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Temozolomide Rechallenge in Patients With Recurrent High-Grade Glioma Treated With Re-Irradiation

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(G) 2 TLN (CTCAE v5.0 criteria) were considered as an event in the modelling process. A collection of 9 clinical and 27 dosimetric parameters was considered for structure wise modelling. After elimination of strongly cross-correlated variables (Spearman correlation coefficient > 0.8), logistic regression models were generated using forward stepwise selection. Bootstrapping was performed to assess parameter selection robustness. Model performance was evaluated via cross-correlation by assessing the area under the curve of receiver operating characteristic curves (AUC-ROC) as well as calibration with a Hosmer-Lemeshow (HL) test statistic. Binary cross-entropy (CE) was calculated to compare the likelihood of our data fitting the different models.

Results: After a median radiological follow-up of 51.5 months (range, 4 − 190), 27 (9 %) patients developed a ≥ G2 TRN. With 11 (41%) patients having bitemporal necrosis, this resulted in 38 events in 598 temporal lobes for structure-wise analysis. After multicollinearity parameter removal, 7 clinical and 7 dosimetrical parameters were used for further analysis. During the Bootstrapping analysis the highest selection frequency was found for prescription dose (PD), followed by Age, Diabetes (DM), Hypertension (HBP) and $D1cc_{Gy}$ and $Dmin_{Gy}$. Changes in Bayes information criterion were minimal for models > 3 parameters. As a result, models with 3 and 4 parameters were chosen for further evaluation. DM and $Dmin_{Gy}$ failed to reach significance in the generated models, so models including HBP, PD, age and $D1cc_{Gy}$ were selected for performance evaluation. During cross validation, Age*PD*$D1cc_{Gy}$ and Age*PD*$D1cc_{Gy}$*HBP were superior in all described test statistics. Full cohort structure wise and patient wise models were built with a maximum AUC-ROC of 0.7931 (structure wise) and 0.7590 (patient wise) for the model including Age*PD*$D1cc_{Gy}$*HBP.

Conclusion: While developing logistic regression NTCP models to predict ≥ G2 TLN, the best fit was found for the model containing Age, prescription dose, $D1cc_{Gy}$ of the temporal lobe and high blood pressure as risk factors. External validation would be the next step to improve generalizability and potential introduction into clinical routine, allowing for patient-specific planning to avoid high grade TLN for high-risk patients.

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3235

Proximity to Brainstem at Recurrence is Associated with Decreased Survival in IDH Wild-Type Glioblastoma

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Purpose/Objective(s): Recent autopsy data from patients with glioblastoma (GBM) has demonstrated that pronounced brainstem infiltration is now a common pattern of disease progression near the end of life. The present study evaluated the association of disease proximity to the brainstem on imaging, both at diagnosis and at recurrence, with overall survival (OS).

Materials/Methods: 140 patients with IDH wild-type GBM treated definitively with resection and adjuvant chemoradiation at a single institution from 2013-2019 were retrospectively analyzed. Disease proximity to brainstem was calculated from measurements made on T1 post-contrast MRI brain obtained at diagnosis postoperatively and at recurrence. Tumor volume was approximated by the resection cavity plus adjacent extrinsic enhancement, measured during target delineation at time of treatment delivery. The Kaplan-Meier method was used to estimate OS, and multivariable analysis was performed using the Cox proportional hazards model. Logistic regression was used to assess the effect of tumor volume on brainstem involvement, and the relationship between tumor volume and proximity to brainstem was assessed by the Spearman correlation.

Results: Median distance of disease to brainstem was 22.4 mm (range 0-54) at diagnosis, with 2.1% (n = 3) having brainstem involvement. At 56-month median follow-up, 87% of patients had recurrence; 2-year OS was 38.6%. Median distance of disease to brainstem was 20.8 mm (range 0-63) at recurrence, with 5.7% (n = 8) having brainstem involvement at recurrence. Controlling for resection status, MGMT methylation, and Karnofsky performance status, there was no noted association of brainstem invasion ($P = .60$) or proximity at diagnosis ($P = .14$) with OS. However, at recurrence, distance from the brainstem was significantly associated with improved OS when measured continuously (HR: .97, 95% CI: .95-.99, $P = 0.001$) and when compared by group (20-40 mm vs. ≤20 mm: HR .59, 95% CI: .35-.99, $P = 0.05$; > 40 mm vs. ≤20 mm: HR .16, 95% CI: 0.05-.55, $P = 0.003$). While volume of tumor at diagnosis was not found to be independently associated with brainstem involvement ($P = .99$) or OS ($P = .90$) at recurrence, tumor volume at diagnosis was found to be significantly associated with disease proximity to brainstem at the time of recurrence ($P = 0.037$), with larger volume disease more likely to recur close to the brainstem.

