RTHP-33. PIK3 MUTATIONS ARE ASSOCIATED WITH DECREASED LOCAL CONTROL IN BRAIN METASTASES TREATED WITH RADIATION

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INTRODUCTION: To compare hyo-fractionated (HyRT) with conventional fractionated radiotherapy (CRT) for good prognosis newly diagnosed nased patients with glioblastoma (GBM). METHODS: HyART, a Phase II trial randomly assigned newly diagnosed GBM patients 1:1 by computer generated randomization chart to HyRT and CRT. Patients of 16 - 65 years, Karnofsky performance score ≥70 and maximal safe tumor volume > 2 cm3 were randomized. SPSS v16, was used for all statistical analysis. RESULTS: 83 patients randomized, 77 were evaluable. Median age 45 years (Range: 16-65). Male: Female ratio was 2.1. 20(25.9%) patients had seizure at presentation. Median symptom duration was 2 months (1 day to 72 months). 49 patients had GTR. Only two patients required hospitalization for features of raised intracranial pressure during radiation and two required long duration steroid after RT in the HyRT arm. Three patients in HyRT arm grade III thombocytopenia during maintenance phase. At a median follow up of 3 years, 31 experienced disease progression. However, none of them have presented a documented radio necrosis as of now. Median PFS was 13.1 months (95% CI: 11.7-14.5 months). Median PFS was significantly better for GTR than STR (14.1 vs 9.6 months; p=0.004). Patients operated at high volume center have better PFS (14.1 vs 9.6 months). Median PFS was better but not significant for IDH mutated patients (16.3 vs 13.1 months). A delay in initiation of RT by more than 6 weeks conferred worse PFS (9.9 vs 14.2 months; p=0.022). There was no difference in PFS for patients treated with HyRT vs CRT. Estimated median OS was 29.6 months (95% CI: 19.1-40.1 months). CONCLUSION: HyRT appears to be well tolerated with no treatment interruption and equivalent survival compared to CRT.

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BACKGROUND: Hyperactivation of the phosphatidylinositol-3-kinases (PI3K) pathway has been reported to be associated with radioresistance in preclinical models. We examined whether PIK3 mutations are associated with poor radiotherapy response in brain metastases (BM). METHODS: We retrospectively reviewed 259 patients with BM treated with RT between 2004-2017 for whom MSK-IMPACT testing data was available for primary or metastatic lesions. MSK-IMPACT analyzes 341 genes, including PIK3CA, AKT1, PTEN, PIK3R1, PIK3R2, PIK3R3, AKT2, and AKT3. Association between clinical factors, mutation status, and local control (LC) was evaluated with Cox regression multivariate analysis. The Kaplan-Meier method was used to assess differences in LC rates and overall survival (OS). RESULTS: 147 patients received stereotactic radiosurgery (SRS) and 112 patients received whole brain radiation (WBRT). The most common histologies were lung (48%) and breast (20%). Eighty-three (32%) patients had PIK3 mutations, and 36 (14%) patients specifically had PIK3CA mutations. Median follow-up was 10.8 months. LC was 82% at 12 months. The presence of any PIK3 mutation (HR=0.4, p=0.003), PIK3CA mutation (HR=0.1, p=0.001) were associated with decreased LC, while age and histology were not. For patients who received WBRT, mutation status resulted in worse LC at 12-months: 42% for PIK3 mutation positive vs. 65% for mutation negative, p=0.001; 30% for PIK3CA mutation positive vs. 40% for PIK3CA mutation negative, p=0.01. Interestingly, for SRS treatments, PIK3CA mutation positivity did not result in worse LC at 12 months (90% vs 93% mutation negative, p=0.17), while PIK3CA mutation positivity did result (76% vs 92% mutation negative, p=0.05). There was no difference in OS on treatment based on PIK3 or PIK3CA mutation status. CONCLUSION: Patients with PIK3 mutations are at significantly higher risk for decreased LC after RT for BM. Specifically, patients with PIK3CA mutations are more likely to develop local recurrence that is not abrogated by SRS.