Neurological manifestations of malignant disease

Jeremy Rees

Neurological complications of cancer are some of the most feared manifestations of malignant disease. Their frequency is increasing with improvements in the treatment of primary systemic disease. This article discusses the approach to patients with neurological complications of cancer and reviews some of the most common causes.

Neurological complications of cancer (NCC) are common, increasing in incidence, serious, potentially disabling and usually treatable when correctly diagnosed (Posner, 1995). The most frequent complaints are pain, confusion, headache and muscle weakness (Clouston et al, 1992). They are the second most common reason for admission to oncology beds after elective chemotherapy. When seeing a patient with a possible NCC, it is useful to consider the following differential diagnosis (*Table 1*). Many different causes can lead to identical clinical presentations and so it is essential to have a systematic approach.

APPROACH TO THE PATIENT WITH A POSSIBLE NCC

The key points detailed in *Table 2* should be elicited from the history and examination to guide appropriate further investigations. Where necessary, the history should be obtained from a close relative, particularly if the patient is suffering from a confusional state. Before documenting the history of the neurological complaint, it is advisable to detail the nature and stage of the underlying cancer together with the treatments so far received.

DIRECT EFFECTS OF CANCER ON THE NERVOUS SYSTEM

The majority of NCC are the result of direct or metastatic spread to the nervous system. This is usually easily diagnosed with appropriate imaging but may be missed if contrast is not given. Although there are common patterns of tumour spread, e.g. bony metastases with breast, bronchus, prostate, kidney and thyroid cancer, almost any malignancy can spread anywhere within the neuraxis.

Direct invasion

Compression or invasion of neurological structures occurs when the primary tumour or a draining lymph node is in direct contact with part of the nervous system (*Table 3*). Tumour invasion is usually associated with severe pain and this may be useful in trying to differentiate between malignant infiltration and the effects of previous treatment. In some cases, e.g. Pancoast tumour, the neurological symptoms may be the presenting complaint. Less commonly, microscopic growth of tumour cells, particularly lymphoma, along nerve sheaths occurs after the primary tumour has been treated.

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TABLE 1.
Differential diagnosis of neurological complications of cancer

Direct effects	Malignant infiltration of the primary tumour or draining lymph nodes		
	Metastasis	Brain	
		Skull base and calvaria	
		Dura	
		Spinal cord	Extradural
			Intradural
			Intramedullary
		Leptomeninges	
		Plexus	
		Perineural	
Indirect effects	Toxic/metabolic encephalopathy		
	Vascular disorders		
	Infections		
	Paraneoplastic neurological syndromes		
Effects of treatment	Chemotherapy		
	Radiotherapy		
	Intrathecal administration		

Metastases

Metastases are a major cause of neurological disability in patients with cancer and are commonly fatal when they involve the CNS. They occur in three different ways: by haematogenous dissemination (the usual mechanism of brain metastases), lymphatic dissemination (usually to peripheral nerve structures) or by dissemination through the CSF (giving rise to leptomeningeal metastases). The likelihood of metastasis increases with increasing primary tumour size. The site to which a tumour metastasizes depends on the anatomy of the venous and lymphatic drainage of the organ harbouring the tumour, the microenvironment of the receiving organ and the molecular phenotype (particularly the propensity to express surface adhesion molecules) of the tumour.

TABLE 2.
Key points in the approach to a patient with neurological complications of cancer

History	Primary tumour, site and grade	
	Presence of known metastases	
	Treatment received, e.g. surgery, radiotherapy, chemotherapy, other	
	Current drug treatment, e.g. steroids, opiates	
	Previous neurological history	
	Presenting neurological symptoms	
	Other symptoms, e.g. bone pain	
Examination	Higher mental functions, e.g. orientation, attention, concentration	
	Language	
	Gait	
	Cranial nerves	
	Limbs	
	Spinal tenderness	
	Systemic examination	
Investigations	Routine blood tests, e.g. full blood count, urea and electrolytes, liver function tests, calcium, glucose, thyroid function tests	
	Specific blood tests, e.g. antineuronal antibodies	
	Imaging	Computed tomography/ magnetic resonance imaging scan
		Radioisotope scans
	Cerebrospinal fluid	Opening pressure
		Microscopy
		Protein
		Glucose
		Cytology
	Electroencephalogram/electromyogram	

