Review Article

Research progress on radiotherapy technology and dose fraction scheme for advanced gliomas

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Abstract: Glioma is the most common central malignant tumor. High-grade glioma (HGG) has high malignancy and a short median survival. Complete surgical resection and comprehensive treatment with postoperative radiotherapy and chemotherapy is the recommended treatment for HGGs at present in clinic. Postoperative radiotherapy can reduce the local recurrence rate and prolong the survival time of patients. In recent years, researchers have made some progress on different radiotherapy technologies and dose fraction schemes. With the continuous development of medical technology, different groups of people should choose different dose fraction schemes, in order to realize the individualization of treatment schemes, and provide more benefits to patients. At present, the optimal radiotherapy dose, the fraction model, and how to achieve individualized radiotherapy remains unclear. In view of the poor prognosis of this disease, patients should be encouraged to participate in properly conducted experimental studies.

Keywords: Glioma; radiotherapy; chemotherapy; malignant tumor; dose splitting strategy

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Introduction

Glioma is the most common intracranial tumor, which accounts for approximately 50% of primary intracranial tumors in adults (1). High-grade gliomas (HGGs, WHO grade III–IV) include anaplastic astrocytoma, anaplastic oligodendrocytoma and glioblastoma (GBM). The annual incidence of HGGs in the world is 6/100,000 (2), these tumors progress, and overall outcomes have not changed much in the past decade. The two most common subtypes of HGGs are anaplastic astrocytoma and GBM, which account for more than 80% of HGGs (3), and the 5-year survival rate is 27% and 5% (4), respectively. Complete surgical resection and comprehensive treatment with postoperative radiotherapy and chemotherapy is the recommended treatment for HGGs at present. The European Organisation for Research and Treatment of Cancer-National Cancer Institute of Canada (EORTC-NCIC) randomized phase III trial published in 2005 confirmed the role of the concomitant and adjuvant addition of temozolomide (TMZ) to radiotherapy (5,6). Radiation therapy occupies an important role in treating gliomas, with the development of new technologies, combination of radiotherapy and multiple imaging modalities will increase the diagnostic accuracy and treatment efficiency of the area at a high-risk of relapse. However, the current situation of

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HGGs therapy faced a choice between efficacy and toxicity. In recent years, researchers have made some progress on different radiotherapy technologies and dose fraction schemes. The present review summarizes the research progress of radiotherapy technology and the dose fraction scheme for HGGs. The details are reported, as follows.

The development and application of radiotherapy technology

Radiotherapy is one of the important treatment methods for HGGs. Radiotherapy performed within 6 weeks after the operation can significantly reduce the local recurrence rate, and prolong the survival of patients (7). With the continuous development of modern radiotherapy technology, radiotherapy regimens for HGG patients have become increasingly accurate, and the clinical effect has also been significantly improved.

Importance of intensity-modulated radiation therapy (IMRT)

With the development of radiotherapy technology, a therapy plan can significantly reduce the radiation dose for normal brain tissues (8,9). At present, IMRT and volumetric modulated arc therapy (VMAT) are the most commonly used radiotherapy technologies for HGGs. IMRT can adjust the output of a standard linear accelerator (LINAC) according to the software, in order to change the radiation intensity across each treatment field. Compared with three-dimensional conformal radiation therapy (3D-CRT), IMRT can increase the target coverage and conformability, reduce the dose of organs at risk, and accordingly reduce adverse reactions (10). Previous studies have revealed that (11-13) patients with HGGs undergoing IMRT presented with low doses in the brain, brainstem and optic chiasm, and a high target coverage, while IMRT did not increase the survival of these patients.

VMAT is one of the IMRTs, in which the radiation source arc rotates around the patient, and emits rays for the radiotherapy. Previous studies have revealed that (14,15) compared with IMRT, VMAT is better in terms of delivery, and the coverage of the target areas of these two are equal. Furthermore, it reduces the machine monitor unit and radiotherapy time, improves the effect and comfort of the treatment. However, there is presently no consensus on which is more advantageous in protecting organs at risk between VMAT and IMRT.

