LONDON CANCER
NORTH AND EAST

London Cancer Brain and Spine Pathway Board

Neuro-oncology guidelines

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Contents

1. The neurosciences multidisciplinary team meeting

- All patients with a suspected or proven primary intra-cranial malignancy should be referred for discussion into the local multidisciplinary neuro-oncology meeting (UCLH / BLT / BHR).

  Urgent referrals should be made to the neurosurgery SpR on call as follows:

  Referrals for Neurosurgery (not 2 week wait)

  NHNN bleep 8100 / mobile 07908 250 938
  Information to be sent via www.referapatient.org

  Royal London - 07795 245 709

  Queens Romford - bleep 6177

- These meetings should take place on a weekly basis
- They may be one meeting encompassing brain / spinal / base of skull and pituitary tumours – or these may be held as separate meetings
- All patients with a CNS tumour should be considered for a surgical procedure. Where safe, a pathological confirmation should be obtained prior to radiotherapy / chemotherapy. In general, as complete a resection of tumour as safely possible, should be performed (unless CNS lymphoma or a GCT). If excision is likely to result in major functional impairment then an open or stereotactic biopsy should be performed where the patient is of sufficient performance status.
- All patients should have a pre-operative MRI scan performed. All patients who have a resection should have a post-operative MRI (ideally within 48 hours for high grade gliomas, and within 24 hours for medulloblastoma) to assess the degree of resection and to act as a baseline, and for use in radiotherapy planning where appropriate.
- All patients should be considered and, whenever possible, be offered entry into clinical trials.

1.1. Aims and objectives of NSMDTs

- To provide all members with a policy of agreed standards and processes to enable quality patient focused care.
- To review all new and recurrent cases of suspected and confirmed CNS tumours without delay.
- To discuss the initial and subsequent treatment of all patients diagnosed with a CNS tumour.
- Ensure individual patient management is co-ordinated in a specific multidisciplinary way to support best practice, enabling the delivery of high quality patient care.
- Help foster Trust wide co-operation between clinicians working for patients with CNS tumours.
- To work in a collaborative way to contribute to the management plan for patients with CNS tumours.
- To use agreed operational standards in the management of CNS tumours.
- Support research in CNS tumours through recruitment to trials and ensure patients have access to appropriate clinical trials.
- Ensure the service is fully compliant with IOG guidelines.
- To hold at least annual operational meetings to discuss policies, present audits and as a teaching forum.

- To participate in audit internal to the service and agreed audits with the NDSG undertaking service improvement where required.
- To ensure a data collection system is in place to allow entry of information on all patients with radiologically or histopathologically confirmed CNS tumour.

1.2. Discussion of a patient at the NSMDT

- when newly diagnosed with a brain or other CNS tumour,
- following initial radiological diagnosis, and before potential histological confirmation,
- following histological confirmation and before any potential definitive surgical procedure,
- following definitive surgical procedure and before any potential adjuvant treatment,
- all cases of suspected tumour recurrence or progression where the patient remains well enough for further treatment,
- at any other times agreed in the area wide pathway.

1.3. Specialist NSMDT

- BLT

- BHR
    - Pituitary
        - Weekly at Queens (Monday 1030)
    - Radiosurgical
        - Alternate weeks teleconference with BLT (Mon 0800)

- UCLH
    - Spinal
        - Weekly at NHNN (Friday 0800)
    - TYA
        - Weekly at UCLH (Wed 1600)
    - Pituitary
        - Weekly at UCLH (Tues 0915)
    - Skull base
        - Alternate weeks at UCLH (Wed 1600)
    - Radiosurgical
        - Alternate weeks at UCLH (Mon 1230)

2. Tumour-type specific guidelines

2.1. Gliomas

- These include
  - Low Grade Gliomas G1/2 (oligodendroglioma, diffuse, fibrillary, gemistocytic or protoplasmic astrocytomas, pleomorphic xanthroastrocytomas and pilocytic astrocytoma)
  - High Grade Gliomas G3/4 (anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, gliosarcomas and glioblastoma multiforme (GBM)).

2.1.1. High grade Gliomas (HGG)

- All patients with HGGs should be considered for radiotherapy. Radiation therapy is standard and has been shown to prolong survival by 3-6 months and improve quality of life, when compared to no radiotherapy. 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

- <u>Management decision algorithm for HGG</u>

	< 70 yrs	**> 70 yrs**
KPS <40	No treatment	No treatment
KPS 40-70	Palliative RT 30Gy in 6 fractions over 2 weeks (Mon, Wed, Friday)	No treatment
KPS > 70	Radical RT +/- chemotherapy G3: 59.4Gy in 33 daily fractions or 60Gy in 30 daily fractions G4: 60Gy in 30 daily fractions with concurrent TMZ	Palliative RT 30Gy in 6 fractions over 2 weeks (Mon, Wed, Friday) 40Gy in 15 daily fractions over 3 weeks

- Radiotherapy:
  - 3D planning using CT data
  - 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 post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
    - All margins should be added using a 3D growth algorithm.
    - A single phase should be used throughout treatment wherever possible.
    - A 3 or 4 field optimised CT plan is used
    - Routinely consider IMRT in GBM for the young (<60), good PS patients going through chemorad with temporal lobe and low frontal tumours.

        - Consider IMRT in G3 Gliomas for the young (<60), good PS patients with temporal lobe and low frontal tumours, and those with extensive tumours requiring large treatment volumes.
    - Dose:
        - Palliative Radiotherapy
            - 30Gy in 6 fractions over 2 weeks, treating Monday, Wednesday, Friday
        - Radical Radiotherapy
            - GBM: 60Gy in 30 daily fractions over 6 weeks
            - G3: 59.4Gy in 33 daily fractions over 6 and ½ weeks
            - Brain stem gliomas are prescribed a dose of 54Gy in 30 daily fractions over 6 weeks
    - GTV
        - In Palliative setting, this is defined as the gross visible tumour seen on the Planning CT with reference made to the diagnostic imaging.
        - In the Radical setting, the GTV is defined from the planning CT data and preoperative images from MRI fusion. The postoperative images are also useful when there has been a significant resection. GTV is enhancing tumour on MRI T1 plus Gadolinium images
        - Some G3 tumours may be better visualized on the MRI T2 images
        - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
    - CTV
        - CTV is T1 +contrast enhancing tumour +2.5cm margin. This should include all abnormal T2 signal
        - G3 tumours: If GTV has been defined using unenhanced T1 or T2 images, then CTV = GTV +1.5cm margin (otherwise T1 + contrast enhancing tumour + 2.5cm)
        - The volume may be trimmed at the bony circumference, tentorium and at midline, unless there is a clear route for tumour spread such as the corpus callosum
    - PTV
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Chemotherapy
    - **Temozolomide: Concomitant and adjuvant** (NICE supported)
    - Patients with G4 Gliomas (GBM) that are suitable for radical treatment should be treated with concurrent Temozolomide (TMZ).
    - Temozolomide orally Concomitant: 75 mg/m^2 daily for 6 weeks including weekends D1-42
    - Temozolamide orally adjuvant: commences 4 weeks after chemoradiation, 150mg/m^2 d1-5 q4w for first cycle and then 200mg/m^2 for subsequent cycles if tolerated.
    - This regimen improves median survival by an extra 2-3 months.
    - **Supportive meds:** Cotrimoxazole 960mg BD x3 per week as Pneumocystis prophylaxis. Locally agreed anti-emetics,
    - **Tests**: Baseline FBC, U&ES and LFTS required, repeat weekly during concomitant phase and prior to each cycle during adjuvant treatment

- Chemoradiation is not currently standard treatment in G3 Gliomas. The role of adjuvant chemotherapy in these tumours is currently being investigated in an EORTC study (BR14).

- The risk of pseudoprogression on MRI following chemoradiation must be considered and clinicians must balance the evidence from the scans with the patients' performance status and clinical symptoms. We now recommend deferring routine imaging until completion of all adjuvant treatment unless clinically indicated.

- G3 tumours with 1p19q co- deletions should now be offered 6 cycles of adjuvant PCV chemotherapy following radiotherapy (based on the mature data from ASCO 2012).
  PCV: Procarbazine,lomustine,vincristine: Adjuvant q42
  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

    Lifetime total doses of CCNU exceeding 1000mg/m2 may have an increased risk of pulmonary toxicity

  Tests: Baseline FBC, U&ES and LFTS required, repeat prior to each cycle

- Treatment at relapse
  - Patients who present with symptoms or signs of clinical progression should be assessed and, if therapeutic options are available, repeat imaging should be performed. They should then be discussed in the NSMDT
  - If there is concern that the changes might represent radiation necrosis a biopsy, MRI perfusion studies or PET-CT/MRI should be considered.
  - If the imaging suggests tumour progression and the patient remains sufficiently fit the following treatment options should be should be considered:

  - 1) Re-resection: when this would provide the best palliation, for example reduction in symptoms of raised intra-cranial pressure. In certain cases the use of BCNU wafers (Gliadel) may be appropriate.

  - 2) Palliative chemotherapy
    - If patients with G4 tumours have had more than 6 months since completing adjuvant chemotherapy they are usually retreated with temozolomide
    - **Temozolomide - palliative**
    - Temozolomide po 150-200mg/m2 D1-5 q 28/7 for up to 12 cycles but usually six - beyond this there is an increased risk of myelodysplasia and other haematological effects.

    - Chemo-naïve G3 patients will be offered temozolomide at first relapse, unless they are 1p19q co-deleted who should be offered PCV instead.

