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ORIGINAL ARTICLE

Acute radiation toxicity in glioblastoma patients undergoing hypofractionated radiotherapy

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Summary

Introduction. Hypofractionated radiotherapy is the preferred regimen for older patients with glioblastoma and those with poor prognostic factors. Acute radiation toxicity remains a concern in these cases.

Aim. We conducted a retrospective analysis aiming to show the acute toxicity profile in patients with glioblastoma treated with hypofractionated radiotherapy, with or without temozolomide.

Material and Methods. This study included 25 patients with diagnosed glioblastoma who underwent a hypofractionated regimen of radiotherapy, with a dose of 40 Gy in 15 fractions or 34 Gy in 10 fractions. Acute radiation toxicity was observed during the treatment and graded according to Common Terminology Criteria for Adverse Events, version 5.0.

Results. Radiation toxicity was found in 60% of the patients. The majority of the patients with toxicity (80%) had toxicity grade 1. Fatigue was the most common grade 1 toxicity that was observed. One patient (6.7%) exhibited grade 3 radiation toxicity (somnolence and worsening of existing neurological condition). No patients had grade 4 radiation toxicity. A statistically significantly higher number of patients who experienced radiotoxicity were predominantly distributed in the group with tumors located in more than one lobe, multifocal or multicentric tumor compared to patients who had a tumor in one lobe ($p < 0.01$).

Conclusions. A hypofractionated regimen of radiotherapy represents a favorable option for the treatment of older patients with glioblastoma or those with poor prognosis, with an acceptable acute radiation toxicity profile.

Keywords: glioblastoma, hypofractionated radiotherapy, acute toxicity

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INTRODUCTION

Since 2005, the standard postoperative treatment for patients with glioblastoma has included concomitant radiotherapy (RT) with temozolomide (TMZ) and adjuvant TMZ, up to 6 cycles (1). Conventional fractionation implies prescribing a radiotherapy dose of 60 Gy in 30 fractions (1). For patients aged ≥ 65-70 years with poor performance status (Eastern Cooperative Oncology Group, ECOG, Performance Status 3 and 4) and with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter, hypofractionated radiotherapy is the preferred regimen (2–4). According to the European Society for Radiotherapy and Oncology and Advisory Committee on Radiation Oncology Practice guideline (ESTRO-ACROP) from 2016 and, guideline ESTRO and European Association of Neuro-Oncology (EANO) (ESTRO-EANO) from 2023, the most recommended radiotherapy dose in the hypofractionated regimen for glioblastoma patients is 40.05 Gy in 15 fractions (3,4). Nevertheless, 34 Gy in 10 fractions and 25 Gy in 5 fractions could be alternative hypofractionated schemes in some cases (3,4). Hypofractionated radiotherapy regimens are recommended for different groups of patients. A recent study investigated a moderately hypofractionated radiation therapy regimen in younger patients with good performance status, with a dose of 50 Gy in 20 fractions (5).

Delineation of the target volumes for hypofractionated radiotherapy should not be different from target volume delineation in those patients with conventional fractionation (3). Radiotherapy can be planned using 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or volumetric-modulated arc therapy (VMAT) (3).

Acute toxicity of the radiation treatment with or without chemotherapy with temozolomide could have a deleterious effect on the quality of life of some patients, and even pause or stop the treatment (6). However, in patients with glioblastoma and other high-grade gliomas, there is not much data about the toxicity profile of the hypofractionated regimen of radiotherapy. Even when there are data, they are poorly described (5). Although the brain is considered late-responding tissue with regard to radiotherapy effects, brain edema is one of the acute radiation toxicities (7) causing different symptoms, especially during hypofractionated radiotherapy (7,8).

This study aims to show the radiation toxicity profile in patients with glioblastoma who underwent hypofractionated radiotherapy with or without temozolomide.

MATERIAL AND METHODS

This retrospective study included 25 patients with histopathology-confirmed glioblastoma, (*isocitrate dehydrogenase*) IDH-*wild type* CNS WHO grade 4, treated with radiotherapy at the Institute for Oncology and Radiology of Serbia and/or with chemotherapy with TMZ at the Institute for Oncology and Radiology of Serbia and Clinic for Neurosurgery, University Clinical Center of Serbia, in the period 2023-2024. All data were obtained from medical records at the Institute for Oncology and Radiology of Serbia. The study was approved by the Ethical Research Committee of the Institute for Oncology and Radiology of Serbia, No 01-1/2024/1188.