Proton radiotherapy

Proton therapy is a commonly used form of particle therapy. Protons have unique physical properties. The application results of proton therapy for different tumors have been confirmed in phase I and phase II clinical trials (16-18). Compared with photon radiotherapy, the proton has a Bragg peak, a better dose distribution in tumors, a higher biological effect, and a lower dose to normal tissues. Local recurrence is the main failure model of HGGs after treatment, and local treatment, which mainly include a secondary operation and re-radiotherapy, is the main treatment for recurrent patients. However, the treatment effect is poor. Furthermore, it induces many complications after treatment, which affects the quality of life of patients, thereby preventing most patients with postoperative recurrence from obtaining an effective treatment. Verma *et al.* (19) investigated the safety and effectiveness of proton radiotherapy for recurrent patients, and it was suggested that proton radiotherapy can be used as an effective rescue treatment for recurrent patients. However, the late toxicity remains to be investigated. Adeberg *et al.* (20) conducted a study on 66 HGG patients, who were treated with conventional postoperative radiotherapy (50 Gy, 2 Gy/f), and subsequently treated with an added proton dose (an equivalent biological dose of 10 Gy, 2 Gy/f). Compared with the conventional treatment group (60 Gy, 2 Gy/f), the progression-free survival (PFS) and overall survival (OS) were similar. Furthermore, in the proton dosage group, the planning target volume (PTV) was significantly decreased ($P<0.001$), and the third-grade side effect was milder. A study on six centers was conducted by Vora *et al.* (21), which had the largest population on HGG proton radiotherapy. In this study, 63 patients were treated from 2009 to 2017, and these patients were followed up (73% of patients were at WHO grade IV, and 27% of patients were at WHO grade III), with a median follow-up duration of 15 months. Among these patients, 89% of these patients received TMZ chemotherapy during the proton therapy, and the mean dose of the proton radiotherapy was 59.4 GyE (40–66 GyE/15–33 f). Furthermore, the median OS was 18.3 months, the 2-year OS was 39%, and >3 levels of toxicity reaction occurred in three patients. These results reveal that proton

radiotherapy has good tolerance, and its prognosis is similar to that of traditional therapy.

The development of imaging technology and HGG radiotherapy

Malignant glioma has no capsule, and infiltrative growth is one of its characteristics. The growth characteristics of HGGs make it difficult to determine the boundary between the tumor and the normal tissue. Pathology has also confirmed that scattered tumor cells infiltrating along the new blood vessel can be found in the peripheral edema area (22). Magnetic resonance imaging (MRI) is the most commonly used examination method for HGGs. In recent years, MRI technologies, including diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS), have been widely used in HGG radiotherapy. The development of other new examination technologies, such as positron emission tomography (PET), has also brought new progress to the radiotherapy of HGGs.

DWI

DWI reveals lesions by detecting the diffusion of water molecules and the apparent diffusion coefficient (ADC). A literature (23) considered that the lower the ADC value is, the higher the cell density and proliferation activity are. Therefore, areas with a low ADC value have high tumor density and obvious infiltration. Another study (24) revealed that DWI can help to define the boundary of glioma and its surrounding infiltration, and the accuracy of the HGG target delineation can be improved by increasing the dose of the high-risk area, according to the changes in the DWI image and ADC value. Park *et al.* (25) delineated the target areas of HGG patients according to the ADC and MRI-T1. They reported that the dose to the optic nerve and brainstem in the ADC-IMRT plan was reduced by 10% and 16%, respectively.

