superior or inferior to TMZ d1-5, and either should be considered in fit patients.	BR12: – Unpublished: showed no difference in QOL, toxicity or overall survival between PCV and TMZ, but TMZ 5d was superior to TMX 21d
Relapsed Glioma Previous chemo XRT	If further surgery performed, Gliadel may be used as above Evidence remains unclear but if relapsing shortly after chemoXRT use PCV, but if reasonable disease progression free interval retreat with TMZ 150 - 200 mg/m^2 d1-5	No trial

Notes: Gliadel should not be used without confirmed pathological diagnosis of a high grade glioma, or if the tumour crosses the midline, basal ganglia, cerebellum, or brainstem. Nor should it be used if there is more than 1 contrast-enhancing lesion or it is multifocal, or is there has been opening of the CSF ventricles during surgery.

6. SUPPORTIVE THERAPY

All patients with brain tumours should be referred to the Macmillan Nurse. Patients may wish to have support from the Macmillan Nurse in the community and they should be told of the opportunity of visiting the Macmillan Centres at Roxburghe House, Macmillan House, Perth or Macmillan Centre at Stracathro.

Dexamethasone to reduce cerebral oedema is often needed by these patients, but the minimum dose required to control symptoms should be used. Gastric protection in the form of a proton pump inhibitor should be prescribed. All patients should carry a steroid card at all times.

7. TREATMENT DEFINITIONS

PCV
Lomustine 100 mg/m² po Day 1
Procarbazine 100 mg/m² po Days 1 -10
Vincristine 1.5 mg/m² iv Day 1 (Max 2mg)
Repeated every 6 weeks

Temozolamide
Concurrent: Temozolamide 75 mg/m² daily throughout XRT

Adjuvant: Temozolamide 150 mg/m² d1-5 cycle 1 commenced 4 weeks after completion of chemoXRT
Temozolamide 200 mg/m² d1-5 q28 cycle 2-6

8. REVIEW

Patients on chemo XRT
Weekly review through chemo XRT by radiotherapy support team, and monthly during adjuvant chemotherapy by Chemo unit staff.

To be seen in clinic 4 weeks after completion of combined chemoXRT with up to date MRI / CT to assess response to treatment, remembering phenomenon of pseudoprogression, and to consider the appropriateness of adjuvant phase. If well, patient collects TMZ same day to commence adjuvant treatment.

Patients treated with XRT alone to be reviewed 4 weeks post treatment in clinic to assess toxicities and 3-4 months time with MRI / CT to assess response to treatment.

9. REFERENCES

(1)Van den Bent, Lancet 2005 Sept 17-23; 366 (9490): 985-90
(2)Shaw LJ, Clin Oncol 2002 May 1:20 (9): 2267-76
(3)Stege, Cancer 2005 Feb 15: 103 (4): 802-9
(4)Stupp, NEJM 2005 Mar 10; 352 (10): 987-96
(5)Whittle, Br J Neurosurg 2002 Aug; 16 (4): 343-7
(6)Hart MG, Grant R, Garside R et al Chemotherapeutic wafers for High Grade Glioma. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD007294

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(on behalf of OHMMG)