Rare Brain and CNS Tumours Guidelines

In collaboration with the

National Cancer Action Team

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

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

Contents

Summary of key recommendations:

1. Unless clinically contra-indicated, such as in a patient of very poor performance status, diagnosis of PCNSL should always be confirmed histologically by image guided biopsy. Steroids are to be avoided pre surgery if at all possible

2. Staging should include measurement of serum LDH; CT scanning of chest, abdomen and pelvis; testicular ultrasonography in elderly males; lumbar puncture for CSF protein/glucose quantification, cytology, flow cytometric analysis and immunoglobulin gene rearrangement studies; and examination of the anterior chamber of the eye, vitreous and ocular fundus. Bone marrow involvement is rare but examination is advised to confirm that intracerebral disease is primary rather than metastatic. Intraocular lesions should be biopsied, and HIV infection should be confirmed or excluded in all patients (grade C, level IV).

3. Biopsy samples for PCNSL and PIOL should be examined in centres or network teams with ready access to suitably qualified neurosurgery, neuropathology, ocular pathology and haematopathology specialists, and access to relevant immunocytochemical and molecular techniques. Typically these patients will be under the care of both a neuroscience and lymphoma MDT.

4. A national register of CNS DLBCL documenting immunophenotype and survival should be considered to allow reliable characterisation of prognostic markers and therapeutic outcome.

5. Baseline neuropsychological tests should be carried out before treatment and repeated during and after treatment (grade C, level IV).

6. A prognostic score should be calculated based upon age >60 years, performance status >1, raised LDH, raised CSF protein and involvement of deep brain matter (grade C, level IV). Patients and relatives should be warned of the risk of neurocognitive deterioration when consent for treatment is being obtained (grade C, level IV)

7. All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD-MTX. The efficacy of HD-MTX has been shown to be improved by using it in combination with cytarabine in a randomised international (IELSG) study. (grade B, level IIa)

8. Consolidation WBRT, 45 Gray in 25 fractions, should be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits (grade B, level IIa).

9. **First line treatment with high-dose chemotherapy and autologous stem cell transplantation should be considered in the setting of a clinical trial (grade B, level III).**

10. **Relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone, temozolomide or second line chemotherapy should be considered for short-term palliation.**

11. **Concurrent intraocular and CNS lymphoma should be treated with systemic HD-MTX-based chemotherapy followed by radiation to both globes. Isolated intraocular disease should be treated in the same way. Intravitreal MTX is an effective treatment option for patients with recurrent disease confined to the eyes (grade B, level III).**

12. **Timely referral to rehabilitation and supportive care services is imperative and is dependent on rapid, comprehensive communication between medical and AHP staff.**

Introduction

Primary central nervous system lymphoma (PCNSL) is usually an aggressive form of non-Hodgkin's lymphoma (NHL) arising in and confined to the brain, spinal cord, and leptomeninges. (Batchelor, 2004; Kluin PM et al., 2008). The intraocular manifestation of PCNSL, which typically occurs in the retina, vitreous humour and, rarely, optic nerve, is termed "primary intraocular lymphoma" (PIOL), although the suitability of this term has been questioned (Coupland and Damato, 2008). PIOL is a variant of PCNSL that can appear prior to, concurrent with, or subsequent to the cerebral disease. Although relatively rare, the incidence of both PCNSL and PIOL seems to be increasing. Over the last three decades survival has improved, mainly because of the introduction of methotrexate (MTX)-based combination chemotherapy. Long-term treatment-related neurological toxicity, however, remains a major problem. The role of consolidation radiotherapy is controversial. These guidelines attempt to provide an evidence-based approach to the diagnosis and management of PCNSL, including its intraocular component.

Methods

These guidelines have been compiled on behalf of the British Neuro-Oncology Society based on the recent British Committee for Standards in Haematology (BSCH) report (Marcus et al., 2007). Recommendations are based on a review of the literature using Medline/Pubmed searches under the heading 'CNS lymphoma' up to April 2007, supplemented where relevant by additional more recent literature.

The guideline group was selected to be representative of UK based medical experts and patients representatives. MEDLINE and EMBASE were searched systematically for publications in English from 1950 - April 2009 using key words: CNS and intraocular

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lymphoma. Criteria for levels of evidence and grades of recommendation are shown in Table 1.

Epidemiology

The incidence of PCNSL has trebled over the last 30 years and, in the USA, is now 4.8 per million population per year. This disease accounts for approximately 5% of all primary brain tumours (Olson et al, 2000). Most series show a slight male preponderance of PCNSL, with most patients aged 60 years or more. A recent European study suggests an incidence of 2.7 per million population (Van der Sanden et al, 2002) and this was supported by a recent UK study, which reported an incidence of 2.8 per million population (Hodson et al, 2005). The increase in the incidence of PCNSL cannot be explained solely by improved diagnostic technology because the incidence of other cerebral tumours has not shown a similar increase. Neither can it be explained by the human immunodeficiency virus (HIV) epidemic since the trend is also observed in populations with a low prevalence of HIV, and it far outpaces the increase seen in other HIV-related malignancies, such as Kaposi's sarcoma (Olson et al, 2000). Nevertheless, within the HIV+ population, NHL is the second most common malignancy, and previously PCNSL accounted for 20% of such cases (Knowles, 2003). Prior to the advent of highly active anti-retroviral treatment, it was estimated that individuals with HIV infection were 3600 times more likely to develop PCNSL than the general population (Cote et al, 1996). Post-HAART the incidence has fallen dramatically (Diamond C 2006; Kreisl T, 2008).

Diagnosis

PCNSL is usually an aggressive high-grade malignant lymphoma, and patients typically present with neurological symptoms developing over a few weeks. A large survey of 248 patients presenting with PCNSL showed that 70% had focal neurological defects, 33% raised intracranial pressure, 14% seizures, and 4% ocular symptoms (Bataille et al, 2000). Headache is a rare complaint, whereas behavioural changes are common. Up to 20% of patients with PCNSL present with ocular involvement, which masquerades as steroid-resistant posterior uveitis. This is usually bilateral, and is often associated with painless loss of vision and/or vitreous "floaters" (Coupland et al. 2004).

Brain imaging in PCNSL usually reveals a mass, which shows contrast enhancement in 80-90% of patients on computerised tomography (CT), and in nearly all patients with magnetic resonance imaging (MRI) (Kuker et al, 2005). Contrast-enhanced brain MRI provides superior lesion characterisation and localisation compared to CT, and is recommended in all suspected cases. The frontal lobe is the most common site of involvement, but PCNSL also has a predilection for the corpus callosum, basal ganglia and deep periventricular structures. Characteristic brain imaging features are of solidly enhancing mass lesions; typically in the periventricular regions, deep grey matter structures and corpus callosum. Lesions are more frequently frontal, and most are in contact with ependyma, meninges or both. A significant proportion are radiologically multifocal, and posterior fossa lesions are well-recognized.

Diffuse signal abnormality without focal mass lesion, and focal non-enhancing parenchymal lymphoma lesions have been reported in the brain on initial imaging at presentation. Haemorrhagic lesions are very rare, and calcification is not reported.

Although radiological appearances of PCNSL may be distinctive, there is considerable overlap with other aggressive intracranial neoplasms such as high grade gliomas and metastases, and inflammatory and infective conditions.

Steroid treatment usually results in marked initial reduction in mass effect and contrast enhancement, and can confound radiological diagnosis and localization of targets for stereotactic biopsy.

Because of the sometimes complex imaging features, experienced neuroradiological review of all imaging is recommended.

Biopsy should only be performed by a neurosurgeon who is a core member of an accredited neuroscience MDT and after discussion of the case in this meeting (except in cases of exceptional clinical urgency). Biopsy should be performed using stereotactic localisation or as an open image guided procedure, and targeting should be undertaken in conjunction with a neuroradiologist. Immediate histopathological diagnostic facilities should be available during this procedure.

Histomorphological Assessment of Suspected PCNSL

Diagnosis of PCNSL requires morphological, immunohistochemical and in relevant cases molecular genetic studies. Tissue is preferentially acquired through stereotactic brain biopsy rather than surgical resection.

In about 90% of cases, PCNSL can be sub-typed as a diffuse large B-cell lymphoma (DLBCL), according to the WHO Lymphoma Classification (Kluin PM et al., 2008). This will be referred to below as **CNS DLBCL**.

PCNSL of T-cell type (referred to here as **T-CNSL**) are less frequent although incidence varies dramatically in different regions (approximately 2-5% of PCNSL in Western counties, 8-14% in Japan and 17% in Korea) (Louis et al, 2007). T-CNSL may have atypical imaging appearances, without contrast enhancement (Dungerwalla et al, 2005). A group of low-grade B-cell PCNSL also exist, including marginal zone B-cell lymphoma and lymphoplasmacytic lymphoma.

Low-grade B-cell PCNSL often present as leptomeningeal or dural associated masses, mimicking meningioma or subdural haematoma (Goetz et al 2002).

Other subtypes of PCNSL are extremely rare and include Burkitt lymphoma, lymphomatoid granulomatosis, plasmacytoma, T-cell rich B-cell lymphoma, and Hodgkin disease (Miller et al, 1994; Jahnke et al., 2005a; Louis et al, 2007).

Leucocyte common antigen (CD45) is useful in distinguishing PCNSL from high-grade glioma and metastatic carcinoma. The typical immunophenotype of CNS DLBCL is CD79a+, CD20+, PAX-5+, BCL-2+, MUM1/IRF4+, BCL-6+/- and CD10-/+, with the tumour cells having a high growth fraction (Ki-67 approximately 90%) (Coupland et al., 2005a).

