



Short Communication

Management of Glioblastoma Multiforme as a Big Challenge for Neurosurgeons and Radiation Oncologists in Covid-19 Era: An Institutional Experience in a Rural Sub-Himalayan Region

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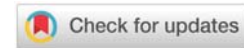
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Abstract

Objectives: To illustrate our institutional experience about the challenges we faced and steps taken in the management of the patients with Glioblastoma multiforme during Covid 19 crises at Dr. R.P.G.MC Tanda.

Methods: In the period of complete lockdown, patients were treated surgically without much delay. Patients with incomplete resection were given radiation while the ones with complete resection were started on tablet temozolamide (TMZ) alone and were sent home after counselling. At the period of partial lockdown patients below 70 years were given option of starting on hypofractionated radiation or tab temozolamide, 55% of the patients preferred radiation over temozolamide while rest continued on tablet temozolamide. Further, the patients above 70 years were continued on tablet temozolamide and were kept on telephonic check for the onset of any neurological symptoms, those developing symptoms were immediately called and started on short course radiotherapy to a dose of 40GY/15#/3 weeks or 34GY/10#/1 weeks or 25GY/5#/1 week or were treated by Stereotactic radiotherapy 8GY/5# by Volumetric Arc Radiotherapy.

Results: In our institute all of our GBM patients below 70 years remained asymptomatic when started on the non standard treatment- on tab temozolamide only post surgery or on hypofractionated course of radiotherapy and only 2% patients above 70 years developed slight symptoms showed progression of disease on check MRI scan were given hypofractionated radiotherapy.

Conclusion: Covid 19 pandemic has resulted in unprecedented global healthcare crises. Our institution has illustrated the challenges we faced in managing patients with highly dreadful Glioblastoma multiforme. Due to the fear of increased risk of Covid 19 infection in the cancer patients which would result in devastating complications and very poor outcome, the non standard strategy of keeping the patients on tab temozolamide only post surgery or on hypofractionated course of radiotherapy resulted in symptomatic relief in patients below 70 years of age and only 2% patients above 70 years who developed slight symptoms showed progression of disease on check MRI scan. . Though, not standard this strategy can be considered in covid-19 crises.

Introduction

On March 11, 2020 Coronavirus disease (Covid-19) was declared as global pandemic by the World health organization [1]. This has resulted in unprecedented challenges and changes in healthcare delivery everywhere so as to reduce exposure to virus and transmission. The brain tumours like Glioblastoma Multiforme (GBM) deserves special attention due to its presentation in older age and being more vulnerable to Covid-19 infection. Dealing with these types of terminal illnesses while keeping lowest burden on healthcare system and especially on intensive care units becomes very challenging. So Neuro-oncology and Radiation oncology departments should immediately develop pessimistic and coordinated approach to ensure best possible oncological care while protecting the patients and staff from the novel Covid-19 infection. Delaying surgical intervention in GBM by the neurosurgeon is non justifiable and he must deal it like an emergency case, on the other hand radiation oncologist can use some other alternatives like short course radiation therapy or some other alternative to decrease number of hospital visits.

Why is counselling GBM patient his Relatives so challenging?

As cancer is taken as stigma in the society, and when patient is diagnosed with brain tumour that too with the most aggressive and lethal tumour he and his relatives become helpless and hopeless. Moreover, in the period of such pandemic when he needs immediate treatment and everything gets shut down even hospital which remains the last hope for him, he becomes completely broken with continuous fear of disease progression and death. Counselling them at this point of time is also very challenging

Why is management of GBM so challenging to the neurosurgeons in this pandemic?

As GBM is the disease of old age and patients usually have co-morbidities which is itself challenging.

Owing to the exponential increase in the number of cases with very high infectivity rate, most of the neurosurgeons had stopped elective interventions in some benign brain tumours, but GBM is a very aggressive tumour with very high proliferative rate and postponement of surgery in any circumstances is not at all justifiable.

Surgical intervention in GBM is not that easy owing to advanced stage, advanced age, co-morbidities, immunosuppression and big tumour size sometimes hampering complete tumour resection resulting in fatal outcome. If surgery is not carried out on time then these tumours would grow very rapidly in short period of time leading to increased neurological morbidity and many times earlier death.

As every patient should be considered as Covid case unless proven otherwise, and these long lasting neurological surgeries results in increased risk to the whole surgical team. Moreover, there are high chances of need of intensive care unit (ICU)

especially if patient turns out to be Covid-19 positive, further burdening the already burdened ICU's.

Why is management of GBM so challenging to the radiation oncologists in this Pandemic?

Post-operative radiotherapy is indispensable for GBM with clear cut survival benefit in randomized studies [2]. In the period of Covid-19 crises it is very difficult to start new patients on machines that too for longer durations when maintaining social distancing and preventing virus transmission is utmost important. Moreover, a situation in which any patient on treatment contracts infection would lead to very bad consequences like hampering the treatment of other patients, need to shut down machine, treatment breaks and further prolongation of treatment leading to poor treatment outcome.

What is the standard management of GBM ?

As per NCCN guidelines: For patients < 70 years, KPS>60- Standard Brain Radiotherapy (60GY/30#/6 weeks) with concurrent and adjuvant Temozolamide is the standard of care.

For patients > 70 years old, KPS< 60-Hyofractionated radiotherapy +/- concurrent or adjuvant temozolamide OR temozolamide alone.

For patient > 70 years: Hypo fractionated Radiotherapy (40GY/15#/3 weeks), Temozolamide alone or best supportive care.

