East Midlands Cancer Alliance

EAST MIDLANDS

Brain & CNS Expert Clinical Advisory Group

Guidelines for the Investigation and Treatment of Brain and CNS Cancer (Including Operational Framework)

Status: **Final**

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Endorsed by:

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Contents **Page**

Summary of Operational Arrangements

The arrangements for the diagnosis and treatment of people with brain and other CNS tumours are governed by the NICE Improving Outcomes Guidance published in June, 2006 and the "Brain tumours (primary) and brain metastases in adults" NICE guideline published in July 2018. The key principles from these documents have been adopted by the Neuro-oncology Services as the Operational Framework within the East Midlands Cancer Alliance (EMCA) as follows:

- Within the EMCA the care of all patients with brain and other central nervous system (CNS) tumours will be coordinated through multidisciplinary assessment and care. For the majority of EMCA this tertiary provision is through the Neuro-sciences Services at Nottingham University Hospitals NHS Trust. For the south of the EMCA (Northamptonshire) this tertiary service is provided by Oxford Radcliffe Hospitals NHS Trust.

- Each Acute Trust within the EMCA has designated a neuro-oncology clinical lead

- The EMCA has developed a model of Alliance Local MDTs to support the ongoing care of patients and their families as close to home as is safe and practical

- The Key Worker Policy has been developed and agreed

- EMCA supported upgrade VTC on an N3 platform, MoVi and the roll out of APC to facilitate image sharing and consultation both within and out of hours to ensure that every patient with imaging that suggests a diagnosis of CNS tumour is discussed by the neuroscience brain and other CNS tumours MDT without delay. This is to ensure that radiological diagnosis is confirmed and advice on further management can be given, regardless of the source of the initial referral or possible need for specialist treatment. Neuropathology reports to the standards defined by the Royal College of Pathologists

- Neuroradiologists report and review examinations to the standards defined by the Royal College of Radiologists.

- There is ready access to a neurosurgical biopsy or resection service, including image localisation and stereotactic techniques through the designated Neurosciences Services

- Preoperative discussions should take place at the neuroscience brain and other CNS tumours MDT to determine the optimum approach to surgery and the processing of tissue specimens, including intraoperative histological evaluation.

- An intraoperative histopathological diagnostic service is available to support surgical interventions with clear procedures in place to inform the clinical team of arrangements for out-of-hours requirement for an intraoperative opinion in non-elective cases. Either smear preparations or frozen sections may be used. In the current imaging era the evidence base for the benefit of the technique is limited and its use in diagnosis varies accordingly.

- Final diagnosis, treatment planning and patient counselling is based on the final report of the paraffin histology and subsequent immunocytochemical and mutational analyses .

- Specialist neuropathology should include autopsy facilities to support both consented and Coroner's examinations such that feedback can be obtained on any post-operative deaths or deaths while on treatment wherever they occur in the Alliance. In the case of

Coroner's autopsies systems should be in place to ensure that relatives are given the opportunity to request formal neuropathological examination in appropriate cases. There should be provision of a post mortem brain examination service to receive material for a clinical diagnostic opinion from local autopsies (authorised by H.M. Coroner or with consent from relatives) as well as referred cases from elsewhere in the Alliance. Material may include whole brain, whole spinal cord, peripheral nerve. Large or small block samples and slides may also be received for clinical opinion. Neuropathologists provide a network service based on one clinical neuroscience centre. They should have time to give clinical advice to colleagues in the Alliance as to the extent of examination and requirements for tissue retention in relation to the neuropathological component of examinations performed in other centres. Information from post mortem examinations should be integrated into regular mortality meeting reviews carried out by the MDT team.

- Healthcare professions have face-to-face communication with patients, their relatives and carers at critical points in the care pathway to discuss diagnosis, prognosis, treatment options (including no treatment), recurrence and end-of-life care. Clear, high-quality and relevant written information material is made available to support patients, their relatives, carers and professionals in this process.

- There is a bereavement service in the Trusts providing services to CNS tumours to assist families in the event of a death

- Clinical nurse specialists are core members of the neuroscience brain and other CNS tumours MDT and the Cancer Alliance brain and other CNS tumours MDTs and may need to work across several geographical sites. They are likely to take on the role of key worker for many patients, especially during the early stages of their clinical care, providing supportive care, information and continuity of care with other healthcare professions.

- There should be ready access to specialist neuropsychology and neuropsychiatry services for assessment and management of complex cognitive, emotional and behavioural problems. This is an area of development.

- There should also be access to specialist healthcare professions as appropriate for any other problems patients may experience, such as epilepsy, headaches and functional loss, for example, speech, language or visual problems.

- Palliative care specialists should be included as members of the neuroscience brain and other CNS tumours MDT and the cancer alliance MDTs.

- There should be rapid access to allied health professional assessment and rehabilitation services, including specialist neurorehabilitation when appropriate as a patient's condition changes.

- There should be immediate access to specialist equipment as necessary.

- Data collection system is in place for information on all patients with a radiologically or histopathologically confirmed CNS tumour.

- Entry into clinical trials is fully supported

1.0 Presentation Pathway

1.1 Referral Arrangements

Patient Pathway attached as **Appendix 1.**

The referral arrangements for patients with suspected brain and CNS cancer cover both newly presenting patients and patients presenting with symptoms suggestive of recurrence.

