Long-Term Risk of Radiation Necrosis Following SRS in ALK-Positive NSCLC in the Era of CNS-Penetrant TKIs

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Background: ALK-positive non-small cell lung cancer (NSCLC) is characterized by a high incidence of central nervous system (CNS) metastases. While contemporary ALK tyrosine kinase inhibitors (TKIs) have significant intracranial efficacy, stereotactic radiosurgery (SRS) remains a key treatment modality. Potential interactions between these highly CNS-penetrant TKIs and SRS-related toxicity remain poorly defined. Treatment-related changes (TRC) can include symptomatic radiation necrosis (RN), which is often associated with diagnostic uncertainty and significant morbidity. We sought to characterize the clinical features and risks associated with TRC in this population.

Methods: We performed a retrospective analysis of advanced ALK+ NSCLC patients treated with SRS at our institution and evaluated clinical features and treatment patterns potentially associated with TRC (defined as radiographic or pathologic changes after SRS not clinically adjudicated as disease progression). Associations between clinical variables and the occurrence of TRC were assessed using Fisher's exact test for p-values and univariable logistic regression for odds ratios with 95% confidence intervals.

Results: A total of 26 patients were included; median age was 51 years (range: 29-77) and 61.5% were male. Alectinib was the most frequent concomitant TKI around the time of SRS (46.2%), followed by crizotinib (23.1%) and lorlatinib (19.2%). The median number of lesions treated with SRS per patient was 5 (IQR: 2-10), at a median dose per lesion of 21 Gy (IQR: 20-24). Eight (30.8%) patients received post-operative SRS. Treatment sites included the cerebral lobes (n=54, 77.1%), deep cerebrum (n=10, 14.3%), cerebellum (n=16, 22.9%)**,** brainstem (n=4, 5.7%) and other (n=2, 2.8%). With a median follow-up of 65.9 months, nine (34.6%) patients developed TRC, including five (19.2%) with histologic confirmation of RN. All five of these patients were symptomatic and required steroid treatment; one patient also received bevacizumab. TRC was observed in 28 (14.4%) of 195 total lesions treated with SRS across all patients. The median time from SRS to TRC of any grade was 19 months (95% CI: 15.1 - 58.2); shorter for asymptomatic TRC (median 18.7 months, 95% CI: 10.4-37.4) than for symptomatic TRC (median 81.7 months, 95% CI: 7.9 - 125.6). Among TRC cases, treatment with a highly CNS-penetrant TKI (alectinib, brigatinib, or lorlatinib) at the time of TRC was associated with symptomatic presentation (55.6% vs 0.0%; OR 11.12, 95% CI: 0.52-236.77, p=0.096). Single-fraction SRS was administered to 60.5% of evaluable lesions and associated with a higher rate of TRC (22.9% vs 1.3%; OR 22.33, 95% CI: 3.51-931.07, p<0.001).

Conclusion: In this single-institution series, ALK-positive NSCLC patients on TKI frequently experienced treatment-related changes after SRS, with higher incidence than historically observed in non-ALK populations. Single-fraction treatment and highly CNS-penetrant TKI use following SRS may increase the risk of TRC. The emergence of symptomatic TRC years after SRS underscores the need for long-term surveillance and continued refinement of risk stratification and treatment sequencing within the evolving TKI–radiation therapeutic paradigm.