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A practical method of target volume delineation based on peritumoral edema in radiation therapy of glioblastoma

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► ***Original article***

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ABSTRACT

Background: To introduce a simple glioblastoma (GBM) target delineation method based on peritumoral edema. ***Materials and Methods:*** A postoperative GBM patient was selected, the target volume was delineated using three methods, including the methods recommended by the Radiation Therapy Oncology Group (RTOG method), by the European Organization for Research and Treatment of Cancer (EORTC method) and by this study (New method), and radiotherapy plans were formulated by the same physicist. The dose distributions of each schedule were compared. Then, patients treated with the delineation method recommended in this study were retrospectively analyzed, and progression-free survival and overall survival were determined. ***Results:*** The distributions of the high-dose regions of the 3 plans were as follows: RTOG method > EORTC method > New method, as was the low-dose region. Thirty-three patients were included in this retrospective study, and the median progression-free survival (PFS) and overall survival (OS) were 12 and 25 months, respectively. ***Conclusions:*** Our study suggested that delineating the target volume for GBM radiotherapy based on peritumoral edema is a good choice.

INTRODUCTION

Glioblastoma (GBM) is a common primary malignant tumor of the brain, and adjuvant chemoradiotherapy plays an important role in the treatment of GBM [1, 2]. There are no uniform target delineation guidelines for radio-therapeutics in GBM. The two methods recommended by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) are preferred [3, 4]. At present, most of the target delineation methods are to first identify the postoperative tumor bed and residual tumor; on this basis, a certain range can be expanded, and then pruning can be performed to determine the irradiation target volume [5-7]. However, clinically, we often find that the tumor bed and residual tumor cannot be accurately identified. The possible reasons are as follows. First, patients do not undergo timely MRI scanning after surgery, or if radiotherapy is delayed, it could lead to deformation of the tumor bed or occlusion of the tumor cavity, and then the tumor bed cannot be correctly identified. Second, there are sometimes low-grade glioma components in the peritumoral edema area, and with the current diagnostic ability, it is often difficult to accurately distinguish between simple edema and low-grade glioma [8, 9]. Third, early metastasis of glioblastoma often occurs in the peritumoral edema area, with no enhancement, and these areas are nonisocentric and even discontinuous with tumor center edema [10]. Therefore, relying solely on the tumor bed and residual tumor delineating the target volume cannot satisfy postoperative radiotherapy for all GBM patients. For these conditions, we sometimes adopt a simpler but practical delineating method, which only considers peritumoral edema. To avoid the uncertainty of target delineation caused by the above situation. Whether peritumoral edema is fully included in the target volume has not yet been determined [11]. Therefore, we conducted this retrospective single-center study to analyze the overall survival (OS) and progression-free survival (PFS) of GBM patients who completed radiotherapy, and the target volume was based on peritumoral edema to determine the feasibility of this target volume delineation method. To our knowledge, this is the first time that GBM has been treated with radiation therapy based solely on peritumoral edema.

MATERIALS AND METHODS

This section has two parts: one is to compare the characteristics of three different sketch methods, and the second is to retrospectively analyze the prognosis

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of 33 patients with GBM who underwent the delineation method recommended in this study.

Comparison of different sketch methods

A patient diagnosed with glioblastoma in the right frontal lobe after surgery was selected. The Varian Eclipse 15.6 system (Varian Company) was used to delineate the target volume and formulate the radiotherapy plan by the same physicist. Three different methods (RTOG, EORTC and this study) were used to delineate the target volume, and the plans adopted methods of intensity-modulated radiotherapy (IMRT). Then, the characteristics of the different radiotherapy plans were compared. The brain volumes enveloped by 60 Gy, 46 Gy and 25 Gy isodose lines (V60, V46 and V25) were used to represent the high-dose, medium-dose and low-dose regions, respectively; the high-dose regions represented the volume of irradiation of the target volume (PTV); and the medium-dose and low-dose regions represented the prophylactic region and irradiated normal brain. The V60, V46, and V25 of the different plans were calculated to compare the size of the target volume and the normal brain tissue exposure. The details of the three delineation methods are shown below.

