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ORIGINAL ARTICLE

Functional image-guided dose escalation in gliomas using of state-of-the-art photon vs. proton therapy

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ABSTRACT

Background: Recurrences of glioma are usually local, suggesting the need for higher tumor dose. We investigated the boundaries for dose escalation of an ^{18}F-fluoro-ethyl-tyrosine positron emission tomography defined target by intensity-modulated photon therapy (IMRT), volumetric modulated arc therapy (VMAT) and intensity-modulated proton therapy (IMPT).

Materials and methods: Standard dose (60 Gy) and dose-escalated plans were calculated for seven patients using IMRT, VMAT and IMPT. The achieved boost dose, the dose to the organs at risk (OAR), the dose homogeneity (defined as overdose volume, ODV) and the ratio of the 30 Gy isodose curve and the boost volume (R30) were compared. The risk of radionecrosis was estimated using the ratio of the dose volume histograms of the brain (range 30–60 Gy).

Results: The mean boost dose was 77.1 Gy for IMRT, 79.2 Gy for VMAT and 85.1 GyE for IMPT. Compared with the standard plan, the ODV was unchanged and the R30 increased (17%) for IMRT. For VMAT, the ODV decreased (7%) and the R30 was unchanged whereas IMPT substantially decreased ODV (61%), R30 (22%), OAR doses as well as the risk of radionecrosis.

Conclusions: Dose escalation can be achieved with IMRT, VMAT and IMPT while respecting normal tissue constraints, yet with IMPT being most favorable.

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Introduction

Gliomas are the most frequent brain tumors in adults with radiotherapy (RT) playing a crucial role in the treatment. Nevertheless, the clinical outcome of patients remains dismal since early local failure is common. Consequently, a higher radiation dose may be needed for sufficient tumor control. However, application of higher radiation doses is often restricted by the neighboring organs at risk (OARs) [1].

Contemporary RT techniques such as intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT) allow for dose escalation, while respecting the constraints to the OAR. Moreover, intensity-modulated proton therapy (IMPT) may significantly reduce both the integral dose and doses to OARs, which is mainly attributed to the characteristic depth dose profile of protons [2]. However, due to the steep dose gradients the precise target volume delineation is of crucial importance, in particular for IMPT. Standard imaging modalities for target volume delineation of gliomas such as CT or MRI are not sufficiently tumor-specific and of limited value in differentiating between viable tumor and edema.

Positron emission tomography (PET) is a functional imaging method that seems promising in the assessment of brain tumors [3,4]. Amino acid PET tracers accumulate in most gliomas due to increased expression of transporters and ^{18}F-fluoro-ethyl-tyrosine (FET)-PET imaging is preferred due to the longer physical half-life of the isotope. Improved target volume delineation by integrating biological imaging has been reported [4]. Furthermore, the pre-irradiation FET uptake was found prognostic in several studies [5–8], which may suggest a dose escalation strategy in order to deliver a higher radiation dose to radio-resistant tumor regions [9].

A radiation dose–effect relationship for gliomas up to 60 Gy has been observed [10], but the only prospective randomized trial so far (RTOG 93-05) failed to demonstrate any survival benefit for patients receiving additional dose using stereotactic radiosurgery [11]. More recently, a prospective non-randomized phase 2 study investigated the feasibility and efficacy of an integrated boost IMRT concept based on FET-PET derived target volume in glioblastoma [12]. The dose escalation with a prescribed dose of 72 Gy and a corresponding equivalent dose in 2 Gy fractions (EQD2) of 74.4 Gy failed to prolong survival. It should be noted, that the study has low power (22 patients included) and the survival data were compared with historical controls, making interpretation of the results difficult. A dose escalation strategy with a proton boost of high-risk areas up to 96.6 GyE has previously been suggested to improve survival in a

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Supplemental data for this article can be accessed here.

highly selected group of patients with high grade glioma, albeit with concerns of increased toxicity [13]. In this series, most recurrences were found outside of the high-dose volume. Similarly, complete coverage of the PET positive target volume was associated with improved outcome in a limited number of patients [14].

Treatment planning studies have been performed to compare the target coverage, dose homogeneity and OAR sparing using IMRT, VMAT and IMPT in patients with gliomas, with overall similar target coverage [15–17]. The target homogeneity was found improved for VMAT and even more for IMPT as compared with IMRT. As expected, a significant sparing of the OAR can be obtained using IMPT. Only one study investigated dose escalation using so-called 4π RT. The mean dose could be increased to about 100 Gy, while respecting the common constraints for OAR. However, dose escalation resulted in a higher radiation dose to the total brain as well [18].

In the present study, we therefore investigated the implications of FET-PET for target definition. We used state-of-the-art RT techniques (IMRT, VMAT and IMPT) for dose escalation of the FET-PET defined target volume and analyzed the consequences for the dose distribution, specifically with regard to the estimation of treatment-induced toxicity.

Materials and methods

Patients and imaging

Seven patients with histologically verified glioma treated with RT from 09/2014 to 07/2015 were included. All subjects received static FET-PET recordings (20–40 min post-injection; 200 MBq) on a Siemens Biograph PET/CT system with the head fixed in a customized head-holder prior to RT. Low-dose CT was used for attenuation correction, and PET data were reconstructed using an iterative reconstruction algorithm. All seven patients also received a gadolinium-enhanced MRI (Gd-MRI) (3 mm slices). The median age of patients was 47 years (range 34–70). Histology included WHO grade II gliomas ($n = 2$) and grade III–IV gliomas ($n = 5$). Biopsy or surgical resection was performed in all cases. Two patients underwent radical resection. Patient characteristics are summarized in Table S1. All data presented were generated in accordance with ethical institutional policies.

Target volume delineation

The biological target volume (BTV) was auto-delineated (MIM v.6.4; MIM Software Inc., Cleveland, OH) from the FET-PET scan and covered the volume of pathological FET uptake with a tumor/brain ratio of $\geq$1.6 for pre- and 2.1 for postoperative scans [5]. Delineation of the gross tumor volume (GTV) and OAR were carried out in the Eclipse treatment planning system (Varian Medical systems, Palo Alto, CA). The GTV was delineated based on MRI T1-weighted gadolineum-enhanced images and encompassed the contrast-enhancing tumor and/or resection cavity. An isotropic margin of 2 cm was added to the GTV to form CTV46, which also included surrounding edema (e.g., areas of T2 weighted flair hyper-intensities). Both the BTV and the CTV46 were checked visually and adapted to anatomic barriers. The planning target volumes, PTV boost and PTV46 were generated by isotropically adding 3 mm to the respective BTV and CTV46. Planning risk volumes (PRVs for OAR) were generated using the same margin.

Treatment planning

First, a standard five to seven field IMRT plan (all beams 6 MV beam quality; one or two non-coplanar fields) was calculated for each patient. The prescribed dose to PTV boost was 60 Gy given in 30 fractions and the prescribed dose to PTV46 was 46 Gy in 30 fractions.

The volume of PTV46 excluding PTV boost was denoted oPTV46, and the over-dose volume of oPTV46 (ODV) was defined as the relative volume receiving more than 107% of the prescribed 46 Gy (e.g., 49.2 Gy). Then three dose escalation plans were calculated for each patient. The IMRT plans were calculated using the same technique as the conventional 60 Gy plan. For the VMAT plans, three arcs were used (all arcs used 6 MV beam quality; two arcs were non-coplanar). For both photon techniques, the fields were defined by high-definition multileaf collimators of 2.5 mm leaf width (Varian HD120). The IMPT plans were calculated using three to four proton beams and there was at least 30 degrees separation between two adjacent beams. For shallow targets, a range shifter of 5.7 g/cm^2 was applied. Multi-field optimization and simultaneous spot optimization were used and the in-layer spot separation was set to 3 mm. The beam angles were chosen in order to maximize plan robustness with regard to patient anatomy.

Dose levels and constraints

Constraints for target coverage and OAR are summarized in Table 1. For the dose escalation plans, the mean and maximum doses to PTV boost were increased maximally until reaching the limit of 90 Gy. No increase of the ODV and the mean doses of the first priority OARs, hippocampi and temporal lobes by more than 1 Gy was allowed, as compared with the standard plan (unless part of or just adjacent to the target). The 1 Gy limit was chosen in order to speed up the planning process, mainly due to the slow iterative process of VMAT optimization. For one patient, the PTV boost overlapped with the PRV brainstem. Therefore, a smaller boost volume was defined as the part of PTV boost which was more than 5 mm apart from PRV brainstem.

Analysis

Dosimetric comparison was performed using the following parameters: near maximum dose (e.g., the dose to 0.027 cm^3 of the body), mean PTV boost dose, ODV, R30 and mean dose to the OAR; R30 and ODV were used for evaluation of the dose homogeneity. R30 was defined as the ratio of the brain volume receiving 30 Gy and the PTV and reflected the dose gradient outside PTV46, while the ODV reflected

Table 1. Dose coverage requirements and dose constraints of OAR for the standard and the dose escalation plans. Maximum doses are defines as the dose to 0.027 cm^3 of the body. The OARs are defined according to Ref. [1].

	Dose constraints	
	Standard plan	Dose escalation plans
PTV boost	Mean dose: 60 Gy Max dose: ≤107% (64.2 Gy) V99%: ≥95% (57.0 Gy)	Mean dose: maximized Max dose: maximized, but ≤90.0 Gy V99%: ≥74.0 Gy
PTV46	V99%: ≥95% (43.2 Gy)	V99%: ≥95% (43.2 Gy)
oPTV46	V107% (ODV): minimized	V107% (ODV): ≤ODV (as derived from the standard plan)
PTV46, more than 5 mm away from PTV boost	None	D2% < 74 Gy
OAR		
Priority 1 spinal cord, brainstem, chiasm and optic nerves	Prioritized above the target coverage	Mean dose <1 Gy as compared with the standard plan
Priority 2 eyes, cochlea and lenses	Prioritized below target coverage	Prioritized below target coverage For hippocampi and temporal lobes, the mean dose <1 Gy compared with the standard plan

the dose gradient outside the BTV. Wilcoxon signed rank tests were used for the comparison and a p value less than 0.05 was considered statistically significant. For ODV and R30, we used the difference between the standard plan and the dose escalation plan. Non-parametric quantile regression was used for comparison of mean dose to the OAR. The volume of the 12 Gy isodose curves (V12) has previously been proposed as the predictor of radionecrosis [19]. Using the linear quadratic model, 12 Gy given in one fraction translates to 41.2 Gy, 47.1 Gy and 55.0 Gy using α/β values of 1 Gy, 2 Gy and 3 Gy, respectively. Due to the uncertainty in the specific value of α/β for brain necrosis and the breakdown of the linear quadratic model with high fraction doses, we compared the ratio between DVH curves of the escalated plans and the standard plan in the range from 30 Gy to 60 Gy, corresponding to a wide range of α/β values.

Results

There was large variation between BTV and GTV of the seven patients. Two patients with a diagnosis of oligodendroglioma grade 2 and anaplastic oligodendroglioma showed no contrast uptake on the MRI. Three patients had a larger GTV than BTV (GTV/BTV: 2.4–11.4) with the BTV included within the GTV. For one patient, the BTV corresponded to the GTV and for one patient there was a very small overlap between BTV and GTV. This patient underwent radical surgery and the GTV corresponded to the resection cavity. However, the postoperative FET-PET showed residual activity localized more profoundly from the resection cavity with no corresponding contrast enhancement on the MRI. The respective median BTV, GTV and PTV46 was 4.3 cm^3 (range: 1.3–24.9 cm^3), 24.0 cm^3 (range: 1.5–45.1 cm^3) and 253 cm^3 (range 154–364 cm^3). There was also a considerable variation in tumor location. Examples of GTV and BTV delineation for four patients are shown in Figure 1 (the remaining three patients are shown in Figure S1).

The dose escalation plans fulfilled all constraints for target coverage, dose spillage and OAR doses. For one patient due to an overlap between PTV boost and PRV brainstem, only a part of the boost volume was escalated. The mean PTV boost dose was increased to 77.1 Gy for IMRT, 79.2 Gy for VMAT and 85.1 GyE for IMPT; the corresponding increase in maximum PTV boost dose was 81.3 Gy, 86.9 Gy and 89.3 GyE (see Table 2).

For both the ODV and the R30, a large spread in absolute values was found, mainly due to a high diversity of target volume and location. Median ODV decreased for all three dose escalation techniques as compared with the standard plan. For IMRT, the decrease was not significantly different (78% vs. 76%, $p = 0.063$). However, a significant reduction by 4 percentage point ($p < 0.05$) and 48 percentage point ($p < 0.05$) was achieved for VMAT and IMPT, respectively. The median R30 of the IMRT escalation plans significantly increased (45%. vs. 52%, $p < 0.05$), while there were no significant differences for VMAT. As expected, IMPT significantly reduced the median R30 (45% vs. 35%, $p < 0.05$) (see Table 2).

The difference in mean dose to the OARs between dose escalation plans and the standard plan is shown in Figure 2. For IMRT, the difference in mean doses to the OARs was in the range −1.0 Gy to 1.2 Gy (the 0.25–0.75 quantiles), which was very similar to the standard plan. For VMAT, a larger spread was observed (range −3.9 Gy to 8.3 Gy). The 0.25 quantiles for first priority organs, the hippocampi and the temporal lobes were above −1 Gy, with the symmetrical distribution of ranges around the zero-line or towards positive values. However, 0.25 quantiles for second priority organs were below −1 Gy with distribution of the ranges towards negative values. Thus, VMAT decreased the dose to the first priority organs, while increasing the dose to the second priority organs. For IMPT, the range was above the zero-line illustrating sparing of all OARs. There were seven cases where mean dose to the OARs increased by more than 1 Gy, mainly due to an overlap or near location between the boost PTV and the OAR. However, for OARs more than 1.5 cm apart from the PTV boost there was no significant difference.

The ratio of the median DVH curves of the brain (range 30 Gy–60 Gy) for IMRT, VMAT and IMPT and the standard as an estimate of brain necrosis is shown Figure 3. For IMRT, the ratio of the DVH curves was above unity for the entire dose range. For VMAT, the ratio of the DVH curves was very close to unity for α/β values around 2 Gy, and for IMPT the ratio was below unity for doses <57.5 Gy.