All patients in the study underwent hypofractionated radiotherapy, with a total dose of 40.05 Gy in 15 fractions or 34 Gy in 10 fractions. Radiotherapy was planned with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) **(Figure 1)**.

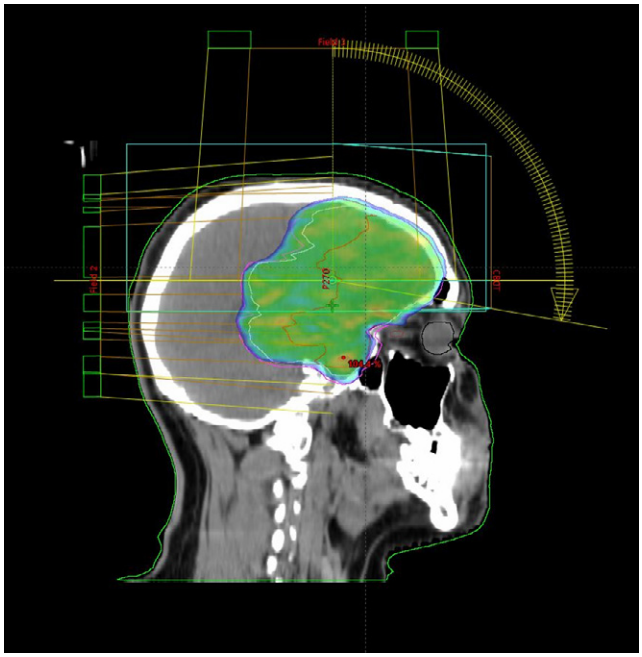

Figure 1. Volumetric modulated arc therapy (VMAT) in patients with glioblastoma treated with a hypofractionated regimen of radiotherapy. The green color in the brain represents 95% of the isodose distribution. The red color inside the green color represents gross tumor volume (GTV), the yellow color represents a margin of the clinical target volume (CTV), and the pink color represents a margin of planning target volume (PTV); a line with divisions and a triangle at the end (arc) of the line VMAT technique and radiation fields (Material from the Institute for Oncology and Radiology of Serbia).

Delineation of the target volumes was contoured according to ESTRO-ACROP guidelines for target delineation of glioblastomas. Patients who were eligible for chemotherapy (patients aged 18-75, ECOG PS < 3, with normal hematological, hepatic, and renal function) were prescribed temozolomide according to the protocol.

Patients were followed minimum once a week during the treatment. Acute radiation toxicity that was observed in patients during the treatment included fatigue, headache, worsening of existing neurological conditions, seizures, somnolence, and confusion. Radiation toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (9). Patients with

hematological toxicity and nausea were not included in this retrospective study. As the assessment of acute radiation toxicity of hypofractionated radiotherapy was our primary goal, we did not assess the overall survival of our patients.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 29.0 (IBM Corporation, Armonk, NY, USA) statistical software. Regarding descriptive statistics, measures of central tendency were used. Categorical data were analyzed using the Chi-square test, and Student's t-test was used for numerical data. P value < 0.05 was considered statistically significant.

RESULTS

Out of 25 patients included in the study, 60% were male. The mean age was 68.1 ± 8.8 years. Fifteen patients (60%) had multifocal, multicentric tumors, or tumor foci in more than one brain lobe. The majority of the patients (92%) included in the study underwent surgical resection (supramaximal resection, total resection, near-total resection, subtotal resection, or partial resection), while 8% of the patients underwent only tumor biopsy. More than half of the patients (56%) had tumor recurrence and/or remaining tumor before radiotherapy. 56% of the patients had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score 1, while 44% of the patients had ECOG PS scores 2 and 3. More than two-thirds of the patients (64%) had multiple comorbidities. Radiation toxicity was experienced in 15 patients (60%), while 80%

