Protocol for Planning and Treatment

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

GLIOBLASTOMA MULTIFORME

Patient information given at each stage following agreed information pathway

1. DIAGNOSIS

Glioblastoma Multiforme WHO Grade 4 is the most common glial tumour (50-60% of primary brain tumours).

Patients may present with a variety of neurological symptoms and signs, depending on the anatomical location.

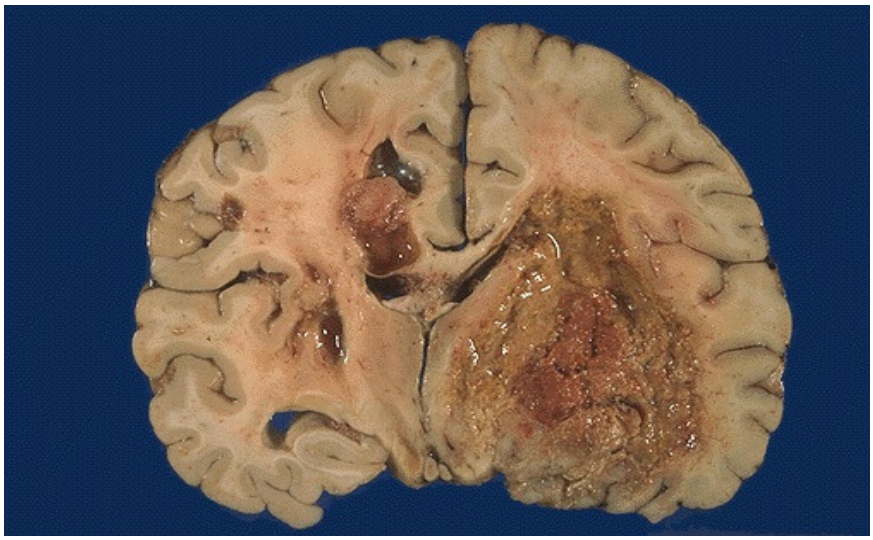
After imaging suggestive of tumour, Tayside neurosurgeons will perform biopsy / debulking surgery and refer tissue samples to Edinburgh for review, where an expert neuropathology diagnosis is provided by Prof J Ironside, Dr C Smith and Dr A Torgersen.

Definitive diagnosis of a GBM is therefore based on the results of biopsy, or occasionally a provisional radiological diagnosis is accepted. MGMT status should be assessed as this is associated with better prognosis and response to treatment [(1)].

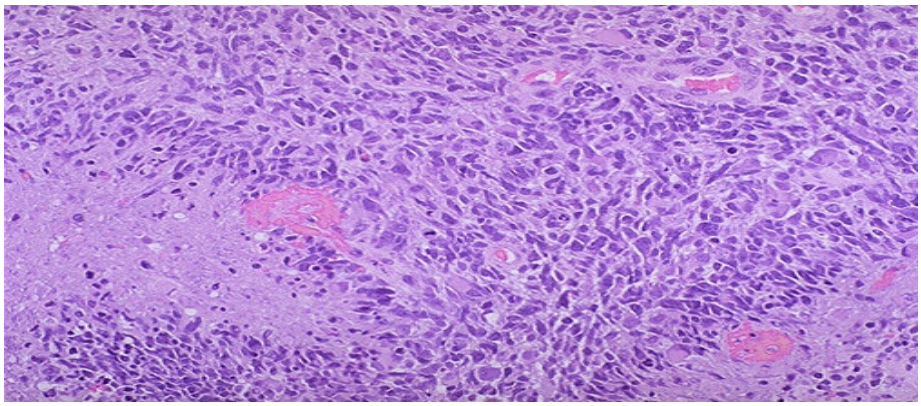
2. STAGING

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

3. HISTOPATHOLOGY



The tumour consists of neoplastic cells with highly pleomorphic nuclei and a high proliferation index (Ki 67). Diagnosis, as per World Health Organization (WHO) criteria, requires presence of tumour cell necrosis and /or microvascular proliferation (angiogenesis).



Definitive diagnosis rests upon the histology.

4. INVESTIGATIONS

CT Brain
MRI Brain
Routine bloods

5. SURGERY AND RADIOTHERAPY

CONSIDER ENTRY INTO AVAILABLE TRIALS AT ALL POINTS

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.

Radiotherapy:

Further treatment will depend on an individual patient's fitness. Known factors influencing outcomes are listed in the MRC Prognostic Index and the higher an individual's score, the poorer the likely outcome.

MRC prognostic index

Prognostic factor	Category	Score
Age	<45	0
	45–59	6
	> 60	12
Clinical performance status	0–1	0
	2	4
	8	
Extent of neurosurgery	Complete resection	0
	Partial resection	4
	Biopsy	8
History of seizures	≥3 months	0
	<3 months	5
	None	10

< 65 years old and PS 0-1: Combined chemo-radiation: 60Gy in 30# over 6 weeks CT planned with fusion of pre-op T1 post contrast axial MRI, 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 [2]

PS 0-1, >65 years old ; < 65 years old and PS 2: Radiation alone: 60Gy in 30# over 6 weeks

Any age PS 2-3: Consider 30Gy in 6 # over 2 weeks treating Mon, Wed and Fri [3], Temozolamide 200mg/m^2 d1-5 q28 days [3], 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.