A high frequency of somatic mutation of the variable region of the immunoglobulin gene (V_H) has been reported in CNS DLBCL and its intraocular counterpart, with a limited germline V_H gene usage (e.g. *V_H4-34)* apparent (Montesinos-Rongen et al., 1999;

Coupland et al., 2005b; Montesinos-Rongen et al., 2009). The high frequency of somatic mutations in the V_H genes, together with the tumour-cell immunophenotype (as above), suggests that CNS DLBCL is derived from mature B cells that have undergone a prolonged interaction with the germinal centre microenvironment and are either at the late germinal centre stage of differentiation or the early post-germinal centre stage. On the basis of the gene expression profiling data available to date, however, it is difficult to place the CNS DLBCL into either the ABC or GCB subtypes, described in systemic DLBCL (Camilleri-Broët et al., 2006; Montesinos-Rongen et al., 2009).

Although morphologically similar, there may be important differences between systemic and CNS DLBCL. For example, a higher proportion of CNS DLBCL express Bcl-2 and MUM-1 than systemic DLBCL (Levy et al 2008; Lin). Similarly, the expression of various immunoglobulin transcription factors is different in CNS DLBCL and systemic DLBCL (Coupland et al 2006; 2005a). Therefore, it would not be appropriate to assume that prognostic markers demonstrated to be of value in the assessment of systemic DLBCL are valid in CNS DLBCL.

Several pathological features have been suggested as possible prognostic markers in PCNSL. The most important is differentiating CNS DLBCL from other types of lymphoma, such as low grade B-cell lymphoma. Within the CNS DLBCL group, there is mixed evidence for several other potential prognostic markers, as outlined below:

- Germinal centre versus activated B-cell immunophenotype is of prognostic significance in systemic DLBCL; however a very high proportion of CNS DLBCL have an immunophenotype comparable to B cells in the transition between germinal centre and post-germinal centre (Levy et al. 2008).

- There have been conflicting results regarding the possible prognostic significance of BCL-6 expression (Braaten et al 2003, Levy et al 2008, Lin et al 2006, Change et al 2003). A recent meta-analysis of 193 patients with CNS DLBCL currently being prepared for publication has found immunohistochemical expression BCL-6 not to be a statistically significant predictor of survival (Galloway, Baber, Bhagavathi, Chang, Lin, Cheng, Levy, Abrey, Braaten, Péoc'h, and Batchelor, 2010, in preparation), although methodological differences between studies makes compaison difficult.

- BCL-2 – two studies of BCL-2 expression have not identified an association with prognosis (Levy et al 2008; Krogh-Jensen et al 1998).

- p27 – One study of 22 patients suggested that expression of p27 was associated with poor prognosis (Kunishio and Nagao, 2006). This has not been assessed in other published studies.

- p53 – Three studies of 33, 37, and 61 patients, respectively, have not demonstrated a significant association between prognosis and p53 expression (Braaten et al 2003; Krogh-Jensen et al 19988; Levy et al 2008). One small study of 14 patients reported a significant negative association between prognosis and p53 expression (Chang et al 2003). The evidence currently available suggests that p53 is not a significant predictor of survival in CNS DLBCL.

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- c-myc expression has been reported to be associated with poor outcome in one small study (Chang et al 2003). Other associations reported by this study (e.g. association between p53 and survival) have not been replicated in larger studies. No further studies assessing this have been reported.

- STAT6 expression by neoplastic and endothelial cells has been reported to be a negative prognostic indicator in a study of 13 patients (Yang et al 2009).

- CD10 – two studies have reported no association between CD10 expression and prognosis (Braaten et al 2003; Levy et al 2008).

- Telomerase activity has been reported to be a significant predictor of prognosis in a small study of 12 patients (Harada et al 1999).

- Vascular endothelial hyperplasia has been reported to be a negative prognostic indicator in one study of 44 patients (D'Haene et al, 2007).

- Higher intratumoural vascular density as assessed with endoglin (CD105) staining, but not with CD34 staining, has been reported to be a poor prognostic indicator in a study of 26 patients (Sugita et al 2006). A study of 32 patients assessing vascularity with factor VIII staining did not find a significant relationship with survival (Roser et al 2004).

- VEGF expression by neoplastic cells has been reported to be associated with better prognosis in one small study of 19 patients (Takeuchi et al 2007), but this was not confirmed in a study of 26 patients (Sugita et al 2007).

- Galectin-3 – One study demonstrated an association between poor prognosis and endothelial expression of galectin-3, but not with expression of galectin-3 by neoplastic cells (D'Haene et al, 2007).

- Tumour cell growth fraction - MIB-1 or Ki-67 labelling index – There is no evidence that this is of prognostic value (Kunishio and Nagao, 2006; Levy et al 2008; Aho et al 1995; Krogh-Jensen et al 1998; Roser et al 2004).

There is no evidence to suggest that morphological subclassification of CNS DLBCL is of prognostic significance (Camilleri-Broet et al 1999). Neither is necrosis (D'Haene et al 2007; Ponzoni et al 2007). A reactive T-cell infiltrate has been reported to be associated with improved survival in one study (Ponzoni et al 2007), not in another (D'Haene et al 2007).

Should ocular manifestation of CNS DLBCL occur prior to detection of cerebral involvement, diagnosis is achieved by performing vitreous biopsy, preferably combined with a sub-retinal aspirate or chorioretinal biopsy. The vitrectomy specimens are notoriously paucicellular and difficult to interpret, so that diagnostic failure rates up to 30% have been reported. These specimens, which should be sent rapidly in cytofixatives, are examined for morphology, immunophenotype and rearrangements of the immunoglobulin and/or T-cell receptor genes using the polymerase chain reaction (IgH and/or TCR-PCR, respectively), depending on the amount of material available for examination (Coupland et

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al. 2004). In patients with visible subretinal deposits, taking additional chorioretinal biopsies and aspirates improves diagnostic accuracy (Coupland et al. 2004).

The diagnosis of patients with suspected PCNSL should be carried out by a centre or network team with ready access to suitably qualified neurosurgery, neuropathology, ophthalmic pathology and haematopathology specialists. Pathologists diagnosing such cases should participate in relevant diagnostic external quality assessment schemes, such as that provided by the British Neuropathological Society and by the British Association of Ophthalmic Pathology. Typically these patients will be under the care of both a neuroscience and lymphoma MDT.

Where clinically safe to do so, steroid therapy should be avoided prior to biopsy, unless there is rapid neurological deterioration when they should be used for a short a period as possible since such treatment may induce rapid transient tumour regression and increase cellular fragility, thereby rendering the biopsy samples difficult to process and to interpret, although a retrospective review from the Mayo Clinic suggested that the diagnostic yield from patients with and without steroid treatment was equivalent (Porter et al 2008).

Recommendation (grade C, level IV): Unless clinically contra-indicated (such as patient of very poor performance status), diagnosis of PCNSL should always be confirmed histologically. Biopsy should be performed by a neurosurgeon who is a core member of an accredited neuroscience MDT and should be performed using a stereotactic localisation apparatus and targeting should be undertaken in conjunction with a neuroradiologist

Biopsy samples for PCNSL and PIOL should be examined in centres or network teams with ready access to suitably qualified neurosurgery, neuropathology, ocular pathology and haematopathology specialists, and access to relevant immunocytochemical and molecular techniques. Where possible, corticosteroid therapy should be avoided prior to biopsy. Typically these patients will be under the care of both a neuroscience and lymphoma MDT.

Recommendation: There is currently insufficient data to allow accurate prediction of prognosis on histopathological grounds for individual patients with CNS DLBCL. There is also insufficient evidence of the prognostic value of any specific histopathological/immunohistochemical feature to recommend routine use in diagnostic practice. A national register of CNS DLBCL documenting immunophenotype and survival should be considered to allow reliable characterisation of prognostic markers.

Staging and other investigations

The International PCNSL Collaborative Group (IPCG) has recently published guidelines on standardized baseline evaluation of patients with newly diagnosed PCNSL (Abrey et al, 2005). Staging has two purposes: to define the extent of CNS involvement and to exclude disease outside the CNS. By definition, systemic disease is not a feature of PCNSL. However, up to 12.5% of patients presenting with disease apparently confined to the CNS

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are found to have extra-neural involvement (O'Neill et al, 1995; Ferreri et al, 1996; Loeffler et al, 1985). A full body CT scan is, therefore, mandatory together with a bone marrow aspirate and trephine biopsy. Elderly males should also undergo testicular ultrasound examination, because testicular lymphoma has a high risk of CNS involvement.

Given the tendency of CNS DLBCL to involve the leptomeninges, a lumbar puncture should be performed unless contraindicated by the risk of coning. The cerebrospinal fluid (CSF) should be analysed cytologically and by flow cytometry, protein and glucose concentrations should be measured and IgH-PCR should be performed. Typical CSF abnormalities include a raised protein concentration, a reduced glucose concentration and a raised white cell count. Cytology reveals abnormal, pleomorphic lymphocytes in 15–31% of cases (Fitzsimmons et al, 2005; Balmaceda et al, 1995), although the frequency is much higher at autopsy (Onda et al, 1999). The finding of a clonal B lymphocytosis in the CSF in conjunction with typical radiology is strongly suggestive of a diagnosis of PCNSL but does not obviate the need for a brain biopsy. Consideration should be given to a single instillation of intra-thecal methotrexate at this time.

Ophthalmic involvement should be sought by non-invasive procedures such as slit lamp examination and ophthalmoscopy, and confirmed by invasive procedures, including vitreous biopsy, subretinal aspiration and/or chorioretinal biopsy, as outlined above (Coupland et al. 2004). Given the strong association with HIV infection, it is important to bear in mind the possibility that intraocular lesions in a patient with PCSNL might be due to opportunistic infection rather than lymphoma. Intraocular biopsy is indicated also when a patient is suspected to have primary or recurrent intraocular lymphoma, for example in the absence of any CNS disease symptoms.

In view of the strong association between PCNSL and HIV infection, HIV serology should also be performed in all patients, who consent to this investigation. Table 1 summarises the baseline investigations recommended by the IPCG.

