

Neuro-oncology Management During the COVID-19 Pandemic With a Focus on WHO Grade III and IV Gliomas

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Abstract

Background

Because of the increased risk in cancer patients of developing complications caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), physicians have to balance the competing risks of the negative impact of the pandemic and the primary tumor. In this consensus statement, an international group of experts present mitigation strategies and treatment guidance for patients suffering from high grade gliomas (HGG) during the coronavirus disease 2019 (COVID-19) pandemic.

Method / Results

16 international experts in the treatment of HGG contributed to this consensus-based practice recommendation including neuro-oncologists, neurosurgeons, radiation oncologists and a medical physicist. Generally, treatment of neuro-oncological patients cannot be significantly delayed and initiating therapy should not be outweighed by COVID-19. We present detailed interdisciplinary treatment strategies for molecular subgroups in two pandemic scenarios, a scale-up phase and a crisis phase.

Conclusion: This practice recommendation presents a pragmatic framework and consensus-based mitigation strategies for the treatment of HGG patients during the SARS-CoV-2 pandemic.

Introduction

The current pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) has significantly disrupted healthcare, including the care of neuro-oncology patients. While the treatment of SARS-CoV-2 patients is delegated to dedicated expert teams, the decisions regarding the most appropriate allocation of resources for risk mitigation and optimal treatment of patients require guidance from medical and surgical teams managing patients from various specialties, including oncology. In this review, we present an international consensus recommendation for the treatment of high grade gliomas (HGG) to inform clinical practice. It is acknowledged that the SARS-CoV-2 pandemic will require center specific discussions of appropriate resource allocation that considers patient and provider safety, resource constraints, and a realistic evaluation of the impact of therapy upon Incurable brain tumors.

Current guidelines provide a framework of evidence-based care that is intended to prolong progression-free and overall survival. However., during the pandemic, physicians are presented with the challenge to strike a balance between the risks of COVID-19 in a vulnerable population and the potential for undertreatment of cancer patients. Furthermore, there is a social need for the protection of healthcare staff and the avoidance of further secondary viral spread to patients. The intent of our recommendations is to prepare physicians for the likely adjustments in neuro-oncology treatment decisions during this pandemic when best practices are simply unavailable, impractical or unsafe. Since neuro-oncology patients with HGG are a vulnerable patient group, the value of treatment must be balanced with risks of exposure to infection / inducing immunosuppression and survival benefit.

During the period of scaling-up in a pandemic, adequate medical resources are still available but there are mandated reductions in surgery and/or consultations in order to free-up intensive care unit (ICU) capacity, reduce use of protective personal equipment (PPE), and decrease hospital traffic to mitigate viral spread within health care settings.¹ This requires physicians to adapt existing guideline recommendations in order to conserve resources, and still provide optimal treatment to patients. During the peak of pandemic crisis (crisis phase), medical resources may be significantly reduced and major decisions with respect to triaging patients for treatment require systems to be in place to ensure appropriate resource allocation for those with the greatest likelihood of a good outcome, while potentially withholding treatment for those facing imminent death. This international multidisciplinary group of experts in HGG provides a risk-adapted framework for decisions in both pandemic scenarios, considering both ethical issues and resource constraints, in order to minimize the irreparable damage associated with withholding necessary treatments.

Glioblastoma (GBM) and other HGG

The optimal treatment for GBM is maximal safe resection followed by concurrent chemo-radiotherapy (CRT) and monthly adjuvant temozolomide (TMZ)^{2,3}. One of the first steps in crisis management in many major university clinics and hospitals in Europe and North America, at the beginning of the SARS-CoV-2 pandemic, was to postpone all elective surgeries and stop in-person interdisciplinary tumor conferences, which are frequently utilized to determine the optimal course of treatment.

Interdisciplinary Decisions

Decisions regarding the treatment of GBM and other HGGs are interdisciplinary as a standard of care, requiring a high level of expert knowledge. During a pandemic crisis,

high-level and complex treatment regimens are being scrutinized due to disruption of traditional workflow. Clinicians are challenged to carry out sophisticated treatments and to mitigate treatment disruptions, while simultaneously managing treatment with reduced access to resources and health care providers. To mitigate disruptions to patient care, we believe that interdisciplinary discussion should continue using healthcare technology such as video-conferencing, phone conferences or other digital methods to maintain expert discussion between disciplines. As this crisis becomes more pervasive, there might be more need for careful assessments, possibly involving but not restricted to administrators with resource oversight and ethics counseling as available.