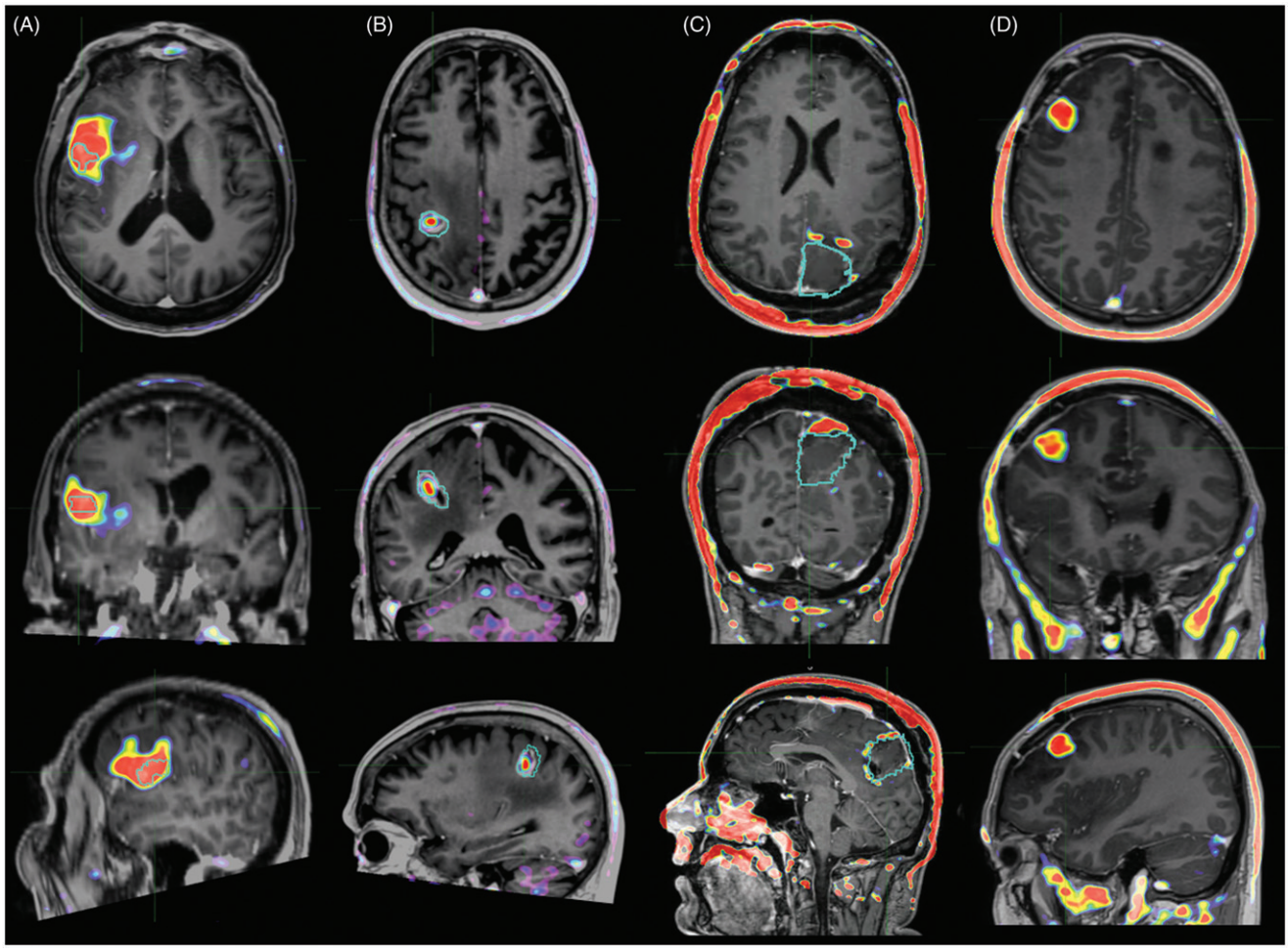

Figure 1. Illustration of the MRI defined GTV (solid line) and the FET PET defined BTV (colorwash/greyscale) for four patients. A) the GTV is smaller than the BTV, B) the GTV corresponds to the BTV, C) the GTV (resection cavity in this case) is larger than the BTV (residual tumor), and D) No contrast enhancement on the MRI.

Table 2. Evaluation parameters for the standard and IMRT, VMAT and IMPT dose escalation plans. Wilcoxon signed rank test was used for the statistical analysis and p values <0.05 considered statistically significant (marked by an asterisk).