For what time radiotherapy can be postponed after surgery?

Ideally Radiation (RT) should not be postponed, it should be given as per guidelines, ASCO guidelines states that RT should be initiated as soon as safely permissible; some trials have started RT within 3-6 weeks of surgery.

One study on 172 patients showed that the addition of every one week (after 2 weeks of surgery) increases the risk of death by 8.9% [3], while another study on 179 patients of malignant glioma showed no effect of waiting time between surgery and radiotherapy on survival [4].

The delay in initiating radiotherapy in GBM leads to detriment in overall survival was shown in three case series [3-5]. In contrast to this there was no reduction in survival with delayed radiation by 6 weeks after diagnosis on analysis of 2855 patients in 16 Radiation Therapy Oncology Group (RTOG) studies [6].

Why Should we consider Hypofractionated radiotherapy in this Pandemic?

Hypofractionated Radiotherapy (HFRT) gets completed early, and thereby, reduces burden on medical resources, patient himself and his relatives [7].

Evidence says that in older patients (>60 years or more) there is no difference in median survival between HFRT and standard course radiotherapy [7-9] and had better survival in



patients of more than 70 year [8]. Further, there is less need of increasing corticosteroids dosage [7]. The another phase II study by Roa, et al. [7] compared 40GY/15# versus 25GY/5 # and found no difference in median Overall survival (7.9 months versus 6.4 months).

The authors suggest that elderly patients (aged >65 years) with glioblastoma should strongly be considered for hypofractionated RT regimens of 40 Gy in 15 fractions [10].

For patients with very poor performance status (PS; Karnofsky PS [KPS] <50 or Eastern Cooperative Oncology Group [ECOG] score 3-4, the authors recommend the palliative regimens like 34 Gy in 10 fractions, 25 Gy in 5 fractions, or temozolomide with the omission of RT, and each regimen was supported by prospective trial data [7,8].

Protocol Followed at out institute at the period of Covid-19

In the period of complete lockdown, patients were treated surgically without much delay. Patients with incomplete resection were given radiation while the ones with complete resection were started on tablet temozolamide (TMZ) alone and were sent home after counselling. In view of still persisting unclarity regarding ideal timing of initiation of radiotherapy in many studies, patients who were taken chance on TMZ were kept on check by teleconsultation. At the period of partial lockdown patients below 70 years were given option of starting on hypofractionated radiation or tab temozolamide, 55% of the patients preferred radiation over temozolamide while rest continued on tablet temozolamide. Further, patients above 70 years were continued on tablet temozolamide and were kept on telephonic check for the onset of any neurological symptoms. Those who developed symptoms were immediately called and were started on short course radiotherapy to a dose of 40GY/15#/3 weeks or 34GY/10#/1 weeks or 25GY/5#/1 week or were treated by Stereotactic radiotherapy 8GY/5# by Volumetric Arc Radiotherapy.

Steps taken in our institute to decrease rush in the outpatient care are given in Table 1.

Table 1: Steps taken in our institute to decrease rush in the outpatient care.

Purpose	Measures
Reducing the risk of patients exposure	The visits were restricted to the patients on active treatment /requiring urgent attention. All the routine follow-ups were postponed and teleconsultation was started. All unnecessary interventions like routine imaging, blood tests, serum markers in asymptomatic patients were postponed limiting the number of patients in waiting area posters pasted in waiting area regarding social distancing
Reducing the exposure to the staff	Only patients were allowed inside the OPDs. Only one attendant (uninfected) was allowed to accompany the patient outside OPDs. To minimize the exposure to the staff, roster was made in which healthcare workers and physicians were not called daily and were assigned specific duty days
Reducing the number of medical staff	Reducing the number of nursing staff. Reducing the number of staff at reception. All the staff to wear gowns, masks and gloves

Precautions taken in the Radiation Zone by our Institute

To protect both the patients and staff, weekly team rotation was done, thereby, reducing the number of workers at this period of crisis. The patients already on treatment, finishing the treatment was the priority while delaying radiation for others. To avoid overcrowding only patients thermal screening and after asking about the symptoms related to Covid-19, were allowed to enter while keeping attendant outside the main door.

Patients were treated in dedicated time slots with staff wearing the protective equipment. The treatment couch was always sanitised after treatment of each patient. The posters regarding measures taken for self care were posted on the walls in Hindi and were advised to read them. The whole area was properly decontaminated and sanitised daily.

Results

All patients whether with completely resected tumour on tablet temozolamide or incompletely resected tumour post hypofractionated radiotherapy remained asymptomatic. All patients below 70 years irrespective of treatment (radiation or temozolamide) remained asymptomatic.

After telephonic conversation with the patients of over age 70 years, we came to know that all patients remained asymptomatic post surgery while on TMZ, except only 2% became anxious on developing symptoms like weakness, giddiness, and these patients showed radiological progression on check MRI Scan, and were given hypofractionated course of radiotherapy.

Conclusion

The present situation forced us to modify our treatment plans by using hypofractionated radiotherapy or temozolamide to minimize the risk of exposure and transmission. We should try our best to provide best possible treatment. Though, starting young patients on hypofractionated radiotherapy or tab temozolamide alone is not the standard, patients can be given hypofractionated radiotherapy or started on tab temozolamide post surgery with active surveillance to decrease burden on radiotherapy treatment machines in Covid-19 era . Thus, options different from current guidelines unlikely to result in major significant negative impact on individual patient can be considered.

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