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Hippocampus Sparing in Whole-Brain Radiotherapy for Brain Metastases Using the Volumetric Modulated Arc Therapy (VMAT) Technique

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Abstract

Brain metastases are a prevalent and serious complication in cancer patients, often requiring whole-brain radiotherapy (WBRT) to manage intracranial disease. Traditional WBRT effectively controls brain metastases but has notable adverse effects on cognitive function, primarily due to radiation exposure to the hippocampus, a critical region for memory and learning. Recognizing the hippocampus's sensitivity to radiation, recent advancements in radiotherapy, such as Volumetric Modulated Arc Therapy (VMAT), have enabled hippocampal sparing to reduce neurocognitive side effects while maintaining therapeutic efficacy. Hippocampal-sparing WBRT with VMAT selectively limits radiation dose to the hippocampus, aiming to preserve memory function, enhance quality of life, and decrease cognitive impairment in patients undergoing treatment. This approach leverages VMAT's precision to deliver targeted radiation to metastatic sites, avoiding unnecessary exposure to healthy brain tissue. This paper examines the theoretical basis for hippocampal sparing, technical considerations in using VMAT, and clinical outcomes, highlighting the promising role of hippocampus-sparing WBRT. By integrating this technique into treatment protocols, clinicians may improve the quality of life for cancer patients, offering an effective balance between disease control and cognitive preservation, ultimately setting new standards in supportive care for those with brain metastases.

Keywords: Brain metastases, (WBRT), Hippocampal sparing, (VMAT), Cognitive preservation

1. Introduction

Brain metastases occur in approximately 20–30% of adult cancer patients, posing a substantial clinical challenge due to both the neurological symptoms of metastatic disease and the cognitive side effects of its treatment. Whole-brain radiotherapy (WBRT) has traditionally been the standard care for patients with multiple metastases, effectively controlling the spread of cancer within the brain. However, WBRT's broad radiation exposure often leads to neurocognitive decline, predominantly due to incidental radiation damage to the hippocampus. This structure, located within the medial temporal lobes, is central to memory formation, spatial navigation, and overall cognitive health. Consequently, damage to the hippocampus during WBRT can result in severe memory impairments and cognitive deficits, affecting the quality of life for cancer survivors.

To address this issue, advancements in radiotherapy, particularly with Volumetric Modulated Arc Therapy (VMAT), have introduced the possibility of hippocampal-sparing WBRT. VMAT is an advanced form of radiation therapy that allows for precise modulation of radiation dose, with the capability to deliver high-intensity doses to specific areas while minimizing exposure to surrounding healthy tissue. In the context of hippocampal-sparing WBRT, VMAT technology enables oncologists to contour and spare the hippocampal region, reducing the dose of radiation it receives while still effectively targeting and treating metastatic lesions throughout the brain.

The hippocampus's radio sensitivity has driven the development of this technique, as studies have shown that minimizing hippocampal radiation exposure significantly reduces the incidence and severity of cognitive decline in patients. This approach requires careful planning and technical precision, as the hippocampus must be clearly identified and contoured on imaging scans to avoid excess radiation. VMAT achieves this by delivering radiation in an arc, allowing radiation beams to be continuously modulated as they circle around the patient, focusing on the metastases and reducing spillover radiation to sensitive areas like the hippocampus.

Clinical trials and studies have demonstrated the benefits of hippocampal-sparing WBRT using VMAT. For example, patients who receive this form of treatment report fewer memory-related side effects and maintain better cognitive function compared to those who undergo traditional WBRT. This preservation of cognitive abilities can be life-changing for patients, particularly those who are younger or have longer life expectancies, as it allows them to retain a greater degree of independence and quality of life after treatment. Moreover, hippocampal-sparing WBRT does not compromise the efficacy of brain metastasis management, as VMAT enables precise targeting of the metastatic sites, maintaining therapeutic effectiveness. The adoption of hippocampal-sparing WBRT using VMAT represents a significant shift towards a more patient-centered approach in oncology, prioritizing not only survival but also the post-treatment quality of life. By balancing disease control with cognitive preservation, VMAT offers an optimized treatment solution for brain metastases. This technology aligns with a growing emphasis on supportive care, focusing on the long-term well-being of cancer patients. However, successful implementation of hippocampal-sparing WBRT requires specialized training, access to advanced technology, and thorough patient evaluation to determine candidacy, as not all patients may benefit equally from this approach.

Overall hippocampal-sparing WBRT via VMAT provides a breakthrough in treating brain metastases by reducing radiation-induced cognitive decline, thus preserving memory and cognitive function in patients. This advancement underscores the importance of integrating innovative radiotherapy techniques into clinical practice to enhance the quality of life for patients undergoing treatment for brain metastases, moving closer to a holistic approach in cancer care.

