



British Neuro-Oncology Society

Rare Brain and CNS Tumours Guidelines

In collaboration with the
National Cancer Action Team

Guidelines on the diagnosis and management of Adult PNETs

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Guidelines on the diagnosis and management of Adult PNETs

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Introduction

The Improving Outcomes for People with Brain and other CNS Tumours (published in June 06) recommended establishing a working group for rarer cancers including adult patients with central nervous system PNETs. The group should produce guidelines allowing a nationally standardised treatment approach in adult patients according to agreed protocols. In addition the group should provide guidance on clinically relevant national research programs. The British Neuro-Oncology Society in conjunction with the Cancer Action Team set up a task force between 2009 and 2010 based on a multidisciplinary approach to provide this guidance.

Summary of key recommendations

1. The definitive surgical management of patients with presumed primary adult CNS PNETs must only be undertaken by designated oncology neurosurgeons in designated neurosurgical centres.
2. The postoperative non-surgical management of patients with primary adult CNS PNETs must be delivered in primary treatment centres having commissioned services for paediatric and/ or teenage and young adults.
3. Preoperative MRI imaging of the brain and whole spine, including post contrast imaging, for cases of suspected PNET is vital for accurate tumour evaluation and staging. This must be performed in line with nationally recommended protocols.
4. Follow-up of patients with primary adult CNS PNETs should be provided based on patient's preference assuming appropriate services are available.
5. Neurosurgical units providing the definitive surgery must have pathways in place to allow regular tissue banking and participation in local and national audits.
6. Timely referral to rehabilitation and supportive care services is imperative and is dependent on rapid, comprehensive communication between medical and AHP staff.
7. Regular long-term follow-up in conjunction with an endocrinologist should be provided.
8. It is good practice for tissue surplus to diagnostic requirement should be banked as frozen samples with a view to further molecular analysis.

Background

Primary central nervous system (CNS) tumours are considered as rare malignancies due to the overall low incidence rate and intrinsic biological diversity. Incidence rates of primary CNS malignancies vary depending on age. While in adults gliomas represent the largest subgroup of primary malignant central nervous system tumours, the commonest malignant CNS tumour in childhood are primitive neuroectodermal tumours (PNETs). Adult PNET is rare and accounts for under 1% of primary CNS malignancy. Whilst exceptional cases of supratentorial PNET have been reported the vast majority of adult PNETs are (like the paediatric population) located in the posterior fossa. The annual incidence rate has been reported as 0.05 per 100,000 per year. PNETs are primitive neuronal tumours accounting for approximately 20% of paediatric malignant brain tumours. There are approximately 80 cases arising in childhood each year in the UK. The majority arise in the cerebellum where they are referred to as medulloblastoma (MB). PNETs may also arise in the supratentorial area (supratentorial PNET, sPNET) or in the pineal area (pineoblastoma). PNETs have a propensity for spread via the cerebro-spinal fluid (CSF), and up to 35% present with radiological evidence of leptomeningeal spread. Patients with disseminated disease have a significantly worse prognosis. The presence of metastatic disease at presentation as diagnosed by the presence of meningeal enhancement on MRI of the brain (Chang Stage M2) or spine (Chang Stage M3) carries a significantly worse prognosis. The negative prognostic significance of Chang Stage M1 disease, in which tumour cells are found within the CSF without radiological evidence of metastasis, is now widely accepted by the North American Children's Oncology Group (COG) and SIOP brain tumour sub committee.

PNETs are characterised by their radiosensitivity and chemosensitivity. While there is a paucity of clinical data available to define the optimal treatment strategy for PNETs in adults, management strategies for children are based on the results of a series of consecutive European and North American multi-institutional trials using upfront craniospinal axis (CSA) radiotherapy (RT) and the routine use of concomitant and adjuvant chemotherapy. Postoperative radiotherapy remains a cornerstone in the management of primary CNS PNETs in order to achieve long term tumour control. Other than selected infants series no published study omitting CSA RT as part of the therapeutic strategy has been able to document a clinically acceptable survival rate and has never been pursued in adult patients with PNETs.

In the UK research for children with PNETs is co-ordinated via the clinical studies CNS subgroup (CSG CNS sub group) of the National Cancer Research Institute (NCRI) and Children's Cancer and Leukaemia Group (CCLG). The results of consecutive prospective clinical trials both in the UK and Europe, which have been either lead by the UK working group or where the UK has been a major contributor, as well as studies from the US have established the benefit of combined modality treatment over radiotherapy alone in paediatric patients with localised disease at diagnosis. In addition for children a lower CSA dose (23.4 Gy) is prescribed compared to the current adult standard. In the adult setting a "standard" dose of 35-36 Gy to the CSA without routine use of chemotherapy is current standard practise in the UK. The benefit of chemotherapy in high risk (metastatic disease) remains controversial both in the paediatric and adult setting. The question of a

prospective study for adults with PNETs has been discussed within the EORTC and the UK, but none has been established to date or in preparation. Published experience for adult patients with PNETs is based on retrospective studies comprising small patient numbers and varying treatments regimens over several decades during which diagnostic procedures, neurosurgical procedures and radiotherapy techniques have changed considerably. In adults the standard management post surgery remains at present the use of postoperative radiotherapy alone. The reported 5 year survival for children with SR medulloblastoma, which constitutes the largest single subgroup of PNETs, is today in the range of 80-85%. Comparable publications reporting outcome of adult populations vary between 50% and 80% but are generally lower than those expected for children.

In addition to the fact that prospective clinical trial data are missing supporting the evidence of a survival benefit for patients with localised PNETs is the fact that the toxicity issues of a combined modality treatment are different in adults compared with children. Young children experience significant long-term neuropsychological consequences of therapy which are age and radiation dose dependant. In addition endocrine and growth deficiencies are of significant clinical relevance in this age group. All current paediatric protocols have been attempting to reduce the dose of craniospinal radiotherapy as one means of trying to ameliorate the long-term sequelae of therapy. The currently established standard dose of CSA RT in children is 23.4 Gy/ 13# compared to 35 Gy/ 21# in adults. For adults there is no convincing rationale for craniospinal radiotherapy dose reduction strategies as they are employed in paediatric protocols. In addition both intensive pre-RT and / or post-RT chemotherapy protocols, as used in children, are difficult to deliver in the adult population. In paediatric patients with standard risk medulloblastoma the current perceived gold standard is the use of upfront craniospinal radiotherapy with concomitant and eight cycles of adjuvant chemotherapy ("PACKER" regime, consisting of cisplatin, vincristine, CCNU) (Packer JCO 99 and Packer JCO 2006). Evidence is lacking if the addition of PACKER chemotherapy to craniospinal radiotherapy improves overall survival compared to RT alone in adults particularly if a CSA dose of 35-36 Gy is prescribed. Additionally there are no prospective information of the acute and long-term toxicity in adults, particularly chemotherapy related nutritional and ototoxic side effects. There is good evidence from paediatric studies that the quality of planning and delivery of craniospinal radiotherapy for PNET impacts on outcome (ref: Carrie et al, 1999). Thus there is concern that centres who are not designated paediatric primary treatment centres and have less experience in delivering such a treatment poorer quality control which in turn may impact on outcome. Given the rarity of employing CSA RT this guideline should ensure a technically uniform approach to the highest standards regardless where adult patients with PNETs are treated.

Despite the use of chemotherapy, various large, multicentre studies including the CCG-921, HIT-91 and PNET-3 have only reported survival figures of between 30% and 40 % for patients with high risk features (M2/M3 status) at diagnosis (Zeltzer, Kortmann, Taylor 2005). Indeed for M2/M3 disease, no reasonably-sized North American or European study has shown survival in excess of 50 % where treatment consists of 35 to 36 Gy with addition of conventional chemotherapy. Thus in order to improve outcome, different approaches are required.

Recently, several studies have shown more encouraging results in the treatment of M2/M3 MB, with survival for M2/3 patients of > 50% (Gajjar 2006, Gandola 2008). It has to be noted that the backbone of the published - and unpublished paediatric studies in HR PNETs (e.g. POG 9031) - rely on a higher total dose of craniospinal axis radiation than used with conventional fractionation. The Milan group successfully treated patients up to the age 34 years with an aggressive combined modality approach including the use of hyperfractionated accelerated radiotherapy. With a median follow-up of 82 months 5 year PFS and OS were 72% and 73% respectively for the entire patient population. This is substantially higher than conventional approaches using radiotherapy alone. All study protocols use a combination of surgery, radiotherapy and chemotherapy of varying intensity. Based on the available data outcomes may be improved by an aggressive multimodality treatment including high dose chemotherapy with stem cell rescue.

Presentation and Diagnosis

Clinical

Neurological symptoms at presentation and their management

"There are few cohorts of patients whose presenting symptoms have been adequately described (table 1). Most (up to 4 in 5) will have headache but papers do not comment as to whether this is recurrent or raised intracranial pressure type. Around half will have an unstable gait due to truncal ataxia, a similar number will have nausea or vomiting, a quarter are dizzy and a fifth have visual symptoms. Up to 1 in 4 present with symptomatic hydrocephalus. This needs to be put in the context that most patients presenting between the age of 16-40 with gait instability and visual disturbance have demyelination (two orders of magnitude more common). These constitute a group of symptoms usually referred to neurologists who would MRI a patient with brainstem signs whereupon the diagnosis would be evident". "Beyond survival and recurrence the information on outcomes is even more sketchy. Clinicians have observed that these patients have neurological, cognitive and endocrinological problems but there is inadequate reporting."

