

Neuro-oncology management during the COVID-19 pandemic with a focus on WHO grades III and IV gliomas

Denise Bernhardt^{1,2,3,✉}, Wolfgang Wick⁴, Stephanie E. Weiss⁵, Arjun Sahgal⁶, Simon S. Lo⁷, John H. Suh⁸, Eric L. Chang⁹, Matthew Foote¹⁰, James Perry¹¹, Bernhard Meyer¹², Peter Vajkoczy¹³, Patrick Y. Wen¹⁴, Christoph Straube^{1,2,3}, Steffi Pigorsch^{1,2,3}, Jan J. Wilkens¹, and Stephanie E. Combs^{1,2,3}

¹Department of Radiation Oncology, Technical University of Munich (TUM), School of Medicine and Klinikum rechts der Isar, 81675 Munich, Germany; ²Department of Radiation Sciences (DRS), Institute of Radiation Medicine (IRM), Neuherberg, Germany; ³Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Site Munich, Germany; ⁴Neurology Clinic, University of Heidelberg and German Cancer Research Center, Heidelberg, Germany; ⁵Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; ⁶Department of Radiation Oncology, Sunnybrook Health Science Centre, Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada; ⁷Department of Radiation Oncology, University of Washington School of Medicine, Seattle, Washington, USA; ⁸Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA; ⁹Department of Radiation Oncology, Keck School of Medicine at University of Southern California, Los Angeles, California, USA; ¹⁰Department of Radiation Oncology, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Queensland, Australia; ¹¹Division of Neurology, Department of Medicine, Odette Cancer and Sunnybrook Health Science Centres, University of Toronto, Toronto, Ontario, Canada; ¹²Department of Neurosurgery, Technical University of Munich (TUM), School of Medicine and Klinikum rechts der Isar, 81675 Munich, Germany; ¹³Department of Neurosurgery, Charité Universitätsmedizin Berlin, 13353 Berlin, Germany; ¹⁴Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts, USA

Corresponding Author: Dr. med. Denise Bernhardt, Department of Radiation Oncology, Technical University of Munich (TUM), Klinikum rechts der Isar, Ismaninger Straße 22, D-81675 München (denise.bernhardt@mri.tum.de).

Abstract

Background. Because of the increased risk in cancer patients of developing complications caused by 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 disease. In this consensus statement, an international group of experts present mitigation strategies and treatment guidance for patients suffering from high grade gliomas (HGGs) during the coronavirus disease 2019 (COVID-19) pandemic.

Methods. Sixteen 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 2 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.

Keywords

COVID-19 | glioblastoma | high-grade glioma | neuro-oncology | SARS-CoV-2

The current pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly disrupted health care, 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 (HGGs) 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 brain cancers which are incurable.

Current guidelines provide a framework of evidence-based care that is intended to prolong progression-free and overall survival (OS). 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 health care 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 the 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 provide 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 and Other HGGs

The optimal treatment for glioblastoma (GBM) is maximal safe resection followed by concurrent chemoradiotherapy (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 health care 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 inform treatment decisions. For example, the knowledge of the O⁶-methylguanine DNA methyltransferase (MGMT) status can be critical in deciding who would benefit from 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 to minimize surgical resources, including 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 workup and specialized testing such as functional MRI 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 latter. 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 was 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 reevaluated with interdisciplinary input on a case-by-case basis.

Diagnostics

Given the relevance of an appropriate histological and molecular diagnosis according to World Health Organization (WHO) criteria for any treatment decision, compromising the diagnostic workup for HGG is not recommended. Of note, since several of the therapeutic considerations require *MGMT*, isocitrate dehydrogenase (*IDH*), and 1p/19q status, the determination of these molecular diagnostics should be prioritized, if feasible.

Clinical Monitoring and MRI

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 in these patients 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 III 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 as it can cause significant anxiety, and a plan should be in place should the center be drastically constrained with respect to imaging resources.

Radiotherapy

Radiotherapy (RT) 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 canceled, 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 evidence-based recommendations.⁸ 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 alone, 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 entail 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 for this population in particular, 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—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 virus.¹⁰ 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 RT, hypofractionated schedules should be used as a standard in older and/or frail poor performance status patients.¹¹ In a prospective trial by Roa et al which was completed in the pre-TMZ era, 100 GBM patients older than 60 years were randomly assigned to receive postoperative standard RT (60 Gy in 30 fractions over 6 wk) 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 RT regimens of 34/35 Gy in 10 fractions have also been shown to be efficacious; however, the addition of TMZ to these fractionation schemes has not been tested in randomized trials compared with 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. 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 versus 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 old 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 (\pm TMZ) (see Table 1). It is our opinion that these recommendations balance the benefits of completing a course of

Table 1 Proposed neuro-oncological treatment algorithm during the SARS-CoV-2 pandemic

