in Cryptogenic Stroke Study. *Circulation* 2002;105:2625–31.
8 Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. The French Study of Aortic Plaques in Stroke Group. *N Engl J Med* 1996;334:1216–21.
9 Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. Review. *Cerebrovasc Dis* 2005;20(Suppl 2):68–74.
10 Meissner I, Khandheria BK, Sheps S *et al.* Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. *J Am Coll Cardiol* 2004;44:1018–24.
11 Wessels T, Wessels C, Ellsiepen A *et al.* Contribution of diffusion-weighted imaging in determination of stroke etiology. *Am J Neuroradiol* 2006;27:35–9.
12 Jauss M, Wessels T, Trittmacher S, Allendörfer J, Kaps M. Embolic lesion pattern in stroke patients with patent foramen ovale compared with patients lacking an embolic source. *Stroke* 2006;37:2159–61.
13 Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. *Clin Sci (Lond)* 2001;100:215–20.
14 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 2000;356:1648–51.
15 Migraine Intervention with STARFlex Technology (MIST) Trial: presented at The American College of Cardiology Scientific Session 2006. www.migraine-mist.org/_content/PDFs/MIST_presentation.pdf
16 Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000;36:181–4.
17 Ho RT, Wicks T, Wyeth D, Nei M. Generalized tonic-clonic seizures detected by implantable loop recorder devices: diagnosing more than cardiac arrhythmias. *Heart Rhythm* 2006;3:857–61.

Neurological problems in cancer

Nick Gutowski BSc MD FRCP, Consultant Neurologist, *Royal Devon and Exeter Hospital; Senior Lecturer, Peninsula Medical School, Exeter*

Clin Med 2007;7:159–64

Several neurological problems can arise in cancer (Table 1). This article will focus on the most challenging presentations. Treatment related complications will not be discussed.

Metastasis

Brain metastases

Brain metastases are common (10–30% of cancer patients). The prevalence is rising as survival improves, the population ages and clinically silent lesions are detected with magnetic resonance imaging (MRI). The most common primaries in adults are lung (50%), breast (15–20%) and melanoma (10%). Lung and melanoma tend to produce multiple metastases, limiting treatment options.[1,2]

The distribution of brain metastases occurs in proportion to blood flow (80% cerebral hemispheres, 15% cerebellum, 5% brainstem). Patients present with headaches, seizures and cognitive dysfunction or progressive focal neurological deficits such as hemiparesis, aphasia or visual field defect. Up to a third of metastases escape detection during life.[3] Brain metastases are associated with a poor prognosis. Depending on age, functional status, extent of systemic disease and number of metastases, median survival is 2.3–13.5 months.[4]

Contrast enhanced MRI is the most sensitive test; if a single metastasis is seen on computed tomography (CT), MRI is required to exclude multiple metastases before planning radical treatment. Initial medical management consists of steroids for oedema and anticonvulsants where appropriate. Further treatment may consist of surgical excision or radiosurgery for a solitary metastasis or whole brain radiotherapy.[5,6]

Spinal cord compression

Approximately 5% of cancer patients develop spinal cord compression, in two-thirds of cases in the narrower thoracic canal. Bony spinal metastases arise from any primary malignancy, the most common being prostate, breast and lung.[5] Spinal pain is common; it presents on average 7–15 weeks before neurological signs develop, most commonly as bilateral pyramidal leg weakness. The site of pain or sensory level does not correlate well with the level of cord compression. A high level of suspicion is required and a spine MRI is the investigation of choice. Treatment is with steroids, usually followed by either surgery or radiotherapy.[5]

Neoplastic meningitis

Neoplastic meningitis (NM), resulting from direct invasion of leptomeninges and/or cerebrospinal fluid (CSF) by

Table 1. Neurological problems in cancer.