Table 1. Patient's clinical characteristics and demographic data

	Frequency (percent) of patients/mean ± standard deviation
Sex	
Male	15 (60%)
Female	10 (40%)
Age	68.1 ± 8.8*
Histopathology	
Glioblastoma, IDH-wild type CNS WHO grade 4	25 (100%)
Tumor site	
1 lobe	10 (40%)
> 1 lobe, multifocal or multicentric	15 (60%)
Surgical treatment	23 (92%)
Biopsy	2 (8%)
Tumor recurrence and/or tumor remaining	14 (56%)
ECOG PS**	
1	14 (56%)
2	8 (32%)
3	3 (12%)
Comorbidity	
1	9 (36%)
≥ 2	16 (64%)
Radiotherapy dose	
40.05 Gy/15 fractions	24 (96%)
34 Gy/10 fractions	1 (4%)
Concurrent TMZ***	15 (60%)
Radiation toxicity	15 (60%)
Grade of radiation toxicity	
1	12 (80%)
2	2 (13.3%)
3	1 (6.7%)

*Age at diagnosis was presented as means ± standard deviation
** ECOG PS - Eastern Cooperative Oncology Group Performance Status
***TMZ - Temozolomide

Table 2. Clinical characteristics of patients with glioblastoma treated with hypofractionated radiotherapy in relation to radiation toxicity

	Radiation toxicity	*p* value
Age		
< 70	7 (46.7%)	0.742
≥ 70	8 (53.3%)	
Tumor remaining/recurrence of the tumor		
No	6 (40%)	0.622
Yes	9 (60%)	
ECOG PS*		
1	7 (46.7%)	0.250
≥ 2	8 (53.3%)	
Tumor site		
1 lobe	3 (20%)	**0.01**
≥ 2 lobes, multifocal/ multicentric tumor	12 (80%)	
Comorbidities		
0, 1	5 (33.3%)	0.734
≥ 2	10 (66.7%)	
	15 (100%)	

* ECOG PS - Eastern Cooperative Oncology Group Performance Status

of the patients with toxicity had toxicity grade 1. The most common grade 1 toxicity observed was fatigue, followed by headache. One patient (6.7%) exhibited grade 3 radiation toxicity in the group with toxicity. This patient experienced grade 3 somnolence, as well as worsening of existing neurological condition. No patients had grade 4 radiation toxicity. Complete patients' clinical characteristics and demographic data are presented in **Table 1.**

We also analyzed whether sex, age (< 70 and ≥ 70), tumor recurrence and the tumor remaining, ECOG PS (1 and ≥ 2), tumor site (1 lobe and more than 1 lobe, multifocal/multicentric tumor) and comorbidities (without comorbidity or 1 comorbidity and ≥ 2 comorbidities) are associated with radiation toxicity. We did not find statistical significance for observed data, except for the tumor site. A statistically significantly higher number of patients who experienced radiotoxicity were predominantly distributed in the group with tumors located in more than 1 lobe, multifocal or multicentric tumor (80%) compared to patients who had a tumor in one lobe (20%) (**p < 0.01**) **(Table 2)**.

DISCUSSION

A hypofractionated regimen of radiation therapy is usually the recommended treatment for patients with glioblastoma and those with bad ECOG or Karnofsky performance status, poor prognosis, and/or for older patients. Given that older patients with glioblastoma tolerate the treatment less effectively compared to younger patients (6), many hypofractionated regimens have been recommended as a standard treatment for these patients. One of the concerns during hypofractionated regimens is acute and late toxicity. In a meta-analysis published in 2017, Liao et al. reported that patients older than 70 years treated with hypofractionated radiotherapy had better overall survival (OS) rates than patients treated with standard (conventional) fractionation, and the toxicity profile was similar between the groups (10). In our study, 15 patients (60%) experienced toxicity. Most of our patients experiencing toxicity (80%) had grade 1 toxicity, while toxicity grade 2 was observed in 13.3% of the patients and grade 3 in 6.7%. All of our patients received uninterrupted treatment. Brandes et al. reported that 25% of the patients treated with standard radiotherapy and concurrent and adjuvant temozolomide experienced mental deterioration. However, mental deterioration was observed immediately after completing concomitant treatment and six months after the treatment. No strictly acute radiation toxicity was observed and reported in these patients (6). Out of 15 patients with glioblastoma with poor prognostic factors included in the study, Jablonska et al. stated that grade 2 acute toxicities were observed in 3 patients during the treatment with hypofractionated radiotherapy and concomitant TMZ (11). The authors reported perilesional brain edema, hematological toxicity, anorexia, and asthenia as observed toxicities (11). These toxicities could be a consequence of concurrent treatment, as all patients in their study had concurrent treatment, while in our study 40% of the patients did not have concurrent treatment. In general, during concurrent treatment, there

can be no clear indication of whether a certain symptom is a result of a single treatment. Nevertheless, hematological toxicity can be related mostly to temozolomide and antiepileptic drugs (12,13).

