ORIGINAL RESEARCH

Study on the Appropriate Timing of Postoperative Adaptive Radiotherapy for High-Grade Glioma

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Purpose: To investigate the appropriate timing of adaptive radiotherapy (ART) for high-grade glioma.

Methods: Ten patients with high-grade gliomas were selected and underwent CT/MRI (CT_1/MRI_1, CT_2/MRI_2, CT_3/MRI_3, and CT_4/MRI_4) scans before RT and during 10-, 20- and 30-fraction RT, and the corresponding RT plans ($plan_1$, $plan_2$, $plan_3$ and $plan_4$) were made. The dose of the initial plan ($plan_1$) was projected to CT2 and CT3 using the image registration technique to obtain the projection plans ($plan_{1-2}$ and $plan_{1-3}$) and by superimposing the doses to obtain the ART plans ($plan_{10+20}$ and $plan_{20+10}$), respectively. The dosimetric differences in the target volume and organs at risk (OARs) were compared between the projection and adaptive plans. The tumor control probability (TCP) for the planning target volume (PTV) and normal tissue complication probability (NTCP) for the OARs were compared between the two adaptive plans.

Results: Compared with the projection plan, the D_2 to the PTV of ART decreased, the conformity index (CI) to the PTV increased, and the D_2/D_{mean} to the brainstem, optic chiasm and pituitary, as well as the V_{20}, V_{30}, V_{40} and V_{50} to the normal brain decreased. The D_2 to the pituitary and optic chiasm as well as the V_{20}, V_{30}, V_{40} and V_{50} to the normal brain in $plan_{10+20}$ were lower than those in $plan_{20+10}$, while the CI to the PTV was higher than that in $plan_{20+10}$. The TCP of the PTV in $plan_{10+20}$ was higher than that in $plan_{20+10}$.

Conclusion: ART can improve the precision of target volume irradiation and reduce the irradiation dose to the OARs in high-grade glioma. The time point after 10 fractions of RT is appropriate for ART.

Keywords: adaptive radiotherapy, high-grade glioma, dosimetry, biophysical model

Introduction

The standard treatments for high-grade gliomas include surgery, postoperative radiotherapy (RT), and synchronous and adjuvant chemotherapy with temozolomide (TMZ). Previous studies have shown that the anatomical structure of normal tissues in the target volume and its surroundings is nonstatic during RT for gliomas. With changes in volume, location and morphology, the dose distribution of RT to the target volume can change to varying degrees.[1–5] If the initial RT planning scheme has been used for the entire irradiation plan, regardless of changes in the size, location and morphology of the target volume and organs at risk (OARs), the tumor segment that needs to be irradiated may be removed from the high-dose area, and the actual dose to the target volume may be reduced. At the same time, normal tissues may enter the high-dose area, and the radiation dose to normal tissue may even exceed its limited dose, thus

aggravating the side effects of RT. Late delayed effects of radiation on the brain mainly included cerebral radiation necrosis and cognitive impairment. Ruben et al[6] performed follow-ups on the 426 patients with gliomas experiencing radiochemotherapy, and 21 cases exhibited radionecrosis (4.9%). The actuarial incidence of brain radiation necrosis stabilized by 13.3% after three years, and the risk factors in the high-risk group were total dose, fraction size, and biologically effective dose (BED). The combined radiochemotherapy obviously enhanced the risk of radiation-induced cerebral necrosis. Keime-Guibert et al[7] evaluated the cognitive function in glioblastoma in the elderly and found 42 cases in the supportive care group and 39 cases in the supportive care plus radiotherapy group. The scores of the mini mental state examination (MMSE) decreased over time in both groups (P<0.007), while the Mattis Dementia Rating Scale (MDRS) score did not change obviously over time, except for progressive deterioration and initiation (P=0.03) and construction (P=0.05). Yan et al[8] first proposed the concept of adaptive radiotherapy (ART). ART refers to a type of RT with improved precision during which CT/MR images and other images are reacquired; anatomical, physiological and other conditions (eg, changes in tumor size, morphology and location) are observed and evaluated; differences between the subsequent RT plan and the original plan are analyzed (upon which the RT plan is redesigned); and the doses after variation in the volume, location and morphology of the target volume as well as normal tissues and organs are modified. This can not only increase the irradiated dose to the tumor but also minimize the irradiated dose to surrounding normal tissues, thus reducing the incidence of radiation complications and improving the long-term quality of life of patients. To date, ART has not been widely used in the study of tumors in the central nervous system. Among such studies, there are few on the use of ART for glioma. Our preliminary work showed that the gross tumor volume (GTV) of gliomas decreased during intensity-modulated radiotherapy (IMRT), which resulted in increased doses to the OARs and normal brain over the course of IMRT;[9] thus, it is necessary that the RT plan be modified to decrease the dose to normal organs during RT. Therefore, we performed a study of ART for malignant glioma to identify the appropriate timing of ART in fixed-field IMRT/helical tomotherapy (TOMO).

Methods

Patient Enrollment

This study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University, and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients prior to the commencement of the study. The inclusion criteria were as follows: patients 18–65 years old with a Karnofsky Performance Status (KPS) score of >80 points, with supratentorial lesions, and who underwent tumor resection by craniotomy and were diagnosed with high-grade glioma based on the 2016 World Health Organization (WHO) pathological classification of central nervous system tumors.[10] All patients were treated with IMRT (Varian 23EX and Varian Trilogy, Varian Medical Systems) or TOMO (TomoTherapy HD System, Accuray, Inc.) and synchronous chemotherapy. The simultaneous chemotherapy regimen was as follows: from the first day to the last day of RT, TMZ was administered daily at an oral dose of 75 mg/m^2.