- 1.Herrlinger JNeurol 2005 252 291-99
- 2.Brandes Cancer treatment reviews 1999 25 3-12
- 3.Spreafico Eur J of cancer 41 2005 1304-10
- 4.Kunschner Neuro-oncology2001
- 5.Abacioglu Int J Radiation Biol Phys 54(3) 855-60 2002
- 6.Chan Neurosurgery 47(3) 2000 623-32

Table 1:

60-83%	headache
40-45%	gait instability

42-73%	nausea and vomiting
23-27%	dizziness
11-27%	visual symptoms

Symptoms at presentation

Radiology

Imaging Features of Primitive Neuro-ectodermal Tumours (PNETs)

Most of the imaging features of PNETs have been described in childhood. There is one report describing the MR imaging features of PNETs in adults (Hajoun et al. MRI features of intracranial primitive neuroectodermal tumours in adults: comparing with histopathological findings, Journal of Huazhong University of Science and technology, Vol 24, pp 99-102, 2004). This reports a small series of cases describing the tumours as relatively large, well defined, lobulated tumours. In this series, there were heterogeneous tumours with cystic and necrotic areas with occasional intra tumoural haemorrhage and calcification. There was little surrounding oedema although most showed marked inhomogeneous contrast enhancement. Yet in general it is assumed that similar radiological features will be present in the adult group. There are certain suggestions in the literature however that the location of the tumour in the posterior fossa may vary between children and adults. Specifically lateral hemispheric medulloblastoma is said to be more common in adults and older children compared to young children. PNETs may also be seen in the supratentorial compartment but these are even rarer than the adult medulloblastoma. Similar imaging patterns may be seen supratentorially

On CT these tumours are often of increased attenuation on pre contrast imaging due to the high nuclear to cytoplasmic ratio. Following contrast there is usually (in 95% of cases) contrast enhancement, which is often variable. Haemorrhage can rarely be seen and some cystic regions with hypodensity may also be visible. Matrix calcification is present in a small proportion of cases. There is usually associated hydrocephalus when compression of the CSF pathways is present.

On MRI these tumours are typically iso to hypointense with grey matter on T1 weighted imaging and iso to hypointense on T2 weighted imaging. Approximately 95% of tumours will show contrast enhancement, particularly of the solid elements, although a relatively small proportion will show either very little or no contrast enhancement. Areas of heterogeneity within the tumour may be seen as a result of cysts, haemorrhage, calcification or necrosis. On diffusion weighted imaging there is restricted diffusion in approximately 95% of cases, but this is often patchy in nature. This manifests as increased signal on diffusion weighted imaging (DWI) with low signal on apparent diffusion coefficient (ADC) maps.

There is one report describing the MR imaging features of PNETs in adults (Haojun et al 2004). This is only a small series of cases that describes these as relatively large, well defined, lobulated tumours. They were heterogeneous tumours with cystic and necrotic areas with occasional intratumoural haemorrhage and calcification. There was little

surrounding oedema although most showed marked inhomogeneous contrast enhancement.

Haojun S, Xiangquan K, Haibo X, Liying X, Dingxi L (2004)

MRI features of intracranial primitive neuroectodermal tumors in adults: Comparing with histopathological findings

Journal of Huazhong University of Science and Technology -- Medical Sciences --Volume 24, number 1, pages 99-102.

Magnetic resonance spectroscopy may be of value. This shows a typical malignant pattern of intracranial tumour with a high choline to NAA ratio (3-4 to 1 ratio). It has also been recently described that taurine is seen to be elevated in PNETs on short echo spectroscopy studies.

Experience with perfusion imaging is as yet relatively limited but early studies shows markedly elevated tumoural cerebral blood volume (rCBV of approximately 5) and vascular permeability, which can be of assistance in differentiating these tumours from other cerebral tumours that may share conventional imaging characteristics but are of lower grade. Perfusion imaging may also be of value in assessing response to treatment interventions. .

Law, M, Kazmi K, Wetzel S, Wang E, Iacob C, Zagzag D, Golfinos JG, Johnson G.

Dynamic susceptibility contrast enhanced perfusion and conventional MR imaging findings for adult patients with cerebral primitive neuroectodermal tumors. AJNR 2004;25:997-1005.

Pre-operative imaging with MRI is important in order to assess CSF dissemination of tumour. CT will only demonstrate gross leptomeningeal dissemination. MRI is far more sensitive for this process. Typical sites of dissemination are locally within the sulci around the cerebellar folia but also within the supratentorial compartment including the suprasellar cistern, Sylvian fissures and within the orbital frontal sulci, and within the ventricles. CSF dissemination into the spinal canal is described in approximately 11% of children at presentation. Post contrast spinal imaging is therefore important in staging patients pre-operatively. Imaging of the spine in the immediate post operative phase is problematical due to the presence of blood products following surgery that could mimic leptomeningeal metastatic disease, and therefore should be done pre-operatively whenever possible.

The childhood cancer and leukaemia group (CCLG) have produced an imaging protocol to reflect best imaging practice and to introduce uniformity of imaging across the UK. This imaging protocol would certainly be applicable to adults with medulloblastoma as well as children. This protocol is currently undergoing revision but the suggested current protocol is as follows (courtesy of Dr Tim Jaspan – personal communication, appendix 1).

Staging and other investigations

The prognosis of PNETS is closely related to the extent of disease at diagnosis and to the dose and volume of radiotherapy. Patients with disseminated disease have a much poorer prognosis than standard risk patients.

With regard to the extent of disease, the presence of metastatic disease at presentation as diagnosed by the presence of meningeal enhancement on MRI of the brain (Chang Stage M2) or spine (Chang Stage M3) carries a poor prognosis. The prognostic significance of Chang Stage M1 disease, in which tumour cells are found within the CSF without radiological evidence of metastasis, is less clear, although several studies demonstrated that patients with M1 disease do have a worse prognosis than those without evidence of such tumour spread (M0). At present the poorer outlook for patients with M1 disease is accepted both by the North American Children's Oncology Group (COG), with these patients being classified as high-risk patients, and the SIOP Brain Tumour Committee, which accepts that patients with M1 disease cannot be regarded as standard risk.

Thus appropriate staging is a vital component of the management of patients with PNETs.

Radiology (MRI brain and spine pre-op)

Preoperative

Current standard practice in paediatric patients with primary posterior fossa tumours which could be suggestive of a primary malignant tumour must undergo a preoperative MRI scan of brain and spine. The childhood cancer and leukaemia group (CCLG) has produced an imaging protocol to reflect best imaging practice and to introduce uniformity of imaging across the UK. This imaging protocol would certainly be applicable to adults with pNETs as well as children. The suggested current imaging protocol recommendations can be found in appendix 1 (courtesy of Dr Tim Jaspan – personal communication).

Postoperative

Residual disease postoperatively is best demonstrated by comparing the patient's pre-operative MRI imaging with one obtained immediately post-operatively. It is accepted practice that postoperative imaging is best performed within 24-48 hours of surgery (ideally immediately postoperatively), after which post-operative changes render interpretation of residual disease very difficult.

Becker JL, Auer D, Jaspan T. Post-operative imaging of paediatric brain tumours - Should the protocol be changed? BSNR annual meeting, Edinburgh 2005

Standard risk patients are defined as those having less than or equal to 1.5 cm² of residual disease (maximum cross sectional area). If post-operative imaging suggest a larger than 1.5 cm² residue consideration needs to be given to further attempted gross total resection. If necessary advice from a neuro-surgical colleague experienced in posterior fossa tumour surgery should be sought. Post operative pre- and post contrast imaging of the spine is

only required if not performed preoperatively, although the interpretation of postoperative spinal imaging to exclude metastatic disease is fraught with difficulties. Hence this should not replace the appropriate preoperative MR imaging due to possible lack of resources. Experience with intraoperative MRI is as yet limited, however indicates the potential for this technique to maximise potential resectability and enable immediate further surgery when residuum is detected.

LP

A lumbar puncture for CSF cytology is a mandatory staging procedure unless deemed clinically unsafe.

A lumbar puncture must generally be performed at least 15 days following surgery. If a lumbar puncture is performed before 15 days and is negative for tumour cells then this will be taken as evidence of non-metastatic disease (M0). If, however, the CSF is positive by lumbar puncture before 15 days then the lumbar puncture will be required to be repeated at 15 days or beyond to determine the M status.

The CSF should be sent to the laboratory as promptly as possible for rapid processing. For this reason, arrangements should be made with the relevant histopathology or cytology laboratory before the sample is taken. Larger volumes of CSF are associated with lower false negative rates and the largest volume considered clinically safe should be sent for cytology.

Involvement of CSF pathways by tumour is defined as the unequivocal identification of tumour cells, on cytological grounds. In difficult cases, immunocytochemistry may assist identification of cells. The cytology should be reported by a histopathologist with a significance interest in brain tumours (typically a neuropathologist).

Pathology and Biology

Pathology

Primitive neuroectodermal tumours of the CNS (CNS PNET) form a group of tumours composed of poorly differentiated neuroepithelial cells that may show differentiation along neuronal, astrocytic and ependymal lines. Medulloblastoma refers to a tumour of primitive neuroepithelial cells of the cerebellum. These tumours correspond to WHO grade IV. They are generally tumours of children, but may occur in adults, where they are seen mostly in younger adults (Giordana, Schiffer et al. 1999). However, cases do occur even in the elderly.

Tumours should be classified according to the latest edition of the WHO classification (Louis, Ohgaki et al. 2007). CNS PNET may be divided into a number of distinct entities CNS PNET NOS, CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma and ependymblastoma. Medulloblastoma may be sub-typed into desmoplastic, classic, large cell, anaplastic and variants with extensive nodularity, with myogenic and with melanotic differentiation, with some evidence that in children the large cell and diffuse anaplastic variants have a worse prognosis. Anaplasia in adult medulloblastomas appears

to be rare and its influence on prognosis less certain, although data is limited by the small number of cases (Giordana, D'Agostino et al. 2005; Rodriguez, Eberhart et al. 2007). Histological subtypes may be associated with different molecular genetic abnormalities and more refined classification may become increasingly important for development of more optimal therapies (Ellison 2002). It would seem good practice to subtype these tumours where possible.

Although classical forms of medulloblastoma and glioblastoma are morphologically distinct, in the context of an adult patient, particularly in older adults in which the relative incidences of the entities is very different to that found in a paediatric setting, there are some borderline cases in which distinction between these categories is difficult. The difficulty is greatest in the setting of supra-tentorial lesions in older adults, in whom unusual glioblastomas are more common than PNETs. A poorly differentiated small cell glioblastoma may only show relatively scanty GFAP expression. It is particularly important not to overinterpret the significance of immunohistochemical positivity for neuronal markers in a tumour which otherwise would be regarded as glioblastoma, as such positivity is frequent and not contributory to diagnosis. Neuropathologists should be aware that a distinction which may appear semantic and arbitrary in some cases on a morphological level will have a major impact on patient management.

It is anticipated that molecular/genetic investigations will play an increasing role in the distinction between small cell glioblastoma and sPNET in this context, although it should be noted that there is evidence that sPNET are genetically distinct from medulloblastoma (Pommeroy et al. Nature 2002).