It includes referral from Primary Care and also from other hospital doctors (who are not members of a brain and CNS MDT or part of the diagnostic service)

Referral arrangements - General Points:

A patient should be referred who presents with symptoms suggestive of brain or CNS cancer to an appropriate specialist.

- Discuss any concerns about a patient's symptoms and/or signs with the local specialist
- If rapid access to scanning is available, consider as an alternative to referral
- Reassessment and re-examination if the patient does not progress according to expectations.

Urgent referral:

Refer urgently patients with:

- Symptoms related to the CNS, including:
  - Progressive neurological deficit
  - New-onset seizures
  - Headaches
  - Mental changes
  - Cranial nerve palsy
  - Unilateral sensorineural deafness

  in whom a brain tumour is suspected

- Headaches of recent onset accompanied by features suggestive of raised intracranial pressure, for example:
  - Vomiting
  - Drowsiness
  - Posture-related headache
  - Pulse-synchronous tinnitus

- Other focal or non-focal neurological symptoms, for example blackout, change in personality or memory

- A new, qualitatively different, unexplained headache that becomes progressively severe

- Suspected recent-onset seizures (refer to neurologist).

Consider urgent referral (to an appropriate specialist) in patients with rapid progression of:

- Subacute focal neurological deficit
- Unexplained cognitive impairment, behavioural disturbance or slowness, or a combination of these

- Personality changes confirmed by a witness and for which there is no reasonable explanation even in the absence of other symptoms and signs of a brain tumour

Non-urgent referral:

Consider non-urgent referral or discussion with specialist for:

- Unexplained headaches of recent onset:
  - Present for at least 1 month
  - Not accompanied by features suggestive of raised intracranial pressure

Suspected Cerebral Metastases

Refer urgently patients previously diagnosed with any cancer who develop any of the following symptoms:

- Recent-onset seizure
- Progressive neurological deficit
- Persistent headaches
- New mental or cognitive changes
- New neurological signs

Investigations:

- In a patient with new, unexplained headaches or neurological symptoms, undertake a neurological examination guided by the symptoms, but including examination for papilloedema. (Note that the absence of papilloedema does not exclude the possibility of a brain tumour).
- When a patient presents with seizure, take a detailed history from the patient and an eyewitness to the event. Carry out a physical examination, including cardiac, neurological and mental state, and developmental assessment, where appropriate.

1.2 Protocol for Emergency Surgical Interventions

The great majority of patients presenting with a primary or secondary brain tumour do not need surgery on an emergency basis. For almost all, advice at the time of referral will include giving (or withholding) steroids , further imaging of the brain or chest/ abdomen and pelvis and a plan for discussion at the next appropriate MDT meeting ahead of any proposed surgery. In the exceptional circumstance that such surgery cannot wait for an MDT discussion , the responsible surgeon will make every possible effort to have discussed the rationale for surgery and the imaging to date with an MDT colleague.

1.3 Referral Guidelines Between Teams

Tertiary Referrals:

Referrals to the tertiary centre at NUH from other trusts within the East Midlands Cancer Alliance were previously agreed in August 2005.

Tertiary referrals are received from a wide area with an estimated population of 4.2 million. This covers Nottinghamshire, Lincolnshire, Derby City and parts of Derbyshire County, the Burton area of South Staffordshire, Leicestershire and Rutland.

Tertiary referrals from Northamptonshire are to Oxford as per the agreed pathway.

Tertiary referrals from North Derbyshire (Chesterfield) have been to Sheffield in the past , but from 1/6/2019 this region is now also included within the East Midlands Cancer Alliance and new clinical links may form in the future.

General Criteria for Referral

- ALL adult patients with suspected Primary Brain and other CNS tumours should be referred to the Neuro-oncology MDT for discussion

- Patients under 16 years of age from across the entire EMCA should be referred to the EM Paediatric Service through the hub at Nottingham University Hospitals

2.0 The Diagnostic Pathway

Patient pathway attached as **Appendix 1.**

Prior to referral to the neurosurgeons at the Neuroscience Centre in Nottingham all patients whether it is a new diagnosis, a suspected recurrence or an unexpected imaging diagnosis of CNS tumour should have an initial diagnostic test which should be:

1. CT scan completed which indicates a positive diagnosis of brain cancer
OR/ (and preferably)
2. MRI scan completed which indicates a positive diagnosis of brain cancer

The main aims of imaging of brain tumours are:-

- Primarily diagnose or refine a suspected diagnosis
- Optimally localise the lesion
- Characterise the lesion
- Assess the lesion's secondary effects and complications
- Plan surgical and radiation treatment including provision of data for neuronavigation
- Recognise post-treatment progress and complications

Where possible the following protocols should be adhered to:

- All CT and MRI brain scans should be reported on by a neuro-radiologist
- Ideally, all scans performed outside the neurosciences centre should be reviewed by the neuroradiological team prior to treatment

All diagnostic imaging suggestive of primary CNS tumours should be referred to the NeuroOncology MDT within 2 working days.

2.1 Diagnosis and Imaging

Brain Primary Tumours

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Imaging objectives

- To detect tumour.
- To characterise tumour.
- To determine extent of tumour.

- To select optimal site for obtaining histological material (preferably where tumour grade is highest and avoiding eloquent areas and those with a large amount of necrosis or not cyst formation).

