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Radiation for Glioblastoma in the Era of COVID-19: Patient Selection and Hypofractionation to Maximize Benefit and Minimize Risk --Manuscript Draft--

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| Abstract: | |

Radiation for Glioblastoma in the Era of COVID-19:

Patient Selection and Hypofractionation to Maximize Benefit and Minimize Risk

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In the midst of the COVID-19 pandemic, minimizing risk of exposure for both patients and healthcare personnel is critical. Early data suggest that cancer patients are particularly susceptible to severe illness due to COVID-19¹. Delivering a course of radiation therapy (RT) involves multiple person-to-person interactions at the individual level over many weeks, including between patients, physicians, nurses, radiation therapists, physicists, and more. Thus, many radiation oncology facilities are identifying measures to reduce exposure of patients and providers to COVID-19. Radiation oncologists are therefore revisiting the role of hypofractionated RT regimens to decrease treatment time and exposure for all involved. To that end, our central nervous system working group at a large tertiary cancer care center has drafted guidance for selecting glioblastoma (GBM) patients who would benefit from hypofractionated RT in the era of COVID-19 (**Figure 1**).

According to the Center for Disease Control and Prevention (CDC), patients aged ≥ 65 years and those with uncontrolled comorbidities (primarily cardiopulmonary conditions; **Figure 1**) are considered at risk for severe illness from COVID-19². Based on these risk factors, we recommend patients with GBM presenting for first-course RT aged ≥ 65 years should strongly be considered for hypofractionated RT regimens, in particular 40 Gy in 15 fractions, as supported by phase 3 data (**Figure 1**)^{3,4}. Special considerations can be made if these older patients have excellent performance status (PS) and are without major medical comorbidities. For patients less than 65 years with good PS (Karnofsky PS ≥ 70), we continue to favor standard fractionation with 60 Gy in 30 fractions⁵. However, individualized risk/benefit considerations should be made for those younger patients, even those satisfactory PS, if they have CDC-identified risk factors associated with increased COVID-related morbidity and mortality; this can be made in a shared decision-making model with patients (**Figure 1**). Together, for patients presenting for first-course RT in the treatment of GBM, our algorithm broadly favors use of hypofractionated RT, halving the total treatment delivery time for many GBM patients.

For patients with very poor PS (Karnofsky PS < 50), palliative regimens of either 34 Gy in 10 fractions⁶ or 25 Gy in 5 fractions⁷, each supported by prospective trial data, can be utilized for patients being considered for first-course RT. Alternatively, best supportive care or TMZ with omission of RT is reasonable (**Figure 1**). For patients with recurrent GBM, we do not generally recommend re-irradiation,

and instead favor consideration of systemic therapies if considered reasonable (**Figure 1**). These therapies may include, but are not limited to temozolomide, bevacizumab, lomustine, and others.

Within our department, a daily multidisciplinary group provides guidance to radiation oncologists on decision-making given the rapidly-changing evidence and protocols in response to the COVID-19 pandemic. This group assesses the appropriateness of safely delaying consultations or treatment, referring patients to local providers as indicated, utilization of telemedicine, and handling of COVID-19 positive patients requiring RT. Given the aggressive nature of GBM, we recommend patients who are asymptomatic, COVID-19-negative, and do not meet criteria for self-quarantine should receive RT in a manner that decreases exposure without compromising clinical outcomes as outlined (**Figure 1**). For patients who have tested COVID-19-negative, we recommend re-testing if the index of suspicion for COVID-19 infection remains high given reports of high false-negative rates (~30%) with current COVID-19 testing⁸. If a patient becomes COVID-19-positive during RT, we recommend holding RT until the patient self-quarantines for 14 days after positive test date. The patient is then screened for symptoms after completion of self-quarantine and the patient's case undergoes multidisciplinary review to determine if he/she can resume RT. Since there is no vaccine, standardized therapy, known immunity, or cure for COVID-19, the rationale for holding oncologic treatment for COVID-19-positive GBM patients, is multifactorial, including: 1) known adverse outcomes of individuals with cancer diagnosis and COVID-19 infection¹, 2) increased risk of exposure of other COVID-19 negative individuals (other immunocompromised cancer patients, RT providers, and front-line staff), or 3) depletion of limited personal protective equipment (PPE) resources. Thus, we believe the decision to resume RT in a clinically recovered, COVID-19-positive patient with anticipated life expectancy of greater than 6 months would require self-quarantine for 14 days after test date, negative for COVID-19 related symptoms after self-quarantine, and multidisciplinary panel review of the patient's case to determine risk-to-benefit ratio of proceeding with oncologic therapy with consideration of hypofractionated RT as clinically feasible.

In conclusion, the COVID-19 pandemic is likely to impact oncologic management in a lasting way, and the recommendations provided here may evolve over time. Other institutions should consider implementing these guidelines in accordance with local institutional, state, and federal regulations and with multidisciplinary discussions with radiation oncology, neuro-oncology, and neurosurgery. Collectively,

we believe these recommendations allow safe, effective, and expedient RT for GBM patients in the era of COVID-19.