The target volume delineation guidelines recommended by the RTOG (RTOG method).

Phase 1 (to 46 Gy in 23 fractions).

Gross tumor volume 1 (GTV1) = surgical resection cavity plus any residual enhancing tumor (postcontrast T1-weighted magnetic resonance imaging (MRI) scans) plus surrounding edema (hyperintensity on T2 or Fluid-attenuated Inversion-Recovery sequences (FLAIR) MRI scans). Clinical Target Volume 1 (CTV1) = GTV1 plus a margin of 2 cm (if no surrounding edema is present), the CTV is the contrast-enhancing tumor plus 2.5 cm. Anatomical barriers, such as the skull, visual pathway/optic chiasm, brainstem, falx and tentorium cerebelli (each 0 mm), and ventricles (5 mm), need to be trimmed. Planning Target Volume 1 (PTV1) = CTV1 plus a margin of 3 mm.

Phase 2 (14 Gy boost in 7 fractions).

GTV2 = surgical resection cavity plus any residual enhancing tumor (postcontrast T1-weighted MR scans). CTV2 = GTV2 plus a margin of 2 cm and restricted from CTV1. PTV2 = CTV2 plus a margin of 3 mm.

The target volume delineation guidelines recommended by the EORTC (EORTC method).

Phase 1 (to 60 Gy in 30 fractions).

GTV = surgical resection cavity plus any residual enhancing tumor (post-contrast T1-weighted MR scans) plus no enhancing areas may be a component of the tumor. CTV = GTV plus a margin of 2 cm. Anatomical barriers, such as the skull, visual pathway/optic chiasm, brainstem, falx and tentorium cerebelli (each 0 mm), and ventricles (5 mm), need to be trimmed. PTV = CTV plus a margin of 3 mm.

The target volume delineation pattern recommended by this study (new method).

Phase 1 (to 50-54 Gy in 25-27 fractions).

CTV2 = surgical resection cavity plus any residual enhancing tumor (post-contrast T1-weighted MR scans) plus surrounding edema (hyper-intensity on T2 or FLAIR MR Scans), but edema caused by surgery was excluded. CTV1 = CTV2 plus a margin of 0-1.0 cm, and the size of the external expansion depended on the size of the peritumoral edema (plus a 1.0 cm margin if there was little peritumoral edema, plus a 0.5 cm margin if there was moderate peritumoral edema, or no margin if there was large patchy edema or distant edema). Anatomical barriers, such as the skull, visual pathway/optic chiasm, brainstem, falx and tentorium cerebelli (each 0 mm), and ventricles (5 mm), need to be trimmed. PTV1 = CTV1 plus a margin of 3 mm.

Phase 2 (6-10 Gy boost in 3-5 fractions).

PTV2 = CTV2 plus a margin of 3 mm.

By utilizing the intensity-modulated radiotherapy-simultaneously integrated boosting (IMRT-SIB) technique, 1.8 Gy PTV1 and 2.0 Gy PTV2 can be prescribed in a total of 30 fractions.

According to the above delineation principles, the target volumes were delineated separately.

The peritumoral edema in this patient was considered moderate, so peritumoral edema with 5 mm marginal expansion formed CTV1 in the target delineation method recommended by this study. The physicist formulated three radiotherapy plans according to the same criteria (figure 1).