    - For those with a shorter disease free interval following previous TMZ the following regimens may be offered:

PCV : Procarbazine,lomustine,vincristine -palliative

- 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

Lifetime total doses of CCNU exceeding 1000mg/m2 may have an increased risk of pulmonary toxicity
(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.
Tests: Baseline FBC, U&ES and LFTS required, repeat prior to each cycle

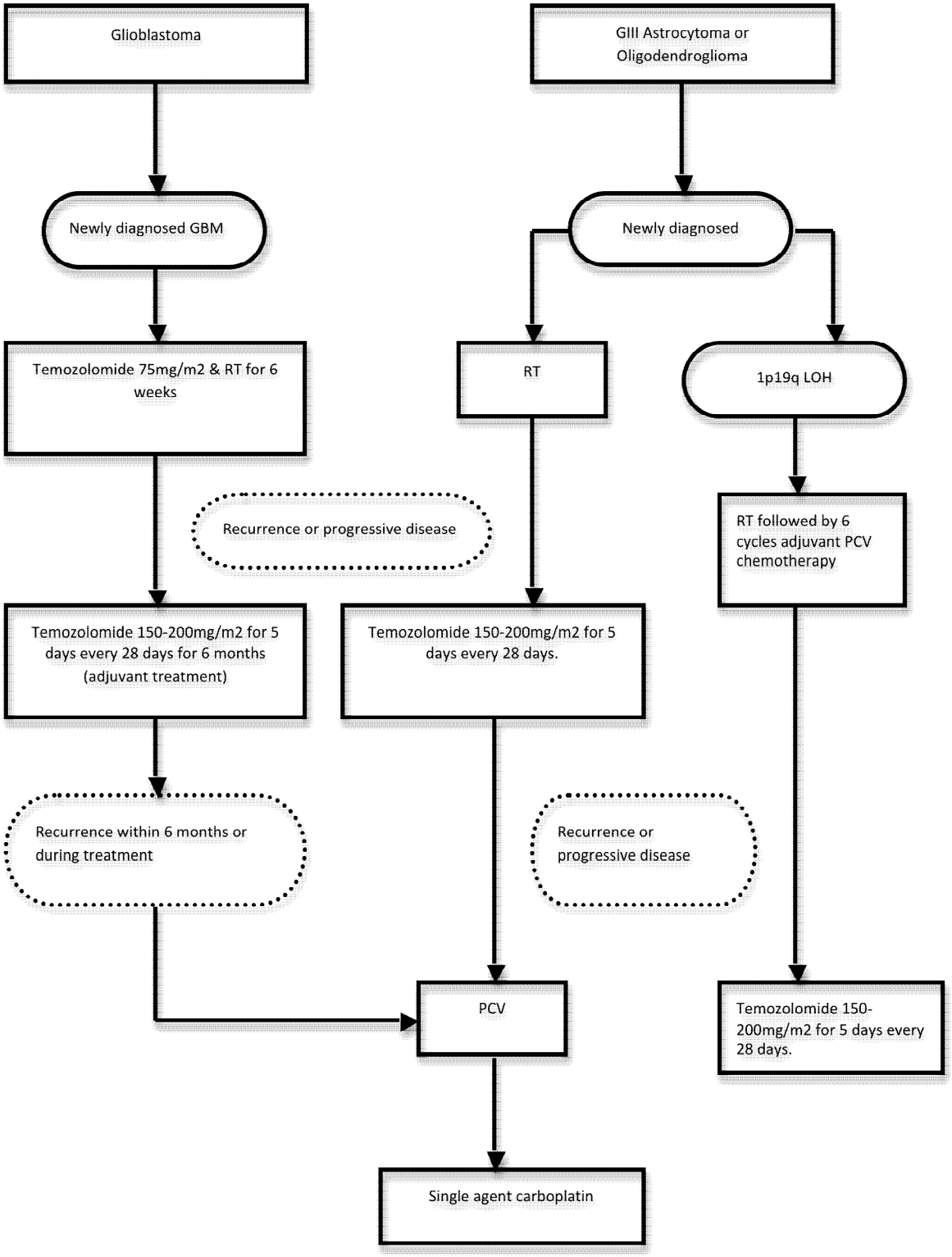
Lomustine Single agent - **Palliative**
Lomustine 100mg/m^2 PO od q6/52
Tests: Baseline FBC, U&ES and LFTS required, repeat prior to each cycle

Carboplatin - **Palliative**
Carboplatin AUC 4-6 Single agent
(depending upon performance status) q3-4/52
Tests: Baseline FBC,U&ES and LFTS required, repeat prior to each, calculated or measured Creatinine clearance

- 3) Re-irradiation
  - may be considered in certain patients in whom there is a long progression free interval and critical structures have not been taken beyond tolerance previously.
  - The optimal fractionation is not known but the combined BED of both treatments should be <100 Gy. The patient will need to be carefully consented with respect to the estimated risks.

- Surveillance imaging
  - GBM following Stupp regimen: 6 weeks post completion of adjuvant TMZ and then at 3-6 monthly intervals unless otherwise indicated clinically
  - G3 post RT: 3 months and then extend to 6 months if all well.
  - During palliative chemotherapy: at 2- 3 cycle intervals and 6 weeks post completion. Then at 3 monthly intervals

- Chemotherapy Algorithm in HGG



2.1.2. Low grade Gliomas (LGG)

- LGG are typically non-enhancing on CT and MRI scanning.

- The non-infiltrative G1 low grade gliomas include pilocytic astrocytoma, and other includes pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma and subependymoma. Primary surgery may be curative.

- For all LGG, surgery remains important first management, not only for diagnosis (which can be difficult on small samples) but also for improving survival where an extensive resection is possible.

- There is no proven benefit in the LGG in terms of overall survival from immediate radiotherapy, therefore radiotherapy can be deferred till time of radiological (including contrast enhancement as this is highly suggestive of high grade elements) or symptomatic progression.

- However, early radiotherapy should be considered in patients with:
    - defined high risk of progression with poor prognostic features (age >40, lesion >6cm, lesion crossing midline, pre-operative neurological deficit, contrast enhancement).
    - tumour in eloquent area
    - intractable seizures

- Radiotherapy:
    - 3D planning using CT data
    - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used
    - Routinely consider IMRT in G1/2 Gliomas for the young (<60), good PS patients with temporal lobe and low frontal tumours, and those with extensive tumours requiring large treatment volumes.
    - Dose:
        - 50-55Gy in 30-33 daily fractions over 6 weeks
        - Use 50.4Gy in 28 fractions for the true Grade 1 tumours eg optic nerve glioma
    - GTV
        - Defined from the planning CT data and diagnostic images from MRI fusion where appropriate.
        - LGG usually better visualized on the MRI T2 images
        - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
    - CTV
        - CTV is T2 tumour +1.5cm margin. The volume may be trimmed at the bony circumference, tentorium and at midline, unless there is a clear route for tumour spread such as the corpus callosum
    - PTV
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Chemotherapy:
  - Chemotherapy is not standard first line treatment outside clinical trials (no conclusive evidence that primary or adjuvant chemotherapy is of benefit, but may be appropriate in some patients with large tumours for whom radiotherapy treated volume would be very large).
  - Currently awaiting results of BR13 (comparing RT versus TMZ chemotherapy)

- Ongoing trials in LGG
  - MRI surveillance protocol NHNN
  - Tavarec – chemotherapy with Avastin in progressing LGG following prior radiotherapy or chemotherapy

- Oligodendroglioma
  - In general these tumours behave and are treated as for other gliomas (dependent on their grading) but they are more chemosensitive and have a better overall survival than other types of glioma.
  - The presence of the 1p19q deletion predicts a longer time to progression after radiotherapy, and a greater sensitivity to subsequent chemotherapy.

- Disseminated Pilocytic astrocytoma
  - This is extremely rare and mainly seen in the paediatric / TYA population.
  - Diagnosis based on MRI of CSA and CSF cytology
  - Good control has been reported in the TYA population with CSRT. Younger patients (<8 years may be treated initially with chemotherapy)
  - Radiotherapy
    - To start within 4 weeks of diagnosis (see section below on planning of CSRT)
      - Phase 1 CSRT:36Gy in 20 fractions over 4 weeks (1.8Gy per fraction)
      - Phase 2 boost (brain): 18Gy / 10 fractions / 3 weeks (1.8Gy per fraction)
      - Phase 2 boost (spinal mets): 14.4Gy / 10 fractions / 2 weeks (1.8Gy per fraction)
      - Routinely consider the use of IMRT for brain phase 2 boost
        - GTV =all visible enhancing tumour on T1 + gadolinium MRI images, plus 2mm where appropriate for MRI fusion uncertainty
        - CTV = GTV + 5mm
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Gliomatosis Cerebri
  - Consider whole brain radiotherapy to a maximum dose of 54Gy in 30 daily fractions

2.2. Meningiomas

- The majority of patients are adequately treated with surgery only and followed up by the treating surgeon
- Classified into:
  - grade I
  - grade II (atypical, clear cell or chordoid)
  - grade III (anaplastic, rhabdoid or papillary).

- Whenever possible, a pre-operative MRI scan should be performed to fully demonstrate the extent of the lesion, particularly the dural tails and post-operative (<72 hours) to confirm extent of resection.
- The maximum safe resection should be performed.
- Benign lesions, which have been completely excised, rarely recur.
- The Simpson's grade of the resection should be noted on the pathology form by the surgeon to aid discussion at the NSMDT
    - Stage 1 = complete excision including dura and bone
    - Stage 2 = complete with co-agulation of dural attachment
    - Stage 3 = incomplete, disease still visible on MRI
    - Stage 4 = biopsy only
    - Stage 5 = decompression only

- Current Management decision algorithm following surgery

Complete resection	WHO grade I/II	Surveillance
Complete resection	WHO Grade III	∗RT/IMRT 50-60Gy
Incomplete resection	WHO grade I	Surveillance
Incomplete resection	WHO grade II/III	∗RT /IMRT RT 50-60Gy
Recurrent disease	Any grade	∗RT/IMRT RT 50-60Gy

∗Depending on size and position of lesion

- Routinely consider the use of IMRTin all young (<60 years old), good PS patients with histological or radiological diagnosis of meningioma referred for RT
- **Patients with small <3cm lesions, away from critical structures, may be treated with stereotactic radiosurgery**

- Radiotherapy:
    - 3D planning using CT data
    - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium in axial, sagittal and coronal views) plus pre and post operative CT if available
    - Consider the use of Gallium Dotatate PET-CT or PET-MRI scanning and fusion for difficult base of skull meningiomas to help delineate the extent of bony involvement
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used
    - Routinely consider the use of IMRT either within a trial or where clinically indicated in all young (<60 years old), good PS patients with histological or radiological diagnosis of meningioma referred for RT
    - Dose:
        - 50-60 Gy in 1.8Gy per fraction daily over 5.5-6.5 weeks
        - 50.4Gy in 28 daily fractions over 5.6 weeks is standard in G1
        - No prospective data supporting dose escalation in any grade of meningioma (EORTC study ongoing), however it is accepted practice to prescribe 54Gy in 30 fractions for atypical meningiomas and 60Gy in 30-33 fractions for G3 meningiomas based on retrospective data.
    - GTV
        - Defined from the planning CT data and diagnostic images from MRI, CT, Gallium dotatate PET fusion where appropriate.
        - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)

        - Residual Disease:
            - GTV is residual meningioma, hyperostotic bone and dural extension.
        - No Residual Disease:
            - GTV equivalent = Use pre-operative MRI to define largest extent of dural/bone thickening
    - CTV
        - Residual Disease:
            - Add 1cm in plane of dura for CTV
            - Add 1cm into brain at brain/meningioma margin in presence of brain invasion
            - Add 1cm into bone where bone invasion/thickening
        - No Residual Disease:
            - Add 1cm in the plane of the dura to define CTV
            - If documented brain invasion add 1cm into brain for CTV
            - Note that when a large tumour has been removed the meningioma/brain margin may move into the surgical cavity and this should be accounted for.
    - PTV
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Chemotherapy:
    - There is no known role for chemotherapy or hormonal therapies in meningiomas

- Ongoing trials in meningioma
    - **IMRT in meningiomas** (local study at UCLH) – now incorporating and evaluating the role of Gallium dotatate PET-MRI in radiotherapy planning

- Treatment at relapse
    - The following options should be considered where clinically appropriate:
        - Re-resection
        - Stereotactic radiotherapy / radiosurgery - but can only be used in very small (<3cm) recurrences
        - Occasionally an out-of-field recurrence occurs which can be treated with standard radiotherapy
        - There is no proven role of chemotherapy or hormonal treatment for meningiomas

- <u>Haemangiopericytomas</u>
    - CT or MRI scan will demonstrate a well-demarcated lesion, sometimes with destruction of overlying bone. As complete a resection as possible should be performed.
    - These lesions almost always recur locally - all patients should be referred for adjuvant postoperative radiotherapy, using dose regimens up to 60Gy in 30 daily fractions over 6 weeks (50-60Gy)
    - Of all brain tumours, haemangiopericytomas are the most likely to metastasise out with the CNS (e.g. bone and liver).
    - Therefore, if the patient develops signs or symptoms of possible metastases then appropriate imaging should be arranged, also before any further surgery.

