Abstract

Gliomas, representing the most common primary brain tumors, derive from cells resembling the CNS’s normal glial components—astrocytes, oligodendrocytes, and ependymal cells. Notably, these tumors vary significantly in their biological aggressiveness. In this context, we explore the challenging journey of a 47-year-old man first diagnosed in 2007 with a grade III anaplastic oligoastrocytoma located in the frontal region. Initial treatment involved surgical resection, but unfortunately the tumor recurred locally four years later. A second surgery achieved complete removal, but histopathological findings confirmed the continued presence of grade III oligoastrocytoma. Following surgery, the patient received two cycles of adjuvant temozolomide chemotherapy. Considering the aggressive nature of the tumor, his age, and existing comorbidities, a combined approach of radiochemotherapy was subsequently adopted, followed by additional adjuvant chemotherapy. However, in 2023, he faced another setback—a second relapse. Subsequent surgical and histopathological evaluations disclosed a progression to grade IV astrocytoma. Postoperative treatment included six weeks of intensive concurrent radiochemotherapy. After completing this phase, he proceeded with ongoing chemotherapy, complemented by regular monitoring through serial brain MRIs. This case underscores the complexity and dynamism of glioma management and illustrates the critical need for tailored therapeutic strategies.

Keywords: glioma, brain tumor, radiotherapy, chemotherapy, recurrence

1. Introduction

Gliomas are the most prevalent type of primary tumors in the central nervous system (CNS). These tumors share histologic features with normal glial cells, such as astrocytes, oligodendrocytes, and ependymal cells, and each type displays a variable range of biological aggressiveness.

Traditionally, the World Health Organization (WHO) classified gliomas into “low-grade gliomas” (grades 1 and 2) and “high-grade gliomas” (grades 3 and 4). However, the WHO now advises against these broad terms, as they encompass diverse tumors with significantly different biological behaviors, prognoses, and treatment responses (1). Grade 4 gliomas, the most common malignant brain...
tumors in adults, are particularly aggressive and invasive, exhibiting high inter- and intra-tumoral heterogeneity (1). These tumors typically arise de novo without evidence of a lower-grade precursor. In 2021, the WHO updated its CNS tumor classification to better reflect these distinctions.

Glioblastomas, the most common type of primary malignant brain tumor in adults, account for about 48.6% of malignant brain and other CNS tumors. The median survival for glioblastoma patients is approximately 15 months, with a 5-year survival rate of less than 10% (3). For patients experiencing tumor recurrence, therapeutic options are limited, and the median overall survival after disease progression is approximately 8 months. This poor prognosis is partly due to the molecular and cellular heterogeneity among tumors, which current therapies do not adequately address. This heterogeneity is likely even more pronounced in recurrent gliomas. Modern therapeutic approaches primarily rely on molecular profiling of tumors, but they often fail short in accurately predicting therapy response.

2. Case report

A 47-year-old man initially presented in 2007 at the Oncology Institute “Prof. Dr. Ion Chiricuta” Cluj-Napoca with a diagnosis of right frontal lobe grade III oligoastrocytoma. He underwent a surgical excision, and no further oncological intervention was advised at that time.

Four years subsequent to the initial treatment, the patient demonstrated a local recurrence. A complete surgical resection was performed, confirming a persistent grade III oligoastrocytoma. Postoperatively, the patient received two cycles of Temozolomide chemotherapy (320 mg/day and 400 mg/day D1-5, q28). Subsequently, age-appropriate conformal radiotherapy was initiated alongside chemotherapy with Temozolomide 75 mg/m²/day (150 mg/day). Additionally, anticonvulsant therapy was commenced as per neurosurgical recommendation. External beam radiation therapy was administered to the tumor bed (TD=60 Gy over 52 days in 30 fractions), which extended over seven weeks due to a technical complication with the linear accelerator. Throughout this period, the patient exhibited no neurological deterioration or signs of intracranial hypertension, and routine laboratory assessments remained within normal limits. After radiochemotherapy, two additional cycles of chemotherapy with Temozolomide were administered at doses of 150 mg/m² (TD=300 mg/day D1-5, q28) and 200 mg/m² (TD=400 mg/day D1-5, q28).

In 2023, the patient experienced another recurrence, this time classified as a grade IV astrocytoma (IDH-mutant grade IV tumor) according to the 2021 WHO classification of brain tumors. Upon re-evaluation in July 2023, concurrent radiochemotherapy was considered the most appropriate treatment approach. Clinically, the patient was completely conscious and oriented X3, with minor neurological impairments, including gait instability, bradypsychia, and bradylalia, though biological parameters remained stable.

Subsequent treatment consisted of external beam radiation therapy employing the VMAT technique at dosages of TD=45 Gy over 25 fractions at the right fronto-temporal level and TD=59.4 Gy over 33 fractions/45 days at the tumor bed. Concurrent chemotherapy included Temozolomide at 75 mg/m², TD=150 mg. The treatment was well tolerated without any acute toxicities or interruptions. The treatment regimen was continued with Temozolomide at increased doses of 150 mg/m² (TD=300 mg/day, D1-5, q28) and subsequently 200 mg/m² (TD=400 mg/day, D1-5, q28), both of which were well tolerated by the patient.

