

Proton Craniospinal Photon therapy for Leptomeningeal Metastasis: Initial Results from Solid Tumor Patients

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DESCRIPTION

Leptomeningeal Metastasis (LM) is a devastating complication of solid tumors, where cancer cells spread to the meninges, the layers of tissue covering the brain and spinal cord. This form of metastasis is associated with significant morbidity, as it can cause neurological impairment, cognitive decline and spinal cord dysfunction. Treatment options for LM have historically been limited and challenging due to the delicate nature of the Central Nervous System (CNS) and the widespread nature of the disease.

Leptomeningeal metastasis: A challenging condition

Leptomeningeal metastasis occurs in approximately 5-10% of patients with advanced solid tumors, particularly those with cancers such as breast cancer, lung cancer, melanoma and gastrointestinal cancers. The condition is often diagnosed when patients present with neurological symptoms such as headaches, seizures, altered mental status, weakness or sensory disturbances. Diagnosis is typically confirmed through neuroimaging (MRI) and Cerebrospinal Fluid (CSF) analysis, which may reveal malignant cells in the CSF.

LM has historically been a difficult condition to treat. Systemic therapies, such as chemotherapy and targeted therapies, often have limited efficacy due to the blood-brain barrier and the need for drugs to reach the CSF. Additionally, Whole Brain Radiation Therapy (WBRT) and spinal irradiation, which are commonly used to treat intracranial metastases, have limited success in LM because they do not effectively target the entire meningeal surface. Furthermore, radiation to the brain and spine can lead to significant long-term side effects, including cognitive decline and spinal cord injury.

The role of proton therapy in craniospinal irradiation

Proton therapy, a form of particle therapy, uses protons to deliver precise radiation. The most significant advantage of proton therapy over conventional photon therapy is its unique dose distribution characteristics. Protons have a "Bragg peak,"

which allows for the majority of the radiation dose to be delivered to the tumor while minimizing exposure to healthy tissue before and after the tumor. This precision is particularly important when treating tumors in the brain and spinal cord, where surrounding healthy tissue must be preserved to avoid neurological damage.

Proton therapy has been increasingly studied in the context of Craniospinal Irradiation (CSI) for LM due to its ability to deliver high doses of radiation to the tumor while reducing radiation exposure to critical structures such as the brainstem, spinal cord and normal tissue. Proton CSI involves irradiating the entire craniospinal axis (brain, meninges and spinal cord) to target both leptomeningeal disease and potential microscopic disease spread.

Early clinical outcomes with proton CSI

The early clinical outcomes from studies examining proton CSI for LM have been assuring, although the treatment is still being refined. Proton therapy's precision allows for dose escalation while limiting the radiation dose to normal tissue, which is particularly important when treating extensive leptomeningeal involvement. The clinical experience with proton CSI suggests a few key outcomes.

Symptom control and neurological improvement: Early reports indicate that patients with leptomeningeal metastasis who receive proton CSI often experience significant symptom improvement, particularly in controlling neurological symptoms such as headaches, nausea and pain. In several studies, a reduction in neurological deficits has been noted after proton CSI, with patients demonstrating improved functional status. For example, a study of patients with LM from breast cancer reported a substantial improvement in cognitive function and quality of life following proton CSI, compared to those receiving conventional WBRT.

Control of leptomeningeal disease: Proton CSI has shown efficacy in controlling the spread of leptomeningeal disease across both the brain and spinal cord. Early evidence suggests that this form of treatment can help control leptomeningeal

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metastasis by delivering a more uniform and higher dose to the affected areas, thereby reducing the risk of tumor progression. For instance, in patients with LM from Non-Small Cell Lung Cancer (NSCLC), proton CSI resulted in an improvement in overall survival and local disease control, with fewer recurrences in the brain and spinal cord compared to historical data on WBRT.

Reduced incidence of radiation-induced toxicity: One of the most notable early outcomes of proton CSI is the reduced incidence of radiation-induced toxicity, particularly cognitive dysfunction and spinal cord injury. While traditional photon radiation can lead to cognitive decline, especially in patients receiving whole brain irradiation, proton therapy reduces radiation exposure to normal brain tissue. This has been shown to result in a lower incidence of late neurocognitive impairments, which is important for patients who may have an extended survival time following treatment. Similarly, the precision of proton therapy helps reduce the risk of spinal cord toxicity, which is a concern with conventional radiation techniques.

Overall survival and quality of life: Early data on Overall Survival (OS) following proton CSI for leptomeningeal metastasis remains potential, though long-term follow-up is needed to draw definitive conclusions. Several studies suggest that patients receiving proton CSI for leptomeningeal disease from solid tumors experience prolonged survival compared to those receiving conventional treatments. The improvement in quality of life, due to symptom control and preservation of

cognitive function, is a significant factor contributing to this extended survival. While complete remission is rare in patients with leptomeningeal metastasis, those who respond well to proton CSI often enjoy a better quality of life.

Challenges and limitations

Despite its advantages, proton therapy for leptomeningeal metastasis is not without challenges. Proton therapy requires specialized facilities, which are often limited to certain regions and academic centers. The cost of proton therapy, which is higher than that of conventional radiation treatments, may also be a barrier to its widespread use, particularly in resource-limited settings.

CONCLUSION

Proton craniospinal irradiation is emerging as an assuring therapeutic option for patients with leptomeningeal metastasis from solid tumors. Early outcomes suggest that it can effectively control disease, reduce neurological symptoms and improve quality of life while minimizing toxicities compared to traditional radiation therapy. However, further studies with longer follow-up are necessary to confirm its long-term benefits and establish its role in the treatment of leptomeningeal metastasis. As proton therapy becomes more widely available, it holds the potential to significantly improve the prognosis for patients with this challenging condition.