Metastases	Cerebral Epidural spinal cord compression
Direct tumour infiltration	Cranial nerves Nerve roots Peripheral nerves
Neoplastic meningitis	Cerebral Cranial nerves Spinal cord and roots
Remote effects of cancer	Paraneoplastic disorders Coagulopathy (eg venous sinus thrombosis)
Effects of treatment	Surgery, radiotherapy and chemotherapy

Table 2. Symptoms and signs in neoplastic meningitis (NM).

Site of NM	Symptoms and signs
Cerebral	Headache Mental change, disturbance of consciousness Nausea and vomiting Papilloedema Seizures Hemiparesis
Cranial nerves	Individual cranial neuropathies in various combinations Symptoms include vision and hearing loss, diplopia, facial numbness and weakness, dysphagia and hoarseness
Spinal cord and individual roots in various combinations	Pain: neck, back, radicular Neck rigidity Weakness – root: lower motor neurone (leg >arm) Paraesthesia – root: dermatomal sensory loss Reflex asymmetry Sphincter disturbance: bladder and bowel

cancer cells, occurs in 3–8% of cancer patients, with a higher incidence at post-mortem. The incidence is increasing because of more accurate MRI imaging and improved prognosis with more effective systemic disease treatments. Interestingly, the incidence is higher for breast cancer (12–34%) than for lung cancer (10–26%), the inverse of brain metastases.[7,8] Other common solid tumour primaries for NM include melanoma and gastrointestinal tumours. NM occurs in 7–15% of non-Hodgkin's lymphoma and 5–15% of leukaemias (mainly acute non-lymphocytic). It is also found in primary brain tumours, particularly ependymoma and medulloblastoma. NM arises via haematogenous spread, direct invasion from metastases, perineural space spread and seeding during surgical resection.

Clinical findings and imaging

Symptoms and signs vary according to the part of the neuroaxis affected (Table 2). The possibility of NM must always be considered in established cancer cases. There should be high clinical suspicion of NM in multifocal neuroaxis disease with 'lymphocytic meningitis' in patients not known to have cancer.

