

Approaching glioblastoma during COVID-19 pandemic: current recommendations and considerations in Brazil

Abordando glioblastomas durante a pandemia pelo COVID-19: recomendações atuais e considerações no Brasil

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ABSTRACT

Background: Cancer patients in general and glioblastoma patients, in particular, have an increased risk of developing complications from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and reaching a balance between the risk of exposure to infection and the clinical benefit of their treatment is ideal. The aggressive behavior of this group of tumors justifies the need for a multidisciplinary team to assist in clinical decisions during the current pandemic. Brazil is now ranked #2 in the number of cases and deaths from COVID-19 pandemic, and existing disparities in the treatment of neuro-oncology patients in Brazil will challenge the clinical and surgical decisions of this population, possibly affecting global survival. **Objective:** To search the literature about the management of glioblastomas during COVID-19 pandemic to guide surgical and clinical decisions in this population of patients in Brazil. **Methods:** We performed a systematic search on the PubMed electronic database targeting consensus statements concerning glioblastoma approaches during COVID-19 pandemic up to July 18, 2020. **Results:** When approaching glioblastoma during the COVID-19 pandemic, important parameters that help in the decision-making process are age, performance status, tumor molecular profile, and patient consent. Younger patients should follow the standard protocol after maximal safe resection, mainly those with MGMT methylated tumors. Aged and underperforming patients should be carefully evaluated, and probably a monotherapy scheme is to be considered. Centers are advised to engage in telemedicine and to elaborate means to reduce local infection. **Conclusion:** Approaching glioblastoma during the COVID-19 pandemic will be challenging worldwide, but particularly in Brazil, where a significant inequality of healthcare exists.

Keywords: Coronavirus Infections; Neuro-Oncology; High-Grade Glioma; Glioblastoma.

RESUMO








Introdução: Pacientes com câncer, em geral, e particularmente pacientes com glioblastoma estão sob elevado risco de desenvolver síndrome respiratória aguda grave devido à infecção pelo SARS-CoV-2, e alcançar um equilíbrio entre risco de exposição à infecção e benefício clínico do tratamento seria o ideal. O comportamento agressivo desse grupo de tumores justifica a necessidade de equipe multidisciplinar para auxiliar nas decisões clínicas durante a pandemia vigente. O Brasil ocupa hoje o segundo lugar em número de casos e óbitos pela COVID-19, e as atuais disparidades no tratamento de pacientes neuro-oncológicos desafiarão as decisões clínicas e cirúrgicas dessa população, possivelmente afetando a sobrevida global. **Objetivo:** Guiar decisões clínicas e cirúrgicas relacionadas ao manejo de glioblastoma durante a pandemia pelo COVID-19 no Brasil por meio de pesquisa em literatura. **Métodos:** Busca sistemática no banco de dados eletrônico da PubMed por estudos ou consensos quanto à abordagem de glioblastoma durante a pandemia por

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COVID-19 até 18/07/2020. **Resultado:** Ao abordar o glioblastoma durante a pandemia pela COVID-19, parâmetros importantes que auxiliam no processo de tomada de decisão são idade, desempenho, perfil molecular tumoral e consentimento do paciente. Pacientes jovens devem seguir protocolo padrão após máxima ressecção cirúrgica, principalmente aqueles com metilação do promotor MGMT. Idosos e pacientes debilitados devem ser cuidadosamente avaliados, e monoterapia deve ser provavelmente considerada. Centros de saúde são orientados a utilizar-se da telemedicina e de meios para reduzir infecção local. **Conclusão:** A abordagem do glioblastoma durante a pandemia por COVID-19 será mundialmente desafiadora, mas particularmente no Brasil, onde ainda existe significativa inequidade no cuidado com a saúde.

Palavras-chave: Infecções por Coronavírus; Neuro-Oncologia; Glioma de Alto Grau; Glioblastoma.