Neurosurgery

Although patients with HGG are incurable, current treatment pathways provide meaningful extensions to both survival and quality of life. Since we know that survival is determined in part by the extent of surgery for HGG, maximal safe surgery should still be considered a priority^{4,5}. Surgery also provides tissue for both the histological and molecular diagnoses which informs treatment decisions. For example, the knowledge of the O⁶-methylguanine DNA methyltransferase (MGMT) status can be critical in deciding who would benefit from temozolomide (TMZ) chemotherapy. We recognize that during the pandemic the challenges of ICU capacity, conservation of PPE, availability of health care professional expertise and the risk for patients' exposure to SARS-CoV-2 may reduce the ability to provide optimal surgical management. Such a situation may force clinical decision-making in the absence of a tissue diagnosis, although we hope that even during the peak of this crisis this situation is minimized.

Neurological deficits caused by the tumor, and from the surgery itself, should be taken into account when making decisions prioritizing which patients need urgent surgery and which patients could be delayed. It is important to identify patients who potentially need ICU or ventilator support, and minimize and minimize surgical resources including the operating time as much as possible. Although there are specialized centers that can conduct awake craniotomies on an outpatient basis allowing for some critical resources to be conserved, this is not widely available. Furthermore, in the crisis phase of the pandemic, the necessary work-up and specialized testing such as fMRI and presence of appropriate technicians may not be available to allow for such procedures.

The surgical intent may also be dramatically altered in the crisis phase of the pandemic with tumor decompression in symptomatic patients as the goal, versus an attempt for gross tumor resection given the higher risk for postoperative ICU surveillance for the later. Therefore, the ICU capacity preservation argument has to be applied on an individual and center basis, and with respect to the phase of the pandemic. In those patients where the extent of surgical resection is limited due to the pandemic, there may be the potential for additional surgery when the pandemic subsides and more resources are available. Therefore, patients should be re-evaluated with interdisciplinary input on a case-by-case basis.

Diagnostics

Given the relevance of an appropriate histological and molecular diagnosis according to WHO criteria for any treatment decision, compromising the diagnostic work-up for HGG is not recommended. Of note, since several of the therapeutic considerations

require *MGMT*, *isocitrate dehydrogenase (IDH)* and 1p19q status, the determination of these molecular diagnostics should be prioritized, if feasible.

Clinical Monitoring and Magnetic Resonance Imaging

As clinical visits at medical centers may be restricted, it is advisable to rely as much as possible on telephone and telemedicine solutions for follow-up and patient guidance. Critical blood tests are often required for monitoring adverse effects of systemic therapy and for monitoring levels of anti-seizure medications, and should continue in local laboratories whenever possible. MRI assessments should adhere to standard guidelines as much as possible to ensure appropriate patient guidance. However, adjustments in the frequency of monitoring are reasonable for lower grade tumors, those patients with stable disease and on surveillance and when the potential risks are outweighed by exposure to SARS-CoV-2 in a hospital that is managing an outbreak. For example, stable *IDH*-mutated grade 3 HGG could be monitored less frequently to avoid viral exposure during the crisis phase. Adjustments in MRI surveillance protocols should be discussed individually with the patient to minimize significant anxiety, and a plan in place should the center be drastically constrained with respect to imaging resources.

Radiotherapy

Radiotherapy is traditionally delivered daily for 6 weeks for most HGG patients and should ideally not be disrupted. During pandemics, it may be challenging to maintain treatments over multiple weeks, and there is greater interest in hypofractionation for all tumor types. Furthermore, radiation oncology departments are vulnerable to unit closures or significant service reduction in the event of a reduction in the workforce or an outbreak on a unit and radiation protection laws must be respected. For example,