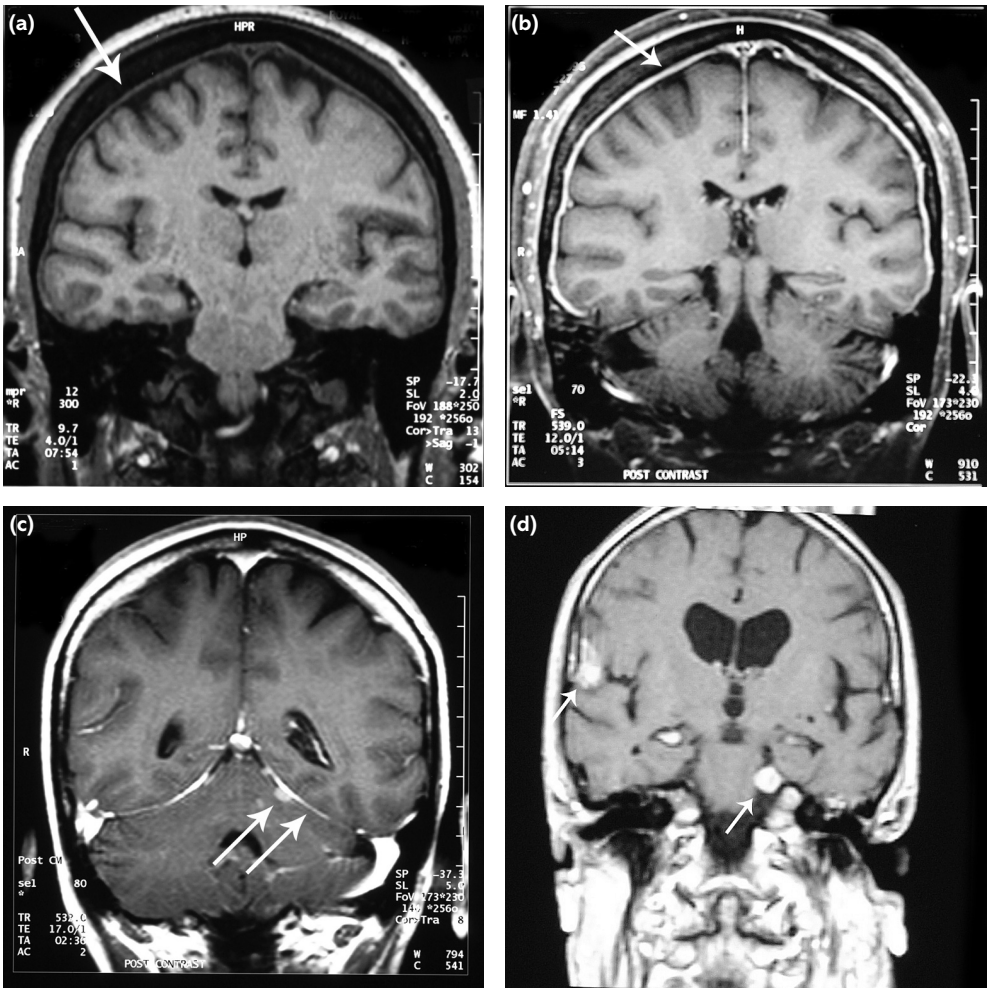

Fig 1. Magnetic resonance images in neoplastic meningitis. T1 coronal image (a) pre- and (b) post-gadolinium showing diffuse meningeal enhancement due to breast neoplastic meningitis (arrow); (c) T1 coronal images post-gadolinium showing nodular and linear meningeal disease (arrows) not demonstrated on pre-gadolinium scans; (d) T1 coronal image post-gadolinium showing metastatic melanoma (arrow) to the left of the pons (V nerve involvement) and right cerebral dura (images courtesy of Dr A Spiers, Royal Devon and Exeter Hospital).

Table 3. Cerebrospinal fluid (CSF) findings in neoplastic meningitis: (a) CSF tests; (b) examples of biochemical markers (usually poor sensitivity and specificity).

(a)

CSF test	Findings	Abnormality (%)
Opening pressure	Elevated	50
Protein	Elevated	75
Glucose	Reduced	25
White cell count	Elevated	50
Cytology	Positive	55–80

(b)

Biochemical marker	Findings	Associated cancer
Ca 125	Present	Ovarian
Ca 15-3	Present	Breast
PSA	Present	Prostate
LDH5	Isoenzyme >2.8% total	Suggests lymphoma/leukaemia
CEA	>1% serum CEA	Suggests neoplastic meningitis
β2-microglobulin	>2 mg/l	Non-specific
β-glucuronidase	>80 mu/l	Non-specific

CEA = carcino-embryonic antigen; LDH = lactate dehydrogenase; PSA = prostate-specific antigen.

Contrast-enhanced MRI is more sensitive than CT (71% *v* 29%)[8] and both linear and nodular enhancement can be found (Fig 1(a) to 1(d)). There can be a lack of correlation between imaging findings and symptoms and signs. An MRI of the brain and spine is required for proper assessment of the full extent of NM.

Cerebrospinal fluid analysis

CSF analysis is the most useful test for diagnosing NM and monitoring treatment. The CSF shows abnormalities in nearly all patients (Table 3).[8,9] Malignant cells may be found at different neuroaxis levels. Lumbar CSF is more sensitive, than CSF from other neurological levels, while positive lumbar cytology correlates better with imaging. There is frequently dissociation (<30%) between CSF white cell count and cytology.[7] The volume of CSF is critical (10 ml is ideal). Initial lumbar CSF is positive in 55% of NM; a second CSF increases this to 80%. Returns diminish with repeated testing, and some cases remain cytology negative.[8]