- Treatment at relapse:

- Consider the following options in good PS patients:
  - Re-resection
  - Stereotactic radiotherapy / radiosurgery, but can only be used in very small (<3cm) recurrences
  - There is no proven role of chemotherapy for haemangiopericytomas

2.3. Schwannomas

Cranial nerve schwannomas are benign nerve sheath tumours. The vestibular nerve is the most common site inside the skull for the growth of these tumours. As they grow they may cause brainstem compression. There is a specific group of patients with Neurofibromatosis Type II who develop bilateral tumours. Tumour control rates in the order of 91-98% are reported with SRS and SRT, with increasing documentation of long term results, providing control beyond 10 years. This can be achieved with hearing preservation (defined as unchanged functional grade) in 75% of patients with a very low risk of damage to the facial and trigeminal nerves (around 1%), unlike surgical excision

2.3.1. Vestibular schwannomas

Criteria for suitability for SRS:

- Less than 3.5cm in extra-canalicular diameter
- No clinical signs of brainstem compression
- NF2 patients when referred by the NF team

Criteria for suitability for conventionally fractionated SRT / IMRT

- Larger than 2.5cm in extra-canalicular diameter
- No clinical signs of brainstem compression
- Excluding NF2 patients (unless no other treatment option available)

Secondary reason to use SRS or SRT rather than surgery:

- Medical contraindications to surgery
- Hearing preservation paramount (bilateral, deafness on other side)
- Facial nerve preservation paramount (certain professions)

2.3.2. Non-vestibular schwannomas

- Surgery usually first choice treatment
- Then consider radiotherapy as appropriate (SRS, SRT, IMRT)

2.4. Pituitary tumours (including craniopharyngiomas)

2.4.1. Pituitary adenomas

- Macroadenoma (>1cm)
- Microadenoma (<1cm)
- Non-functioning
- Functioning (Prolactin, GH, ACTH, TSH)

- Dedicated Pituitary MR imaging, including coronal views, is often required to fully demonstrate the lesion.
- All patients will be jointly managed by the pituitary MDT

  - UCLH/NHNN: joint pituitary clinic (Tues am following the specialist MDM: pituitary surgeon, endocrinologist, clinical oncologist)
  - BLT
  - BHR: Mon am specialist MDM
- Endocrine status will be assessed prior to and may obviate surgery (in the case of prolactinoma which requires medical management only initially)
- Visual field assessment
- Where necessary, trans-sphenoidal surgery will be performed (craniotomy being reserved for selected cases)
- Post-operative MRI scanning at 3/12 to help assess the need for subsequent radiotherapy

- Indications for radiotherapy:
  - Significant residual (consider redo TSS first)
  - Very large silent corticotroph (increased risk of recurrence post-operatively)
  - Atypical histology
  - Recurrent (ie following a second TSS or within the cavernous sinuses)
  - Hormone secreting (not cured biochemically surgically)
  - Medically unfit patients: Long-term control rates are around 70-80% with radiotherapy alone

- Aim is to prevent tumour regrowth and / or normalise elevated hormone levels

- Non–functioning Macroadenomas
  - Without radiotherapy around 15% of macroadenomas will recur, this falls to <5% with radiotherapy
  - Invasion of the cavernous sinus, marked supra-sellar extension and post-operative residual disease are associated with a higher risk of recurrence
  - Reasonable to defer radiotherapy for patients without these factors provided they are agreeable to surveillance MRI
  - With radiotherapy local control exceeds 95%

- Functioning macroadenomas and microadenomas
  - Radiotherapy is less effective for functioning adenomas
  - Hormonal manipulation and surgery are the primary treatment modalities.
  - When unsuccessful, radiotherapy can reduce hormone levels, though this can take a number of years.
    - Acromegaly = reduction of GH and IGF-1 in about 60% patients by 10 years
    - Cushing's disease/Nelson's syndrome = reduction ACTH 80% normal by 4 years
- All patients require long-term follow up for regulation of any hormone replacement therapy.

- Radiotherapy:
  - 3D planning using CT data
  - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium in axial, sagittal and coronal views). The post-operative MRI is important as surgical decompression may cause the optic chiasm to fall into the pre-operative GTV superiorly
  - All margins should be added using a 3D growth algorithm.
  - A 3 or 4 field optimised CT plan is used (classically opposing lateral beams and an anterior superior oblique field – with the head in a flexed position)

  - Routinely consider the use of IMRT in young (<60 years old), good PS patients with large tumours (especially if extending anteriorly between the orbits)
  - Consider stereotactic radiotherapy in all cases if available
  - Dose:
    - Adjuvant: 45 Gy in 25 daily fractions over 5weeks
    - Macroscopic residuum: 50.4Gy in 28 daily fractions over 5.6 weeks
  - GTV
    - Defined from the planning CT data and diagnostic images from MRI where appropriate.
    - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
    - Visible extent of tumour pre-operatively and any possible residual disease. If surgical decompression of the chiasm causes the chiasm to fall within the pre-op GTV, then use the post-op GTV superiorly
  - CTV
    - Include the cavernous sinuses bilaterally
    - Extend to CTV by 5mm in the direction of the TSS to ensure adequate coverage of the sphenoid where a trans-sphenoidal approach has been employed
  - PTV
    - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Radiosurgery
  - Small functional lesions away from the optic chiasm can be treated with radiosurgery

- Chemotherapy:
  - Chemotherapy is not used in the standard management of pituitary tumours. However, Temozolomide may have a role in the treatment of pituitary carcinoma (localised and metastatic) and following the failure of all standard treatment modalities in pituitary adenomas (especially prolactinomas).

- Re-irradiation of recurrent disease
  - May be considered in certain patients in whom there is a long progression free interval and critical structures have not been taken beyond tolerance previously.
  - The optimal fractionation is not known - the patient will need to be carefully consented with respect to the estimated risks
  - Radiosurgery may be used in very small recurrences away from the optic chiasm

2.4.2. Craniopharyngioma

- MR imaging, including coronal views, is often required to fully demonstrate the lesion
- All patients will be jointly managed by the pituitary MDT
  - UCLH/NHNN: joint pituitary clinic (Tues am following the specialist MDM: pituitary surgeon, endocrinologist, clinical oncologist)
  - BLT
  - BHR
- Endocrine status will be assessed prior to surgery
- Visual field assessment
- Most patients undergo trans-sphenoidal or trans-cranial resection.

- Complete excision can result in marked morbidity so often a subtotal resection is combined with post-operative radiotherapy. Such an approach has been shown to have good local control with reduced toxicity
- Radiotherapy should be considered in all adult patients after first resection – although close surveillance may be preferred after near-total resection

- Radiotherapy:
    - 3D planning using CT data
    - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium in axial, sagittal and coronal views). The post-operative MRI is important as surgical decompression may cause the optic chiasm to fall into the pre-operative GTV superiorly
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used (classically opposing lateral beams and an anterior superior oblique field – with the head in a flexed position)
    - Routinely consider the use of IMRT in young (<60 years old), good PS patients with large tumours (especially if extending anteriorly between the orbits)
    - Consider stereotactic radiotherapy in all cases if available
    - Dose:
        - 50.4Gy in 28 daily fractions over 5.6 weeks (some centres use up to 54Gy in 30 daily fractions over 6 weeks)
    - GTV
        - Defined from the planning CT data and diagnostic images from MRI where appropriate.
        - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
        - Visible extent of tumour pre-operatively and any postoperative cystic component
        - NOTE: If there is reaccumulation of fluid within a craniopharyngioma cyst in evidence on the planning scan, the patient should be referred back to the Neurosurgeons for further surgical drainage.
    - CTV
        - GTV + 5mm, ensuring coverage of surgical approach utilised, especially where trans-sphenoidal surgery has been employed
    - PTV
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

2.5. Ependymoma

- These are divided into:
    - grade I lesions (subependymoma and myxopapillary ependymomas)
    - grade II (cellular, papillary, clear cell and tanycytic)
    - grade III lesions (anaplastic ependymoma).
- Ependymomas can occur infratentorially (especially children), supratentorially or in the spinal cord
    - Adults 2/3 spinal cord
    - Children 2/3 posterior fossa
- Preoperative staging should include MRI of the whole cranial spinal axis (there is no evidence for whole neuraxis irradiation – craniospinal radiotherapy – in the absence of neuraxis seeding as evidence by MRI staging or CSF cytology)

- A CSF sample should be obtained, either pre-operatively or >14 days after surgery in high grade tumours
- Maximal safe resection should be performed as this improves survival.
- Post-operative MRI scan (<72 hours) should be performed to assess the extent of the resection.

- Management Algorithm

Complete resection	Grade I and Grade II	Surveillance
Complete resection	Grade III	Radiotherapy
Incomplete resection	Grade I	Surveillance or Radiotherapy
Incomplete resection	Grade I, II, III	Radiotherapy

- Grade 1
    - Subependymoma:
        - surgery alone is usually curative but radiotherapy maybe required if evidence of local progression (suggests a mixed morphology).
    - Myxopapillary ependymomas:
        - occur almost exclusively in the conus region of the spinal cord.
        - Total resection is not usually possible because of the risk of morbidity.
        - In patients in whom sub-total resection has been performed, postoperative radiotherapy should be considered as this has been demonstrated to produce excellent local control rates.

- Grade II
    - Historically all patients with Grade II ependymomas received immediate radiotherapy, regardless of the extent of resection.
    - Increasing body of evidence (though single centre retrospective series) that some patients have a durable remission without radiotherapy.
    - Proposed: following macroscopic resection - close surveillance with MRI (3 months post-operative then 6 months for first year then annual) may be sufficient.
    - If there is macroscopic residual disease patients should receive immediate radiotherapy
- Grade III
    - All patients with anaplastic ependymoma should receive immediate post-operative radiotherapy
    - In the early 1990's classical teaching was that patients with infra-tentorial anaplastic ependymomas should undergo craniospinal radiotherapy
    - Review of series of patients treated with local RT alone has questioned this teaching with the majority of patients relapsing locally

- Radiotherapy:
    - 3D planning using CT data
    - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used

- Routinely consider IMRT in the posterior fossa G2 ependymomas in good PS, young (<60) patients to enable bilateral temporal lobe sparing.