Head Immobilization and CT/MRI Scanning

All the patients lied in the supine position with their head fixed with a thermoplastic mask and received enhanced CT simulation (SOMATOM Definition AS, SIEMENS AG) at a thickness of 0.3 cm and a scanning range from the vertex to 10 cm below the foramen magnum. MRI simulation (Discovery MR750w, GE Healthcare) was also performed with contrast-enhanced T_1, T_2 and fluid-attenuated inversion recovery (FLAIR) scans at a thickness of 0.4 cm. Each patient underwent the abovementioned simulated CT/MRI scans four times, namely, before RT (CT_1/MRI_1) and during 10-fraction RT (CT_2/MRI_2), 20-fraction RT (CT_3/MRI_3) and 30-fraction RT (CT_4/MRI_4).

Target Volume Contouring and RT Planning

The target volume and OARs were outlined according to the European Organization for Research and Treatment of Cancer (EORTC) guidelines.[11] The simulated enhanced CT image was fused with the simulated enhanced MRI T_1 image. The gross tumor volume (GTV) included the gross tumor volume of the tumor bed or surgical cavity (GTV_{tb}) and the gross tumor volume of the residual tumor (GTV_r). The GTVr was outlined according to the MRI contrast-enhanced T1 image. The vascular infarction and damaged brain areas after the operation, if not considered as part of the original

tumor volume, were excluded from the GTVr. The clinical target volume (CTV) was the GTV with an extended edge of 2 cm, the edge of which may have been shrunken due to the effects of natural barriers that hinder tumor growth, such as the skull, ventricle wall and cerebral falx; however, the "fixed" barriers, such as the skull and cerebral falx, could be reduced to 0 mm, and the "nonrigid" barriers, such as the brain stem and ventricle wall, could be reduced to as low as 5 mm. The planning target volume (PTV) was the CTV with an extended edge of 0.5 cm. The Radiation Therapy Oncology Group (RTOG) protocol was referred to when determining the dose limits of the OARs.[12] The maximum dose (D_{max}) to the brain stem, lens, optic chiasm, optic nerve and pituitary was ≤54 Gy, ≤7 Gy, ≤56 Gy, ≤55 Gy and ≤50 Gy, respectively. For IMRT and TOMO, treatment plans were designed on two treatment planning systems: Varian Eclipse and Accuray TomoTherapy. The target volume was outlined on the CT1/MRI1 image, and the initial RT plan ($plan_1$) was designed. The prescribed dose to the PTV was given at 60 Gy for 30 fractions, 2 Gy each fraction.

The dose of the initial RT plan ($plan_1$) was projected to CT_2/CT_3 to obtain the projection plans ($plan_{1-2}$ and $plan_{1-3}$), which indicated that if the RT plan was not modified, the radiation dose distribution would be developed to 30 fractions of irradiation according to the initial plan in CT_2/CT_3. Then, ART $plan_{10+20}$ was obtained by superimposing the 10-fraction RT doses of $plan_1$ and the 20-fraction RT doses of $plan_2$, while ART $plan_{20+10}$ was obtained by superimposing the 20-fraction RT dose of $plan_1$ and the 10-fraction RT dose of $plan_3$, which indicated the cumulative dose distribution obtained by modifying the RT plans after 10 and 20 fractions of RT, respectively.

Biophysical Parameter Calculation

We compared the tumor control probability (TCP) of the PTV and normal tissue complication probability (NTCP) of the OARs between adaptive $plan_{10+20}$ and adaptive $plan_{20+10}$.

An in-house MATLAB code was developed to calculate the TCP and NTCP values. To calculate the TCP of the PTV, the modified linear quadratic-Poisson model was used.[13] The concept of the equivalent uniform dose (EUD) was adopted to estimate the quantitative biophysical measure of tumor dose.[14] The following parameters were used to calculate the TCP: α/β=10 Gy, SF_2=0.5, D_{ref}=2 Gy, n=30, and D=EUD. The Clongen cell density (CCD), which refers to millions of tumor cells per cubic centimeter of the PTV, was assumed to be 0.5 M/cm^3. The NTCP of the OARs was calculated using the Lyman–Kutcher–Burman model.[15,16] The tissue tolerance dose parameters and OAR endpoints were employed from the data of Burman et al[17] as shown in Table 1.

Statistical Methods

Statistical analyses were performed using the IBM SPSS Statistics 22 software package (SPSS, Inc.; Chicago, IL, USA). The target volume and dosimetric data of the target volume and OARs are expressed as the mean ± standard deviation (X±s). The TCP and NTCP are also expressed as the mean ± standard deviation (X±s). A two-sided paired t-test was used for comparisons. Statistical significance was defined as P<0.05.

Results
Clinical Data

From February 2018 to July 2018, ten patients with high-grade gliomas in the Department of Oncology, Xiangya Hospital, Central South University (nine males and one female, with a mean age of 41.8 years (age range, 18~55 years), were enrolled in this study. Of these patients, 6 received TOMO and 4 received IMRT. The clinical data are shown in Table 2.

Changes in Target Volume

A comparison of $plan_2$ with $plan_1$ revealed that the GTV, GTV_{tb}, CTV and PTV decreased by 17.06%, 24.16%,

Table 1 OAR Endpoints and Tolerance Dose Parameters

OARs	n	m	TD$_{50}$ (Gy)	Endpoint
Brain stem	0.16	0.14	65	Necrosis/infarction
Optic chiasm	0.25	0.14	65	Blindness
Lens	0.30	0.27	18	Cataract requiring intervention
Optic nerve	0.25	0.14	65	Blindness
Normal brain	0.25	0.15	60	Necrosis/infarction

Abbreviations: n, volume effect; m, slope of the curve for complication probability; OARs, organs at risk; TD50, 50% tolerance dose for uniform irradiation of the partial volume.

Table 2 Clinical Data

No.	Sex	Age (Years)	Duration of RT (Days)	Interval Between the Operation and RT (Days)	Side	Invaded Area (Lobes)	WHO Grade	Degree of Resection	Treatment Modality
1	M	51	43	51	R	<3	IV	STR	TOMO
2	M	18	42	42	L	≥3	IV	STR	TOMO
3	M	36	43	25	R	<3	IV	GTR	TOMO
4	M	49	43	31	L	≥3	IV	GTR	IMRT
5	M	51	44	28	L	≥3	IV	STR	TOMO
6	F	47	47	28	R	<3	IV	GTR	TOMO
7	M	51	43	23	R	≥3	IV	STR	IMRT
8	M	55	40	41	R	<3	III	GTR	IMRT
9	M	33	57	21	L	<3	IV	GTR	TOMO
10	M	27	42	42	R	≥3	III	GTR	IMRT

Abbreviations: M, male; F, female; R, right; L, left; STR, subtotal resection; GTR, gross tumor resection; IMRT, intensity-modulated radiotherapy; TOMO, tomotherapy; WHO, World Health Organization; RT, radiotherapy.