Recommendation (grade C, level IV): Staging should include CT scanning of chest, abdomen and pelvis; testicular ultrasonography in elderly males; lumbar puncture for CSF protein/glucose quantification, cytology, bone marrow examination with flow cytometric analysis and examination of the anterior chamber of the eye, vitreous and ocular fundus. Intraocular lesions should be biopsied, and HIV infection should be confirmed or excluded in all patients.

Neuropsychological tests

A neuropsychological baseline evaluation should be carried out before treatment and repeated during and after treatment. Cognitive dysfunction is present in 83% of patients at the time of diagnosis. Improvement in cognitive function is observed in approximately 59% of patients who achieve CR after primary chemotherapy (Fleissbach K et al, 2005). However radiotherapy and chemotherapeutic agents are neurotoxic and the neurocognitive risk is increased when modalities are combined. A battery of recommended standardised neuropsychological tests have been suggested in a recent literature review (Correa DD et al, 2007).

Prognostic scoring systems

The prognosis of patients with PCNSL varies markedly between different reported series. Patients considered unfit for chemotherapy have a median survival of just six weeks (Hodson 2005). Those treated with radiotherapy alone have a median survival of about 12 months while the most successful chemotherapy regimens achieve a median survival of up to 60 months (De Angelis et al, 2000). Much of this variability in prognosis is probably caused by selection bias. To compare different studies and to predict the outcome for individual patients, some form of prognostic scoring stratification is required.

The International Prognostic Index (IPI) used for systemic lymphoma is of limited use in PCNSL because two variables – stage and number of extranodal sites - will by definition be constant in all cases. Bessell et al (2004) proposed the Nottingham/Barcelona scoring system to generate a score between 0 and 3 based on the following:

- *age >60 years*
- *ECOG performance status >2*
- *extent of disease (multifocal versus unifocal)*

This scoring system was examined retrospectively in 77 patients with PCNSL treated with either BVAM (carmustine, vincristine, cytarabine and MTX) or CHOD (cyclophosphamide, doxorubicin, vincristine, dexamethasone)/BVAM and whole brain radiotherapy (WBRT). Poor survival correlated with a higher score, median survivals being 55, 41, 32 and 1 month for scores of 0, 1, 2, and 3 respectively.

Ferreri et al. (2003) proposed an alternative prognostic scoring system using the following:-

- *age >60 years*
- *ECOG performance status >1*
- *raised lactate dehydrogenase (LDH)*
- *raised CSF protein*
- *tumour involvement of deep brain matter.*

This was applied retrospectively to a larger number of 378 immunocompetent PCNSL patients treated at 23 centres. Risk of death was categorized as high (score 4-5), medium (score 2-3) or low risk (score 0-1). Two-year overall survival rates were 15%, 48% and 80% respectively. Although potentially useful, this prognostic index requires confirmation using a separate cohort of patients.

Recommendation (grade C, level IV): A prognostic score should be calculated based upon age >60 years, performance status >1, raised LDH, raised CSF protein and involvement of deep brain matter.

PCNSL: Neuropsychological Evaluation

Cognitive status has important implications for quality of life, particularly with regards professional and social functions. One of the most significant issues influencing the development of new therapies for PCNSL is concern about the cognitive impact of current therapies (Abrey et al, 2005).

Cognitive impairments in patients with PCNSL are common due to a number of factors including the effects of the tumour itself and treatment-related neurotoxicity. Although there is a paucity of prospective studies which have included cognitive outcome measures, cognitive impairment has been reported in 83% of patients before treatment (Fliessbach et al, 2005) and in the majority of PCNSL patients after treatment with whole-brain radiotherapy (WBRT) and HD-MTX or with WBRT and blood-brain barrier disruption (BBBD) chemotherapy (Correa et al, 2009; Harder et al, 2004). Patients treated with WBRT with or without chemotherapy have been reported to have more pronounced cognitive impairment than patients treated with MTX-based chemotherapy alone (Correa et al, 2009). Improvement in cognitive functioning has also been observed in patients who achieve CR after primary chemotherapy (Fliessbach et al, 2005). The cognitive domains most frequently impaired include attention, executive functions, memory, naming and psychomotor speed. However, widely used screening instruments such as the Mini-Mental State Examination (MMSE) have low sensitivity and have been reported to grossly underestimate the degree of cognitive impairment in these patients (Fliessbach et al, 2005). Moreover, the MMSE does not assess the cognitive domains typically compromised such as psychomotor speed and executive functions.

Baseline neuropsychological assessment and follow-up assessments are crucial to determine the contributions of tumour to cognitive impairment and gauge the benefit of treatment as well as monitor treatment-related cognitive decline. A recent literature review (Correa et al, 2007) recommended neuropsychological evaluation before treatment (baseline) and in patients with CR at 6 month intervals following treatment completion for the initial 2 years and subsequently annual assessments to capture delayed treatment effects. Although there is no standard battery of neuropsychological tests, the cognitive domains deemed essential to be evaluated as part of a core battery of tests include attention, executive functions (i.e. working memory, sequencing abilities, processing speed), verbal memory and psychomotor speed and to include an estimate of premorbid level of functioning. In order to minimize the problem of content-specific practice effects, neuropsychological test batteries should include tests with alternative versions where possible.

Treatment of CNS DLBCL

The optimal treatment for patients with CNS DLBCL is poorly defined, because of a lack of randomised phase III trials. Most CNS DLBCL trials have been small single-arm phase II studies. Comparing such studies is fundamentally flawed as differences in outcome could be biased by patient selection criteria.

Therapeutic options for CNS DLBCL include steroid therapy, radiotherapy and chemotherapy. A proposed treatment algorithm is shown in Figure 1. Standardized

response assessment criteria have recently published by the IPCG (Abrey et al, 2005) (Table 3). One of the most important adverse effects of CNS-directed radiotherapy and combined modality therapy is neurocognitive impairment. A key objective in treating CNS DLBCL is to achieve the right balance between long-term disease control and neurotoxicity. This is a particular issue with older patients.

Recommendation (grade C, level IV). Patients and relatives should be warned of the risk of neurocognitive deterioration when consent for treatment is obtained.

Glucocorticoids. CNS DLBCL tends to be highly sensitive to steroid therapy (Weller et al, 1999). Radiographically, resolution of disease is detectable within 48 hours of treatment. This response is usually short lived, however, with disease recurrence occurring soon after steroid withdrawal (DeAngelis et al, 1990). A response to steroid is not diagnostic of CNS DLBCL, as similar improvement can be seen in patients with conditions such as neurosarcoidosis and multiple sclerosis. Steroid treatment should, if possible, be avoided before tissue biopsy, because the treatment can interfere with histopathological assessment. To prevent a false-negative result, biopsy should be performed only after a steroid-free interval. This approach risks a recurrence of tumour, which may progress before formal chemotherapy can be started.

Recommendation (grade C, level IV): Dexamethasone is the treatment of choice for short-term palliation but where possible should be avoided before biopsy.

Radiotherapy. Because CNS DLBCL is almost always multifocal, radiotherapy is usually given to the entire brain. A multi-centre prospective trial of whole brain radiotherapy (36-40 Gy) as primary therapy in 41 patients with PCNSL showed an overall response rate of 90%, with nearly 50% of patients achieving complete remission (CR) or near CR. However, 61% of patients relapsed within the radiation field, and the median survival was only 11.6 months (Nelson et al, 1992). In a recent Japanese review of 132 patients with PCNSL treated with WBRT, the median overall survival was 18 months with 39% of patients surviving at least two years. It is difficult to draw firm conclusions from this study, however, as it was retrospective and the radiotherapy was not standardised (Shibamoto et al, 2005).

The main disadvantage of WBRT is its neurotoxicity. This presents as dementia, ataxia and urinary incontinence, and is associated with MRI evidence of leucoencephalopathy, which tend to develop after a delay of several years (DeAngelis et al, 2001; Fitzsimmons et al, 2005; Batchelor & Loeffler, 2006).

Because of its limited long-term efficacy, the benefits of chemotherapy and its propensity to cause delayed neurotoxicity, WBRT alone cannot be recommended as first-line treatment of CNS DLBCL except as palliation in patients unfit to receive chemotherapy.

We recommend WBRT 36 Gy in 20 fractions with an option for a 9 Gy boost to the tumour bed where clinically indicated.

Recommendation (grade B, level III): Whole brain radiotherapy can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy.

CHOP-like chemotherapy. The addition of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) to radiotherapy improved survival in localised aggressive NHL occurring outside the brain. Several studies have examined this approach in CNS DLBCL but have not demonstrated a survival advantage. A prospective RTOG trial treated patients with CHOD and WBRT, achieving a median survival of 16.1 months (Schultz et al, 1996). An MRC randomised trial (Mead et al, 2000) of 53 PCNSL patients showed a trend towards worse survival in the group randomised to CHOP and WBRT compared with those receiving WBRT alone (median survival 14 vs 26 months). Lahance et al, (1994) showed that although CHOP may induce an initial tumour response it was associated with a median survival of only 8.5 months.

Recommendation (grade A, level 1b): There is no role for CHOP-like chemotherapy in the treatment of primary CNS lymphoma.

High-dose systemic methotrexate (HD-MTX). Autopsy studies of CNS DLBCL patients reveal widespread microscopic lymphoma deposits throughout areas of the brain that are apparently normal on MRI (Lai et al, 2002). To be effective, therefore, chemotherapy must be able to cross the normal blood-brain barrier and penetrate the brain parenchyma. This is possible with systemic MTX, in contrast to CHOP-like chemotherapy. To achieve therapeutic concentrations of MTX in the brain, high doses are required (i.e. at least 1.5g/m^2). The steady-state blood:CSF ratio is about 30:1 (Shapiro et al, 1975), so that tumoricidal levels in the CSF are achieved with doses above 3.5 g/m^2. A three-hour infusion achieves higher CSF levels than slower infusions (Higara et al, 1999). CSF penetration is important because of the high frequency of meningeal involvement, even in the absence of a detectable CSF lymphocytosis.