Tumours should be reported according to standards in the Royal College of Pathologists Dataset for tumours of the central nervous system, 2nd edn (Wharton, Hilton et al. 2008). Definitive histological diagnosis is based on sections from formalin-fixed, paraffin-embedded material and should be supported by an appropriate panel of current immunohistochemical markers. Immunohistochemistry is particularly important to define differentiation and exclude differential diagnoses. Peripheral PNETs and other “small blue cell tumours” may also metastasise to CNS or meninges. More common in this age group is the need to establish differential diagnosis from other more common tumours with a small cell phenotype, including metastatic small cell carcinoma and glioblastoma with a small cell pattern. In addition to these relatively common tumours, it is increasingly recognised that areas of PNET-like differentiation may arise within high grade gliomas (based on both morphology and immunophenotype), probably through a metaplastic process (Perry, Miller et al. 2009).

Given on-going developments, molecular and cytogenetic analysis may in future contribute to more refined diagnostic classification, although these are not routine at present. Where the specimen is of sufficient size, consideration should be given to flash freezing and archiving a portion of fresh tissue -70/80C, which could be available for future retrospective diagnostic/prognostic. Good communication with the laboratory prior to surgery is important where circumstance permit, to allow optimum use of material. With appropriate consent, this may also form an invaluable research resource for this rare tumour type.

The biopsies should be reported by an accredited pathologist, defined as recommended by the NICE improving outcomes guidelines for brain tumours (NICE 2006). They should be registered as a neuropathologist or histopathologist, who has specialist expertise in neuro-oncology and takes part in the national External Quality Assurance scheme for neuropathology organised by the British Neuropathological Society (www.bns.org.uk). The reporting pathologist should be a member of the neuro-oncology MDT and cases should be discussed in that forum, both for biopsy planning and discussion of the diagnosis. Correlation of the pathological findings with neuroimaging and clinical findings is important and the 'final' diagnosis should take account of this information.

CSF cytology may be of aid in demonstrating leptomeningeal disease at presentation or recurrence and is useful therefore for diagnosis and staging. At least in the paediatric age group, studies have shown that CSF cytology improves detection of leptomeningeal disease compared to MRI alone, and lumbar CSF is superior to ventriculoperitoneal shunt CSF for detection of leptomeningeal metastases (Fouladi, Gajjar et al. 1999; Gajjar, Fouladi et al. 1999).

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Biology

Abnormalities of chromosome 17 and loss of 9q22

Using an interphase FISH method on tumour nuclei extracted from paraffin wax embedded tissue this study will test the hypothesis that loss of 17p, gain of 17q, i(17q) or a combination of these abnormalities is a prognostic marker for adult medulloblastoma. As a distinctive desmoplastic variant of medulloblastoma, the medulloblastoma with extensive nodularity (9q22), occurs mainly in infancy and is associated with a good outcome, the hypothesis that loss of 9q22 is associated with a particular morphophenotype and biological behaviour in adult cases.

MYC oncogene amplification

Available data suggest that around 6% of primary medulloblastomas harbour amplification of the MYCC and MYCN oncogenes. Several studies have reported an adverse effect of MYCC and MYCN amplification on clinical outcome, including studies on tumours derived from the PNET3 cohort. Further, evidence of an association between aggressive tumour behaviour and MYC amplification has been provided by Scheurlen et al (1998), who reported a MYC amplification rate almost three times that observed in other studies (17%, n=5/29) in an analysis which included samples from clinically high risk patients.

Wnt/Wg pathway activation

The occurrence of medulloblastoma in type 2 Turcot's syndrome, in which patients have multiple colonic polyps and germline mutations in the APC tumour suppressor gene, suggested that abnormalities of the Wnt/Wingless (Wnt/Wg) pathway could be involved in the development of sporadic medulloblastomas. Subsequently, mutations in components of the Wnt/Wg pathway, including APC and CTNNB1 (encoding beta-catenin), have been consistently demonstrated in approximately 15% of sporadic medulloblastomas, and are predicted to cause aberrant pathway activation. The critical downstream effector of the canonical Wnt/Wg pathway is beta-catenin, and nuclear accumulation of beta-catenin is a marker for physiological or abnormal Wnt/Wg pathway activation. Recent evidence from a cohort of 109 tumours collected from the PNET3 cohort has demonstrated that nuclear accumulation of beta-catenin (ie. Wnt/Wg pathway activation) is strongly associated with mutation of the CTNNB1 gene, and is an independent prognostic marker of favourable outcome in medulloblastoma.

Array profiling of genomic and gene expression aberrations

Recent data collected using array-based technologies to disclose genomic imbalances and gene expression profiles indicate that childhood PNETs are characterised by distinct sets of abnormalities that not only reflect histopathological differences, but also abnormal activation of signalling pathways. Much of this data has been gathered by studying PNETs from children older than 3 years. To understand better the biological, clinical, and histopathological features of adult PNETs, it is essential to undertake similar comparative studies on PNETs from the adult population. Frozen tissue is required for extraction of high

quality DNA and RNA, which will be profiled using Affymetrix arrays. Data from these arrays will be analysed using standard bioinformatics methodologies.

In the light of the importance of a better understanding of the underlying biology of adult PNETs for improving treatment and outcome, it should be mandatory for any centre undertaking the definitive surgery to have a procedure in place to allow for tissue banking of sufficient quantities of the resected specimen.

Prognostic factors

Pathology

Based on the reported histological phenotypes, and the observed differences in their clinical behaviours, the current WHO classification of CNS tumours (**Giungaspero**) define the following histopathological variants of medulloblastoma

- (i) classic medulloblastoma,
- (ii) desmoplastic/nodular medulloblastoma,
- (iii) medulloblastoma with extensive nodularity (MBEN),
- (iv) anaplastic medulloblastoma (if anaplasia severe and diffuse)
- (v) large cell medulloblastoma.

Both diffuse anaplasia and a large cell variant of medulloblastomas are currently perceived as independent high risk features.

Widespread and severe anaplasia is observed in about 15% of cases and in current reports are possibly associated with a poorer prognosis than that for classic, desmoplastic/nodular and MBEN (**Ellison 2002, Eberhart, McManamy**). The situation is, however, complicated by a number of factors:

- Variability in the criteria adopted by groups and individual institutions for the diagnosis of the anaplastic phenotype.
- Overlap with the large cell medulloblastoma phenotype (anaplasia is frequently seen in cases of large cell medulloblastoma).
- The confounding impact of tumour biology e.g. MYC amplification.

Hence the published evidence is inconclusive as e.g. the German HIT 91 study found no negative impact of anaplasia in its own of prognosis (Kortmann et al.)

Large cell medulloblastoma is a rare and phenotypically distinct medulloblastoma subtype that accounts for less than 5% of cases. It is an international consensus that based on the evidence available large cell medulloblastoma is associated with a worse outlook (**Ellison 2002**).

Stage

Standard risk

Several large prospective studies have demonstrated the prognostic importance of achieving a gross total or near gross total surgical excision albeit uncontested at present only for patients with posterior fossa PNETs. This was initially demonstrated in the CCG-921 study, which showed a survival advantage for patients having less than 1.5 cm² residual disease on immediate post-operative imaging as compared to those patients with greater or equal to 1.5 cm². Only a small minority of patients today have significantly sub-total tumour resection. The COG define standard-risk patients with medulloblastoma in respect of local disease as those having less than or equal to 1.5 cm² (maximum cross-sectional area) of residual disease after surgery. The SIOP PNET4 protocol used the same criteria and a current preliminary analysis confirms the lower risk of these patients.

Metastatic disease

The current staging classification still relies in part on the definitions as established by Chang et al. 1969. (Chang CH, Housepian EM, Herbert C Jr: An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastomas. *Radiology* 93;1351-1359 1969), updated by Hariasadis in 1977 (ref: Hariasadis L, Chang CH "Medulloblastoma in children: a correlation of staging with results of treatment. *Int J Radiat Oncol Biol* 9:833-84, 1977). While the use of T staging has been abandoned due to the lack of a prognostic value the M staging component is still relevant today. Patients with no visual tumour outside the primary tumour area and negative CSF cytology are classified as M0. Patients with a negative MRI and a positive cytology finding are classified as M1. Macroscopic metastatic disease within the intracranial compartment (usually leptomeningeal or intraventricular) is called M2 while macroscopic disease within the spinal area as M3. Extremely rarely and usually never at first diagnosis metastatic spread can be identified outside the cranio spinal axis (extraneural, M4).

It is acknowledged that patients with M1-4 disease carry a significantly worse outlook and justify the use more intensified primary treatment strategies.

As opposed to standard/average risk disease, metastatic disease regardless of the primary site must be considered a poor prognosis tumour and until recently little progress has been made in terms of improving outcome. Previous treatments consisted of surgical excision of the primary tumour followed by conventional radiotherapy with doses of radiotherapy of 35 to 36Gy to the craniospinal axis together with a boost of 18 to 20Gy to the posterior fossa. In addition, further boosts to sites of metastatic disease are frequently administered.

General principles of management

As the guidance is technically covering the age groups of both late teenagers and young people and adults (16/18 years to 24 years and over 24 years old) close cooperation between the paediatric and adolescent MDT and its team members is required. In case that for a given patient an open clinical trial is available - either by the national working group (NCRI brain tumour group or CCLG CSG CNS sub-group or a correlating European

working group (e.g. SIOP or EORTC) preference should be given to offer treatment within this context. Assuming that the patient is able and willing to consider this, this should be recommended even if this may mean referring this patient to a different and more distant unit.

Surgery

As a consequence evidence about the potential role of radical resective surgery is limited to retrospective case series only. The largest series to date is outcome data from 17 independent tumour registries (464 patients treated from 1973-2004) recently analysed by the American Cancer Society. The US Surveillance, Epidemiology and End Results (SEER) Program (SEER*Stat) was used to calculate observed and relative 2-, 5-, 10-, 15-, and 20-year survival and Cox Proportion Hazard Regression modelling was used to evaluate prognostic variables. In multivariable regression modelling, gross total resection was found to be an independent favourable prognostic factor. ['Survival of patients with adult medulloblastoma: A population-based study'. Lai R. *Cancer* 2008. 112:1568-1574].

