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Sequential proton boost after standard chemoradiation for high-grade glioma

Sebastian Adeberg [a,b,c,d,*], Denise Bernhardt [a,c,d], Semi Ben Harrabi [a,b,c,d], Matthias Uhl [a,c,d], Angela Paul [a,b,c,d], Nina Bougatf [c,d], Vivek Verma [e], Andreas Unterberg [f], Wolfgang Wick [g], Thomas Haberer [c,d], Stephanie E. Combs [h,i], Klaus Herfarth [a,b,c,d], Juergen Debus [a,b,c,d], Stefan Rieken [a,b,c,d]

[a] *University Hospital of Heidelberg, Department of Radiation Oncology;* [b] *Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg;* [c] *Heidelberg Ion-Beam Therapy Center (HIT);* [d] *Heidelberg Institute for Radiation Oncology (HIRO), Germany;* [e] *Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, USA;* [f] *University Hospital of Heidelberg, Department of Neurosurgery;* [g] *University Hospital of Heidelberg, Department of Neurooncology;* [h] *Technische Universität München, Department of Radiation Oncology; and* [i] *Institut für Innovative Radiotherapie (iRT), Department of Radiation Sciences (DRS), Helmholtz Zentrum München, Germany*

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ABSTRACT

Purpose: To retrospectively assess the feasibility and safety of a sequential proton boost following conventional chemoradiation in high-grade glioma (HGG).

Method and materials: Sixty-six consecutive patients with HGG were treated with 50.0 Gy photons (50.0–50.4 Gy) in 2.0 Gy (1.8–2.0 Gy) fractions, followed by a proton boost with 10 Gy equivalent (Gy(RBE)) in 2.0 Gy(RBE) fractions. Patients were matched one to one with 66 patients with HGG undergoing conventional radiation therapy (RT) with 60.0 Gy photons (59.4–60.0 Gy) in 2.0 Gy fractions (1.8–2.0 Gy). Matching criteria were age, WHO grade, Karnofsky's performance status, PTV size, temozolomide therapy (each $p > 0.1$). The study assessed progression-free survival (PFS), overall survival (OS), acute treatment-related toxicity (CTCAE v.4.03) and pseudoprogression (RANO criteria).

Results: Median PFS and OS were similar in both treatment groups (bimodality RT, PFS: 8.8 months [2–32 months], OS 19.1 months [4–41 months]; photon-only RT, PFS: 7.2 months [2–39 months], 20.9 months [3–53 months]; $p = 0.430$ and $p = 0.125$). The median PTV of the proton boost was significantly smaller than the photon plan PTVs (each $p < 0.001$). Acute toxicity was mild. Toxicity ≥grade 2 was observed in 6 patients (9%) receiving bimodality RT and 9 patients (14%) receiving photon-only RT. Two types of severe adverse events (CTCAE grade 3) occurred solely in the photon-only group: severe increase in intracranial pressure (5%); and generalized seizures (3%). Pseudoprogression was rare, occurring on average 6 weeks after radiotherapy, and was balanced in both treatment groups ($n = 4$ each; 8%).

Conclusion: Delivering a proton boost to significantly smaller target volumes when compared to photon-only plans, yielded comparable progression and survival rates at lower CTCAE grade 3 acute toxicity rates. Pseudoprogression occurred rarely and evenly distributed in both treatment groups. Thus, bimodality RT was at least equivalent regarding outcome and potentially superior with respect to toxicity in patients with HGG.

Summary: Treating patients with HGG with 50.0 Gy photons in 2.0 Gy fractions, followed by a proton boost with 10 Gy(RBE) in 2.0 Gy(RBE) fractions, is safe and feasible. Severe radiation-induced acute toxicity and pseudoprogression were rare in both treatment groups. Therefore, in this clinical setting, combined proton radiotherapy might be beneficial in terms of further risk reduction for treatment-related side effects. Interestingly, treatment volume reduction using a proton boost led to comparable survival and progression rates with decreased severe treatment-related toxicity compared to conventional photon radiotherapy.

 Radiotherapy and Oncology xxx (2017) xxx–xxx

High-grade gliomas are relatively common primary cerebral neoplasms that, together with treatment, are often associated with substantial compromises in functioning and quality of life (QOL). Presently, the most accepted treatment for high-grade glioma (HGG) is surgical resection followed by photon radiotherapy with 60 Gy in 30 fractions and concomitant temozolomide [1,2]. Importantly, in the era of technological advances in systemic therapies and options for recurrence in HGGs, long-term survival is not uncommon in this patient population [3], thereby increasing the

* Corresponding author at: University Hospital of Heidelberg, Department of Radiation Oncology, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany.
E-mail address: Sebastian.adeberg@med.uni-heidelberg.de (S. Adeberg).

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demand for optimized radiation techniques to maintain functionality and QOL.

To this extent, novel radiotherapeutic modalities such as charged particle radiotherapy provide attractive treatment opportunities. Irradiation with charged particles offers distinct physical and biological advantages, due to a favorable low dose distribution in the beam path, a reduced integral dose (ID), and an inverted dose profile transfer into steep dose gradients with a high degree of local dose deposition [4]. Using these benefits, dose exposure for surrounding organs at risk (OARs) and non-target tissue can be reduced significantly compared to photon radiotherapy. This is especially apparent in patients with complex target volumes in the proximity of critical OARs, and/or that may warrant dose-escalation. Indeed, though numerous studies have shown similar effects between both modalities on both normal and tumor tissue [5–7], a token benefit of proton radiotherapy may translate to reduced incidences of treatment-related side effects. Thus, in patients with limited life expectancies, maintenance of neuronal (and physical) functionality and QOL could be arguably just as important as other endpoints. Several studies have been performed to confirm the safety of particle radiotherapy with respect to critical OARs, including the supratentorial non-target brain tissue, brainstem, spinal cord, and optic apparatus [8–11].