Ferreri et al. (2003) examined 45 patients treated with MTX (doses between 1 and 3.5 g/m^2) and showed that outcome correlated positively with calculated area under the curve, which was in turn affected by creatinine clearance, MTX dose, rate of administration and dosing intervals (more or less than 3–4 weeks). Glass et al. (1994) showed dosing intervals of 10 days and 3 weeks to be equivalent. These findings support the use of MTX > 3 g/m^2 delivered over not more than 3 hours at 2-3 week intervals. Although HD-MTX as a single agent without radiotherapy is effective at inducing remission, two recent studies have shown a high rate of early relapse with median times of 12.8 months (Batchelor et al, 2003) and 13.7 months (Herrlinger et al, 2002). Glass et al. (1994) treated 25 patients with 1 – 6 courses of MTX 3.5g/m^2 prior to radiotherapy and achieved a median survival of 33 months. O'Brien et al. (2000) treated 46 patients (median age 58 years) with two courses of MTX prior to WBRT and reported a median survival of 36 months.

HD-MTX can be safely given to elderly patients provided that due attention is given to creatinine clearance. In a report by Jahnke et al. (2005), 154 patients received 619 cycles of HD-MTX followed by leukovorin rescue. MTX was given at 4g/m^2 but with attenuation if the creatinine clearance was reduced. Toxicity was generally mild and not significantly higher among the 89 patients aged > 60 years, although older patients received a lower dose. The EORTC 26952 trial examined single-agent HD-MTX in 50 patients over the age of 60 years with PCNSL. The main complication was myelosuppression, with grade III/IV neutropenia occurring in 19% of cases. The CR rate was 48%, one-year progression-free survival 40% and median overall survival time 14.3 months. Most patients improved or preserved their cognitive function until relapse (Hoang-Xuan et al, 2003). These results compare favourably with those achieved with WBRT.

Combination chemotherapy based on HD-MTX. Bessell et al. (2002) reported a median survival of 38 months in 31 consecutive patients (median age 59 years) treated with one cycle of CHOD followed by two cycles of BVAM (carmustine, vincristine, cytarabine and MTX 1.5g/m^2) followed by radiotherapy. Abrey et al (2000) treated 52 patients (median age of 65 years) at a single centre with five cycles of MPV (MTX 3.5g/m^2, procarbazine 100mg/m^2/d and vincristine 1.4 mg/m^2) followed by WBRT and 2 courses of cytarabine (3g/m^2 days 1 & 2). The overall median survival was 60 months. Using a similar regimen but a lower dose of MTX (2.5 g/m^2) followed by high dose cyatarabine DeAngelis et al. (2002) treated 102 patients in a multicentre study and achieved a median survival of 36.9 months. Poormans et al. (2003) treated 52 patients in a multicentre trial with two cycles of MBVP (MTX 3 g/m^2, teniposide, carmustine and methylprednisolone) and reported a median survival of 46 months. Moreton et al. (2004) have proposed a CNS-targeted regimen: IDARAM (idarubicin, dexamethasone, cytarabine and MTX 2 g/m^2) that has been piloted in a few patients, with encouraging preliminary results.

The efficacy of HD-MTX has been shown to be improved by combining it with the CNS-penetrating chemotherapeutic agent, cytarabine, in a multicentre Phase II study, involving 79 patients, performed by the IELSG (Ferreri, Lancet Oncology 2009). After chemotherapy, 7 MTX and 18 MTX+araC pts achieved CR (18% vs. 46%; p=0.0002); and 9 MTX and 9 MTX+araC pts achieved PR (ORR: 40% vs. 69%; p=0.0002). At a median follow-up of 25 months, 31 MTX and 22 MTX+araC pts experienced failure (PD, relapse, death), with a 3-yr event-free survival (EFS) of 20% and 38% (p=0.01), respectively. Fifteen MTX and 21 MTX+araC pts were alive at interim analysis, with a 3-yr OS of 34% vs. 47% (p=0.12). Although previously results have been complicated by the fact that consolidation radiotherapy was not offered to all patients, stratification in this study was based on IELSG score and administration of WBRT. Although the majority of patients received WBRT, centres were allowed to omit this to patients >60 years in CR after chemotherapy, and this variable was incorporated into the outcome analysis.

In summary, although HD-MTX is widely accepted as the single most important agent in the treatment of PCNSL, improved efficacy has been observed when the drug is used in combination with other agents that penetrate into the CNS. The optimum combination of chemotherapeutic agents, however, remains unclear.

Recommendation (grade B, level IIa): All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD-MTX (3-5 doses of $\geq$ 3g/m^2 delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks). The efficacy of HD-MTX appears to be improved by using it in combination with cytarabine but such treatment should be based on established protocols.

Chemoradiotherapy. Many of the therapeutic regimens outlined above involve MTX-based chemotherapy followed by WBRT. Combined modality therapy can be very effective but is also associated with age-related neurotoxicity. In one retrospective study of 226 patients, many of whom received combined modality treatment, late neurotoxicity was observed in 26% of patients after a median follow-up of six years. However, since the study was retrospective, this figure may be an under-estimate. In addition to its adverse effect on quality of life, neurotoxicity was also associated with a poor prognosis. Thus, patients who developed late neurotoxicity in this series survived a median of 12 months from onset of neurotoxicity despite ongoing tumour remission.

The risk of delayed neurotoxicity is generally thought to be greatest in elderly patients. Abrey et al (1998) showed that late neurotoxicity developed in all patients older than 60 years receiving combined modality treatment, with symptoms developing after a median of 13 months. However, neurotoxicity can also occur in younger patients with CNS DLBCL. Harder et al (2004) performed neuropsychological assessment on a cohort of 19 patients aged less than 60 years in remission following treatment with MBVP and consolidating radiotherapy. Cognitive impairment was found in twelve patients, and was severe in four. The patients were not assessed psychologically before treatment, so it is not possible to establish how much of the cognitive impairment was caused by the original tumour and how much was iatrogenic.

Patients who have received consolidation WBRT are more likely to develop neurotoxicity, thereby providing indirect evidence that those receiving combined modality therapy are more likely to develop this complication from the WBRT than from chemotherapy. Pels et al. (2003) treated 65 consecutive patients with MTX combination chemotherapy without elective radiotherapy. Response rates and duration were similar to those seen in studies employing chemoradiotherapy. The incidence of neurotoxicity was substantially lower, however, with only two patients developing severe cognitive dysfunction. MRI changes of leucoencephalopathy were seen in one third of patients but these were not associated with cognitive dysfunction, confirming the lack of correlation between clinical and radiological features of post-treatment neurotoxicity. Fleissbach (2003) performed a prospective neuropsychological assessment of ten patients from the above series with follow-up for a median of 36 months and demonstrated no decline in function following treatment. Correa et al. (2004) also compared the cognitive performance of patients in remission following chemotherapy alone against that of patients treated with chemoradiotherapy. Those treated with chemotherapy alone developed significantly less impairment of cognitive function than those treated with chemoradiotherapy. Indeed, chemotherapy alone can actually improve or stabilise cognitive function despite altering the MRI appearance of the white matter (Fliessbach et al, 2005; Neuwelt et al, 2005).

Omitting radiotherapy apparently reduces the risk of neurotoxicity but may increase the rate of tumour relapse. The relative importance of these two factors seems to be influenced by patient age. Abrey et al (2000) treated 22 patients aged >60 years with MTX-containing chemotherapy without cranial irradiation and compared these individuals to a similar group of 12 elderly patients who received both chemotherapy and cranial irradiation. The latter group were less likely to relapse but had a higher mortality from neurotoxicity, resulting in equivalent median survivals of 33 and 32 months, respectively. Bessell et al (2002) compared 31 patients treated with chemotherapy and WBRT (45Gy) with 26 patients who received chemotherapy and a reduced dose of consolidating WBRT (30.6Gy). In patients under 60 years of age, the reduction in radiation dose resulted in an increased rate of relapse at 3 years from 25% to 81%. There was no significant difference in relapse rate in patients aged 60 years or over. In a large retrospective analysis, Ferreri et al. (2002) was unable to detect a survival benefit from consolidating WBRT amongst patients who had achieved complete remission following MTX based chemotherapy.

Taken together, these data suggest that consolidation radiotherapy is beneficial in patients with CNS DLBCL less than 60 years old after HD-methotrexate, who have had a CR to treatment

A dose of 45 Gray in 25 fractions is recommended. Lower doses may result in a greater risk of relapse.

However, patients aged 60 years or over, the balance between earlier relapse and neurotoxicity is less clear. Radiotherapy should only be considered after considering the patients current neurocognitive condition and a discussion of the risks of neurocognitive decline with the patient and carers.

Recommendation (grade B, level IIa): Consolidation WBRT, up to 45 Gray total dose should be considered in patients under the age of 60 responding to MTX-based chemotherapy: to patients unless there is a significant neurocognitive deficit following chemotherapy, but in patients aged 60 years or over, the neurocognitive side-effects are more likely to outweigh the potential benefits.

Autologous stem-cell transplantation (ASCT). High dose therapy with stem cell rescue has been investigated in the hope of dispensing with consolidation radiotherapy in patients achieving CR after MTX-based chemotherapy. Abrey et al (2003) treated 28 patients with MTX-cytarabine induction. Fourteen patients subsequently received high-dose therapy with BEAM and stem cell rescue. The median event-free survival of these 14 patients receiving ASCT was 9.3 months. Cheng et al. (2003) also used TBC in seven patients, resulting in one toxicity-related death. The median event-free survival was not reached at 24 months. Recently 11 of 13 patients (age 38-67 years) underwent high-dose carmustine/thiotepa conditioned ASCT after methotrexate and cytarabine/thiotepa induction-chemotherapy. Seven patients were subsequently in CR and 4 in PR, and WBRT was restricted to those in PR. With a median follow-up of 25 months, 3 year DFS and OS was 77% (Illerhaus 2008). Taken together these data suggest a role for ASCT in first line therapy. This will be evaluated in an IELSG randomised clinical trial where outcome after consolidation with WBRT or ASCT will be compared.

