# Central Nervous System Complications of Oncologic Therapy

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**KEYWORDS**

• Neurotoxicity • Chemotherapy • Radiation therapy • Magnetic resonance imaging • Cancer

**KEY POINTS**

- Neurotoxicity related to cancer treatment is increasing in frequency related to improvements in cancer treatment and patients surviving longer.
- Neurotoxicity is a widely recognized adverse effect of cancer treatment and can result from radiation therapy, traditional chemotherapeutic agents, and newer biologic and immunotherapeutic agents used to treat cancer.
- MRI is the main imaging modality used to assess patients with cancer with new symptoms referable to the CNS.
- CNS complications of oncologic treatment can have variable imaging appearances and in some cases mimic cancer progression or recurrence.

## INTRODUCTION

Neurotoxicity is a widely recognized adverse effect of cancer treatment and can result from radiation therapy (RT), traditional chemotherapeutic agents, and newer biologic and immunotherapeutic agents used to treat cancer.[1] Although the exact incidence of treatment-related neurotoxicity is unknown, its frequency is thought to be increasing.[2] Higher doses of chemotherapeutic agents are being administered because of advances in supportive care, with escalating doses resulting in neurotoxicity. Additionally, improvements in cancer treatment have led to patients with cancer living longer. Thus, treatment-related neurotoxicity with a long latency between treatment and symptom onset is increasingly recognized.[2] After myelosuppression, neurotoxicity is the most common dose-limiting factor of cancer treatment.[3] It was once thought that the blood-brain and blood-cerebrospinal fluid barriers and the

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nondividing central nervous system (CNS) cells would protect the CNS from the toxic effects of RT and chemotherapy. However, it is now known that the CNS contains stem cells that replenish some neuron populations and that glial cells do divide. Although the pathophysiologic mechanisms are not fully known, traditional chemotherapeutic agents and RT can directly damage neural structures and cause indirect damage through injury to the vasculature. Newer immune and biologic agents can affect the CNS through a heightened immune response or cross reactivity with nervous system cells.[1] When patients with cancer develop new neurologic symptoms it is important to distinguish symptoms related to the cancer itself from those related to other causes, such as paraneoplastic syndromes, infection, or treatment-related toxicity. Although attributing symptoms to neurotoxicity is generally a diagnosis of exclusion, it is important to recognize so that further injury is prevented by dose adjustment or treatment cessation.[1,4] MRI is the main imaging modality used to assess patients with cancer with new symptoms referable to the CNS. It is important to be aware of the common neurotoxic syndromes that can occur as a result of cancer treatment, the agents responsible for them, and the imaging findings to allow prompt diagnosis.

## RADIATION-INDUCED CENTRAL NERVOUS SYSTEM COMPLICATIONS

RT to the brain and spinal cord is used to treat a variety of primary and metastatic tumors and may be administered prophylactically to prevent the development of metastases. The brain may also be included in the RT port of patients with other cancers, notably head and neck cancers.[5] Injury to the CNS can occur after whole brain RT, involved field RT, or focal RT, such as stereotactic radiosurgery and brachytherapy.[5,6] Radiation can directly affect the CNS or indirectly induce vasculopathy, endocrinopathy, or carcinogenesis.[4,5,7] Risk factors associated with radiation-induced injury include energy of radiation, total dose, fraction size, time between fractions, treatment volume, and previous or concurrent chemotherapy.[4,5,8,9] Patient-specific factors, including age, sex, genetic predisposition, pre-existing CNS damage, systemic disease, and lifestyle choice, also impact the risk of radiation-induced injury.[5,7]

Radiation injury to the brain is typically classified into three phases based on the time of onset after radiation. Acute injury occurs during or shortly after radiation, subacute or early delayed injury occurs weeks to months after radiation, and late-delayed occurs months to years after radiation.[10]

Acute injury presents clinically with headache, nausea, vomiting, lethargy, and worsening of pre-existing neurologic symptoms.[11,12] This is most commonly seen following large fractions (>3 Gy) delivered to large brain volumes in patients with increased intracranial pressure. The pathogenesis is likely related to disruption of the blood-brain barrier by endothelial apoptosis leading to increased edema and possibly an increase in intracranial pressure.[13,14] The incidence and severity of this type of injury has decreased with prophylactic steroid use, surgical debulking, and careful treatment planning with conventional fractionation (1.8–2 Gy per fraction) and the symptoms are usually reversible.[6,8,11,15] Although acute brain swelling has been reported, typically no computed tomography (CT) or MRI findings are present with this type of injury.[16,17]

In patients receiving RT for high-grade gliomas, particularly in combination with temozolamide (Temodar), a temporary increase in brain edema and enhancement in the RT treatment volume can occur that is believed to be an early delayed effect of treatment. This usually occurs on the first MRI done within 2 to 3 months after treatment and has been termed “pseudoprogression,” because the imaging findings mimic