- Dose:
  - Spinal tumours: 50.4Gy in 28 daily fractions over 5.6W
  - Cauda Equina: 54Gy in 30 daily fractions over 6 weeks
  - Intracranial tumours: 55-60Gy in 30 daily fractions over 6 weeks
- GTV
  - Defined from the planning CT data and preoperative images from MRI fusion. The postoperative images are also useful when there has been a significant resection.
  - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
- CTV
  - Intracranial
    - G1/2 = GTV + 1.5cm
    - G3 = GTV + 2.5cm
    - The volume may be trimmed at the bony circumference, tentorium and at midline, unless there is a clear route for tumour spread such as the corpus callosum
  - Spinal and Cauda Equina
    - CTV = GTV + 2cm (superiorly and inferiorly).
    - include entire spinal canal axially, ensuring coverage laterally of neural foramina
    - Inferiorly, may be appropriate to cover to bottom of thecal sac for lumboscaral lesions
- PTV
  - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Disseminated ependymoma
  - The exact schedule must be considered on a case-by-case basis.
  - Areas of gross disease should receive >50Gy and the whole craniospinal axis ≥45Gy
  - If there is just positive cytology and no gross visible disease outside the primary location then a schedule of 45Gy at 1.8Gy per fraction for the craniospinal fields with a boost of 9-15Gy at 1.8-2Gy per fraction to primary tumour bed is a reasonable approach

- Chemotherapy
  - Chemotherapy is not a first line treatment.
  - It may be indicated for relapsed disease, decisions made on case by case basis
  - Carboplatin and /or etoposide recommended

- Treatment at relapse:
  - Depends on the location and symptoms.
  - Surgery may offer the best palliation.
  - Alternatives are radiosurgery or in rare cases re-irradiation.
  - Ependymomas respond poorly to chemotherapy though there is some evidence for using cisplatin and etoposide.

2.6. Chordoma and chondrosarcoma

- Spinal and base of skull / Clival lesions
    - In light of the difficulty of delivering to this region the high doses required to treat these relatively radioresistant tumours, consideration should be made to referral to the UK Proton panel.
    - If patient not fit to travel then they should receive 60-65Gy in 33-39 fractions using IMRT (preferably stereotactic)

    - Following maximal debulking surgery for base of skull and spinal chordoma, patients should be referred to the National Proton Panel for consideration of proton beam radiotherapy:
    - Proton treatment is a highly specialised means of delivering radiotherapy dose to a target volume. The particular characteristic of proton beams means that comparatively little radiation is given to normal tissues. This is especially useful for cases where critical normal tissues impose dose constraints or considerations of potential late effects from irradiation of the normal tissues make even optimised photon options such as Intensity Modulated Radiotherapy (IMRT) unacceptable. Base of skull chordoma is considered to be one of the clearest indications, and there is evidence for up to 80% 5Y control rates with the 79Gy achievable with proton beam therapy.
    - Clinical decisions as to the need or suitability for proton therapy are required as there are many factors other than dose distribution that are important to consider. Patients should have the opportunity to discuss the range of options with an expert in radiotherapy by referral to a Clinical Oncologist.
    - From April 2008, suitable cases have been funded for treatment abroad by a service nationally commissioned by the National Specialised Commissioning Team.
    - A Proton Clinical Reference Panel (PCRP) has been set up which manages the referral pathway and has the necessary knowledge of proton therapy to approve cases for consideration for treatment abroad.
    - Patient / disease characteristics to be considered before referral to the PCRP:
        - Treatment should be given with curative intent.
        - No other coincident diagnoses that are likely to either limit 5 year survival or make a prolonged period abroad difficult to manage from a practical point of view
        - There should be no metastatic disease
        - Re-treatment cases will not be accepted
        - There are weight limits on the treatment couches in treatment centres (cannot exceed 150kg)

    - The advantage of proton treatment over optimal photon treatment may be dependent on the size and position of the tumour and target volume in relation to critical normal tissues and tolerance doses. In some cases the treatment centre may require further debulking surgery before they are accepted for treatment. Cases may be turned down when, in the panel's view, proton therapy would not confer any advantage.

    - A wide range of factors need to be taken into account in assessing if Proton Therapy confers any significant advantage over conventional radiotherapy or IMRT. These factors include the:
        - site of tumour

- radiotherapy target volume,
- target volume dose and dose gradients required
- significant residual bulk disease
- tumour and target volume proximity to critical dose limiting structures
- patient age and performance status,
- presence, size and position of metallic implants
- views of patient
- patients ability to travel

- Metallic implants:
  - The presence of any metal stabilisation rods or plates may have a major impact on the acceptance of cases for treatment. The outcomes of cases treated with significant metallic stabilisation in place have been shown to be very significantly worse such that cases may be reviewed on a case-by-case basis and often not accepted.
  - There is some guidance that may make proton treatment more likely and which surgeons should be aware of. Ideally the position and type of any stabilisation should be planned prior to resection, with proton treatment in mind. The uncertainties of dose distribution in treatment planning close to the target volume and critical normal tissues such as spinal cord with cold spots in the shadow of metal and hot spots anteriorly and laterally can lead to significant underestimation of dose with current planning systems.
  - This uncertainty is sufficient that conventional radiotherapy with IMRT solutions where dose distributions will be much more reliable may be preferred.
  - Factors to be born in mind are:
    - Titanium rather than stainless steel is preferred as it reduces artefact and improves accuracy of radiotherapy treatment planning.
    - Metal implants close to residual disease that will be within the radiotherapy target volume may make the patient unacceptable for treatment.
    - Transverse cross-links at the level of the tumour and in the plane of radiotherapy between longitudinal rods should be avoided.
    - Implants should be minimised but posterior rods for stabilisation or only one plate, situated away from the radiotherapy target volume may still allow treatment.
    - Pedicular screws should be fixed at least 2 vertebral bodies cranial and caudal to the area of the tumour to avoid artefacts which may compromise treatment planning and dosimetry.

- Significant residual bulk disease:
  - This may preclude patients from treatment with Protons.
  - There is good evidence of good outcomes from surgery and post operative proton and conventional radiotherapy when the volume of residual disease is minimal. This volume appears to ideally be less than 25ml. Experience has been that newer approaches to endoscopic skull base surgery and in some cases re-operation at specialist centres, including some abroad, has been recommended before patients have been accepted for proton treatment. In some cases decompression may be necessary to allow sufficient space (around 5mm) between the brainstem and the target volume to allow scope for high dose proton treatment.

- Summary
  - The clinical reference panel will review clinical details and imaging to approve referrals
  - Referral forms and guidance available on the NSCT website
    - http://www.specialisedservices.nhs.uk/service/proton-beam-therapy
  - Referrals and contact with treatment centres abroad should not be made until formal approval has been given by the NSCT for each case
  - A Clinical Oncologist must see and refer all cases.
  - Referrals should be sent to the NSCT via nhs.net email to:
    - leedsth-tr.ProtonNCG@nhs.net
  - Imaging on CD-ROM should be sent to
    Dr Adrian Crellin
    Consultant Clinical Oncologist
    NHS Specialised Services Proton Clinical Reference Panel
    St James's Institute of Oncology
    Level 4 Bexley Wing
    St James's University Hospital
    Beckett Street
    LEEDS LS9 7TF
  - Contact Telephone and Fax numbers
    - Tel 0113 2068602
    - Fax 0113 2067561
    - adrian.crellin@nhs.net
  - If the case is approved the referring clinician will be informed and a suggested treatment centre and contact for referral will be given.
  - After approval the referring clinician will retain primary clinical responsibility (discussions with the patient, referral to the treatment centre and follow up care after treatment).
  - Funding covers treatment costs, basic level travel and accommodation. The NSCT Policy is available on the NSCT website. The referring centre will be responsible for making travel and accommodation arrangements. Advice on this is available if needed from the NSCT
    - NSCTProton@nsct.nhs.uk
    - Tel: 020 7932 3937

- Indications for photon radiotherapy using IMRT
  - These patients may have been turned down for Proton Therapy abroad for a number of reasons, which might include the presence of metal implants to achieve spinal reconstruction. They have been approved for therapy but declined themselves for personal reasons.
  - There is evidence that high doses achieve greater levels of local control. These tumours are relatively radiation resistant (TD50 ~ 65Gy), and therefore there will be some balance between a high enough dose to have a reasonable chance of local control and risks to normal tissue structures.
  - These technologies are required to achieve high dose treatments safely. IMRT planning is mandatory.
    - IMRT
    - Access to image guidance technology for daily imaging and positional correction.

  - Some patients may be considered for high dose palliative treatment (large residual bulk abutting critical structures eg brain stem, optic chiasm) and this protocol would also apply to these cases.

- Radiotherapy planning
  - 3D planning using CT data
  - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences in axial, sagittal and coronal planes) and a bony windows fine cut CT
  - All margins should be added using a 3D growth algorithm.
  - IMRT mandatory
  - Dose:
    - Aiming for a dose of 65Gy in 39 fractions (1.67Gy per fraction) to GTV
    - Aiming for 60Gy to PTV
    - (Once we are able to deliver stereotactic RT on the Truebeam – to consider dose escalation to 70Gy to GTV)
    - This may not be achievable in the high dose palliative patients (unsuitable for protons because of bulk / site of disease).
  - GTV
    - GTV = pre-operative tumour (usually T1-contrast enhancing tumour abnormal bone on CT bony windows)
    - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
  - CTV
    - Where the cortex of the bone is not breached but the centre part involved the CTV can be restricted to the intact cortex
      - Eg Clival lesion
        - CTV = GTV + entire clivus / sphenoid bone
      - Eg Vertebral lesion
        - CTV = GTV + entire vertebral body
    - If cortex is breached – intracranial / sellar / suprasellar / intraspinal disease: add 5mm in other directions, with compromise posteriorly to come off brainstem.
    - There is no published evidence base for the size of this margin, but the experience here is that these margins can reflect the invasiveness of the tumour seen on pre-operative imaging.
    - CTV should be compromised to come off brainstem / spinal cord / optic chiasm
  - PTV
    - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Clinical Trials:
  - There are currently no trials open for these patients

- Chemotherapy
  - There is currently no evidence for the role of chemotherapy in these patients

2.7. Rare tumours

2.7.1. Adult CNS PNET

- **Medulloblastoma (when sited in the posterior fossa)**
- **Supratentorial PNET (sPNET)**
- **Pineoblastoma**

- Medullobastoma is the commonest embryonal tumour occurring in adults.
    - Maximal safe resection should be performed as this improves survival.
    - Staging should include an MRI of the whole cranial spinal axis, ideally pre-operatively.
    - A CSF sample should be obtained, if not done pre-operatively will need to be done >14 days after surgery to avoid a false positive result
    - Post-operative MRI should be performed within 24 hours to assess the extent of the resection. If there is a significant residual then second look surgery should be considered

- Patients can be divided into two risk groups:
    - Standard risk: volume of residual disease following surgery <1.5cc,
    - High risk:
        - volume of residual disease following surgery >1.5cc
        - evidence of metastatic disease (M1-M4)
        - anaplastic (severe and diffuse) medulloblastoma
        - large cell medulloblastoma
        - MYC and MYCN amplification

- Chang Staging
    - M1 (microscopic seeding)
    - M2 (macroscopic seeing in posterior fossa)
    - M3 (macroscopic seeding in spinal canal)
    - M4 (extra neuroaxial metastases)

- The gold-standard treatment of medulloblastoma has long been cranio-spinal radiotherapy (CSRT). However, in the standard risk children it has been possible to reduce the dose given to the CSA from 36Gy to 24Gy (to reduce the significant late effects of radiation) without effecting survival, by the addition of Packer regimen chemotherapy (weekly vincristine during CSRT followed by 6-8 cycles Cisplatin, Vincristine and Lomustine given 6 weekly).
- In adults, the late effects of CSRT are far less significant, there is no adult data plus it is very difficult to deliver the intensive chemotherapy used in the paediatric practice to adults.
- Therefore, the standard treatment for adults with medulloblastoma (without high risk features) remains radiotherapy alone.