INTRODUCTION

The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has wholly changed healthcare worldwide, including the care of neuro-oncology patients with high-grade gliomas. In this review, current recommendations for the treatment of high-grade gliomas during the pandemic are presented to guide clinical practice. COVID-19 pandemic will require individual centers to shift their focus and resources to allocate patients and provide a safe environment. It will also demand physicians to employ clinical care in different manners and to an interdisciplinary extent.

Current publications provide mostly a framework of evidence-based care to prolong overall survival and progression-free survival. Each health service should manage resources to avoid the potential for undertreatment of cancer. During the current pandemic, neuro-oncology treatment decisions will challenge clinicians, surgeons, and hospitals, and the best efforts to deliver treatment should prevail.

High-grade gliomas comprise a heterogeneous group of aggressive and incurable tumors, usually requiring maximal safe surgical resection, radiotherapy, and chemotherapy as an upfront treatment to reach the best overall survival and progression-free survival. COVID-19 pandemic broke the traditional workflow employed during neuro-oncology therapy in many centers. Glioblastoma patients are usually offered the standard treatment protocol established since 2005 (Stupp protocol). Still, aged patients or patients with poor performance status may benefit from hypofractionated protocols or even monotherapy with radiotherapy or temozolomide. Molecular changes like O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and Isocitrate dehydrogenase (IDH) mutation should be used to stratify best treatment among older patients.

Here, a group of Brazilian neuro-oncology experts gathered together to suggest treatment approaches during the COVID-19 pandemic in Brazil.

GLIOBLASTOMA

Glioblastoma is currently treated according to EORTC-NCIC (Stupp protocol), where maximal safe resection is followed by concurrent chemo-radiotherapy (CRT) and six cycles of adjuvant chemotherapy with temozolomide¹

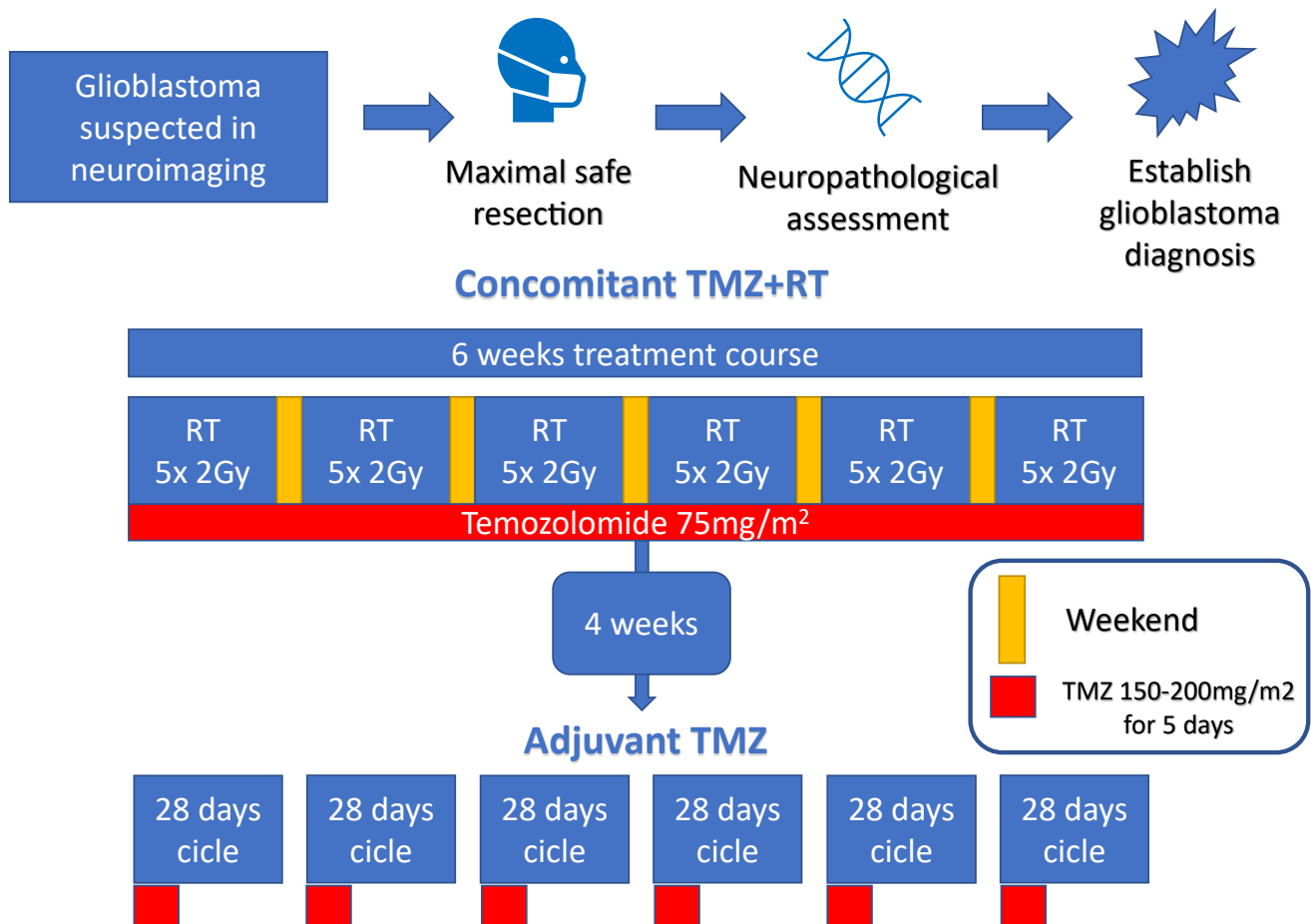
(Figure 1). Patients with MGMT promoter methylation status reached better overall survival than unmethylated ones, with about 50% longer median survival for those treated with temozolomide^{2,3}. Aged patients generally have a worse prognosis and are less tolerant to toxicities. Still, a recent study demonstrated that hypofractionated radiotherapy (40Gy/15 fractions of 2.67Gy over three weeks) is as effective as the standard 60Gy over six weeks. The association of temozolomide showed better overall survival when compared to radiotherapy alone⁴. Treatment with either temozolomide or radiotherapy alone is an option, mainly for those with poor performance status, and it should be guided by MGMT promoter methylation whenever possible⁵.

