

PIK3 mutations are associated with increased local failure in patients with brain metastases treated with stereotactic radiation

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Purpose: Hyperactivation of the phosphatidylinositol-3-kinases (PI3K) pathway has been associated with radioresistance. It is unclear whether radioresistant mutations confer suboptimal local intracranial control for patients who receive stereotactic radiosurgery (SRS) for brain metastases. Our objective was to examine whether PIK3 mutations are associated with poor response to SRS in brain metastases.

Methodology: We retrospectively reviewed 60 identified patients with 155 brain metastases treated with SRS from 2003 to 2015 for whom MSK-IMPACT testing data was available for primary or metastatic lesions. MSK-IMPACT analyzes 341 genes by whole exome sequencing, including PIK3C2G, PIK3C3, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2 and PIK3R3. Patients with mutations of the above listed genes were considered to be positive for PIK3 mutations in this analysis. Association between clinical factors, including PIK3 mutation status (positive vs. negative), and local control was evaluated with univariate and multivariate Cox regression analysis. The Kaplan-Meier method was used to assess differences in local failure rates based on PIK3 mutation status.

Results: The most common tumor histology was lung (43.2%), followed by melanoma (18.1%) and breast (12.3%). Nineteen patients (31.7%) had a PIK3 mutation identified by IMPACT. The median lesion size was 0.8 cm (range, 0.2 – 5.8 cm). A total of 138 lesions (89%) were treated with single fraction SRS and 17 lesions (11%) were treated with hypofractionated SRS over 5 fractions. The median dose was 21 Gy (range 18 – 30 Gy). Most lesions were treated definitively (85.8%), while 22 lesions were treated post-operatively. Twenty-one patients (13.5%) had received prior radiation at the SRS site. Median follow-up was 8.5 months (range, 1.0 - 142.7 months). Local failure was observed for 16 lesions (10.3%). The median time to local failure was 4.9 months (range, 1.0 – 34.3 months). On univariate analysis, the presence of PIK3 mutation and lesion size were associated with local failure ($p=0.039$ and $p=0.006$, respectively), while primary tumor histology (lung vs. other), prior radiation received at SRS site, single fraction versus fractionated SRS, and definitive versus post-operative SRS were not. On multivariate analysis, PIK3 mutation remained predictive for local failure (HR 3.56 [95% CI 1.18-10.75], $p=0.024$), while lesion size was not ($p=0.828$). Using Kaplan-Meier method, local failure in lesions with PIK3 mutations was 16.0% vs. 8.8% in lesions without mutations ($p=0.030$). Lesions with PIK3 mutations were associated with a decreased time to local failure (mean 18.7 months [95% CI 16.7 – 20.7 months]) compared to absence of PIK3 mutation (mean 70.0 months [95% CI 36.8 – 103.2 months]).

Conclusions: Patients with PIK3 mutations are at higher risk for local failure after stereotactic radiosurgery for brain metastases. This data needs to be validated in a larger patient cohort. Future directions also include examining PIK3 mutations and local failure for patients treated with whole brain radiation.