Recommendation (grade B, level III): First line treatment with high-dose chemotherapy and autologous stem cell transplantation has been shown to be feasible and effective. Further evaluation should be conducted in the setting of a prospective randomised clinical trial.

Intrathecal chemotherapy. Most regimens involving intrathecal (IT) chemotherapy in CNS DLBCL have reported no benefit if sufficient doses of systemic MTX were used. Glantz et al (1998) measured MTX concentrations in the CSF of patients treated with IT versus systemic high-dose MTX and found peak levels to be equivalent but more prolonged in patients receiving MTX by the intravenous route. Ferreri et al (2001) omitted intrathecal chemotherapy in a small single arm trial of 13 patients treated with MTX $3g/m^2$, vincristine, procarbazine and consolidating WBRT. Results were in line with other MTX-containing regimens and no meningeal relapses were reported. Ferreri et al (2002) also retrospectively analysed a cohort of 370 patients and found that intrathecal chemotherapy did not improve outcome amongst those receiving systemic MTX. This lack of correlation was consistent on subgroup analysis of patients, both with and without CSF involvement.

Recommendation (grade B, level III): There is no evidence supporting a role for intrathecal chemotherapy unless there is evidence of meningeal (CSF) involvement at diagnosis, as an adjunct to high-dose intravenous MTX in patients with PCNSL.

Rituximab. As mentioned above, almost all PCNSL express the B-cell antigen, CD20. Unfortunately, however, intravenous, rituximab has poor penetration of the intact blood-brain barrier.

Shultz et al. (2004) reported the use of intraventricular or intrathecal administration of 10 – 40 mg of rituximab in six patients. A response was seen in all four patients with meningeal disease. The effectiveness and toxicity of intraventricular rituximab in relapsed CNS lymphoma has also been examined in a prospective phase I dose escalation study. Ten patients were allocated to receive 9 intraventricular injections of rituximab at doses of 10mg, 25mg or 40mg over a 5-week period. The maximum tolerated dose was found to be 25mg. Six of the 10 patients had cytological improvement of the CSF, with complete clearance of malignant cells in 4 cases. Two patients had improvement of intraocular manifestations and brain parenchymal disease regressed in one patient (Rubenstein et al. 2007). There is some evidence to suggest that the therapeutic efficacy of rituximab when given via the intrathecal route might be improved by co-administration of autologous serum (Takami et al, 2006). Taken together, these findings suggest that there may be role for intraventricular or intrathecal rituximab in the treatment of relapsed PNCSL, especially if disease is largely confined to the meninges. However, in view of the current paucity of data its use remains experimental at the present time.

Recommendation (grade B, level III): Rituximab administered via the intrathecal or intraventricular route should not be used in the routine treatment of CNS DLBCL except in a clinical trial.

Disruption of the blood brain barrier. A few centres have evaluated chemical disruption of the blood-brain barrier, in an attempt to increase penetration of chemotherapy into cerebral tissue. Hypertonic mannitol was infused into the carotid or vertebral artery under general anaesthesia, to produce a transient osmotic disruption of the blood-brain barrier.

Doolittle et al. (2000) combined intra-arterial mannitol and chemotherapy in a multicentre trial including 53 PCNSL patients and demonstrated its safety and efficacy. CR was seen in 75% patients but survival data were not reported. Tyson et al. (2003) treated 37 relapsed PCNSL patients with intra-arterial carboplatin and blood-brain barrier disruption (BBBD). The same group is investigating the role of BBBD in combination with immunotherapy and radioimmunotherapy. Although this approach may lead to promising developments in the future, the current survival data are not significantly better than those achieved with current intravenous HD-MTX regimens; therefore, they do not justify the technical complexity and associated risk involved in administration.

Recommendation (grade B, level IIb): Pharmacological disruption of the blood-brain barrier should not be performed as part of the treatment of CNS DLBCL unless as part of a clinical trial.

Relapse/salvage treatment. Patients who fail MTX-based treatment and who have not previously received WBRT can receive WBRT as salvage therapy. Nguyen et al (2005) examined WBRT in 27 consecutive patients who had failed MTX-based chemotherapy. Median radiation dose was 36 Gy, and seven patients also received a boost of 19–40 Gy. Thirty-seven percent of patients achieved a CR and 37% a partial remission (PR). Median progression-free survival was 57 months for patients with CR and nine months for those achieving PR. Median overall survival was 10.9 months. This compares favourably with results achieved using WBRT as primary therapy and suggests that MTX resistance is not necessarily associated with radio-resistance.

Soussain et al. (2008) examined the use of salvage chemotherapy with cytarabine and etoposide followed by intensive chemotherapy (thiotepa, busulphan and cyclophosphamide) and stem-cell rescue in 43 patients with relapsed (n=22) or refractory (n=17) disease. Twenty seven patients proceeded to ASCT, 15 of whom were chemosensitive to induction chemotherapy and 12 patients who were refractory. Overall two-year survival probablility was 45% in the whole population and 69% among the 27 patients who proceeded to ASCT. Other groups have attempted salvage therapy with further MTX, high-dose cytarabine or PCV (procarbazine, lomustine, vincristine) with some success. More recently, temozolomide (Reni et al, 2004), topotecan (Fischer et al, 2004) and intra-arterial carboplatin (Tyson et al, 2003) have been evaluated in a few patients with response rates of 26-37%. Arellano-Rodrigo et al. (2003) investigated the used of etoposide, ifosfamide and cytarabine in 16 patients refractory to or relapsed after treatment with CHOD/BVAM: six patients achieved a CR. The survival at 12 months was 41%. Glucocorticoids play a useful a role in short-term palliation, and there are case reports of steroids alone producing long-term disease control (Weller et al, 1999).

Recommendation (grade B, level III): Relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone should be considered for short-term palliation. Alternative chemotherapeutic regimens such as temozolomide or combination chemotherapy with autologous stem cell transplantation show some promise but require further evaluation in clinical trials.

HIV Lymphoma

The incidence of HIV lymphoma has fallen dramatically since the introduction of HAART and is now of the order of 1 per 1000 patient years (Bower et al 2006) Although patients frequently present with more extensive multi focal disease and a generally poorer performance status than non_HIV positive patients , there are recent data suggesting that useful disease free survival can be achieved by optimisation of antiretroviral therapy and High dose Methotrexate based regimens , with median response durations in some small series of approximately eighteen months. (Bower et al 2008) In those patients not suitable for such approaches , palliative whole brain RT may produce useful albeit short term benefit

Recommendation: Grade C Level III :HIV positive patients presenting with PCNS lymphoma should undergo the same investigations and as those with HIV negative disease . Patients should receive optimal HAART therapy and then receive the same therapy as non- HIV positive patients in similar prognostic groups and with similar performance status

Treatment of Primary Intraocular Lymphoma (PIOL)

Although considered a variant of PCNSL, PIOL is associated with therapeutic considerations of its own. As with PCNSL, there is a paucity of data on which to base treatment recommendations, which therefore remain controversial.

Historically, the mainstay of treatment for PIOL was ocular radiotherapy (30–45 Gy to both eyes). High response rates were achieved but most patients relapsed in the eye and brain, the median survival being only 12-20 months (Ferreri et al., 2002; Nelson, 1999; Margolis et al, 1980). In patients who survived for longer periods, ocular complications such as radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, loss of limbal stem cells, cataracts and glaucoma were common.

Systemic chemotherapy alone offers the possibility of simultaneous treatment of intracranial and intraocular disease without the risk of radiation-induced toxicity. Consequently, some centres have proposed this approach for combined PIOL/PCNSL (DeAngelis, 2001; Valluri et al., 1995). Most systemic chemotherapy regimens are based on HD-MTX and/or cytarabine because of their ability to penetrate the blood-brain barrier

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and blood-ocular barrier (Plowman et al., 1993; Valluri et al., 1995; Batchelor, 2003a and Batchelor, 2003b).

The efficacy of systemic chemotherapy as a treatment for PIOL depends on intraocular pharmacokinetics. For example, seven of nine patients with PIOL treated with HD-MTX alone (8g/m² body surface area) showed a good ocular response, with persisting remission in four patients after 8 to 36 months (Batchelor et al., 2003b). Micromolar MTX concentrations were present in both ocular chambers four hours after the infusion in all eight patients. Following systemic treatment with high dose cytarabine, therapeutic levels in intraocular fluids as well as responses exceeding 15 months have been documented (Baumann et al., 1986). However, several studies (Soussain et al., 2001; Strauchen et al., 1989) have shown that CNS lymphoma may respond differently from intraocular disease. This suggests that penetration of chemotherapeutic agents into these two compartments may differ, and that the maintenance of sufficient levels of MTX in the vitreous humour is difficult. Systemic MTX and cytarabine can both cause ocular side-effects, which include periorbital oedema, conjunctivitis, keratitis, and photophobia (Valluri et al. 1995). To avoid these complications, some authors have suggested that MTX and/or cytarabine should be administered intrathecally instead of systemically (Mason and Fischer, 2003).

Combined modality therapy, including CNS-penetrating systemic chemotherapy, intrathecal MTX, and radiation to the brain, orbits and spinal cord is associated with a relatively long median survival of 36 months from diagnosis (Char et al. 1981). However, up to 50% of patients treated in this way relapse in the eyes, and delayed neurotoxicity is common (Abrey et al., 1998; DeAngelis et al., 2002). Once tumour relapse occurs, additional treatment with systemic chemotherapy is often required, exacerbating any pre-existing toxicity (Plowman et al., 1993). As with PCNSL without overt ocular involvement, the beneficial anti-tumour effect in PIOL of consolidation radiotherapy to the eyes and brain needs to be carefully balanced against the risk of radiation-induced toxicity.

