The Prevalence and Impact of Neurological Disease in Cancer

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Abbreviations

APL	Acute promyelocytic leukemia
CAR T-cell	Chimeric antigen receptor T-cell
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
DIC	Disseminated intravascular coagulation
FDA	Food and Drug Administration
JC virus	John Cunningham virus
HER2	Human epidermal growth factor receptor 2
MEK	Mitogen-activated protein kinase enzyme
MS	Multiple sclerosis
PRES	Posterior reversible encephalopathy syndrome

Introduction

Cancer is a leading cause of disability and death throughout the world. Though regional variations in environmental risk factors and genetic propensities affect the incidence of each type of cancer, as an illness, it afflicts all age and socioeconomic groups worldwide [1]. In the United States, 1 in 4 deaths are due to cancer, making it the second leading cause of death [2]. This sobering statistic is offset by a decline in cancer death rates by as much as 20% over the past 20 years as a result of early treatment and medical advancements which have resulted in some cures, and delays in progression among those with advanced disease.

A large percentage of the cancer population will develop a neurologic complication of their disease. Up to 25% of cancer patients develop a central nervous system (CNS) metastasis over the course of their illness [3]. Many more develop chemotherapy-associated neuropathy; it occurs commonly in patients receiving both conventional cytotoxic chemotherapy—with an incidence that approaches 100% among patients treated with vincristine—and novel agents, such as the small molecule inhibitor, bortezomib.

For these reasons, in the mid-1980s, almost 50% of patients on a solid tumor service were admitted with a neurologic complaint; Table 1.1 details the most common chief complaints and neurologic diagnoses identified by an inpatient neurology consultant in a population of patients with cancer [4, 5]. During this same time period, a cancer hospital in the Netherlands referred about 15% of their patients for neurologic evaluation [6]. Because patients are living longer after their cancer diagnosis, the number of neurologic complications has increased and more patients suffer the diverse, late effects of treatment and the disease itself.

An estimated 1.7 million Americans will be diagnosed with cancer in 2015, of whom 68% will be alive at 5 years [7]. Many of these 1.2 million cancer survivors will have a neurologic symptom or disability and would benefit from

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Table 1.1 Categorization of 2137 inpatient neurology consults at a large cancer center by chief complaint and neurologic diagnosis

	Number of patients	Percentage of consults
Chief complaint		
Back pain	385	18
Headache	192	9
Other pain	160	7
Altered mental status	521	24
Weakness	395	18
Sensory deficit	173	8
Ataxia/gait instability	156	7
Seizures	156	7
Vision deficit	54	2
Speech deficit	52	2
Neurologic diagnosis		
Parenchymal brain metastasis	407	19
Epidural metastasis	298	14
Leptomeningeal metastasis	224	10
Other metastasis	407	19
Toxic metabolic encephalopathy	275	12
Cerebrovascular disease	169	8
Headache	67	3
Syncope	45	2
Peripheral neuropathy	40	1
Epilepsy	34	1
Paraneoplastic syndrome	7	0.3
Other	246	12

Patients may have more than one chief complaint or neurologic diagnosis
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neurologic expertise. This book seeks to address the broad scope of these issues and the large unmet clinical needs of these patients.

Management of the Neurologic Complications of Cancer

Neurooncology is the subspecialty of neurology that deals with the neurologic complications of cancer. Neurologic symptoms may arise from primary malignancies of the brain, and for that reason, one focus of neurooncology is the management of gliomas and other primary tumors of the CNS. A second, equally important focus is the diagnosis and management of neurologic complications of systemic cancer and its treatment which is the core of this book. This second focus extends far beyond brain metastases, a problem that is already ten times more common than malignant gliomas [3, 7].

The first step in managing a neurologic complication of cancer is the correct identification of the underlying problem. A cancer patient with a change in gait may have loss of proprioception from prior chemotherapy, disease within the CNS, or severe pain that limits function. Correct diagnosis and treatment of the patient's complaint is contingent upon the same principles of neurology that apply to the non-cancer population. A careful history and detailed exam localizes the deficit in the nervous system to a focal, multifocal, or diffuse process. From that localization, a neurologic differential diagnosis can be developed that is based on specialized knowledge of the characteristic propensities of each cancer, the off-target effects of a wide array of conventional cytotoxic, novel small molecule and biologic therapeutics, and the complications of radiotherapy and surgical treatments. The most common neurologic complications of cancer and their association with different malignancies and treatment are provided in Table 1.2.