MRI is the investigation of choice in the evaluation of primary cerebral neoplasms. It is superior to CT for tumour detection due to better contrast resolution, which gives a high sensitivity to any alteration in the nature of brain tissue. However, CT can provide unique information not readily available on MRI (e.g. the presence of calcification) and is still used in the primary investigation of non-specific neurological presentations, which may occasionally be caused by the tumour. If a mass-like lesion is detected on CT, MRI should be undertaken for further characterisation and to assess the full extent of disease. Nevertheless, MRI is unable to predict tumour type and histological grade reliably. Signal intensity and contrast enhancement characteristics may assist the surgeon in choosing a site for biopsy and imaging may be used for guiding stereotactic biopsy procedures. Proton MR Spectroscopy (^{1}H-MRS), single photon emission computed tomography (SPECT) and positron emission tomography (PET) remain experimental procedures in the evaluation of brain tumours. High resolution CT is useful in addition to MRI in pre-operative assessment and follow up of skull base tumours.

Imaging should be able to discriminate between tumours and other intracranial mass lesions, e.g. infarcts, haemorrhage or inflammatory/demyelinating lesions. Some tumours have characteristic features on imaging which allow a definite diagnosis to be reached prior to biopsy. However, most tumours will need to be biopsied for histological classification.

Unlike tumours elsewhere in the body a biopsy is not usually obtained prior to definitive surgery. Intra-operative histological evaluation by a specialist neuropathologist is, however, commonly obtained. A decision will be made on imaging as to whether image-guided, open biopsy or resection is most appropriate for patient management. In some instances, it will be decided that biopsy is neither feasible nor clinically appropriate. Depending on the presumed diagnosis, these patients may have surveillance follow up imaging or referral for palliative radiotherapy.

Immediate pre- and intra-operative imaging

Both CT and MRI are used for directing image-guided biopsy. This will be performed in dedicated neurosurgical units. Additional sequences that aid in surgical planning may need to be performed. These will include DWI, MR angiography (MRA), MR venography (MRV) and CT angiography (CTA). MRS, SPECT and PET are techniques that may help in identifying the area of highest grade of malignancy and, thus influence choice of biopsy site. Ultrasound imaging is used extensively during intrinsic brain tumour resections to assist in achieving a maximal safe resection. Intraoperative MRI will be available in Nottingham from early 2021 and will be used in selected appropriate cases to assess the extent of resection and check for any missed residual tumour.

Post-operative imaging

It will be beneficial to obtain an early post-operative scan, usually with MRI , in the majority of patients to confirm the extent of resection and note the location of any residual tumour , thus enabling planning of appropriate further therapy at the neuro-oncology MDT. This scan should ideally be carried out within 48 hours of surgery to give best image quality.

Follow up

Patients may be treated by complete or partial resection, radiotherapy, chemotherapy or by adopting a wait and watch policy. The requirement for follow up imaging of different CNS

tumours is variable and the Neuroscience and Cancer Network MDT will usually determine follow up protocols.

In obtaining any follow up imaging, care should be taken to obtain sequences in an identical manner to previous investigations including the same scanning plane (including angle), slice thickness and sequence type.

Brain Metastases

Clinical Background

All malignant tumours can metastasise to brain with lung, breast and melanoma doing so most frequently. Brain metastases from gastrointestinal (GI) and genitourinary tract (GU) tumours occur less commonly. The majority of metastases (80%) are supratentorial. However, GI and GU tumour metastases are more common in the posterior fossa, 50% being infratentorial. Within the cerebral hemispheres the grey/white matter junction is the most common site of metastases. Diagnosis is usually made on the basis of multiple lesions but solitary brain metastases occur and may be resectable. Multiple lesions are treated with chemotherapy which will include the use of corticosteroids or radiotherapy which may be to whole brain or to individual lesions (stereotactic external beam radiotherapy or gamma knife irradiation). Metastases are usually of high signal intensity on T2W imaging and of intermediate signal intensity on T1W imaging, although this signal pattern is sometimes reversed in haemorrhagic metastases, and mucinous adenocarcinoma. There is usually surrounding oedema and the degree may be variable but it is often disproportionate to the size of the lesion. Metastases situated in the grey matter tend to be associated with less oedema than those found in the white matter. Enhancement with contrast medium is typical and may be seen throughout the lesion or only at its rim.

Meningeal metastatic disease is diagnosed by the presence of multiple enhancing nodules in the leptomeninges. Dural enhancement may be normal within the cranial cavity particularly after a CSF tap. Meningeal metastatic disease may be present in the absence of meningeal enhancement and confirmed by cytology even when MRI is entirely normal. Conversely, no malignant cells may be found on cytology despite abnormal meningeal enhancement.

Who should be imaged?

All patients with a previous history of malignancy and symptoms or signs suggesting metastatic disease to the brain should be imaged initially with MRI or CT

Imaging objectives

- To detect the presence of brain metastases.
- To identify the number of metastases.
- To determine tumour extent

2.2 Diagnosis and Pathology

Primary tumours of the nervous system are classified and graded according to the latest 2016 WHO grading scheme**.**

Definitive diagnosis of a brain tumour requires histological examination of representative tissue from the lesion by a qualified and experienced neuropathologist. Diagnosis based on clinical and or radiological findings alone should be viewed as presumptive and should not

form the basis for definitive treatment or further clinical management unless there are compelling clinical considerations that preclude biopsy.

