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ISNO Position Statement on Treatment Guidance in Neuro-oncology During Pandemics

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Abstract:

The entire world including India is currently fighting the coronavirus disease 19 (COVID-19) pandemic that threatens to disrupt healthcare systems globally in terms of capacity and resources. This outbreak necessitates an urgent review of existing management guidelines for commonly encountered tumors of the brain and central nervous system (CNS). Such a review should include a reassessment of benefit-risk ratio to align with local, national, and international priorities without compromising on delivery of care in terms of safety, compassion, efficiency, and effectiveness. Towards this end, the Indian Society of Neuro-Oncology (ISNO) constituted an online expert panel with adequate representation from all major treatment modalities (neuro-surgery, radiation oncology, and pediatric/medical oncology) to formulate a "COVID-19 context" position statement to guide the care of neuro-oncology patients during the ongoing crisis. The ISNO position statement suggests graded prioritization (based on clinical presentation, type of tumor, expected prognosis, and relevance of immediate therapy) for efficient utilization of resources and provides a framework through a set of general considerations, treatment modality-based considerations, and disease-specific considerations for the guidance of healthcare professionals involved in the delivery of care and services to patients with CNS tumors. The views expressed herein represent the current consensus of key opinion leaders from within the Indian neuro-oncology community and should not be in any case considered binding medically or legally to individual physicians and/or hospitals who may formulate their guidelines based on local setup and health-environment and update them periodically based on emerging evidence through the COVID-19 pandemic.

Kev Words:

COVID-19, neuro-oncology, pandemics, prioritization

Key Message:

Widespread disruption of healthcare systems caused by COVID-19 pandemic mandates urgent reassessment of benefit-risk ratio of standard treatment guidelines with a view to formulate pragmatic COVID-context neuro-oncology care considerations and recommendations.

Tumors of the brain and central nervous system (CNS) though relatively rare, comprising <2% of the overall cancer burden, are a substantial source of cancer-related morbidity and mortality worldwide. [1,2] Significant heterogeneity in the disease spectrum, diverse biological behavior, and highly variable prognosis mandate specialized and skilled multidisciplinary care to guide therapeutic decision-making in neuro-oncology. [2] The outbreak of a contagious viral pandemic such as the coronavirus disease 19 (COVID-19) with high infectivity threatens to disrupt healthcare systems globally in terms of capacity and resources. [3] With several thousand confirmed

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COVID-19 positive cases in India at the time of writing of this report, the coming few weeks/months are likely to witness community transmission of disease in the country resulting in an exponential increase in the number of such infected individuals needing hospitalization, intensive-care, and ventilatory support putting an unprecedented burden on healthcare systems. Older patients, particularly those with comorbid conditions such as diabetes, hypertension, and cancer and resultant immunocompromised state are far more vulnerable and susceptible to getting infected and developing severe forms of the disease with higher mortality rates. [4] This outbreak necessitates an urgent review of existing

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management guidelines for various cancers^[5,6] including the commonly encountered CNS tumors. Such a review should include a reassessment of benefit-risk ratio to align with local, national, and international priorities without compromising on delivery of care in terms of safety, compassion, efficiency, and effectiveness. Documented response to the severe acute respiratory syndrome (SARS) outbreak in Singapore resulted in the prepare, communicate, operate, and compensate strategy^[7] to mitigate and fight such pandemics. Institutions and departments need to have proper contingency planning to create capacity and continue to provide essential services despite reduced workforce. Appropriate triage of neurosurgical as well as oncological referrals with considered change in existing treatment paradigms are likely to be necessary to tide over the present crisis. The European Association of Neuro-Oncology (EANO), Royal College of Radiology (RCR), and British Neuro-Oncology Society (BNOS) have recently formulated guidance documents[8-10] for consideration of daily care in neuro-oncology as well as treatment-modality and disease-based considerations for common CNS tumors during the COVID-19 pandemic to help the neuro-oncology fraternity worldwide. There is a hierarchy of needs and what measures need to be implemented, when and how would vary with the severity of the pandemic and the local capacity.

Position Statement

Indian Society of Neuro-Oncology (ISNO), the premier-most academic forum for promoting and advancing the field of neuro-oncology in the country stands strongly with the world community in this hour of crisis. Coping with a crisis requires strong leadership, war-like preparedness, efficient use of resources, and clear communication with all relevant stakeholders. Towards this end, ISNO constituted an online expert panel comprising of its senior leadership, with adequate representation from all major treatment modalities (neuro-surgery, radiation oncology, and pediatric/ medical oncology) to formulate a "COVID-19 context" position statement to guide the care of neuro-oncology patients during the ongoing pandemic. The expert panel reviewed available resources through online discussions and deliberations to create this guidance document for healthcare professionals involved with the delivery of neuro-oncology care and services. The views expressed herein represent the current consensus of key opinion leaders from within the Indian neuro-oncology community and should not be in any case considered binding medically or legally to individual physicians and/or hospitals who may formulate their guidelines based on local setup and health-environment and update them periodically based on emerging evidence through the COVID-19 pandemic.