10.80% and 8.76% on average, respectively, while the GTV_r increased by 10.30%. A comparison of $plan_3$ with $plan_1$ revealed that the GTV, GTV_{tb}, CTV and PTV decreased by 22.40%, 31.96%, 14.40% and 12.13% on average, respectively, while the GTV_r increased by 14.56%. A comparison of $plan_4$ with $plan_1$ revealed that the GTV, GTV_{tb}, CTV and PTV decreased by 20.50%, 35.29%, 14.92% and 14.49% on average, respectively, while the GTV_r increased by 36.54%. There was a statistically significant difference in the GTV, GTV_{tb}, CTV and PTV before and at the end of RT (P<0.05), as shown in Table 3. The changes in the GTV, CTV and PTV of patient No. 10 based on $plan_1$, $plan_2$ and $plan_3$ are shown in Figure 1.

Comparison of Dosimetric PTV Data Between the Adaptive and Projection Plans

Compared with projection $plan_{1-2}$ and $plan_{1-3}$, the mean value of the near maximum dose (D2) to the PTV in adaptive $plan_{10+20}$ and $plan_{20+10}$ was reduced by 1.74% and 2.39%, respectively, showing statistical significance (P<0.05). There was no statistically significant difference in the dose received by 95% of the PTV (D_{95}) and volume

of the PTV receiving 110% of the prescribed dose (V_{110}) to the PTV between projection $plan_{1-2}$ and $plan_{1-3}$ and adaptive $plan_{10+20}$ and $plan_{20+10}$ (P > 0.05), as shown in Table 4. The distribution of the dose delivered to patient No. 10 in $plan_1$, $plan_{10+20}$, $plan_{1-2}$, $plan_{20+10}$, and $plan_{1-3}$ is shown in Figure 2.

Comparison of Dosimetric OAR Data Between the Adaptive and Projection Plans

Compared with projection $plan_{1-2}$, the D_2/mean dose (D_{mean}) to the brain stem, pituitary, and optic chiasm, as well as V_{20}, V_{30}, V_{40} and V_{50} to normal brain tissue in adaptive $plan_{10+20}$, was significantly reduced by 6.38%, 5.54%, 9.57%, 5.76%, 6.69%, 4.12%, 4.71%, 7.34%, 14.60% and 24.07%, respectively (P<0.05). Compared with projection $plan_{1-3}$, the values of D_2/D_{mean} to the brain stem, pituitary and optic chiasm, D_2 to the contral-ateral optic nerve, and V_{20}, V_{30}, V_{40} and V_{50} to normal brain tissue in adaptive $plan_{20+10}$ were significantly reduced by 5.56%, 5.42%, 6.75%, 4.58%, 4.99%, 3.83%, 5.93, 4.75%, 7.41%, 11.66% and 14.86%, respectively

Table 3 Changes in Target Volume (cm^3) Planned Before and at the End of RT (X±s)

	Plan₁	Plan₂	Plan₃	Plan₄	T	P
GTV	70.73±38.20	59.25±37.48	54.89±35.95	56.23±35.53	2.388	0.041
GTV_r	14.56±28.22	16.65±36.76	17.03±36.5	19.88±37.46	−1.132	0.287
GTV_{tb}	56.17±35.30	42.6±31.71	38.22±30.44	36.35±29.87	5.565	<0.001
CTV	311.83±99.15	282.06±100.33	267.91±97.90	265.30±103.03	2.474	0.035
PTV	420.84±120.03	389.5±131.27	370.49±130.58	359.88±136.50	3.340	0.009

Note: The T value and P value represent the corresponding values of the paired *t*-test for the target volumes of CT_1 and CT_4.
Abbreviations: GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; GTV_{tb}, GTV tumor bed; GTV_r, GTV residual.
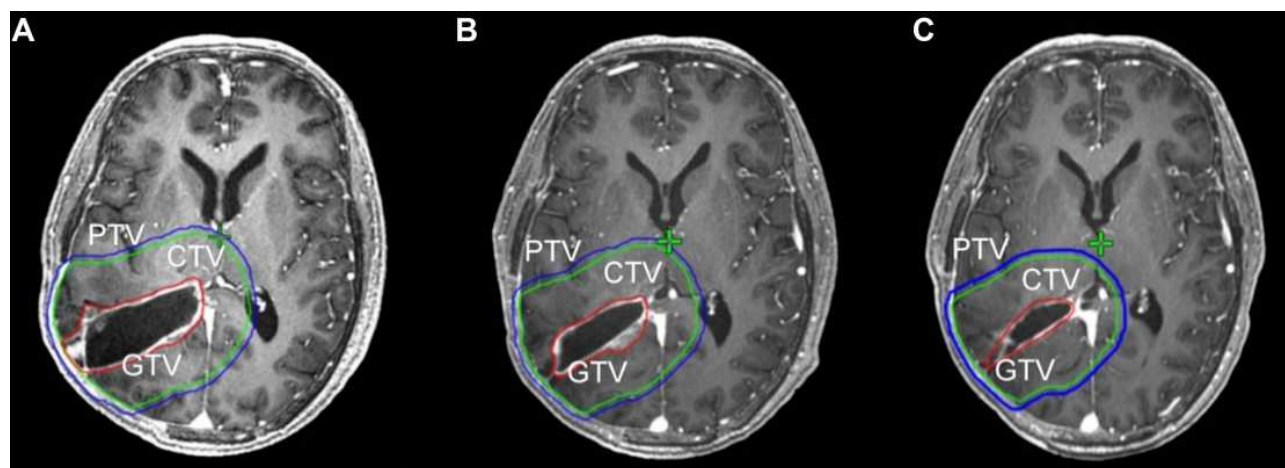
Figure 1 Target volumes on MRI$_1$, MRI$_2$ and MRI$_3$ are displayed in (**A–C**), respectively. The GTV, CTV and PTV are shown as red, green and blue solid lines, respectively.
Abbreviations: MRI$_1$, before RT; MRI$_2$, during 10-fraction RT; MRI$_3$, during 20-fraction RT; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; RT, radiotherapy.

(P<0.05). For the D$_2$/D$_{mean}$ to both the contralateral and ipsilateral lenses and D$_{mean}$ to the ipsilateral optic nerve, there were no differences between the adaptive and projection plans, as shown in Table 5.

Changes in the Conformity Index (CI) and Homogeneity Index (HI) of the PTV Between the Adaptive and Projection Plans

In the equation CI=(V$_{T,ref}$/V$_T$)*(V$_{T,ref}$/V$_{ref}$), V$_T$ is the target volume, V$_{ref}$ is the total volume enclosed by the reference isodose line and V$_{T,ref}$ is the target volume enclosed by the reference isodose line. The greater the CI is, the better the conformity.[18] In this study, 95% of the prescribed dose (ie, 57 Gy) was taken as the reference isodose line. HI=D$_5$/D$_{95}$ indicated the ratio of the irradiated dose to 5% of the target volume to the irradiated dose to 95% of the target volume. The closer the HI is to 1, the better the homogeneity.[19]

Compared with plan$_{1-2}$, the CI to the PTV in plan$_{10+20}$ increased by 11.76%, while the HI was reduced by 1.77%,

showing statistical significance (P<0.05). Compared with plan$_{1-3}$, the CI to the PTV in plan$_{20+10}$ increased by 9.23%, while the HI was reduced by 4.35%, showing statistical significance (P<0.05) (Table 6).

Timing for ART

Compared with plan$_{20+10}$, in plan$_{10+20}$, the values of D$_2$, D$_{95}$ and V$_{110}$ to the PTV increased by 0.05%, 0.35% and 0.13%, respectively, while the D$_2$/D$_{mean}$ to the brain stem, pituitary, and optic chiasma, as well as the V$_{20}$, V$_{30}$, V$_{40}$ and V$_{50}$ to normal brain tissues, were reduced by 2.70%, 1.73%, 4.57%, 1.82%, 2.37%, 1.62%, 5.08%, 8.54%, 11.43% and 18.66%, respectively, corresponding to a significant reduction in the D$_2$ to the pituitary and optic chiasm as well as the V$_{20}$, V$_{30}$, V$_{40}$ and V$_{50}$ to normal brain tissues (P<0.05). Compared with plan$_{20+10}$, in plan$_{10+20}$, the CI to the PTV increased by 7.04%, showing statistical significance (P<0.05), while the HI to the PTV increased by 0.91%, indicating no statistical significance (P>0.05) (see Table 7).

The TCP of the PTV in plan$_{10+20}$ was higher than that in plan$_{20+10}$ (0.77±0.32 vs 0.73±0.33, P<0.05), while the

Table 4 Comparison of Dosimetric PTV Data Between the Adaptive and Projection Plans

PTV	Plan$_{10+20}$	Plan$_{1-2}$	Plan$_{20+10}$	Plan$_{1-3}$	T$_1$	P$_1$	T$_2$	P$_2$
D$_2$ (Gy)	63.28±0.84	64.40±1.36	63.25±0.76	64.80±1.93	−2.687	0.025	−3.071	0.013
D$_{95}$ (Gy)	56.81±3.40	56.82±3.17	56.61±4.01	56.42±3.41	−0.150	0.998	0.492	0.635
V$_{110}$ (%)	0.13±0.42	2.62±6.38	0.00±0.01	17.90±46.87	−1.318	0.220	−1.207	0.258

Notes: T$_1$/P$_1$ represents the statistical value of the paired *t*-test for plan$_{10+20}$ and plan$_{1-2}$. T$_2$/P$_2$ represents the statistical value of the paired *t*-test for plan$_{20+10}$ and plan$_{1-3}$. P<0.05 was considered statistically significant.
Abbreviations: D$_2$, near the maximum dose; D$_{95}$, dose received by 95% of the PTV; V$_{110}$, volume of the PTV receiving 110% of the prescribed dose.
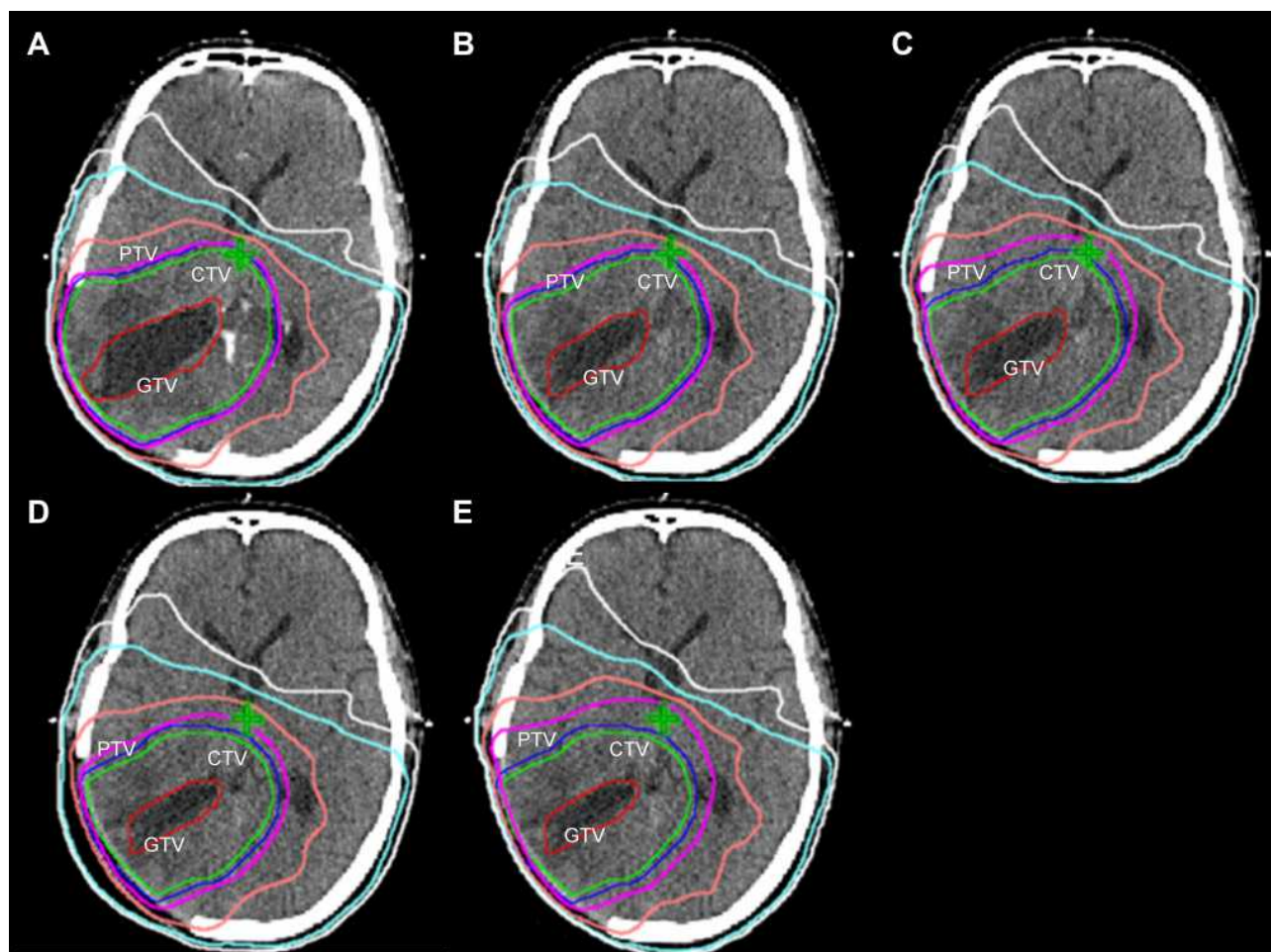
Figure 2 Dose distributions according to plan$_1$, plan$_{10+20}$, plan$_{1-2}$, plan$_{20+10}$ and plan$_{1-3}$ (initial RT plan$_1$, plan sum of the 10-fraction RT doses of plan$_1$ and the 20-fraction RT doses of plan$_2$, projection plan of initial plan$_1$ to CT$_2$, plan sum of the 20-fraction RT dose of plan$_1$ and the 10-fraction RT dose of plan$_3$, and projection plan of initial plan$_1$ to CT$_3$, respectively) are shown in (**A–E**), respectively. Isodose levels of 60, 48 30 and 20 Gy are shown as magenta, pink, cyan and white solid lines, respectively.
Abbreviations: plan$_1$, initial RT plan; plan$_2$, RT plan in 10 fraction; plan$_3$, RT plan in 20 fraction; RT, radiotherapy; CT$_2$, during 10-fraction RT; CT$_3$, during 20-fraction RT; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume.

NTCP of the brain stem, optic chiasm, ipsilateral optic nerve and normal brain tissue in plan$_{10+20}$ was lower than that in plan$_{20+10}$, without statistical significance ($P > 0.05$). The NTCP of the contralateral and ipsilateral lens was almost equal between plan$_{10+20}$ and plan$_{20+10}$ ($P > 0.05$). The NTCP of the contralateral optic nerve in plan$_{10+20}$ was higher than that in plan$_{20+10}$, without statistical significance ($P > 0.05$) (Table 8).

Discussion

Some studies have shown that in the process of RT for gliomas, the location, volume and morphology of the target volume and surrounding normal tissues change due to a reduction in the tumor bed/surgical cavity and disease progression. If the initial RT plan before treatment is used continuously during the treatment, missed irradiation of the tumor and irradiation of normal tissues may be increased.

By comparing changes in the GTV$_{pre}$ and GTV$_{mid}$ displayed on the MR images before and during RT for 15 patients with glioblastomas, Manon et al[1] found that the location of the GTV$_{mid}$ changed to varying degrees in 12 patients, among whom the GTV$_{mid}$ was beyond CTV1 but did not exceed CTV2 in 8, the GTV$_{mid}$ was beyond CTV2 in 4, and the GTV$_{mid}$ did not overlap with the GTV$_{pre}$ completely but did not exceed CTV1 in 3 patients, all indicating that the location of the GTV changes accordingly during RT and that there may be missed irradiation of the target volume when the location changes dramatically.

After observing CT scans on day 1 after surgery (CT0), on the first day of RT (CT1) and after 5 weeks of RT

Table 5 Comparison of Dosimetric OAR Data Between the Adaptive and Projection Plans