High-dose chemotherapy with thiotepa, busulfan and cyclophosphamide (TBC) followed by autologous bone marrow transplantation was administered in 12 patients with refractory or recurrent PIOL or PCNSL (Soussain et al., 1996). Nine of these patients achieved CR in the brain and the eye. Median overall survival was 53 months after relapse. However, the therapy was highly toxic and proved fatal in five out of seven patients older than 60 years (Soussain et al., 1996).

Intravitreal MTX has been used to treat patients with isolated and recurrent intraocular lymphoma. Successful conservation of vision has been achieved in patients who had previously received systemic chemotherapy, with or without radiation (Helbig et al., 2003). Repeated intravitreal injections of MTX are necessary to achieve a good local tumour response. Complications include keratitis, conjunctivitis, ocular hypotony, macular oedema and cataract. The major drawback of intravitreal treatment is that it does not prevent death from CNS involvement.

A range of therapeutic agents are currently being investigated for treatment of PIOL. These include oral trofosfamide (Jahnke et al., 2004) and monoclonal antibody therapy directed against B-cell antigens (e.g. rituximab). However, owing to paucity of data, these should be regarded at experimental at the present time.

Recommendation (grade B, level III): Concurrent intraocular and CNS lymphoma should be treated with systemic HD-MTX-based chemotherapy followed by radiation to both globes and possibly also the brain if the patient is less than 60 years old. Isolated intraocular disease should be treated in the same way. Intravitreal MTX is an effective treatment option for patients with recurrent disease confined to the eyes.

Primary CNS lymphoma of T-cell type (T-CNSL).

T-CNSL is currently a poorly understood group of entities (Ferracini R et al., 1995; Shenkier et al., 2005; Levin et al., 2008). Most correspond to peripheral T-cell lymphoma, unspecified; however, rare examples of anaplastic large cell T cell lymphoma and NK/T-cell lymphoma have also been described (Shenkier et al., 2005). T-CNSL are associated with a very wide range of clinical symptoms (Levin et al., 2008) as well as histomorphological features: consequently, there is often a delay in the diagnosis in these patients. Exceptionally rarely, intraocular lymphoma of T-cell type can arise primarily in the retina and vitreous body, and may or may not be associated with cerebral disease (Coupland et al., 2005c)

The histopathological features of T-CNSL are very diverse, ranging from infiltrates of overtly atypical T cells, to a pattern of granulomatous inflammation associated with relatively inconspicuous neoplastic T cells. They may be associated with a reactive B-cell infiltrate. T-cell PCNSL may express CD4, CD8, both, or neither antigen. Given the histological similarity between some cases of T-CNSL or T-PIOL and reactive inflammatory conditions, a low threshold for obtaining T-cell receptor studies on the cerebral or intraocular biopsies is advisable (Shenkier et al., 2005). This should involve TCR-PCR for both gamma and beta receptors, if possible.

Because of the rarity of the disease, the treatment of T-CNSL is not standardised. In the largest study by Shenkier et al, which reports 45 cases of T-PCNSL, the patients were treated by chemotherapy followed by irradiation (53%); chemotherapy alone (7%); intra-arterial chemotherapy with BBBD (4%); and irradiation alone (24%). MTX was the most commonly used agent (n=29 patients), either alone (n=11) or in combination with other agents (n=18). The MTX dosage ranged from 2g/m2 to 8g/m2 per month, with the number of courses ranging from one to 12 (median, 4.5. courses). One patient had high-dose chemotherapy and autologous peripheral blood stem-cell transplantation following MTX and irradiation. Further, 17 patients received IT MTX either alone (n=8) or alternating with IT cytarabine (n=9). Irradiation was administered to 35 (78%) patients. This consisted of WBI in 34 patients, with a boost to the tumour bed in 12 patients.

Although some studies suggest that the outcome of T-CNSL is better than that of CNS DLBCL (Ferracini R et al., 1995), this is not supported by all investigators (Shenkier et al., 2005). With respect to prognosis prediction within T-CNSL, few published series are available to provide information. Multivariate analysis of the data provided by Shenkier et al suggests that performance status (greater than 2) and MTX use were significantly associated with a better outcome with hazard ratios of 0.2 (95% CI, 0.1 to 0.4) and 0.4 (95% CU, 0.2 to 0.8), respectively.

An unpublished audit of a series of T-cell PCNS undertaken at Great Ormond Street Hospital, The Royal Free Hospital, and The National Hospital For Neurology and Neurosurgery, supplemented by data from published cases from other centres identified nine cases in which the expression of CD4 and CD8 antigens could be compared with survival (Jacques TS, Cave J, Galloway M, Dogan A, unpublished data). Although the number of cases are insufficient for meaningful formal statistical assessment, 5/5 patients with a CD4+/CD8- immunophenotype were alive 18 months following diagnosis, compared with 2/4 patients with a CD8+/CD4- immunophenotype. A previous study of non-CNS T-cell lymphomas has suggested a worse prognosis for patients with CD8+/CD4- than CD8-/CD4+ lesions. A much larger series of T-cell lymphomas with immunophenotypic profiling and clinical follow-up are required to determine pathological indicators of prognosis in T-cell PCNSL.

Recommendation – (grade C, level IV) T-CNSL is often a very difficult histological diagnosis, and an experienced neuropathologist, ocular pathologist and/or a haematopathologist should be involved in the investigation of these cases. In addition to immunohistochemistry, T-cell receptor studies may help to confirm the diagnosis. (grade C, level IV) T-CNSL is a rare entity for which reliable prediction of prognosis is not currently possible. Large series with detailed immunophenotypic studies are required. A national register of patients with T-cell PCNSL should be developed.

CNS lymphoma – Low Grade B-cell Lymphomas of the Dura/ Leptomeninges

Approximately 3-4% of PCNSL is reported to be histologically low grade (Jahnke et al 2006). Low grade PCNSL are not a homogenous entity. An international review of 40 patients with low grade PCNSL found B-cell lymphomas cases diagnosed as lymphoplasmacytic lymphoma (n=11), follicular lymphoma (n=1), 'small lymphocytic lymphoma, low grade' or 'poorly differentiated lymphocytic, low grade (n=20) (Jahnke et al 2006). 20% of cases were diagnosed as low-grade T cell lymphomas. Four patients had leptomeningeal involvement which was exclusive in two cases. The median overall survival in these patients was 79 months. Two patients who received surgical resection as the only therapeutic modality were alive without evidence of recurrent disease after 42 and 20.5 months.

Low-grade B-cell lymphomas occurring arising in the dura or the leptomeninges are considerably rarer than CNS DLBCL, appearing in the literature as either single case reports or as small case series (Kumar et al. 1997; Itoh et al 2001; Goetz P et al., 2002; Tu et al., 2005) Although other low-grade B-cell lymphomas have been described arising primarily in the CNS, the most common of these neoplasias are extranodal marginal zone B-cell lymphomas (CNS EMZL), and usually in association with the dura. They demonstrate similar morphological and immunophenotypical characteristics of EMZL in other locations. That is, they consist of a mixture of centrocyte-like cells, monocytoid cells and plasmacellular-differentiated cells located in the marginal zone surrounding reactive

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follicles. In some extreme examples of CNS EMZL with plasmacellular differentiation, amyloid deposition may be seen. The immunophenotype of CNS EMZL is: CD20+, CD43 +/-, IgM+. Trisomy 3, t(14;18) and t(3;18) were reported to be the most common chromosomal abnormalities in these tumours (Kumar et al. 1997; Goetz P et al., 2002; Tu et al., 2005).

Studies suggest that CNS EMZL most commonly occur in middle-aged females, with or without autoimmune disease, as single isolated masses, and tend to clinically mimic the symptoms and signs of meningiomas. Indeed, many of the patients with CNS EMZL were treated with radiosurgery for meningioma, and it was only on histological examination that the true diagnosis was established (Kumar et al. 1997; Itoh et al 2001; Goetz P et al., 2002; Tu et al., 2005). Low-dose and limited volume radiotherapy has been recently recommended in these patients (Puri et al., 2008).

Similar to these lymphomas in other sites, CNS EMZL are characterized by an indolent clinical course. They are not associated with systemic dissemination or ocular involvement, although the primary intraocular counterpart can occur independently in the choroid (Coupland and Damato, 2008).

Recommendation – (?grade C, level IV) Low grade PCNSL is inhomogeneous and relatively rare. Literature on response to therapy is largely anecdotal, however it should be noted that some patients respond very well to surgical resection, or local radiation.

CNS lymphoma - Intravascular Lymphoma subtype.

Intravascular B-cell lymphoma (syn. malignant angioendotheliomatosis and angiotropic lymphoma) is a rare subtype of DLBCL, characterised by the presence of tumour cells in blood vessels, especially capillaries (Gatter et al., 2002). This type of lymphoma is frequently seen in skin and the central nervous system and can present with vague systemic symptoms. While in the skin it presents with skin plaques and nodules, rash and unexplained fever, in the CNS it is associated with multiple peripheral infarcts due to obstruction of the small blood vessels by the tumour cells. During late stages, there may be an extravascular component, and may therefore present as a cerebral mass lesion (Imai et al., 2004). Intravascular DLBCL can present at any age but typically occurs in the seventh decade of life with no gender preference.

It can be subdivided into the a) "classic" variant of intravascular DLBCL, although exceptionally rarely they can be of T-cell type; and the b) "Asian variant", characterised by a large admixed proportion of histiocytes and haematophagocytosis. In some cases, there is an association with Helminthic infections (e.g. Fasciola and Anisakis) as well as with viruses (e.g. HTLV-1 and EBV). In 15% of patients, there is an association with either a previous or concomitant malignancy, including another NHL.