Gross total surgical resection rates reported in the literature range from 36% to 73% ['Medulloblastomas-primitive neuroectodermal tumours in the adult population'. Smee RI. Williams JR. *Journal of Medical Imaging & Radiation Oncology* 2008. 52:72-6.], ['Adult medulloblastoma: Clinical profile and treatment results of 18 patients'. Menon G. et al. *Journal of Clinical Neuroscience* 2008. 15:122-126]. The average reported gross total resection rate in 8 reported series is around 54%.

Definitive surgery for adult PNET should, like the more common primary CNS malignancies, only be performed by a neurosurgeon spending more than 50% of his programmed activities in neuro oncology as directed by the current NICE IOG for CNS tumours. Ideally planned surgical resection will be carried out in most cases by a surgeon experienced in intra axial posterior fossa surgery, but this is unlikely to be an issue if the surgeon has already a substantial neuro oncology workload.

Where practically possible all cases of suspected adult PNET should be formally discussed preoperatively in an accredited neuro-oncology MDT, such that complete imaging of the neuraxis for staging, and a provisional global treatment plan is implemented prior to surgery on the primary focus of disease.

The individual technical challenges of the surgical procedure for a patient presenting with a suspected PNET should be left to the discretion of the operating surgeon. Where at all possible CSF diversion with a shunt system should be avoided to minimise the risk of systemic spread of disease outwith the CNS.

All such surgical procedures should only be performed within centres with immediate access to neuropathology reporting (smear or frozen section) of intra operative biopsy material to guide the operating surgeon. Where possible surplus material to diagnostic purposes should be stored frozen for subsequent genetic analysis.

Post operative MRI imaging with and without contrast to determine the extent of surgical resection should be performed within 24-48 hours of the surgical procedure. If possible the

use of 'Surgicel' should be avoided by the surgeon as early enhancement of brain tissue adjacent to the 'Surgicel' can be misinterpreted as residual tumour. The use of surgicel or any other haemostatic material should be recorded on the request card for the post operative imaging to inform the radiologist of its presence.

Radiotherapy

Standard risk

Pre-treatment assessment for RT should include access to the pre-operative CSA imaging (MRI), the pathological and operative report and the immediate postoperative CT/ MRI scan. Baseline pre-treatment investigations must include a diagnostic post-operative LP, FBC, and routine biochemistry. In addition depending on age and patients preferences fertility counselling/ sperm banking and pregnancy test must be considered. If a patient is considered a candidate for adjuvant chemotherapy furthermore a GFR and a pure tone audiogram are required.

Based on current UK practice the dose prescription for patients with localised PNETs should be 35 Gy in 21 daily fractions, followed by a second radiotherapy phase of 20 Gy in 12 fractions to the posterior fossa for patients with a localised medulloblastoma or otherwise to the primary tumour (if biopsied only) or any postoperative residual tumour and /or the primary tumour bed with an appropriate margin.. Preliminary data from paediatric studies are suggestive that it might be sufficient in patients with SR medulloblastomas to define the PTV of the boost as the postoperative tumour bed plus an adequate margin. Such an approach has not been considered for adult patients. The craniospinal radiotherapy protocol is adapted from the HIT/SIOP PNET-4 study and subsequent CCLG guidelines with respect to target volume definition and dose specification but not dose prescriptions (see appendix 3).

In accordance with The Improving Outcomes for People with Brain and Other Central Nervous System Tumours document radiotherapy should be delivered in a centre providing radiotherapy services for paediatric and/or young adult patients. The delivery of CSA RT is complex and the technical quality of radiotherapy is closely related to outcome (Carrie et al 1999, Saran et al 1998). Centres offering a paediatric and/or young adult service will see a significantly higher number of patients requiring CSA RT and thus the team will be more familiar with the practical details of the technique required.

High Risk

In HR patients (e.g. localised large cell or diffuse anaplastic PNETs, pineoblastomas or supratentorial PNETs) a CSA dose of 35 Gy/ 21# should be prescribed. In all other patients with HR disease who have proven metastatic spread, a dose increase to the CSA up to 40 Gy/24# should be strongly recommended. Where feasible, individual macroscopic metastases outside the primary tumour site, will receive a radiotherapy boost to deliver a total dose of 45 - 50 Gy in an additional 6-9 fractions (see appendix 3). The primary tumour area will be boosted to a standard total dose of 55 Gy (i.e. 15 Gy/ 9#).

Alternatively a combined modality treatment including hyperfractionated and accelerated radiotherapy as published by the Milan group should be considered particularly in young adults (Gandola et al JCO 2009). Detailed advice can be found in the interim guidelines issued by the CCLG PNET group.

Chemotherapy

Standard risk

There is currently no randomised data available supporting the routine use of adjuvant or neo-adjuvant chemotherapy in adult patients with primary PNETs. Nevertheless recently published contemporary studies have report survival rates for adult patients with PNETs in a similar range as published paediatric series. The survival rates in these studies were higher than commonly reported by retrospective series using a RT approach only. It is currently unclear in how far the improved survival rates are solely related to the use of adjuvant chemotherapy or are a result of improved imaging and staging procedures, surgical and post-surgical care as well improved radiotherapy quality assurance.

Based on a consensus among the working group adjuvant platinum based chemotherapy can be offered to standard risk patients (particularly in the young adult spectrum) But given the lack of randomised data an individual assessment has to be made in each case balancing risks and benefits of such an approach and these will have to be discussed with the patient in detail.. Current published trial use a combination of concurrent vincristine chemotherapy with 8 cycles of adjuvant vincristine, cisplatin and lomustine starting 6 weeks after completion of radiotherapy. The contribution of the concomitant vincristine to the curative potential of the combined modality treatment is unclear and any planned future contemporary studies of the European SIOP group elected to omit this component. In addition it is clinically accepted that the acute toxicity associated with concomitant VCR is closely related to the age at the time of treatment - with older patient exhibiting a noticeably increased toxicity. The guidance group therefore recommends omitting the concomitant VCR phase and using the time interval of radiotherapy (6 ½ weeks) and subsequent break until the potential commencement of adjuvant chemotherapy (6 weeks) to counsel the patient in more depth about the potential therapeutic options and its implication for the patient.

In current published paediatric series approximately 70% of patients require dose modification of the adjuvant cisplatin based chemotherapy predominantly due to evolving oto-toxicity, myelotoxicity, weight loss or others. Given the lack of familiarity with his regime it has to be stressed that clinicians delivering adjuvant chemotherapy for SR PNETs need to follow the available chemotherapy guidelines strictly or have a close link with the local paediatric and adolescent teams. Given the substantial and cumulative toxicity of the adjuvant chemotherapy it is a frequent experience that in this clinical setting, adult patients will rarely tolerate the 8 adjuvant cycles as published in the paediatric setting and consideration could be given to limit the number of cycles to 6. In case that the patient elects to proceed with the adjuvant chemotherapy local trust policies of delivering cytotoxic therapies apply - including access to counselling and fertility services.

High Risk

Chemotherapy is generally accepted as having an important role in treatment of metastatic medulloblastoma, although the optimal chemotherapy regimen has yet to be defined.

No reliable data are available for guiding the management of adult patients with high risk PNETs and thus no formal recommendations can be made albeit consideration should be given to consider a more aggressive multi modality approach. Consideration should be given to consult with current guidelines issued by the CCLG PNET working group and advice from clinicians with larger experience in the management of this rare disease in the paediatric setting. As for radiotherapy, if an approach according to the published study from Milan is considered, the interim guidelines of the CCLG PNET group should be consulted.

Follow-up Recommendations

Imaging

The benefit of regular surveillance imaging remains controversial in the literature as in the case of established recurrences only in exceptional circumstances can long term control be achieved with currently available salvage strategies (Bartels et al 2006, Bouffet et al 1998, Torres et al 1994, Saunders et al. 2003, Yalcin et al 2002), as it is more likely to achieve a longer term remission with localised recurrences amenable to further surgical resection and repeat radiotherapy (Saran et al 2008). Thus consideration should be given to a surveillance imaging strategy limited to the brain every 6 months during the first and second year after treatment and annually until the 5th year after treatment. Due to a lack of evidence of a patient derived benefit regular spinal imaging is not recommended and should only be performed in case of clinical suspicious symptoms or evidence of a local recurrence.

Endocrinology

Endocrine function in patients with rare CNS tumours may be affected either by direct impact of the tumour on the hypothalamic-pituitary axis (HPA) or secondarily as a consequence of treatment with surgery and/or radiotherapy and/or chemotherapy.

The major secondary damage to the HPA is by **cranial irradiation** whereas a potential damage by chemotherapy is currently undefined. Radiation effects are delayed and may surface up to 10 - 15 years after initial therapy. The likelihood of a radiotherapy induced HPA dysfunction critically depends on the total hypothalamic / pituitary irradiation dose and its fractionation. Young children are more sensitive to irradiation than adolescents or adults. A threshold dose of > 60 Gy or a fraction dose of > 1.8 Gy to the HPA leads to a 80-100 % chance of pituitary dysfunction. The various axes differ in sensitivity with growth hormone deficiency being most sensitive and the posterior pituitary function most resistant to irradiation.

The gonadotropic axis is peculiar as low doses in prepubertal children may induce precocious puberty predominantly in girls whereas higher dosage > 60 Gy induce gonadal failure.

Late metabolic changes are increasingly recognized following treatment.

The effects of **chemotherapy** are not yet conclusively defined. Large series of childhood cancer survivors suggest an increased frequency of endocrine late effects in patients treated with a combination of radiotherapy and chemotherapy. However, a consistent and independent direct effect of chemotherapy on the hypothalamic-pituitary regulation has not been determined. Only the gonadal axis appears to be sensitive to damage via certain chemotherapeutic agents inducing primary gonadal failure (Schmiegelow 2001, Gurney 2003). The toxicity is dose-dependent and associated with alkylating agents (including procarbazine, cisplatin, and vinblastine) or with drugs acting directly on the gonads (including doxorubicin, cyclophosphamide, melphalan, and chlorambucil) (Stava 2007). In addition, the posterior pituitary function may be altered by cancer therapy (Yeung 1998). Cytotoxic treatments with vinca alkoids, cisplatin, cyclophosphamide, and melphalan may stimulate secretion of antidiuretic hormone (ADH) (Stava 2007).