General considerations

- Patients should be actively discouraged to visit hospitals/ clinics for routine checkups and follow-up assessments unless clinically indicated
- Physicians should reduce the frequency of surveillance neuroimaging, which should be done only to guide clinical decision-making
- 3. Physicians should adopt remote consultation (telephonic, video, or online)^[11] to avoid unnecessary overcrowding by applicable local/national laws and telemedicine guidelines^[12]

- 4. Hospitals should recommend high levels of carefulness in patients and staff (personal hygiene and social distancing) including the use of personal protective equipment (PPE)
- 5. Hospitals and departments should devise and review contingency plans periodically to deal with the ongoing crisis
- Physicians and hospitals should ensure the continuation of ongoing therapy with appropriate modifications as desirable
- Physicians should liaise and coordinate with colleagues within the city/region to ensure uninterrupted and timely completion of active ongoing therapy in the likely event of partial or complete shut-down of services at their institute
- 8. Physicians and hospitals should create a graded and tiered priority-list [Figure 1] based on the type of tumor, recommended therapies, expected prognosis, risks, and current resources, which may vary dynamically over time
- 9. A multidisciplinary team (MDT) should discuss "standard advice" as well as "COVID-context advice" with patients and caregivers clearly explaining the differences between the two with appropriate documentation. Physical attendance at such MDT meetings should be avoided or restricted to key decision-makers only. Hospitals should strongly consider conducting virtual tumor boards through online resources
- 10. COVID-context regimens need not necessarily be based on high-quality (level I) evidence from randomized controlled trials, but could be supported by prospective phase II data, retrospective studies, or even personal/institutional experience.

Priority levels [Figure 1]

- Low priority: small benign brain tumors (meningioma, pituitary adenoma, or acoustic schwannoma); and low-grade glioma (LGG)
- Low-medium priority: elderly glioblastoma; recurrent/ progressive glioblastoma; and metastatic disease in the brain and/or spine
- Medium priority: high-risk and/or metastatic medulloblastoma; high-grade glioma (HGG) including glioblastoma in the non-elderly; primary CNS lymphoma; and craniopharyngioma

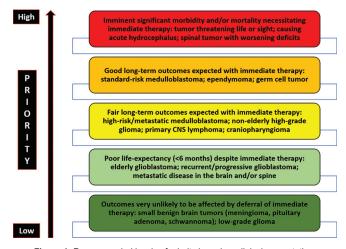


Figure 1: Recommended levels of priority based on clinical presentation, type of tumor, expected prognosis, and relevance of immediate therapy. Note the color-coding as green (lower priority), yellow (medium priority), and orange-red (higher priority)

- High-medium priority: standard-risk/nondisseminated medulloblastoma; ependymoma; and intracranial germ cell tumor (GCT)
- 5. High priority: Large benign tumors presenting with acute life or sight-threatening symptoms including posterior fossa tumors (benign or malignant) causing gross obstructive hydrocephalus; intradural extramedullary spinal tumors with threatening/worsening neuro-deficits.

Treatment modality-based considerations *Neurosurgery*

Neurosurgical oncologic emergencies such as large intracranial tumor with significant mass effect, midline shift, and neuro-deficits; posterior fossa lesion causing symptomatic obstructive hydrocephalus; arteriovenous malformation (AVM) with recent bleed; and primary spinal tumors with threatening/ worsening neuro-deficits would still need to be considered for urgent neurosurgical intervention. However, appropriateness of surgery has to be reviewed on an individual basis, based on the availability of the intensive-care facility, and the likelihood of receiving further adjuvant therapy. Consider temporary cerebrospinal fluid diversion through endoscopic third ventriculostomy or ventriculoperitoneal shunt in the pineal and/or posterior third ventricular tumors to relieve symptoms of obstructive hydrocephalus and defer definitive surgery. Consider less invasive approaches such as stereotactic biopsy or mini-craniotomy that may be accomplished as day-care procedures without the need for an overnight stay or prolonged hospitalization to reduce procedure-related morbidity and burden on in-patient services. Consider postponement of elective surgery for benign tumors such as meningioma, schwannoma, pituitary adenoma, and LGG without mass effect.

Radiotherapy

It is extremely important to ensure the continuation of ongoing radiation therapy (RT) with modifications as appropriate but without unwarranted treatment interruptions. At the same time, it is equally important to triage new referrals for RT such that patients who are likely to derive the maximum benefit are accorded the highest priority. Consider omitting adjuvant RT for tenuous indications such as meningioma (benign and atypical), pituitary adenoma, schwannoma, and LGG. Consider the use of hypofractionated schedules (40 Gy/15 fractions/3-weeks, 30-35 Gy/10 fractions/2-weeks, or even once-weekly RT) in appropriately selected patients with HGG including children with diffuse intrinsic pontine glioma,[13-16] which not only reduces the number of hospital visits thereby reducing exposure-risk to patients but also imposes a lesser burden on the already constrained healthcare system. Children with medulloblastoma, ependymoma, and intracranial GCT should continue to receive standard of care RT as usual. Consider postponement of stereotactic radiosurgery (SRS) for asymptomatic AVM by few months. Consider best supportive care alone with the omission of whole-brain radiation therapy (WBRT) in patients with multiple brain metastases and limited life-expectancy (<3-6 months). Consider deferral of adjuvant RT for primary spinal tumors in minimally symptomatic patients or patients with stable neuro-deficits. Consider single-fraction palliative RT with adequate and appropriate pharmacotherapy (analgesics, anti-inflammatory, and steroids) for bone metastases/metastatic spinal cord

Systemic therapy

Age, Eastern Co-operative Oncology Group (ECOG) performance status (PS), isocitrate dehydrogenase (IDH) mutation, and methylation of the O6-methyl-guanine methyltransferase (MGMT) gene promoter should be considered for decision-making regarding chemotherapy in adult diffuse glioma. Consider omitting chemotherapy in patients where the benefit is marginal or modest at best such as IDH-wild type^[17] and/or unmethylated MGMT, [18] but, poses significant risks particularly in the context of immune-suppression and risk of acquiring infections. Consider oral and less toxic chemotherapy such as temozolomide instead of procarbazine, lomustine (CCNU), vincristine (PCV) regimen in patients with lower-grade gliomas. Systemic chemotherapy should be offered with due risk in patients with a consistent and high benefit such as primary CNS lymphoma, embryonal CNS tumor, and intracranial GCT. Given the lack of clinically significant and meaningful benefit, the use of targeted therapy, and immunotherapy should be avoided in recurrent/progressive HGG during this time.

Disease-specific considerations

- (i) Glioblastoma in the elderly (≥65 years) and/or frail (ECOG PS ≥ 2) patients:
 - -consider the best supportive care alone in the elderly and frail patients.
 - -consider temozolomide (TMZ) monotherapy in selected patients with methylated MGMT.
- (ii) Glioblastoma in young (<65 years) and fit (ECOG PS 0–1) patients:
 - -consider surgery with due precautions followed by appropriate adjuvant therapy.
 - -could occasionally consider therapy without tissue diagnosis in selected patients (clinico-radiologically consistent with glioblastoma).
 - -consider using hypofractionated RT regimens wherever possible.
 - -consider the omission of adjuvant TMZ chemotherapy in unmethylated tumors.
- (iii)Diffuse grade III glioma (IDH-mutant and 1p/19q co-deleted):
 - -consider deferral of RT for 3-6 months.
 - -consider using systemic chemotherapy till deferral of RT. -consider using TMZ monotherapy instead of the PCV regimen.
 - -consider switching to TMZ from the next cycle, if the patient already on the PCV regimen.
 - -consider using reduced-dose single-agent CCNU orally, if switching to TMZ is not feasible.
- (iv)Diffuse grade III glioma (IDH-mutant but 1p/19q non-co-deleted):
 - -consider standard RT with or without concurrent TMZ chemotherapy.
 - -consider deferral of adjuvant TMZ chemotherapy for 3–6 months.
 - -consider avoiding PCV or single-agent CCNU.
- (v) Diffuse grade III glioma (IDH-wild type):
 - -consider standard RT alone without concurrent or adjuvant TMZ chemotherapy.
 - -consider avoiding PCV or single-agent CCNU.
- (vi)Medulloblastoma and other embryonal CNS tumors: -consider risk-stratified adjuvant RT and chemotherapy as appropriate.

-consider only best supportive care in patients with widespread leptomeningeal dissemination.

(vii) Germ cell tumors:

-consider platinum-based chemotherapy and RT as appropriate.

(viii) Primary CNS lymphoma:

-consider treatment on presumptive clinico-radiological diagnosis, if a biopsy is difficult.