should a substantial number of employees be unable to work due to exposure and quarantine measures, then a unit/center may not be able to be staffed and treatment would be interrupted or cancelled resulting in compromised patient outcomes^{6,7}. Unfortunately, the evidence on how to mitigate treatment interruptions specific to HGG is sparse, as is evidence on the impact on survival. Although data exist from previous disasters such as Hurricane Maria in Puerto Rico, the number of affected patients was too low to make general evidenced based recommendations⁸. In a pandemic, the risk of exposure increases with each day of treatment since a patient has to be transported to a radiation facility either themselves, with family, or with a transportation service, and may need to be hospitalized requiring hospital based transfers which generally should be avoided. In addition, most centers are restricting all visitors, which can put additional strain and safety concerns for patients with HGG who are often cognitively impaired. Older patients may be more vulnerable and impacted by these considerations and, in particular, for this population the risk of exposure and potential complications of infection should be balanced against the absolute benefit of the treatment. As epidemiologic data are lacking, evidence-based recommendations are not possible and, hence, the need for expert consensus recommendations^{9,10}. It is recognized that cancer patients are at higher risk for infection by SARS-CoV-2 infection and developing more serious complications, underscoring the importance of minimizing exposure to the virus¹⁰. However, for HGG patients with rapidly progressing tumors, the risk of delay or termination of treatments may outweigh the risk of SARS-CoV-2 exposure or infection.

To minimize exposure, reduce the risk for infection and increase the chance of completing a course of radiotherapy, hypofractionated schedules should be used as a standard in older and/or frail poor performance status patients¹¹. In a prospective trial

by Roa et al., which was completed in the pre-TMZ era, 100 patients with GBM >60 years of age were randomly assigned to receive post-operative standard RT (60 Gy in 30 fractions over 6 weeks) or a shorter course of RT (40 Gy in 15 fractions) ¹². There was no difference in median survival rates between patients receiving standard RT or short-course RT. Shorter course radiotherapy regimens of 34/35 Gy in 10 fractions have also been shown to be efficacious; however, the addition of TMZ to these fractionation schemes have not been tested in randomized trials as compared to the 40 Gy in 15 fraction regimen where a survival advantage was reported with the addition of TMZ in the elderly ¹³⁻¹⁵. An even shorter regimen of radiation alone was tested by the *International Atomic Energy Agency (IAEA)*. Roa et al. compared the previously tested 40 Gy in 15 fractions against 25 Gy in 5 fractions in a phase III non-inferiority trial ¹⁶. With a median OS of 7.9 vs 6.4 months ($p = 0.988$), this very abbreviated regimen did not result in an OS disadvantage. Given the significant OS advantage of a combined modality regimen, short course regimens of RT alone (40 Gy in 15 fractions, 34 Gy in 10 or 25 Gy in 5 fractions) should be reserved for elderly and frail poor performance status patients, and the addition of TMZ to 40 Gy in 15 fractions considered on a case by case basis. Unfortunately, there are limited data available supporting hypofractionation in HGG patients <60 years with a good performance status^{17,18} and, as such, we make expert based consensus statements in this cohort with respect to considering hypofractionated RT (+/- TMZ) in Table 1. It is our opinion that these recommendations balance the benefits of completing a course of treatment with a potential adverse survival impact, as compared to simply adhering to standard management in non-pandemic conditions. .

Generally, we recommend maintaining standard treatment for patients less than 60-65 years in age with a good performance status, and *MGMT* hypermethylated

tumors. However, if the ability to offer a full course of CRT is compromised due to effects of the pandemic crisis, hypofractionation with 40 Gy in 15 fractions with TMZ offers a less resource intensive treatment course, and is unlikely to significantly compromise survival outcomes. Furthermore, in the current situation, patients may prefer a radiation schedule that minimizes the number of visits when dealing with an incurable cancer. Ultra-short fractionation (25 Gy in 5 fractions) has limited worldwide experience in general, and applies only to patients with relatively small volume disease. Care must be taken before recommending radiation fractionation shorter than the 40 Gy in 15 regimen which has been in clinical practice for the better part of a decade in several countries including Europe and North America.

Chemotherapy

Currently, there is no evidence to support blanket changes or withholding of chemotherapy in cancer patients during the pandemic, although precautions are warranted and guidelines needed to inform care. Acute respiratory distress syndrome (ARDS) is the leading cause of mortality from SARS-CoV-2 accompanied by hemophagocytic lymphohistiocytosis with a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia leading to multiorgan failure^{9,19}. Patients suffering from chemotherapy associated toxicities, such as lymphopenia, are at high risk for severe complications during the pandemic and, therefore, practical recommendations are needed to ensure patient safety.