Objective:

To present a case demonstrating the effectiveness of hippocampus-sparing WBRT using a VMAT plan & Evaluate the Dosimetric parameter and OAR constrains, and also its impact on clinical outcomes and cognitive preservation.

Case Description:

A 35 year-old male patient with metastatic brain lesions underwent WBRT as part of her treatment regimen. Prior to treatment, a VMAT plan was developed with a focus on sparing the hippocampi while delivering an adequate dose to the target PTV. The VMAT plan aimed to optimize dose distribution and minimize radiation exposure to critical structures.

2. Theoretical Basis for Hippocampal Sparing

2.1 Neuroanatomy and Radiation-Induced Cognitive Decline

Neuroanatomy plays a pivotal role in understanding radiation-induced cognitive decline, especially for patients undergoing brain radiation therapy, such as Whole Brain Radiation Therapy (WBRT) for treating brain metastases. The brain’s complex structure, particularly regions like the hippocampus, frontal lobe, and temporal lobe, significantly influences cognitive abilities, including memory, attention, executive function, and emotional regulation.

Radiation exposure, however, affects these critical regions differently, with the hippocampus being highly vulnerable due to its role in neurogenesis and memory consolidation. The hippocampus, integral to forming new memories and spatial navigation, is sensitive to radiation, making it a primary site of damage in patients receiving WBRT. This sensitivity often results in memory deficits, affecting both short-term memory and learning capacity. Additionally, the frontal and temporal lobes, which are crucial for executive functions, emotional control, and language processing, are also susceptible to radiation-induced injury, contributing to broader cognitive and functional impairments in patients.

Radiation-induced cognitive decline is thought to result from multiple mechanisms, including inflammation, direct neuronal damage, and disruption of neurogenesis, particularly in the hippocampus. When radiation induces inflammation within brain tissue, it releases cytokines that can damage neuronal cells and support cells like oligodendrocytes, which are essential for maintaining white matter integrity. This degradation of white matter can disrupt communication pathways between brain regions, further contributing to cognitive deficits. In addition, radiation affects the brain's blood-brain barrier, increasing permeability and allowing harmful substances to reach sensitive areas, exacerbating inflammation and neuronal damage.

The cognitive effects of radiation often manifest gradually, with some patients experiencing delayed cognitive decline months or even years after treatment. These effects can include problems with processing speed, attention, executive function, and verbal memory, all of which impact daily life and independence. Advances in neuroprotective strategies, such as hippocampal-sparing techniques, aim to limit radiation exposure to specific regions like the hippocampus, which has shown promise in reducing memory-related side effects in clinical studies. By focusing radiation on tumor-affected areas while sparing critical neuroanatomical structures, these techniques strive to balance effective cancer treatment with the preservation of cognitive function.

Understanding the neuroanatomical basis of radiation-induced cognitive decline has led to these innovations, enabling clinicians to make more informed decisions on treatment planning to mitigate cognitive risks. As research advances, a more precise targeting approach combined with neuroprotective interventions holds potential for preserving cognitive health in cancer survivors, ensuring that treatment not only prolongs life but also maintains quality of life and cognitive integrity.

2.2 Role of Hippocampus in Cancer Patients Undergoing WBRT

The hippocampus plays a crucial role in memory formation and spatial navigation, and its function becomes a major consideration for cancer patients undergoing Whole Brain Radiation Therapy (WBRT). WBRT is commonly used to treat brain metastases; however, it poses significant risks to cognitive health, particularly memory impairment, which can severely impact a patient's quality of life. The hippocampus is highly sensitive to radiation, and exposure during WBRT can lead to neurocognitive decline, including issues with short-term memory, learning, and processing information. As a response, advanced techniques like hippocampal-sparing WBRT have been developed to mitigate these effects. This approach specifically limits radiation exposure to the hippocampal region while still targeting metastatic sites across the brain, aiming to preserve cognitive function as much as possible. Studies have shown that patients receiving hippocampal-sparing WBRT experience fewer memory-related side effects compared to those undergoing traditional WBRT, which does not differentiate between brain regions. Protecting the hippocampus during WBRT represents a promising advance in supportive cancer care, offering a balance between effectively managing brain metastases and preserving cognitive function, which is essential for maintaining patient independence and overall well-being during and after treatment.

