

## Stereotactic Radiosurgery and Radiotherapy for Brainstem Metastases – An International Multicenter Analysis

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### Background and objective

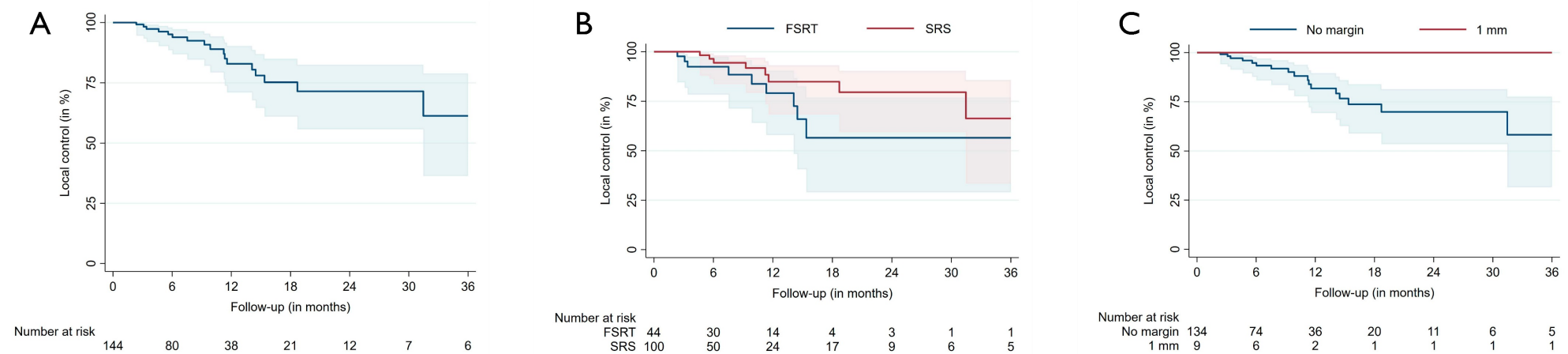
Brainstem metastases (BSM) present a significant neuro-oncological challenge, resulting in profound neurological deficits and poor survival outcomes. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) offer promising therapeutic avenues for BSM, despite their precarious location and high single doses. This international multicenter study investigates the efficacy and safety of SRS and FSRT for the treatment of BSM.

### Materials and methods

This retrospective international multicenter study included patients treated with SRS or FSRT (up to five fractions) for BSM between 2005 and 2022. BSMs had to be located in the pons, mesencephalon, or medulla oblongata. Metastases on the brainstem's surface or with presumed invasion from outside were excluded. All patients underwent SRS or FSRT using the CyberKnife robotic radiosurgery platform (Accuray Inc., Sunnyvale, CA, USA). The choice of prescription dose, the number of fractions, and applied margin were at the discretion of managing physicians in the nine participating institutions. Patient follow-up was conducted both radiologically and clinically. Local control (LC) was defined as unchanged or decreased tumor volume on follow-up imaging, while local failure was defined as increased tumor volume during follow-up. In cases of multiple BSM treatments during the disease course, the first treatment was considered for overall survival (OS). Data analyses utilized the Kaplan-Meier estimator and multivariable Cox proportional hazards models.

### Results

A total of 136 patients with 144 BSM treated at nine institutions from 2005 to 2022 were included. The median radiographic and clinical follow-up periods were 6.9 and 9.4 months, respectively. Predominantly, patients with BSM were managed with SRS (69.4%).



A) Overall local control, A) local control stratified for SRS and FSRT, A) local control stratified by total treatment margin. 95% confidence intervals represented by shaded areas.

The median prescription dose and isodose line for SRS were 18 Gy and 65%, respectively, while for FSRT, the median prescription dose was 21 Gy with a median isodose line of 70%. The 12-, 24-, and 36-month local control (LC) rates were 82.9%, 71.4%, and 61.2%, respectively. Corresponding overall survival rates at those time points were 61.1%, 34.7%, and 19.3%.

In the multivariable Cox regression analysis for LC, only the minimum biologically effective dose was significantly associated with LC, favoring higher doses for improved control (in Gy, hazard ratio (HR): 0.86,  $p < 0.01$ ). Regarding overall survival, good performance status (Karnofsky performance status,  $\geq 90\%$ ; HR: 0.43,  $p < 0.01$ ) and prior whole brain radiotherapy (HR: 2.52,  $p < 0.01$ ) emerged as associated factors.

In 14 BSM (9.7%), treatment-related adverse events were noted, with a total of five (3.4%) radiation necrosis.

### Conclusion

Given the scarcity of comprehensive prospective data, larger studies, and remaining uncertainties concerning the normal tissue tolerance of the brainstem, this international multicenter analysis suggests that SRS and FSRT for BSM are effective and time-saving treatment options with an acceptable risk profile. Stereotactic treatment with a sufficient dose should be offered to patients with small to medium-sized BSM, given the favorable LC rates. Inclusion of BSM in prospective trials on SRS and FSRT appears justified.