The addition of TMZ to the upfront treatment of GBM provided an OS benefit of approximately 10% at five years. This benefit is more pronounced in patients with hypermethylated *MGMT* promoter²⁰. However, 14% of patients were observed to experience grade 3 or 4 hematologic toxicities, including 4% with grade 3 or 4

neutropenia and 11% with grade 3 or 4 thrombocytopenia ². Therefore, the possible long-term OS benefit associated with the addition of TMZ must be carefully balanced against a potential risk of severe complications if exposed to SARS-CoV-2 infection. This may be particularly relevant for patients who do not have a hypermethylated *MGMT* promoter status, as there is limited potential gain with additional TMZ ²⁰.

Can we or should we withhold TMZ treatment? Irrespective of the current pandemic situation, the National Comprehensive Cancer Network (NCCN) guidelines offer the option for the omission of TMZ ²¹. While this is particularly helpful in the assessment of new agents in clinical trials, it also is reasonable during the pandemic to consider withholding TMZ in all unmethylated *MGMT* patients. This is clear in elderly and more frail patients who are more prone to worse outcome with a SARS-CoV-2 infection ¹⁹. Therefore, a pragmatic approach is to prioritize TMZ for patients with *MGMT* hypermethylation and/or IDH mutated tumors, and pay specific attention to toxicities associated with previous chemotherapy cycles. For patients whose tumors are not methylated, the difference in overall survival favoring the TMZ and radiotherapy group was only marginally significant with a median OS of 12.7 months amongst those GBM patients assigned to TMZ and radiotherapy, vs. 11.8 months among those assigned to radiotherapy alone²⁰. However, given the additional toxicities associated with TMZ, a discussion of risks vs. benefits even in *MGMT* promoter methylated patients must also be considered, and informed patients decisions made. It is also noteworthy to consider that adjuvant TMZ can always be given if the risk vs. reward of providing concurrent RT and TMZ are outweighed by the of the pandemic in those with known *MGMT* hypermethylation, in an effort to reduce the potential for immunosuppression during the radiation.

TMZ monotherapy in *MGMT* methylated patients is an option for older HGG patients^{13,22}. In the NOA-08 trial, TMZ alone was non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma including GBM. However, we would only recommend this if radiotherapy is unavailable or treatment completion is at risk.

Oligodendroglial tumors are currently recommended to receive RT with adjuvant PCV^{3,21}, and they may be able to switch from IV chemotherapy to oral therapies. Switching PCV to temozolomide, or leaving out vincristine may decrease the risk for exposure by reducing clinic visits and the potential for hematological toxicity. Furthermore, procarbazine as well as lomustine can cause pulmonary fibrosis as a side effect, which should be considered when prescribing this treatment in the context of a possible SARS-CoV-2 related lung fibrosis²³.

An of risk adapted decisions for HGG and use of chemotherapy can be derived from considering the CeTeG/NOA-09 trial. Herrlinger et al. investigated the effect of lomustine plus TMZ vs. the standard TMZ regimen for newly diagnosed *MGMT* methylated GBM undergoing radiation in the setting of a randomized phase 3 trial²⁴. The results suggested that lomustine-TMZ chemotherapy may improve OS compared with TMZ standard therapy in patients with a methylated *MGMT* promoter. However, the hematological side effects were significantly greater in the experimental treatment group. Given that more toxic and potentially harmful chemotherapy regimens should be viewed critically during the pandemic, the use of this regimen is not recommended. Physicians should also be cautious about a possible shortage of transfusion treatments during a pandemic, which might hamper a supportive treatment in case of

grade 4 hematologic toxicities. In addition, focus on guideline supported treatments seems preferable to less conventional approaches in a time of limited resources.

We believe the clinical decision to withhold or interrupt chemotherapy should be individualized with consideration of the molecular parameters, the individual risk stratification, the available resources and the regional phase of the pandemic crisis (scale-up vs. crisis phase, Table 1). Patients and caregivers should be included in the decision-making process as much as possible, and this should include all relevant data on chemotherapy and radiotherapy, as well as the individual risk profile associated with a potential SARS-CoV-2 infection.

Tumor Treating Fields (TTFields)

In 2015, Stupp et al. demonstrated that the addition of TTFields (Optune) to maintenance TMZ chemotherapy resulted in a statistically significant improvement in survival for GBM patients^{25,26}. Although Optune treatment is reimbursed and recommended in some regions, it is not universally prescribed, and this is an ongoing area of discussion because of the high treatment costs and the potential intrusiveness of wearing the device on the patients' quality of life. However, since TTFields can be used at home with minimal viral exposure, some patients can continue wearing the device during the pandemic as long as the support teams are in place.