Direct Effects of Cancer on the Nervous System

Cancer frequently metastasizes to the nervous system, primarily to the brain, dura, subarachnoid space, spinal cord,

Table 1.2 Neurologic complications of cancer

Location	Complication	Cancer or treatment related causes	
Brain			
Direct complications	Brain metastasis	Lung, melanoma, renal, breast, and colon cancer	
	Primary brain tumor	Meningioma, glioma, pituitary adenoma, and schwannoma	
	Leptomeningeal metastasis	Breast, lung, melanoma, and gastrointestinal cancer	
Complications associated with cancer	Epilepsy/status epilepticus	Brain metastasis, primary brain tumor, paraneoplastic limbic encephalitis, and meningitis/encephalitis	
	Paraneoplastic limbic encephalitis	Anti-VGKC	SCLC and thymoma
		Anti-NMDA	Ovarian teratoma
		Anti-Hu	SCLC and gynecological cancer
		Anti-Ma2	Testicular germ cell
	Paraneoplastic cerebellar degeneration	Anti-Yo	Ovarian and breast cancer
		Anti-Tr	Hodgkin lymphoma
		Anti-Hu	SCLC and gynecological cancer
	Meningitis/encephalitis	Cancer-mediated immunosuppression	Hodgkin lymphoma, CLL, multiple myeloma, and Waldenstrom macroglobulinemia
	Ischemic stroke	Hyperviscosity	Multiple myeloma, Waldenstrom macroglobulinemia, and leukemia
		Cancer-mediated hypercoagulability	Pancreatic cancer, adenocarcinomas
		Tumor emboli	Rhabdomyosarcoma
		DIC	Sepsis from cancer-mediated immunosuppression
		Vasculopathy	Intravascular lymphoma
			Infectious vasculopathy (VZV) from cancer-mediated immunosuppression
	Hemorrhagic stroke	Coagulopathy/DIC	APL
			Sepsis from cancer-mediated immunosuppression
			Liver metastases
		Thrombocytopenia	Leukemia, lymphoma, and multiple myeloma
		Hemorrhage from a metastasis	Renal cell carcinoma, melanoma, choriocarcinoma, and papillary thyroid cancer
Treatment complications	Encephalopathy	Methotrexate, ifosfamide, and 5-FU	
	PRES	Bevacizumab, sorafenib, cyclophosphamide, high-dose corticosteroids, L-asparaginase, cisplatin, gemcitabine, and tacrolimus	
	Ischemic stroke	Bevacizumab, sunitinib, sorafenib, and cisplatin	
		Radiation-induced vasculopathy from treatment of head and neck cancers	
		Infectious vasculopathy and DIC from treatment-induced immunosuppression	
	Hemorrhagic stroke	Chemotherapy-induced thrombocytopia	
		Bevacizumab	
		Hemorrhage due to vascular changes secondary to radiotherapy	
	Venous sinus thrombosis	L-asparaginase	
	Pseudoprogression	Radiation to a primary or metastatic brain tumor	
	Radiation necrosis	Radiation to the head and neck; SRS to brain metastases	
	Bacterial meningitis/abscess/empyema	Neurosurgical procedure	VP shunt, burr hole, craniotomy, transsphenoidal resection, and laminectomy
		Treatment-induced immune suppression	Cytotoxic chemotherapy, hematopoietic stem cell transplant, and immune-modulating biologics

(continued)

Table 1.2 (continued)