DTI is one of the DWIs, which can evaluate the structure and physiological state of tissues by detecting the diffusion of water molecules. Anisotropic fraction (FA) is the most commonly used index of DTI. The decrease in FA value reflects the abnormality of white matter tracts. DTI can be used to distinguish between low-grade gliomas and HGGs, and it can also be used to distinguish between gliomas and brain metastasis (26). Jena *et al.* conducted a study (27), in which conventional radiotherapy and a radiotherapy plan with reference to the DTI were compared in HGG patients. The mean PTV of the target area in the DTI radiotherapy plan decreased by 35% (18–46%), and the toxicity in the two groups was similar during the treatment. Therefore, they considered that the application of DTI technology is expected to achieve individualized radiotherapy, and that the curative effect may be more significant. However, further studies are needed to determine how to make it play a better role. In a study conducted by Bian *et al.* (28), the DTI and FA measurement of the bilateral hippocampus were performed on 23 HGG patients before and after the radiotherapy, and the results revealed that after radiotherapy, the FA values of the bilateral hippocampus decreased, and this decrease in FA was prior to the occurrence of cognitive impairment. Therefore, DTI and FA value measurement of the hippocampus may be an effective examination method for radiation-induced neurocognitive impairment.

MRS

MRS is an MRI technology that can reflect the disease situation by detecting the concentration of metabolites in the body. The substances detected by MRS mainly include creatine (Cr), choline (CHO), lipid (LIP), lactic acid (LAC), acetyl aspartic acid (NAA), etc. The CHO signal reflects the formation and change of the cell membrane. NAA is a neural marker, which reflects the integrity of neurons (29). A previous study (30) revealed that compared with normal brain tissues, for HGGs, the CHO value was elevated, but the NAA and Cr values decreased. Furthermore, the sensitivity of MRS to tumor invasion was better, when compared to traditional enhanced MRI. MRS can also be used to distinguish between brain injury and tumor recurrence caused by radiotherapy. A study reported that (31) the sensitivity and specificity of CHO/NAA and NAA/Cr for tumor recurrence were 86% and 90%, and 93% and 70%, respectively. However, further studies are needed to determine how MRS guides radiotherapy and target delineation.

PET/computed tomography (CT)

PET can remedy the shortcomings of MRI and other anatomical images by reflecting the HGG situation from molecular and metabolic aspects. The most commonly used contrast in PET is ^{18}F-fluorodeoxyglucose (^{18}F-FDG). However, due to the high intake of glucose by the brain,

^{18}F-FDG is not sensitive enough to produce the imaging picture of glioma. Other contrasts include amino acids, choline, acetic acid, nucleic acid, neuroreceptors, and amino acids is more commonly used than others. Compared with ^{18}F-FDG, amino acids, including ^{11}C-methionine (^{11}C-MET), O-(2-[^{18}F] fluoroethyl)-L-tyrosine (^{18}F-FET), can show the proliferation and metabolism of the tumors at the metabolic and receptor level, and it's absorbed more in the tumor than normal tissues, thus is better in the imaging of glioma (32). ^{18}F-FET has longer half-life (109.8 min) than ^{11}C-MET, so it's more used in clinic (33-35). Munck *et al.* (36) performed ^{18}F-FET PET and MRI scans on 54 HGG patients, and delineated the target areas. The volume of the target area based on the PET was larger in WHO grade IV patients (P<0.001), but smaller in patients with larger and more complete surgical resections (P=0.004). Therefore, researchers have speculated that target areas based on the PET may benefit patients at grade IV. However, this needs to be verified through a randomized prospective study.

Target volume definition for HGG during initial radiotherapy may yield significantly differing results depending upon the imaging modality. CT and MRI can show bony structure and soft tissue, respectively, and the combination of PET with CT or MRI can better distinguish tumor and normal brain tissue. PET/MRI fusion is more comprehensive than single examination in the diagnosis of glioma (37) and can more accurately define the target area, thereby making the radiotherapy of HGG patients more accurate. Researchers compared the radiotherapy plans of 44 patients with recurrent HGG, and found that the survival time of patients treated with the PET/MRI fusion radiotherapy plan was longer, when compared to patients treated with the CT/MRI radiotherapy plan (9 *vs.* 5 months) (38).