Steroids

Previous data suggested that caution should be exercised with the use of corticosteroids in neuro-oncology. Several studies suggest a detrimental effect of dexamethasone on GBM survival outcomes²⁷. Although available data are

inconclusive and mainly retrospective with inherent bias, steroids should be used as needed but with caution during the SARS-CoV-2 pandemic. A recent publication outlined the detrimental effects and the clinical outcomes of corticosteroid use in coronavirus and similar outbreaks as a reference ²⁸. The authors concluded that it cannot be expected that patients with SARS-CoV-2 infection will benefit from corticosteroid treatment, and they may be more likely to be harmed with such treatment. They concluded that corticosteroid treatment should not be used for the treatment of SARS-CoV-2-induced lung injury, or shock, outside of a clinical trial. Detrimental outcomes of corticosteroid therapy included delayed clearance of viral RNA from respiratory tract, delayed clearance of viral RNA from blood, avascular necrosis in survivors, and complications such as psychosis and worsening of a preexisting diabetes, and an overall increased mortality in influenza patients ²⁸.

While the reasons for steroid use are different in cancer patients compared to patients suffering from ARDS and acute viral infections, the beneficial anti-inflammatory and anti-edematous effects should be weighed against the potentially detrimental effects of inhibiting antiviral immunity and immunosuppression during the SARS-CoV-2 pandemic. Independent of the pandemic, it is recommended to use the lowest dose compatible with symptom control in HGG patients.

Experimental Treatments and Clinical Trials

There are official statements by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the conduct of trials in the time of a pandemic ²⁹. Importantly, there is no general rule to stop any follow-up or new enrollments into the trial. Most important is the communication both from the sponsor

to the investigator and from the investigator to subsites and patients, as well as active discussions within cooperative groups and study teams. Since trials, especially for the vulnerable population of HGG patients are regarded an essential option, there is an ethical obligation to maintain these options if possible. However, to offer phase I trials with a minimal likelihood of a patient benefit during a pandemic, given the additional monitoring and consequent risks to patients and healthcare providers, should be evaluated critically. Importantly, safety of patients and trials staff have first priority, and the integrity of the study comes next. On a practical note, new enrollments/accrual may be held especially during the peak of the crisis to protect subjects and the study integrity, i.e. since there may be shortage in the availability and/or restricted delivery of the study drug, restrictions to some safety measures, losses to follow-up, or incomplete administration of study interventions. We advise study coordinators /sponsors to actively address this topic now in their respective trial(s), and closely monitor the evolution in their trial sites which may be different especially in multinational studies. With a higher priority, currently enrolled subjects where safe and feasible within jurisdictional constraints should be continued. However, relevant risks with respect to safety should be discussed, which may occur with staff shortage or specific examinations not being available.

SARS-CoV-2 positive patients

Currently, we are unable to make general recommendations on how to proceed with SARS-CoV-2 positive patients as this is greatly dependent on individual hospital policies and jurisdictional issues. From the oncological point of view, continuation of treatment (at least radiotherapy) seems appropriate in asymptomatic or stable

patients, but will depend on the resources of each facility, the number of positive tested patients in one facility, and sometimes even based on governmental legislations. The use of PPE is essential to protect the staff, as the safety of staff and other patients is paramount³⁰. On the other hand, a substantial number of SARS-CoV-2 positive tested patients are asymptomatic and the oncological disease might be the more imminent threat. In patients who recovered from COVID-19, all available data suggest that continuation of treatment should be initiated.

Proposed strategy for GBM and other HGG

To inform interdisciplinary decisions, we recommend the use of digital solutions for patient tumor boards and conferences during the pandemic. Standard treatment should be offered when possible. However, we recognize in many jurisdictions this is already no longer manageable because of compromised resources, risk of infection or treatment interruption. We therefore suggest alternative treatment options that balance the capacity of affected health care systems versus best possible treatment standards in Table 1.