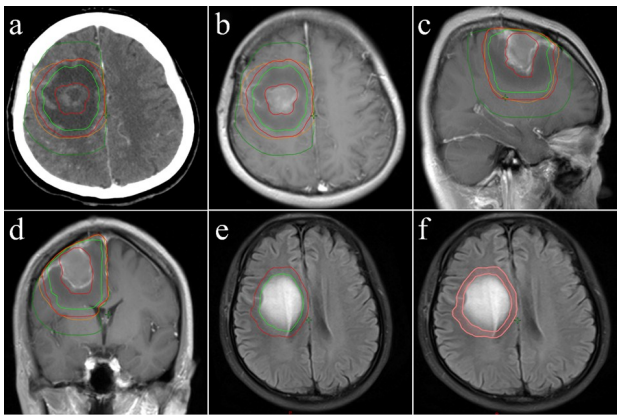


Figure 1. The target volumes were delineated by the RTOG method, EORTC method and New method. The red contour line in the center represents the surgical resection cavity plus any residual enhancing tumor (postcontrast MR T1WI). The light green contour line in the outer layer represents peritumoral edema. The outside three lines represent peritumoral edema expanding 5 mm (red), the resection cavity and residual tumor expanding 2 cm (orange), and peritumoral edema expanding 2 cm (outermost green). These lines can be seen on a, b, c, and d images (**a:** axial CT, **b:** axial MRI T1WI enhancement, **c:** sagittal MRI T1WI enhancement, and **d:** coronal MRI T1WI enhancement). These expanded contours are all trimmed). Figure e shows the peritumoral edema delineated on the FLAIR MRI sequence (light green line plus 5 mm in this study to produce the outline of the preventive target volume). The red shaded area in panel f is the preventive target volume excluding peritumoral edema.

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Retrospective study

Patients who met the following criteria were included in this retrospective study: newly diagnosed with glioblastoma or glioma containing World Health Organization (WHO) grade IV components, total or partial surgical resection, Karnofsky performance status of at least 70, and no contraindications to radiotherapy. We enrolled 33 eligible patients, all North Chinese Asians, who were treated at the General Hospital of Northern Theater Command between July 2014 and January 2020, and the target volumes of all of them were delineated using the methods recommended in this study. Concurrent chemoradiotherapy began 3 to 16 weeks after surgery. Informed consent was obtained from all subjects and/or their legal guardian(s). Radiotherapy was performed by three-dimensional conformal radiation therapy (3D-CRT) or IMRT-SIB with a prescribed dose of 50-60 Gy. According to Stupp [12], concurrent with radiotherapy, oral temozolomide chemotherapy is administered at a dosage of 75 mg per square meter of body surface area per day. Sequential temozolomide chemotherapy was started 1 month after the end of concurrent chemoradiotherapy, in accordance with 150-200 mg per square meter of body surface area per day, for 5 days, 28 days for a cycle, and in fact, each patient completed between 3 and 40 cycles (average: 12 cycles). The general information of the patients is shown in table 1. The radiotherapy facility included a computer tomography (CT) simulator (Philips MX4000dual; Philips Company) and two linear accelerators (Siemens Primus M4044; Siemens Company) and Tomotherapy (Accuray Company). Target delineation was performed using the Pinnacle^3 system (Philips Company). Temozolomide was obtained from two companies (Tasly and Merck Company) that chose the drug brand according to the patient's wishes. The diagnosis of tumor recurrence was based on head MR images, including plain, postcontrast, magnetic resonance spectroscopy (MRS), and perfusion weighted imaging (PWI) images, and some patients were confirmed by reoperation. Approval for the conduct of this retrospective study was obtained from the Ethics Committee of the General Hospital of Northern Theater Command on May 5, 2022, number NO.Y (2020)089. All procedures implemented in patients were in accordance with the Declaration of Helsinki. Guidelines for target delineation and detailed information on radiotherapy and chemotherapy in retrospective analyses can be found in the *Protocol* file in the supplemental material.

Statistical analysis: OS and PFS were calculated by the Kaplan–Meier method with GraphPad Prism 8.0 software.