Diagnosis, prognosis and treatment

A pathological definition of NM is positive CSF cytology, irrespective of neuroimaging. NM is clinically defined when CSF cytology is negative but there is pathologically proven cancer and a clinical syndrome consistent with NM.[7] It is important to exclude mimicking conditions such as infections.[9]

Clinical condition is important in determining prognosis, encephalopathy being a poor prognostic sign.[10] Most NM patients present with advanced disease and are best offered supportive palliative care which might include radiotherapy for focal disease and anticonvulsants. Overall survival is short (2–6 months). The mainstays of aggressive therapy, where indicated, are intrathecal and systemic chemotherapy (Table 4); the former may require surgery to implant an Ommaya reservoir.[8]

Table 4. Chemotherapy in neoplastic meningitis.

Chemotherapy	
Intrathecal	Mainstay of treatment for suitable patients: • high performance status • absent or limited controlled systemic cancer • breast and haematological malignancies The three most commonly used agents are: • MTX • cytarabine • thio-TEPA MTX and cytarabine are active for lymphomas and leukaemias MTX and thio-TEPA are active for breast cancer None of these agents is active against lung cancer or melanoma
Systemic	Often fails due to difficulty achieving cytotoxic CSF levels High-dose iv MTX, cytarabine and thio-TEPA can be effective Chemosensitive tumours (eg breast, lymphomas) can respond Hormonal therapy for breast and prostate cancer
A number of novel intrathecal and systemic agents are being trialed	

CSF = cerebrospinal fluid; iv = intravenous; MTX = methotrexate; thio-TEPA = triethylene thiophosphoramide.

Paraneoplastic neurological disorders

Paraneoplastic neurological disorders (PND) represent less than 1% of neurological cancer complications but are important as they usually occur before a cancer diagnosis.[11,12] The underlying cancer is almost always localised, therefore the chances of cure are highest. PND can affect any part of the nervous system (Table 5), causing significant morbidity and mortality. In some PNDs associated with certain cancers antibodies are found in serum and CSF (Table 6), supporting the hypothesis that the cause is an autoimmune response against common antigens to the cancer and neurones, leading to remote cancer effects. Lambert-Eaton myasthenic syndrome is

Table 5. Paraneoplastic neurological disorders (PNDs).

Site	PND
Central nervous system	Encephalomyelitis Limbic encephalitis Brainstem encephalitis Cerebellar degeneration Stiff-person syndrome Retinal degeneration Motor neurone diseases
Peripheral nervous system	Sensory neuronopathy Sensorimotor neuropathies Neuromyotonia
Neuromuscular junction and muscle	Lambert-Eaton myasthenic syndrome Myasthenia gravis Dermatomyositis and polymyositis

the most common PND, occurring in 2–3% of small cell lung cancer (SCLC) cases. PND rarely occurs in young people,[13] although this depends on the peak incidence for the associated cancer.

The most common cancers associated with PND are SCLC, breast, gynaecological and lymphoma. In up to 20% of PND no cancer is found at post-mortem, the hypothesis being that host immunity has fully controlled the tumour.

PND can affect a single neural component or several simultaneously. In the relatively common encephalomyelitis the areas most frequently involved are the hippocampus, brainstem, spinal cord and dorsal root ganglia. There is an underlying SCLC in more than 85% of cases. The differential of PND may include granulomatous, vasculitic, inflammatory and infective conditions. PND more commonly affects the peripheral nervous system, where it tends to be of gradual onset, than the central nervous system (CNS) where onset can be rapid usually over weeks to months.

Central nervous system

Limbic encephalitis presents with recent memory loss and altered mental state, which can progress to agitation, dementia and seizures. An important differential is herpes simplex encephalitis. MRI can be normal or show medial temporal lobe signal changes (Fig 2(a) and 2(b)) and the CSF may show elevated protein and lymphocytosis. The most common association is with SCLC and anti-Hu antibodies or sometimes anti-Ma1 or ANNA-3. Other antibody associations are anti-Ma2 or anti-CV2 antibodies (Table 6).