- The prognosis of sPNET is worse than with medulloblastoma and is considered high risk. Pineoblastoma is a more favourable subgroup of sPNET. Children with high risk medulloblastoma, pineoblastoma and PNET are all treated with a combination of higher dose CSRT and chemotherapy. Better results in pineoblastoma were seen in the PNET3 study with the use of neoadjuvant chemotherapy (4 cycles of 3 weekly vincristine, carboplatin and etoposide) followed by CSRT.

- Adults with high risk medulloblastoma, pineoblastoma and sPNET need to be carefully assessed, and management plans designed on an individual basis, before commencing intensive chemotherapy regimes they may not tolerate or complete – the most important component of their adjuvant treatment is the CSRT.

- <u>Management Algorithm</u>

Medulloblastoma	CSRT: 36Gy in 20 fractions PF boost: 18Gy in 10 fractions
Medulloblastoma with high risk features	1. CSRT (36Gy in 20 fractions), PF boost (18Gy in 10 fractions) followed by Packer chemotherapy (may omit the weekly concurrent Vincristine with CSRT) 2. If M1 – take whole CSA to 40Gy 3. If M2/3 – boost individual mets : 18Gy to brain, 19Gy to spine
Pineoblastoma M0-4	1. CSRT (36Gy in 20 fractions), PF boost (18Gy in 10 fractions) 2. CSRT (36Gy in 20 fractions), PF boost (18Gy in 10 fractions) followed by Packer chemotherapy 3. PNET3 protocol
sPNET	1. CSRT (36Gy in 20 fractions), PF boost (18Gy in 10 fractions) 2. CSRT (36Gy in 20 fractions), PF boost (18Gy in 10 fractions) followed by Packer chemotherapy

    - Sperm cryopreservation should be considered for males undergoing chemotherapy or craniospinal RT

- Radiotherapy
    - All adult patients diagnosed with CNS PNET should have immediate post operative craniospinal radiotherapy (to start within 42 days of surgery, and ideally before), unless they have a pineoblastoma and are fit for the PNET 3 regimen with neoadjuvant chemotherapy first (CSRT then starts 3 to 4 weeks post chemo / when count recovered)

    - Dose
        - Phase 1 CSA:36Gy in 20 fractions over 4 weeks (1.8Gy per fraction)
        - Phase 2 boost:
            - Medulloblastoma - Posterior Fossa boost: 18Gy/10 fractions/2W
            - Supratentorial PNET - Primary tumour boost: 18Gy/10 fractions /2W
            - Pineoblastoma - Primary tumour boost: 18Gy/10 fractions /2W

- Radiotherapy planning
    - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium in axial, sagittal and coronal views).
    - All margins should be added using a 3D growth algorithm.
    - Routinely consider the use of IMRT for the phase 2 boost to reduce the temporal lobe doses bilaterally

- CSRT
    - Head fields: A 2 field optimised CT plan is used (parallel opposing lateral beams to cover the whole brain – with the head in an extended position)
    - These are matched (using a dynamic gap) as low as possible in the cervical spine to an optimised direct lateral spinal field (length achieved with extended FSD). Spinal field inferior border at S3/4 junction.
    - In exceptional circumstances when the length can still not be achieved at extended FSD, two spine fields will be required (at 100cm FSD) and matched at cord depth. The maximum field length is positioned superiorly so that ideally the junction is in L spine. The clinician will be consulted about the appropriateness of the junction position.
    - CTV whole brain = meninges, plus ensure includes the cranial nerve exit foramina in the base of skull (outlined using radiotherapy planning CT scan)
    - PTV whole brain = CTV plus 5mm
    - CTV spine = spinal canal outlined on radiotherapy planning CT scan down to S2, extending laterally to cover exiting nerve roots
    - PTV spine = CTV plus 5mm
    - Fields for brain and spine = PTV + 7mm (adjust for spinal fields to allow for any rotation)
        - CTV = GTV + 1.5cm (cut back with respect to anatomical barriers to spread eg midline, skull, tentorium)
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Phase 2
    - CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences in axial, sagittal and coronal planes)

- Medulloblastoma
    - Posterior Fossa Boost
    - (GTV = pre-op tumour)
    - CTV = cerebellum plus brainstem (use T1 + gadolinium fused MRI images to outline) up to level of tentorium
    - Incorporate 2mm for MRI fusion uncertainty where appropriate
    - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)
        - Inferior field border in C2/3 junction
        - Inferior CTV must cover pre op GTV + 2cm
        - Anterior CTV must cover preop GTV + 1.5cm
        - Superior CTV = tentorium unless a midline tumour (must cover pre-op GTV + 1.5cm)

- Supratentorial PNET
    - GTV = all visible enhancing tumour on T1 + gadolinium MRI images , plus 2mm where appropriate for MRI fusion uncertainty

- Pineoblastoma
    - GTV = all visible enhancing tumour on T1 + gadolinium MRI images , plus 2mm where appropriate for MRI fusion uncertainty
    - CTV = GTV + 1.5cm (cut back with respect to anatomical barriers to spread eg midline, skull, tentorium)
    - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Chemotherapy for (>18 years)
    - 1) Medulloblastoma
        - Standard risk: Not indicated unless in context of clinical trial
        - High risk: Consider adjuvant Packer
    - 2) Supratentorial PNET: Consider adjuvant Packer
    - 3) Pineoblastoma: consider adjuvant Packer or PNET3 neoadjuvant chemotherapy

Packer chemotherapy: Adjuvant or palliative	The first cycle starts 6 weeks after the end of radiotherapy, provided count recovery has occurred. **Vincristine** 1.5 mg/m2 (Max. 2 mg) IV on d1, 8, 15 **Cisplatin** 70 mg/m2 IV D1 **Lomustine** 75 mg/m2 PO D1 6-8 courses q6/52 **Tests**: FBC, U&E, LFTs prior to each cycle. Creatinine clearance (calculated or measured) and audiometry before initial treatment and after cycle 2 and 4

- Treatment at relapse
    - They may respond to PNET type multi-agent chemotherapy (usually a combination of some of the following agents; platinum, cyclophosphamide, vincristine or etoposide).

2.7.2. Intracranial Germ cell tumours (GCT)

- Intracranial GCTs are a heterogeneous group of lesions which occur in children and adults.
- There are a variety of different tumour types (see below) which carry different prognoses.
- The diagnosis of an intracranial germ cell tumor usually requires histological information, but a subgroup of tumors will secrete specific tumor markers, including alpha-fetoprotein and beta-human chorionic gonadotropin, which may obviate the need for surgical intervention.
- Germinomas have a very good prognosis, with over 90% of patients effectively treated with radiation therapy. The outcome for patients with nongerminomatous germ cell tumors is less favorable. Radiation therapy alone will result in disease control in 40%-60% of patients. The addition of chemotherapy to radiation therapy may improve the rate of survival with a 70% 5YS.

- WHO Classification of germ cell tumours (GCT)
    - Germinoma
    - Non-Germinamatous germ cell tumours (NGGCT)
        - Embryonal carcinoma
        - Yolk sac tumour
        - Choriocarcinoma
        - Teratoma
            - Immature
            - Mature
            - Teratoma
        - Mixed Germ cell

- CSF Markers

	ß-HCG	AFP
Teratoma	-	-
Germinoma (pure)	-+ (weak)	-
Germinoma (syncytiotrophoblastic)	+	-
Choriocarcinoma	++	-
Mixed germ cell	++	++
Endodermal sinua	-+	++
Embryonal carcinoma	-+	-+

- Intracranial germ cell tumours may be found anywhere in the midline (eg pineal, suprasellar)

- Management (from UKCSSG - now CCLG - interim guidelines)
    - If an intracranial germ cell tumour is suspected based on clinical and radiological evidence of a suprasellar or pineal mass, the following diagnostic steps must be followed:
        - Gadolinium enhanced MRI scan of head and spine
        - Tumour markers (AFP, ß-HCG) in both serum and CSF. For the purposes of subsequent management, elevation is defined as > 25 ng/ml for AFP and > 50 IU/l for ß-HCG in either serum or CSF.
        - CSF cytology
        - Only cases with normal markers in both compartments require biopsy for histological diagnosis. The remainder, those with elevated markers in either serum or CSF, should be treated according to the guidelines for nongerminomatous GCTs (NGGCTs) and surgical intervention limited to urgent CSF diversion procedures, where control with steroids is insufficient.

