Commentary: Long-Term Update of Stereotactic Radiosurgery for Benign Spinal Tumors

Benign spinal tumors (BSTs) including meningiomas, schwannomas, and neurofibromas have historically been treated with surgical resection, or fractionated conventional radiotherapy in those patients with unresectable disease, medically unfit for surgery or patient preference, or as salvage therapy for multiply recurrent tumors when surgery is no longer feasible. However, single fraction, or hypofractionated stereotactic radiosurgery (SRS) has been increasingly used to treat BSTs with the intent to improve upon patient convenience and potentially efficacy, as a result of increasing comfort in our understanding of spinal cord tolerance to SRS and the certainty in delivery with millimetric precision inherent to modern image-guided radiotherapy delivery systems.

The incorporation of SRS into BST management requires a multidisciplinary approach, as several contraindications exist including spinal instability, symptomatic cord compression, and multilevel (>3 spinal segments) involvement. Additional safety considerations beyond those for intracranial SRS are necessary given the reduced spinal cord tolerance relative to the brain/brainstem and inability to immobilize the body with a rigid system as in intracranial SRS. Finally, the optimal contouring approach, delineation sequences, and planning margins for BSTs have yet to be established. Contouring guidelines exist for malignant spine SRS, however, differences in patterns of failure and margin considerations suggest different approaches are needed.

Given the long natural history, decades of follow-up is required to understand long-term treatment efficacy and late toxicities, compared to patients with spinal metastases with shorter survival. Specifically, secondary malignant neoplasms (SMNs) and malignant degeneration of neurofibromas are late toxicities unique to radiotherapy that may alter the risk/benefit ratio relative to surgery. Lastly, low patient numbers limit the power to make meaningful comparisons.

Chin et al published an update to their experience with BSTs, which addresses several limitations of previous studies. In this analysis, 120 patients with 149 BSTs were reviewed, of whom 26% had an existing tumor predisposition. Median follow-up was 49 mo, with 61 and 24 treatment courses having >5 yr and >10 yr of follow-up, respectively. Fractionated regimens were standardized using a single fraction equivalent dose (SFED), reporting outcomes with an alpha/beta ratio of 3 and 4. The primary endpoint was local failure (LF), defined as radiographic tumor progression compared to the immediate pretreatment magnetic resonance imaging (MRI), with or without clinical symptom progression. Considering the known phenomena of transient tumor enlargement or pseudoprogression, tumor growth within the first year after SRS was not considered a LF. Secondary endpoints included tumor shrinkage, symptom response, toxicity, and SMN. Imaging follow-up occurred at 6 and 12 mo, then yearly thereafter.

The cumulative incidence of LF at 3, 5, and 10 yr was 2%, 5%, and 12%, respectively, improving to 1%, 2%, and 8%, respectively, for radiation-naïve patients. The median time to LF was 51.3 mo, without associated correlated patient or dosimetric factors. Surgical salvage was required in 11 patients (3 with LF, 7 with stable or decreasing disease extent, and 1 with tumor swelling compressing cord within 1 yr requiring surgery). Patients presenting with pain experienced improvement in 36% of cases but worsening in 11%. One patient experienced transient myelopathy, and none developed SMNs.

This study confirms, with a large cohort with extended follow-up, that patients with BSTs can achieve excellent local tumor control. However, comparisons among studies remain challenging due to methodological differences. Over time, fractionated SRS has played a larger role in treating BSTs given the favorable dose gradients required across the tumor and at-risk spinal cord. In situations where large tumors are intimately associated with the spinal cord or thecal sac, stereotactic radiotherapy (SRT) using a total dose of 50 to 54 Gy in 1.8 to 2.0 Gy/fraction...
may be the safest approach given a differential dose gradient is not required. Among those treated with SRS, throughout the literature, there has been no unified method of quantifying delivered doses independent of fractionation. Despite its known limitations in SRS, the linear quadratic model does provide insight into comparative outcomes across various fractionation schemes, and Chin et al\textsuperscript{4} use this to better describe their cohort. Further work may corroborate the findings of Kalash et al,\textsuperscript{6} wherein tumor control was similar when patients were compared according to biological equivalent doses above and below 30 Gy\textsuperscript{10}.

Next, a meaningful consensus on treatment failure has yet to be established, in part due to pseudoprogression. Although Chin et al\textsuperscript{4} used a cutoff of 12 mo, pseudoprogressions have been documented to last even longer.\textsuperscript{7} Therefore, whether pseudoprogression should be considered a LF and the timing of such an event is unknown.

Finally, LF itself may not be as meaningful an endpoint as desired. Among patients with BSTs treated with SRS, MRI characteristics indicating tumor control (ie intramural enhancement and high T2 signal intensity) may be present even within enlarging lesions, suggesting that underlying SRS induced cellular damage may be sufficient, but radiographic tumor growth may be related to an increased cystic component rather than the tumor itself.\textsuperscript{8} In this setting, the most meaningful endpoint may be one that incorporates late tumor enlargement and tumors requiring intervention due to progressive symptoms, with or without radiographic failure. This highlights the need to explore the use of functional imaging sequences for BSTs and derive more meaningful endpoints in tumors that tend to stay stable and dormant.

Due to limited patient numbers and follow-up, there has also been little progress in our understanding of the individual BST histologies, their indications for and response to treatment, and the impact of tumor predisposition syndromes on outcomes. It has been postulated that neurofibromas may have worse symptomatic treatment outcomes due to their association with neurofibromatosis type 1, and consequently higher frequency of multilevel disease, larger-sized lesions, and infiltrative qualities.\textsuperscript{9–11} Also, SMN or malignant degeneration of neurofibromas remain worrisome, especially among patients with tumor predispositions and long life expectancies; larger patient cohorts with longer follow-up will be critical in ascertaining these risks. For now, proceeding with SRS with adequate informed consent remains reasonable, particularly among those without surgical options. Moving forward, understanding these principles may help us improve patient selection, avoid unnecessary treatments, and improve outcomes for this complex group of patients.

Disclosures
Dr Sahgal has received personal fees for past educational seminars from Elekta AB, Accuray Inc, and Varian Medical Systems; has received a research grant from Elekta AB; and has received fees for travel accommodations/expenses from Elekta and Varian Medical Systems for work performed outside of the current study. Dr Sahgal also belongs to the Elekta MR-Linac Research Consortium. Dr Chang has received speaker’s honorarium from Brainlab. Dr Lo belongs to the Elekta AB ICON expert group. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES