PURPOSE: To develop a valid treatment strategy for recurrent high-grade gliomas using stereotactic hypofractionated reirradiation based on biologic imaging and temozolomide. PATIENTS AND METHODS: The trial included a total of 44 patients with recurrent high-grade gliomas (1 patient with anaplastic oligodendroglioma, 8 with anaplastic astrocytoma, 33 with glioblastoma multiforme, and 2 with gliosarcoma) after previous surgery and postoperative conventional radiotherapy +/- chemotherapy. For fractionated stereotactic radiotherapy (SFRT) treatment planning, the gross tumor volume was defined by (11)C-methionine positron emission tomography (MET-PET) or (123)I-alpha-methyl-tyrosine (IMT) single-photon computed emission tomography (SPECT)/computed tomography (CT)/magnetic resonance imaging (MRI) fusion in 82% of the patients and by CT/T1+gadolinium-MRI image fusion in 18% of the patients. Six fractions of 5 Gy were administered in 6 days. In 29 of 44 patients (66%), chemotherapy with temozolomide (200 mg/m² body surface/day) was given in one to two cycles before and four to five cycles after SFRT. The patients were evaluated in follow-up by clinical investigators and MRI or CT every 3 months after SFRT until
death. In cases suspicious for radiation necrosis, a MET-PET or IMT-SPECT investigation was performed. RESULTS: The median survival time in the whole group was 8 months. Treatment planning based on PET(SPECT)/CT/MRI imaging was associated with improved survival in comparison to treatment planning using CT/MRI alone: median survival time 9 months vs. 5 months ($p = 0.03$, log-rank). Median survival time were 11 months for patients who received SFRT based on biologic imaging plus temozolomide and significantly lower, 6 months for patients treated with SFRT without biologic imaging, without temozolomide or without both ($p = 0.008$, log rank). The most important prognostic factor in univariate analysis was a long interval between initial diagnosis and recurrence ($p = 0.0002$, log-rank). In the multivariate model, time interval to retreatment ($p = 0.006$) and temozolomide ($p = 0.04$) remained statistically significant. No acute neurologic toxicity Grade 3 or higher and no Grade 4 hematologic toxicity was observed. CONCLUSION: This is the first study of biologic imaging optimized SFRT plus temozolomide in recurrent high-grade gliomas. It demonstrates the feasibility and safety of this approach. The most striking result of the trial is the statistically significant longer survival time in the univariate analysis for patients reirradiated using MET-PET or IMT-SPECT/CT/MRI image fusion in the treatment planning, in comparison to patients treated based on MRI/CT alone. Multivariate analysis confirmed a significant survival benefit from multimodal treatment (i.e., addition of temozolomide), despite the limited number of patients. Whether treatment planning with SPECT/PET independently influences survival has to be studied in a larger series of patients.