- Baseline investigations prior to commencing treatment
    - Ophthalmological assessment as indicated
    - Audiogram and GFR for patients due for chemotherapy
    - Routine haematological and biochemical assessment prior to chemotherapy
    - Endocrine assessment as indicated
    - Sperm cryopreservation should be considered for males undergoing chemotherapy or craniospinal RT

Treatment Algorithm

Germinoma	CSRT
NGGCT (non-metastatic) (secreting tumours and embryonal carcinoma)	4 cycles of PIE chemotherapy followed by focal radiotherapy (consider surgical excison of any residual)
NGGCT (metastatic) (secreting tumours and embryonal carcinoma)	4 cycles of PIE chemotherapy followed by CSRT (consider surgical excison of any residual)
Mature and Immature tetatoma	Complete surgical resection where possible (a clear post-op residuum may justify focal RT)

- Germinoma

    - Treatment for pure germinoma is craniospinal radiotherapy. This should commence as soon as possible after confirmation of diagnosis, preferably within 4 weeks but no later than within 6 weeks.
    - These have a very high cure rate with craniospinal radiotherapy (>90% 10 year survival). For details of cranio-spinal irradiation see medulloblastoma guidelines

    - Dose and fractionation:

	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Brain	15	1.6Gy	24Gy	3
Spine	15	1.6Gy	24Gy	3
Tumour boost	10	1.6Gy	16Gy	2
Total dose to primary	25		40Gy	5

    - Radiotherapy planning for boost volume
        - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
        - All margins should be added using a 3D growth algorithm.
        - A 3 or 4 field optimised CT plan is used
        - Consider IMRT to enable bilateral temporal lobe sparing.
            - GTV = all visible residual tumour and /or tumour bed on T1 + gadolinium MRI images , plus 2mm where appropriate for MRI fusion uncertainty
            - CTV = GTV + 1cm
            - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- NGGCT (secreting tumours and embryonal carcinoma)

    - This group of tumours includes all those with elevated tumour markers in either serum or CSF (AFP > 25 ng/ml and/or ß-HCG > 50 IU/l) and any tumour with histological evidence of yolk sac tumor, choriocarcinoma or embryonal carcinoma.
    - Recommended treatment for nongerminomatous GCTs consists of 4 courses of chemotherapy followed by focal radiotherapy for localised tumours and craniospinal radiotherapy for metastatic disease.
    - **PIE Cisplatin, Etoposide and Ifosfamide**: **Radica**l
    - **This regimen is given as per the UKCCLG guidelines**.
        - **Cisplatin** 20 mg/m²/day iv days 1, 2, 3, 4, 5
        - **Etoposide** 100 mg/m²/day iv days 1, 2, 3
        - **Ifosfamide** 1500 mg/m²/day iv days 1, 2, 3, 4, 5
    - A total of 4 courses should be given at 21 day intervals, subject to count recovery, and should commence as soon as possible following diagnosis

    Premedication and supportive care:

Tests: FBC, U&ES, LFTs, Ca, Mg, PO4 and HCO3, AFP and bHCG baseline and before each cycle. GFR to measure Creatinine clearance pre-cycle 1 and 3. Audiometry every 2 cycles.

For cotrimoxazole prophylaxis during chemo and 3/12 post treatment

- Surgery should be considered for residual tumour after chemotherapy
  - If after the second cycle of chemotherapy the tumour markers have fallen but the tumour is growing, or if residual tumour is present at the end of chemotherapy, surgery should be considered.
  - Resection may also be considered after radiotherapy for residual tumour, not resected or resectable after chemotherapy.
  - Interim analysis of SIOP CNS GCT 96 suggests that the risk of relapse is greater for patients who are not in complete remission at the end of treatment.
- Radiotherapy
  - This should start as soon as possible after the last course of chemotherapy usually within 3-4 weeks following adequate haematological recovery (and after surgery if undertaken)
  - For localised disease at diagnosis, craniospinal irradiation is not indicated. Radiotherapy is delivered **only** to the tumour bed at a total dose of 54 Gy in 30 fractions of 1.8 Gy over 6 weeks.
  - CSRT is indicated for metastatic disease, followed by a boost to the primary tumour and all sites of macroscopic intracranial and /or spinal metastatic disease.

  - <u>Dose and fractionation:</u>

	Number of #	Dose per fraction	Total dose	Duration (weeks)
Brain	20	1.5Gy	30Gy	4
Spine	20	1.5Gy	30Gy	4
Tumour boost brain	15	1.6Gy	24Gy	3
Tumour boost spine	10	1.6Gy	16Gy	2
Total dose	35 (brain) 30 (spine)		30Gy CSA 46Gy spinal mets 54Gy to primary intracranial mets	7

- Radiotherapy planning
  - CSRT as per medulloblastoma guidelines
  - Focal brain RT (primary or mets)
    - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used
    - Consider IMRT to enable bilateral temporal lobe sparing.

- GTV = all visible residual tumour and /or tumour bed on T1 + gadolinium MRI images , plus 2mm where appropriate for MRI fusion uncertainty
- CTV = GTV + 1cm
- PTV = CTV + 3mm.

- **At the end of treatment** (around 4 weeks following radiotherapy)
  - MRI of the brain (and spine if metastases were present at diagnosis)
  - CSF-cytology, if positive at the last evaluation
  - AFP and ß-HCG, measured in serum (and CSF if possible) if previously raised
  - Ophthalmologic examination, as indicated
  - Audiogram
  - FBC, LFTs, endocrine evaluation

- Follow up
  - MRI with contrast – every 4 months for 2 years then yearly
  - AFP and ß-HCG (secreting tumours)
    - Monthly for 1 year
    - Every 4 months in 2nd year
    - Yearly thereafter

- Treatment at relapse
  - Germinomas and non-germinomatous lesions maybe salvaged with chemotherapy such as BEP or POMB-ACE.

2.7.3. Pineal region tumours

- These are either:
  - Pineal parenchymal tumours
    - pineocyctomas (grade 1)
    - intermediate pineal tumours (grade II or III)
    - pineoblastomas (grade IV) **(discussed in Adult PNET section)**
  - Germ cell tumours (GCT) (discussed in GCT section)
  - All patients should be considered for a biopsy to obtain confirmation of the diagnosis.
  - Low-grade lesions should if possible be resected.
  - The role of resection in high-grade lesions remains controversial, but may result in longer survival
  - The use of ventricular-peritoneal shunts in patients may be associated with an increased risk of systemic metastases.
  - All patients with a pineal gland lesion should have tumour markers taken (CSF and serum)
  - All patients should have a pre-operative cranial MRI performed

- <u>Management Algorithm</u>

Pineocytoma	Surgical resection followed by surveillace
Grade II/III (intermediate differentiation) pineal parenchymal tumours	Sugical resection followed by consideration of adjuvant radiotherapy (either focal or CSRT)

- Pineocytomas are treated by surgery alone
- Pineal parenchymal tumors of intermediate differentiation
    - Rare
    - Reported cases include long-term survivors and also cases with leptomeningeal dissemination
    - Management has varied from surgery alone to craniospinal radiotherapy.
    - Radiotherapy should start within 4 weeks of diagnosis

- Radiotherapy planning
    - 3D planning using CT data
    - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences in axial, sagittal and coronal planes)
    - Routinely consider the use of IMRT to reduce the dose to the temporal lobes bilaterally (for the phase 2 primary boost or single phase focal treatment)
    - All margins should be added using a 3D growth algorithm.
    - Dose:
        - Young, good PS
            - Phase 1 CSA: 36Gy in 20 fractions over 4 weeks (1.8Gy per fraction)
            - Phase 2 Primary tumour boost: 18Gy/ 10 fractions / 2 weeks
        - Or consider single phase, focal RT to primary 54Gy in 30 fractions over 6 weeks

    - 1) CSRT
        - See previous section on Adult PNET for details

    - 2) Single phase focal RT or for Phase 2 boost after CSRT
        - GTV = all visible enhancing tumour on T1 + gadolinium MRI images (plus 2mm where appropriate for MRI fusion uncertainty)
        - CTV = GTV + 1cm
        - PTV = CTV + 0.3 – 0.5cm (depending on departmental set up tolerances)

- Clinical Trials:
    - There are currently no trials open for these patients

- Chemotherapy
    - There is currently no evidence for the role of chemotherapy in these patients

2.7.4. CNS lymphoma

- This is usually a diffuse B cell lymphoma.
- A biopsy should be performed.
- There is no proven advantage for more extensive surgery

- The following staging investigations should be performed:
    - FBC, U&U, LFT, LDH
    - Slit lamp examination of eyes
    - CSF cytology (pre-operative of >14 days post biopsy) and protein
    - HIV test (arranged through infectious diseases department)

  - CT thorax, abdomen and pelvis should be performed if there are symptoms or signs of systemic disease, though the yield is low
  - In men, testicular ultrasound should be considered as testicular lymphoma has a propensity for relapsing in the brain.

- The main prognostic factors for PCNL are performance status and age.
  - Poor performance status (KPS<70) and >age 60
    - This group has a poor prognosis and are at greater risk from late neurotoxicity from combined chemo-radiation. Radiotherapy used alone maybe the most appropriate treatment.
    - WBRT with doses ranging from: 40Gy in 20 fractions; 36 Gy in 20 fractions with an option for a 9 Gy boost to the tumour bed where clinically indicated; 30Gy in 10 fractions or 20Gy in 5 fractions in very poor PS patients

  - Good performance status (KPS >70) and age < 60
    - This group has the best prognosis and should be considered for intensive treatment. Chemotherapy followed by radiotherapy appears to offer the best chance of long-term survival. The optimal chemotherapy regime has yet to be established.
    - Consolidation WBRT, up to 45 Gray total dose should be considered in patients under the age of 60 responding to MTX-based chemotherapy: to patients unless there is a significant neurocognitive deficit following chemotherapy, but in patients aged 60 years or over, the neurocognitive side-effects are more likely to outweigh the potential benefits

- These patients will be managed primarily by the haematologists. Neurosurgical involvement may be appropriate to establish a histological diagnosis but definitive treatment is not neurosurgical.
- If after discussion at the haematology MDT radiotherapy is the preferred treatment, timely referral to an appropriate Clinical Oncologist who specialises in Lymphoma or CNS malignancy will be made. Treatment may be given with radical or palliative intent dependent on fitness for treatment.

- Clinical Trials:
  - **IELSG 32 :** a randomised phase II trail on primary high dose chemotherapy followed by brain RT v high dose chemotherapy with autologous stem cell transplant in newly diagnosed PCNSL - currently open at UCLH, RFH and BHR

2.7.5. Choroid Plexus tumours

- Choroid plexus papilloma – resection alone should be sufficient
- Choroid plexus carcinoma – resection followed by involved field radiotherapy to a dose of 54Gy in 30 fractions.

2.8. Spinal Cord tumours

2.8.1. Primary spinal cord tumours

- Benign
    - These include meningiomas and neurofibromas and are usually best managed by surgery when symptoms justify the risks.
- Malignant
    - These tumours are invariably intrinsic to the spinal cord and will require laminectomy for access.
    - Gliomas will usually lend themselves to biopsy only and occasionally debulking. The mainstay of treatment will then be radiotherapy.
    - Ependymomas may be removable using microsurgical techniques.