Primarily, a hypofractionated regimen of radiation therapy may cause toxicity in the late-responding neural tissue (14). However, possible acute radiation toxicity should not be neglected. Radiation brain injury could be explained by processes such as blood-brain barrier breakage, neural progenitor cell death, and astrocyte senescence, leading to a neuroinflammation cascade and causing multiple symptoms and clinical signs (15).

Chang et al. investigated the outcomes of patients with glioblastoma treated with hypofractionated radiotherapy (16). The authors did not report significant acute toxicity in the observed group of patients (16). They assessed acute toxicity according to the daily dosage of corticosteroid therapy, and a median dose of dexamethasone was 16 mg per day. In our study, acute toxicity was not assessed according to the usage of the steroids. Rather, acute toxicity was assessed during the treatment and graded according to CTCAE, version 5.0. Nevertheless, in their study, the hypofractionated regimen involved a radiotherapy dose of 50 Gy in 20 fractions (2,5 Gy per day), and the radiotherapy was carried out in two phases, which differs from our study. In our study, radiotherapy was carried out in a single phase, and the daily radiation dose per fraction was slightly higher (2.67 Gy/day in twenty-four patients, and 3.4 Gy/day in one patient). A higher daily dose could potentially increase acute radiation toxicity. Steroids are often prescribed in patients receiving whole-brain radiotherapy (WBRT) or partial brain radiotherapy for primary brain tumors. The important question arises whether all patients undergoing hypofractionated radiotherapy should receive steroids in advance, even before starting radiation. The above-mentioned study reported no significant acute toxicity during radiotherapy (16), but in our study, most of the patients had grade 1 toxicity (80%) and steroids were prescribed individually. Marantidou et al. concluded that in patients with malignant glioma, bad performance status at the beginning of radiation therapy, and unresected tumors are the predictive factors of steroid use (17).

Older age (18) and poor performance status are recognized as factors for increased toxicity in patients who underwent chemoradiotherapy (19). Concerns for increased toxicity in older patients with glioblastoma are multiple comorbidities and different geriatric conditions, such as malnutrition (20). Furthermore, we analyzed whether clinical and demographic characteristics had an impact on acute radiation toxicity. Comparing the two groups, with and without tumor recurrence and the remaining tumor, there was no significant difference in occurrence of toxicity. Similarly, we did not find any statistically significant differences when comparing age, ECOG performance status, and comorbidities between the groups regarding occurrence of toxicity. However, patients with tumors extended in more than one lobe, and those with multifocal and multicentric tumors, experienced toxicity significantly more than patients with tumors located in one brain lobe. Treatment volumes and irradiated volumes could have a significant influence on the toxicity profile. Larger treatment volumes carry a higher risk of toxicity and radiotherapy-induced edema (7), and poor tolerance to the treatment. Brain tolerance to ionizing radiation is directly related to the radiation volume and the radiation dose (21). The blood-brain barrier disruption could cause acute leukoencephalopathy which is manifested by symptoms such as fatigue and headache (17). In addition to tumor cells, in tumors, there are numerous components such as immune cells, blood vessels, and metabolites (22). After radiation, the microenvironment can change, and proinflammatory cytokines are released, even from dying tumor cells (22). Proinflammatory mediators such as Interleukin-1, Interleukin-6, Tumor Necrosis Factor-α, and Transforming Growth Factor-β are observed after exposure to ionizing radiation in several organs, including the brain (21). It should be noted that patients with glioblastoma who receive temozolomide, may experience increased acute radiation toxicity. One reason is that temozolomide, in addition to its other mechanisms of action, acts as a radiosensitizing agent on glioma cells and fibroblasts (23). Additionally, worsening of neurological conditions of the patients, seizures and other symptoms may happen independently of radiation therapy. Tumor progression and neurological damage can also cause a patient's bad condition during the treatment, which can be difficult to assess.