Whilst neuropathology has historically been primarily dependent on histopathological characterisation of tumour phenotype , growing understanding of the genetic basis of tumorigenesis has led to the incorporation of molecular data into the current 2016 classification system and full diagnosis now often takes the form of a combination of phenotypic and genotypic information. Methylation array profiling and other techniques may provide supplementary information for tumours which otherwise difficult to classify with confidence.

Where initial diagnostic evaluation by the specialist neuropathology service indicates that a tumour is not a primary CNS tumour then the case and material will be referred to a specialist pathologist in the relevant cancer MDT in the alliance. Primary bone tumours other than those affecting the skull base are referred to the specialist orthopaedic pathology service in Birmingham.

Where local laboratory facilities do not offer a particular diagnostic test then material will be referred to another laboratory that has CPA accreditation.

In cases of diagnostic difficulty cases will be referred for an external opinion to another UK specialist neuropathology service. The main services used are:-

- Neuropathology Section, Institute of Neurology, Queen Square, London
- Orthopaedic pathology service, Birmingham

Cases presented at the MDT will be reviewed before the meeting by specialist neuropathology review. The purpose of this review is to check on accuracy of diagnosis and ensure that the report meets the standards specified for a minimum dataset. Where possible a pathologist other than the original reporting pathologist will undertake a review.

Intra-operative opinions will be provided where requested by the surgical team for elective cases.

3.0 The Treatment Pathway

Patient pathway attached as **Appendix 1.**

The Treatment Pathway covers the process of active treatment delivery up to, but not including, referral for follow up. It covers this process whether it is with radical or palliative intent and whether it is for treatment of a first presentation or of a recurrence. It also covers the situation where the treatment plan is to offer palliative and supportive care only, rather than active tumour removal or cytoreductive therapy.

3.1 Surgical Management of Patients

Management for a particular patient will depend on multidisciplinary discussion at the MDT taking into account all relevant clinical factors but working in accord with the broad guidelines below.

Surgical Guidelines

Tumour Type	Aims of Surgery	Operation Performed
Adult High Grade Glioma	Tissue diagnosis Cytoreductions (esp if ↑ICP) Maximal resection where feasible	Biopsy – stereo/IG or debulking as appropriate 5ALA should be used to ensure maximal resection where MDT feels this is feasible. Gliadel wafers may be used if 90% or greater resection and with prior MDT agreement
***Rationale**:- tissue diagnosis required prior to radiotherapy . Radiotherapy better tolerated if ICP addressed. Improved outcome now established for greater than 90% resections on post op MRI* **Reoperation** – Limited role – drainage of cysts, occasional further debulking after MDT discussion especially for patients surviving well and with good performance status a year or more after initial surgery		
Adult Low Grade Glioma	Tissue diagnosis Resection or maximal debulking where feasible	Biopsy – stereo/IG Resection/Lobectomy Consider value of Awake surgery
***Rationale**:- Increased use of adjuvant therapies now in patients with Grade II tumours following up front surgery , depending on molecular stratification .* *Detection of de-differentiation or unfavourable molecular status – eg IDH1 wild type at first opportunity possible.* *Improved prognosis with resection of polar lesions* **Reoperation** – Indicated where recurrence or concerning appearances on surveillance scans/deterioration in appearances or suggestions of dedifferentiation. MDT may agree that there is good evidence of progression to higher grade without biopsy being mandatory		
Meningioma	Tissue diagnosis Maximal resection ± margins	Maximal feasible resection (with involved dura and bone). Increasingly acceptable to leave limited residuum e.g. along cavernous sinus recognising a role for stereotactic radiosurgery
***Rationale**:- recurrence correlates with extent of resection*		

Recurrent Meningioma		Resection if symptomatic or growth of tumour on serial imaging. Stereotactic radiosurgery in appropriate cases Reresection for atypical cases
***Rationale**:- surgery the most effective treatment in disease control*		
Intracranial Metastasis	Tissue Diagnosis. Symptom control	Resection Stereotactic radiosurgery for smaller mets / those in eloquent areas. Should be preceded by full staging and discussion in metastasis MDT and appropriate site specific MDT
***Rationale**:- control symptoms and prolong survival where disease elsewhere under control. Large metastases or those causing significant oedema may be better managed surgically*		
Multiple Intracranial Metastasis	Tissue diagnosis symptom control	Resection of at most 2 mets or largest metastasis Stereotactic radiosurgery if mets and site specific MDTs agree on suitability for radical treatment
***Rationale**:- intracranial disease will cause more symptoms and kill patients before disease elsewhere)*		
Paediatric Cerebellar Pilocytic Astrocytoma	Tissue diagnosis. Possible cure.	Resection
***Rationale**:- resection associated with high chance of cure with surgery alone*		
Residual/Recurrent Pilocytic Astrocytoma		Consider further resection taking into account reason for incomplete resection in first instance. Either re-resect or await development of symptoms
***Rationale**:- surgery by far the most effective treatment for this localised disease*		
Paediatric post fossa Ependymoma	Tissue diagnosis Cytoreduction Symptom control	Maximal resection feasible taking into account neuraxis staging
***Rationale**:- pre-eminent role of surgery in disease control recognised*		
Residual/Recurrent Ependymoma		Consider 2nd look surgery for localised disease.
***Rationale**:- pre-eminent role of surgery in disease control recognised*		