Table 1. Patient characteristics

Characteristics	N = 33
median age (range) - years	57 (27-75)
Sex - no. (%)	
Male	19(57.6)
Female	14(42.4)
Pathological diagnosis - no. (%)	
Glioblastoma	15(45.5)
Astrocytoma (WHO Grade III-IV)	18(54.5)
Temozolomide	
Concurrent radiochemotherapy	100%
Adjuvant chemotherapy	3-40 Circles
Radiotherapy (%)	
3D-CRT	3(9.1)
IMRT-SIB	30(90.9)
Expansion of peritumoral edema (%)	
0 mm	9(27.3)
5 mm	19(57.6)
10 mm	5(15.1)

WHO: World Health Organization; 3D-CRT: three-dimensional conformal radiation therapy IMRT-SIB: intensity-modulated radiotherapy-simultaneous integrated boosting.

RESULTS

Comparison of radiotherapy schedules

We selected this patient as a 33-year-old female with glioblastoma. The tumor was completely removed one month after surgery. The tumor was located in the right frontal parietal lobe, deep in the brain parenchyma, and had moderate peritumoral edema around it, which could better reflect the different characteristics of the different delineation methods. The volume of the whole brain of this patient was 1490.71 ml. By delineating the target volume of the same patient and calculating the volumes of V60, V46, and V25 and their proportions in the whole brain, the radiation exposure of tumor lesions and normal brain tissues with different delineation methods could be clearly determined to compare the advantages and disadvantages of each delineation method. Figure 1a-d shows the target volume delineated using the three methods displayed in different cross sections: CT axis (a), MRI axis (b), MRI sagittal (c), and MRI coronal (d). The lines from the inside to the outside are the tumor bed (red), peritumoral edema (light green), peritumoral edema with an external expansion of 5 mm (red, CTV1 of the new method), the tumor bed with an external expansion of 2 cm (orange, CTV2 of the RTOG method and CTV of the EORTC method), and peritumoral edema with a 2 cm outward expansion (green, CTV1 of the RTOG method). The RTOG plan was calculated separately in two phases, and then the two plans were combined to calculate the overall isodose line. The EORTC plan was scheduled to be administered directly at the prescribed dose of 60 Gy to 2 cm around the tumor. The IMRT-SIB method was used in

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the planning of the new method. CTV2 was set up in the peritumoral edema area, and a prescription dose of 60 Gy was given. Then, a prescription dose of 54 Gy was given as the preventive target volume with an expansion of 5 mm (CTV1) (figure 1e-f). The radiotherapy plan is shown in Figure 2. In the RTOG plan (Figure 2a1-3, a1 in axial, a2 in coronal, a3 in sagittal), the brain volumes enveloped by 60 Gy, 46 Gy and 25 Gy isodose lines (V60, V46 and V25) were 239.6 ml, 481.5 ml and 867.2 ml, respectively, accounting for 16.1%, 32.3% and 58.2% of the whole brain volume, respectively. In contrast, in the EORTC plan (figure 2b1-3), V60, V46 and V25 were 194.1 ml, 296.5 ml and 609.7 ml, 19%, 38.4% and 29.7%, respectively, lower than those in the RTOG plan. According to the new method plan of this study (figure 2c1-3), the volumes of V60, V46 and V25 were 156.4 ml, 256.6 ml and 544.7 ml, respectively, which were decreased by 34.7%, 46.7% and 37.2%, respectively, from the RTOG plan and decreased by 19.4%, 13.5% and 10.7%, respectively, from the EORTC plan. The data for the comparison of the three plans can be found in Table 2. In the three plans, regardless of the distribution of the high-dose region (V60), medium-dose region (V46) or low-dose region (V25), there was a trend of RTOG > EORTC > new method.