Dose fraction scheme

Fractionated external irradiation is the standard treatment for HGGs. Its survival rate is almost twice as surgery alone (39), but whether and how radiation therapy should be applied depends on characteristics specific to tumor and patient, including age and performance status. The suggested dose for HGGs is 60 Gy/30 f, or 59.4 Gy/33 f; for tumor with larger size or WHO grade III astrocytoma, dose can be decreased to 55.8–59.4 Gy, 1.8 Gy/f, or 57 Gy/30 f. If boost dose is used, radiation dose can be increased by 14 Gy (2.0 Gy/f) or 9–14.4 Gy (1.8 Gy/f) after treatment at 46 Gy (2 Gy/f) or 45–50.4 Gy (1.8 Gy/f) (40). When depicting gross tumor volume (GTV), it's suggested to use MRI T1 enhanced phase and T2 fluid-attenuated inversion recovery (FLAIR) phase. For WHO grade III tumors, clinical target volume (CTV) is 1–2 cm outside GTV, but for GBM, CTV is 2–3 cm outside GTV. However, HGGs have high malignancy and a high postoperative recurrence rate, and 90% occurs within 2 cm of the primary tumor, so it's important to optimize the local radiotherapy (41). Researchers found that when split dose remains the same, increasing total dose does not bring more benefit to patients (42). Therefore, researchers have explored various fraction methods and radiotherapy regimens, including stereotactic radiosurgery (SRS), stereotactic radiotherapy (SRT), hypofractionated radiotherapy (HFRT), simultaneous integrated boost IMRT (SIB-IMRT).

SRS

The radiation sensitivity of HGGs remains unsatisfactory. In theory, it is better to use a large dose. SRS is a single high-dose radiotherapy technology, which is mostly used for small intracranial lesions. In 2004, RTOG9305 published the results of a multicenter randomized controlled trial (43). In this trial, patients with GBM were randomly divided into two groups: one group of patients received conventional radiotherapy (60 Gy/30 f), while the other group of patients received routine external radiation immediately after treatment with SRS (15–24 Gy/f). Patients in both groups were treated with carmustine chemotherapy. The results revealed that there was no significant difference in median survival time. However, this trial was discussed, because SRS was conducted before external radiation, and carmustine was not used as a routine treatment in GBM patients. Some subsequent retrospective studies on SRS revealed that SRS can be used as a safe and effective treatment for HGG patients with small recurrent tumors (44-46). Morris *et al.* (47) reported that 45 patients with recurrent GBM were treated with SRS and bevacizumab. The median tumor volume was 2.2 cm^3, and the average dose of SRS was 17 Gy (13–24 Gy), PFS and OS were 5.2 and 13.3 months after SRS, respectively. Abbassy *et al.* also reported that (48) recurrent GBM patients treated with SRS and bevacizumab, PFS and OS were 7.5 and 13 months, respectively. These studies reveal that SRS is beneficial for increasing the dose of HGG radiotherapy, and provides a new treatment approach for recurrent HGGs. However, in these studies,

the sample sizes were small. The best population to benefit from SRS, the choice of the best dose of treatment, and the determination of when to intervene the SRS needs to be determined through further studies.

SRT

SRT is a non-coplanar, multi-field, 3D and multi-fractionated radiation mode developed on the basis of SRS. SRT is similar to SRS in terms of dose, but the dose gradient is not as large as that of SRS. Therefore, compared to SRS, SRT can be used to treat large tumors and multiple fractionated radiation can also reduce the radiation damage to normal tissues (49). Compared with the conventional treatment regimen, SRT can reduce the treatment time to 2 weeks and the shortened treatment time would significantly improve the quality of life of patients.