The **diagnosis** of a defect in the HPA may be suggested by the clinical scenario, although symptoms of pituitary insufficiency may be non-specific particularly in adults (e.g. fatigue). Dynamic tests are necessary to assess the endocrine axes and to decide on **replacement therapy**. In children endocrine assessment are necessary every 6 months whereas in adults yearly to biannual intervals are sufficient. A joint follow-up with a specialist endocrinologist should be attempted. (For details see appendix 5)

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Supportive care, rehabilitation and general palliative care

Provision of appropriate supportive care is mandatory in all patients. Patients treated for CNS PNETs must be discussed in the appropriate site specific MDT(s). Any tertiary treatment centre has to demonstrate a robust pathway for accessing and providing the necessary support services.

When considering the supportive care for patients with primary CNS lymphoma, PNET, optic glioma, and pineal tumour, few centres and clinicians will gain wide experience in their management because of their rarity (NICE 2006). This means these patients present particular problems in management and service co-ordination. They may need long-term monitoring due to problems associated with their disease and/or its treatment e.g. physical and cognitive impairment. (See Appendix 6)

Patients diagnosed with these tumours require input from a well co-ordinated multi-professional team (NICE 2006:Table 8: 37), to support their complex changing care needs throughout the patient pathway. This approach does not differ from other patient groups with disease affecting their CNS (NICE 2004; NSF 2005; NICE 2006; RCP, NCPC & BSRM 2008).

“Supportive Care is an umbrella term encompassing the work of a broad range of healthcare professionals to address the changing needs of patients, their relatives and carers throughout the patient journey” (NICE 2006: 100). This has been extensively described in previous (NICE 2004: Ch10; 2006: Ch8) and current national guidance (NCAT 2010) in order to optimise patients’ quality of life. Support services will include Allied Health Professionals (AHP) and other professionals within the multi professional team:

Core Members of Supportive Care services

- Physiotherapists
- Occupational Therapists
- Speech & Language Therapists
- Dietitians

Extended members of Supportive Care services

- Nurses
- Primary healthcare team
- Neuropsychology, neuropsychiatry and psychological therapy
- Social services and care managers/ continuing care manager

- Orthotic/appliance officer
- Wheelchair and other equipment services
- Chaplaincy and bereavement services
- Ophthalmologist services
- Complementary therapy services (NICE 2006:111)

Referral to supportive care services should not be dependent on diagnosis, but on patient need (NCAT 2010, NICE 2006). Intervention may be required at any stage of the patient's disease trajectory dependent on presentation of their symptoms: pre – diagnosis, diagnosis, initial treatment, post treatment, disease progression and end of life care (NCAT 2010, NICE 2006, NICE 2004) – see appendix 6 (Symptom related referral pathway to supportive care services for patients with CNS tumours). Observational studies show patients with 1° CNS tumours can benefit from rehabilitation intervention (NCAT 2010). This is predominantly identified in inpatient multi-professional units (Geler-Kulcu et al 2009, Tang et al 2008, Greenberg *et al.* 2006, Giordana & Clara 2006, Garrard et al 2004, Huang et al 1998, 2000, 2001 a & b, Mukand et al 2001, Marciniak et al 2000, Sliwa & Marciniak 1999, O'Dell et al 1998, Marciniak et al 1996) and some out patient settings (Giovagnoli et al 1999, Sherer et al 1997). All demonstrate the importance of rehabilitation to improve function and facilitate discharge to the community for these patients. Current evidence regarding timing of rehabilitation in relation to medical treatment e.g. radiotherapy treatment, is inconclusive (Marciniak 1996, Huang *et al.* 2001). However, based on theoretical evidence concerning neuroplasticity and brain tumours (Duffau 2006, 2008) and parallel literature concerning therapy intervention (DH 2007), rehabilitation intervention should begin as early as possible to optimise rehabilitation opportunities and functional participation in society (NCAT 2010).

The importance of timely access to appropriate rehabilitation services is dependent on rapid, comprehensive communication between AHPs. This is discussed in NICE 2006 and echoed in other evidence based guidance for patients with long-term neuro-degenerative conditions (MNDA 2004; MSS 2008; NCP & BSRM 2008; RCP; NCAT 2010). These recommend early referral to specialist rehabilitation services when patients present with symptoms affecting their independence and/or participation in their current environment. They advocate ongoing, comprehensive assessment and provision of support according to patient's changing needs. This may include integrated care planning by health, social services and the voluntary sector.

According to their individual diagnosis and treatment, the particular clinical features of these patients will fluctuate, change and ultimately deteriorate. These may be as a consequence of the patient's disease, prognosis and/or treatment related side effects. To ensure a holistic approach, it is essential that local service provision provides specialist rehabilitation including: vocational/leisure interests, equipment, environmental adaptation, and psycho-social support (RCP, NCP & BSRM 2008, DH & Macmillan Cancer Support 2009). Ongoing re-assessment at key stages of the patient pathway is recommended (NICE 2004; NICE 2006; NCAT 2010). NICE 2004 also acknowledges the need for

patients to obtain reliable information about complementary therapy services and empower them to make informed decisions regarding their use.

The need for psychological support services including neuropsychology and neuropsychiatry for patients with CNS disease is advocated in previous guidance (NICE 2004; NSF 2005; NICE 2006; MSS 2008; NCPC & BSRM 2008; RCP).

The emotional and spiritual needs of the patient, family and carers must be recognised by the multi professional team throughout the patient pathway from pre-diagnosis to end of life care. Additionally, patients may substantially benefit from early contact (as soon after diagnosis as possible) with dedicated brain tumour-specific charities and not-for-profit organisations which offer face-to-face, telephone and online support opportunities as well as a wide range of comprehensive, practical information regarding brain tumours. Talking through the challenges of brain tumours with other patients and caregivers who are on the same journey can provide a unique level of emotional support and hope. Appropriate local spiritual support and bereavement care services support should be accessed (NICE 2004, NICE 2006).

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Specialist palliative care

The World Health Organization (WHO) has defined palliative care as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” [1]. Palliative care “is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications” [1]. This philosophy is endorsed in the NHS Cancer Plan [2], the Improving Supportive and Palliative Care for Adults with Cancer document [3], and the Improving Outcomes for People with Brain and Other Central Nervous System Tumours document [4].

Palliative care specialists have a particular role in the management of “difficult-to-control” symptoms, and in the planning and provision of end of life care. The remit of specialist palliative care services is discussed in detail in the Improving Supportive and Palliative Care for Adults with Cancer document [3], whilst the Department of Health’s guidance on end-of-life care is set out in detail in the End of Life Care Strategy document [5].

The management of difficult-to-control symptoms involves adequate assessment, appropriate treatment, and adequate re-assessment (i.e. review of the efficacy and tolerability of the treatment). The objective of assessment is to determine the aetiology of the symptom. Thus, many of the symptoms associated with PNETs are non-specific (e.g. headache, nausea and vomiting), and patients may also experience these symptoms as a consequence of the anticancer treatment, the supportive care treatment, or a co-existent medical condition [6,7]. Inadequate assessment may result in the initiation of inadequate or inappropriate treatment, which will inevitably result in continuation of the problem (and possibly loss of confidence in the ability of members of the MDT by the patient and their carers).

Headache due to tumour or raised intracranial pressure may be effectively managed in the short term by corticosteroids, and / or conventional analgesic drugs. However, corticosteroids are rarely effective in other causes of headache (e.g. migraine, “tension type headache” [6]), and although conventional analgesic drugs may be effective for many causes of headache, they may not be the most appropriate treatment for specific causes of headache [6]. It should be noted that there is almost no data on the management of specific symptoms in patients with adult PNETs, and so treatment strategies need to be extrapolated from patients with other CNS tumours (and indeed patients with other types of cancer).

In addition to providing advice and assessment of difficult-to-control physical symptoms throughout the disease trajectory, referral may be particularly beneficial in patients with advanced disease. In this situation, management of challenging physical symptoms (e.g. pain, sleep disturbance, seizures at the end of life) and any associated psychosocial or spiritual symptoms can be addressed. Planning for the future is imperative as patients with PNETs may undergo progressive cognitive impairment, personality changes and communication difficulties. Advance care planning – the voluntary process of discussing wishes and preferences for future care, should be offered early whilst the patient has the capacity to make those decisions. National guidance is available on how to manage advance care planning in clinical practice from the Royal College of Physicians [8] and Advanced Care Planning section of the National End of Life Care Programme [9].

When a patient has entered the terminal phase of their illness and it is recognised that a patient is actively dying, integrated pathways for the care of the dying, such as the Liverpool Care Pathway of the Dying Patient [10], should be considered. These can be used in any setting, and the use of such pathways has been recommended by the End of Life care programme and more recently in the End of Life Care Strategy [5]. There is a paucity of data specific to the management of patients with brain tumours and the end of life. Local palliative care teams can provide guidance on specific symptoms e.g. continuing regular opioid analgesia or anticonvulsant medication via the subcutaneous route when the oral route is not possible.

Patients with advanced PNETs who are approaching end of life may still be on long term maintenance doses of steroids. If they become unable to take oral medication, the decision needs to be taken whether or not the steroids should be discontinued abruptly, weaned or given parenterally. There is no evidence on the best practice and the decision needs to be made on an individual basis, although symptoms that might arise as a result of withdrawal can usually be dealt with by adjusting the patient's other medication (e.g. in a subcutaneous syringe driver), thus ensuring optimal symptom control continues.

References

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[10] Liverpool Care Pathway for the Dying Patient (LCP). Available from: <http://www.mcpcil.org.uk/liverpool-care-pathway/index.htm>

Survivorship / Living with cancer

The supportive care issues and recommendations outlined in the NICE guidance 'Supportive Care and Continuing Care of People with Brain and Other CNS Tumours' (NICE 2006) and 'Improving Supportive and Palliative Care for Adults with Cancer' (NICE 2004) should be referred to and followed for adults with Adult PNET tumours. Similarly, the Cancer and Palliative Care Rehabilitation Care Pathways (NCAT 2010), due for publication, should be followed.

The Department of Health National Cancer Survivorship Initiative Vision document (2010) sets out that all cancer survivors should have:

- A personalised assessment and care plan;
- Support to self-manage their condition;
- Information on the long-term effects of living with and beyond cancer; and
- Access to specialist medical care for complications that occur after cancer.