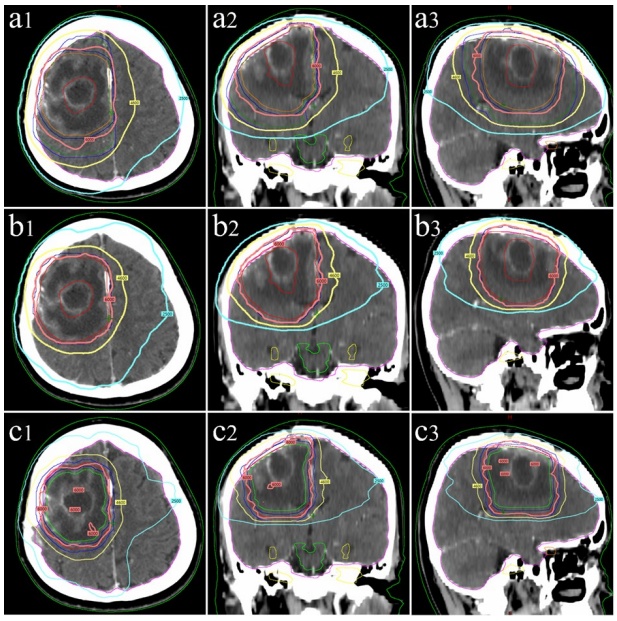


Figure 2. Equimetric curve distribution of radiation therapy plans obtained by three different delineation methods. Panels **a1**, **a2**, and **a3** show the isodose curves obtained via the RTOG method by merging two-phase axial, coronal and sagittal planes, respectively. Panels **b1**, **b2**, and **b3** are the EORTC methods, and panels **c1**, **c2** and **c3** are the methods used in this research. The radiotherapy plans are displayed by isodose contours of 60 Gy (thick red line), 46 Gy (thick yellow line) and 25 Gy (thick blue line).

The volume of the whole brain of this patient was 1490.71 ml. Regardless of the V60, V46 or V25, the RTOG method had the largest difference, followed by the EORTC method, and the new method recommended in this study had the smallest difference.

Table 2. Dose-volume comparisons in the brain produced by three different target volume delineation methods.

Target volume delineation methods	Brain volume, ml (%)		
	60 Gy	46 Gy	25 Gy
RTOG	239.6 (16.1)	481.5 (32.3)	867.2 (58.2)
EORTC	194.1 (13.1)	296.5 (19.9)	609.7 (40.9)
New method	156.4 (10.5)	256.6 (17.3)	544.7 (36.6)

RTOG: Radiation Therapy Oncology Group; EORTC: The European Organization for Research and Treatment of Cancer.

Retrospective study results

In this retrospective study, 33 eligible patients were enrolled, including 19 males and 14 females with a median age of 57 years, 15 patients diagnosed with GBM and 18 patients diagnosed with astrocytoma (WHO grade III-IV). For postoperative radiation therapy, 30 patients were treated with a one-phase IMRT-SIB approach, and 3 patients were treated with a two-phase 3D-CRT approach. The new method recommended by this study was used to delineate the target volume in these patients. According to the extent of peritumoral edema, 19 patients had a 5 mm expanded margin as the preventive target volume, 5 patients had a 10 mm expanded margin, and 9 patients had no preventive target volume. The concrete target delineation rules are described in the first part of the Materials and Methods section. All patients received concurrent chemoradiotherapy and subsequent maintenance chemotherapy with temozolomide.

Patients were followed up until January 2023. The median PFS and OS of the 33 patients were 12 and 25 months, respectively, and the average PFS and OS were 17.85 and 30.67 months, respectively (figure 3a, c). Since 18 patients who were diagnosed with astrocytoma (WHO Grade III-IV) were included in the study, they were compared with GBM patients. There was no significant difference in PFS or OS between the two groups, and GBM patients even had some advantages in prognosis (hazard ratio: 0.62 for PFS and 0.59 for OS) (figure 3b, d). Up to the follow-up period, 4 patients survived, 2 patients experienced no recurrence, 1 patient was treated with a gamma knife after recurrence, and 1 patient survived with a tumor after two rounds of radiotherapy plus a temozolomide dose-intensive regimen and low-dose bevacizumab. Five patients died of other diseases, including coronary heart disease, demyelinating disease, septic shock, acute cerebral infarction, and coronavirus disease 2019 (COVID-19). During our follow-up, if recurrence occurred within the 60 Gy irradiated volume, it was labeled the internal field; if recurrence occurred in the 50/54-60 Gy range, it was labeled the margin; and if recurrence occurred outside the prescribed dose, it was labeled the out-of-field. A total of 28 patients were detected for recurrence, including 17 patients (63%) in the irradiated field alone, 5 patients (18.5%) in the irradiated field accompanied by margin or out-of-