OARs	Plan$_{10+20}$	Plan$_{1-2}$	Plan$_{20+10}$	Plan$_{1-3}$	T$_1$	P$_1$	T$_2$	P$_2$
Brain stem (Gy)								
D$_2$	46.92±6.90	50.12±6.46	48.22±5.29	51.06±6.30	−7.190	<0.001	−3.746	0.005
D$_{mean}$	29.49±9.69	31.22±9.75	30.01±8.81	31.73±9.33	−4.719	0.001	−3.854	0.004
Optic chiasm (Gy)								
D$_2$	44.69±17.15	49.42±18.94	46.83±17.62	50.22±17.66	−4.626	0.001	−5.833	<0.001
D$_{mean}$	41.54±17.96	44.08±18.93	42.31±18.13	44.34±18.59	−3.674	0.005	−5.124	0.001
Pituitary (Gy)								
D$_2$	41.97±19.26	44.98±19.92	42.99±19.89	45.25±20.19	−4.805	0.001	−3.104	0.013
D$_{mean}$	40.03±19.38	41.75±19.50	40.69±19.64	42.31±19.71	−3.655	0.005	−3.810	0.004
Contralateral lens (Gy)								
D$_2$	5.50 ± 2.37	5.55 ± 2.37	5.73 ± 2.39	6.05 ± 2.47	−0.244	0.813	−1.410	0.192
D$_{mean}$	5.09 ± 2.20	5.08 ± 2.13	5.21 ± 2.21	5.23 ± 2.06	0.030	0.977	−0.177	0.864
Ipsilateral lens (Gy)								
D$_2$	5.94 ± 2.68	6.03 ± 2.95	6.08 ± 2.76	6.20 ± 2.69	−0.438	0.672	−0.862	0.411
D$_{mean}$	5.47 ± 2.61	5.46 ± 2.72	5.54 ± 2.68	5.58 ± 2.65	0.119	0.908	−0.335	0.745
Contralateral optic nerve (Gy)								
D$_2$	29.09 ± 20.32	29.26 ± 20.00	28.69 ± 20.07	30.50 ± 20.82	−0.333	0.747	−2.592	0.029
D$_{mean}$	20.87 ± 15.67	20.52 ± 14.43	19.59 ± 13.90	20.13 ± 13.21	0.397	0.701	−0.761	0.466
Ipsilateral optic nerve (Gy)								
D$_2$	38.97 ± 20.56	40.28 ± 21.72	38.66 ± 20.48	40.54 ± 21.42	−0.900	0.392	−2.082	0.067
D$_{mean}$	26.46 ± 14.50	26.04 ± 16.98	25.81 ± 14.62	26.55 ± 16.06	0.270	0.793	−0.503	0.627
Normal brain tissues (cm^3)								
V$_{20}$	608.67±147.30	638.76±129.29	641.23±145.72	673.20±150.34	−2.481	0.035	−3.917	0.004
V$_{30}$	396.62±109.42	428.04±108.30	433.67±114.78	468.36±126.01	−2.789	0.021	−3.816	0.004
V$_{40}$	249.97±78.49	292.72±90.84	282.24±88.10	319.50±103.10	−4.478	0.002	−3.603	0.006
V$_{50}$	123.68±40.88	162.88±57.11	152.06±50.55	178.60±66.23	−3.767	0.004	−2.425	0.038

Notes: T$_1$/P$_1$ represents the statistical value of the paired *t*-test for plan$_{10+20}$ and plan$_{1-2}$. T$_2$/P$_2$ represents the statistical value of the paired *t*-test for plan$_{20+10}$ and plan$_{1-3}$. P<0.05 was considered statistically significant.
Abbreviations: OARs, organs at risk; D$_2$, near the maximum dose; D$_{mean}$, mean dose; V$_n$, normal brain tissue volume receiving at least n Gy of radiation.

Table 6 Comparison of the CI and HI of the PTV Between the Adaptive and Projection Plans

PTV	Plan$_{10+20}$	Plan$_{1-2}$	Plan$_{20+10}$	Plan$_{1-3}$	T$_1$	P$_1$	T$_2$	P$_2$
CI	0.76±0.07	0.68±0.09	0.71±0.08	0.65±0.11	7.126	<0.001	4.400	0.002
HI	1.11±0.08	1.13±0.07	1.10±0.10	1.15±0.10	−2.491	0.034	−2.909	0.017

Notes: T$_1$/P$_1$ represents the statistical value of the paired *t*-test for plan$_{10+20}$ and plan$_{1-2}$. T$_2$/P$_2$ represents the statistical value of the paired *t*-test for plan$_{20+10}$ and plan$_{1-3}$. P<0.05 was considered statistically significant.
Abbreviations: PTV, planning target volume; CI, conformity index; HI, homogeneity index.

(CT2) in 19 patients undergoing gross total resection of glioblastomas, the GTV1/CTV1 and GTV2/CTV2 were drawn according to CT1 and CT2, respectively, and Kim et al[4] developed radiation plan$_1$ and plan$_2$ accordingly. Their research suggested that the GTV reduction rate was 14.4–51.3% between CT0 and CT1 (median, 29%) and 7.9–71.9% between CT1 and CT2 (median, 34.9%), and the volume of normal brain tissue around the surgical cavity covered by the 95% isodose line in plan$_2$ was much smaller than that in plan$_1$, where the CTV2 of 5 patients exceeded the range covered by the 95% isodose line in plan$_1$, which would result in missed irradiation of the target volume. This result indicated that the GTV decreased to varying degrees during RT and that the

Table 7 Comparison of Dosimetric Parameters of the Target Volume and OARs Between Adaptive Plan$_{10+20}$ and Plan$_{20+10}$

Dosimetric Parameter	Plan$_{10+20}$	Plan$_{20+10}$	T	P
PTV				
D$_2$ (Gy)	63.28±0.84	63.25±0.76	0.371	0.719
D$_{95}$ (Gy)	56.81±3.40	56.61±4.01	0.506	0.625
V$_{110}$ (%)	0.13±0.42	0.00±0.01	0.991	0.347
CI	0.76±0.07	0.71±0.08	7.960	<0.001
HI	1.11±0.08	1.10±0.10	0.855	0.415
OARs (Gy)				
Brain stem				
D$_2$	46.92±6.90	48.22±5.29	−2.250	0.051
D$_{mean}$	29.49±9.69	30.01±8.81	−1.121	0.291
Optic chiasm				
D$_2$	44.69±1.71	46.83±1.76	−3.373	0.008
D$_{mean}$	41.54±1.80	42.31±1.81	−1.980	0.079
Pituitary				
D$_2$	41.97±19.26	42.99±19.89	−2.633	0.027
D$_{mean}$	40.03±19.38	40.69±19.64	−1.698	0.124
Contralateral lens				
D$_2$	5.50 ± 2.37	5.73 ± 2.39	−1.847	0.098
D$_{mean}$	5.09 ± 2.20	5.21 ± 2.21	−1.238	0.247
Ipsilateral lens				
D$_2$	5.94 ± 2.68	6.08 ± 2.76	−1.117	0.293
D$_{mean}$	5.47 ± 2.61	5.54 ± 2.68	−0.845	0.420
Contralateral optic nerve				
D$_2$	29.09 ± 20.32	28.69 ± 20.07	0.571	0.582
D$_{mean}$	20.87 ± 15.67	19.59 ± 13.90	1.365	0.205
Ipsilateral optic nerve				
D$_2$	38.97 ± 20.56	38.66 ± 20.48	0.367	0.722
D$_{mean}$	26.46 ± 15.00	25.81 ± 14.62	0.619	0.551
Normal brain tissue (cm^3)				
V$_{20}$	608.67±147.30	641.23±145.72	−4.801	0.001
V$_{30}$	396.62±109.42	433.67±114.78	−6.413	<0.001
V$_{40}$	249.97±78.49	282.24±88.10	−6.834	<0.001
V$_{50}$	123.68±40.88	152.06±50.55	−6.075	<0.001

