Response assessment in recurrent high grade glioma treated with carbon ion irradiation using diffusion weigthed MRI

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Abstract: Response assessment is crucial for evaluation of carbon ion radiotherapy in recurrent high-grade glioma, due to the need for distinction between further tumor growth from within the irradiated volume and additionally appearing tumorous tissue from prior existing micro-invasion. In a retrospective study on 15 patients, ADC values from diffusion MRI were evaluated within radiotherapy target volumes at treatment planning and tumor volumes after irradiation. Results show, that ADC could be used to assess response to irradiation and further tumor growth.

Introduction

High-grade glioma (HGG) is a devastating disease, due to their infiltrative nature and rapid growth, which lead to poor overall survival and early tumor recurrence after radiotherapy (RT) (1). For recurrent HGG, where re-irradiation has to be performed cautiously due to prior dose burden from primary tumor treatment, carbon ion irradiation is a promising new therapy option, since it offers steep dose gradients and enhanced biological effectiveness (2,3). Therefore, response assessment is currently of special interest. In cases of tumor progression after therapy, the question arises, whether continuing tumor growth occurs due to therapy ineffectiveness or as a result of an initial underestimation of tumor micro invasions and thus the true tumor extent.

Diffusion weighted MRI (DWI) offers means for non-invasive imaging that does not rely on application of a contrast agent or the use of ionizing radiation (4). It allows for the determination of the apparent diffusion coefficient (ADC), which has been correlated with tissue density and cellularity (5). Since tumors generally present with increased cellular density compared to healthy tissue, diffusion MRI poses a promising tool to assess response to therapy and formation of tumor progression. In the presented study, changes in ADC values within irradiated tumor volumes before and after therapy and their correlation with clinical progression of the tumor were investigated.

Methods

Retrospective data of 15 patients with recurrent HGG was investigated, 8 with grade III tumors and 7 with grade IV tumors. Patients were irradiated with carbon ions of 10, 11 or 13 fractions (3 GyE each). MRI was acquired at treatment planning and follow-up (one month after end of therapy). T_1 weighted contrast enhanced (T_1 CE) MPRAGE and DWI (single-shot spin-echo echo-planar sequence, applied sequentially in x, y and z direction with b=0, 1200 s/mm^2) were acquired on a 3T MR scanner. Pre- and post-radiotherapy ADC maps were co-registered with the treatment planning T_1 CE MRI. The gross tumor volume (GTV) was mapped onto the ADC image, as shown in Fig. 1. Resection cavities were subtracted manually from GTV if applicable. Follow-up T_1 CE MRI was used to delineate the further grown tumor (GTV_{FU}) in patients showing progress of the tumor after irradiation. The progress volume after irradiation was determined as: $P = GTV \setminus GTV_{FU}$

Median ADC values were determined within the GTV from treatment planning and follow-up DWI images. Furthermore, for progressive patients, median ADC was determined within the progressed volume P.

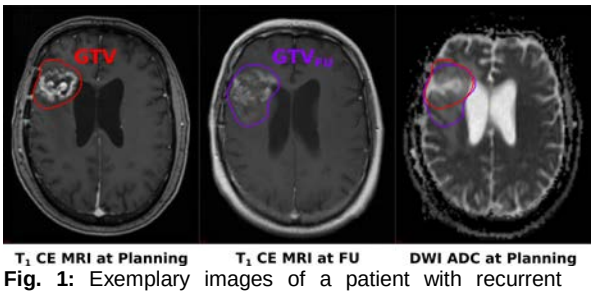

Fig. 1: Exemplary images of a patient with recurrent glioblastoma. The T_1 CE MRI at treatment planning (left) and follow-up (middle) were used to delineate the analysis contours GTV and GTV_{FU}. These contours were mapped onto the DWI ADC map for analysis (right).

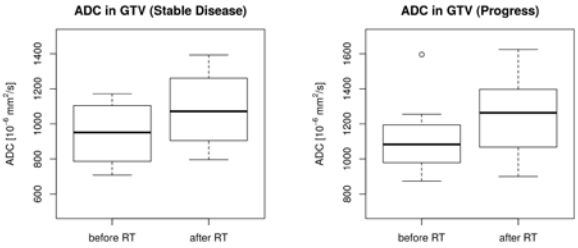

Fig. 2: Median ADC values within GTV at planning (before RT) and follow-up (after RT), for patients exhibiting stable disease and progression after therapy respectively.

Results

Median follow-up was 13 month. 11 patients showed confirmed progression of the tumor after therapy according to RECIST criteria. 4 patients with grade III tumors presented with stable disease and local tumor control. 5 patients with grade III tumors showed an increased ADC (>10%) in GTV at follow-up compared to planning. In the other 3 patients ADC values remained stationary or decreased after irradiation. In grade IV tumors, 4 patients presented with increased ADC at follow-up.

Figure 2 shows results of median ADC values before and after RT, in patients with stable disease versus progression of the tumor. It can be observed, that patients with progressed tumors show a tendency to higher ADC values within the GTV after RT compared to ADC values at planning (p=0.101, paired t-test), whereas almost no difference can be found between pre- and post irradiation in patients with stable disease. Furthermore, ADC values tend to be higher prior to RT in patients, who later exhibited progression of the tumor.

At follow up, 6 out of 7 patients with grade IV gliomas showed decreased ADC values (>5%) within the progressed tumor volume P compared to GTV, whereas in grade III tumors only one patient showed a lower ADC within volume P=GTV \ GTV_{FU} and 3 patients presented with similar or increased values in P compared to GTV. Figure 3 shows median ADC values after irradiation within the irradiated volume (GTV), compared to the further grown tumor P that might have been underdosed. For grade III tumors, only 4 of the 8 exhibited progression of the tumor after therapy. In grade IV tumors, lower ADC values can be observed within the volume P compared to GTV (p=0.0356, paired t-test).

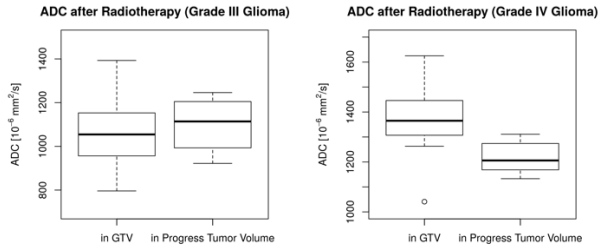

Fig. 3: Median ADC values at follow-up MRI within the irradiated volume (GTV) and the further grown tumor (P), for patients with grade III and grade IV tumors respectively.

Discussion

In this study, response to irradiation with carbon ions in recurrent high grade glioma was investigated using ADC values from diffusion MRI. Our results show an increased ADC within the irradiated volume after therapy, indicating a decrease in cellularity and thus response to therapy.

Furthermore we found, that in grade IV tumors, ADC after irradiation was lower in the progression volume than in the irradiated GTV. Hence, it could be concluded that progression of the tumor is not due to continued growth of the initial tumor but rather originates from micro-invasions that were not assessed at treatment planning and thus did not receive sufficient dose. Further studies should include larger patient cohorts.

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