The RTOG0023 (50) included 76 patients with GBM, and these patients were treated with conventional fractionated radiotherapy with a total dose of 50 Gy. SRT (5–7 Gy/f) was added weekly during the 3–6 weeks of treatment. The median survival was 12.5 months and had no significant survival benefit when compared with the historical RTOG data. Many studies after RTOG0023 suggest that for relapse and elderly HGG patients, the benefits of SRT would be more significant. Fogh *et al.* investigated (51) the toxicity and efficacy of SRT (35 Gy/10 f, 3.5 Gy/f) in 147 patients with recurrent HGGs. The results revealed that SRT was well-tolerated and the median survival time after SRT was 11 months. Young patients, patients with small GTV sizes, and patients with short intervals between diagnosis and recurrence may have significant survival benefits. SRT is recommended for HGG patients who relapse within 6 months after traditional treatment. RTOG1205 (52) is the first multicenter, randomized controlled phase II clinical trial for recurrent GBM. Patients in this trial were divided into two groups: SRT (35 Gy/10 f, 3.5 Gy/f) + bevacizumab (10 mg/kg, once every 2 weeks) group and bevacizumab alone (10 mg/kg, once every 2 weeks) group. A total of 182 patients were enrolled in this study. There was no significant difference in median survival time between these two groups. In the SRT + bevacizumab group, PFS increased to 6 months (54% *vs.* 29%; HR 0.42, 95% CI: 0.34–0.50, P=0.001).

HFRT

HFRT pertains to the administration of a large fractionated dose in a short time, and a single fractionated dose is greater than 2.5 Gy/f (for example, 60 Gy is fractionated into 15–20 times). HFRT is more frequent, and has fewer single doses, when compared to SRT. Various studies have revealed that elderly patients with GBM can benefit from HFRT. In the Nordic Trail (53), 342 elderly patients were randomly assigned to three groups: TMZ treatment (200 mg/m^2, d1–d5, q28d) group, HFRT (34 Gy/10 f) group, and conventional radiotherapy (60 Gy/30 f) group. The OS of patients in the TMZ group and HFRT group was similar (8.4 *vs.* 7.4 months), and this significantly improved, when compared to that in the conventional radiotherapy group (6 months). This study suggests that conventional radiotherapy is not the best choice for elderly patients, especially for patients >70 years old. Furthermore, TMZ and HFRT should be used as a standard treatment for elderly GBM patients. Biau *et al.* (54) conducted a study on elderly patients with GBM, who were treated with HFRT + TMZ. This study also confirmed that HFRT + TMZ can benefit elderly patients with GBM, and TMZ treatment was recommended, regardless of the methylation of the O^6-methylguanine-DNA-methyltransferase (MGMT). Roa *et al.* (55) conducted a study on 98 GBM patients (aged or frail), who were randomly divided into two groups (25 Gy/5 f and 40 Gy/15 f). The differences in OS, PFS and quality of life between these two groups were not statistically significant. The median survival time was 7.9 and 6.4 months, respectively. Considering the treatment time, the 25 Gy/5 f regimen was preferred. In the EORTC/NCIC/Trans-Tasman Radiation Oncology Group (TROG) phase III clinical trial (56), 562 GBM patients (over 65 years old) were randomly divided into two groups: HFRT (40 Gy/15 f) group and HFRT + TMZ group. The OS of patients in these two groups was 7.6 and 9.3 months, respectively, and the PFS was 3.9 and 5.3 months, respectively. The differences were statistically significant. This study concluded that HFRT combined with TMZ can be recommended as a standard treatment for new GBM in the elderly.

SIB

Glioma has the characteristics of recurrence *in situ*, and its local recurrence is closely correlated to the survival of HGG patients (10). SIB-IMRT can irradiate different doses to different targets at the same time without increasing the toxicity to normal tissues (57). Cho *et al.* (58) treated 40 HGG patients with SIB-IMRT. The PTV dose per time

