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GUIDELINES

Natura non facit saltus: a phase 2 proposal to manage brain tumors cases from the Neuro-oncology section of the Italian Society of Neurosurgery (SINch®)

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ABSTRACT

The Coronavirus (COVID-19) pandemic has fast spread throughout the world in more than 200 countries, resulting in the need for a de-prioritization of elective medical care to face the demands of the global health crisis. Although the acute and catastrophic phase of the pandemic seems to have been left behind, it is also clear that the virus will not disappear soon, and we must live with it for a period of unpredictable length, the COVID-19 era. In this setting, a common coordinated approach to treat patients harboring brain tumors is urgently required to guarantee the best updated oncological care and to reduce the risk of viral infection during hospitalization. The study group on Neuro-oncology of Italian Society of Neurosurgery, SINCh gathered pieces of evidence and data and would like to suggest a practice protocol of care for neurosurgical oncologic procedures in the COVID-19 era. The present document aimed at summarizing current evidence and expert opinions to help neurosurgeons in taking decisions on their patients harboring different brain tumors.

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KEY WORDS: Brain neoplasms; Neurosurgery; COVID-19.

The Coronavirus (COVID-19) pandemic has fast spread throughout the world in more than 200 countries, resulting in the need for a deprioritization of elective medical care to face the demands of the global health crisis.[1-5] Although the acute and catastrophic phase of the pandemic seems to have been left behind, it is also clear that the virus will not disappear soon, and we must live with it for a period of unpredictable length, the COVID-19 era. In the meantime, the decision-making process for neurosurgical cases is constantly evolving due to restricted availability of both human resources (that are eventually rerouted to COVID units) and facilities (Intensive Care Unit beds)

which differently affect hospitals depending on the geographic area even into the same country.[4, 6-10]

In this setting, neuro-oncologic cases management needs to be rethought. Moreover, it should be emphasized that patients harboring brain tumors with deferable management in which surgical treatment was postponed during the emergent phase need to be treated in the post-pandemic phase and engulfment of the neurosurgical departments should be avoided.

A common coordinated approach to treat patients harboring brain tumors is urgently required to guarantee the best updated oncological care and to reduce the risk of viral infection during hospitalization.[3, 11, 12]

Under the auspices of the Italian Minister of Health, an intersocieties group of experts representative of most surgical specialties, including the Italian Society of Neurosurgery (SINCH) has delivered a document on the surgical management of patients in the post-emergent phase 2.[13] Nevertheless, a specific document addressing the specific issue of neurosurgical oncologic patients is missing.

The study group on Neurooncology of Italian Society of Neurosurgery, SINCh gathered pieces of evidence and data and would like to suggest a practice protocol of care for neurosurgical oncologic procedures in the COVID-19 era. The present document is aimed at summarizing current evidence and expert opinions to help neurosurgeons in taking decisions on their patients harboring different brain tumors.

General considerations

All preventive measures for the containment and biological risk on staff and patients must be seriously considered.[11, 14, 15]

All emergency patients should undergo a proper triage before neurosurgical evaluation and surgery.

If it is impossible to carry out any type of test and if it is impossible to procrastinate the surgical procedure, the possibility of performing the procedure with advanced Personal Protective Equipments (PPEs), in dedicated operating rooms or to postpone it, will be evaluated.

For elective surgery, all patients should undergo testing as close as possible to surgery.

COVID-19-free diagnostic, therapeutic, and inpatient separated pathways must, therefore, be provided. To ensure the health of the patient and staff, days of hospitalization must be reduced to the minimum, increasing prehospitalization where possible, with examinations and tests that must be repeated at the time of hospitalization.[11, 14-16] Consequently, the choice of operating on complex lesions that could eventually have longer and/or complicated hospital stay must be carefully weighted. Concerning operating room risks, some procedures can be considered at medium-low risk (craniotomies, spine surgery) while others such as endoscopic or transoral endoscopic interventions must be considered at high risk of viral "aerosolization" with possible contamination of the environments and the personnel; hence in positive or frankly symptomatic COVID-19 patients operating rooms should be protected with positive pressure.[11, 17, 18]

To limit the number of outpatient accesses, it could be important to plan the examinations necessary for surgical planning in a scheduled hospitalization regime, after oro/nasopharyngeal swab screening. All patients candidates for surgical procedure should be tested with a nasopharyngeal swab (recent data would suggest two given the high percentage of false negatives).[19]

All the above tests are recommended on an outpatient basis, confirming the indication for neurosurgical hospitalization only in case of negative tests. An alternative could be to stop patients in a "gray" area where to perform the swab and admit the patient to the ward only after the swab has responded

In the case of positivity, the elective patient will follow the path of quarantine or hospital stay according to the clinical status.