Intravascular DLBCL is characterised by a B-cell immunophenotype (CD79a, CD20 and PAX5) and immunoreactivity for BCL-2, MUM1/IRF4 and BCL-6 Gatter et al., 2002). The

angiotropic property of the tumour cells is postulated to be due to loss of adhesion molecules such as CD29 and CD54 (Ponzoni et al 2000).

Despite some reports of complete remission and long-term survival in patients with intravascular DLBCL (DiGiuseppe et al., 1994), the prognosis is usually dismal as the disease responds poorly to chemotherapy. The chemotherapy usually includes anthracyclines (Ferreri et al., 2004); however, better responses may be attained with the inclusion of Rituximab (Ferreri et al., 2008). The role of intensive CNS directed therapy is unclear.

Recommendation – A national register should be developed and linked to treatment given and outcomes through the NCIN. Patients are to be treated with systemic Rituximab containing chemotherapy (eg. R-CHOP) and primary CNS prophylaxis.

CNS Hodgkin Lymphoma

Involvement of the CNS by Hodgkin Lymphoma is very rare. The largest series currently reported described 16 patients with CNS involvement by Hodgkin disease. 8 patients presented with CNS involvement at presentation, 2 of whom had disease limited to the CNS (Gerstner et al 2009). 8 patients developed CNS involvement at relapse. Median overall survival for all 16 patients was 60.9 months from first diagnosis of lymphoma and 43.8 months from diagnosis of CNS involvement. As only 2 patients had primary CNS Hodgkin Lymphoma the data should be regarded with caution; however, it is noteworthy that one of these patients (treated with resection, whole brain radiotherapy – 35 Gy and no chemotherapy) was reported to be in complete remission over 90 months following diagnosis.

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Table 1. Levels of evidence and recommendation

Classification of evidence levels	
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study*
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.
Classification of recommendations	
A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels Ia, Ib).
B	Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III).
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

* refers to a situation in which implementation of an intervention is outwith the control of the investigators, but an opportunity exists to evaluate its effects.

Table 2. BNOS guidelines for baseline evaluation.

Pathology	Clinical	Laboratory	Imaging
Report by histopathologist with expertise in neuropathology, ocular pathology and/or haematopathology and access to specialist neuropathology, ocular pathology and/or haematopathology	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI scan (CT if MRI contraindicated)
Immunophenotyping and where appropriate molecular testing	Dilated eye examination, including slit lamp examination and fundoscopy	Vitreous biopsy +/- chorioretinal biopsy, immunohistochemistry, IgH-PCR[1], serum LDH level	CT of chest, abdomen and pelvis
	Record prognostic factors (age, performance status)	CSF cytology, flow cytometry, IgH-PCR	Bone marrow aspirate and trephine biopsy
	Serial evaluation of cognitive function	24-hour urine collection for creatinine clearance if HD-MTX planned	Testicular ultrasound in elderly males

[1] Polymerase chain reaction for detection of immunoglobulin heavy chain rearrangements.

Table 3. IPCG response criteria

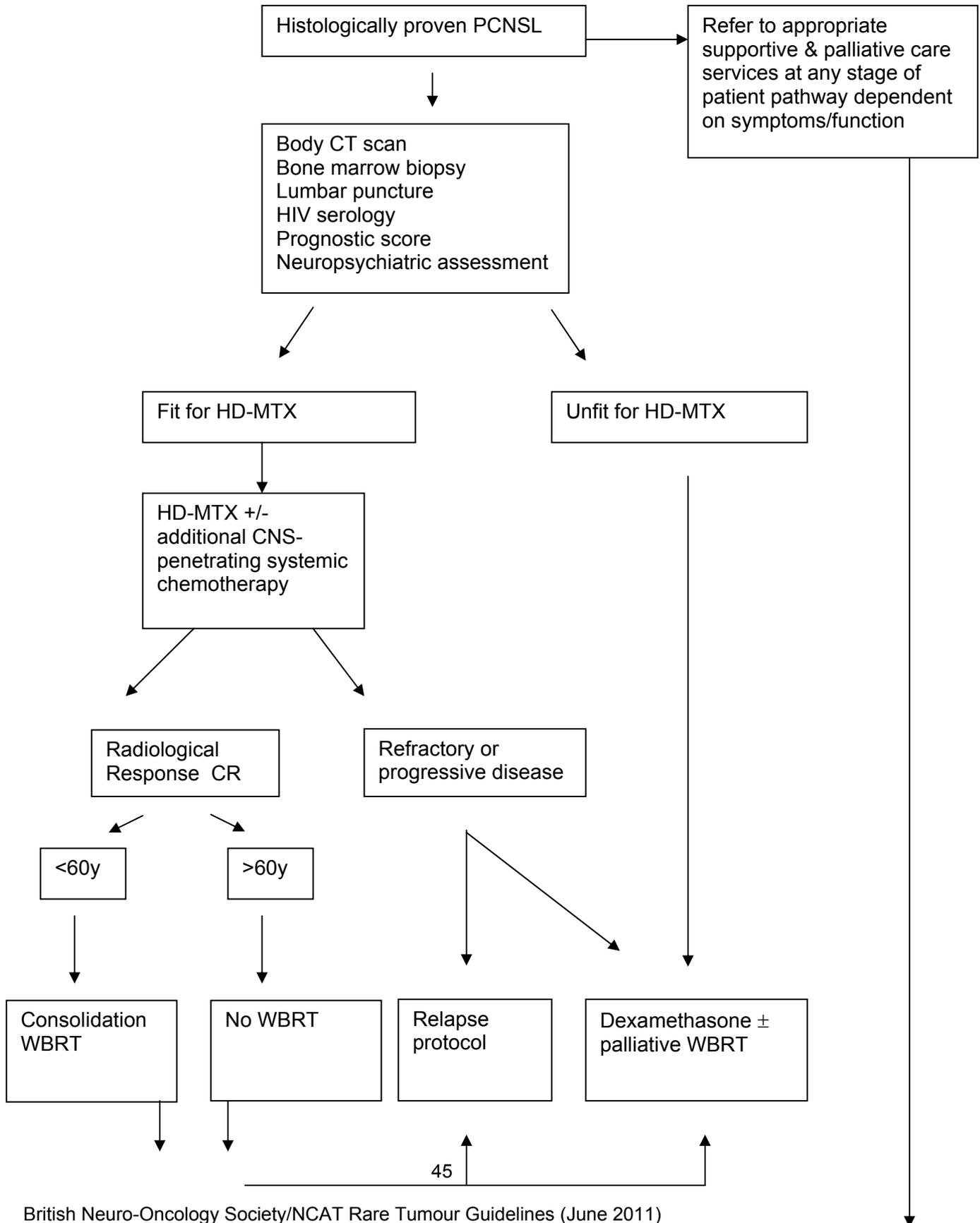| Response	Brain imaging	Glucocorticoid dose	Eye examination	CSF cytology
CR	No enhancing disease	None	Normal	Negative
uCR	No enhancing disease	Any	Normal	Negative
	Minimal enhancing disease	Any	Minor RPE[1] abnormality	Negative
PR	50% decrease in enhancement	NA	Minor RPE abnormality or normal	Negative
	No enhancing disease	NA	Decrease in vitreous cells or retinal infiltrate	Persistent or suggestive of disease
PD	25% increase in enhancement Any new site of disease	NA	Recurrent or new disease	Recurrent or positive
SD	All scenarios not covered by responses above			

[1] Retinal pigment epithelium

Prognostic Markers in CNS DLBCL

Marker	Author	Marker of positive prognosis (+), negative prognosis (-) or non-significant (NS)	Number of cases involved in study	
p27	Kunishio and Nagao, 2006	-	22	
p53	Braaten et al 2003	NS	33	
	Chang et al 2003	-	14	
	Levy et al 2008	NS	61	
	Krogh-Jensen et al 1998	NS	37	
c-Myc	Chang et al 2003	-	14	
MIB-1 or Ki67	Kunishio and Nagao, 2006	NS	22	
	Levy et al, 2008	NS	60	
	Krogh-Jensen et al 1998	NS	41	
	Aho et al 1995	NS	30 PCNSL (not all DLBCL)	
	Roser et al 2004	NS	32	
BCL-6	Braaten et al 2003	+	33	101 vs 14.7 months survival in patients treated with high dose methotrexate
	Chang et al 2003	NS (but worse OS)	14	
	Levy et al 2007	Significant + PFS, NS trend to better OS	66	
	Lin et al 2006	NS trend to better OS	51	
BCL-2	Levy et al 2008	NS	61	
	Krogh-Jensen et al 1998	NS	39	
CD10	Braaten et al 2003	NS	32	
	Levy et al, 2008	NS	60	
CD44	Braaten et al	NS	31	

	2003			
Vs38c	Braaten et al 2003	NS	33	
Morphological subclassification of DLBCL	Camilleri-Broet et al 1999	NS	72	
	Braaten et al 2003	NS	33	
Endothelial hyperplasia	D'Haene et al, 2007	-	44	
Vascular density	Sugita et al 2006	_	26	CD105 (endoglin) labelled vessels associated with survival but not CD34 stained vessels.
	Roser et al 2004	NS	32	Labelled with factor VIII
Necrosis	D'Haene et al, 2007	NS	44	
	Ponzoni et al 2007	NS		
Reactive perivascular T-cell infiltrate	D'Haene et al, 2007	NS	44	
	Ponzoni et al, 2007	+		
Galectin-1	D'Haene et al, 2007	NS	44	
Galectin-3 (endothelial expression)	D'Haene et al, 2007	-	44	
Galectin-3 (neoplastic cell expression)	D'Haene et al, 2007	NS	44	
VEGF (expression on neoplastic cells)	Takeuchi et al 2007	+	19	
	Sugita et al 2007	NS	26	
Telomerase activity	Harada et al 1999	-	12	
CDKN2A/p16 delections	Braaten et al 2003	NS	31	
COX-2 expression	Sugita et al 2007	NS	26	
STAT6	Yang et al 2009	-	13	

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Figure 1. Suggested treatment algorithm for first-line therapy (including reference to supportive/palliative care)

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Relapse

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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 long term control can 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. Spinal imaging should only be requested in case of clinical suspicious symptoms.