As a summary of principles, neurosurgical decisions should be individualized based on the oncological necessity, the extent of the surgery, and ICU capacity. Radiotherapy principles should focus on hypofractionation where possible. Chemotherapy should be critically evaluated at regular intervals and patients should be monitored closely. In older patients, and in patients with known unmethylated *MGMT* status, the addition of TMZ should be viewed critically. However, withholding chemotherapy for all patients is not recommended and must be evaluated daily considering the extent of the crisis, the available resources, and the individual patient

risk. Withholding TMZ is also an option in specific subtypes of HGGs depending on the molecular pattern and the pandemic state. In general, patients should wear PPE as recommended by local public health authorities, and visits to clinics should be virtual whenever safe and feasible.

The intent of the recommendations in Table 1 is to deliver adequate treatment to patients with WHO grades III and IV gliomas, while minimizing the risk of exposure to SARS-CoV-2 (Table 1). Recommendation for practice are summarized below and in Table 1.

1. GBM patients and WHO grade III gliomas IDH-wt with good prognosis and younger age:

Generally, we would recommend maintaining standard treatment for patients less than 60-65 years of age with good performance status and *MGMT* hypermethylated tumors, recognizing that during the COVID-19 pandemic decisions must be adapted day-to-day given the fluidity of the situation in each area. If the situation deteriorates (crisis phase), 40 Gy in 15 fractions for all newly diagnosed GBM irrespective of age is reasonable practice with consideration of TMZ on a case by case basis. For WHO grade 3 tumors, we recommend the use of standard therapy as long as possible. TMZ should be reviewed individually. Standard fractionation may be given if resources allow it, however, discussion with the patient as to potential pros and cons of hypofractionated RT should be considered.

2. GBM patients with poor prognosis, frail and poor performance status:

Short course radiation such as 25 Gy in 5 fractions per Roa et al., or 34 Gy in 10 fractions may be appropriate. Hospice and best supportive care (BSC) may be

preferable to radiotherapy in selected patients who are unlikely to benefit meaningfully from treatment.

3. Anaplastic Astrocytoma over age 65/ 70:

IDH-wt: Hypofractionation with 40 Gy in 15 fractions +/- TMZ can be offered, potentially dependent on *MGMT* status and status of resource limitation or patient risk.

IDH mutated: Standard fractionation may be given if resources allow, however, discussion with the patient as to potential pros and cons of hypofractionated radiotherapy should be equally considered.

4. WHO Grade 3 IDH-1 mutated or 1p19q codeleted tumors:

Conventional 60 Gy in 30 fractions or 59.4 Gy in 33 fractions radiotherapy with TMZ is reasonable, but the patients should be included in the decision-making process (risk of exposure vs. potential benefit of conventional fractionation). Using TMZ in place of PCV can minimize toxicity likely without significant compromise to overall outcomes.

Conclusion and Disclaimer

As an international team of neuro-oncologists, neurosurgeons, medical physicists and radiation-oncologists, our aim was to review the scientific evidence and provide recommendations for clinical use in the COVID-19 pandemic. These recommendations are a guide and not meant to be prescriptive; ultimately, each physician will need to make treatment decisions based on discussions with the patient and taking into account their own local guidelines and treatment approach. Generally,

our goal is to treat all brain tumor patients with the most advanced and effective approach, without compromising patient safety and care. The current situation challenges us to adapt treatments, to shorten radiotherapy fractionation (hypofractionate), to modify chemotherapy to minimize immunosuppression, and in some cases to omit treatment if patients are tested SARS-CoV-2 positive. Since these guidelines may change over time as we navigate through this pandemic and learn best practices, the present summary provides possibilities and alternatives which physicians may choose to consider during the SARS-CoV-2 pandemic.

Ethics approval and consent to participate

Ethics approval was not necessary for the comprehensive review article. All co-authors have agreed to participate.