The specialised requirements for treatment of this rare tumour type require a key worker to co-ordinate treatment across both local and potentially distant specialised treatment centres, in order to develop and deliver such a personalised approach to the care of the brain tumour patient.. This role should be available throughout the patient pathway, and the patient and their family should be informed if their key worker changes.

Ongoing emotional support is required for these patient groups and their families/carers. In addition, well co-ordinated treatment and appointments are essential, especially if patients

require treatment at different centres and departments. Patient hand-held records may clarify who is responsible for various aspects of their care, and identify who to contact if they have changes in symptoms or concerns of any kind.

To ease the general financial burden, proactive advice should include comprehensive and supportive information. If treatment is required at a non-local specialised centre, travel and accommodation costs warrant discussion with patients and their families.

The key worker role should provide support and signposting to appropriate services:

- local health authority,
- charitable institutions which may provide grants for such purposes.
- state benefits
- Disability employment advisors at local Job Centres, for those patients fit enough to return to work

The welfare and support of the patient's primary carer and immediate family need to be considered at key points throughout the patient pathway. This must include appropriate management of the point of diagnosis, the end of each round of treatment, disease recurrence, the terminal phase and bereavement care (ref NICE 2004).

References:

NCAT (2010) Cancer and Palliative Care Rehabilitation Care Pathways (draft). Cancer Action Team. London

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Research recommendations

1. Given the paucity of adequate information on presenting symptoms, the incidence of presenting symptoms in which there is classification of headache type (International Classification of Headache), "dizziness" and type of gait disturbance should be investigated.

2. Given the controversial data on the contribution of systemic chemotherapy to cure in primary adult CNS PNETs a national clinical trial exploring this question should be initiated.
3. The relevance and frequency of regular follow-up imaging should be explored as part of a prospective clinical trial.
4. Given the known increased long-term cardiovascular morbidity of long term survivors and mortality, research is needed to clarify the pathophysiological basis and to define early risk markers.

Appendices

Appendix 1: Imaging

It is essential that all new brain tumour cases are imaged using a consistent and comprehensive protocol. This is to ensure that optimal diagnostic information can be obtained, consistency is maintained, studies are directly comparable and that all brain tumour cases can be recruited into national tumour studies. It is equally important that follow up imaging is undertaken in a consistent and timely manner. Lack of a consistent protocol has led to very significant difficulties in analysing imaging of patients enrolled into tumour studies from different centres in the UK.

In future, lack of adherence to the national imaging protocol will exclude new cases being recruited to studies. The protocol given below is based upon the imaging protocol published in 2001¹ but reflects recent advances in imaging techniques (DTI, perfusion MRI, MRS). Not all centres can or will wish to use these newer techniques, which remain experimental in nature, and therefore these are given as optional sequences. Many centres will have their own preferred imaging sequences and this protocol is not intended to be proscriptive or to exclude other sequences and techniques, however it is essential that a standardised basic set of sequences is adopted nationally.

Newly diagnosed patients:

Brain

Standard sequences

- Axial T1, T2
- Coronal FLAIR
- DTI and/or DWI (with ADC maps)
- Post Gd Ax, Cor, Sag T1 – 1.5T
- Post Gd Ax T1, Ax 3D T1 volume – 3T

Optional sequences (according to local capacity/availability or CCLG trial involvement)

- Cor/Sag T1, T2 or FLAIR
- Perfusion MRI (requires placement of blue or pink cannula)
- MRS

Spine

Standard sequences

- Sag T1 (post Gd)
- Ax T1 through any equivocal focal abnormality

Optional:

- Sag T2

Immediate post-op (within 48 hours)

Brain

Standard sequences

- Ax T1, T2
- Coronal FLAIR
- DTI and/or DWI (with ADC maps)
- Post Gd Ax, Cor, Sag T1 – 1.5T
- Post Gd Ax T1, Ax 3D T1 volume – 3T

Spine (only if not obtained prior to surgery)

Standard sequences

- Sag T1, T2 (pre and post Gd – note that both brain and spine need to be imaged pre contrast if no pre-operative spinal imaging)
- Ax T1 through any equivocal focal abnormality

Follow-up examinations

Brain

Standard sequences

- Axial T1, T2
- Coronal FLAIR
- DTI and/or DWI (with ADC maps)
- Post Gd Ax, Cor, Sag T1 – 1.5T
- Post Gd Ax T1, Ax 3D T1 volume – 3T

Optional (according to local preference or CCLG trial involvement)

- Cor/Sag T1, T2 or FLAIR

- Perfusion MRI (requires placement of blue or pink cannula)
- MRS if tumour size >1.0cm (and dependent on tumour type/protocol)

Spine (indicated if spinal symptoms develop or evidence of intracranial leptomeningeal dissemination)

Standard sequences

- Sag T1, T2 (post Gd)
- Ax T1 through any equivocal focal abnormality

Reference

Thiesse P, Jaspan T, Couanet D, Bracard S, Neuenschwander S, Griffiths PD. Un protocole d'imagerie des tumeurs cerebrales de l'enfant (A protocol for imaging pediatric brain tumors). J Radiol 2001;82:11-16.

Appendix 2: Radiotherapy

Timing of Radiotherapy (RT)

Following definitive surgery - all patients shall begin RT and ideally no later than 30 days after surgery. Patients with CNS PNETs are recognised by the Royal College of Radiologists as Category 1 patients.

Equipment

Patients must be treated using conformal radiation therapy treatment planning and delivery techniques. IMRT techniques will be possible assuming that appropriate departmental QA procedures are available. All patients must be treated on isocentric linear accelerators with a minimum source-to-axis distance (SAD) of 80 cm. Megavoltage photons with a nominal energy ≥ 4 MV must be used. Treatment with ^{60}Co is not permitted.

The use of electron spinal fields will be acceptable provided a beam of sufficient energy is available to ensure adequate irradiation of the target volume allowing for tissue heterogeneity and the junction between the photon cranial fields and spinal electron field can be precisely calculated and implemented.

Energy

The cranial (whole brain) fields shall be treated with megavoltage photons with energies in the range of 4-6 MV. Energies higher than 6 MV should be avoided due to the risk of under-dosing the lateral meninges. The tumour bed RT can be given with a higher energy. Photons of 4-6 MV will generally be used for spinal irradiation but electrons of suitable energy or protons can be used as an alternative.

Treatment position

Patients should be immobilised using an immobilisation device according to departmental policies. The patient should be maintained in the same position for the cranial and spinal components of CSRT for the duration of this treatment phase.

RT planning

A planning CT is mandatory for the definition of the target volumes of both craniospinal axis and tumour bed. It is strongly recommended that the CT slice thickness should be no greater than 0.5 cm in the region of the cribriform fossa, base of skull, primary tumour area and cranio-cervical field junction, and no greater than 1.0 cm elsewhere within the craniospinal axis.

If the spinal field is treated with electron beams the dose along the entire spinal axis should be calculated with an appropriate correction for tissue heterogeneity.

Treatment volume anatomical description

Target Volume

Target volumes will be defined according to ICRU 50/62 guidelines. Delineation of all target volumes is based on a planning CT with i.v. contrast and or CT-MR image fusion and will be outlined on each slice of the planning scan.

Craniospinal Axis

The Clinical Target Volume (CTV) for CSRT comprises the whole brain as well as the spinal cord and thecal sac as identified by the preoperative MRI scan.

Whole Brain Volume

The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. In order to include the cribriform fossa within the CTV, and allowing an additional appropriate margin for PTV, the edge of the field (i.e. the geometric edge of the shielding block) will in many cases include the lenses.

The geometric edge of the shielding should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull. The margin between the shielding and the anterior border of the upper cervical canal should be a minimum of 1.0 cm. The lower border of the cranial fields should form a precise match with the upper border of the spinal field.

The CTV should include any herniation of the meninges through the craniotomy scar.

Cervical Spinal Volume

The spinal field should extend superiorly to form an accurate match with the border with the lower borders of the cranial fields.

Dorso-Lumbar Spine Volume

The inferior limit of the spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MR performed as part of the staging process. The treatment field edge will set 1 cm below the lowest point of the thecal sac.

Width of the Spinal Volume

The aim is to include the entire subarachnoid space including the extensions along the nerve roots as far as the intervertebral foramina. Thus the spinal CTV should extend laterally to cover the intervertebral foramina. An additional margin, generally 1.0 cm on either side should be added for PTV, and an appropriate field width chosen to allow for this. The use of a 'spade' shaped field to treat the lumbo-sacral spine is not recommended.

Tumour Bed Volume

The GTV includes all gross residual tumour and/or the walls of the resection cavity at the primary site, based on the initial imaging examination that defines the tissue initially involved with disease anatomically and the post-operative and pre-irradiation neuro-imaging examinations. The GTV will have to take into account any anatomical shift or changes after surgery.

The CTV includes the GTV with an added margin that is meant to treat sub-clinical microscopic disease and is anatomically confined (i.e. the CTV is limited to the confines of the bony calvarium and tentorium where applicable). The CTV is defined as the GTV plus a 1.0 cm margin except at bone or tentorial interface where it remains within the confines of the posterior fossa.

The PTV is defined as the CTV plus an additional 0.3 - 0.5 cm margin. The size of the required margin will depend on the quality of the immobilisation device chosen and the departmental reproducibility records for the patient position and chosen device. If a local investigator feels that a 0.5 cm margin is insufficient as a CTV/PTV margin, an appropriate margin according to his own experience should be chosen and the radiotherapy principal investigator informed. CAVE: In patients with standard risk medulloblastoma the final PTV should be not extending beyond the boundaries of a "classical" PTV when the entire posterior fossa is defined as CTV unless clinically indicated.

A field arrangement using complex coplanar or non-coplanar beam arrangements (e.g. 2-4 posterior oblique fields) is strongly recommended. The purpose of this is to minimise the RT dose to the temporal lobes and cochleas.

Organs at risk (OR)

The following OR should be considered when defining the tumour bed boost for 3-D conformal radiation therapy or IMRT planning:

- Supratentorial brain
- Posterior fossa (infratentorial brain)
- Cochlea (left and right)
- Hypothalamus
- Pituitary

Dose Specification

Dose Definition: All doses will be specified according to ICRU 50/ICRU 62.

Dose specifications

Brain

If the brain is treated by a pair of parallel opposed fields, the dose should be defined at the midpoint of the central axis.

Spine

The dose to the spine should be prescribed along the central axis at a depth representing the posterior margin of the vertebral bodies.