Location	Complication	Cancer or treatment related causes	
Spinal cord			
	Leptomeningeal Metastasis	Breast, lung, melanoma, and gastrointestinal cancers	
	Cord compression/cauda equina syndrome	Lung, breast, prostate, renal, colorectal, and hematologic malignancies	
	Paraneoplastic myelopathy	Anti-amphiphysin	Breast cancer
		Anti-CRMP5	SCLC and thymoma
		Anti-Hu	SCLC and gynecological cancer
		Anti-ANNA-3	SCLC
		Anti-NMO	Carcinoma and lymphoma
	Radiation myelopathy	Radiation to the vertebral column, thorax, abdomen, or neck	
	Radiculomyelitis	Cancer-mediated and treatment-induced immunosuppression	
Plexus			
	Neoplastic infiltration	Brachial	Breast and lung cancer
		Lumbosacral	Prostate, colorectal, cervical, bladder cancers, and retroperitoneal sarcoma
	Radiation plexopathy	Radiation near the plexus	
Peripheral nerve			
	Neoplastic infiltration	Leukemia, lymphoma, Waldenstrom macroglobulinemia, prostate cancer, and squamous cell of head and neck (to cranial nerves)	
	Drug-associated neuropathy	Platinum agents, vinca alkaloids, thalidomide, bortezomib, and ipilimumab	
	Immune-mediated neuropathy	POEMS syndrome, MGUS, and multiple myeloma	
	Paraneoplastic neuronopathy	Anti-Hu	SCLC and gynecological cancer
	Peripheral nerve hyper-excitability	Anti-VGKC	SCLC and thymoma
Neuromuscular junction			
	Myasthenia gravis	Anti-acetylcholine receptor	Thymoma
	Lambert–Eaton myasthenic syndrome	Anti-Ca channel	SCLC
Muscle			
	Steroid myopathy	Pituitary adenomas/carcinomas, adrenal adenomas/adrenocortical carcinomas, and exogenous steroids	
	Dermatomyositis/polymyositis	Cervical, lung, ovarian, pancreatic, bladder, and gastric cancer	

Abbreviations APL acute promyelocytic leukemia, *CLL* chronic lymphocytic leukemia; *DIC* disseminated intravascular coagulation, *MGUS* monoclonal gammopathy of unknown significance, *POEMS* polyneuropathy organomegaly endocrinopathy M-protein skin-changes, *PRES* posterior reversible encephalopathy syndrome, *SCLC* small cell lung cancer, *SRS* stereotactic radiosurgery, *VP shunt* ventriculoperitoneal shunt, *VZV* varicella zoster virus, 5-*FU* 5-flurouracil

and plexus. Considered together, the direct complications of cancer on the nervous system are responsible for a major burden of disability and death. Ironically, enhanced therapeutics and longer systemic disease control may be responsible for increasing the incidence of these complications, making the need for better therapeutics for CNS disease ever more pressing.

The elucidation of the molecular drivers of cancer has in certain cancer subtypes significantly improved tumor control. For example, trastuzumab, a monoclonal antibody directed against the HER2 receptor which is overexpressed in 25–30% of breast cancers has markedly improved the prognosis of patients with stage IV breast cancer by reducing the hazard rate of relapse by one-half [8, 9]. Unfortunately, the improved systemic control afforded by trastuzumab in appropriately selected patients with HER2 overexpression has not translated into the same degree of control within the CNS. Several retrospective studies have reported an incidence of clinically evident brain metastasis of 25–40% in patients with HER2 positive breast cancer receiving

trastuzumab compared with an incidence of only 10–15% in HER2 negative patients with advanced disease [10]. One explanation is that HER2 positive breast cancer has a tropism for seeding the CNS; alternatively, the CNS may function as a sanctuary site because trastuzumab does not penetrate the blood–brain barrier effectively and prolonged systemic control may permit sufficient time for brain metastases to become evident [11]. Both of these and other factors may play a role, and altering this natural history will require unraveling the mechanisms by which it and other malignancies metastasize and circumvent the blood–brain barrier.

Basic and translational research have revealed that the development of metastatic disease is a highly inefficient process; large numbers of circulating tumor cells leave the primary tumor with only a small percentage (<0.01% of metastatic clonal cells in experimental models) surviving and establishing themselves at a distant site, including the brain [12]. The inefficiency of this process is due to the obstacles that these circulating tumor cells must overcome. Some of these obstacles apply to the development of metastases at any organ site, and others appear to be host organ specific.