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Table 1: Proposed neurooncological treatment algorithm during the SARS-CoV-2 pandemic

	Criteria	Scale-up phase	Crisis phase	Caveat
Surgery	Operable tumors or tumors in need of decompression	Max. safe resection	Individual assessment of resources and necessity	Salvage surgery should be discussed after pandemic
WHO Grade III				
Grade III IDH mutant	1p/19q non-cod.	RT (+/-TMZ) → TMZ	RT → TMZ	TMZ should be reviewed individually Crisis phase: Standard fractionation may be given if resources allow, however, discussion with the patient as to potential pros and cons of Hypofx RT can be considered.
	1p/19q cod.	RT → PCV or RT + TMZ → TMZ	RT + TMZ → TMZ	TMZ in place of PCV can minimize toxicity/ exposure Crisis phase: Standard fractionation may be given if resources allow, however, discussion with the patient as to potential pros and cons of Hypofx RT can be considered.
Grade III IDH WT	Favorable: Age <65/70 years and KPS _≥ 70	RT + TMZ → TMZ	Hypofx RT (40.05 Gy/ 15 fx) + TMZ → TMZ	TMZ should be reviewed individually Crisis phase: Hypofx RT alone with 40.05 Gy in 15 fractions with delayed TMZ to adjuvant phase when <i>MGMT</i> known and hypermethylated or shorter course Hypofx RT alone as opposed to withholding treatment
	Favorable age but unfavorable KPS (between 50 to 70)	Hypofx RT (40.05 Gy/ 15 fx) +/- TMZ	Hypofx RT alone (34 Gy/ 10 fx); Ultra-Short course RT (25 Gy/ 5 fx)	TMZ should be reviewed critically; can consider BSC
	Age >65/70 <i>MGMT</i> promotor non-meth.	Hypofx RT with 40.05 Gy/ 15 fx	Hypofx RT (34 Gy Gy/ 10 Fractions); Ultra-Short course RT (25 Gy/ 5 fx)	no TMZ; can consider BSC if poor KPS
	Age >65/70 <i>MGMT</i> promotor methylated	Hypofx RT (40.05 Gy/ 15 fx) + TMZ → TMZ	Hypofx RT 40.05Gy/15 fx with delayed TMZ to adjuvant alone or shorter course hypofx RT alone (34 Gy in 10 fx or ultra-short course RT with 25 Gy/ 5 fractions) depending on KPS	TMZ should be reviewed critically; can consider BSC if poor KPS
	Very unfavorable KPS<50	Hypofx RT (40.05/ 15 fx or 34 Gy/10 fx or 25Gy/5 fx)	ultra-short course RT with 25 Gy/ 5 fractions; TMZ alone if methylated <i>MGMT</i> or BSC	BSC should be considered and TMZ should be reviewed critically even in <i>MGMT</i> meth.
WHO Grade IV				
	Favorable: Age <65/70 years KPS _≥ 70	RT + TMZ → TMZ (+/-TTF)	Hypofx RT (40.05 Gy/ 15 fx) +/- TMZ	TMZ should be reviewed individually and should be considered if <i>MGMT</i> known positive, Hypofx RT alone with 40.05 Gy in 15 fractions with delayed TMZ to adjuvant phase if <i>MGMT</i> unknown, individually review initiation of TTF
	Favorable age with unfavorable KPS between 70 and 50	Hypofx RT alone with 40.05Gy/ 15 fx +/- TMZ	Hypofx RT alone with 34 Gy/ 10 fractions or ultra-short course RT (25 Gy / 5 fractions) or BSC	TMZ should be reviewed individually and should be considered if <i>MGMT</i> known positive, Hypofx RT alone with 40.05 Gy in 15 fx with delayed TMZ to adjuvant phase if <i>MGMT</i> unknown
	Age >65/70 <i>MGMT</i> promotor non-meth.	Hypofx RT (40.05Gy/ 15 fx)	Hypofx RT (34 Gy/ 10 fx) or ultra-short course RT (25 Gy / 5 fractions)	Consider BSC for poor performance status
	Age >65/70 <i>MGMT</i> promotor methylated	Hypofx RT (40.05Gy/ 15 fx) +/- TMZ	Hypofx RT alone (34 Gy/ 10 fx or 25 Gy/ 5 fx) or BSC	TMZ should be reviewed critically BSC for poor performance status
	Very unfavorable KPS<50	Hypofx RT (34 Gy/10 fx or 25 Gy / 5 fx) alone or BSC or TMZ	25 Gy/ 5 fx or BSC	BSC should be considered and TMZ should be reviewed critically even in <i>MGMT</i> meth.

		alone if <i>MGMT</i> meth.		
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Abbreviations:

Fx: fractions

RT: radiotherapy

Hypofx: Hypofractionation

BSC: Best supportive care

TMZ: temozolomide

MGMT: O⁶-methylguanine DNA methyltransferase

PCV: procarbazine,

CCNU, vincristine

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