	Standard	IMRT	VMAT	IMPT
PTV boost				
Dose max (Gy/GyE)	61.2 (60.9–62.4)	81.3 (78.7–82.1)	86.9 (79.3–89.2)	89.3 (87.6–89.9)
Mean dose (Gy/GyE)	60	77.1 (76.3–78.3)	79.2 (76.3–82.4)	85.1 (84.4–85.6)
ODV				
Median (%)	78.2 (64.5–85.9)	76.2 (61.9–85.9)	72.4 (59.9–82.1)	30.4 (23.3–63.3)
Difference (percentage point)		1.3	3.8 (*)	47.8 (*)
R30				
Median	44.7 (12.6–79.2)	52.3 (14.4–80.1)	35.6 (11.9–89.4)	34.9 (9.5–65.0)
Difference		−2.6 (*)	0.6	10.6 (*)

Discussion

To our knowledge, this is the first dosimetric study investigating the dose escalation of the functional imaging based targets in gliomas. Functional imaging (e.g., FET-PET) is known to provide additional information for target volume definition of this disease [3,4,20]. The accuracy for detecting tumor tissue, as evaluated by stereotactic biopsy specimens, is higher for FET-PET than for MRI and CT [21]. In the present study, two patients exhibited residual FET-PET uptake near the resection cavity, despite the postoperative MRI showing gross total resection. Another two patients displayed considerable different FET-PET activity compared with the volume defined by MR. In the remaining three patients the FET-PET defined volume was contained within the MR defined volume but considerably smaller. Our findings, although based on very limited number of patients, support the suggestion that integrating FET-PET imaging add additional information to the target volume. Especially in patients with gross total resection, pre-irradiation FET-PET provided supplementary information of residual tumor.

Previous treatment planning studies in gliomas have showed that IMPT is superior to IMRT and VMAT with regard to the dose homogeneity in the target and OAR. The present study expands on these findings. We found that IMPT still spared the OARs even when increasing the mean boost dose to 85 GyE. Furthermore, IMPT had the lowest value of ODV and R30, suggesting better sparing of the normal brain as

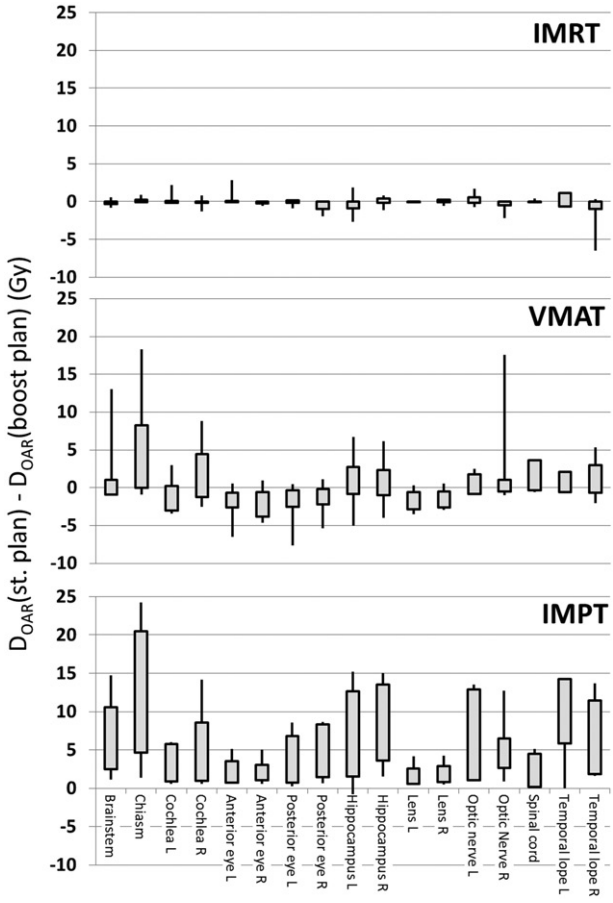

Figure 2. The difference in the mean dose to the OAR between the dose escalating plans (IMRT, VMAT and IMPT) and the standard plan. Boxes represent 0.25 and 0.75 quantiles and lines represent ranges.