	Criterion	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 (\pm TMZ) \rightarrow TMZ	RT \rightarrow 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 \rightarrow PCV or RT + TMZ \rightarrow TMZ	RT + TMZ \rightarrow 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 IDHWT	Favorable: Age <65/70 years and KPS \geq 70	RT + TMZ \rightarrow TMZ	Hypofx RT (40.05 Gy/15 fx) + TMZ \rightarrow 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 and 70)	Hypofx RT (40.05 Gy/15 fx) \pm 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> promoter non-meth.	Hypofx RT with 40.05 Gy/15 fx	Hypofx RT (34 Gy/10 fx); ultra-short-course RT (25 Gy/5 fx)	No TMZ; can consider BSC if poor KPS
	Age >65/70 <i>MGMT</i> promoter methylated	Hypofx RT (40.05 Gy/15 fx) + TMZ \rightarrow 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 25 Gy/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 y KPS \geq 70	RT + TMZ \rightarrow TMZ (\pm TTF)	Hypofx RT (40.05 Gy/15 fx) \pm 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 fields
	Favorable age with unfavorable KPS between 70 and 50	Hypofx RT alone with 40.05 Gy/15 fx \pm TMZ	Hypofx RT alone with 34 Gy/10 fractions or ultra-short course RT (25 Gy/5 fx) 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> promoter non-meth.	Hypofx RT (40.05 Gy/15 fx)	Hypofx RT (34 Gy/10 fx) or ultra-short course RT (25 Gy/5 fx)	Consider BSC for poor performance status
	Age >65/70 <i>MGMT</i> promoter methylated	Hypofx RT (40.05 Gy/15 fx) \pm 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 alone if <i>MGMT</i> meth.	25 Gy/5 fx or BSC	BSC should be considered and TMZ should be reviewed critically even in <i>MGMT</i> meth.

Abbreviations: fx, fractions; hypofx, hypofractionated.

treatment with a potential adverse survival impact, compared with simply adhering to standard management in nonpandemic conditions.

Generally, we recommend maintaining standard treatment for patients younger than 60–65 years 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 are 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 multi-organ 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 5 years. This benefit is more pronounced in patients with hypermethylated *MGMT* promoter.²⁰ 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 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 OS favoring the TMZ and radiotherapy group was only marginally significant, with a median OS of 12.7 months among those GBM patients assigned to TMZ and radiotherapy, versus 11.8 months among those assigned to radiotherapy alone.²⁰ However, given the additional toxicities associated with TMZ, a discussion of risks versus benefits even in *MGMT* promoter methylated patients must also be considered and informed patient decisions made. It is also noteworthy to consider that adjuvant TMZ can always be given if the risk versus reward of providing concurrent RT and TMZ are outweighed by the effects 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 RT alone in the treatment of elderly patients with malignant astrocytoma including GBM. However, we would only recommend this if RT is unavailable or treatment completion is at risk.

Oligodendroglial tumors are currently recommended to receive RT with adjuvant procarbazine/lomustine/vincristine (PCV),^{3,21} and they may be able to switch from i.v. chemotherapy to oral therapies. Switching PCV to TMZ 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 fibrosis.²³

An example 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 versus the standard TMZ regimen for newly diagnosed *MGMT* methylated GBM undergoing radiation in the setting of a randomized phase III trial.²⁴ 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, guideline-supported treatments seem preferable to less conventional approaches in a time of limited resources.

We believe that 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 versus 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

In 2017, Stupp et al demonstrated that the addition of tumor treating fields (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 on patients' quality of life of wearing the device. 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 outcomes.²⁷ 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 pre-existing diabetes, and an overall increased mortality in influenza patients.²⁸

While the reasons for steroid use are different in cancer patients compared with 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. Independently 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 FDA and the 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 as 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 health care providers, should be evaluated critically. Importantly, safety of patients and trial 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, 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 RT) 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 governmental legislation. The use of PPE is essential to protect the staff, as the safety of staff and other patients is paramount.³⁰ 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 HGGs

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 that 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 (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](#)). Recommendations for practice are summarized below and in [Table 1](#).

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

Generally, we would recommend maintaining standard treatment for patients younger than 60–65 years 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 patients irrespective of age is reasonable practice with consideration of TMZ on a case-by-case basis. For WHO grade III 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 \pm 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 RT should be equally considered.

4. WHO grade III IDH1 mutated or 1p/19q codeleted tumors:

Conventional 60 Gy in 30 fractions or 59.4 Gy in 33 fractions RT with TMZ is reasonable, but the patients should be included in the decision-making process (risk of exposure versus 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 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 RT fractionation (hypofractionate), to modify chemotherapy to minimize immunosuppression, and in some cases to omit treatment if patients tested positive for SARS-CoV-2. 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.

Funding

The work was funded by the participating departments. No external funding is related to this manuscript.