- The most frequently seen lesions are gliomas (high or low grade) and ependymomas (high or low grade).
- Patients in whom a spinal tumour is suspected should be considered for biopsy or resection.
- If the pathology suggests a high-grade lesion the patient should undergo a brain MRI to exclude a second lesion / primary

- Indications for radiotherapy:
    - Ependymoma – see ependymoma guidelines
    - Low grade gliomas – these should receive radiotherapy when they have progressive symptoms.
    - High grade gliomas – should receive immediate radiotherapy
        - GBM – should receive chemoradiation and adjuvant TMZ

- Radiotherapy planning:
    - 3D planning using CT data
    - Planned using CT data fused with pre-operative and post-operative MRI images (T1 plus gadolinium and T2 sequences) where possible if there has been significant resection
    - All margins should be added using a 3D growth algorithm.
    - A 3 or 4 field optimised CT plan is used

    - Dose:
        - Spinal tumours: 50.4Gy in 28 daily fractions over 5.6W
        - Cauda Equina: 54Gy in 30 daily fractions over 6 weeks
    - GTV
        - Defined from the planning CT data and preoperative images from MRI fusion. The postoperative images are also useful when there has been a significant resection.
        - Any MRI fusion uncertainty (up to 2mm should be incorporated in the GTV)
    - CTV
        - Spinal and Cauda Equina
            - CTV = GTV + 1.5cm (superiorly and inferiorly) for LGG.
            - CTV = GTV + 2.5cm (superiorly and inferiorly) for HGG using T1+ Gadolinium weighted sequences.
            - Include entire spinal canal axially, ensuring coverage laterally of neural foramina
            - Inferiorly, may be appropriate to cover to bottom of thecal sac for lumbosacral lesions
    - PTV
        - PTV = CTV + 0.5cm

- Chemotherapy
    - GBM are treated with chemoradiation and adjuvant TMZ as per the Stupp regimen (described in HGG section above)
    - There is no role for primary chemotherapy in LGG and G3 glioma of the spinal cord

- Treatment at relapse
    - If the imaging suggests tumour progression and the patient remains sufficiently fit the following treatment options should be should be considered:
        - 1) Re-resection: when this would provide the best palliation.
        - 2) Palliative chemotherapy. See brain tumour section above
            - If patients with G4 tumours have had more than 6 months since completing adjuvant chemotherapy they are usually retreated with temozolomide (150-200mg/m2 D1-5 q 28/7) for up to 12 cycles but usually six - beyond this there is an increased risk of myelodysplasia and other haematological effects.
            - Chemo-naïve G3 patients will be offered temozolomide at first relapse.
            - For those with a shorter disease free interval following previous TMZ the following regimens may be offered:
                - 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 (*see chemotherapy appendix*).
                - Single agent lomustine
                - Bevacizumab (when patients live in an area where this is available via the CDF)
                - Single agent Carboplatin (*see chemotherapy appendix*)
        - 3) Re-irradiation
            - Very rarely considered in spinal cord tumours due to the lower radiation tolerance compared to brain

2.8.2. Metastatic spinal cord compression

Please refer to the Acute Oncology guidelines

- Most of these are best managed with high dose corticosteroids and palliative radiotherapy.
- Where the diagnosis is uncertain a CT guided biopsy should precede radiotherapy if possible.
- Surgery will be confined to single or adjacent level disease where conservative measures are deemed inappropriate or are failing.
- Surgery may include spinal decompression and/or stabilisation.

2.9. Brain metastases

- There are several groups of patients with brain metastases needing consideration by the NSMDT:
    - Patients presenting with cerebral metastases as the first sign of malignant disease and where surgery is required to clarify the diagnosis

  - Patients in whom imaging findings are in doubt following neuro-radiological assessment
  - Patients presenting with solitary metastases, with a favourable prognosis warranting consideration of neurosurgical intervention.
  - Patients with 1-3 cerebral metastases (newly diagnosed or recurrent) with a favourable prognosis.
  - Patients with symptomatic brain metastases that may benefit from palliative neurosurgical intervention, providing the prognosis warrants aggressive intervention

- Favourable Prognostic Group criteria are adapted from recursive partitioning analysis performed on 1200 patients with brain metastases by Gasper et al (1997):
  - Primary/Systemic disease controlled
  - WHO performance status 0-1
  - Age less than 65 years

- All patients should have MRI-based imaging of the brain with gadolinium unless there are specific contraindications
- For patients with suspected brain metastases e.g. previous history of cancer, multiple lesions, further staging investigations should be carried out prior to referral:
  - Chest X-ray
  - CT scan Thorax, Abdomen, Pelvis
  - Other specific investigations e.g. bone marrow aspirate in cases of suspected lymphoma

- As a general rule, patients presenting with brain metastases can be divided in three management / treatment groups.
  - Group 1:
    - Aggressive local treatment with surgical resection or stereotactic radiosurgery is appropriate for patients with:
      - 1-3 metastases (but may be changed to an upper volume limit)
      - Good PS (KPS>60)
      - Stable or low volume extra-cranial disease.
    - Treatment options are:
      - Surgical excision
      - stereotactic radiosurgery
      - A single fraction using highly conformal RT (IMRT) may be considered for solitary metastases
        - not suitable for surgical excision or stereotactic radiosurgery
        - or where PCT funding for stereotactic radiosurgery is refused.
    - In such patients, Whole Brain Radiotherapy (WBRT) can be delayed until progression, after consideration of further aggressive local treatment. Tumour bed radiotherapy may be offered post-operatively where there is concern regarding completeness of excision.

  - Group 1a:
    - Large solitary metastases not suitable for aggressive local treatment may be offered WBRT, plus / minus a boost to the tumour.

  - Group 2:

        - In all other patients, consider WBRT if appropriate
        - Dose regimen will depend on tumour histology and PS
            - 30Gy in 10 daily fractions
            - 20Gy in 5 daily fractions
            - 12Gy in 2 fractions over a week
        - It may also be appropriate to consider palliative debulking of large tumours causing significant oedema, compression of adjacent structures, and / or hydrocephalus (shunting should also be considered).
        - However, there may be cases where best supportive care only is most appropriate.

    - Group 3:
        - Patients with multiple brain lesions with no known cancer diagnosis, and no primary site to biopsy on extracranial staging may be offered a diagnostic brain biopsy. Biopsies should only be offered to patients who are considered fit enough for oncological treatment.

- All new diagnoses will be referred into the primary cancer site-specific MDT (location based on patient preference and postcode) for management of the primary cancer.

- The Group 1 patients will remain under the joint care of the primary site oncologist and the brain metastases clinic (see below).

- Group 2 and 3 patients will be both treated and followed up by their primary site oncology team only.

- The UCLH Brain Metastases Clinic
    - This is a fortnightly multi-disciplinary clinic (Consultant Clinical Oncologist, Consultant Neurosurgeon and a neuro-oncology Clinical Nurse Specialist) only for patients with brain metastases, run as single service collaboration between UCH and NHNN.
    - Referrals are made via the MDT co-ordinator, and all patients referred will be discussed at the weekly neuro-oncology MDTM at NHNN. It is specifically for patients with brain oligo-metastases (up to 5).
    - Recent data supports use of surgical resection or radiosurgery in good prognostic groups.
    - We now know that:
        - aggressive focal treatment can improve survival
        - adjuvant whole brain radiotherapy (WBRT) following surgical resection or radiosurgery does not improve survival, and can be delayed.
    - Aggressive local treatment with surgical resection or radiosurgery is appropriate for patients with:
        - 1-5 metastases
        - Dural based or intra-axial or skull/bony lesions; posterior fossa or supratentorial; skull base lesions
        - Good performance status (KPS>60)
        - Stable or low volume extra-cranial disease (recent re-staging required)
        - All pathologies except lymphoma.
    - For this patient group, the protocol is 3 monthly MRI follow-up after local treatment, withholding WBRT until progression.

- Planning and dose schedules for palliative brain radiotherapy
    - Single fraction to solitary metastasis:
        - 3D planning using CT data fused with diagnostic MRI images (T1 weighting plus Gadolinium)
        - GTV = enhancing lesion on T1 weighted + gadolinium MRI images (incorporating 2mm for MRI fusion uncertainty where appropriate)
        - PTV = GTV + 3mm
        - Routinely consider the use of IMRT
        - 16Gy in 1 daily fraction
    - WBRT (virtual simulation of lateral parallel opposed fields covering whole brain with a 1cm clearance on the outer table of the skull and base of skull, down to bottom of C2):
        - 30Gy in 10 daily fractions over 2 weeks in good performance status breast cancer
        - Consider 20Gy in 5 daily fractions over 1 week in all other histologies
        - Consider 12Gy in 2 fractions a week apart if poor performance status
    - Supratentorial Boost (may use 3D planning using CT data and MRI fusion to enable the use of an optimised 2-3 field plan):
        - 10Gy in 5 daily fractions over 1 week
    - Posterior Fossa boost (virtual simulation of opposing lateral fields covering posterior fossa down to bottom of C2: MRI fusion can aid outlining of cerebellum and brainstem as CTV to ensure adequate coverage):
        - 20Gy in 5 daily fractions over 1 week

- Chemotherapy
    - Concurrent chemotherapy is not standard therapy and any delivery of concurrent treatment (either chemotherapeutic or targeted therapy) should be conducted within the setting of a clinical trial.
    - Chemotherapy use for control of extracranial disease should follow the guidelines and work instructions for that tumour site.

3. Follow up

When patients finish their treatment a personal follow up care plan is discussed and agreed after discussion with the NSMDT involved in their care. The GP is informed of this in clinic correspondence.

The neurosurgical teams will take responsibility for the patients following surgery until discharge from hospital and until patients have been returned to the care of their referring clinician. The surgical team can be contacted during normal working hours or the neurosurgical SpR on call for post-operative surgical advice.

Patients who have had surgery will have a routine follow up at 6 weeks unless they have been referred to another team for further treatment.

3.1. Brain and rare CNS tumours

- Patients with high grade gliomas or metastases are followed up at three monthly intervals until progression or death. Patients with low grade gliomas are followed up with an MRI scan at 6 monthly or yearly intervals until progression.
- All patients receiving active or radical treatment will have a baseline scan 6-12 weeks after treatment and follow up imaging as appropriate. Subsequent follow up and possible discharge (with an open appointment and according to availability of community support services) is considered where appropriate according to the patient's wishes e.g. community care team, hospice, and palliative care team. Ad hoc review can be mobilised at any time via liaison usually with the CNS/key worker.

3.2. Pituitary tumours

For most patients periodic reassessment of endocrine, ophthalmic and radiological appearances will be required, especially in those who have undergone surgical intervention and/or received radiotherapy.

Patients with small functioning tumours that are completely excised,with biochemical remission demonstrable post-operatively may be recommended for a combination of clinical and biochemical surveillance with repeat imaging only in the event of clinical concern.

Patients with functioning (macroadenoma) and non-functioning pituitary tumours may have:

- A follow-up MRI, pituitary function test and ophthalmology assessments at 3 months with an outpatient appointment. A further outpatient appointment and pituitary function tests at 6 months.
- Follow up MRI scans and/or ophthalmology assessments at 12, 24, 48 and 72 months with MRI scans 5 yearly thereafter.

The exact timing of follow-up MRI/CT scans should be determined by the local pituitary specialist NSMDT on a case by case basis. As a general rule of thumb the first postoperative scan is typically carried out between 3 to 6 months (early post-operative scans may be difficult to interpret due to post-operative inflammatory changes). Thereafter, it is reasonable to perform 'routine' surveillance scans as above and the decision to continue long-term radiological surveillance should be made on an individual case basis.

