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Research Article

Evaluation of the Impact of Magnetic Resonance Imaging (MRI) on Gross Tumor Volume (GTV) Definition for Radiation Treatment Planning (RTP) of Inoperable High Grade Gliomas (HGGs)

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Aim and Background. Inoperable high-grade gliomas (HGGs) comprise a specific group of brain tumors portending a very poor prognosis. In the absence of surgical management, radiation therapy (RT) offers the primary local treatment modality for inoperable HGGs. Optimal target definition for radiation treatment planning (RTP) of HGGs is a difficult task given the diffusely infiltrative nature of the disease. In this context, detailed multimodality imaging information may add to the accuracy of target definition in HGGs. We evaluated the impact of Magnetic Resonance Imaging (MRI) on Gross Tumor Volume (GTV) definition for RTP of inoperable HGGs in this study. *Materials and Methods*. Twenty-five inoperable patients with a clinical diagnosis of HGG were included in the study. GTV definition was based on Computed Tomography- (CT-) simulation images only or both CT-simulation and MR images, and a comparative assessment was performed to investigate the incorporation of MRI into RTP of HGGs. *Results*. Median volume of GTV acquired by using CT-simulation images only and by use of CT and MR images was 65.3 (39.6-94.3) cc and 76.1 (46.8-108.9) cc, respectively. Incorporation of MRI into GTV definition has resulted in a median increase of 12.61% (6%-19%) in the volume of GTV defined by using the CT-simulation images only, which was statistically significant ($p < 0.05$). *Conclusion*. Incorporation of MRI into RTP of inoperable HGGs may improve GTV definition and may have implications for dose escalation/intensification strategies despite the need for further supporting evidence.

1. Introduction

High-grade gliomas (HGGs) refer to World Health Organization (WHO) grades III and IV gliomas including glioblastoma (GB), anaplastic astrocytoma, and anaplastic oligodendroglioma [1]. GB, the most common primary brain tumor in adults, remains to be a formidable challenge to the treating physicians with a dismal prognosis despite multimodality management [2, 3]. Several studies have focused on strategies for improving the poor outcome in the setting of newly diagnosed or recurrent disease by use of dose escalation, radiosensitization, immunotherapy, radiosurgery, and evolving intensified treatment approaches [4–10]. Maximal surgical removal of the tumor followed by chemoradiotherapy has been the standard of care for newly diagnosed GB patients after the landmark trial of European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) in 2005 and has been widely practiced worldwide [11]. This practice-changing study has demonstrated prolonged overall survival with the addition of temozolomide (TMZ) to conventionally fractionated radiation therapy (RT) and paved the way for future trials for further achievements [11]. Nevertheless, there is still room for improvement, and there is extensive research on management of GB [12].

Radiation treatment planning (RTP) for HGGs is typically accomplished by use of Computed Tomography- (CT-) simulation. This practice allows for achieving improved

precision compared to conventional planning methods utilized before the modern RT era. However, optimal target definition for RTP of HGGs is a difficult task given the diffusely infiltrative nature of the disease. In this context, detailed multimodality imaging information may add to the accuracy of target definition in HGGs. The usefulness of neuroimaging with Magnetic Resonance Imaging (MRI) for several purposes including diagnosis, lesion characterization, presurgical planning and navigation for preservation of eloquent brain regions and fiber tracts, brain tumor segmentation, disease monitoring, and discrimination of tumor progression from adverse effects of irradiation has been widely addressed in the literature [13–18]. Nevertheless, there is paucity of data on its utility for RT target definition for the distinct group of patients with inoperable HGGs. In this study, we evaluated the impact of MRI on Gross Tumor Volume (GTV) definition for RTP of inoperable HGGs.

2. Materials and Methods

Twenty-five patients with a clinical diagnosis of HGG based on MR spectroscopy and imaging features were included in this study to investigate the impact of MRI for GTV definition in RTP of inoperable HGGs. All patients were deemed to be medically inoperable due to comorbidities and/or poor performance status and were referred for definitive RT after detailed assessment by a multidisciplinary team of experts from neuroradiology, neurosurgery, and radiation oncology. Treatment with RT was decided after thorough evaluation of the patients taking into account symptomatology, lesion size, location, and association with critical neurovascular structures. Patients were informed about the details of the RT procedure including potential benefits and adverse effects. Written informed consents were obtained from all patients before RT and the study was conducted in compliance with the principles of Declaration of Helsinki. All patients had a pre-RT MRI within 1 week before CT-simulation including T1-gadolinium (Gd-DTPA, gadolinium diethylenetriaminepentaacetic acid, Magnevist®) enhanced images along with T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) images, and CT-simulations were performed at the CT-simulator (GE LightSpeed RT, GE Healthcare, Chalfont St. Giles, UK) available at our institution. Immobilization was secured by use of a thermoplastic mask for all patients. Thin-slice planning CT images including the region from the vertex to the 2 cm below the cervical spine were acquired at CT-simulation and were then transferred to the delineation workstation (SimMD, GE, UK) for contouring of treatment volumes along with neighbouring critical structures such as the brainstem, optic apparatus, cerebellum, hippocampus, and cerebral hemispheres. GTV definition was based on CT-simulation images only or both CT-simulation and MR images, and a comparative assessment was performed to investigate the incorporation of MRI into RTP of HGGs. For the purpose of this study, ground truth GTV was generated by collaboration and consensus of the board-certified radiation oncologists after detailed assessment of available imaging data of all patients. Ground truth GTV was utilized for RT of patients and was also used as a reference for comparison with GTVs defined based on CT-simulation images only or both CT-simulation and MR images. Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) software (version 15.0) was used for data analysis with the level of significance set at $p < 0.05$.

