Supplements

Supplement S1: Details of Image acquisition

Patients were instructed to abstain from protein containing meals 6 h prior to PET. PET/MRI was performed on a 3Tesla Ingenuity TF PET/MRI scanner (Philips Healthcare, Best, The Netherlands), equipped with an 8-channel head coil. Concerning MRI, the 3D T1w, 2D FLAIR, 2D T2w and 3D T1w post-contrast MRI sequences were acquired according to the consensus recommendations for standardized brain tumor imaging in clinical trials [1] with two deviations, as the protocol of this study was defined several years before the consensus paper was published: for the 3D-T1w flip angle 8 degrees was used that was outside of the recommended range 10-15, and for FLAIR TI being 2800 ms instead of 2500 ms. Attenuation correction was performed by a non-diagnostic T1-weighed fast field echo scan, covering the entire brain and upper maxillofacial area. An MR-based attenuation map was reconstructed via segmentation of air and soft tissue with assignment of the respective attenuation values. The effect of the head coil on the PET image is taken care of by implementation of a vendor provided attenuation template integrated into the final attenuation map. The PET acquisition protocol had a duration of 40 min (12x 10s, 2x 30s, 2x 60s, 2x 150s, 6x 300s), starting with intravenous injection of the PET tracer [11C]MET (300 MBq +/- 53 MBq, in house production HZDR, modified according to [2]). MRI-diagnostic scans, the scan for attenuation correction, and the PET-scan were taken in identical head position after rotation of the patient bed in the respective position of the scanner (PET-ring resp. MRI-ring of the scanner). During time-out due to relocation of the PET/MR machine, PET scans were performed on a Biograph 16W PET/Computed Tomography (CT) (Siemens Medical Solution Inc., Knoxville TN, USA) with identical dynamic PET protocol with the MRI taken separately on a dedicated MRI scanner.

Supplement S2: Slight changes in overall treatment time or combined treatments

There were only a few days of uncompensated radiotherapy interruptions mainly due to public holidays or technical problems and maintenance (mean 1.3, median 0, range 0-6 days) except one patient with 18 days of interruption due to surgery of a progressive tumor (scored as early recurrence). Simultaneous TMZ was interrupted or terminated early in 22 patients due to toxicity (hematotoxicity: 13, severe hepatotoxicity: 4, worsening of general condition: 4, infection: 1). Because of early progression or death, adjuvant TMZ was not given in 15 and terminated early in 10 patients (after median 3, range 1-5 cycles). In 7 patients, less than six cycles or reduced doses of adjuvant TMZ were administered due to toxicity (median 4 cycles, range 0-6). Two patients received TMZ in slightly different dosage or timing or in combination with another drug. Two patients received Tumor-Treating-Fields (TTF) during adjuvant TMZ or after early recurrence [3,4].

Fourteen patients took part in other clinical trials in parallel, most of them in register trials, trials applying standard radiochemotherapy or dealing with a confounding disease, thus not interfering PETra treatment. Four patients took part in other interventional trials during radiochemotherapy and thus, in addition to standard radiochemotherapy, received CCNU (Lomustine, CeTeG-Trial, NCT01149109; n=1) or DCVax®-L (NCT00045968; n=3). After the end of radiochemotherapy, two patients participated into a phase I vaccination trial (NOA-16, NCT02454634; n=1) and in the CUSP-9-study (NCT02770378; n=1) on safety of repurposed drugs in addition to adjuvant metronomic TMZ. All mentioned interventional trial data are still unpublished.