3. VMAT Technique in Hippocampal Sparing WBRT

3.1 Overview of VMAT

Volumetric Modulated Arc Therapy (VMAT) is an advanced radiation therapy technique designed to treat cancer with precision and efficiency. It delivers targeted radiation doses to tumors while minimizing exposure to surrounding healthy tissue. VMAT uses a rotating linear accelerator that moves in a 360-degree arc around the patient, continuously adjusting the intensity of the radiation beam. This capability allows for highly modulated treatment, precisely conforming to the tumor's shape, which is particularly beneficial for treating cancers in complex or sensitive areas like the head, neck, and prostate. Unlike traditional Intensity-Modulated Radiation Therapy (IMRT), which requires multiple fixed beams and longer treatment times, VMAT achieves its objectives faster by delivering radiation in a single or multiple arcs. This reduction in treatment time not only enhances patient comfort but also reduces the potential for patient movement, which can lead to more accurate treatment. VMAT is often used in adaptive radiation therapy, where treatment plans can be adjusted to

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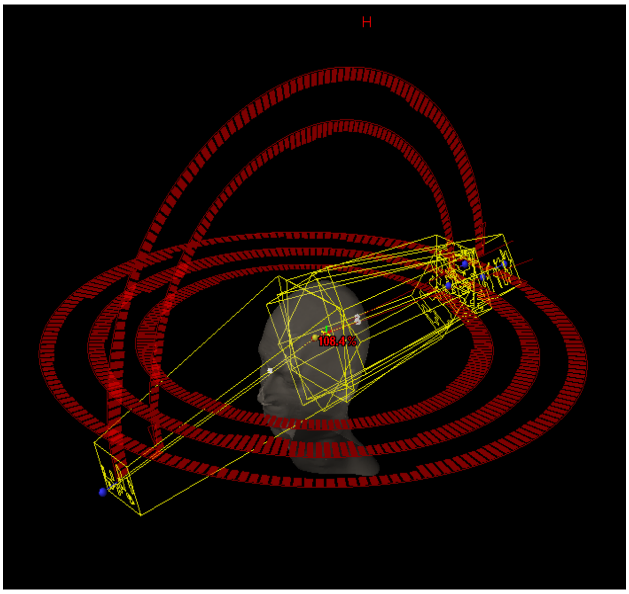
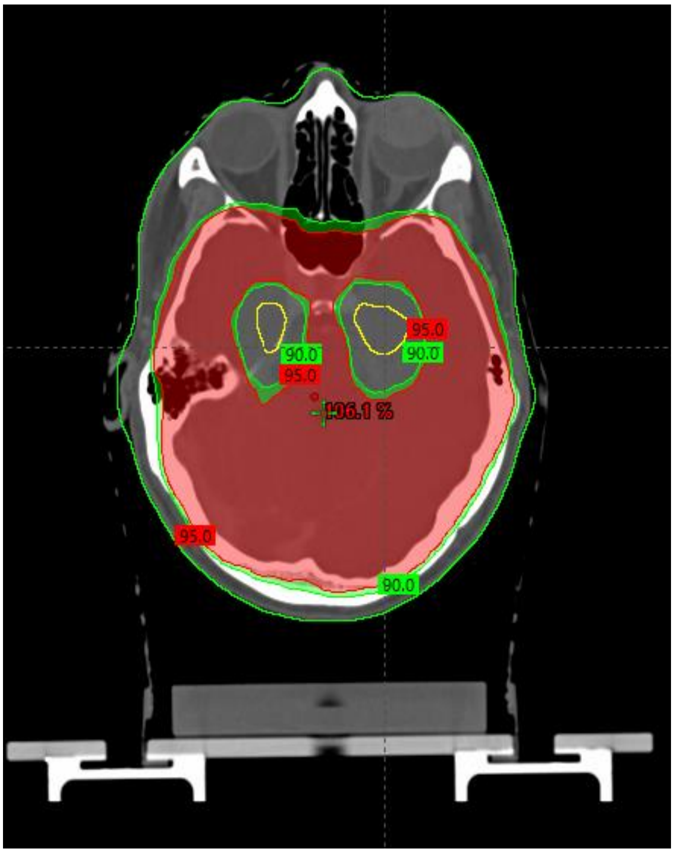
accommodate daily changes in patient anatomy. While it's generally more accessible and cost-effective than other advanced options like proton therapy, VMAT's suitability depends on the specific tumor characteristics and patient factors, making it a versatile yet personalized approach in modern oncology.