Table 1: Patient and tumor characteristics.

Characteristic	Number	%
Clinical diagnosis		
HGG	25	100
Gender		
Male	16	64
Female	9	36
Tumor location (lobe)		
Frontal lobe	11	44
Temporal lobe	8	32
Parietal lobe	5	20
Occipital lobe	1	4
Median age (range)	66 (53-75) years	

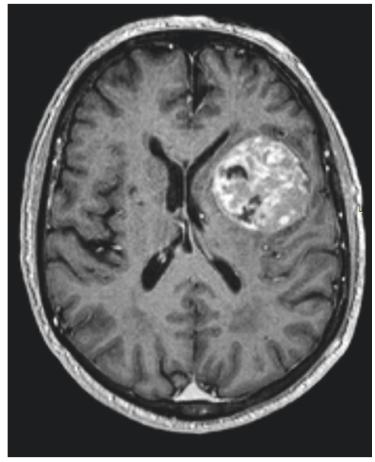

Figure 1: Axial T1-weighted postcontrast MR images of a patient with HGG used for RTP.

3. Results

A total of 25 patients referred for definitive RT at our institution for inoperable HGG were assessed for GTV definition based on CT-simulation images only or both CT-simulation and MR images. Patient and tumor characteristics are shown on Table 1.

Axial, coronal, and sagittal images were used for determination of GTV as areas of contrast enhancement on CT and postcontrast T1-weighted MR images. Axial, coronal, and sagittal MR images of a patient used for RTP are shown in Figures 1, 2, and 3, respectively.

Median volume of GTV acquired by using CT-simulation images only, by use of CT and MR images, and by consensus of the treatment team was 65.3 (39.6-94.3) cc, 76.1 (46.8-108.9) cc, and 75.7 (46.3-108.3) cc, respectively (Figure 4).

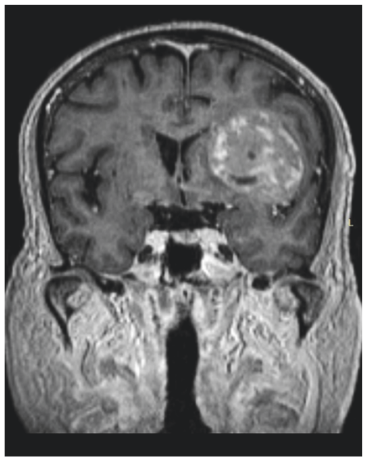

Figure 2: Coronal T1-weighted postcontrast MR images of a patient with HGG used for RTP.

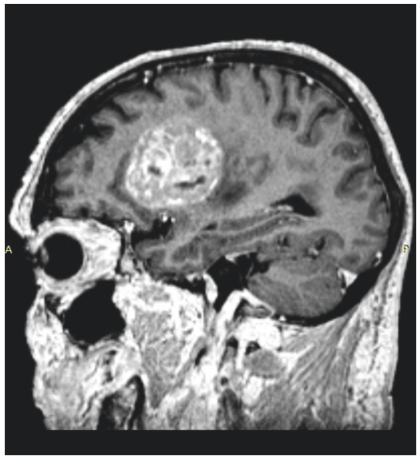

Figure 3: Sagittal T1-weighted postcontrast MR images of a patient with HGG used for RTP.

Table 2 shows volumetric comparison of GTVs defined by CT-simulation images only, CT-simulation and MR images, and consensus of the treatment team.

When compared to GTV acquired by use of CT and MR images and by consensus of the treatment team, there was a 12.61% (6%-19%) and 12.11% (5.6%-18.63%) increase, respectively, in volume of GTV acquired by using CT-simulation images only, both with statistical significance ($p < 0.05$) (Table 2). There was a median decrease of 0.49% (0.37%-0.95%) in GTV based on CT-simulation and MR images compared to GTV defined by consensus of the treatment team, without statistical significance ($p > 0.05$) (Table 2).