Notes: T/P represents the statistical value of the paired *t*-test for plan$_{10+20}$ and plan$_{20+10}$. $P<0.05$ was considered statistically significant.
Abbreviations: OARs, organs at risk; PTV, planning target volume; D$_2$, near the maximum dose; D$_{95}$, dose received by 95% of the PTV; D$_{mean}$, mean dose; V$_{110}$, volume of the PTV receiving 110% of the prescribed dose; CI, conformity index; HI, homogeneity index; V$_n$, normal brain tissue volume receiving at least n Gy of radiation.

location of the GTV changed correspondingly with a reduction in the GTV. The normal brain tissue around the target volume gradually entered the high-dose irradiation area, and the volume of the normal brain tissue exposed to high-dose irradiation increased gradually.

By analyzing the daily MR images of 3 patients with grade IV gliomas during postoperative RT, Mehta et al[5] observed that the volume of the surgical cavity was reduced in 3 patients (2 who underwent gross total resection and 1 who underwent subtotal resection) during RT and was gradually stable in 2 of these patients after 20 fractions of RT. The residual GTV (GTV$_r$) of patients undergoing subtotal resection did not change significantly during RT, while the edema volume decreased at the beginning of RT but began to increase with the progression of RT and decreased again after 13 fractions of RT. This study showed that the volume of the surgical cavity tended to decrease during RT.

Table 8 Comparison of Radiobiological Parameters of the Target Volume and OARs Between Adaptive Plan$_{10+20}$ and Plan$_{20+10}$

Radiobiological Parameter			Plan$_{10+20}$	Plan$_{20+10}$	T	P
PTV (TCP)			0.77±0.32	0.73±0.33	2.889	0.018
OARs (NTCP, %)						
	Brain stem		0.06±0.06	1.06±3.18	−0.996	0.345
	Optic chiasm		4.91±6.22	6.84±9.67	−1.050	0.321
	Normal brain tissue		0.28±0.24	2.02±4.8	−1.316	0.221
	Lens					
		Contralateral	0.07±0.07	0.07±0.06	0.021	0.984
		Ipsilateral	0.09±0.09	0.09±0.09	−1.372	0.203
	Optic nerve					
		Contralateral	0.79±2.44	0.35±1.05	1.007	0.340
		Ipsilateral	0.19±0.50	0.35±1.05	−0.897	0.393

Notes: T/P represents the statistical value of the paired *t*-test for plan$_{10+20}$ and plan$_{20+10}$. P<0.05 was considered statistically significant.
Abbreviations: TCP, tumor control probability; OARs, organs at risk; PTV, planning target volume; NTCP, normal tissue complication probability.

By comparing changes in the GTV (including the GTVtb and GTVr) displayed on MR images before and at the end of RT in 15 patients with gliomas, Yang et al[9] found that the GTVtb shrank significantly while the GTV$_r$ did not change significantly during RT and thought that the reduction in the surgical cavity (tumor bed) was the main reason for the decrease in the GTV. They also discovered that the irradiated doses to the OARs and normal brain tissues in the initial RT plan were significantly higher than the replanned doses at the end of RT. Therefore, it is necessary for patients with gliomas to undergo ART during RT.

Our study indicated that decreases in the GTV, CTV and PTV were more significant before 10 fractions of RT than after 20 fractions of RT, while the decreases in the GTV, CTV and PTV slowed dramatically after 20 fractions of RT. The shrinkage of the GTV and corresponding target volume was relative to the shrinkage of the GTVtb, which shrank gradually, and the shrinkage of the GTVtb was associated with the interval between the operation and postoperative MRI examination. The GTVtb may shrink quickly during a period of time after surgery; however, over time, when the GTVtb is reduced to a certain size, the rate of GTVtb shrinkage slows. Our research also indicated that the GTV increased gradually during RT, and the mean GTV at the end of RT was slightly higher than the GTV after 20 fractions of RT (56.23±35.53 cm^3 vs 54.89±35.95 cm^3) based on

a comparison of RT replans among different fraction intervals; this result may be associated with a change in the target volume of the blood brain barrier or tumor progression during RT. At the same time, it was found that a reduction in the surgical cavity or tumor bed was the main reason for the decrease in the GTV, CTV and PTV, similar to the conclusion of Yang et al.[9]

By comparing the dosimetric data of the target volume and OARs between projection plan$_{1-2}$ and adaptive plan$_{10+20}$, as well as between projection plan$_{1-3}$ and adaptive plan$_{20+10}$, it was determined that ART was not obviously superior to projection RT for increasing the irradiated dose to the target volume, but it could increase the precision of irradiation and reduce the irradiated dose to the OARs to a certain extent.