TABLE 3.
Common syndromes caused by spread of primary tumour cells

Source	Primary tumour	Syndrome
From tumour itself	Pancoast tumour (apical bronchial carcinoma)	T1 radiculopathy
	Nasopharyngeal carcinoma	Cranial neuropathy
	Paravertebral lymphoma/ neuroblastoma	Cord compression
From lymph nodes	Breast cancer	Brachial plexopathy
	Testicular cancer	Lumbosacral plexopathy
Perineural invasion	Lymphoma	Polyradiculopathy

Brain metastases: The commonest primary tumours that spread to the brain are lung, breast and melanoma (Cairncross et al, 1980). Brain metastases are usually intraparenchymal and supratentorial, although pelvic and gastrointestinal tumours have a predilection for the cerebellum. They present clinically with either a seizure, symptoms and signs of raised intracranial pressure, or an evolving focal deficit. Radiologically they are solitary or multiple enhancing mass lesions with surrounding vasogenic oedema occurring at the grey/white matter interface where the arterial supply terminates. Metastases may be haemorrhagic, particularly from melanomas, colonic carcinomas and testicular tumours.

Spinal cord metastases: Unlike brain metastases, spinal cord metastases are rarely intraparenchymal but cause compression of the cord from the epidural space, usually as a result of haematogenous dissemination to the vertebral bodies. As a result, most patients with spinal cord compression have identifiable abnormalities of the vertebral body on plain X-ray at the site of compression. Pain is the earliest and most frequent presenting symptom followed by limb weakness, sensory loss and sphincter disturbance.

Failure to diagnose cord compression when pain is the only symptom may result in progressive and untreatable paraplegia and incontinence. Thus any patient with a known malignancy and new back pain, particularly if waking at night, should have at least a plain X-ray of the affected area. Occasionally spinal cord compression presents as gait ataxia without pain.

Leptomeningeal metastases: Malignant cells, particularly from carcinoma of the breast and lung, melanoma and leukaemia/lymphoma, may seed the leptomeninges. The symptoms and signs are legion, reflecting the multifocal nature of leptomeningeal metastases (*Table 4*). The diagnosis should be suspected if there is clinical involvement of more than one

anatomical area. Cytological examination of the CSF is the most valuable diagnostic test. A minimum of 4 ml CSF should be collected and immediately taken to the laboratory to minimize the time for autolysis of malignant cells to occur. At least three samples should be taken if necessary to increase the sensitivity up to 90%.

Other characteristic abnormalities, in the absence of malignant cells, include a raised opening pressure, elevated CSF white cell count and protein concentration and reduced glucose concentration. Imaging is helpful and is useful to exclude intraparenchymal mass lesions. Computed tomography (CT) or magnetic resonance imaging (MRI) scans showing contrast enhancement in the basal cisterns (*Figure 1*) or cauda equina provide sufficient confirmation to start treatment in the absence of identifiable malignant cells.

Treatment of metastatic disease: The decision to treat a patient with metastatic disease depends on the status of the primary tumour and the patient's overall physical condition. In general, metastases to the CNS are associated with a median survival of weeks to months, although exceptions to the rule occur, particularly in patients with breast cancer and acute lymphoblastic leukaemia.

If the primary disease is well controlled and the patient is reasonably well, then the options for treatment will be determined by the site and the number of metastases. In general, a solitary brain metastasis (as determined by MRI scanning) is best treated by surgical resection or stereotactic radiotherapy/radiosurgery. Similarly a solitary spinal cord metastasis may be treated surgically, particularly if there is evidence of spinal instability, although in most cases localized radiotherapy will be given. Patients with multiple brain or spine metastases should be given palliative radiotherapy. Corticosteroids (dexamethasone 16 mg daily) should be started as soon as the diagnosis is made to reduce vasogenic oedema and mass effect.

The treatment of leptomeningeal metastases involves a combination of radiotherapy and intrathecal chemotherapy (methotrexate or cytosine arabinoside) via an Ommaya reservoir connected to the lateral ventricles or via repeated lumbar punctures. Some irradiate only the symptomatic site while others treat the entire neuraxis with craniospinal radiotherapy. This latter option is associated with considerable morbidity, which may be unacceptable in patients with such a poor prognosis. As with intraparenchymal metastases, corticosteroids provide useful palliation.