Paediatric post fossa Medulloblastoma	Tissue diagnosis Cytoreduction Symptom control	Maximal safe resection feasible taking into account neuraxis staging
***Rationale**:- Outcome improved with more extensive resection or minimal residual disease recognising that in some cases with tumour invasion leaving a small residuum may be preferable in terms of minimising risks of cerebellar mutism syndrome*		

Pineal and Tectal Plate Lesions	Tissue diagnosis Symptoms control	Hydrocephalus treatment CSF markers first Biopsy – endoscopic or stereotactic – of small lesions Resection of larger lesions
***Rationale*:-** *diverse range of lesions requiring diverse treatments so should establish a tissue diagnosis where possible; tumour markers **may** obviate need*		

Paediatric Brain Stem Glioma	Tissue Diagnosis?	No surgery in classic cases "radiological diagnosis" Biopsy in atypical cases or as part of clinical trial
***Rationale**:- biopsy carries risk of complications and of sampling error in heterogeneous tumours. Dreadful prognosis*		

Pituitary Macroadenoma (non-functioning)	Preserve/improve vision Maximal clearance of tumour	Transphenoidal surgery, endoscope or microscope
***Rationale**:- adequate surgery decompresses anterior visual pathways and minimises risk of longer term recurrence* **Re-operation**:- for recurrence may be considered if feasible and if considered appropriate after pituitary MDT discussion. All patients managed in conjunction with endocrinologists		

Pituitary Microadenoma (functioning)	Biochemical cure	Transphenoidal surgery, endoscope or microscope
***Rationale**:- to correct excess morbidity mortality with pituitary hypersecretion syndromes e.g. Cushings, acromegaly* **Re-operation**:- for recurrence may be considered if feasible and if considered appropriate after pituitary MDT discussion. All patients managed in conjunction with endocrinologists		

Vestibular schwannoma	Complete tumour removal for growing tumours either when too large for radiosurgery or when patient prefers surgery	Retrosigmoid or translabarynthine surgery
***Rationale**- microsurgical resection offers complete tumour removal with resultant long term cure. Aside from conservative management it is the only option for large tumours and is preferred by some patients with smaller tumours.* Management would be under a neuro-otology neurosurgical team, taking in mind non-surgical options and with skull base MDT discussion.		

Skull base tumours in general	Heterogeneous indications for surgery Tissue diagnosis Symptoms control where	Biopsy (often endoscopic) Skull base approach and debulking/maximal resection

	cure not feasible Attempt at cure with maximal resection and adjuvant treatment
Tissue diagnosis is always desirable due to range of possible diagnoses, more extensive surgery either as symptoms control strategy or as curative strategy considered within head and neck MDT or skull base MDT	

SPINAL TUMOURS

Tumour Type	Aims of Surgery	Operation Performed
Extradural	Symptom Control Tissue Diagnosis	Neurological decompression Bony stabilisation – Bony support - PLASTYS
Overlap with MSCC Orthopaedic Spinal Surgery		
Intradural	Symptom Control Tissue Diagnosis Cure	Minimal bony resection Complete Resection where possible Curative Surgery
Complete resection expected to be curative except syndromic or residual disease		
Intramedullary	Symptom Control Tissue Diagnosis Cytoreduction Possible Cure	Decompressive bony resection ± dural expansion ± fusion Debulking to complete resection where possible Biopsy if no plane/unsafe
Tissue diagnosis often difficult by radiology/intraoperative histology: extent of resection determined by presence of distinct tumour/intraoperative findings		
NF2	Symptom Control Tissue Diagnosis Cyto Reduction	Maximal resection depending on site of tumours etc.
Genomic Syndrome Overlap with acoustic/skull base/other CNS tumours Centralised multidisciplinary decisions (± treatment in hubs)		
Sarcomas	Symptoms Control Tissue Diagnosis Cyto Reduction	Maximal resection depending on site of tumour etc.
Overlap with Sarcoma MDT		

3.2 Oncological Treatment of Brain and CNS Cancer

Introduction

- This guidance has been written to provide guidance on the treatment of brain and CNS cancer in the East Midlands Cancer Alliance (EMCA).
- See Alliance chemotherapy prescribing proformas for details of chemotherapy/anti-cancer regimens.
- All patients will be considered for entry into a clinical trial where appropriate
- All patients should be discussed within a multidisciplinary team meeting (MDTM) before commencing initial treatment.
- All chemotherapy regimens listed within this document are delivered at:
    - Nottingham University Hospitals NHS Trust
        - City Hospital Campus
    - United Lincolnshire Hospitals NHS Trust
        - Lincoln County Hospital
    - United Hospitals of Leicester NHS Trust
        - Leicester Royal Infirmary
        - Northampton General Hospital
    - University Hospitals of Derby & Burton NHS Trust
        - Royal Derby Hospital
        - Queens Hospital, Burton

Patients are referred from the neuro-sciences MDTM. Typically, they will have had a biopsy or debulking surgery. Subsequent treatment intent will depend on performance status, but early input of palliative care services is recommended in all cases.

Radiotherapy is the primary non-surgical modality of treatment. However, the addition of chemotherapy has been shown to improve outcome in selected patients with GBM.

Glioma

Glioblastoma multiforme (GBM) – Grade 4

Treatment decisions should be based on known prognostic factors such as age and performance status. Patients with a poor prognosis maybe better managed with active supportive care.