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 2)

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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 2).

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 1 (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 mutli-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 AHP's. 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, NCPC & 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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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 primary CNS Lymphoma. 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).

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Specialist palliative care for PCNS Lymphoma

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 CNS lymphomas 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 CNS lymphomas, 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

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with CNS lymphomas 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 CNS lymphomas 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.

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Appendices

Appendix 1: Endocrinology

Endocrine consequences in rare brain tumours

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.

Among the treatment options, **surgical interventions** for tumours related to the HPA e.g. (removal and/or decompression of cystic tumours) may cause immediate detrimental effects on the function of the HPA.

Cranial irradiation

Damage to the HPA by **cranial irradiation** is well established (Duffner 1985, Sanaan 1987, Clayton & Shalet 1991, Oberfield 1997). The effects are delayed and may surface many years after 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 (Brauner 1986). 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 (Littley 1989). The various axes differ in sensitivity with posterior pituitary function being very resistant to irradiation (Vladyka et al 2003).

Outcome related to tumour type

There are few data on specific brain tumours and their relation to endocrine dysfunction. The questionnaire based American childhood cancer survivor study (CCSS) provided the most extensive set of data (Gurney 2003). With a mean cranial irradiation dose of 50-55 Gy **medulloblastomas and gliomas** appear to be associated with the highest rate of both hypothyroidism and GH deficiency (GHD), averaging 29% and 39% of patients. For **ependymomas** and **astrocytomas** the rate averaged at 11% and 11.5% for hypothyroidism and 11% and 16.5% for GHD respectively. In all tumours the rate of **osteoporosis** was at 3-5% (Gurney 2003).

Radiation effects on specific endocrine axes

I. GH

The sensitivity of the different endocrine axes towards radiation varies considerably. Growth hormone (GH) secretion is most frequently affected with the lowest irradiation doses followed by gonadotrophins, ACTH and TSH whereas diabetes insipidus is very rarely a problem (Littley, 1989, Clayton & Shalet 1991, Schmiegelow 1999, 2000). GH deficiency, particularly in children, occurs frequently after irradiation doses in excess of 30 Gy. But even with doses as low as 10 Gy a substantial proportion of children have defects

in their GH secretion (Costin 1988, Ogilvy-Stuart 1992, Brennan 1998). The interval between irradiation and pituitary dysfunction varies widely and appears to be linked to the dose applied to the hypothalamus.

II. Gonadotrophins

Other hormone axes are less sensitive. The gonadotropin axis may be transiently or permanently affected and is of particular interest because of its dual response to irradiation. Doses as low as 18 Gy applied to prepubertal children induce premature puberty, predominantly in girls. Higher doses up to 50 Gy may similarly affect both sexes (Leiper 1987, Ogilvy-Stuart 1994, Lannering 1997). A further increase in radiation dose to the HPA results in gonadal failure in children and adults. Thus, dose and timing of irradiation determine effects on puberty (Oberfield 1996). The time interval between radiotherapy and the manifestation of gonadal dysfunction may be many years (Pasqualini 1987, Sanders 1983, Schmiegelow 2001).

III. ACTH and TSH

The frequency of ACTH or TSH deficiencies (21 % and 9 % respectively) is comparable in children and adults (Agha 2005), and is dependent on dose (up to 35 % for ACTH with doses > 50 Gy) and time interval after radiotherapy (Samaan 1982, Lam 1991, Constine 1993). The observation that TSH deficiency is reported with a much lower incidence (Samaan 1982, Chen 1989, Pai 2001) may be explained by the diagnostic approach and highlights the importance of sensitive diagnostic tools to assess pituitary function. It is well known that bioactivity of TSH decreases as a result of hypothalamic-pituitary problems when immunoreactive TSH remains normal or high. This is believed to be based on the glycosylation of the molecule which is controlled by TRH (Beck-Peccoz 1985). For that reason TSH is no longer a sufficiently reliable marker in patients with suspected central hypothyroidism and the diagnosis should rely entirely on free thyroxine.

Metabolic late effects

Hypothalamic damage due to the primary tumour, surgery or irradiation with a dose exceeding 50 Gy is a major risk factor for the development of obesity in CNS tumour survivors. It may be associated with hyperphagia or reduced physical activity (Harz et al 2003). The presence of hormone deficiencies, particularly GH deficiency but also gonadal and thyroid failure contribute to the changes in body composition (Lustig et al 2003; Ahmet et al 2006). Long-term survivors of childhood brain tumours irradiated with doses of 45 Gy or higher have an increased risk of elevated systolic blood pressure and a less favorable lipid profile (Heikens 2000). The resulting risk of metabolic syndrome is supported in the large CCSS cohort. When comparing patients to their siblings, patients demonstrated an excess increase in BMI of 0.41 kg/m^2/yr in females and 0.29 kg/m^2/yr in males, giving an average excess weight gain in female patients of more than 6 kg. These effects are seen over a broad range of irradiation doses (Garmey 2008, Shankar 2008).

Table: Risk factors for cancer-related disruption of pubertal timing (Fernandez 2009)

- Female sex

- Radiation fields involving the hypothalamic region. Doses > 18 Gy can cause early puberty in girls and GHD. Doses > 24 Gy can cause early puberty in boys

- Age at radiaton exposure < 6 years

- Scattered radiation to the thyroid bed (Primary hypothyroidism) can delay puberty

- Doses to the gonads > 20 Gy: high risk of primary hypogonadism with pubertal failure. Greater risk in males with prepubertal radiation exposure

- Neoplasms in the hypothalamic region: tumour compression, surgical injury and radiation toxicity cause delayed or absent puberty

- b-HCG secreting tumours: germ cell tumours secreting b-HCG can induce pubarchia and phallic enlargement in male children, but do not induce early puberty in girls

- Chemotherapy regimens with known gonadal toxicity: chlorambucil, melphalan, busulfan, cyclophosphamide, chlorambucil, melphalan and ifosfamide

References for Pubertal disorders in Cancer survivors: Nathan & Palmert 2005, Cohen 2005, Gleeson & Shalet 2004

Chemotherapy

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 can be induced by alkylating agents (including procarbazine, cisplatin, and vinblastine) or by 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).

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

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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 oligoamenorrhoea 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 et al 2002, Hartman et al 2002, Ghigo et al 2007)*	IGF-I (Hartman et al 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 et al 2002, Clayton et al 2005, Maghnie et al 2005a)	-Sensitivity 89%, Specificity 95% for a cut-off of 9 mU/l (Biller et al 2002) in adult patients - In the transition period, cutoffs of 15 mU/l (Clayton et al 2005) and 18 mU/l (Maghnie et al 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 et al 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 et al 2000, Davis & Tate 2001)
	Glucagon Test (Leong et al 2001, Gomez et al 2002, Conceicao et al 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 resrve - Contraindicated if fasting >48 hours or clinical suspicion of phaeochromocytoma or insulinoma - Lack of normative data for the transition period and obese patients
	GHRH + Arginine (Aimaretti et al 1998, Darzy et al 2003, Ghigo et al 2007)	- 95% Sensitivity and 85% Specificity for a cut-off of 13.8 mU/l (Biller et al 2002) -100% Sensitivity and Specificity for a cut-off of 27 mU/l (Aimaretti et al 1998)	- Safe and accurate - Body mass index-related normative data are available - Less sensitive than ITT in initial phases of radiation-induced GHD (Darzy et al 2003) - Optimal performance requires specific cut-offs (Aimaretti et al 1998, Ghigo et al 2007)
Gonadotroph deficiency (Verga 2002, Bhasin et al 2006, Kazi et al 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

  o Disorders of the gonadal axis such as delay in menarche, pubertal development, oligo-, amenorrhea, infertility or loss of libido.

  o Uncharacteristic symptoms like fatigue indicative of other pituitary dysfunction such as central hypothyroidism or GH deficiency

- In patients treated with brain irradiation

  o Weight, blood pressure, serum glucose and lipid levels should be monitored regularly.

  o 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.

  o 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.

  o In children, evaluation of growth velocity and pubertal development should be undertaken at least 6 monthly with pituitary function testing if there is any concern. It is important to recognise that early puberty may lead to a relatively normal growth rate in the presence of GH deficiency.

  o 10 years after radiotherapy, treatment should be stratified according to symptoms indicative of pituitary dysfunction.

Appendix 2: Symptom related referral pathway to supportive and palliative care services for patients with PCNSL tumours

Referral to appropriate supportive care services 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)	PCNSL Tumour	
	Symptom	**Support services**
Pre-diagnosis	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech/language & swallow ↓ cognition psychosocial issues	PT/OT OT/SS SLT OT/PS/SLT SS
Diagnosis	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech /language & swallow ↓ cognition psychosocial issues	PT/OT OT/SS SLT OT/PS/SLT SS
Initial/during treatment	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living/anxiety ↓ speech/language & swallow ↓ cognition ↓ appetite/weight change hair loss emotional /mobility/pain issues psychosocial issues	PT/OT OT/SS SLT OT/PS D A CT/PS/C SS/PC PC
Post treatment	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living /anxiety ↓ speech/language & swallow ↓ cognition ↓ appetite/weight change hair loss emotional /mobility/pain issues psychosocial issues	PT/OT OT/SS SLT OT/PS D A CT/PS/C SS/PC PC
Disease progression	Weakness/↓balance/↓mobility/fatigue/↓ex tol ↓ Activity of Daily Living /anxiety ↓ speech/language & swallow ↓ cognition ↓ appetite/weight change emotional /mobility/pain issues psychosocial issues	PT/OT OT/SS SLT/PC OT/PS D CT/PS/C 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   - psychosocial issues & welfare benefits
SLT = Speech & Language Therapy   - ↓ speech/language/swallow function

Appendix 3: 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	