TABLE 4.
Symptoms and signs of leptomeningeal metastases

Cerebral	Headache
	Confusion
	Nausea and vomiting
	Gait ataxia
	Seizures
Cranial nerves	Diplopia
	Visual loss
	Deafness
	Facial weakness
	Dysphagia
Spinal	Pain: neck, back, radicular
	Weakness
	Paraesthesiae
	Sphincter disturbance
	Meningism
	Areflexia

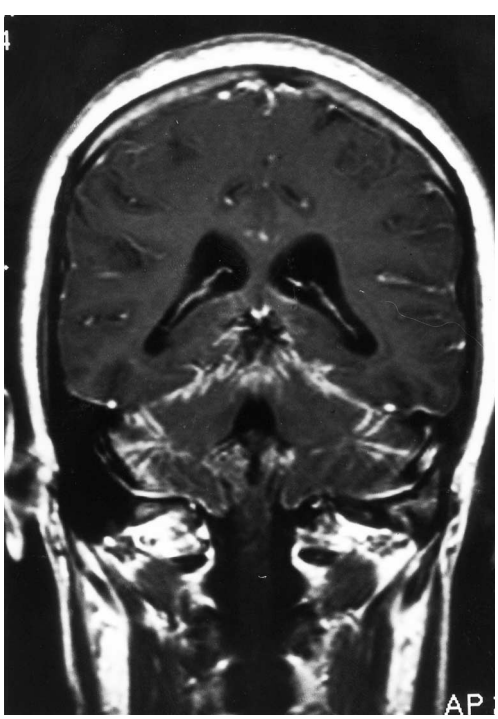

Figure 1. Coronal T1-weighted magnetic resonance image of the brain with gadolinium showing diffuse leptomeningeal enhancement outlining the cerebellar folia in a 60-year-old woman with treated breast cancer presenting with deafness and ataxia.

INDIRECT EFFECTS OF CANCER ON THE NERVOUS SYSTEM

Toxic/metabolic encephalopathy

Toxic/metabolic encephalopathy is a frequent occurrence in cancer patients and presents, when fully developed, as delirium or an acute confusional state. There are numerous causes (*Table 5*) and therefore a thorough evaluation is required, particularly as most are reversible. The earliest manifestations are subtle deficits of concentration and attention which progress to the full-blown state of delirium, characterized by either a state of lethargy and apathy (quiet delirium) or by hyperactivity and restlessness, similar to that seen in the delirium tremens of alcohol withdrawal.

In general these patients will not have focal neurological signs, although hypoglycaemia may cause hemiplegia. Specific neurological signs include tremor and asterixis, which are usually symmetrical. Investigation of these patients consists of excluding a primary neurological cause such as brain or leptomeningeal metastases and identifying a treatable extracerebral condition. A careful drug history is mandatory.

Vascular disorders

Cerebrovascular complications are relatively common in cancer patients and are either a direct effect of a tumour or its treatment on blood vessels, or are the result of a coagulopathy indirectly caused by the neoplasm. Cerebral haemorrhage may be the presenting symptom of a metastasis, particularly from melanoma, germ cell tumours or colonic carcinomas. It may also occur as a result of thrombocytopenia caused by either tumour invasion of bone marrow, the effects of chemotherapy or radiotherapy or when disseminated intravascular coagulation develops.

TABLE 5.
Causes of toxic/metabolic encephalopathy

Drugs*	Opioids, benzodiazepines, corticosteroids
Sepsis*	Pneumonia, urinary tract infection, intra-abdominal abscess
Hypoxia*	Pneumonia, pulmonary emboli
Electrolytes	Hypercalcaemia, hyponatraemia, hypophosphataemia
Endocrine	Adrenal insufficiency, e.g. rapid steroid withdrawal
Hepatorenal	Uraemia, hepatic failure
Nutritional	Thiamine deficiency (Wernicke's encephalopathy)

* particularly common in cancer patients

A hypercoagulable state leading to cerebral thrombosis is usually seen in patients with widespread disease as a result of the multiple procoagulant effects of cancer on platelet function and coagulation factors. Occasionally drug therapy causes abnormal coagulation, the classical example being sagittal sinus thrombosis associated with L-asparaginase in acute leukaemia (Feinberg and Swenson, 1988). Rarer causes of cerebral infarction include tumour emboli, nonbacterial thrombotic endocarditis, thrombotic microangiopathy and cerebral vasculitis. All of these can present with a diffuse brain syndrome caused by multiple small infarcts. Venous sinus occlusion may result from compression or invasion by metastatic tumour, particularly breast cancer and lymphoma.