4. Discussion

A critical issue in RT of HGG is optimal target definition. There may be variations in institutional practices on definition of target volumes even among cooperative group trials and large-scale studies [11, 12, 22–28]. Whole-brain irradiation (WBI) has been considered in earlier studies given the diffusely infiltrative nature of GB; however, this practice has been widely abandoned after comparative trials reported no advantage of WBI over partial brain irradiation with recurrences typically occurring within 2-3 centimeters of the original tumor [29–32]. Considering a relationship between adverse radiation effects and irradiated volumes, the rationale behind focusing on smaller target volumes is avoidance of excessive treatment related toxicity [33–35].

Since the main challenge for HGG treatment remains to be nearly inevitable recurrence in overwhelming majority of the patients typically within the vicinity of original tumor, precise definition of GTV for RTP is of utmost importance for the medically inoperable patient group with a worse prognosis compared to patients with tumors amenable to complete/maximal resection [36, 37]. Radiation dose escalation strategies may be more strongly considered for this patient group given the relentless disease course in patients with excessive tumor burden. Focusing on the GTV harboring the cancer stem cells, which may be responsible for radioresistance and aggressive progression, is an area of extensive research.

Besides its usefulness in brain tumor diagnosis, treatment response assessment, differentiation of adverse radiation effects from recurrence, and detection and characterization of lesions with the capability of functional imaging techniques, a very critical and relevant benefit of MRI is in RTP. Utility of MRI for GTV definition in RTP of inoperable HGGs has been poorly addressed in the literature, and our study supports its incorporation into the RTP process for this specific group of patients to improve precision in target delineation. In our study, incorporation of MRI into GTV definition has resulted in a median increase of 12.61% in the volume of GTV defined by using the CT-simulation images only, and this difference was statistically significant (Table 2). There was no statistically significant difference in target definition by consensus of the treatment team as the ground truth GTV and by incorporation of MRI, supporting the utility of MRI for improved GTV definition. Ground truth GTV defined by collaboration and consensus of the board-certified radiation oncologists after assessment of all available imaging data of the patients has been used for RT of patients in our study. This ground truth GTV has also served as a reference for comparison purposes, since interobserver variations may lead to substantial diversity in definition of target volumes for HGGs. Several studies have also used the ground truth target volume defined by experienced physicians and experts as a reference for comparison [15–17]. Ground truth GTV was used for RT of patients and for validation of the results in our study, consistent with the methodology of aforementioned studies [15–17]. Given the negligible and statistically insignificant difference between GTV defined by incorporation of MRI and ground truth GTV, we suggest that incorporation of MRI into RTP of inoperable HGGs improves target definition.

Although not focusing on the inoperable HGG patient group exclusively, several studies have investigated the utility of MRI in RT target volume definition for brain tumors and typically reported larger GTVs when MRI was incorporated [19–21]. Table 3 shows selected series assessing target definition in HGGs with incorporation of MRI into RTP.

Table 2: Volumetric comparison of GTVs defined by CT-simulation images only, CT-simulation and MR images, and consensus of the treatment team.

	Imaging data used for GTV definition			Median % increase in GTV based on CT-simulation images only with incorporation of MRI in target definition (range)	Median % increase in GTV based on CT-simulation images only with incorporation of consensus of the treatment team (range)	Median % decrease in GTV based on CT-simulation and MR images with incorporation of consensus of the treatment team (range)
	CT-simulation images only	CT-simulation and MR images	Consensus of the treatment team			
Median GTV in cc (range)	65.3 (39.6-94.3) cc	76.1 (46.8-108.9) cc	75.7 (46.3-108.5) cc	12.61% (6%-19%) $p < 0.05$	12.11% (5.6%-18.63%) $p < 0.05$	0.49% (0.37%-0.95%) $p > 0.05$