was 2.0 Gy, the planning gross tumor volume (PGTV) dose per time was 2.4 Gy, a total of 25 times of treatment was given. The median survival time was 14.8 months. It has been proven that SIB-IMRT is safe and feasible, and that its survival is equivalent to that of traditional radiotherapy. However, the best fractionated dose and its effect still needs to be further explored. Some scholars (59) have studied the maximum tolerable dose of SIB in HGG patients. The dose for PTV1 (operated cavity and residual tumor) started from 2.8 Gy, and was increased in each group by 0.4 Gy, in order to carry out a dose climbing test. A total of 20 f was set. PTV2 (PTV1 + 2 cm) was given at 2.5 Gy at a time, for a total dose of 50 Gy, TMZ was concurrently given during the treatment. The results reveal that the maximum single-tolerance dose of SIB when combined with TMZ was 3.6 Gy/f (72 Gy/20 f), and that the median OS and PFS were 19 and 16 months, respectively. In the phase II clinical study conducted by Mallick *et al.* (60), 89 GBM patients, who were treated from 2011 to 2017, were randomly divided into two groups: traditional radiotherapy group (60 Gy/30 f) and SIB group. In the SIB group, a single dose per time was 3 Gy for high-risk PTV and 2.5 Gy for low-risk PTV, and a total of 20 fractions were given. The median OS of patients in the two groups was similar (18.07 *vs.* 25.18 months, P=0.3), patients <40 years old with complete resection and isocitrate dehydrogenase 1 (IDH1) mutation had better OS. After 2 years, 60% of patients in the SIB group survived, while merely 24% of patients in the traditional radiotherapy group survived. After 2 years, 30% of patients in the SIB group did not progress, while patients in traditional treatment group all progressed. In an ongoing phase III clinical trial (61), GBM patients were divided into two groups: conventional STUPP treatment group and SIB radiotherapy combined with TMZ group. In the SIB group, the target area was delineated according to MRS. When CHO/NAA was >2, the dose for the operated cavity and MR-enhanced area were simultaneously added. The single dose was 2.4 Gy, and the total dose was 72 Gy (30 fractions). These results were as expected.

Biomarkers

Prognosis of HGG is related to many factors, including age, surgery, Karnofsky Performance Scale (KPS) score and pathology results. Detection of biomarkers can provide more information (62,63). MGMT is very important in the decision of treatment regimen. MGMT is a DNA modification enzyme; methylation of its promoter can decrease its expression; thus, DNA reparation will be prevented, and the tumor will become sensitive to chemotherapy. Hegi *et al.* found that methylation of its promoter in patients can lead to better treatment results and prognosis of TMZ (64). Patients with IDH1/2 mutation usually also have MGMT promoter methylation (65-67). ATRX (α thalassemia/mental retardation syndrome X-linked) mutation is the biomarker of neuroastrocytoma; patients with this mutation have better prognosis. Other biomarkers include telomerase reverse transcriptase (TERT) mutation, epithelial growth factor receptor (EGFR) mutation, P53 mutation, and all have diagnosis values.

Radiation toxicity

Radiation toxicity include early and late stage toxicity, the former being reversible, which the latter being irreversible. Radiation will kill the newborn neuros, causing the loss of brain functions. Early toxicity of fractionated external irradiation include fatigue, anorexia, dermatitis, cephalgia, nausea. Late effects include radiation necrosis, neuroendocrine dysfunction, cognition disorders (68). Precise radiation has greatly decreased the occurrence of radiation toxicity after HGGs. The factors that can affect radiation toxicity include the volume of normal tissues that are involved in the radiation, total dose and fraction methods, tolerance of the patients, etc. HGG patients have a short median survival and high rate of recurrence at the original site. Many of the therapeutic strategies tend to increase the radiation dose to the target therefore increased the risk of radiation damage to the nearby normal brain structures, which would be associated with toxicity or even shortened survival (69-73).

Summary

HGGs are common central malignant tumors in clinic, which have the characteristics of high malignancy, short median survival time and high recurrence rate. Surgery, radiation, and chemotherapy remain the standard treatment options for patients with HGGs. With the continuous development and innovation of medical technology in recent years, the clinical treatment of HGGs has made some progress. Different groups of people should choose different dose fraction schemes, in order to realize the

individualization of treatment schemes, and provide more benefits to patients. For older patients, preliminary data suggest that using a shorter course of radiotherapy may benefit. For HGG patients, it is feasible to integrate different imagings, such as PET and MRI, with precise radiotherapy planning. At present, the optimal radiotherapy dose, the fraction model, and how to achieve individualized radiotherapy remains unclear. Hence, further research is still needed. In view of the poor prognosis of this disease, patients should be encouraged to participate in properly conducted experimental studies.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1891). The authors have no conflicts of interest to declare.

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