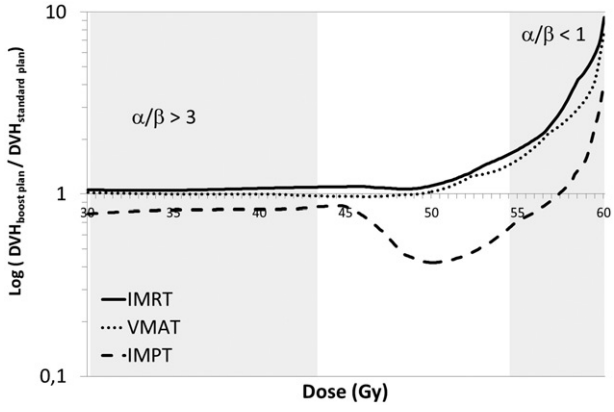

Figure 3. Ratio between the median DVH curve of the brain for IMRT, VMAT and IMPT and the standard plan. Doses corresponding to α/β values >3 are below 41.2 Gy. Doses above 55.0 Gy correspond to α/β values <1. Values below unity illustrate that the volume of brain receiving the specific dose is lower in the dose escalation plan than in the standard plan.

well, which may eventually improve the neuro-cognitive functioning of patients. Nguyen et al. investigated 4π RT for dose escalation to around 100 Gy [18]. However, the dose escalation was accompanied with the increase of the dose to the normal brain. Besides the concern of the increased brain toxicity, another limitation of 4π RT may be the prolongation of the treatment delivery time. The results of our study indicate that mean doses of around 80 Gy to a biological defined target using IMRT, VMAT and IMPT can be given with no expected increase of radiation-induced toxicity.

Results from previous clinical dose escalation studies in patients with gliomas are limited and contradictory. Survival prolongation was reported for patients treated with conventional RT and either a concomitant proton boost or followed by a carbon boost to the respective boost dose of 77.1 GyE and 112 GyE [13,22]. However, due to several limitations of this early phase 1/2 trial, any conclusions should be drawn cautiously. On the contrary, dose escalation using simultaneous integrated boost of 60 Gy in addition to 40 Gy given in 20 fractions (corresponding to EQD2 = 105 Gy, for α/β = 10) failed to improve survival [23]. In the present study, the mean boost dose was increased to 77.1 Gy for IMRT, 79.2 Gy for VMAT and 85.1 GyE for IMPT, which is comparable to the previously used boost doses.

Another concern of delivering high radiation doses to the brain is the risk of late side effects like radionecrosis and impaired neurocognition. For standard fractionation, a 5% and 10% risk of symptomatic radiation necrosis at 5 years is predicted to occur at an EQD2 of 72 Gy and 90 Gy [24]. The brain is especially sensitive to fraction sizes >2 Gy. Besides the high radiation dose, treatment volume and volume of brain receiving 10 Gy and 12 Gy have shown to be additional predictive factors [25]. In the present study, the ratio of the brain DVH of the IMRT escalation and the standard plan was above unity, which might indicate an increased risk of brain necrosis (see Figure 3). However, the ratio became close to unity for α/β values below 2. For VMAT, the ratio was very close to unity for all doses <50 Gy, indicating no expected increase of radionecrosis (when assuming α/β close to or above 2). For IMPT, all α/β values above 1 Gy suggest a reduced risk of brain necrosis compared with the standard plan.

The main limitation of our study is the small number of patients with different histology, tumor size and location contributing to a large variability. On the other hand, the heterogeneity is advantageous due to the explorative nature of the study. For the same reason, treatment planning was uniform for all patients. From a clinical point of view there might be some additional issues of concern such as whether both GVT and BTV need to be included in the boost volume or whether the prescribed dose is clinically sufficient. These questions are beyond the scope of our study and may be addressed in properly designed clinical trials.