Infections

CNS infections are uncommon complications of cancer and are almost always seen in patients suffering from haematological malignancies. Nevertheless they are important to keep in mind because these patients rarely have the florid symptoms and signs seen in immunocompetent patients, e.g. the temperature may be only mildly elevated. In addition the causative organisms are different. *Cryptococcus neoformans* and *Listeria monocytogenes* are the major causes of meningitis in cancer patients while *Toxoplasma gondii*, *Aspergillus fumigatus* and *Nocardia asteroides* are the major causes of brain abscesses (*Figure 2*). Gram-negative organisms, e.g. *Pseudomonas aeruginosa* and *Escherichia coli,* are common causes of meningitis in neutropenic patients.

The paranasal sinuses should always be considered as a possible source of CNS infection, especially in neutropenic patients. It is essential to make an accurate microbiological diagnosis in order to institute vigorous and appropriate antibiotic therapy. Patients with cancer and depressed cellular immune function may develop progressive multifocal leucoencephalopathy, an opportunistic infection of white matter caused by reactivation of a JC virus.

COMPLICATIONS OF CANCER TREATMENT

Chemotherapy

Certain chemotherapeutic drugs are neurotoxic and cause neurological dysfunction, particularly neuropathy and encephalopathy (*Table 6*). In many instances, the diagnosis of a treatment-induced complication is based on clinical experience and exclusion of other causes. Frequently combination therapy may cause previously unrecognized syndromes as drugs may act syner-

gistically with other drugs or with radiotherapy. The best example of this is the combination of methotrexate and cranial irradiation causing an irreversible leucoencephalopathy (Cruz-Sanchez et al, 1991) (*Figure 3*). Neurotoxicity from cancer chemotherapy is more frequent and more severe in patients with pre-existing neurological disease.

Peripheral neuropathy: This is usually a pure sensory neuropathy, often painful, and most commonly associated with vinca alkaloids, taxol and cisplatin. Motor neuropathies are rare but are occasionally seen with suramin and vincristine. They are usually reversible on cessation of the drug.

Encephalopathy: Almost any drug can cause an acute encephalopathy characterized by seizures and confusion. A chronic encephalopathy, characterized by a progressive and usually subcortical dementia, is most commonly seen with methotrexate in combination with cranial radiotherapy (see above).

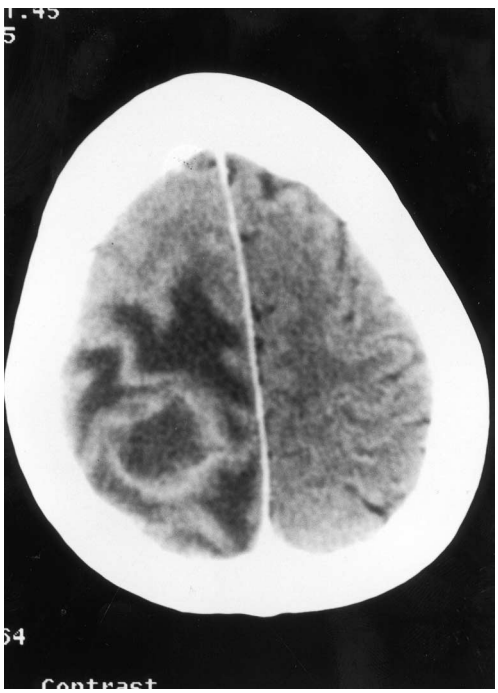

Figure 2. Computed tomography scan brain with contrast enhancement showing a solitary ring enhancing right parietal lesion in a patient who had received a stem cell transplant for relapsed stage IVb non-Hodgkin's lymphoma. The patient presented with focal motor seizures and a decreased level of consciousness. Biopsy of the lesion confirmed an abscess although no organisms were grown. The patient made an excellent recovery with broad spectrum antibiotics and antifungal agents.