6.CHEMOTHERAPY

N.B. *In patients who undergo a > 90% resection, Glaidel wafers (carmustine) [,5,6,7] are approved by NICE and SMC for insertion into the operative cavity, at first diagnosis and at relapse. Data on the use of temozolamide and radiotherapy after this is limited, but toxicities appear to be well tolerated [3] and outcomes improved [4]. SANON have drawn up guidelines on their use.*

1) If <60 years old and PS 0-1:

Temozolamide with radiotherapy [2]

Concurrent: Temozolamide 75 mg/m² daily throughout XRT (60Gy in 30# over 6 weeks)

Give concomitant co-trimoxazole 960mg po Mon, Wed, Fri throughout, and continue if lymphocyte count <0.5 until recovered.

At completion, one month off treatment and to be seen in clinic with MRI result. If responding or stable disease and well:

Adjuvant: Temozolamide 150 mg/m² d1-5 cycle 1 commenced 4 weeks after completion of chemoXRT, followed by

Temozolamide 200 mg/m² d1-5 q28 cycle 2-6

Give co-trimoxazole 960mg po Mon, Wed, Fri only if lymphocyte count <0.5, until recovered.

N.B. GBM has a very rapid doubling time. As radiotherapy planning takes up to 3 weeks to complete, it is reasonable to commence TMZ 1 cycle upfront during this planning time.

Temozolamide 150 mg/m² d1-5 cycle

Give co-trimoxazole 960mg po Mon, Wed, Fri only if lymphocyte count <0.5, until recovered.

2) Any age PS 2-3

Consider Temozolamide TMZ 200mg/m^2 day 1-5 cycle q28d x 6 [3] as an alternative to XRT.

Rationale: In Nordic study median survival TMZ 8.3 months vs 7.5 months with 34Gy in 10# vs. 6.0 months with 60Gy in 30#)

3) At relapse and if PS 0-2:

Consider surgical intervention +/- gliadel - discuss at MDT.

i) f progression free interval > 12 months, or did not receive TMZ with XRT

Consider retreating with TMZ 200mg/m^2 day 1-5 cycle q28d until progression of disease or toxicity requires discontinuation.

Give co-trimoxazole 960mg po Mon, Wed, Fri only if lymphocyte count <0.5, until recovered

ii) If disease free interval < 12 months and PS 0-2 consider PCV [8].

PCV :

Procarbazine 100 mg/m² po Days 1 -10
Lomustine 100 mg/m² po Day 1
Vincristine 1.5 mg/m² iv Day 1 (Max 2mg)

Repeated every 6 weeks until progression of disease or toxicity requires discontinuation.

4) At further relapse or unsuitable for PCV:

consider single agent CCNU(Lomustine)

CCNU 120mg/m^2 po d1 q42 days

3) At next relapse and if PS 0-2:

Consider surgical intervention– discuss at MDT.
Consider PCV or TMZ, according to previous chemotherapy history. Do NOT repeat exposure to PCV.

4) If PS 3 - 4 at any time point:

Best supportive care

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7. SUPPORTIVE THERAPY

All patients with brain tumours should be referred to the Macmillan Specialist 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 Stracathrom and Maggie's Centre in Dundee.

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 Rantidine 150mg bd should be prescribed. Patients should carry a steroid card at all times.

8. REVIEW

1. Patients on chemo XRT

Weekly review throughout chemo-XRT by radiotherapy support team, and monthly during adjuvant chemotherapy by Chemotherapy 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.

Further clinic review 4-6 weeks after completion of adjuvant phase of treatment, with repeat MRI / CT available.

2. 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.

3. Patients treated with palliative chemotherapy

If receiving TMZ, for CT / MRI 3 monthly or if symptomatic progression, and to be seen in clinic with results.

If receiving palliative PCV, for CT / MRI 3 monthly and to be seen in clinic with results.

9. REFERENCES:

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3. Roa W et al Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial JCO May 1, 2004 vol. 22 no. 9 1583-1588

4. Malmstrom et al ASCO 2010 Nordic trial abstract

5. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, et al.Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet. 1995 Apr 22;345(8956):1008-12. http://www.ncbi.nlm.nih.gov/pubmed/7723496

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7. McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, Laterra J, Kleinberg LR, Grossman SA, Brem H, Quiñones-Hinojosa A. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme.. J Neurosurg. 2009 Mar;110(3):583-8. http://www.ncbi.nlm.nih.gov/pubmed/19046047

8. A.C. Kappelle et al "PCV chemotherapy for recurrent glioblastoma multiforme" Neurology 2001;56;118-120 http://www.neurology.org/cgi/content/full/56/1/118