Molecular pathology including MGMT status, IDH1 and IDH2 status and 1p19q loss may guide management

Management decision algorithm for Glioblastoma:

Up to the age of 70:

- PS 0-1: chemoradiotherapy using the Stupp regimen regardless of MGMT mutation status.
- PS 1-2: will be considered for radiotherapy alone.
- PS 3-4: will be considered for active best supportive and palliative care.

Patients >70:

- PS 0: Will be considered on an individual basis for chemoradiotherapy given the increase in toxicity with this regimen. 40Gy in 15# with concurrent temozolomide has been shown to have equivalent efficacy so can be considered as an alternative to the Stupp schedule.
  (In MGMT methylated pts consider chemotherapy (Temozolomide) as a single agent)
- PS 1-2: will be considered for radiotherapy alone.
- PS 3-4: will be considered for active best supportive and palliative care.

Multicentric:

- Should receive palliative radiotherapy. Those who maintain their general condition 4 weeks after treatment completion will considered for palliative chemotherapy.
- In pts where the volume is too large for palliative RT then first line palliative chemotherapy should be considered if PS 0-2.

Radiotherapy:
Palliative patients may be Virtually Simulated with wide lateral opposed fields or CT planned. Radical patients should be planned using CT data fused with pre-operative and postoperative MRI images where possible if there has been significant resection. In order to avoid delays on their treatment, in the absence of postoperative imaging patients should be planned with pre-operative MRI only.

Dose:

- Palliative Radiotherapy: 30 Gy in 6 fractions over 2 weeks.
- Radical Radiotherapy:
  - 60Gy in 30 daily fractions over 6 weeks.
  - If >70 consider 40 Gy in 15 fractions over 3 weeks (+/- temozolomide).
  -

Volumes:

- CTV = GTV + 2 cm margin.
- PTV = CTV + 0.3-0.5cm margin (depending on local centre set up audit data).

Chemotherapy

Radical radiotherapy with concurrent temozolomide chemotherapy (daily 75mg/m2) for 6 weeks.

The schedule can be used with the 40Gy in 15# radiotherapy regimen. The doses are the same, but the concurrent phase is for 3 weeks – chemo and RT should both stop together.

If pts remain well and blood counts are satisfactory then 4 weeks post concurrent phase should be considered for up to 6 cycles of adjuvant / maintenance temozolomide chemotherapy.
(Cycle 1: 150mg/m2 for 5 days, repeated every 28 days. Consider dose escalation to 200mg/m2/day for subsequent cycles if counts and toxicity allow).

Consideration of continuing the chemotherapy up to a total of 12 cycles could be considered for those patients who are otherwise tolerating therapy and have evidence of continued disease response.

Temozolomide causes lymphopenia and hence patients should be given prophylaxis against PCP during the concurrent phase (cotrimoxazole). If patients remain on dexamethasone alongside the adjuvant chemotherapy, then consider continuing the prophylaxis.

Treatment at relapse

If patients have progressed during primary treatment further active treatment has a very low chance of benefit which must be discussed with the patient.

At disease progression following completion of initial active treatment, patients of good PS will be considered for further active treatment, usually chemotherapy but sometimes surgery has a role to play and patients will be reviewed by the neurosciences MDM. Re-irradiation has no established role upon relapse and is not done routinely. There is no standard dose and schedule for reirradiation and if it is considered on an individual patient basis then risks and benefits must be carefully considered and relayed to the patient. Consider clinical trials locally and nationally.

Patients undergoing surgery should go ahead with chemotherapy as soon as recovered from the operation.

1st line chemotherapy:

- First line palliative chemotherapy will usually be with PCV – Procarbazine Lomustine (CCNU) and Vincristine (6 weekly – up to 6 cycles)
- Consider rechallenge with temozolomide if progression more than 6 -12 months of finishing primary treatment.

2nd line chemotherapy:

- Change to Temozolomide/PCV – whichever was not given as first line treatment.

3rd line chemotherapy:

- Carboplatin single agent may be used (AUC 4 to 6 every 4 weeks) depending on renal function and bone marrow reserve.
- Carboplatin (AUC 4 IV on D1) and Etoposide (100mg/m2 IV on D1) every 3-4 weeks.

Glioma Grade 3

Management of this group of patients will be defined by 1p19q deletion status:

- 1p19q co-deleted: Anaplastic oligodendroglioma. Surgical resection if feasible followed by adjuvant radiotherapy then to consider up to 6 cycles adjuvant PCV chemotherapy.

  PCV is currently the recommended adjuvant chemotherapy for these tumours based on the trial evidence and NICE guidance however the substitution of temozolomide could be considered for individual patients due to its proven activity in glial tumours in the adjuvant setting for Gd 3 (non-codeleted) and GBM. In addition, there are trials showing non-inferiority between the two chemotherapy schedules in glioma patients

- 1p19q non co-deleted: Anaplastic astrocytoma. Surgical resection if feasible then adjuvant radiotherapy then to consider up to 12 months of adjuvant temozolomide as per BR14 trial / NICE guidance.

Radiotherapy

Dose: 60Gy in 30# (consider 59.4Gy in 33#) over 6-7 weeks.
Volumes:

- CTV = GTV + 1.5-2 cm margin.
- PTV = CTV + 0.5cm margin.