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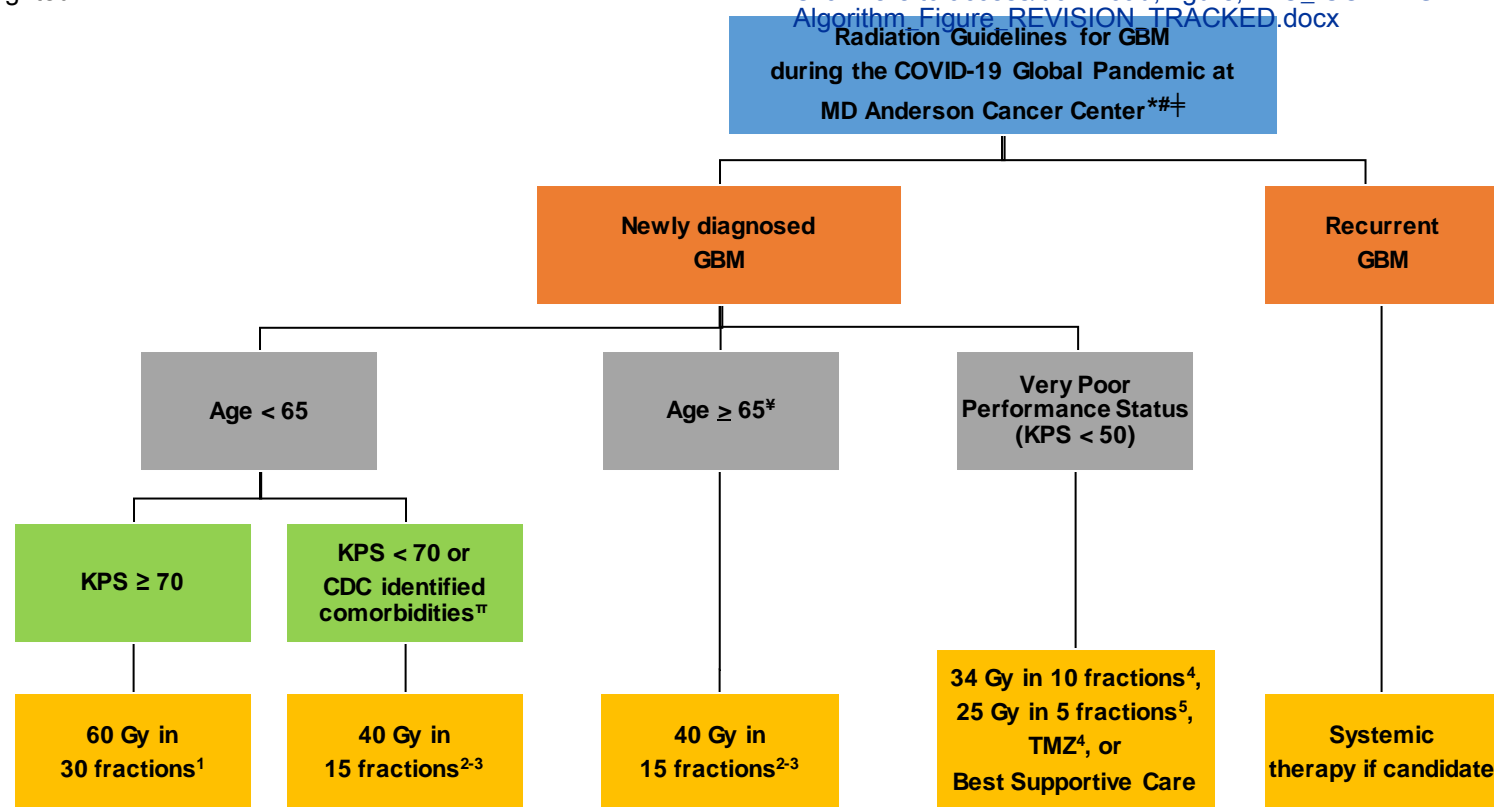


Figure 1: Algorithm of Radiation Guidelines for GBM during the COVID-19 Global Pandemic at MD Anderson Cancer Center: Radiation recommendations regarding GBM in asymptomatic, COVID-19 negative, and/or patients not requiring self-quarantine at a major tertiary cancer center.

*: Healthcare guidelines during COVID-19 pandemic are dynamic and application of the guidelines outlined should be in accordance with local institutional, state, and federal guidelines. Consider travel restrictions for new patients and use of a telemedicine platform to monitor patients for side-effects while on treatment.