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field, and 5 patients (18.5%) in margin and/or out-of-field relapses but cleaned in the internal field. For one patient who recurred, no information on her recurrence location could be obtained, so she was not included in the recurrence pattern statistics. The recurrence patterns are shown in table 3.

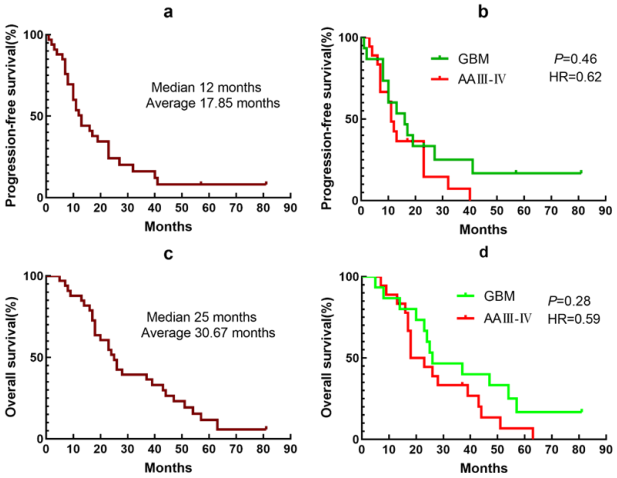


Figure 3. K–M estimates of progression-free survival and overall survival. Panel a shows the total PFS. The median PFS was 12 months, and the average PFS was 17.85 months. Panel b shows the PFS of patients with GBM and astrocytoma (WHO grade III-IV) (labeled AAIII-IV in the figure). The hazard ratio for progression among GBM patients, compared with astrocytoma (WHO Grade III-IV) patients, was 0.62 (P=0.46). Panel c shows the total OS. The median OS was 25 months, and the average OS was 30.67 months. Panel d shows the OS of patients with GBM and astrocytoma (WHO grade III-IV) (labeled AAIII-IV in the figure). The hazard ratio for progression among GBM patients, compared with astrocytoma (WHO Grade III-IV) patients, was 0.59 (P=0.28).

Table 3. Recurrence patterns in this study.

Recurrence patterns	n=27	%
Int	17	63
Int + Out	4	14.8
Int + Mar	1	3.7
Int + Mar + Out	0	
Mar	0	
Out	4	14.8
Mar + Out	1	3.7

Int: internal field; Mar: margin; Out: out-of-field.

Among the 33 patients, 28 relapsed. Except for 1 patient who could not undergo imaging examination after recurrence, the other 27 patients had MRI images taken during recurrence. After careful comparison with the images obtained during radiotherapy, it was possible to distinguish patients with in situ recurrence, internal field recurrence (within V60), marginal recurrence (within V50/54-60), and out-of-field recurrence (in the brain outside the above areas). In situ recurrence occurred in the internal field group.