Owing to these reasons, we performed this retrospective study following our institution's prospective CLEOPATRA trial (NCT01165671), which compares the impact of a carbon ion boost with a proton boost using intensity-modulated raster scanning in patients with glioblastoma (GBM) who underwent subtotal resection and standard chemoradiation with TMZ [12]. As an adjunct to this trial, the aim of this specific study is to demonstrate the safety and efficacy of proton radiotherapy as a sequential boost in patients with high-grade gliomas.

Materials and methods

Patient selection

Between October 2011 and October 2015, 66 consecutive patients with HGG (63 GBM, 2 anaplastic astrocytoma, and 1 anaplastic oligodendroglioma) received a sequential proton boost following photon chemoradiation at the Department of Radiation Oncology, University Hospital Heidelberg, Germany. Inclusion criteria encompassed histologically confirmed supratentorial primary HGG, and subtotal surgical resection or biopsy. Patients with Karnofsky's performance status (KPS) score $\geq$70 were selected in order to avoid biases in survival analysis from known poor-prognostic factors. In order to avoid cases with treatment delays, it was required that the proton boost start within 4 days after completion of photon irradiation. In order to ensure uniform doses and volumes, patients were excluded if dosing was not 50.0 Gy (range: 50.0–50.4 Gy) and target volumes were not delineated as below.

Next, a matched-pair analysis was performed, comparing the study group (n = 66) to a standard (60 Gy) photon-only group (n = 66). Matched patients were selected among the pool of patients with HGG during the same treatment period (63 GBM, 2 anaplastic astrocytomas and 1 anaplastic oligodendroglioma). Overall, patient matching was performed according to KPS ($\geq$70), age (20–78 years), resection status (macroscopic residual tumor on postoperative magnetic resonance imaging (MRI)), temozolomide therapy, and photon planning target volume (PTV) dimension (117–712 ml). Patient characteristics are depicted in Table 1.

Table 1
Patient characteristics of glioblastoma patients undergoing photon radiotherapy or bimodal radiotherapy with photons followed by a proton boost. Numbers in brackets represent percentages and refer to the absolute values in front.

Patient characteristics			
Cofactors	Photon RT n = 66	Bimodal RT n = 66	p-Value
Gender			
Male	38 (57.6)	42 (63.6)	0.59
Female	28 (42.4)	24 (36.4)	
Median age in years (range)	57.9 (21.6–77.9)	57.9 (20.0–77.0)	0.76
Median Karnofsky's Performance Status in % (range)	90 (70–100)	90 (70–100)	0.65
Temozolomide	58 (87.9)	62 (93.9)	0.36
MGMT promoter methylated	24 (36.4)	22 (33.3)	0.42
MGMT promoter not methylated	22 (33.3)	28 (42.5)	
MGMT not determined	20 (30.3)	16 (24.2)	
1p/19q codeletion	1 (1.5)	0 (0.0)	1
Biopsy only	10 (6.6)	13 (19.7)	0.65
Photon volume of PTV in ml (range)	369.4 (123–710)	394.6 (117–712)	0.76
Proton volume of PTV in ml (range)	–	134.7 (26–553)	

Abbreviations: MGMT = O6-methylguanine methyltransferase; PTV = Planning target volume.

Treatment planning

Computed tomography simulation and pre- and postoperative MRI imaging were used for target volume delineation in all patients. Photon radiation therapy was carried out with 3D-conformal radiation therapy (3D-CRT) technique. Treatment planning for 3D-CRT was performed on the Oncentra MasterPlan®, Version 4.5 planning system (Elekta, Stockholm, Sweden) using a collapsed cone algorithm. Beam directions were individually selected in each case and consisted of 3–5 coplanar and non-coplanar fields and (if necessary) subfields using a field-in-field (FIF) technique.

Syngo PT Planning, Version 13 (Siemens, Erlangen, Germany) was used for proton plans with ion beams of one to two coplanar or non-coplanar beams using either a fixed horizontal beam or gantry.

Radiation therapy

The study group received a median dose of 50.0 Gy (50.0–50.4 Gy) photons in 25 fractions (25–28 fractions) to the resection cavity, contrast-enhancing lesions on T1-weighted MR-imaging, T2-FLAIR hyperintense low grade-portions, and edema (GTV). A safety margin of 2–3 cm was added respecting anatomical borders (CTV) (Fig. 1).

Proton beam delivery utilized an active rasterscan system. Five fractions of 2.0 Gy equivalent (Gy(RBE)) were administered for the proton boost to the area of contrast enhancement on T1-weighted MR-imaging (GTV), adding a safety margin of 5 mm (CTV) after treatment with 50.0 Gy of photons. Boost treatment planning aimed for treatment volume coverage by the 95% isodose line. A safety margin for technical inaccuracies of 3mm was added to the CTV in both treatment groups.

The matched-pair cohort received a median dose of 60.0 Gy (59.4–60.0 Gy) in 2.0 Gy (1.8–2.0 Gy) per fraction prescribed according to the target volume and with the same techniques and methods used in the study group's base plan. All 122 patients completed the treatment schedule. Temozolomide was applied as concomitant and adjuvant therapy in both treatment groups according to the Stupp scheme [2].

Follow-up

All patients were monitored at regular follow-up intervals, including contrast-enhanced MRI. Progression-free survival was

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