An emerging concept is that there is a strong and complex interplay between normal brain tissue and tumor cells that develop into brain metastases. For example, it has been recognized that tumor cells thwart the brain's defense against the development of metastases by disrupting the normal function of plasmin. Plasmin is made in the brain to support synaptic plasticity; however, it also protects against the establishment of a metastasis once a tumor cell has extravasated into the brain parenchyma. Plasmin prevents tumor cells from binding to the abluminal surface of brain capillaries and interferes with the required co-option of the cerebral vasculature by the cancer cell to sustain growth [13]. By overexpressing plasminogen activator inhibitory serpins, which inhibit the conversion of plasminogen to plasmin, a subset of tumor cells are able to overcome this obstacle, and they are the cells that successfully develop into a brain metastasis.

Brain and all CNS metastases typically occur late in the cancer course. In autopsy studies, it has been shown consistently that about 30% of individuals with breast cancer have CNS metastases. The rate is even higher for lung cancer and melanoma at 34 and 72%, respectively [14] Cancers with a lower rate of intracranial metastasis include colon and pancreatic cancers; nevertheless, brain metastases develop even in these subtypes (Table 1.3). All told, approximately 25% of all patients with cancer have CNS metastases at death, and in approximately 40% of these patients, the brain is the sole metastatic site [14].

In addition to developing parenchymal brain metastases, patients can develop disease in the subarachnoid space resulting in leptomeningeal metastasis. Leptomeningeal metastasis is another direct complication of cancer that occurs commonly, either in the presence or absence of parenchymal brain metastases. It is found in 4–8% of patients at autopsy and is a particularly challenging diagnosis to establish because the symptoms are highly variable, relatively subtle and nonspecific, and diagnostic tests have a high rate of false negative results [5, 14]. Moreover, outside of cancer, the symptoms of leptomeningeal disease are rarely encountered, except in patients with chronic meningitides, making it more difficult to recognize the clinical syndromes. Leptomeningeal metastasis frequently presents with temporary, postural neurologic symptoms that occur with changes in body position from lying to standing. By history alone, the symptoms seem orthostatic in etiology, but in reality they are due to impaired cerebrospinal fluid (CSF) reabsorption which results in transient, marked elevation in intracranial pressure, typically lasting 5–20 min, known as plateau waves [15]. Alternatively, it may present with symptoms that localize anywhere along the neuraxis such as leg cramping, cranial nerve palsies, radiculopathy, headache, diplopia, and cognitive impairment; the symptoms may occur either alone or in combination.

Metastasis to the CNS contributes significantly to morbidity and mortality in patients with cancer. Unfortunately, the treatment of parenchymal and leptomeningeal metastases has lagged behind the development of treatments for systemic tumors, as trials have historically excluded these patients due to their poor prognosis. Fortunately, this is now beginning to change, particularly for patients with parenchymal brain metastases. There is growing recognition of the need to develop both preventative and therapeutic approaches to metastases in the CNS. Clinical trials are investigating laboratory assays that permit earlier diagnosis, innovative approaches for delivering therapy across the blood–brain barrier, and novel drugs that draw from new insights into the pathogenesis of brain metastases.

Indirect Effects of Cancer on the Nervous System

While neurologic complications of cancer can develop as a consequence of direct metastases to the nervous system, cancer also affects the nervous system indirectly.

Cancer induces an inflammatory state, and certain tumors secrete procoagulant substances. For these reasons, patients with cancer, particularly adenocarcinomas, are at a higher risk for ischemic stroke accounting for the 14.6% incidence of cerebrovascular disease found in an autopsy study [16]. A common mechanism by which individuals with cancer develop ischemic strokes is through the development of nonbacterial thrombotic endocarditis (or marantic endocarditis), but it can be caused by other mechanisms as well

Table 1.3 Prevalence of a primary or secondary brain tumor estimated for 2015

Primary cancer	New cases [7]	Number of deaths [7]	Percentage with intracranial tumor at autopsy [5, 14]	Projected number with intracranial tumor at death
Lung	221,200	158,040	34	53,734
Breast	234,190	40,730	30	12,219
Melanoma	73,870	9940	72	7157
Urinary system	138,710	30,970	23	7123
Leukemia	54,270	24,450	23	5624
Colon	93,090	49,700	7	3479
Non-Hodgkin lymphoma	71,850	19,790	16	3166
Pancreas	48,960	40,560	7	2839
All sites	**1,658,370**	**589,430**	**24**	**141,463**
Brain and spinal cord	**22,850**	**15,320**	**100**	**15,320**

including tumor emboli, infarction secondary to sepsis, and treatment-related hypercoagulability and vasculopathy.