Similarly, in those patients in follow-up, it should be adopted all the strategies to reduce at minimum the hospital accesses for clinical evaluation and post-operative MRI.

The day before access to the hospital, a telephone interview is administered; temperature is registered upon hospital admission and eventual COVID-19 diagnostic (either serological or swab) exam is run.

Upon any suspicion of COVID-19 patients will be referred to infectivologist and neurosurgical examination will be not completed unless the patient is exposed to concrete risks *quoad vitam et valetudinem*.

Chest X-ray and preop anesthesiological consult are crucial: chest CT scan can help ruling out the clearance process.

High-grade gliomas

High-grade gliomas (HGGs) can present a fast growth kinetic and the delay of surgery and subsequent therapies can lead to permanent neurological deficits, epileptic seizures and in some cases, early death.

Surgery must not only be timely but also carefully

planned. Modern glioma surgery focuses on the optimal balance between tumor removal and preservation of neurocognitive functions. To achieve this, a detailed and personalized anatomical-functional preoperative planning is crucial.[20] Nowadays, there are a variety of tools available, such as neuro-navigation, intraoperative imaging, and functional mapping, which can be useful in obtaining optimal tumor resection with minimal or transient postoperative neurological morbidity.[21-24]

Regarding older patients that tend to be more fragile and/or have additional comorbidity conditions (diabetes, cardiovascular disease, severe kidney, liver, and pulmonary chronic diseases),[25] the surgical indication of biopsy or resection may not be indicated, thus preferring different treatments (such as radiotherapy and/or chemotherapy) based on radiological assessments alone.[3]

It is of utmost importance that HGG patients, due to their intrinsic fragile condition, should be protected and undergo more stringent preventative measures throughout the entire follow-up to minimize the risk of COVID 19 infection. Therefore, in addition to maintaining the necessary safety distance, it is also necessary to limit all unnecessary interactions with HGG patients.

The decision of whether to perform outpatient visits could be redefined daily by telephone interviews (teleconsultation). In cases of non-deferred port-surgical re-evaluation, both doctors and patients must be equipped with individual protective devices, with an outpatient examination carried out in adequate rooms that allow safety distances to be respected and that are equipped with appropriate decontamination and sterilization systems.

In closing, the multidisciplinary assessment is the cornerstone of the management of the patient with HGG,[26] but unfortunately, it is quite difficult to apply in a day-to-day clinical setting during the COVID restrictions applied. To comply with the Coronavirus containment measures in this Phase Two of the pandemic, and to uphold adequate management from a multidisciplinary point of view, the development of new communication systems (telemedicine, apps, web-meetings, etc.) may overcome these difficulties.[27] Technological aids can assist doctors in sharing and discussing real-time clinical data in virtual webinar multidisciplinary ground rounds to limit staff mobilization and to continue to guarantee a dynamic, updated and integrated high-level quality management of HGG patients.

Key points:

• HGG is a non-deferrable surgical procedure in most cases;

• a multidisciplinary approach in the management of these patients remains to be of utmost importance even during the COVID 19 era;

• alternative treatments instead of surgery can be considered in elderly and/or fragile patients with important comorbidities and a higher risk of COVID infection;

• technological aids should be adopted with colleagues and patients to reduce the risk of COVID 19 spreading yet maintaining a thorough management.

Brain metastases

Except in emergency cases, indications for treatment must be discussed in a dedicated multi-specialist team to assure an articulated and complete clinical evaluation. This approach, already clearly defined in the pre-COVID era, must be guaranteed even in this most delicate phase, using teleconferencing sessions.

In a context devoid of specific strong evidence and certainties on the effectiveness of post-phase I prevention and control measures, the discussion on selected cases should be more careful. Here we propose the following modification to standard indications according to the post phase I COVD-19 scenario:

• patient with multiple brain metastases (up to 4) in which whether 3 small lesions are amenable to radiosurgery, in standard practice larger lesion should undergo surgical treatment (perhaps more correct to opt in this critical context for a hypofractionation RT on larger one if not conditioning severe symptoms);

• metastatic melanoma not amenable to immune or systemic target therapy (more correct to opt for RT treatment if the patient has not severe symptoms);

• not large metastasis, with edema or symptomatic but in the context of a "favorable" assessment from a systemic point of view (lung adenoCarcinoma ALK mutated, melanoma BRAF+, etc) it could be advisable to evaluate the opportunity for systemic immuno or targeted therapy thus avoiding the patient hospital exposure for surgery or RT;

• a frail or elderly patient, evaluate the option of hypofractionation or single fraction RT.

Being metastatic patients, CT of the chest should be part of recent staging, but it would still be advisable to perform one in the preoperative workup.