#: recommend multidisciplinary discussion with radiation oncology, neuro-oncology regarding systemic therapy, and neurosurgery

‡: In patients who have tested COVID-19 negative, we recommend re-testing if the index of suspicion for COVID-19 infection is high. If a patient becomes COVID-19 positive during RT, we recommend holding RT until the patient tests negative until the patient self-quarantines for 14 days after positive test date. The patient is then screened for symptoms after completion of self-quarantine and the patient's case undergoes multidisciplinary review to determine if he/she can resume RT.

‡: consider 60 Gy in 30 fractions with excellent performance status and without high risk CDC identified COVID-19 comorbidities.

™: consider risk/benefits of hypofractionated RT if patient has the following uncontrolled comorbidities as identified by the CDC: chronic lung disease, moderate to severe asthma, serious heart conditions, immunocompromised, severe obesity, diabetes, chronic kidney disease undergoing dialysis, liver disease

Abbreviations: Glioblastoma (GBM); Karnofsky Performance Status (KPS); Center for Disease Control and Prevention (CDC); TMZ (temozolamide); Radiation treatment (RT)

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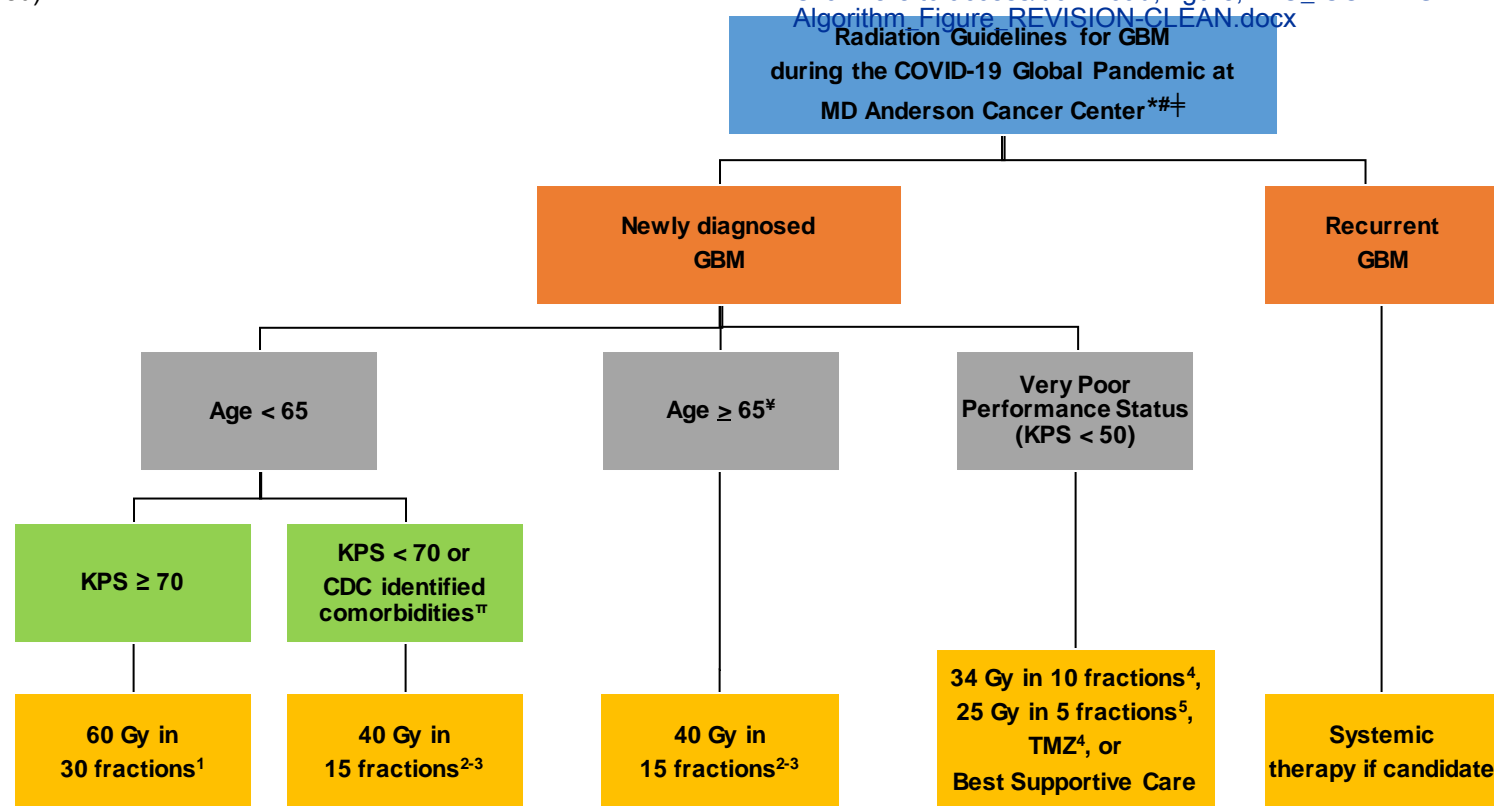


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