Neurosurgery

Maximal safe resection is recommended for glioblastoma, and since it offers a benefit in overall survival (OS) and quality of life (QOL), it should be considered a priority^{6,7}. Surgery also makes histological and molecular analysis possible, which might inform treatment decisions.

When admitting neuro-oncological patients, some safety issues should always be considered, such as active screening for flu symptoms, reverse transcription polymerase chain reaction (rt-PCR) for the COVID-19 test, and getting an epidemiological history focusing on COVID-19. The staff is guided to wear additional Personal Protective Equipment (PPE), such as N95 and face shields⁸. Some centers also recommend acquiring a pulmonary computed tomography (CT) for preliminary diagnosis of COVID-19 before hospitalization^{9,10}. For patients whose tests came out negative, hospital admission should be through a particular lane to avoid cross-infection, and individual accommodation with rigorous quarantine should be applied. Infected patients should have surgery postponed until infection ceases. Patients with life-threatening conditions can bypass all these steps, they should be kept in individual accommodations after surgery, and later analysis would guide different paces. All postoperative patients should be regarded as suspected cases, and quarantine for at least two weeks is recommended⁹.

Awake craniotomy is a crucial procedure to achieve maximum safe resection in some patients with high-grade gliomas, but this technique can be considered high-risk in COVID-19 pandemic times. Patients require very close and direct contact between the neurophysiologist during stimulation and a lot of technical personnel. Patients infected with



TMZ: temozolomide; RT: radiotherapy; Gy: gray.
Figure 1. EORTC-NCIC protocol (Stupp protocol).

SARS-CoV-2 should not be referred to awake craniotomy, and the infection should be treated first¹¹.

Regarding reoperations, probably other therapies should be preferred for the treatment of recurrent glioblastoma (GBM).

