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Research Article

OPTIMIZING TUMOR CONTROL IN BRAIN METASTASES: THE ROLE OF DOSE ESCALATION IN STEREOTACTIC RADIOSURGERY

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Abstract: Brain metastases (BM) affect approximately 20% to 40% of cancer patients and are associated with considerable morbidity and reduced survival. Stereotactic radiosurgery (SRS) has become a pivotal treatment option due to its ability to deliver high-dose, targeted radiation to brain lesions while minimizing exposure to surrounding healthy tissue. Unlike whole-brain radiation therapy (WBRT), which is linked to cognitive decline and suboptimal local control, SRS offers a more focused and effective approach, particularly in patients with a limited number of metastases.

One of the emerging areas of interest in SRS is dose escalation—administering higher radiation doses to improve local tumor control. While promising, this approach carries the risk of radiation-induced necrosis, highlighting the importance of defining safe thresholds for neurotoxicity. Recent studies suggest that carefully controlled dose escalation can lead to improved tumor suppression without significantly increasing adverse effects, especially when patient selection and lesion characteristics are properly considered.

This paper evaluates current evidence on dose escalation in SRS, drawing from recent data, including 2023 studies, to assess its impact on tumor control rates, overall treatment efficacy, and associated complications. The analysis underscores the need for continued refinement of SRS protocols, including personalized dosing strategies that balance maximal therapeutic benefit with minimal risk. Our findings contribute to the evolving framework for the management of brain metastases, supporting the strategic use of dose escalation in selected cases to enhance patient outcomes.

Keywords: Brain Metastases, Stereotactic Radiosurgery, Dose Escalation, Tumor Control, Neurotoxicity

Introduction

Brain metastases (BM) occur in approximately 20%–40% of cancer patients, significantly impacting survival and quality of life. Stereotactic radiosurgery (SRS) has emerged as a crucial treatment modality, providing precise high-dose radiation to metastatic brain tumors with minimal collateral damage. Traditional approaches have prioritized balancing tumor control with neurotoxicity prevention. However, the potential for dose escalation to improve local control rates is an ongoing area of investigation.

While whole-brain radiation therapy (WBRT) was historically the standard treatment, its association with cognitive decline and limited efficacy in local control has led to a shift toward SRS. Studies suggest that dose

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escalation can improve tumor control rates but may increase the risk of radiation-induced necrosis. Thus, understanding the threshold for neurotoxicity is crucial for optimizing treatment strategies.

This paper explores recent advancements in dose escalation strategies, analyzing their effects on tumor control, treatment efficacy, and potential risks. We incorporate data from 2023 to provide the most updated insights into best practices for SRS in managing brain metastases.

1. Literature Review

Several recent studies have explored the efficacy of dose escalation strategies in SRS for brain metastases. Below is a summary of key findings:

Study	Key Findings	Dose Strategy	Neurotoxicity Risk
Kleinberg et al. (2023)	Dose escalation improves local control rates but increases neurotoxicity in tumors >3 cm	24–30 Gy in single fraction	15% risk of radionecrosis
Ladbury et al. (2023)	Multi-session SRS reduces neurotoxicity compared to single-fraction dose escalation	3x9 Gy fractions	5% neurotoxicity
Shen et al. (2023)	Adaptive dosing strategies improve tumor control with limited neurotoxicity	Variable dose based on tumor size	8% neurotoxicity
Milano et al. (2023)	High-dose SRS improves survival in patients with controlled systemic disease	27 Gy in single fraction	12% neurotoxicity

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These findings suggest that while dose escalation improves local control, it is associated with increased risks. Multi-fraction SRS appears to mitigate neurotoxicity while maintaining efficacy.

2. Dose Escalation and Tumor Control

2.1 Relationship Between Dose and Tumor Control

Several clinical trials have demonstrated that increasing the radiation dose correlates with better local tumor control. The Radiation Therapy Oncology Group (RTOG) 90-05 study, a landmark dose-escalation trial, found that local tumor control improved significantly with higher doses, but the risk of grade 3–4 neurotoxicity also increased.

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2.2 Comparative Analysis of Dose Escalation Strategies

Dose Strategy	Local Control Rate	Neurotoxicity Rate
18 Gy (standard dose)	65% at 12 months	5%
24 Gy (moderate escalation)	75% at 12 months	10%
30 Gy (high escalation)	85% at 12 months	15%

3. Strategies to Mitigate Neurotoxicity

3.1 Fractionated Stereotactic Radiotherapy (FSRT)

FSRT delivers the radiation dose over multiple sessions rather than a single fraction. Studies have shown that fractionation reduces the risk of radiation necrosis while maintaining tumor control.

Key Findings:

- **3×9 Gy** fractionation regimen led to **75% local control at 12 months** with only **5% neurotoxicity**.
- A **5×7 Gy regimen** provided similar tumor control but further reduced neurotoxicity.

Biomarkers for Predicting Radiation Toxicity

Emerging research suggests that imaging biomarkers, such as diffusion tensor imaging (DTI), may predict neurotoxicity risk. Studies indicate that **patients with high pre-treatment edema levels** are at greater risk of developing radiation necrosis.

3.2 Adjunctive Therapies

- **Steroid Therapy:** Dexamethasone is commonly used to reduce inflammation postSRS.
- **Bevacizumab:** An anti-VEGF agent that reduces radiation necrosis by improving vascular stability.

4. Future Directions in SRS Dose Optimization

4.1 Radiomics and AI in Treatment Planning

Machine learning models are increasingly being utilized to optimize SRS dosing. AIbased algorithms can predict the optimal dose based on tumor characteristics, patient genetics, and prior treatment response.

4.2 Combination Therapies

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Emerging evidence supports combining SRS with systemic therapies such as:

- **Immunotherapy (Checkpoint Inhibitors)**: Enhances tumor response but increases neurotoxicity risk.
- **Targeted Therapy (TKIs, EGFR inhibitors)**: Shows promise in improving SRS efficacy for specific mutations.

4.3 Adaptive Radiation Therapy

Real-time imaging and dose adaptation allow for dynamic treatment planning based on tumor response. This approach is expected to reduce over-treatment and unnecessary neurotoxicity.

5. Conclusion

Dose escalation in stereotactic radiosurgery for brain metastases improves local tumor control but comes with an increased risk of neurotoxicity. Strategies such as multi-fraction SRS, imaging biomarkers, and adjunctive therapies help mitigate this risk. Advances in AI-driven

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Treatment planning and combination therapies offer promising pathways to optimize outcomes while minimizing adverse effects.

Future research should focus on refining dose thresholds, integrating personalized treatment strategies, and improving long-term neurocognitive outcomes in patients undergoing SRS.

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