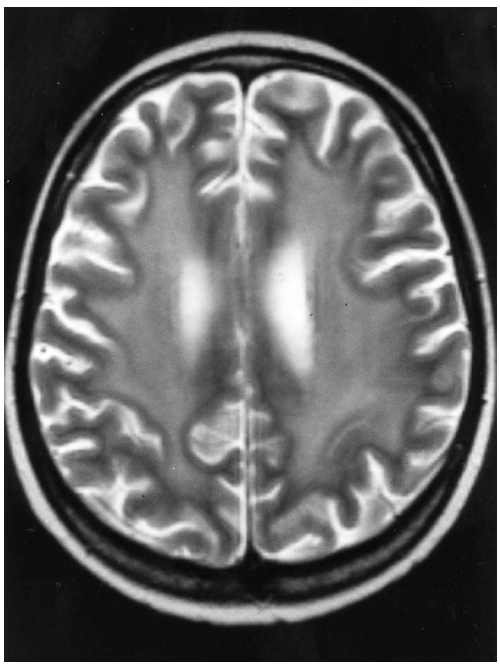

Figure 3. Axial T2-weighted magnetic resonance imaging brain scan showing diffuse subcortical white matter signal change in a young woman presenting with dementia, rigidity and incontinence 3 months after a bone marrow transplant for Philadelphia positive acute lymphoblastic leukaemia in second complete remission. The patient had previously received a combination of intrathecal methotrexate and brain radiotherapy as part of her conditioning protocol. The diagnosis was of a methotrexate-induced leucoencephalopathy. She died within 3 weeks of the scan.

TABLE 6.
Chemotherapy-related neurotoxicity

Acute encephalopathy	Methotrexate, cisplatin, vincristine, asparaginase, ifosfamide
Chronic encephalopathy	Methotrexate, 5-fluorouracil/levamisole
Cerebellar syndrome	5-fluorouracil, cytosine arabinoside, cyclosporin, vincristine
Visual loss	Tamoxifen (retinopathy), cisplatin (cortical blindness)
Deafness	Cisplatin
Myelopathy/aseptic meningitis	Intrathecal methotrexate, cytosine arabinoside
Neuropathy	Vinca alkaloids, cisplatin, taxol, suramin, mitoxantrone

Radiotherapy

Radiation damages all parts of the nervous system and its effects are conventionally classified into acute (within days), early delayed (weeks to months) or late delayed (months to years).

Encephalopathy: Acute encephalopathy occurs in patients with raised intracranial pressure who are given large fractions of brain radiation (above 300 cGy). This is rarely seen nowadays as lower dose fractions are given and patients are almost always pretreated with corticosteroids.

Early delayed encephalopathy begins within 1–3 months of finishing brain radiotherapy and is characterized by excessive fatigue (somnolence syndrome) and worsening of a pre-existing deficit or seizure disorder. The pathology is inflammatory demyelination and is usually reversible with corticosteroids.

Late delayed effects include a dementia, leucoencephalopathy and radiation necrosis, which may be clinically and radiologically indistinguishable from recurrent tumour (although single photon emission tomography and positron emission tomography scanning may be helpful in distinguishing the two).

Myelopathy: Radiation myelopathy is usually late delayed and presents either as a progressive myelopathy or as a lower motor neurone syndrome. This is most commonly seen in patients with Hodgkin's disease given mantle radiotherapy. Patients treated with axillary radiotherapy for breast cancer may develop a late delayed radiation plexopathy of the brachial plexus, which can be distinguished from tumour recurrence by the absence of pain and the presence of myokymic discharges on electromyography.

Secondary tumours: In addition to these direct neurotoxic effects, radiotherapy can cause secondary tumours, in particular meningiomas, gliomas and schwannomas, developing years after treatment.

Vasculopathy: Radiotherapy also causes accelerated large vessel atherosclerosis, most commonly seen in young adults presenting with internal carotid artery occlusions who have been treated for childhood optic nerve or hypothalamic gliomas.

Paraneoplastic syndromes

These are uncommon NCC but are important because they frequently present before the malignancy becomes symptomatic and because they cause severe neurological disability. They are thought to be caused by an autoimmune attack triggered by tumour antigens and any part of the nervous system may be affected (*Table 7*). Some CNS syndromes are associated with specific serum antineuronal antibodies which, when detected by a combination of immunohistochemistry and Western blotting, prompts a search for an underlying malignancy. The detection of such a small tumour may be difficult because of the limitation of conventional imaging techniques.

