Leptomeningeal disease following local brain irradiation: a new frontier

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See the article by Nguyen et al. in this issue, pp. 84–93.

Radiation therapy as a component of the treatment of patients with brain metastases has undergone dramatic changes over the last 20 years. While whole brain radiation therapy (WBRT) has been long used as an effective palliative therapy for patients with brain metastases, in recent years it has been called into question. The risks of WBRT, specifically its potential cognitive detriment, are now widely accepted, compared with local irradiation techniques like stereotactic radiosurgery (SRS).^{1–3} Likewise, the perceived benefit of WBRT continues to be re-defined as prospective evidence emerges to suggest that WBRT offers no benefit in overall survival or quality of life compared with supportive medical therapy for select patient populations with poor prognosis.⁴

The recent decrease in WBRT utilization is, in part, related to the adoption of alternative local irradiation techniques, namely SRS.^{5,6} However, while the goal of WBRT is total intracranial tumor control, SRS by its nature is unable to target unknown subclinical disease elsewhere in the brain. This change in irradiation intent over time has led to a parallel change in intracranial patterns of failure.^{2,3} Interestingly, there are reported series that describe that local irradiation alone after neurosurgical resection may be associated with an increased rate of “pachymeningeal seeding,” ie, disease scattered throughout the surgical bed region but outside of the radiosurgical target.⁷ The relationship between tumor resection and meningeal failure, even with modern neurosurgical techniques, is presumably related to microscopic tumor spill at the time of surgery outside of the radiosurgery field.

Nguyen and colleagues provide a large analysis of patients with brain metastases treated with hypofractionated stereotactic radiotherapy (HSRT) in an attempt to report HSRT outcomes and to identify predictors for leptomeningeal disease (LMD) following irradiation.⁸ In their study, 235 patients with brain metastases were treated with HSRT (typically to 30 Gy in 5 fractions) to both intact tumors and

postoperative cavities (320 intracranial targets in total). Rates of local tumor control and radionecrosis were similar to previously published results, with over 80% tumor control at 12 months and less than 10% rates of symptomatic radionecrosis, despite relatively large average tumor/cavity volumes. While other series of “fractionated stereotactic radiosurgery” have been published, this series serves as a large report of patients treated with this technique to further validate this approach.

In their series, the overall rate of LMD was 19.2%, with a median time of 7.7 months from HSRT to the development of LMD.⁸ In an effort to subcategorize LMD into unique cohorts, the authors went on to classify LMD into one of 4 clinicopathologic groups (with respective frequency): diffuse nodular (44%), diffuse classic (27%), focal nodular (16%), and focal classic (13%). While survival outcomes after the development of LMD were poor, they did not differ by LMD subclassification. Interestingly, the only predictor for LMD after controlling for potential confounders included surgical resection (odds ratio = 2.30, $P = 0.008$). Another thought-provoking finding identified by Nguyen et al was an association between novel systemic agents (targeted agents and immunotherapy) and protection from subsequent LMD. Although it is an interesting area for future study, care should be taken when applying these novel agent data from such a heterogeneous group of patients.

It is noteworthy that reports such as the one provided by Nguyen et al should not be used to support a strictly non-operative approach to brain tumors, as the benefits of immediate neurosurgical decompression and pathology tumor evaluation cannot be challenged by any irradiation technique. Nonetheless it is indeed prudent to consider that additional perceived benefits of resection should be carefully evaluated. The idea that improved intracranial tumor control through a “more is more” approach is likely ill-advised. However, we

suspect that further study in this area will result in advancements in neurosurgical technique and instrumentation that could limit the risk of tumor spread during resection.

In summary, it is clear that the pathophysiology and treatment of patients with LMD from brain metastases has been an understudied area and is now ripe for further research. The authors posit that preoperative SRS could reduce the rate of subsequent LMD by “sterilizing” the surgical cavity such that any tumor spill that does happen during resection will not take root. Indeed, there are several prospective trials under way or in development that will formally evaluate the risks and benefits of preoperative radiosurgery, as well as many novel drug therapies for patients with LMD. It will be a race among medical specialties to provide advancements in surgical technique, radiotherapy technique, and systemic therapy delivery that could each prove to improve the outcome in patients with this dismal disease process. As a brain tumor community, we must work together to improve the care of these patients.

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