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## Abstract

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## Normal Tissue Complication Probability and Dose/Volume Tolerance of the Brain after Three-Fraction Radiosurgery for Brain Metastases: A Large Single-Institutional Analysis

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## Abstract

### Objectives:

Stereotactic radiosurgery (SRS) is the current standard of care in patients with brain metastases and controlled extracranial disease. Radiation necrosis (RN) is the dose-limiting side-effect of SRS but the brain dose constraints are poorly defined. Fractionated SRS can decrease risk of RN over single fraction SRS while maintaining high rates of survival. We assessed the survival and risk of RN after three-fraction SRS with a goal to identify specific dose-volume constraints associated with grade 3 or higher RN using normal tissue complication probability (NTCP) modeling.

### Methods:

A single-institutional retrospective review of patients treated with 3-fraction SRS from 2015 to 2020 was performed. Tissue volume (target + 1 cm brain margin) around each target lesion was contoured in a consistent manner and volumetric doses per lesion were recorded. Our primary endpoint was grade 3 or higher RN. RN was defined using biopsy or MRI with perfusion as available and graded using CTCAE version 5.0. We performed NTCP modeling of grade 3 or higher RN using a simplified Lyman-Kutcher-Burman (LKB) model, to calculate TD50 and TD5, the respective uniform doses which resulted in a 50% and 5% complication risk respectively. MATLAB v2022a and SPSS v23.0 was used for statistical analyses.

### Results:

From 2015 to 2020, a total of 434 patients underwent 539 courses of 3-fraction linac-based SRS, treating a total of 2559 metastatic lesions (range 1-94, and median = 3 lesions per course). Median age of patients at RT was 61.3 years (IQR 52.5 – 69.6). Median RT dose per fraction was 8 Gy (range 5-9 Gy). 12.1% patients received prior whole brain radiation (WBRT). Median follow-up after RT was 8 months (IQR 3-18m). The median overall survival (OS) after RT was 9.3m (95% CI 8.0 – 10.7m) while the median PFS was 5.5m (4.1m – 6.9m). A total of 113 patients (125 lesions) developed RN with 24 (32), 27 (35), 40 (56) and 2(2) patients (lesions) developing grade 1, 2, 3 and 4 RN respectively. Grade 3 or higher RN was observed in 7.8% patients. On per lesion analysis, rate of any RN and grade 3 RN was 4.9% and 2.3% respectively. Median time to RN was 11.3m (range 0.7 – 38.4). Preliminary NTCP modeling revealed a TD50 of 31.4 Gy, with a 5%, 10% and 20% risk of RN at an estimated dose of 22 Gy, 24 Gy and 27 Gy respectively. Mean V10, V12 and V15-24 in patients who developed Grade 3 or higher RN was significantly higher than the entire cohort (specifically, V20: 30.3 cc vs 9.4 cc, p=0.000). On applying receiver operator curve (ROC) characteristics, the rate of RN was < 5% at V20 < 5 cc and < 7.5% at V20 < 12 cc.

### Conclusion(s):

In patients receiving 3 fraction SRS, grade 3 or higher RN was seen in 7.8% patients and 2.3% lesions treated. With preliminary NTCP modeling, we were able to identify an estimated cutoff dose of 22 Gy, and a V20 < 5cc to be associated with < 5% risk of grade 3 or higher RN.