A follow-up brain MRI conducted three months post-treatment displayed no tumor progression and a reduction in the brain edema. (Fig. 3)
Figure 1. Brain MRI before chemoradiation, T1 with contrast

Figure 2. Brain MRI before chemoradiation, T1 with contrast

Figure 3. Brain MRI after chemoradiation, section T1 with contrast
Figure 4. Treatment planning system images

Figure 5. Dose-volume histogram

Figure 6. Treatment planning system images
3. Discussion

The case presented here has several notable aspects. First, the aggressive nature of malignant brain tumors is associated with a poor prognosis, with the median survival of patients diagnosed with grade IV gliomas being approximately 15-20 months from the date of diagnosis. Our patient was first diagnosed with a malignant brain tumor in 2007. Despite multiple relapses and the eventual diagnosis of grade IV glioma, he continues chemotherapy to this day. Secondly, despite numerous surgeries and two courses of full-dose irradiation, the patient remains conscious and oriented temporally and spatially, with minimal cognitive and neurological impairment. Although the patient did not undergo specialized neurocognitive tests after completing the radiochemotherapy course, no significant cognitive deficits were detected during periodic oncological follow-ups. He presents with only minor neurological symptoms, including gait impairment, bradypsychia, and bradylalia.

When treating a patient with radiation therapy, the delivered dose is constrained by the surrounding normal tissues, known as organs at risk (OARs). In this case, it was essential to spare several critical organs, including the brainstem and the optic structures (optic nerves, optic chiasm, and optic tracts). During the initial course of radiation therapy, which employed 3D Conformal techniques, the dose delivered to these organs was significant. Unfortunately, due to technical issues, recovering data on the delivered dose to the brainstem and other critical OARs from 2011 was not possible.

Advancements in radiation technology now allow for the precise targeting of tumors, thereby reducing doses to critical organs at risk (OARs), though these organs still present considerable challenges. In the case discussed the patient has undergone two courses of high-dose radiation with minimal impact on the critical organs thus far. Continuous surveillance is maintained to monitor any long-term adverse effects that may arise from the radiation therapy.

A 2018 study shed light on re-irradiation strategies for recurrent brain tumors, specifically examining the roles of stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT) as salvage treatments for high-grade gliomas. Utilizing linear accelerator (LINAC)-based techniques for radiosurgery and fractionated therapy, the study found that SRS and fSRT are safe feasible and effective options for managing recurrent high-grade gliomas. Furthermore, it highlighted that the treatment volume could indicate local control in these challenging salvage scenarios.

From 2010 to 2017, 25 patients aged 23-74 were re-irradiated with LINAC-based SRS and fSRT, receiving a median dose of 25 Gy in 5 fractions. After the initial diagnosis, the median overall survival (OS) was 39 months, with 1-, 3-, and 5-year OS rates of 88%, 56%, and 30%, respectively. After treatment with SRS or fSRT, the median OS was 9 months with a 1-year OS rate of 29%. Local control was assessed in 28 tumors, with rates of 57% at 6 months and 39% at 1 year. Three patients experienced local failure. No evidence of toxicity was observed following SRS or fSRT during the follow-up period (1). In this patient's case, however, the re-irradiation volume was large (see Figures 1 and 2), making him unsuitable for SRS or fSRT.

Vascular damage following radiation therapy induces high levels of vascular endothelial growth factor (VEGF) expression, a key mechanism in the development of radiation-induced brain necrosis. Bevacizumab alleviates symptoms of brain edema caused by radiation-induced brain necrosis by inhibiting VEGF and acting on the vascular tissue surrounding the necrotic area. Numerous studies have confirmed that bevacizumab effectively relieves symptoms of brain necrosis, improves patients' Karnofsky performance status (KPS) scores, and enhances brain necrosis imaging. However, necrosis is irreversible, and hypoxia and ischemia localized in the necrotic area can lead to recurrent radiation brain necrosis after bevacizumab is discontinued (5). Bevacizumab has also been used in other neuro-oncology settings, including concurrent administration with re-irradiation for recurrent high-grade gliomas (HGG) (6). In this patient's
case, however, bevacizumab was not administered during re-irradiation.

The two relapses present in this patient, highlight the need for a functional phenotypic profile of the tumor and genomic analyses, which can facilitate personalized treatment and improve response rates. Given the poor survival outcomes with currently approved treatments for grade IV gliomas, new therapeutic strategies are urgently needed. Genetic and epigenetic profiling of these tumors and description of interactions within the brain microenvironment with the immune system have lead to several novel interventions that are currently explored in clinical trials. Immunotherapy approaches, including immune checkpoint blockade, chimeric antigen receptor T (CAR T) cell therapy, oncolytic virotherapy, and vaccine therapy, have shown potential to improve outcomes for glioblastoma multiforme (GBM) in selected patients. Ongoing studies are exploring combined therapies to minimize adverse side effects and enhance antitumor immune responses. Additionally, clinical trials are testing techniques to overcome the blood-brain barrier for targeted delivery in patients with recurrent high-grade gliomas (7).

Abbreviations
CNS – central nervous system
MRI – magnetic resonance imaging
WHO – World Health Organisation
TD – total dose
OARs – organs at risk
LINAC – linear accelerator
SRS – stereotactic radiosurgery
fSRT – fractionated stereotactic radiotherapy
OS – overall survival
VEGF – avascular endothelial growth factor
GBM – glioblastoma multiforme (old term)

Statements
Authors’ contribution: BH and MZ analyzed the existing data on the case, and took lead in writing the manuscript. DS and ZF revised the accuracy of the medical data in the manuscript. BH made the final approval. All authors provided critical feedback and helped shape the manuscript.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.”

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References