Fluoro-deoxyglucose-positron emission tomography (FDG-PET) scanning permits the visualization of tumours down to a resolution of 6–8 mm anywhere within the body and is

TABLE 7.
Paraneoplastic neurological syndromes

Site	Syndromes	Malignancy	Antibodies
Brain	Limbic encephalitis	SCLC	Anti-Hu
		Testis	Anti-Ma2
	Brainstem encephalitis	SCLC	Anti-Hu
		Testis	Anti-Ma2
	Cerebellar degeneration	SCLC	anti-Hu
		Breast, ovary	Anti-Yo
		Hodgkin's	Anti-Tr
	Opsoclonus-myoclonus	SCLC	
		Breast	Anti-Ri
		Neuroblastoma	
Dorsal root ganglia	Sensory neuronopathy	SCLC	Anti-Hu
Neuromuscular junction	Lambert–Eaton myasthenic syndrome	SCLC	Anti-VGCC
	Myasthenia gravis	Thymoma	Anti-AchR
Muscle	Dermatomyositis	Many	
	Polymyositis		

AchR = acetylcholine receptor antibodies; SCLC = small cell lung cancer; VGCC = voltage-gated calcium channel

sometimes positive when chest X-ray and CT are negative (*Figure 4*). Most paraneoplastic syndromes respond poorly to immunomodulatory treatment although occasional improvement is seen when the underlying tumour is treated. The exception to this rule is Lambert–Eaton myasthenic syndrome which presents with fatigueable limb weakness, autonomic disturbance and is associated with an underlying small cell lung cancer in about 60% of patients.

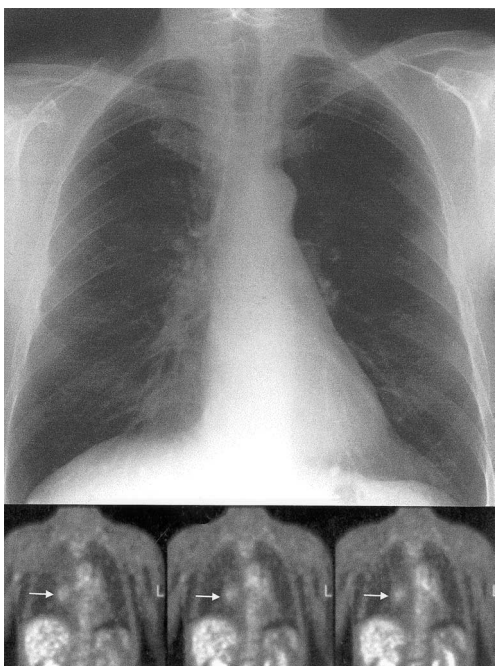

Figure 4. Chest X-ray and fluoro-deoxyglucose-positron emission tomography (PET) scan of a man presenting with a subacute progressive brainstem syndrome and memory loss. The diagnosis of a paraneoplastic encephalomyelitis was made after detection of serum anti-Hu antibodies. Both chest X-ray and computed tomography of the thorax were negative but the PET scan shows a clear focus of increased activity around the right hilum consistent with a carcinoma of the bronchus. The patient died before bronchoscopy could be carried out.

CONCLUSIONS

NCC are common and serious conditions which may be difficult to diagnose. They present a unique challenge to the physician and offer compelling insights into the biological relationship between cancer and the nervous system. Most NCC are treatable, but only if diagnosed before irreversible neurological damage has occurred. Further research is needed to improve on current treatments of these devastating complications. HM

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KEY POINTS

- Neurological complications of cancer (NCC) are common, disabling and often treatable.
- NCC may be caused by a direct effect of the tumour or metastases or by indirect effects which may be metabolic, infective, vascular or paraneoplastic.
- NCC, particularly neuropathies and encephalopathies, may be caused by cytotoxic chemotherapy.
- Radiotherapy-induced damage to the nervous system may present many years after treatment.
- Paraneoplastic neurological syndromes, although rare, are important to diagnose as they prompt the clinician to search for an occult malignancy.