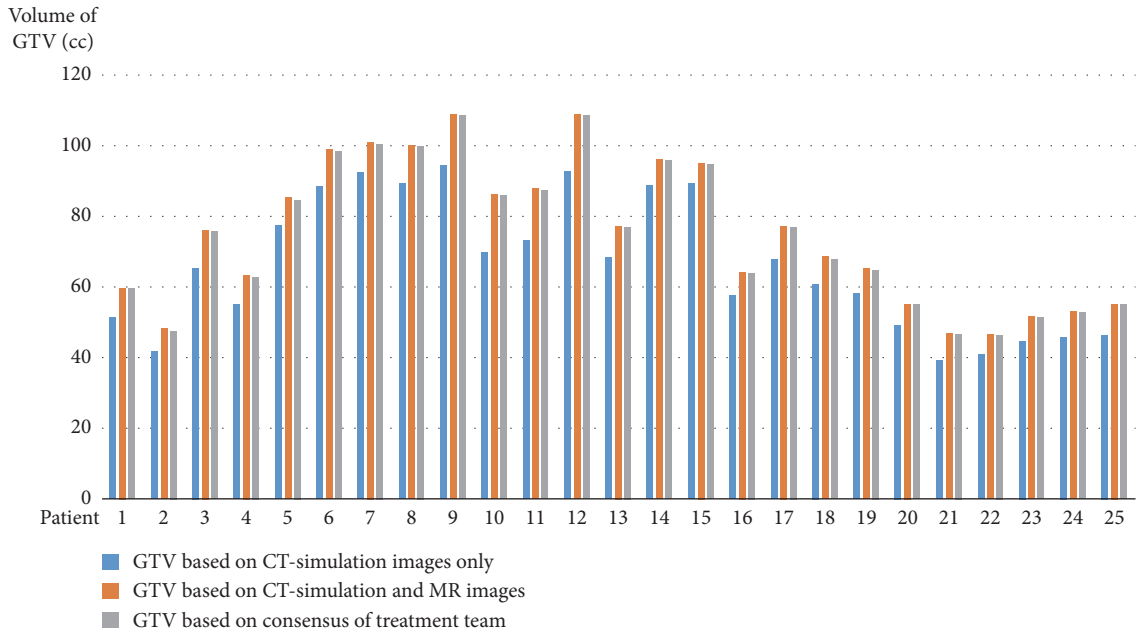

Figure 4: Volumes of GTV based on CT-simulation images only, CT-simulation and MR images, and consensus of treatment team.

Table 3: Selected series assessing target definition in HGGs with incorporation of MRI into RTP.

Authors	Study year	Number of patients with HGG	Mean/median volume of GTV defined on CT only (cc)	Mean/median volume of GTV defined on CT and MRI (cc)	p
Weltens et al. [19]	2001	5	59.5 cc	69.6 cc	< 0.05
Datta et al. [20]	2008	16	50.72 cc	62.35	0.044
Fiorentino et al. [21]	2013	30	36.48 cc	52.44	0.0003
Current study		25	65.3 cc	76.1 cc	< 0.05

Results of our study are consistent with the literature supporting the utility of MRI for GTV definition of HGGs [19–21]. While irradiation of smaller target volumes may improve the toxicity profile of RT with a typically lower risk of adverse radiation effects such as cognitive decline and radionecrosis, vigilance is required for avoiding any geographical misses which may lead to marginal failures and fatal disease recurrences [23, 38, 39]. This is a challenging trade-off between toxicity and treatment failure, and decision-making should take into account individualized consideration of patient and disease characteristics at referral treatment centers.

While MRI may offer several advantages over CT with its distinctive capabilities such as functional imaging, superior soft tissue contrast, and ability to acquire various different image contrasts of identical anatomy, there is still room for improvement [40, 41]. Clearly, image quality and performance of the scanners may affect the usefulness of MRI for RTP. A recent study by Regnery et al. compared a 7 Tesla FLAIR sequence with clinical FLAIR imaging at 3 Tesla for RTP of GB [42]. The study revealed that high-resolution 7 Tesla FLAIR imaging may add to the accuracy of target volume and critical organ delineation for RTP of GB [42]. The technology is evolving with further refinements in neuroimaging by MRI [18, 42, 43]. Although ground truth GTV defined by experienced physicians and experts has been used as a reference for comparison in our study to validate the results, target volume definition may have been affected by image quality and performance of the scanners. Nevertheless, our study adds to the existing body of evidence by reporting improved definition of GTV through incorporation of MRI into RTP for a distinct group of patients with inoperable HGGs.

In conclusion, inoperable HGGs comprise a specific group of brain tumors portending a very poor prognosis. In the absence of surgical management, RT offers the primary local treatment modality for inoperable HGGs. Incorporation of MRI into RTP of inoperable HGGs may improve GTV definition and may have implications for dose escalation/intensification strategies despite the need for further supporting evidence.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest, financial or otherwise.

Authors' Contributions

Omer Sager contributed to study conception and design, data collection, data analysis and interpretation, and manuscript drafting. Ferrat Dincoglan contributed to study conception and design, data collection, and manuscript drafting. Selcuk Demiral contributed to study conception and design, data collection, and data analysis and interpretation. Hakan Gamsiz contributed to study conception and design, data analysis and interpretation, and manuscript drafting. Bora Uysal contributed to data collection, data analysis and interpretation, and manuscript drafting. Fatih Ozcan contributed to data collection, data analysis and interpretation, and manuscript drafting. Onurhan Colak contributed to data collection, data analysis and interpretation, and manuscript drafting. Bahar Dirican contributed to study conception and design, data analysis and interpretation, and manuscript drafting. Murat Beyzadeoglu contributed to study conception and design, data collection, and data analysis and interpretation.

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