Chemotherapy:

- PCV (cycles q6/52), a maximum six cycles are usually delivered however, often patients are unable to receive this many cycles due to bone marrow toxicity:
  - Procarbazine 100mg/m2 (max 200mg) PO od days 1-10
  - CCNU (lomustine) 100mg/m2 PO day 1 (max 200mg)
  - Vincristine 1.4mg/m2 IV (maximum 2mg) day 1
- Temozolomide: 150mg/m2 D1-5 q4w first cycle and then 200mg/m2 for subsequent cycles if tolerated for up to 6 cycles.

Treatment at relapse

At disease progression following completion of initial active treatment, patients of good PS will be considered for further active treatment, usually chemotherapy but sometimes surgery has a role to play and patients will be reviewed by the neurosciences MDM.
Patients undergoing surgery should go ahead with chemotherapy as soon as recovered from the operation.

1st line chemotherapy:

- First line palliative chemotherapy will usually be with temozolomide but patients may be considered for PCV re-challenge if they progress after 12 months of finishing primary treatment.

2nd line chemotherapy:

- Temozolomide/PCV depending on first line treatment.

3rd line chemotherapy:

- Carboplatin single agent may be used (AUC 4 to 6 every 4 weeks) depending on renal function and bone marrow reserve.
- Carboplatin (AUC 4 IV on D1) and Etoposide (100mg/m2 IV on D1) every 3-4 weeks.

Low Grade Glioma – Grade 2

Newly diagnosed:

Early surgery will be encouraged at neurosciences MDM, especially for patients presenting with a large mass or extensive neurologic symptoms.

Surgery alone is not curative and additional oncological therapy is ultimately required in all patients. The optimal timing of additional therapy is uncertain, however, and the decision to proceed with immediate versus delayed postoperative therapy must be individualized.

Radiotherapy and adjuvant PCV chemotherapy should be offered to patients with:

- Gd 2 Oligodendroglioma (1p 19q deleted, IDH-1 mutated) if 40 years upwards OR have residual tumour
- Gd 2 Astrocytoma (non co-deleted, IDH-1 mutated) if 40 years or older OR residual tumour

PCV is currently the recommended adjuvant chemotherapy for these tumours based on the trial evidence and NICE guidance however the substitution of temozolomide could be considered for individual patients due to its proven activity in glial tumours in the adjuvant setting for Gd 3 (non-codeleted) and GBM. In addition, there are trials showing non inferiority between the two chemotherapy schedules in glioma patients.

If patients are < 40 yrs with either oligo or astrocytoma (IDH-1 mutated) with no residuum then close active monitoring is recommended.

Patients with low grade glioma but IDH-1 wild type and other molecular features of high-grade tumour should be considered for treatment as GBM.

Previously diagnosed LGG:

In patients who have had previous surgery / pathological confirmation of grade 2 glioma should be considered for radiotherapy +/- chemotherapy if evidence of radiological progression or intractable seizures.

Patients with previously diagnosed surgically confirmed glial histology on follow up with MRI that start showing enhancing features in MRI, should be treated as grade 4 glioma or glioblastoma without the need of another biopsy.

Radiotherapy for LGG:

Dose: 50 to 54 Gy in 28-30 daily fractions over 6 weeks
Volumes:

- CTV = GTV + 1.5 cm margin.
- PTV = CTV + 0.5cm margin.

Meningioma

Surgery is the primary treatment modality for meningioma. Elderly patients considered unfit for surgery are very unlikely to be suitable for radiotherapy as hypo-fractionated courses are not of benefit in meningioma.

Grade 1:

- Newly diagnosed: Will not receive adjuvant therapy regardless of extent of resection.
- Recurrent: Radiotherapy will be considered as an alternative to surgery if another resection is considered not to be feasible.

Radiotherapy
Dose: 50 to 54 Gy in 28-30daily fractions over 6 weeks.
Volumes:

- CTV = GTV + 1 cm margin.
- PTV = CTV + 0.5cm margin.

Grade 2:
Patients should be encouraged to participate in ROAM trial. (randomised controlled trial comparing observation with adjuvant RT in atypical meningioma following complete resection.

If there is evidence of brain invasion, adjuvant radiotherapy after resection should be considered.

If patient declines the trial:

- In the absence of brain invasion: Consider adjuvant treatment if tumour located in the skull base due to difficulty of proceeding with further surgery if it recurs.
- If due to location second surgery could be feasible then there is currently no evidence for recommending adjuvant radiotherapy after complete resection.

Radiotherapy
Dose: 54 Gy in 30 daily fractions over 6 weeks.
Volumes:

- CTV = GTV + 1 cm margin.
- PTV = CTV + 0.5cm margin.

Grade 3:
All patients should receive adjuvant radiotherapy regardless of extent of resection.

Radiotherapy
Dose: 60 Gy in 30 daily fractions over 6 weeks.
Volumes:

- CTV = GTV + 2 cm margin.
- PTV = CTV + 0.5cm margin.

Stereotactic Radiotherapy/ SRS

Patients are referred for stereotactic radiosurgery or stereotactic radiotherapy if lesions in eloquent areas or for localised recurrence – **following discussion at the MDT**

Systemic therapy

Chemotherapy and endocrine therapies have no proven benefit but may be considered in individual cases. The use of endocrine therapy will be guided by progesterone receptor (PR) status.

Pituitary

Patients will be referred to the dedicated pituitary/craniopharyngioma MDT

This MDT is held on a Wednesday – every four weeks.