Clinical follow-up and magnetic resonance imaging

Clinical visits are vital to patient guidance and for monitoring the adverse effects of systemic therapy. Neuro-oncologists should rely on feasible telemedicine solutions for follow-up, and patients should have their blood tested in local laboratories whenever possible. In Brazil, most centers that treat neuro-oncological patients are inside tertiary hospitals, private hospitals, and many other public hospitals, making cross-infection an issue of concern in this fragile population. Therefore, clinical visits should be reserved for those patients who cannot be followed remotely or with urgent symptoms¹².

Magnetic resonance imaging (MRI) is essential during treatment follow-up and is also critical for decision making. Imaging units should employ safety strategies for receiving patients during the pandemic, and adjustments in MRI surveillance protocols could be discussed individually with the

patient who has a stable condition and an excellent molecular profile^{12,13}.

Radiotherapy

Radiation therapy (RT) has an essential role in the treatment of high-grade gliomas. It is performed through daily applications of ionizing radiation directed to a specific brain area to control the primary tumor or avoid local recurrence after surgical resection. During the coronavirus disease 2019 (COVID-19) pandemic, some strategies have been used to restrict the exposure of patients and healthcare professionals to COVID-19.

Radiation Oncology services around the world have been considering three main strategies to restrict this exposure:

- postpone the start of RT whenever possible;
- 2- avoid RT when another treatment can replace it or when the indication of RT is not proven to be beneficial;
- employment of shorter RT duration through hypofractionated regimens.

To minimize exposure and reduce the risk of infection, older, frail, or patients with poor performance status should

receive hypofractionated schedules instead of a six-week traditional radiotherapy course. Data supporting this recommendation come from earlier trials concerning older patients, and non-inferiority results reinforce some of the current suggestions¹². Roa et al. reported results of a prospective study which randomized 100 patients with GBM and aged 60 years old or older to receive standard RT fractionation (60 Gy in 30 fractions) or a hypofractionated regimen (40 Gy in 15 fractions). They found no difference in survival between patients receiving standard RT or short-course RT¹⁴. The International Atomic Energy Agency (IAEA) conducted an international prospective and randomized trial to compare two RT regimens (40 Gy in 15 fractions and 25 Gy in 5 fractions) on the outcome of 98 patients with GBM and aged 50 years old or older. They found no differences in OS time, progression-free survival time, and QOL between patients receiving the two RT regimens. The authors concluded that a short 1-week RT regimen might be recommended as a treatment option for aged or frail patients with newly diagnosed GBM¹⁵. Perry et al., through a prospective and randomized study involving 562 patients with GBM and aged 65 years old or older, showed median OS benefit when combining CT with temozolomide (TMZ) to hypofractionated RT with 40 Gy in 15 fractions (9.3 vs. 7.6 months; $p < 0.001$)⁴.

For patients younger than 60–65 years of age and with good performance status and MGMT methylated tumors, maintaining standard treatment with 60Gy in 30 fractions according to Stupp Protocol is reasonable. However, patients should be offered the possibility of reducing the number of visits, mainly because they are dealing with an incurable type of cancer¹².

Chemotherapy

The leading cause of mortality from SARS-CoV-2 is the acute respiratory distress syndrome (ARDS) and many events surrounding a hyperinflammatory syndrome leading to multiorgan failure¹⁶. In a retrospective, multicenter cohort study in Wuhan, the presence of lymphopenia in hospitalized patients with COVID-19 was a risk factor for death and usually seen in severe cases¹⁷. Currently, temozolomide is the main chemotherapy used to treat glioblastoma patients, employed in the concurrent and adjuvant phase, and can even be given after disease recurrence^{1,2,3}. Temozolomide added in the upfront treatment of glioblastoma resulted in OS benefit, mainly for those harboring an MGMT promoter methylation status³, but also determined about 14% of grade 3 or 4 hematologic toxicities in the studied cohort of patients¹. Therefore, the decision to keep or withhold chemotherapy should be carefully studied after many considerations, like the presence of a good molecular profile, the local situation despite COVID-19 pandemic, patients' decision and patient adherence to treatment and risk of hematologic toxicities.