Brainstem encephalitis is usually life-threatening, with a combination of long-tract signs, cranial nerve, eye movement, cerebellar and ventilatory dysfunction, sometimes with a movement disorder (eg chorea or parkinsonism). MRI may show signal change. Antibody associations are with anti-Ri, anti-Ma1 and anti-Ma2 antibodies. A variant is opsoclonus-myoclonus syndrome. Opsoclonus is an irregular, continuous, conjugate eye movement disorder in all directions; myoclonus affects the limbs and trunk.

Cerebellar degeneration presents with gait unsteadiness, progressive dysarthria, dysphagia, eye movement disorders and vertigo. Within a few weeks patients can be wheelchair-bound, but then stabilise. Rarely, there is improvement when associated with Hodgkin's disease. Initially,

Table 6. Well characterised paraneoplastic neurological disorder antibodies.

Paraneoplastic antibody	Paraneoplastic neurological syndrome	Associated cancer	Site of action
Anti-Hu (ANNA-1)	Encephalomyelitis Sensory neuronopathy Subacute pancerebellar syndrome	SCLC Other carcinomas	All neuronal nuclei Neurone RNA binding proteins
Anti-Yo (PCA-1)	Subacute pancerebellar syndrome	Ovarian Breast	Purkinje cells ? Gene transcription regulation
Anti-Ri (ANNA-2)	Brainstem encephalitis ± opsoclonus	Breast SCLC Gynaecological	All CNS neuronal nuclei, not dorsal root ganglia Neurone RNA binding proteins
Anti-CV2 (CRMP-5)	Encephalomyelitis Chorea Uveitis Optic neuropathy	SCLC Thymoma	Oligodendrocyte cytoplasm, diffuse neuropile CRMP-5
Anti-Ma2 (Ta)	Limbic encephalitis Brainstem encephalitis	Testicle (germ cell)	Neuronal nucleolus, perikaryon ? mRNA biogenesis
Anti-amphiphysin	Stiff-person syndrome Encephalomyelitis	Breast SCLC	Presynaptic CNS nerve terminals Clathrin-mediated synaptic-mediated endocytosis

CNS = central nervous system; CRMP = collapsing response-mediator protein; SCLC = small cell lung cancer.