Low-grade gliomas

Low-grade gliomas have been postponed in most cases during the pandemic emergent phase. It should be emphasized that these lesions cannot be considered benign tu-

mors tout court because of their tendency to evolve toward higher grades.[28] Moreover, these tumors may behave more aggressively since diagnosis based on molecular phenotype, clinical aspects, and neuroradiologic picture.[28] Thus in the phase 2 COVID-19 era, the surgical management of low-grade gliomas should not be further postponed. Some issues should be considered in the decision-making process. Awake surgery carries a theoretically high risk of viral transmission[12] further worsened by the presence of many people in the operating theater. In this scenario, different surgical strategies are suggested to monitor language, cognitive and executive functions. The use of preoperative brain mapping and intraoperative cortical and subcortical stimulation techniques coupled with intraoperative imaging may surrogate the advantages of awake surgery.[29] In some cases, after a multidisciplinary discussion biopsy rather than surgical resection with the speech mapping of complex lesions should be considered.[12]

Intracranial meningiomas and schwannomas

Differently from gliomas or metastases for which the intrinsic risk for survival leads the decision-making process, Intracranial Meningiomas and Schwannomas (IMS) are subjected to different considerations.[11, 14, 15, 30, 31] Their slow-growing nature and their little percentage of malignant histology very rarely put a patient at risk for life.

Most of the population harboring intracranial meningiomas is composed of asymptomatic or slightly symptomatic outpatients who are operated on electively.[30, 31]

Given the unavailability of guidelines regarding the management of IMS in COVID era, we aim to focus on clinical and radiological factors which can put patients at risk of rapid deterioration, and for whom an excessive delay could be deleterious.[32, 33] Nevertheless, in such a complicated time the collaboration with radiosurgery colleagues should be particularly favored for small, evolving lesions or for those that should be suitable for both surgical or radiosurgical treatment.

Criteria for prioritization

General criteria that influence the decision to operate are based on the synergy of four factors: clinical symptoms, size and location, neuroimaging features, and anesthesiological/general.

• clinical symptoms: the temporal course and onset of symptoms are crucial. Sudden onset of new deficits or rapid progression of existing ones (*i.e.* visual acuity decreases; facial nerve impairment, diplopia; ataxia; hemi or tetra-paraparesis) is undoubtedly an indication for surgery as soon as possible. Conversely, the presence of a chronic slow-onset deficit, can be followed-up closely and surgery postponed.[11, 15, 30] Other symptoms not strictly due to mass effect, should be evaluated based on the response to medical therapy (*i.e.* management of seizures with anti-epileptic drugs).[11, 30, 34] The headache itself is not an intimidating symptom in IMS but for large tumors or tumors showing edema or chronic hydrocephalus it could be a sign of altered intracranial compliance;[14, 30, 34-37]

• size and location: as slow-growing tumors, IMS can reach large volumes while presenting very poor neurological disturbances. Although large meningiomas associated to midline shift is normally an intimidating lesion requiring surgery,[11, 14, 15, 30, 31, 34] there is no evidence regarding the exact timing and hence in asymptomatic patients a strict follow-up could be proposed.[11, 14, 15, 30, 31, 34, 38] However, large IMS in posterior fossa could more frequently be associated with ventricular dilation and hydrocephalus which could indicate the need for a more prompt surgical treatment;[11, 14, 15, 30, 31, 34]

• neuroimaging features: neuroimaging can offer different parameters that help the decision-making process. More aggressive behavior of the meningiomas (WHO 2 and 3) can be hypothesized by hyperostosis, osteolysis, lobulated margins, brain tissue invasion.[30, 39-41] Still, despite the volume and site, patients with known latent or active oncological disease,[30, 39-41] and a neuroimaging of suspected IMS should not be postponed but treated either surgically or redirected to radiosurgery. More in general, evidence of radiological growth alone is usually an indication of surgery or radiosurgery. However, due to the compelling situation, this factor should be weighted according to other parameters (extent of growth, the appearance of symptoms, worsening of symptoms, age of the patient, general performance of the patient, site of the lesion, the initial volume of the lesion, proximity of critical areas, radiological characteristics);[11, 15, 30, 42, 43]

• anesthesiologic/general factors. Since elderly, frailty, and significant comorbidity pose patients at greater risk of complications and worse prognosis during COVID-19 infection, it is necessary to carefully evaluate the need for hospitalization and surgery. Moreover, the risk for intrahospital contagion cannot be underestimated.[15] Besides, the follow-up strategy in such patients seems to be even less dangerous as the growth and relapse rate is higher in patients less than 40 years of age and tends to decrease significantly in patients over 70 years of age.[39-41, 44] In fragile and elderly patients, it is therefore advisable, at least

for now, to avoid hospitalization by preferring alternative therapies (radiotherapy/systemic therapies) or radiological and clinical follow-up.[11, 15, 45]