The National Comprehensive Cancer Network (NCCN) guidelines claim that temozolomide's omission during

glioblastoma treatment is possible, mainly for those MGMT unmethylated patients and the elderly with comorbidities, but could also be reasonable during this pandemic¹⁸. In Brazil, temozolomide is still not widely available in most states¹⁹, and patients with health insurance are those with the possibility of acquiring treatment. Access to MGMT promoter status is also not widely available for most patients, which could harden clinical decisions.

It is reasonable to prioritize temozolomide for patients with MGMT methylated status³ and IDH mutated tumors²⁰, while keeping close attention to treatment toxicities and scheduling regular blood exams. High-grade gliomas that harbor a mutation in IDH might benefit from the addition of temozolomide to the treatment protocol; the EORTC phase III CATNON trial demonstrated that IDH mutation was predictive of a significant benefit from adjuvant temozolomide, with even the benefit of using it in concurrency^{20,21}.

The CeTeG/NOA-09 trial recently investigated the effect of lomustine (CCNU) with temozolomide vs. the standard regimen for newly diagnosed MGMT methylated glioblastomas undergoing radiotherapy in a phase III trial²². This study suggested that this combination might improve OS compared to temozolomide alone in MGMT-methylated patients, but the toxicities when both agents were combined were significantly higher. The decision to employ this strategy during the COVID-19 pandemic should be critically reviewed, and is probably not recommended¹².

The use of corticosteroids

Glioblastoma frequently presents with symptomatic peritumoral vasogenic edema, and dexamethasone alleviated neurological deficits and signs of increased intracranial pressure. Low doses administered once or twice daily are sufficient in most cases²³. Many studies suggest that caution should be used when employing steroids in neuro-oncology due to a detrimental effect on survival outcomes. In an independent analysis of three patients' cohorts, Pitter et al. showed that the use of corticosteroids during radiotherapy is an independent indicator of shorter survival in glioblastoma patients. Probably dexamethasone-induced anti-proliferative effects can protect the tumor from radiation or chemotherapy-induced genotoxic stress²⁴.