DISCUSSION

High-grade glioma, especially glioblastoma, has a poor prognosis, and radiotherapy is an important postoperative treatment. However, there are some differences in the radiotherapy target volume [11]. Whether peritumoral edema should be irradiated has not been determined. Some people believe that peritumoural edema contains dense tumor cells, so it is recommended to include it in the target volume [13]. Korean radiation oncologists from 15 independent institutions outlined clinical target volumes (CTVs) after careful examination of enhanced T1-weighted and T2/FLAIR sequence MR images from nine different cases of glioblastoma. Most of them recommend that peritumoral edema be fully contained within the target volume [14]. It has also been shown that the absence of deliberate edema in the target volume does not result in a different recurrence pattern [15]. There are also some problems in the delineation methods currently recognized and accepted by most radiation oncologists, such as the RTOG and EORTC delineating methods [3, 6]. For example, the RTOG method showed that the high-dose area was larger, especially the "normal" brain tissue outside the peritumoral edema area, which was exposed to an increased range of high-dose or low-dose areas, resulting in increased side effects. In addition, phased irradiation increased the intensity of clinical work. The EORTC method is based on the tumor bed and the residual tumor as the gross tumor volume (GTV), with uniform three-dimensional expansion of 2-3 cm. Most patients have peritumoral edema within the V60 range, but there may be an overinclusion of normal brain tissue and an insufficiency of peritumoral edema. In addition, in clinical practice, it is also common to see some conditions affecting the outlining of the GTV, such as the failure to perform a timely enhanced magnetic resonance scan within 72 hours, resulting in tumor residue, gliosis or injury from surgery that cannot be evaluated; alternatively, if the patient has a long time to start radiotherapy after surgery and if the tumor bed has been deformed, collapsed, or was unevaluable. Studies have also shown that tumor cavity changes during different periods of radiotherapy can reach 1.9-34.4 mm [16]. Sometimes, there may be low-grade tumor components in the edema area, but how can one determine whether it is a low-grade tumor? There is still no unified standard for imaging evaluation. If the tumor bed is simply expanded without complete coverage of the peritumoral edema, omission of the radiotherapy target may occur. The new method recommended in this study takes peritumoural edema as the target volume of the high-dose area, which is simple and easy to achieve in clinical practice, easy to unify the standards, and can avoid the above problems. The external expansion of 0-10 mm around edema acts as a high-risk preventive zone (figure 1e and f), limiting the dose to 50-54 Gy as a buffer to prevent potential radiation omission [17]. On the other hand, it also reduces the target dose in general and plays a role in limiting the low dose zone and average dose in the

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whole brain, thus reducing nerve and vascular injury. In the case shown in the figure, the tumor bed area is small; the peritumoral edema is evenly expanded, without eccentricity of the tumor bed or edema; and the area of edema is large, resulting in the size of the tumor bed expanding 2 cm and peritumoral edema, especially in this study, as the peritumoral edema was basically coincidentally expanded 5 mm. However, clinically, it is more common for us to have a larger tumor bed area and smaller peritumoral edema, which leads to a smaller high-dose area of the delineation method in this study, especially with the 60 Gy area, which is undoubtedly favorable for the protection of normal brain tissue.

Not only the size of the high-dose zone but also the size of the low-dose zone is an important factor affecting the adverse effects of radiation therapy in brain tumor patients. Studies have shown that higher out-of-field doses of radiotherapy for high-grade gliomas may increase radiation-related side effects [18]. Reportedly, the 25 Gy-exposed brain volume is significantly correlated with acute lymphocytopenia and patient survival [19]. Therefore, in addition to the 60 Gy and 46 Gy isodose lines, we also provided 25 Gy isodose lines. The 25 Gy brain volume in this study was also smaller than that of the other two methods (37.2% less than that of the RTOG method and 10.7% less than that of the EORTC method). This also shows that it is important to delineate a prevention area for reducing low-dose volume.

The traditional target delineation method determines the target edge based on the following methods: the T1WI enhanced area is 2–3 cm outside, which is the most densely populated area of tumor cells, usually 60 Gy; the T2WI abnormal signal area, microscopic infiltration area or subclinical focus area or tumor cell low density area, is generally irradiated with 45–50 Gy [20]. An actual retrospective study revealed that 80% of recurrences occurred within 2 cm of the tumor bed. However, some studies have shown that reducing the irradiated field does not increase marginal recurrence, and the recurrence pattern is still mainly in the central or internal field with fewer metastases in the margin or out-of-field [21]. In this retrospective study, we also discussed the recurrence pattern. There were 17 cases of recurrence in the field alone, that is, in the edema area, and these cases accounted for 63% and 81.5% of the cases of recurrence in the internal field with or without margin or out-of-field, respectively; these findings still confirmed past studies and did not increase the proportion of margin or out-of-field recurrence due to the reduction in radiotherapy volume [21]. There was one case (3.7%) of marginal recurrence with intracerebral metastasis and no case of marginal recurrence alone, indicating that the prophylactic dose of 50–54 Gy given outside the edema area did not increase the local failure rate, and such a prophylactic zone could promote an intracerebral dose drop and reduce the volume of the intracerebral low-dose zone.