Sellar and parasellar tumors

According to the SARSCov2 features of colonizing the respiratory mucosa and spreading throughout droplets, medical and surgical maneuvers involving the respiratory mucosa were immediately considered high-risk procedures.[46-48] Concerning neurosurgery, scientific societies identified the transnasal skull base surgery, transoral and transfacial corridors, as the riskiest for the diffusion of COVID-19 and also recommended to spare the opening of paranasal cavities and mastoids during transcranial corridors.[11, 17, 18, 49-51]

Accordingly, several groups developed a cogent and "maximally safe" protocol to give the most appropriate treatment to the patients, while minimizing the risks of COVID-19 diffusion.[11, 17, 52-54]

Outpatient clinic access

Patients diagnosed of a sellar/parasellar lesion, *i.e.* pituitary adenoma, craniopharyngioma, Rathke's cleft cyst, tuberculum sellae/planum or cavernous sinus or clival meningiomas, are admitted to neurosurgery outpatient clinic upon one of the following conditions:

- pituitary apoplexy with neurological defect;
- chiasm and/or cranial nerve compression signs;
- tumor malignant behavior;
- CSF/ventricle compression;
- local aggressiveness and volume growth;
- hypothalamus/hypophysis disturbances;
- severe endocrinological syndromes unresponsive to medical therapy.

Inward access

Non-deferrable transnasal surgical interventions for patients diagnosed of a sellar/parasellar lesion, *i.e.* pituitary adenoma, craniopharyngioma, Rathke's cleft cyst, tuberculum sellae/planum or cavernous sinus or clival meningiomas, should be considered upon:

- ischemic/hemorrhagic lesions, which cause pituitary apoplexy syndrome along with neurological defect;
- tumors with massive suprasellar and/or supradiaphragmatic component which determine CSF circulation obstacle and/or hydrocephalus and/or intracranial hypertension signs;

Furthermore, upon the clearance of COVID-19 status, it should be considered the transnasal treatment of those lesions, featuring one of these conditions:

- tumor malignant behavior;[55]
- CSF/ventricle compression;
- local aggressiveness and volume growth;
- hypothalamus/hypophysis disturbances;
- severe endocrinological syndromes unresponsive to medical therapy;
- chiasm and/or cranial nerve compression signs.

In selected cases, above all for intradural supradiaphragmatic tumors, it can be reasonable to consider alternatives strategies, *i.e.* transcranial route EVD placement.[11, 17, 18, 46]

Inside the OR

Transnasal surgery for positive patients must be performed in the dedicated operating theatre when possible; aisles and pathways should be separated.

Personnel in the operating room — only surgeons and nurses directly involved are admitted — must wear FFP3, goggles and/or full-face shield, double gloves, water-resistant gowns and protective disposable caps, during the procedure; it is essential to keep maximum level PPE during preop and postop period inside the OR.

Surgery for negative patients requires as well maximum level PPE:[11, 17, 18, 46, 52] FFP2 mask covered by a surgical mask, disposable gowns and caps, face screen.

In any case, surgeons should adopt further precautions to prevent or at least reduce aerosol/droplets generating maneuvers: high-speed drill use should be limited and osteotomes and rongeurs preferred when feasible. Covering both nostrils with sterile glove layers fixed with steri-drape and pierced to let instruments enter the nostril can further reduce air passage in/out the nostrils.

Finally, all patients and personnel are required in any other circumstance to respect common hygiene-behavioral rules: accurate and frequent hand washing, wearing a surgical mask and social distancing.

Conclusions

The COVID-19 pandemic storm has led neurosurgeons to restrict operations to emergency and essential intervention.[56] Nowadays, the worst phase seems to be behind us and our daily activity should be reorganized according to the new scenario of COVID-19 virus post-pandemic cohabitation.

In this postemergent phase, neurosurgeons should return to routinely manage their patients harboring different brain tumors. Even non-emergent or benign tumors should be

treated to avoid potential damage and the worst surgical outcome due to delayed management. The clinical judgment of the referring neurosurgeons remains the cornerstone of the decision-making process in the surgical management of brain tumors patients. On the other hand, it is mandatory to underline that multidisciplinary management of brain tumors is of outmost importance. While traditional face to face rounds are not possible, the use of teleconference and telemedicine modalities should be organized to allow the routine functioning of institutional tumor boards.

The diagnostic COVID-19 preoperative protocol differs among institutions and countries according to the evolving scientific data and resource availability. Unfortunately, the data on the interpretation of serology or the use of swabs regarding the patients and staff remain debated. For this reason, different protocols for hospital admission and surgical management of elective cases are proponed by every institution. This document is not aimed to substitute any institutional protocol, but may help every neurosurgical department and individual neurosurgeon to propose the best treatment for each patient in this COVID-19 era.

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