3.2 Methods:

The hippocampus was contoured, and hippocampal avoidance regions were created using a 5mm volumetric expansion around the hippocampus. VMAT treatment plans were generated for a prescription dose of 30 Gy in 10 fractions. The VMAT plan was designed using advanced treatment planning software Eclipse, incorporating image-guided techniques to ensure precision. The treatment plan was evaluated for dose conformity and hippocampal sparing. Dosimetric analysis was performed to assess the radiation dose received by the hippocampi and other critical structures. Cognitive assessments were conducted before and after treatment to monitor any changes in cognitive function. Treatment Planning and Dose Constraints



(A)



(B)

Fig. (A & B) Clinical Outcomes of Hippocampus-Sparing VMAT in Brain Metastases

Results:

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The hippocampal avoidance volume was 42 cm3, occupying 2.2% of the whole brain planned target volume. Spared the hippocampus, with a median dose of 11.45 Gy and maximum dose of 16.72Gy.The VMAT plan successfully spared the hippocampi while delivering the prescribed dose to the brain. Dosimetric analysis revealed a significant reduction in the dose received by the hippocampi compared to conventional WBRT plans. Post-treatment cognitive assessments indicated stable cognitive function, with no significant decline observed in memory or other cognitive domains.

Clinical Goals

Plan			VMAT,F,A
Total Dose			3000.0 cGy
Clinical Goal Summary			0 | 0 | 12
GTVm 1	P1	D 95.0 % > 95.0 %	100.45 %
GTVm 2	P1	D 95.0 % > 95.0 %	100.38 %
PTV PLAN 30GY	P1	D 95.0 % > 95.0 %	96.88 %
Brain	P2	Dmax < 5800 cGy	3250.57 cGy
	P2	Dmax < 6000 cGy	3250.57 cGy
BrainStem	P2	Dmax < 5400 cGy	3202.80 cGy
Eye_R	P2	Dmean < 1500 cGy	1222.43 cGy
	P2	Dmax < 4800 cGy	2213.34 cGy
Hippocampus_L	P2	Dmax < 1700 cGy	1591.48 cGy
	P2	Dmean < 1300 cGy	1162.69 cGy
Hippocampus_R	P2	Dmax < 1700 cGy	1672.13 cGy
	P2	Dmean < 1300 cGy	1150.14 cGy

According to American Association of Physicists in Medicine (AAPM) it is recommended that if prescription dose is 30 Gy in 10, and coverage criteria is D95 % > 95% then hippocampus Dmax should be 16 - 18Gy and Dmean, 12 - 15Gy , similarly if coverage criteria is D95 % > 90% , then hippocampus Dmax should be 14 - 16Gy and Dmean, 9 - 12Gy ,

4. **Quality of Life Improvements**

The preservation of cognitive function is directly correlated with improved quality of life in patients undergoing WBRT. Hippocampus-sparing VMAT has been associated with fewer disruptions in activities of daily living, social interactions, and overall mental health, thus representing a valuable advancement in supportive care for cancer patients. Patient-reported outcomes further emphasize the benefits of this technique, as many patients report lower levels of fatigue, depression, and cognitive disturbance following hippocampus-sparing radiotherapy.

5. Challenges and Future Directions

5.1 Technical and Dosimetric Limitations

While VMAT offers a feasible approach to hippocampal sparing, challenges remain in achieving consistent dose sparing across patient populations, especially in cases of large or irregularly shaped metastases. Additionally, the presence of metastases near the hippocampal region poses difficulties, as the need to balance tumor control with neurocognitive preservation becomes increasingly complex.

5.2 Long-Term Neurocognitive Outcomes and Biomarkers

There is a need for more longitudinal studies examining the effects of hippocampal-sparing WBRT on long-term cognitive outcomes. Furthermore, the identification of biomarkers that can predict cognitive decline or resilience in patients undergoing WBRT would be instrumental in individualizing treatment. Research on neuroimaging techniques to assess hippocampal integrity pre- and post-WBRT may also enhance patient selection criteria for hippocampal sparing.

5.3 Integration with Emerging Therapies

The integration of hippocampus-sparing WBRT with emerging treatments, such as immunotherapy and targeted therapies, presents a promising avenue for enhancing outcomes in patients with brain metastases. Future research is needed to assess the combined effects of these therapies on both tumor control and cognitive preservation.

Conclusion

Hippocampus-sparing WBRT using VMAT represents a significant advancement in the treatment of brain metastases, offering a feasible approach to reduce neurocognitive side effects without compromising therapeutic efficacy. The utilization of VMAT in hippocampal sparing exemplifies the evolving paradigm in radiotherapy, emphasizing patient-centered care that seeks to enhance quality of life alongside clinical outcomes. Ongoing research and technological innovations will continue to refine this approach, potentially setting new standards in the radio therapeutic management of brain metastases.

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