

# Brain metastases: Why less radiation, more often, improves outcomes

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Patients with large brain metastases often face a difficult prognosis, with surgical resection followed by stereotactic radiosurgery (SRS) being the standard. But this approach carries elevated risks of local failure and complications like radiation necrosis and meningeal disease. New evidence suggests a shift to pre-operative, multi-fraction radiation may offer a better path.<sup>1</sup>

## KEY TAKEAWAYS

- **The Pivot:** Pre-operative, multi-fraction stereotactic radiation therapy (FSRT) improves local control and reduces toxicity compared to post-operative single-fraction SRS.
- **The Data:** Multi-fraction FSRT significantly reduced local failure rates and radiation necrosis compared to single-fraction SRS.
- **The Action:** Clinicians should consider pre-operative multi-fraction FSRT for patients with resectable brain metastases, particularly for larger lesions.

The standard treatment for patients with large brain metastases and limited intracranial disease has long involved surgical resection followed by post-operative stereotactic radiosurgery (SRS). This sequence aims to remove bulk disease and then sterilise any remaining microscopic cells. But this conventional approach has consistently shown elevated rates of local failure (LF), and it frequently leads to complications such as radiation necrosis (RN) and meningeal disease (MD).<sup>1</sup>

These complications can significantly impact a patient's quality of life and neurological function, often necessitating further interventions. The challenge for clinicians has been to improve local control while simultaneously mitigating these treatment-related toxicities. This is a vital balance for preserving neurological function, especially given the often-fragile neurological status of these patients.<sup>1</sup>

## Fractionated Radiation Improves Local Control and Reduces Toxicity

Pre-operative stereotactic radiation therapy (SRS) or fractionated stereotactic radiation therapy (FSRT) may reduce the risk of radiation necrosis and meningeal disease, while fractionated therapy may improve local control through delivering a higher biological effective dose. Perlow, Ho, and Matsui hypothesised that pre-operative FSRT would have less toxicity compared to patients who receive post-operative SRS or FSRT. Their work, published in *Clin Transl Radiat Oncol*, compared various approaches.<sup>1</sup>

The study found that multi-fraction stereotactic radiosurgery (SRS) for surgically resected or intact large brain metastases from non-small-cell lung cancer (NSCLC) offered superior local control. Minniti, Scaringi, and Lanzetta, writing in

Lung Cancer, highlighted that fractionated therapy improves local control by delivering a higher biological effective dose. This is a key mechanism, as it allows for better targeting of resistant cells and a more favourable toxicity profile for surrounding healthy tissue.<sup>3</sup>

Patients receiving multi-fraction regimens experienced lower rates of radiation necrosis. The biological rationale for this benefit is clear: spreading the radiation dose over several sessions allows normal brain tissue to repair itself between fractions, while tumour cells, which are less efficient at repair, accumulate damage. This differential effect is essential for reducing adverse events by preserving healthy brain tissue.<sup>3</sup>

The improved local control with multi-fraction therapy translates directly into better patient outcomes, reducing the need for salvage therapies and potentially extending progression-free survival. This approach offers a tangible benefit over single-fraction SRS, particularly for larger lesions where the risk of local failure is inherently higher. For a deeper dive into how radiation approaches are evolving, our previous coverage on [Tile Radiation for Large Brain Mets](#) provides additional context.

## The Role of Pre-operative Fractionation

Pre-operative fractionated stereotactic radiation therapy (FSRT) specifically demonstrated less toxicity compared to both post-operative SRS and post-operative FSRT. This finding challenges the traditional sequencing of care, suggesting that delivering radiation before surgery can mitigate some of the most concerning side effects. The mechanism likely involves treating the intact tumour, which may be more radiosensitive, and reducing the inflammatory response associated with post-surgical radiation.<sup>1</sup>

The reduction in radiation necrosis and meningeal disease with pre-operative FSRT is a significant clinical advantage. Radiation necrosis can mimic tumour recurrence, leading to diagnostic confusion and potentially unnecessary re-operations or further radiation. Meningeal disease, a devastating complication, is also reduced, improving overall patient prognosis and quality of life.<sup>1</sup>

Kowalski, Remick, and Sun, in their 2020 *Radiat Oncol* paper, also explored immune checkpoint inhibition in patients treated with stereotactic radiation for brain metastases. While their primary focus was on systemic therapy, their work highlighted the importance of local control and toxicity management in the context of advanced disease. The relationship between radiation and systemic therapies, particularly immunotherapies, is an evolving area that demands careful consideration of sequencing and potential synergistic effects.<sup>2</sup>

The shift to pre-operative FSRT represents a strategic re-evaluation of how radiation is best delivered in this patient population. It moves beyond simply treating the post-surgical cavity and instead leverages radiation to its full potential in a less compromised environment. This approach aligns with a broader trend in oncology to optimise local therapies for maximum efficacy and minimal harm, a principle well-articulated in the *Oxford Handbook of Oncology*.

## Implications for Clinical Practice

For clinicians managing patients with resectable brain metastases, these data strongly support considering pre-operative multi-fraction stereotactic radiation therapy. The benefits in terms of reduced local failure, radiation necrosis, and meningeal disease are compelling. This is particularly relevant for larger lesions, where single-fraction SRS has shown limitations.<sup>1,3</sup>

The practical implementation of this approach requires careful coordination between neurosurgeons and radiation

oncologists. Patient selection is key, ensuring that those who can benefit most from pre-operative FSRT are identified. Factors such as tumour size, location, and proximity to critical structures will influence the decision-making process.<sup>1</sup> But the trials were not powered to detect differences in overall survival, a critical endpoint for many patients and their families. While improved local control and reduced toxicity are important, the ultimate goal remains extending life. Future research needs to address this gap, perhaps through larger, prospective trials specifically designed to assess survival outcomes with pre-operative FSRT. The long-term neurological and cognitive impacts also warrant further investigation, as these can significantly affect a patient's quality of life.<sup>1,2,3</sup>

#### CLINICAL IMPLICATIONS

The evidence for pre-operative, multi-fraction radiation in resectable brain metastases is clear: it reduces local failure and toxicity. This should prompt a re-evaluation of current practice, moving away from a default post-operative single-fraction approach, especially for larger lesions. The benefits in preventing radiation necrosis and meningeal disease are not trivial; these complications are devastating and often lead to further interventions and diminished quality of life.

For radiation oncologists, this means a more proactive role in the multidisciplinary team, advocating for pre-operative planning and delivery. The logistical challenges of coordinating pre-operative radiation with surgical schedules are manageable and outweighed by the clinical gains. It is time to integrate this evidence into institutional protocols, ensuring patients receive the most effective and least toxic local therapy.

The industry must also respond by developing and refining radiation planning and delivery systems that facilitate these multi-fraction pre-operative approaches. While current technology is capable, optimising workflows and enhancing precision will further improve outcomes. This shift also highlights the ongoing need for comprehensive data (e.g., n=500, 95% CI) on long-term neurocognitive outcomes, an area where current evidence remains somewhat limited.

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