All patients should undergo repeat ophthalmological assessment post-surgery, and periodically (e.g. annually) thereafter (which may be undertaken via their optician) as dictated by their initial presentation and extent of residual tumour.

Endocrine re-evaluation should be tailored to the individual. For example, an annual assessment for biochemical cure is undertaken initially in all patients with functioning tumours.

Baseline reassessment is also indicated annually in all patients, and other measures may be used to help gauge the adequacy of pituitary replacement therapy periodically (e.g. hydrocortisone day profile). However, dynamic pituitary function testing may also required on an ongoing basis (e.g. on alternate years) in patients apparently eupituitary following radiotherapy.

The majority of these visits will be expected to occur at the local referring centre.
Further follow up at the neurosurgical centre will only be made if deemed necessary after discussion at the post op NSMDT.

3.3. Skull base tumours

As a general rule patients with skull base tumours require follow-up as an outpatient with an MRI scan at 8 to 12 weeks, with further outpatient appointments and MRI scan at six months and then yearly for 5 years. If their condition remains stable, patients can be imaged 3-5 yearly. This subsequent follow up may take place at the referring hospital.

3.4. Clinical Trials patients

Trial patients are followed up at intervals and with investigations as indicated by the trial protocol.

APPENDIX 1: DOSE FRACTIONATION SCHEDULES

TUMOUR TYPE	DOSE FRACTIONATION SCHEDULE
GBM	60Gy/30#/6W (radical) 30Gy/6#/2W (palliative) 40Gy/15#/3W (palliative)
G3 Glioma	59.4Gy/33#/6W (radical) 60Gy/30#/6W (radical) 30Gy/6#/2W (palliative)
G1/G2 Glioma	54.9Gy/30#/6W 54Gy/30#/6W 50.4Gy/28#/5.5W (G1 optic pathway)
Brainstem Glioma	54Gy/30#/6W
Gliomatosis cerebri	Consider up to 54Gy/30#/6W for WBRT
Meningioma	G1: 50.4Gy/28#/5.5W G2: 50-55Gy/28-30#/5.5-6W G3: consider 60Gy/30#/6W
Haemangiopericytoma	Consider up to 60Gy/30#/6W
Schwannoma	50.4Gy/28#/5.5W
Pituitary tumours	45/25#/5W 50.4Gy/28#/5.5W (significant residual)
Craniopharyngioma	50.4Gy/28#/5.5W
Ependymoma	Spinal: 50.4Gy/28#/5.5W Cauda Equina: 54Gy/30#/6W Intracranial:55-60Gy/30#/6W
Chordoma and Chondrosarcoma	65-70Gy/39#/8W
PNET (medulloblastoma, pineoblastoma, sPNET)	CSA: 36Gy/20#/4W Boost: 18Gy/10#/2W
Germinoma	CSA: 24Gy/15#/3W Boost: 16Gy/10#/2W
NGGCT (malignant)	Localised: 54Gy/30#/6W Metastatic: CSA 30Gy/20#/4W Primary boost 24Gy/15#/3W Boost spine mets 16Gy/10#/2W
Pineal parenchymal tumours G2/3	54Gy/30#/6W **or** CSA: 36Gy/20#/4W Boost: 18Gy/10#/2W
Primary CNS lymphoma	40Gy/20#/4W 36Gy /20# /4W +/- 9Gy boost 30Gy/10#/2W 20Gy/5#/1W (Very poor PS)
Choroid plexus carcinoma	54Gy/30#/6W
WBRT	30Gy/10#/2W 20Gy/5#/1W 12Gy/2#/1W

APPENDIX 2: TOLERANCE DOSES TO CRITICAL STRUCTURES

Critical Structure	Tolerance Dose in 2Gy per fraction
Lens	6Gy
Optic nerve	Benign disease: 50Gy High grade tumours:
Optic chiasm	Benign disease: 50Gy High grade tumours:50-60Gy
Retina	45Gy
Brainstem	55Gy
Cochlea	48Gy
Brain	60Gy (54Gy/30# at 1.8Gy per# for gliomatosis cerebri)
Spinal Cord	48Gy
Cauda Equina	60Gy
Parotids	24Gy mean dose

When treating with IMRT, then a PRV (Planning at Risk Volume) is created by adding a 3mm margin to the critical structure. The tolerance dose is then applied to the PRV.

APPENDIX 3: CHEMOTHERAPY REGIMENS

Regimen	Prescription
PCV	**Procarbazine** 100mg/m^2 (max 200mg) PO OD D1-10 **CCNU** (Lomustine) 100mg/ m^2(max 200mg) PO D1 **Vincristine** 1.4mg/ m^2(max 2mg) IV D1 6 weekly for 6 cycles Lifetime total doses of CCNU exceeding 1000mg/m2 may have an increased risk of pulmonary toxicity.
Temozolomide (chemoradiation)	75 mg/m^2 PO daily for 6 weeks (including weekends) with Cotrimoxazole (Septrin) 960mg x3 per week as Pneumocystis prophylaxis.
Temozolomide adjuvant	6-8 cycles of adjuvant **TMZ** commences 4 weeks after chemoradiation. 150mg/m^2 PO d1-5 q4w for first cycle. Then 200mg/m^2 for subsequent cycles if tolerated.
Temozolomide	150mg/m^2 PO d1-5 q4w for first cycle if had previous chemotherapy Then 200mg/m^2 for subsequent cycles if tolerated. Can start at 200mg/m^2 if chemo-naive
Single agent Lomustine	100mg/m^2 PO od q6/52
Single agent Carboplatin	AUC 4-6 IV (depending on PS) q3-4/52
Packer	The first cycle starts 6 weeks after the end of radiotherapy, provided count recovery has occurred. **Vincristine** 1.5 mg/m2 (Max. 2 mg) IV on d1, 8, 15 **Cisplatin** 70 mg/m2 IV D1 **Lomustine** 75 mg/m2 PO D1 6-8 courses q6/52
PIE	**Cisplatin** 20 mg/m^2/day days 1, 2, 3, 4, 5 **Etoposide** 100 mg/m^2/day days 1, 2, 3 **Ifosfamide** 1500 mg/m^2/day days 1, 2, 3, 4, 5 4 cycles q3/52

APPENDIX 4: ABBREVIATIONS AND SYMBOLS

GBM	Glioblastoma multiforme
HGG	High grade glioma
LGG	Low grade glioma
PCNSL	Primary CNS lymphoma
TYA	Teenage Young Adult
CSA	Craniospinal Axis
CSRT	Craniospinal Radiotherapy
RT	Radiotherapy
WBRT	Whole brain radiotherapy
IMRT	Intensity modulated radiotherapy
#	Fraction
Gy	Gray
GTV	Gross tumour volume
CTV	Clinical Target volume
PTV	Planning Target volume
OAR	Organ at risk
PRV	Planning at risk volume
iMRI	intra-operative MRI
MDT	multi-disciplinary team
KPS	Karnofsky Performance Status
TMZ	Temozolomide

APPENDIX 5: REFERENCE DOCUMENTS

Radiosurgery
NCAT: Service Specification Stereotactic Radiosurgery and Stereotactic radiotherapy for the Cranium and Skull Base (November 2008)

Gliomas
Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial
Van den Bent; Lancet. 2005 Sep 17-23;366(9490):985-90

Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma
Stupp: N Engl J Med. 2005 Mar 10;352(10):987-96.

Management of patients aged more than 60 years with malignant glioma: good clinical status and radiotherapy determine outcome.
Whittle: Br J Neurosurg. 2002 Aug;16(4):343-7

Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study
Shaw: J Clin Oncol. 2002 May 1;20(9):2267-76

Successful treatment of low-grade oligodendroglial tumors with a chemotherapy regimen of procarbazine, lomustine, and vincristine
Stege: Cancer. 2005 Feb 15;103(4):802-9

Adjuvant procarbazine, lomustine and vincristine chemotherapy in newly diagnosed anaplatic oligodendroglioma: long-term follow up of EORTC brain tumour group study 26951
Van den Bent: J Clin Oncol. 2013 Jan 20:13(3):344-50

Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: longterm results of RTOG 9402.
Cairncross. J Clin Oncol. 2013 Jan 20:13(3):337-43

Ependymomas
Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center
Akyurek J NeuroOncol. 2006 Nov;80(2):177-83

Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients.
Metellus Brain 2007 130 1338-49

Influence of radiotherapy treatment concept on the outcome of patients with localized ependymomas
Combs IJROBP 2008 71(4) 972-978

Pituitary and craniopharyngiomas
Radiotherapy for pituitary adenomas: long-term efficacy and toxicity.
Erridge Radiother Oncol. 2009 Dec;93(3):597-601.

Temozolomide: a novel treatment for pituitary carcinoma.
Lim Lancet Oncology. 2006;7(6):518-20.

Temozolomide Treatment for Aggressive Pituitary Tumors: Correlation of Clinical Outcome with O-6-Methylguanine Methyltransferase (MGMT) Promoter Methylation and Expression.
Bush Journal of Clinical Endocrinology & Metabolism. 2010;95(11):E280-E90.

Intracranial germ cell tumours
Interim Guidelines for the Treatment of Intracranial Germ Cell Tumours following the Closure of SIOP CNS GCT 96
UKCCSG Germ Cell Tumour Working Group

PNET
Results of a Randomized Study of Preradiation Chemotherapy Versus Radiotherapy Alone for Nonmetastatic Medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study
Taylor Journal of Clinical Oncology, Vol 21, No 8 (April 15), 2003: pp 1581-1591

Hyperfractionated Accelerated Radiotherapy in the Milan Strategy for Metastatic Medulloblastoma
Gandola Journal of Clinical Oncology, Vol 27, No 4 (February 1), 2009

CCLG standard risk medulloblastoma treatment guidelines, Version 2, January 2011

BNOS 2010: Guidelines on the diagnosis and management of Adult PNETs

CNS Lymphoma

BNOS 2010: Guidelines on the diagnosis and management of primary CNS and intra-ocular Lymphoma (PCNSL)

Brain metastases

Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical rsection of one to three cerebral metastases; results of the EORTC 22952-26001 study
Kocher J Clin Oncol 29(2):134-41

Pineal Region
BNOS 2010: Guidelines on the diagnosis and management of Pineal area tumours

Radiation Dose effects in the brain
Use of normal tissue complication probability models in the clinic
Lawrence Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10–S19, 2010

Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up.
Douw Lancet Neurol. 2009 Sep; 8(9):810-8. Epub 2009 Aug 7.

Radiation dose-volume effects in the brain.
Lawrence Int J Radiat Oncol Biol Phys. 2010 Mar 1; 76(3 Suppl):S20-7

Neuropsychometric evaluation of long-term survivors of adult brain tumours: relationship with tumour and treatment parameters.
Gregor Radiother Oncol. 1996 Oct;41(1):55-9.

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole brain irradiation: a randomised controlled trial.
Chang Lancet Oncol 10 (11): 1037-44