Not only is there a higher incidence of ischemic stroke, population studies also show a higher risk of intracerebral hemorrhage [17, 18]. Primary and secondary brain tumors may hemorrhage; particularly high risk tumors are oligodendrogliomas and brain metastases from choriocarcinoma, melanoma, papillary thyroid cancer, or renal cell carcinoma [19]. Alternatively, cancer can lead to spontaneous intraparenchymal hemorrhage by causing coagulopathy, as in acute promyelocytic leukemia (APL) [20]. Patients with this condition usually have disseminated intravascular coagulation (DIC) at presentation, and until the recent development of effective therapies, death from massive intracranial hemorrhage was common.

A disordered immune response directed against the tumor but cross-reacting with nervous system proteins is another mechanism whereby cancer affects the nervous system. In 1948, Derek Denny-Brown published an early description of a prototypic paraneoplastic neurologic syndrome characterized by a rapidly progressive, debilitating sensory neuronopathy in individuals with small cell lung cancer [21]. The antibody mediating this paraneoplastic syndrome was later identified from the serum of patient H.U. (giving rise to the name anti-Hu); this antibody was found to cause dysfunction at nearly every level of the nervous system. It is associated with limbic encephalitis, cerebellar degeneration, brainstem encephalopathy, autonomic dysfunction, and motor neuron dysfunction [22]. Moreover, anti-Hu co-associates with other paraneoplastic antibodies such as anti-calcium channel antibodies which primarily affect the neuromuscular junction and give rise to the Lambert–Eaton myasthenic syndrome [23].

The true incidence of paraneoplastic syndromes involving the nervous system is unclear, but they are rare. For all cancers, it may be as low as one per 10,000 patients [24]. For tumors with neuroendocrine proteins, such as small cell lung cancer, the rate is higher, occurring in about 3–5% of patients. In individuals with thymoma and immune dysfunction, myasthenia gravis and other paraneoplastic syndromes are commonplace, occurring in 15–20% of these patients.

Complications of Cancer Treatment

Another category of neurologic dysfunction is the short- and long-term effects of cancer therapies, such as radiotherapy, chemotherapy, and the many procedures that are prescribed. This category of dysfunction may be even more diverse than the others considered.

Peripheral neuropathy is the most common complication of cancer chemotherapy as it affects 30–70% of all patients [25]. Neuropathy can have profound effects on patient function, quality of life, and in one study, was the most troublesome symptom of treatment for one-third of patients with cancer [26]. Importantly, it is also a major dose limiting toxicity of chemotherapy that frequently results in either dose reduction or the premature discontinuation of otherwise effective treatment, and as a consequence, it can adversely affect outcomes.

Conventional cytotoxic chemotherapies are myelosuppressive; hence, treatment may be complicated by hemorrhage from thrombocytopenia or infection due to chronic immunosuppression which may be further compounded by bone marrow suppression and immune dysfunction from the disease itself, as in multiple myeloma. Patients receiving treatment are susceptible to a wide variety of pathogens and often develop more severe disease than is seen in the general population from the same infectious agent. As an example, people who were previously able to clear the West Nile virus with few clinical symptoms may develop a fulminant

meningoencephalitis or a poliomyelitis-like syndrome [27]. They can also develop viral, fungal, or atypical bacterial infections such as varicella zoster virus vasculopathy, cytomegalovirus radiculitis, human herpes virus 6 limbic encephalitis, herpes simplex virus meningoencephalitis, aspergillosis, or nocardiosis.

Bacterial meningitis can also occur. Cancer patients who have undergone neurosurgical procedures are susceptible to infections from uncommon bacterial organisms such as gram-negative bacteria; moreover, because their immune response is frequently blunted, clinical manifestations may be subtle and they may not exhibit the classic tetrad of headache, fever, nuchal rigidity and altered mental status, thus delaying recognition and early institution of appropriate antibiotic therapy [28].