Previous literature has reported that the median PFS and OS of glioblastoma patients are generally 6-8 months and 12-18 months [2, 6, 12, 22] and 16.7 and 30.4 months, respectively, in patients with DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT)-methylated patients [23]. The OS of patients with anaplastic astrocytoma (WHO Grade III) after treatment is twice as high as that of patients with GBM, usually by 1-2 years [24]. Although astrocytoma WHO grade III-IV patients were included in this study, the survival rate of this group of patients at follow-up was even worse than that of patients with GBM, but the P value was not statistically significant. Neither PFS nor OS significantly decreased and were even greater than those in past studies. At present, the delineation of radiotherapy target volumes for solid tumors in all parts of the body is being reduced, mainly due to advances in systemic therapy, such as targeted therapy and immunotherapy. Systemic treatment of glioma is also progressing gradually [24-26]. Whether to leave room for other treatments or to reduce the neurotoxicity of radiotherapy, we are required to reduce the radiotherapy target volume without affecting the effect. Therefore, this method of target delineation for glioblastoma radiotherapy based on peritumoral edema is a good choice.

Limitations: 1. As in other studies, the identification of peritumoural edema as cytotoxic or angioedema requires an experienced physician, and different physicians may give different definitions of the scope of edema. Postoperative edema needs to be removed when sketched. When postoperative edema is severe, the judgment is not necessarily accurate. 2. In this retrospective study, 18 patients (54.5%) were pathologically diagnosed with WHO Grade III-IV; the lesions could not be completely determined to be glioblastoma, and the diagnosis was based on histological diagnosis and the 2007-2016 World Health Organization Classification of Tumors of the Central Nervous System [27] without providing molecular diagnostic information, such as isocitrate dehydrogenase (IDH), 1p19q, MGMT, epidermal growth factor receptor (EGFR), telomerase reverse transcriptase (TERT), cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B), etc., because most of the patients had incomplete data. This may affect the estimation of prognosis. 3. The delineation method recommended in this study is not suitable for patients with large angioedema caused by surgery. 4. This was a retrospective one-arm study with a small number of patients, and it was adopted when doctors believed that it was difficult to correctly delineate the GTV. As a result, research bias exists, which requires further expansion of the sample size and prospective research for confirmation.

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CONCLUSIONS

Our study provides a target volume delineation scheme for glioblastoma or high-level glioma radiotherapy based on peritumoral edema, which is a good option. Although we cannot prove that this method is superior to current delineation methods, our limited data show that it is not inferior to current mainstream delineation methods.

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Conflicts of interest: The authors declare that they have no competing interests.

Ethical consideration: Approval for the conduct of this retrospective study was obtained from the Ethics Committee of the General Hospital of Northern Theater Command on May 5, 2022, number NO.Y (2020)089. Informed consent was obtained from all subjects and/or their legal guardian(s). All procedures implemented in patients were in accordance with the Declaration of Helsinki. Guidelines for target delineation and detailed information on radiotherapy and chemotherapy in retrospective analyses can be found in the *Protocol* file in the supplemental material. The original data and follow-up information for all 33 patients can be found in the *raw data* file in the Supplementary material.

Authors' contributions: SHH, YX, YS and PZ were mainly responsible for case follow-up and data collation. DFY was responsible for the production of the radiotherapy plan. HBZ and YY TW were responsible for the target volume sketch, manuscript writing and overall planning. All the authors have read and approved the final manuscript.

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