Conclusion: GBM proximity to the brainstem at diagnosis was not found to be prognostic, whereas disease proximity to the brainstem at recurrence was associated with worse OS. Tumor volume at diagnosis was found to be associated with disease proximity at recurrence, with higher volume disease at diagnosis associated with greater proximity to the brainstem at recurrence. These findings may have ramifications for upfront and salvage radiation treatment design.

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3236

Temozolomide Rechallenge in Patients With Recurrent High-Grade Glioma Treated With Re-Irradiation

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Purpose/Objective(s): To evaluate the clinical role of temozolomide rechallenge (TMZ) in patients with recurrent high-grade glioma (HGG) treated with re-irradiation (re-RT) regardless of surgical status.

Materials/Methods: Single-center retrospective review of patients with a primary diagnosis of World Health Organization (WHO) Grade III anaplastic astrocytoma or Grade IV GBM treated from 2008 to 2016 for disease recurrence with re-RT (35 Gy in 10 fractions) with and without temozolomide rechallenge. Baseline characteristics were analyzed with pairwise tests. OS/PFS were assessed with the Kaplan-Meier method and multivariable cox regression models for OS.

Results: Two hundred and thirty patients were treated with re-irradiation (n = 67 with and n = 163 without concurrent TMZ), with a median follow-up of 13.4 months. Baseline characteristics were similar between the two groups. TMZ rechallenge did not improve OS (HR 0.81 [0.51-1.3] $P = 0.39$). Univariate regression analysis showed that higher KPS both at diagnosis and recurrence correlated with improved survival, whereas increasing histology grade of initial and recurrent disease and volume of recurrence were correlated with worse OS. Multivariate regression analysis showed primary tumor location to be a significant predictor of OS

($P = 0.004$) with occipital lobe lesions ($P < 0.001$) and in-field recurrence ($P < 0.001$) to be most favorably correlated with OS.

Conclusion: TMZ rechallenge in patients with recurrent HGG treated with re-irradiation offered no survival benefit. Our findings suggest that patient selection may be important in TMZ rechallenge. Further studies in identifying this group of patients are warranted.

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3237

Quantification of Target Volume Changes on Radiation Planning MRI in IDH-Wildtype Glioblastoma

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Purpose/Objective(s): IDH-wildtype glioblastoma (GBM) has an exceptionally poor prognosis due to its rapid growth. Delaying post-operative radiation therapy (RT) more than 6 weeks after surgery negatively impacts prognosis. Post-operative magnetic resonance imaging (MRI) is commonly used to assess the extent of surgical resection followed by a delayed MRI for RT planning. In a heterogeneous population of high-grade gliomas treated in the pre-molecular era, significant resolution of edema and a trend towards increase in surgical cavity sizes were observed. Post-operative volumetric changes in IDH-wildtype GBM have not been described and we suspect these tumors may demonstrate higher rates of recurrence or regrowth during the latent period before the initiation of RT.

Materials/Methods: 30 patients with IDH-wildtype GBM treated with post-operative RT from our institution were identified. Patients with RT planning MRIs obtained between 3-6 weeks after biopsy or surgical resection were included. RT target volumes were contoured and compared between post-operative and RT planning MRIs. Volumetric changes in GTV2 (surgical cavity + residual enhancing disease) and GTV1 (edema + GTV2) were calculated. Progression-free survival (PFS) and overall survival (OS) were measured.

Results: The mean time between post-operative and RT planning MRI was 29.4 days (range: 21-42 days). When comparing post-operative and RT planning MRIs, the mean decrease in GTV1 was 25.8cc or 14.7% ($P = 0.011$) and the mean increase in GTV2 was 10.21cc or 39.6% ($P = 0.0013$). GTV1 decreased at an average rate of 0.5% per day and GTV2 increased at an average rate of 1.4% per day. The proportional growth was similar to a rate of historical controls of mixed high-grade gliomas. Median PFS and OS in our group were 5.6 and 11.2 months, respectively. A delay of more than one month between post-operative and planning MRI was associated with worse median OS of 8.0 months compared with 11.5 months ($P = 0.044$).