Several ongoing research initiatives aim to investigate further hypofractionation schemes in glioblastoma driven by the belief in the positive radiobiological effect of hypofractionation in glioblastoma, such as overcoming the radioresistance of glioblastoma cells and reduced toxicity. FLASH radiotherapy, with an ultra-high dose rate (more than 40 Gy per second), is one of the possible future treatments (24). FLASH radiotherapy was investigated on animal models (mice) with glioblastoma, and the authors reported that FLASH radiotherapy with hypofractionated regimens can reduce neurotoxicity (25).

Limitations

Our study has a few limitations. First of all, it is a retrospective study. We believe that by conducting a prospective study more precise data could be obtained. Also, we observed 25 patients treated with hypofractionated therapy with or without temozolomide. With a larger number of patients, the study results would be stronger. Considering acute toxicity, we tried to focus on and observe symptoms and signs that were more related to radiotherapy. We did not include patients who had any hematological toxicity. However, temozolomide is a radiosensitizing

agent, so we cannot claim that all observed toxicity is associated with radiotherapy only.

CONCLUSIONS

A hypofractionated regimen of radiotherapy represents a favorable option for the treatment of older patients with glioblastoma or those with poor prognostic features. Acute toxicity of the hypofractionated regimen in our study was acceptable and did not require pausing or stopping the treatment. Since there are no clear recommendations for steroid use during hypofractionated radiotherapy, this study opens new questions about steroid use and steroid dosage in these patients. We encourage other researchers to further investigate hypofractionated radiotherapy and proper supportive therapy in patients with glioblastoma.

Conflicts of interest: None to declare.

Author contribution: Aleksandar Stepanović, Marina Nikitović, and Tatjana Arsenijević contributed to the conception and design of the work; Aleksandar Stepanović, Aleksandar Tomašević and Katarina Kopčalić contributed to the acquisition, analysis and interpretation of data; Aleksandar Stepanović, Ivan Bogdanović, and Bojana Poparić-Banđur contributed to the conception and design of the manuscript and preparation of the draft of the manuscript.

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AKUTNA RADIJACIONA TOKSIČNOST KOD PACIJENATA SA GLIOBLASTOMOM KOJI SU LEČENI HIPOFRAKCIONISANOM RADIOTERAPIJOM

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Sažetak

Uvod. Hipofrakcionisana radioterapija je preporučeni režim radioterapije za starije pacijente sa glioblastomom, kao i za pacijente sa nepovoljnim prognostičkim faktorima. Pojava akutne radijacione toksičnosti je jedna od dilema kod primene hipofrakcionisanog režima radioterapije.

Cilj. Sproveli smo ovu retrospektivnu studiju sa ciljem da prikažemo profil akutne toksičnosti kod pacijenata sa glioblastomom lečenih hipofrakcionisanim režimom radioterapije, sa ili bez primene temozolomida.

Materijal i metode. Ova studija je obuhvatila 25 pacijenata sa dijagnostikovanim glioblastomom koji su bili lečeni hipofrakcionisanom radioterapijom, sa ukupnom dozom od 40 Gy u 15 frakcija ili 34 Gy u 10 frakcija. Akutna radijaciona toksičnost koja je zabeležena tokom tretmana, gradirana je prema *Common Terminology Criteria for Adverse Events, version 5.0*.

Rezultati. Akutna radijaciona toksičnost je zabeležena kod 60% pacijenata. Većina pacijenata sa toksičnošću (80%) imala je gradus 1 toksičnosti. Najčešća toksičnost gradusa 1 koju su pacijenti imali bio je zamor. Jedan pacijent (6,7%) je imao radijacionu toksičnost gradusa 3 (somnolenciju i pogoršanje postojećeg neurološkog deficita). Nije zabeležena radijaciona toksičnost gradusa 4. Statistički značajno veći broj pacijenata koji su imali radiotoksičnost bili su raspoređeni u grupi pacijenata koji su imali tumor u više od jednog moždanog režnja, multifokalni ili multicentrični tumor, u poređenju sa pacijentima koji su imali tumor u jednom moždanom režnju ($p < 0.01$).

Zaključci. Hipofrakcionisani režim radioterapije predstavlja povoljnu opciju za lečenje starijih pacijenata sa glioblastomom ili onih pacijenata sa lošom prognozom, sa prihvatljivim profilom akutne radijacione toksičnosti.

Ključne reči: glioblastom, hipofrakcionisana radioterapija, akutna toksičnost

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