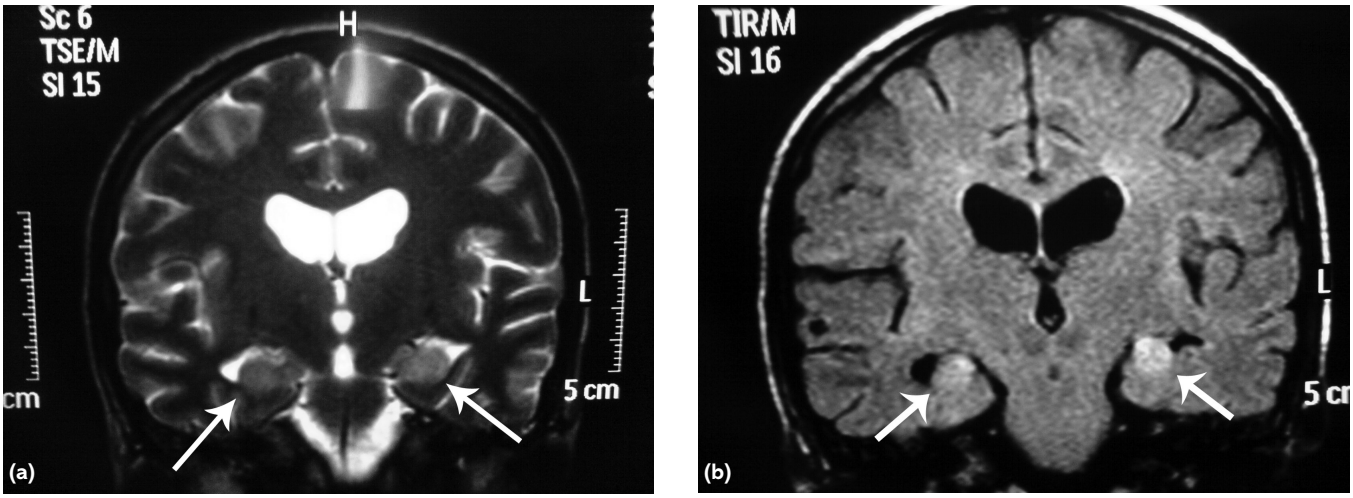

Fig 2. Magnetic resonance images in limbic encephalitis: (a) T2 and (b) fluid attenuated inversion recovery (FLAIR) coronal images from a case of limbic encephalitis with characteristic high signal demonstrated in the hippocampus (arrows) bilaterally in (b). For comparison, the hippocampus is also marked with arrows in (a) (images courtesy of Dr A Mohd Nor, Derriford Hospital).

MRI can be normal but later shows cerebellar atrophy. Common antibody associations are anti-Yo and anti-Hu, less well characterised antibodies associated with Hodgkin's disease are anti-Tr and anti-mGluR1.

Stiff-person syndrome. This syndrome is characterised by axial muscle stiffness, superimposed painful muscle spasms and continuous muscle activity on electromyography. Rare cases are paraneoplastic. Anti-amphiphysin antibodies can be found.

Retinal degeneration causes bilateral, painless visual failure and is associated with antirecoverin antibodies, SCLC and gynaecological cancers.

Motor neurone diseases. The concept of these disorders as a PND is unresolved.[12]

Peripheral nervous system

Sensory neuronopathy involves the dorsal root ganglia. It is usually a rapidly progressive, asymmetrical painful sensory disturbance, with joint position and vibration sense impairment causing pseudoathetosis and sensory ataxia. CSF typically shows an elevated protein and lymphocytosis. On neurophysiology there are reduced sensory nerve action potentials but normal motor studies. It is associated with anti-Hu and ANNA-3 antibodies.

Sensorimotor neuropathies. These neuropathies are recognised in many different cancers. Neurophysiology usually shows a sensory and motor axonal neuropathy. Occasionally there is a demyelinating neuropathy; this may resemble chronic inflammatory demyelinating polyneuropathy but is resistant to usual treatments.

Neuromyotonia. In this disorder there are muscle cramps, twitching, stiffness, abnormal relaxation and sweating. Neurophysiology shows high frequency repetitive muscle action potentials. It may be autoimmune, but if paraneoplastic may be associated with SCLC or thymoma.

Neuromuscular junction and muscle

Lambert-Eaton myasthenic syndrome. There is fatiguable muscle weakness, usually primarily of proximal lower limbs, with autonomic features (dry mouth, impotence and constipation), reflexes are reduced/absent and potentiated after brief muscle contraction.

Key Points

Brain metastases are common, with a rising prevalence; enhanced magnetic resonance imaging (MRI) is the most sensitive test

Bony spinal metastases can cause spinal cord compression. Initially, spinal pain is common, followed by bilateral pyramidal leg weakness. The site of pain or sensory level does not correlate well with the level of cord compression. Spine MRI is the investigation of choice

Neoplastic meningitis is direct invasion of leptomeninges and/or cerebrospinal fluid (CSF) by cancer cells. Symptoms and signs vary: there should be high clinical suspicion in multifocal neuroaxis disease with 'lymphocytic meningitis' in patients not known to have cancer

Paraneoplastic neurological disorders (PNDs) are rare but important as they usually occur before a diagnosis of cancer. The underlying cancer is almost always localised, therefore the chances of cure are highest.