Conflict of interest statement. The authors declare there are no competing interests. Lo SS Research support from Elekta AB for Gamma Knife ICON Expert Group. Suh JH. Consultant for Philips and Abbvie. AS: Advisor/consultant with Abbvie, Merck, Roche, Varian (Medical Advisory Group), Elekta (Gamma Knife Icon), BrainLAB, and VieCure (Medical Advisory Board). Board Member: International Stereotactic Radiosurgery Society (ISRS). Past educational seminars with Elekta AB, Accuray Inc, Varian (CNS Teaching Faculty), BrainLAB, Medtronic Kyphon. Research grant with Elekta AB Travel accommodations/expenses by Elekta, Varian, BrainLAB. AS also belongs to the Elekta MR Linac Research Consortium, Elekta Spine, Oligometastases and Linac Based SRS Consortia. WW has received study drug support from Apogenix, Pfizer, and Roche and consulted for MSD and Roche with all financial reimbursement to the University Clinic. MF: Research and travel support Elekta AB, Consultant Varian. DB: Research grant with

Accuracy, travel expenses by Accuray, Novocure. Grants by Heidelberg University, spouse employee at Roche.

Authorship statement. Ethics approval was not necessary for the comprehensive review article. All co-authors have agreed to participate. All co-authors have approved the final manuscript.

References

- Institute of Medicine. 2010. Crisis Standards of Care: Summary of a Workshop Series. Washington, DC: The National Academies Press.
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987–996.
- Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol.* 2017;18(6):e315–e329.
- Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas: clinical article. *J Neurosurg.* 2011;115(1):3–8.
- Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. *J Neurosurg.* 2012;117(6):1032–1038.
- Mukherjee RK, Back MF, Lu JJ, Shakespeare TP, Wynne CJ. Hiding in the bunker: challenges for a radiation oncology department operating in the severe acute respiratory syndrome outbreak. *Australas Radiol.* 2003;47(2):143–145.
- Severe Acute Respiratory Syndrome (SARS) Investigation Team from Defense Medical and Environmental Research Institute (DMERI), Singapore General Hospital. Strategies adopted and lessons learnt during the severe acute respiratory syndrome crisis in Singapore. *Rev Med Virol.* 2005;15(1):57–70.
- Gay HA, Santiago R, Gil B, et al. Lessons learned from Hurricane Maria in Puerto Rico: practical measures to mitigate the impact of a catastrophic natural disaster on radiation oncology patients. *Pract Radiat Oncol.* 2019;9(5):305–321.
- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* March 2020:1–3.
- Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol.* 2020.
- Liao G, Zhao Z, Yang H, Li X. Efficacy and safety of hypofractionated radiotherapy for the treatment of newly diagnosed glioblastoma multiforme: a systematic review and meta-analysis. *Front Oncol.* 2019;9(Oct):1017.
- Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol.* 2004;22(9):1583–1588.
- Malmström A, Grönberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol.* 2012;13(9):916–926.
- Phillips C, Guiney M, Smith J, Hughes P, Narayan K, Quong G. A randomized trial comparing 35Gy in ten fractions with 60Gy in 30 fractions of cerebral irradiation for glioblastoma multiforme and older patients with anaplastic astrocytoma. *Radiother Oncol.* 2003;68(1):23–26.
- Perry JR, Laperriere N, O’Callaghan CJ, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N Engl J Med.* 2017;376(11):1027–1037.
- Roa W, Kepka L, Kumar N, et al. International atomic energy agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol.* 2015;33(35):4145–4150.
- Navarria P, Pessina F, Tomatis S, et al. Are three weeks hypofractionated radiation therapy (HFRT) comparable to six weeks for newly diagnosed glioblastoma patients? Results of a phase II study. *Oncotarget.* 2017;8(40):67696.
- Gaber MH, Sakr AY, Salama DH, Hashem WB, EL-Zawahry IM. Short course versus standard course of radiotherapy in glioblastoma multiforme. *J Nucl Med Radiat Ther.* 2018;9(6):1–6.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020. doi: [10.1016/s0140-6736\(20\)30566-3](https://doi.org/10.1016/s0140-6736(20)30566-3)
- Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10). doi: [10.1056/NEJM0A043331](https://doi.org/10.1056/NEJM0A043331)
- Nabors LB, Portnow J, Ammirati M, et al. Central nervous system cancers, version 1.2017 featured updates to the NCCN guidelines. *JNCCN J Natl Compr Cancer Netw.* 2017;15(11):1331–1345.
- Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol.* 2012;13(7):707–715.
- Lehne G, Lote K. Pulmonary toxicity of cytotoxic and immunosuppressive agents. A review. *Acta Oncol.* 1990;29(2):113–124.
- Herrlinger U, Tzaridis T, Mack F, et al.; Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet.* 2019;393(10172):678–688.
- Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA.* 2017;318(23):2306.
- Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA.* 2015;314(23):2535–2543.
- Cenciari M, Valentino M, Belia S, et al. Dexamethasone in glioblastoma multiforme therapy: mechanisms and controversies. *Front Mol Neurosci.* 2019;12:65.
- Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395(10223):473–475.
- Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic. <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html>. Accessed March 29, 2020.
- ESTRO News. <https://www.estro.org/About/Newsroom/News/Radiotherapy-in-a-time-of-crisis>. Accessed March 25, 2020.