Post primary treatment

Radiotherapy for:-

- Recurrence post resection
- Bulky residuum
- Persistent endocrine dysfunction

Craniopharyngioma

Post Primary Treatment

Radiotherapy for:-

- Postoperative residuum
- Recurrence

Primary brain lymphoma

Dr C Fox, Consultant Haematologist, based at Nottingham City Hospital administers chemotherapy to this group of patients and Dr K Foweraker, Consultant Clinical Oncologist, will be administering radiotherapy.

3.3 Palliative Care

Despite recent advances in diagnosis and treatment, primary brain tumours remain incurable for the majority of patients. These patients have significant symptoms and concerns, posing considerable burdens on relatives, carers and health professionals. Palliative care is co-ordinated medical, nursing and allied services for people with life-limiting disease, delivered where possible in the environment of the person's choice and which provides physical, psychological, emotional and spiritual support for patients and for patients' families and friends. The provision of hospice and palliative care services includes grief and bereavement support for the family and other carers during the life of the patient and continuing after death. A palliative approach involving attention to symptom control and the psychological, social and spiritual wellbeing of the patient and their family is relevant at all stages of the disease and especially in the terminal phase. Although focussing on quality of life, palliative care is also concerned with the quality of dying.

Palliative care utilises advance planning rather than crises interventions. It offers a multidisciplinary model of care that is focused on the whole person within their social and emotional context, rather than just the disease.

Standards for the provision of quality palliative care:-

- Care, decision-making and care planning are based on a respect for the uniqueness of the patient, their carer and family.

- The holistic needs of the patient, their carers and families are acknowledged in the assessment and care planning processes and strategies are developed to address their needs.

- Ongoing and comprehensive assessment and care planning are undertaken to meet the needs of the patient, their carers and family.

- Care is co-ordinated.
- The patient, their carers and family have access to bereavement care, information and support services.
- Community capacity to respond to the needs of people who have a life-limiting illness is built through effective collaboration and partnerships.
- Access to palliative care is available for all people based on clinical need and is independent of diagnosis, age, cultural background or geography

3.4 Rehabilitation

Patients whose medical condition is stable should be referred to a rehabilitation service if they have ongoing problems affecting everyday life. Rehabilitation may include any of the following or a combination of:-

- Physiotherapy – focussing on a patient's movement, strength, coordination, balance and ability to walk.
- Occupational therapy – focussing on everyday tasks with a view to the patient becoming as independent as possible
- Social Workers – to improve the patients social situation and arrange access to services
- Speech and Language therapy – swallowing, communication etc.
- Clinical Psychologists

4.0 The Follow Up Pathway

Patient pathway attached as **Appendix 1.**

The follow up required varies between tumour types and will involve a combined approach to symptom management and disease surveillance.

Imaging is an integral part of follow up for patients with brain tumours and, ideally, it should be reserved for patients in whom the result of the scan is going to alter management. The frequency of scans is determined by the MDT and some useful guidance on frequency and duration of follow up scans in low grade tumours is available in the NICE NG99 2018 guideline.

Members of the neuroscience MDT held at Queens Medical Centre are responsible for deciding on the most appropriate surgical aspects for the management plan and adjuvant therapy for each individual patient based on neuropathological diagnosis. All other care including:-

- Chemotherapy
- Radiotherapy
- Co-ordination of supportive care

Follow up should be the responsibility of the cancer alliance MDT. Locally agreed guidelines for follow up are agreed locally.

The optimal frequency of follow up visits is determined by the patient's clinical condition. However, a routine follow up schedule of one to three monthly check-ups for patients with high grade disease and initial three to six monthly visits for patients with low grade disease is appropriate. The exact schedule will vary according to the patients condition.

Key points:-

- The aim of follow up for patients is to evaluate tumour control, monitor and manage symptoms from tumour and treatment and provide psychological support
- The optimal frequency of follow up visits varies and should be determined by the patient's clinical condition
- Follow up should be undertaken in a setting where the patient has access to members of the MDT
- The patient's GP is involved in caring for a patient with a brain tumour
- Co-ordinated care is the standard approach for caring for patients with brain tumours due to the complex needs involving several different specialists
- The patient should know which team member to contact at any time between visits.
- Telephone follow up may be preferable for some patients who are stable and live some distance from their managing unit, particularly regarding annual scan results .

5. Treatment of Brain Metastases

The spread of a primary cancer to the brain (cerebral metastases) is not uncommon. Although the incidence of the disease is not known, it has been estimated to occur in around 20 to 40% of all primary cancer cases. If a patient develops cerebral metastatic disease it significantly worsens their overall survival prognosis.

Patients with a known primary tumour elsewhere now presenting with single or multiple brain metastases and those patients presenting with multiple metastases de novo should be referred to and discussed at the BrainMetsMDT in the first instance rather than the general NeuroOncology MDT. A separate proforma exists for this and it is important for the MDT to have full information on staging and treatment plan for the primary tumour as well as performance status and estimated life expectancy for the patient. This enables the team to determine the appropriateness of radical therapy for the patient. Decisions on surgery versus SRS for a particular metastatic tumour will be made on an individual basis but governed by factors such as tumour size and volume, degree of mass effect and eloquence of location. Suitable patients may be considered for both resective surgery for a larger metastasis and SRS to a limited number of other smaller metastases. If there is doubt either surgically or radiologically on postoperative scan about the extent of completeness of resection of a metastatic tumour , consideration may be given to cavity SRS at the site of the resection.

APPENDIX 1 – Patient Pathways