In the case of electron RT to the spine the anterior border of the target volume (posterior aspect of the vertebral bodies) must be encompassed within the 85% isodose.

Tumour bed boost

The primary tumour bed should be treated, using a suitable technique that allows for the least amount of normal brain tissue and organs to be at risk from exposure to high dose irradiation. The prescription point should be the isocentre unless an IMRT technique is used.

Sites of macroscopic metastatic spread

GTV +1.0-1.5 cm to PTV institutional policies.

Dose prescription

Localised disease

- Brain – 35 Gy in 21 daily fractions of 1.67 Gy
- Spine –35 Gy in 21 daily fractions of 1.67 Gy
- Primary tumour boost – 20 Gy in 12 daily fractions of 1.67 Gy

Total dose to primary – 55 Gy in 33 daily fractions of 1.67 Gy

Metastatic disease

- Brain – 40 Gy in 24 daily fractions of 1.67 Gy
- Spine - 40 Gy in 24 daily fractions of 1.67 Gy
- Primary tumour boost – 15 Gy in 9 daily fractions of 1.67 Gy

Total dose to primary – 55 Gy in 33 daily fractions of 1.67 Gy

Boost to macroscopic sites of disease – 5-10 Gy in 3-6 daily fractions of 1.67 Gy

Fractionation

All fields should be treated daily (conventional RT) 5 days per week.

Dose uniformity

Dose variations across the target volume should be within + 7% and – 5% of the prescription point according to ICRU 50/62 recommendations. If technically achievable, the dose variation should preferentially be kept within $\pm 5\%$. An effort should be made where clinically acceptable to spare the cochlea and middle ear.

Field shaping

The use of customised divergent beam blocks or multi-leaf collimators using beam's eye view facilities is mandatory.

Treatment verification

Regular treatment verification according to institutional policies is required. As a minimum standard, weekly portal images must be performed and the set-up variations recorded.

Rests

There will be no planned rests. Delays due to machine services and bank holidays should be avoided and patients are treated in accordance with the RCR guidance as category 1 patients. Patients should be treated as category 1 patients and treatment interruptions compensated according to institutional policies.

Treatment Technique

Cranial RT

The cranial fields will be treated with lateral opposed fields.

Spine Irradiation

If possible the spinal volume should be treated with a single posterior field. If necessary the spinal field can be treated at an extended FSD. The exit from the spinal field should not include the oral cavity.

Junctions

Junctions of abutting fields should be moved either on a daily rotating basis or weekly (moving junction technique).

Primary Tumour Bed Volume

It is mandatory that this volume is treated conformally. The field arrangement will be chosen to provide a high conformity index and to minimise the RT dose to OARs.

Intensity Modulated Radiotherapy (IMRT)

It is likely that during the lifespan of this guidance, IMRT planning and delivery techniques will be increasingly employed. As an example, this may be used as an option for reducing the radiation dose to the cochlea. IMRT has also been used to improve homogeneity of spinal RT. If centres employ IMRT then it will be essential to observe strict criteria for immobilisation and departmental quality assurance.

Treatment Modifications due to Haematological Toxicity

Treatment will not be interrupted for anaemia, leucopaenia or thrombocytopenia unless life threatening. Blood product or growth factor support should be instituted according to institutional guidelines. Irradiated blood products should be used at all times. Transfusions should be considered recommended when the haemoglobin levels fall below 10 g/l. Platelets should be transfused as clinically indicated when counts are $\leq 25 \times 10^9$. Growth factors should be considered if the absolute neutrophil count is $\leq 0.5 \times 10^9$.

Patients should be treated as category 1 patients and treatment interruption compensated according to institutional policies.

Appendix 3: Chemotherapy

Chemotherapy will commence six weeks following the completion of radiotherapy provided blood count recovery has taken place. Six cycles of chemotherapy will be delivered at 6-weekly intervals. Each cycle will consist of:

- CCNU (lomustine) oral - 75 mg/m² per cycle
- Vincristine IV – 1.4 mg/m² (maximum 2 mg)
- Cisplatin IV – 70 mg/m²

The administration of this chemotherapy will involve monitoring of renal function and audiology. Chemotherapy will include strict adherence to a hydration regimen to minimise the risk of cisplatin nephrotoxicity. There will be a dose modification regimen for haematological toxicity and also for cisplatin based on changes in renal or auditory function. Although in children, vincristine is also administered concurrently with craniospinal radiotherapy, severe constipation has been experienced by many older children and it is proposed to avoid vincristine given concurrently with craniospinal radiotherapy for adults.

Chemotherapy

LCV₃ ("Packer")

Week	1	2	3	4	5	6
Lomustine (CCNU)	x					
Cisplatinum	x					
Vincristine	x	x	x			

- CCNU 75 mg/m² po nocte - Day 0
- Repeat cycle 6 weekly up to a maximum of 6 cycles
- Cisplatinum 70 mg/m² IV infused over 6 hours in 1 litre NaCl 0.9% – + 20 mmol KCl - Day 0
- Vincristine 1.5 mg/m² IV bolus, max. 2.0 mg - Days 0, 7, 14

Hydration Regime:

- 1 litre NaCl 0.9% + 20mmol KCl over 6 hours x 2 (2 litres in 12 hours) before and following Cisplatinum
- Mannitol 10% 200 ml over 30 minutes immediately prior to Cisplatinum
- Antiemetics as per RMH protocol

Carboplatin (substitution for cisplatinum if toxicity)

Carboplatin 400 mg/m² is to be given as a 1 hour infusion in 5% dextrose – with no pre- or post hydration.

Modification to Chemotherapy based on Ototoxicity

High frequency hearing loss progressing to involve the speech frequency range (500-3,000 Hz) is a major toxicity of cisplatin. It is clear that the ototoxicity is dependent upon the

cumulative dose of cisplatin, but other factors such as the dose per course and drug scheduling may be important.

Monitoring of hearing loss during chemotherapy is a fundamental and mandatory part of clinical practice.

Brock / CTC (SIOP) Grading:

0	Loss < 40 db on all frequencies
1	Loss at least 40 db at 8000 Hz
2	Loss at least 40db at 4000 Hz
3	Loss at least 40 db at 2000 Hz
4	Loss at least 40 db at 1000 Hz

Note: Grading for Audiometry is based on loss in both ears – Thus the grading (including that for modification of chemotherapy) is based on the Lowest Grading i.e. the ‘best ear’.

Grade	<u>Chemotherapy Modification</u>
0 & 1	None
2	Substitute carboplatin 400 mg/m ² for cisplatin
3 & 4	Omit platinum

Modification to chemotherapy based on nephrotoxicity

Creatinine clearance < 80 ml/min/1.73 m ² or serum creatinine >1.5x upper limit of normal:	Delay chemotherapy for 1 week and repeat creatinine clearance
If no recovery after 1 week and GFR ≥ 60 - 80ml/min /1.73m ² :	Substitute carboplatin 400 for cisplatin for that course
GFR < 60 ml/min /1.73m ² :	Omit platinum for that course

Modification to Chemotherapy based on Haematological Toxicity

Prior to each course of chemotherapy the following apply:

Neutrophils < 0.5 x 10 ⁹ /L or platelets < 100 x 10 ⁹ /L	Delay chemotherapy for at least one week.
If lack of count recovery after > 2 weeks (neutrophils < 0.5 x 10 ⁹ /L or platelets < 100 x 10 ⁹ /L)	Give cisplatin & vincristine above (omit CCNU for that or course)
If recovered prior to next course	Reintroduce CCNU at a reduced dose of 50 mg/m ²
If neutrophils < 0.5 x 10 ⁹ /L and episode of neutropenic fever at any time (nadir).	Reduce CCNU to 50 mg/m ² in the next course and all subsequent courses.
If further episode of neutropenia	Reduce cisplatin to 50 mg/m ² and fever. (<

	0.05 x 10 ⁹ /L) in the next and all subsequent courses.
If platelets < 30 x 10 ⁹ /L and/or platelet transfusion	Reduce CCNU to 50 mg/m ² .in the next course and all subsequent courses.
If further episode of thrombocytopenia (platelets < 30 x 10 ⁹ /L)	Omit CCNU in the next course and all subsequent courses.

Modifications to chemotherapy based on neurotoxicity of vincristine

Vincristine associated seizures or ileus. N.B. Rule out SIADH as a cause of seizures.	Omit vincristine during current course of chemotherapy and reduce to 1mg/m ² for next course. If seizures or ileus do not recur, then return to full dose.
Parasthesia, weakness, abdominal pain or constipation	Omit next vincristine dose but on recovery reintroduce at a reduced dose of 1mg/m ² increasing to full dose if symptoms do not return

Appendix 4: Endocrinology

Clinical assessment and diagnostic tools

The diagnosis of a defect in the HPA may be suggested by the clinical scenario, although symptoms of pituitary insufficiency may be non-specific particularly in adults (e.g. fatigue). Thus assessment based on questionnaires focussing on symptoms such as those used in the CCSS will underestimate the true rate of HPA deficiencies. However in children, growth failure, weight gain or loss, precocious or delayed puberty may provide clinical clues.

1. Symptoms of pituitary dysfunction

a. GH deficiency

- i. In all patients muscle mass and strength may be decreased, visceral fat may be increased, patients are fatigued with a decreased quality of life, impairment of attention and memory. Children have a reduced growth velocity.

b. Gonadotrophin deficiency

- i. Female patients show abnormalities of their cycle with oligo- or amenorrhea, infertility, loss of libido, and dyspareunia.
- ii. Males lose their libido and show impaired sexual function. There may be mood changes and signs like loss of facial, scrotal, and truncal hair and decreased muscle mass.
- iii. Children have a delayed or absent puberty.

c. ACTH deficiency

- i. Patients may complain of weakness, nausea, vomiting, anorexia and/or weight loss. There may be circulatory problems such as hypotension, dizziness or collapse.
 - ii. Children may fail to thrive.
- d. TSH deficiency
 - i. The main symptoms and signs are tiredness, cold intolerance, constipation, hair loss, dry skin, hoarseness and cognitive slowing.
 - ii. A significant sign in children is a reduced growth velocity and weight gain.