-consider high-dose methotrexate-based chemotherapy in young and fit patients; could consider reducing methotrexate dose to somewhat lesser intensive levels.

-consider avoiding rituximab during methotrexate-based induction and even in consolidation.

-avoid high-dose chemotherapy and autologous stem-cell transplantation (ASCT).

-consider WBRT as consolidation instead of ASCT.

- (ix)Benign brain tumors (meningioma, pituitary adenoma, schwannoma):
 - -consider deferral of surgery for 3-6 months.
 - -consider deferral of postoperative adjuvant RT for 3–6 months.

(x) Brain metastases:

-consider alternatives to neurosurgical resection such as SRS or WBRT as appropriate.

-consider best supportive care alone omitting palliative WBRT in patients with multiple brain metastases with limited life-expectancy.

(xi)Spinal tumors:

-consider surgical decompression for primary spinal tumors with worsening neuro-deficits.

-consider deferral of surgery for patients with radiculopathy only and/or minimal symptoms.

-consider deferral of adjuvant RT for patients with minimal symptoms and/or stable deficits.

-consider single-fraction palliative RT for bone metastases/metastatic spinal cord compression.

Discussion

The COVID-19 pandemic has created an unprecedented strain on medical resources throughout the world necessitating prioritization to balance acuity of medical needs with available resources and capacity. A consensus statement on neurosurgery and neurology practices during the COVID-19 pandemic was recently published from India.^[19] Briefly, it states that every patient should be considered as a potential asymptomatic infected case. Categorization for treatment should be based on perceived priority as acute, subacute, or chronic. Non-essential elective surgeries and routine outpatient visits should be avoided as far as possible. High risk of aerosol dispersion during intubation and certain neurosurgical interventions (particularly those involving drills and endoscopes) mandates that these procedures be performed in appropriately modified operating rooms wearing full PPE to mitigate risks and reduce exposure.[19] The Tumor Section of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) and the Society for Neuro-Oncology (SNO) have jointly proposed a framework to provide general guidance to neuro-oncology practitioners towards outpatient and inpatient case prioritization amidst the COVID-19 pandemic. [20] In the resource-constrained environment (some resources available for non-COVID care), their recommendations are generally similar to the ISNO position statement. In the event of all hospital resources being devoted to COVID care, they recommend that neuro-oncologic treatments be considered only for true emergencies such as life-threatening mass effect with imminent herniation, impending paraplegia, hematoma, and infections. [20] More specifically, urgent considerations for the neuro-oncologic treatment of patients with gliomas during the COVID-19 pandemic have also been proposed.^[21] Briefly, these recommendations include offering a standard of care therapies for newly-diagnosed MGMT methylated glioblastoma and IDH-mutant anaplastic astrocytoma, while considering short-course RT and avoidance of TMZ for unmethylated and/or IDH-wild type diffuse gliomas. For patients with IDH-mutant low-grade astrocytoma and oligodendroglioma (with codeletion of 1p/19q), therapy could be deferred in asymptomatic patients and individual case by case decision in symptomatic cases. For recurrent high-grade gliomas, bevacizumab should be considered only for palliation of neurologic symptoms and all treatments with no evidence of survival benefit should be avoided. [21] In parallel, the European Neuro-oncology Community has also outlined its framework for the management of patients with high-grade glioma during the pandemic.[22] Standard of care therapy should be offered wherever possible; however, if this is not possible due to compromised resources, alternative treatment options need to be considered that balance healthcare capacity with the current standard approach. Briefly, neurosurgical decisions need to be individualized based on necessity, urgency, and capacity. Principles of RT should focus on the use of hypofractionation where possible. It is not recommended to withhold chemotherapy for all patients, which must be evaluated based on the extent of the crisis, available resources, and benefit-risk ratio.[22] Withholding TMZ chemotherapy could be an option in specific situations depending on the molecular profile (unmethylated MGMT, IDH-wild-type), poor prognosis category (elderly, frail patients), and pandemic state (late-stage).

Conclusions

The global neuro-oncology community including in India should exercise all reasonable and appropriate precautions to protect themselves as well as their staff and patients in the delivery of care and clinical decision-making during the COVID-19 pandemic. Precautions may include but not necessarily be restricted to pre-procedural testing for COVID-19, use of appropriate PPE, and maintenance of a conducive care-delivery environment while providing care to infected or suspected patients. Physicians should reassess the benefit-risk ratio of existing treatments and discuss COVID-context decisions with patients and family, emphasizing the temporary nature of these recommendations to tide over the crisis. Such decisions are likely to be affected by prioritization, availability of healthcare resources, local/national guidelines, and applicable statutory requirements.

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Conflicts of interest

There are no conflicts of interest.

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