In conclusion, this study has showed that functional image-guided dose escalation in gliomas can be achieved with IMRT, VMAT and IMPT while respecting normal tissue constraints, with IMPT being the most favorable technique.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

[1] Scoccianti S, Detti B, Gadda D, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. Radiother Oncol. 2015;114:230–238.
[2] Jiang GL. Particle therapy for cancers: a new weapon in radiation therapy. Front Med. 2012;6:165–172.
[3] Gotz I, Grosu AL. [(18)F]FET-PET imaging for treatment and response monitoring of radiation therapy in malignant glioma patients – a review. Front Oncol. 2013;3:104.
[4] Grosu AL, Weber WA, Riedel E, et al. L-(methyl-11C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. Int J Radiat Oncol Biol Phys. 2005;63:64–74.
[5] Albert NL, Weller M, Suchorska B, et al. Response assessment in neuro-oncology working group and European association for neuro-oncology recommendations for the clinical use of PET imaging in gliomas. Neuro Oncol. 2016;18:1199–1208.
[6] Piroth MD, Pinkawa M, Holy R, et al. Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas. Results of a prospective phase II study. Strahlenther Onkol. 2012;188:334–339.
[7] Suchorska B, Jansen NL, Linn J, et al. Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM. Neurology. 2015;84:710–719.
[8] Walter F, Cloughesy T, Walter MA, et al. Impact of 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine PET/CT on managing patients with brain tumors: the referring physician's perspective. J Nucl Med. 2012;53:393–398.
[9] Madani I, Duthoy W, Derie C, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68:126–135.
[10] Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. Int J Radiat Oncol Biol Phys. 1979;5:1725–1731.
[11] Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys. 2004;60:853–860.
[12] Piroth MD, Pinkawa M, Holy R, et al. Integrated-boost IMRT or 3-D-CRT using FET-PET based auto-contoured target volume delineation for glioblastoma multiforme – a dosimetric comparison. Radiat Oncol. 2009;4:57.
[13] Mizumoto M, Tsuboi K, Igaki H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010;77:98–105.
[14] Mahasittiwat P, Mizoe JE, Hasegawa A, et al. l-[METHYL-(11)C] methionine positron emission tomography for target delineation in malignant gliomas: impact on results of carbon ion radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70:515–522.
[15] Munck Af Rosenschold P, Engelholm S, Ohlhues L, et al. Photon and proton therapy planning comparison for malignant glioma based on CT, FDG-PET, DTI-MRI and fiber tracking. Acta Oncol. 2011;50:777–783.
[16] Shaffer R, Nichol AM, Vollans E, et al. A comparison of volumetric modulated arc therapy and conventional intensity-modulated radiotherapy for frontal and temporal high-grade gliomas. Int J Radiat Oncol Biol Phys. 2010;76:1177–1184.
[17] Wagner D, Christiansen H, Wolff H, et al. Radiotherapy of malignant gliomas: comparison of volumetric single arc technique (RapidArc), dynamic intensity-modulated technique and 3D conformal technique. Radiother Oncol. 2009;93:593–596.
[18] Nguyen D, Rwigema JCM, Yu VY, et al. Feasibility of extreme dose escalation for glioblastoma multiforme using 4π radiotherapy. Radiat Oncol. 2014;9:239.
[19] Sneed PK, Mendez J, Vemer-van den Hoek JG, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. J Neurosurg. 2015;123:373–386.
[20] McDonald MW, Shu HK, Curran WJ, Jr, et al. Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. Int J Radiat Oncol Biol Phys. 2011;79:130–136.
[21] Pauleit D, Stoffels G, Schaden W, et al. PET with O-(2-18F-fluoroethyl)-L-tyrosine in peripheral tumors: first clinical results. J Nucl Med. 2005;46:411–416.
[22] Mizoe JE, Tsujii H, Hasegawa A, et al. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: Combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. Int J Radiat Oncol Biol Phys. 2007;69:390–396.
[23] Panet-Raymond V, Souhami L, Roberge D, et al. Accelerated hypofractionated intensity-modulated radiotherapy with concurrent and adjuvant temozolomide for patients with glioblastoma multiforme: a safety and efficacy analysis. Int. J Radiat Oncol Biol Phys. 2009;73:473–478.
[24] Lawrence YR, Li XA, el Naga I, et al. Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys. 2010;76:20–27.
[25] Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol. 2011;6:48.