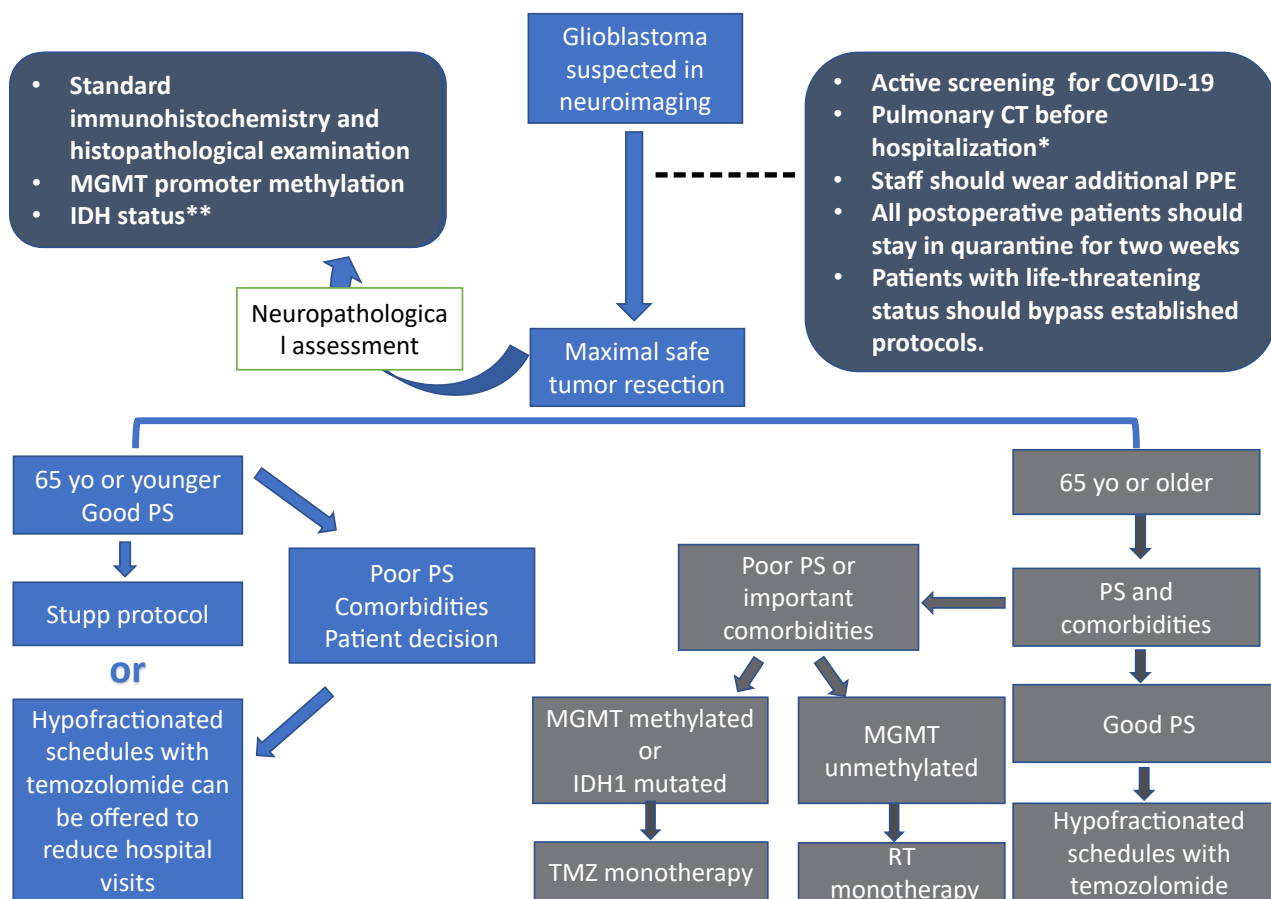
The RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial recently announced that dexamethasone given once daily at the dose of 6mg once per day (either by mouth or intravenous injection) for ten days reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving oxygen only²⁵. Previous data suggested that patients with SARS-CoV-2 infection would not benefit from corticosteroid treatment, and its usage should be cautioned considered²⁶.

Regardless of the current pandemic, the beneficial anti-inflammatory and anti-edematous effects should be cautiously weighed against the potential adverse effects in

glioblastoma treatment and the lowest dose capable of controlling symptoms should be chosen.

Approaching glioblastoma patients during the COVID-19 pandemic will be challenging in most centers that treat neuro-oncological patients. In Brazil, significant disparities in healthcare among states will confront physicians to make proper treatment decisions. Patients with good performance status and good molecular profile (mainly MGMT promoter methylation and IDH mutation) should receive the standard protocol of treatment with maximal safe resection followed by concurrent chemo-radiotherapy and

adjuvant chemotherapy with temozolomide whenever possible. Older patients and those with poor performance status should be carefully treated, and probably a monotherapy regimen might best fit during the COVID-19 pandemic, in case patients with good performance status and no comorbidities could benefit from hypofractionated protocols with temozolomide (Figure 2). The current situation challenges us, and delivering the best healthcare and employing new ways to communicate with our patients is essential. All efforts should focus on safety and not compromise patient care and survival.



MGMT: 0⁶-Methylguanine-DNA methyltransferase; CT: computer tomography; yo: years-old; PS: performance status; IDH: isocitrate dehydrogenase; TMZ: temozolomide; RT: radiotherapy; *some hospitals are using it as a preliminary COVID-19 diagnosis before hospitalization; **IDH status should first be assessed through immunohistochemistry assays.

Figure 2. Proposed flowchart for the treatment of patients with glioblastoma during COVID-19 pandemic.

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