Conclusion: To our knowledge, this is the largest volumetric study of the impact of post-operative MRIs in a uniform group of IDH-wildtype GBM. RT planning MRIs performed 3-6 weeks after biopsy or surgical resection of IDH-wildtype GBM demonstrate significant volumetric changes. Similar to previously published data on a heterogenous population of high-grade gliomas, decreases in GTV1 signify a resolution of edema, however, increases in GTV2 imply recurrence or regrowth of disease over a relatively short time. While this was not statistically significant in a previously published analysis of a heterogeneous population of high-grade gliomas, our analysis of a homogeneous population of IDH-wildtype GBM demonstrates a statistically significant increase in GTV2. Delaying planning MRI more than one month post-operatively was associated with worse OS. These findings support the need for RT planning MRIs and confirm the association between delayed treatment and worse survival. Radiomic analysis of cavity regression vs. tumor regrowth is forthcoming.

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3238

Soluble Programmed Death-Ligand 1 (sPD-L1) as a Novel Biomarker for the Combination of Anti-PD-L1 Antibody and Radiotherapy for Glioma Patients

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Purpose/Objective(s): In our previous study, it has been proven that high level of soluble programmed death-ligand 1 (sPD-L1) is considered a predictor of negative clinical outcomes in glioma. However, the expression of sPD-L1 can change dynamically during radiotherapy (RT), and the effect of sPD-L1 has not been thoroughly elucidated. The purpose of this study was to uncover the dynamics of circulating sPD-L1 levels in glioma patients undergoing RT and to investigate the significance of plasma sPD-L1 levels as a biomarker for combining anti-PD-L1 antibody and RT.

Materials/Methods: Glioma patients treated with RT between October 2019 and September 2020 were prospectively recruited and sPD-L1 levels were measured using enzyme-linked immunosorbent assay (ELISA). Blood samples were obtained before RT (0f), during RT (15 ± 2f) and RT end (30 ± 2f). Flow cytometry were used to address whether circulating sPD-L1 molecules can affect the CD8+ T cells activation and function in the adaptive immune response. Glioma murine model were used to validate whether combine RT and anti-PD-L1 antibody can be a promising therapeutic strategy in gliomas.

Results: Thirty-two GBM patients treated with RT were included. The proportions of grade I, II, III, and IV gliomas were 6.2%, 28.1%, 21.9%, and 43.8%. RT significantly increased the mean level of sPD-L1 (0f **vs.** 15 ± 2f: 55.7 ± 19.2 **vs.**76.7 ± 38.8, $\boldsymbol{P} = 0.008$; 0f vs. 30 ± 2f: 55.7 ± 19.2 vs.80.94 ± 44.9, $\boldsymbol{P} = 0.005$). However, there was no significantly difference between during RT (15 ± 2f) and RT end (30 ± 2f). We performed the CD8+ T cells suppression analysis using mice plasma **in vitro**. The plasma from mice after anti-PD-L1 treatment (the concentration of sPD-L1 could not be detected) didn't show any suppression activity. Instead, the plasma from the mice without anti-PDL1 treatment exhibited the remarkable CD8+ T cell suppression capacity. These results indicated that the sPD-L1 can play an important role in T cell suppression. Furthermore, the glioma murine model indicated that the combination of irradiate (IR) and anti-PD-L1 significantly reduced tumor growth than either IR or anti-PD-L1 antibody monotherapy (anti-PD-L1 **vs.** IR plus anti-PD-L1: 789.67 ± 55.86 mm^3 **vs.** 292.16 ± 102.98 mm^3 on day 31, $\boldsymbol{P} < 0.001$; IR vs. IR plus anti-PD-L1: 697.02 ± 12.98 mm^3 **vs.** 292.16 ± 102.98 mm^3 on day 31, $\boldsymbol{P} < 0.001$).

Conclusion: This study reported that sPD-L1 might be a potential biomarker in glioma patients receiving RT. This finding means that compensation for the potential sequestration of antibodies needs to be considered in the optimization of PD-L1 blockade therapies. Because not all administered anti-PD-L1 immunotherapeutic antibodies may reach the surface of tumor cells, with a potentially appreciable proportion being sequestered by sPD-L1 within the circulation. The elevated level of sPD-L1 after RT suggested that the strategy of a combination of immune checkpoint inhibitors and RT might be promising for glioma patients.

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