Mainstays of cancer treatment, such as methotrexate and ifosfamide, sometimes precipitate encephalopathy syndromes and can be associated with specific neurologic complications, such as venous sinus thrombosis among patients treated with L-asparaginase and posterior reversible leukoencephalopathy syndrome (PRES) among patients receiving cyclophosphamide or cisplatin [5]. With the advent of molecular medicine, a new generation of drugs has emerged that act on cancer by a variety of mechanisms. As these drugs are being tried on an investigational basis and achieve wider use, neurooncologists are being confronted with an unprecedented diversity of unanticipated adverse effects. An illustrative example is the focal neck extensor weakness that can be caused by selumetinib, a MEK inhibitor [29].

Rituximab, a monoclonal antibody against CD20 that revolutionized the treatment of B-cell lymphoma, was Food and Drug Administration (FDA) approved in 1997, but the association between its chronic use and the development of progressive multifocal leukoencephalopathy (PML), a devastating demyelinating condition caused by reactivation of the John Cunningham (JC) virus, was not recognized until 2011 [30]. This association was finally reported by a neurologist with an interest in understanding the development of PML in patients treated with natalizumab, a drug for multiple sclerosis (MS). Research on natalizumab has shown that JC virus serostatus can be used to risk stratify the development of PML [31]. Insights like this from general neurology can form the management of patients with cancer; lymphoma patients on maintenance rituximab and other immunomodulatory drugs may one day benefit from similar serological testing.

Activating the immune system can also have significant neurologic toxicity, as sometimes occurs following the administration of ipilimumab. Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA4); this drug mobilizes the immune system by inhibiting this molecule's ability to downregulate the T-cell response. It extends survival in patients with metastatic melanoma, and has activity against other cancers with high mutational loads and a large number of neoantigens to which the immune system can react [32]. Ipilimumab may cause a number of different autoimmune neurologic syndromes such as hypophysitis (resulting in central hypothyroidism, adrenal insufficiency, and hypogonadism), an axonal motor-predominant polyradiculoneuropathy resembling Guillain–Barre, myasthenia gravis, transverse myelitis, and an inflammatory myopathy [33].

Treatment-related neurotoxicity can also occur following radiotherapy and surgery. These treatments place patients at risk for stroke, radiation necrosis and other forms of direct damage to nearby structures, such as the brachial plexus. Finally, novel treatments are having unanticipated effects on the nervous system by mechanisms that are not completely understood as found in some patients who have received infusions of chimeric antigen receptor T-cells (CAR T-cells) [34]. CAR T-cells are genetically engineered lymphocytes that attack tumor cells and appear highly active against hematologic cancers. Patients treated with this form of cell-based immunotherapy can develop a cytokine storm, which results in striking neurologic symptoms that start with aphasia and progresses to severe encephalopathy, even obtundation, with or without seizures [35]. When the cytokine storm and seizures are appropriately managed, this treatment-related neurologic toxicity is often reversible, but failure to implement treatment rapidly can result in permanent damage, particularly from uncontrolled seizures.

Because neurologic complications of cancer treatments are so common, any team endeavoring to treat these medically complicated patients requires a neurologist to correctly localize the deficit and identify the underlying cause. This is of particular importance in the context of clinical trials because investigational agents commonly have unexpected neurologic consequences which need to be clearly and completely defined so that the safety profile can be assessed adequately and reported.

Conclusion

The nervous system is both a uniquely protected and uniquely vulnerable organ system. Neurologic complications of cancer are common and increasingly prevalent, as patients are surviving longer and are able to experience both the acute and delayed consequences of the disease and its treatment. Compromise of the nervous system by cancer or its therapy is often serious but frequently treatable, particularly if recognized early before serious deficits are fully established, making accurate diagnosis essential. This is where the neurooncologist plays a fundamental role.

Mobility, functional independence, and freedom from pain are of the utmost importance to patients. The

neurooncologist works to help patients accomplish these goals, and in this way, neurooncologists strive to improve not only the quantity, but also the quality of life for their patients with cancer. This book was written to provide the neurooncologist, the general neurologist, and the oncologist with a framework for the early recognition and management of the most frequent neurologic complications of cancer, thus minimizing their effect on the increasingly longer life enjoyed by many with this disease.

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