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Irradiation of the Potential Cancer Stem Cell Niches in the Adult Brain Improves Progression-free Survival of Patients with Malignant Glioma.

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Abstract

ABSTRACT: BACKGROUND: Glioblastoma is the most common brain tumor in adults. The mechanisms leading to glioblastoma are not well understood but animal studies support that inactivation of tumor suppressor genes in neural stem cells (NSC) is required and sufficient to induce glial cancers. This suggests that the NSC niches in the brain may harbor cancer stem cells (CSCs), Thus providing novel therapy targets. We hypothesize that higher radiation doses to these NSC niches improve patient survival by eradicating CSCs. METHODS: 55 adult patients with Grade 3 or Grade 4 glial cancer treated with radiotherapy at UCLA between February of 2003 and May of 2009 were included in this retrospective study. Using radiation planning software and patient radiological records, the SVZ and SGL were reconstructed for each of these patients and dosimetry data for these structures was calculated. RESULTS: Using Kaplan-Meier analysis we show that patients whose bilateral subventricular zone (SVZ) received greater than the median SVZ dose (=43Gy) had a significant improvement in progression-free survival if compared to patients who received less than the median dose (15.0 vs 7.2 months PFS; P=0.028). Furthermore, a mean dose >43Gy to the bilateral SVZ yielded a hazard ratio of 0.73 (P=0.019). Importantly, similarly analyzing total prescription dose failed to illustrate a statistically significant impact. CONCLUSIONS: Our study leads us to hypothesize that in glioma targeted radiotherapy of the stem cell niches in the adult brain could yield significant benefits over radiotherapy of the primary tumor mass alone and that damage caused by smaller fractions of radiation maybe less efficiently detected by the DNA repair mechanisms in CSCs.

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