Paraneoplastic antibodies are found in serum and CSF in some PNDs associated with certain cancers

KEY WORDS: metastasis, neoplastic meningitis, paraneoplastic neurological disorders, spinal cord compression

Neurophysiology shows presynaptic neuromuscular dysfunction (small compound muscle action potentials, with an incremental response at high frequency stimulation). Serum P/Q voltage-gated calcium channel antibodies are found. Many cases (60%) are associated with SCLC, sometimes with cerebellar and encephalomyelitic involvement, while the rest are autoimmune.

Myasthenia gravis. In 10% of myasthenia gravis cases there is an underlying thymoma, particularly in elderly men. Removal may not influence the myasthenia.

Dermatomyositis and polymyositis. In elderly patients there may be an underlying malignancy, particularly in dermatomyositis, for which screening is required.

Diagnostic tests

Standard blood tests, MRI scans, CSF analysis and clinical neurophysiology are used primarily to exclude other diagnoses. PND is confirmed by the presence of known paraneoplastic antibodies and/or an underlying cancer.[14] Screening for an underlying cancer may need to continue for three years when initially negative.

Paraneoplastic antibodies (Table 6) are produced by an autoimmune response against common antigens to cancer and neuronal cells. Direct evidence that these antibodies are pathogenic is lacking except in Lambert-Eaton myasthenic syndrome (LEMS) and myasthenia gravis.

Underlying cancer may be smaller than CT resolution limits, but 18F-fluoro-2-deoxyglucose-positron emission tomography can identify small lesions and guide further investigation.[15]

Treatment and prognosis

Treatment is primarily targeted at the underlying tumour which may also reduce the risk of spread. Generally CNS PNDs respond less well than other PNDs, such as LEMS, to immunomodulatory treatments (steroids, azathioprine and intravenous immunoglobulin).[11,12] Patients with a CNS PND can be stablised but may remain disabled, probably due to irreversible neuronal cell death.

References

1 Shaffrey M, Mut M, Asher A *et al.* Brain metastases. *Curr Probl Surg* 2004;41:665–741.
2 Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: a comprehensive review. *Crit Rev Oncol Hematol* 2004;52:199–215.
3 El Kamar FG, Posner JB. Brain metastases. *Semin Neurol* 2004;24:347–62.
4 Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys* 2000;47:1001–6.
5 Gerrard G, Franks KN. Overview of the diagnosis and management of brain, spine, and meningeal metastases. *J Neurol Neurosurg Psychiatry* 2004;75(Suppl 2):ii37–42.
6 National Institute for Health and Clinical Excellence. *Improving outcomes for people with brain and other CNS tumours.* London: NICE, 2006.
7 Chamberlain MC. Neoplastic meningitis: a guide to diagnosis and treatment. Review. *Curr Opin Neurol* 2000;13:641–8.
8 Chamberlain MC. Neoplastic meningitis. Review. *J Clin Oncol* 2005;23:3605–13.
9 Pavlidis N. The diagnostic and therapeutic management of leptomeningeal carcinomatosis. *Ann Oncol* 2004;15(Suppl 4):iv285–91.
10 Chamberlain MC, Tsao-Wei D, Groshen S. Neoplastic meningitis-related encephalopathy: prognostic significance. *Neurology* 2004;63:2159–61.
11 Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. Review. *N Engl J Med* 2003;349:1543–54.
12 Bataller L, Dalmau J. Paraneoplastic neurologic syndromes. Review. *Neurol Clin* 2003;21:221–47.
13 Candler PM, Hart PE, Barnett M, Weil R, Rees JH. A follow up study of patients with paraneoplastic neurological disease in the United Kingdom. *J Neurol Neurosurg Psychiatry* 2004;75:1411–5.
14 Graus F, Delattre JY, Antoine JC *et al.* Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135–40.
15 Rees JH, Hain SF, Johnson MR *et al.* The role of [18F]fluoro-2-deoxyglucose-PET scanning in the diagnosis of paraneoplastic neurological disorders. *Brain* 2001;124:2223–31.