2. Biochemical tests of HPA

- a. GH axis
 - i. As measurement of IGF-I alone is not sufficiently sensitive to define the status of the GH axis, dynamic tests are also necessary to delineate GH function. The insulin tolerance test (ITT) is still regarded as the gold standard for the evaluation of the GH axis. In brain tumour patients with epilepsy the ITT may be contraindicated. There are a number of other tests such as the arginine and glucagon stimulation tests that can be used, with the latter also being used (like the ITT) to evaluate the adrenal axis.
- b. Gonadotrophin secretion
 - i. Delayed or absent puberty with prepubertal levels of gonadotrophins and sex steroids indicate gonadal dysfunction
 - ii. Precocious puberty may be a direct consequence of low irradiation doses in prepubertal children.
 - iii. In adults oligomenorrhoea in females with oestradiol levels of <100 pmol/L and inappropriately low LH and FSH levels or lower than expected gonadotrophin levels in postmenopausal females confirm the diagnosis. In men testosterone levels are decreased (<10–12 nmol/L) with inappropriately low LH and FSH levels.
- c. ACTH secretion
 - i. Low morning levels of cortisol (< 100 nmol/l) would suggest the diagnosis.
 - ii. A stimulation test with a low peak cortisol (< 500 nmol/L in the ITT or in a short synacthen test with 250 µg ACTH) confirms the diagnosis.
- d. TSH secretion
 - i. TSH levels cannot reliably be used as a diagnostic marker. A free thyroxine levels < 11 pmol/L on more than one occasion suggests central hypothyroidism.
- e. Prolactin secretion
 - i. An increased prolactin level obtained under stress free conditions suggest hyperprolactinemia.
- f. ADH secretion

- i. A urine volume of ≥ 40 ml/kg bodyweight per day with a urine osmolality of < 300 mOsm/kg water would suggest diabetes insipidus.
- ii. Water deprivation test until 12 noon following complete fluid restriction after midnight can confirm the diagnosis (urine osmolality < 700 mOsm/kg; ratio of urine to plasma osmolality < 2)

The demanding nature of these tests warrants referral to an endocrinologist whenever symptoms indicate a potential problem.

Diagnosis of Hypopituitarism (Fernandez 2009)

Pituitary function	Tests	Diagnostic value	Comments
Growth Hormone Deficiency (Biller <i>et al</i> 2002, Hartman <i>et al</i> 2002, Ghigo <i>et al</i> 2007)*	IGF-I (Hartman <i>et al</i> 2002)	41-69% Sensitivity, 95% Specificity	A normal result does not exclude GHD, but a low value in patients with multiple pituitary deficiencies makes a stimulation test unnecessary
	Insulin Tolerance Test (ITT) (Biller <i>et al</i> 2002, Clayton <i>et al</i> 2005, Maghnie <i>et al</i> 2005a)	-Sensitivity 89%, Specificity 95% for a cut-off of 9 mU/l (Biller <i>et al</i> 2002) in adult patients - In the transition period, cutoffs of 15 mU/l (Clayton <i>et al</i> 2005) and 18 mU/l (Maghnie <i>et al</i> 2005) have been advocated	- Gold standard for the diagnosis of GHD - Evaluates cortisol and growth hormone reserve - Only valid if nadir glucose value <2.2 mmol/l, close supervision required (Greenwood <i>et al</i> 1966) - Contraindicated in patients with stroke, epilepsy, coronary heart disease or heart failure - Lack of body mass index-adjusted reference values - Repeated hypoglycaemias can offset the stimulatory input of ITT in non growth hormone deficient subjects (Davis <i>et al</i> 2000, Davis & Tate 2001)
	Glucagon Test (Leong <i>et al</i> 2001, Gomez <i>et al</i> 2002, Conceicao <i>et al</i> 2003)	Sensitivity 97-100%, Specificity 88-100% for a cut-off of 9 mU/l	- Safe and accurate alternative to ITT - Evaluates cortisol and growth hormone reserve - Contraindicated if fasting >48 hours or clinical suspicion of pheochromocytoma or insulinoma - Lack of normative data for the transition period and obese patients
	GHRH + Arginine (Aimaretti <i>et al</i> 1998, Darzy <i>et al</i> 2003, Ghigo <i>et al</i> 2007)	- 95% Sensitivity and 85% Specificity for a cut-off of 13.8 mU/l (Biller <i>et al</i> 2002) - 100% Sensitivity and Specificity for a cut-off of 27 mU/l (Aimaretti <i>et al</i> 1998)	- Safe and accurate - Body mass index-related normative data are available - Less sensitive than ITT in initial phases of radiation-induced GHD (Darzy <i>et al</i> 2003) - Optimal performance requires specific cut-offs (Aimaretti <i>et al</i> 1998, Ghigo <i>et al</i> 2007)
Gonadotroph deficiency (Verga 2002, Bhasin <i>et al</i> 2006, Kazi <i>et al</i> 2007)	-Men: 9 am Total Testosterone, FSH, LH - Clinical assessment of symptoms of androgen deficiency	Low testosterone values in at least 2 consecutive measurements are required for diagnosis	- Prior to biochemical measurements, intercurrent illnesses need to be excluded - Drugs and conditions affecting sex-hormone-binding globulin values can interfere with total testosterone levels. Estimated free testosterone index is recommended in those instances -Age-related total testosterone reference ranges currently lacking
	-Premenopausal women: FSH, LH, Oestradiol + Menstrual History (Verga 2002)	- Low oestradiol levels + low/normal FSH and LH levels in the follicular phase of the menstrual cycle - Oligoamenorrhoea	Clinically and/or biochemically oriented exclusion of other causes of menstrual disorders is required: functional hypothalamic hypogonadism, hyperprolactinaemia, primary ovarian failure (premature, menopausal), hyperandrogenism and drug interference

Minimal requirements for endocrine follow-up

- It is desirable that pituitary hormones are measured before the initial tumour therapy in all cases where the tumour affects hypothalamic or pituitary structures and may thus have induced pituitary dysfunction.
- Patients, who received chemotherapy only, should be scrutinized for
 - Disorders of the gonadal axis such as delay in menarche, pubertal development, oligo-, amenorrhea, infertility or loss of libido.
 - Uncharacteristic symptoms like fatigue indicative of other pituitary dysfunction such as central hypothyroidism or GH deficiency
- In patients treated with brain irradiation
 - Weight, blood pressure, serum glucose and lipid levels should be monitored regularly.
 - Basal pituitary function should be checked at 2-yearly intervals even in the absence of any symptoms during the first 10 years following radiotherapy. Minimal evaluation in adults should include morning cortisol, TSH, fT4, and IGF-I. Females should be screened for changes in regular menstrual cycles. In males morning testosterone levels needs to be assessed.
 - As early HPA dysfunction may be difficult to diagnose further dynamic testing of the pituitary axis may be warranted in all subjects with any of the non-specific clinical symptoms or signs of an endocrine disorder. Referral to a specialist in endocrinology should be mandatory.
 - 10 years after radiotherapy, treatment should be stratified according to symptoms indicative of pituitary dysfunction.

Appendix 5: Symptom related referral pathway to supportive and palliative care services for patients with PNET tumours

Referral to appropriate supportive/ palliative care services can be made at any stage of the patient pathway dependent on symptoms/function (refer to NCAT rehabilitation pathways 2010 for more detail).

Stage of pathway (NICE 2004)	PNET / Medulloblastoma	
	Symptom	Support services
Pre-diagnosis	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech & swallow psychosocial issues	PT/OT OT SLT SS
Diagnosis	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech & swallow psychological issues psychosocial issues	PT/OT/SS OT/SS SLT PS SS
Initial/during treatment	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech & swallow ↓ appetite/weight change hair loss emotional /mobility/pain issues psychosocial issues	PT/OT OT SLT D A CT/PS/C/PC SS
Post treatment	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech & swallow ↓ appetite/weight change hair loss emotional /mobility/pain issues ↓ cognition psychosocial issues	PT/OT/ OT/SS SLT D A CT/PS/C/PC OT/PS SS/PC
Disease progression	Weakness/↓balance/↓mobility/fatigue ↓ Activity of Daily Living/anxiety/↓ex tol ↓ speech & swallow ↓ appetite/weight change emotional /mobility/pain issues ↓ cognition psychosocial issues	PT/OT OT/SS/PC SLT D CT/PS/C/PC OT/PS SS/PC
End of life care	↓ function &ADL/ ↓ swallow/nutrition emotional /mobility/pain issues psychosocial issues	PT/OT/ SLT/D/PC CT/PS/C/PC SS/PC

Key:

- | | |
|-------------------------------------|---|
| A = Appliances | - requiring appliances – prosthetics/wigs |
| C = Chaplaincy | - spiritual/emotional issues |
| CT = Complementary Therapy | - emotional/mobility/pain issues |
| D = Dietitian | - ↓ appetite/weight changes |
| OT = Occupational Therapy | - ↓ ADL/ cognitive deficits/ anxiety issues |
| PC = Palliative Care | - Symptom Control, Advance Care Planning, end of life care |
| PS = Psychological Support Services | - psychological issues/anxiety/ depression |
| PT = Physiotherapy | - weakness and/ or sensory deficits/↓ balance/ ↓ exercise tolerance/ fatigue affecting functional mobility & arm function |

SS = Social Services
SLT = Speech & Language Therapy

- psychosocial issues & welfare benefits
- ↓ speech/language/swallow function

Appendix 6: Additional support for brain tumour patients and carers

Patients and carers may substantially benefit from early contact (as soon after diagnosis as possible) with brain tumour-specific charities and not-for-profit organisations which offer face-to-face, telephone and/or online support opportunities as well as a wide range of comprehensive, practical information regarding brain tumours. Talking through the challenges of brain tumours with other patients and carers who are on the same journey can provide a unique level of emotional support and hope.

Brain tumour charities and not-for-profit organisations:

Brain Tumour Research (an umbrella group of UK brain tumour charities, many of which provide information and support)	http://www.braintumourresearch.org/	01296 733011
Brain Tumour UK (provides information and support)	http://www.braintumouruk.org.uk/	0845 4500 386
International Brain Tumour Alliance (IBTA) (maintains links on its website to numerous brain tumour support groups)	http://www.theibta.org	01737 813872
Samantha Dickson Brain Tumour Trust (provides information and support)	http://braintumourtrust.co.uk/	0845 130 9733
Virtualtrials.com (an international website providing information and online support/discussion groups)	http://www.virtualtrials.com	