As the cognitive impairment caused by RT in most cases generally occurs a few years later, ART has obvious advantages in patients with low-grade gliomas. Patients with low-grade gliomas have a median survival duration of 10 years and can survive for even longer time periods.[20–22] ART can reduce the sequelae of RT and improve the quality of life of these patients. However, for patients with glioblastomas, the 5-year survival rate of those receiving postoperative RT with synchronous and adjuvant 6-cycle TMZ chemotherapy is only 9.8%.[23] Therefore, regarding cognitive function, patients with lower-grade gliomas can benefit more from ART than

patients with higher-grade glioblastomas. The study from Tsien et al[24] indicated that IMRT with an escalated dose could improve the survival of glioblastoma patients. The PTV1 (GTV+1.5 cm) received 60 Gy/30 fractions, and the PTV2 (residual tumor or surgical cavity) received 66–81 Gy using simultaneous integrated boosts with concurrent and adjuvant TMZ chemotherapy. The median overall survival (OS) and progression-free survival (PFS) durations were 20.1 and 9.0 months, respectively, which was superior to the results of Stupp's protocol.[23] ART improved the irradiation precision of the PTV in high-grade gliomas and reduced the radiation dose to the OARs and normal brain tissue. If ART is used to escalate the radiation dose to the GTV in glioblastoma after a standard dose was given, it may improve patient prognosis. Whether ART can increase the local control rate of high-grade gliomas and reduce radiation toxicity to the OARs and normal brain tissue should be further studied.

ART is also beneficial to some glioma patients who have disease progression during RT, which leads to a corresponding increase in the GTV during RT compared with the GTV in the original RT plan. By comparing the changes in GTV_{pre} (GTV before RT) and GTV_{mid} (GTV during 3 weeks of RT) in 19 patients with high-grade gliomas, Tsien et al[2] observed that GTV_{mid} decreased in 14 patients (including 2 with a reduction rate of over 50%), did not change significantly in 2, and increased in 3. Similarly, by comparing the changes in GTV displayed on the MRI before postoperative RT and during 5 weeks of RT for 15 patients with high-grade gliomas, Shukla et al[3] found that 12 patients had decreased GTV (median, 54.85 cm³), 4 of whom had decreased GTV by more than 50% and 3 of whom had increased GTV (median, 14 cm³). The above two studies showed that the GTV of some patients with high-grade gliomas increased by varying degrees during radiotherapy. The increase in GTV during radiotherapy may be due to the true progression or pseudoprogression of the tumor. Pseudoprogression is related to the therapeutic effect of radiotherapy and chemotherapy, but not the real tumor progression. With the application of synchronous and adjuvant chemotherapy using TMZ, the incidence of pseudoprogression increases, especially in patients with methylguanine methyltransferase (MGMT) promoter methylation. The neuroimaging of pseudoprogression showed localized blood brain barrier disruption, T1 contrast enhancement, a mass effect and strong T2 or FLAIR signals of peritumoral vasogenic edema on MRI images.[25] When the GTV increases to

a certain extent, the PTV in the original plan cannot cover the changed PTV; if RT is completed according to the original plan, the probability of tumor recurrence may increase. Therefore, for patients with progressive disease, MRI can be used repeatedly during RT to evaluate the GTV. If the GTV increases dramatically, it is necessary to modify the RT plan.

Regarding modifications of the planned time points, we found that compared with $plan_{20+10}$, the D_2, D_{95} and V_{110} to the PTV increased to varying degrees, while the D_2 /D_{mean} to the brain stem, pituitary, and optic chiasm, as well as the V_{20}, V_{30}, V_{40} and V_{50} to normal brain tissues, were reduced to varying degrees, and the CI to the PTV increased in $plan_{10+20}$. The decreases in D_2 to the pituitary and optic chiasm, as well as V_{20}, V_{30}, V_{40} and V_{50} to normal brain tissues, together with the CI to the PTV, were statistically significant ($P<0.05$). Therefore, we conclude that the irradiated dose to the target volume can be increased slightly in $plan_{10+20}$, showing no statistical significance. Regarding the increased precision of RT and reduced irradiated dose to some OARs and normal brain tissue, $plan_{10+20}$ was significantly superior to $plan_{20+10}$.

Furthermore, our results demonstrated that the value of the TCP in $plan_{10+20}$ was higher than that in $plan_{20+10}$ (0.77±0.32 vs 0.73±0.33, $P<0.05$), showing that the RT plan modified after 10 fractions of RT was more appropriate than that modified after 20 fractions of RT. MacDonald et al[13] suggested that the TCP for high-grade gliomas treated with IMRT was as high as 92.57%, which is much higher than that in our study. We adopted the same modified TCP model based on EUD,[14] which was derived using Poisson statistics and the linear quadratic (LQ) model. This difference between the value of the TCP in our study and MacDonald's is related to the PTV. The PTV cone down (PTVcd) in MacDonald's study ranged from 18.9 cm³ to 383.5 cm³, but we found that the initial mean volume of the PTV was 420.84±120.03 cm³. The patients in our study had a larger PTV than those in MacDonald's study. In the TCP model, the greater the PTV is, the smaller the TCP value. The NTCP values of the normal brain tissue, brain stem, optic chiasm, contralateral lens and ipsilateral optic nerve in $plan_{10+20}$ were slightly lower than those in $plan_{20+10,}$ although there was no significant difference. However, these results still show that $plan_{10+20}$ is more advantageous in terms of the protection of normal tissue.

Finally, there are many limitations to this study. First, only ten patients were enrolled, and the sample size was too small. Second, we performed only simulated CT/MRI after 10, 20 and 30 fractions of RT and concluded that the

modified RT plan after 10 rounds of RT was better than that after 20 rounds of RT; however, we did not explore changes in the volume size or RT-irradiated dose to the target volume and OARs at other time points, such as after 15 rounds of RT. Most importantly, our study was carried out only to explore the effect of ART on the size of the target volume and radiation dosimetry and biophysical parameters of the target volume and OARs. The effect of ART on the OS rate and PFS rate of high-grade glioma patients has not yet been investigated. We will focus on this area in the future.

Conclusion

The GTV and PTV in patients with high-grade gliomas decreased with a reduction in the GTV_{tb} accordingly during postoperative RT. By using ART, the precision of the target volume can be improved, the irradiated dose to some OARs can be reduced, and the TCP of the PTV can be increased. We conclude from this study that it is more appropriate to modify the RT plan after 10 fractions of RT than after 20 fractions of RT.

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Disclosure

The authors report no conflicts of interest in this work.

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