

Glioblastoma Multiforme in The COVID-19 Era: How Italy Managed to Surgically Treat the Neuro-Oncological Patient Despite the Pandemic

Parlato C*, De Prisco F and Rotondo M

Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania Luigi Vanvitelli, CTO Hospital, Naples, Italy

*Corresponding author:

Ciro Parlato,
Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania Luigi Vanvitelli, CTO Hospital, Naples, Italy,
E-mail: ciro.parlato@unicampania.it

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1. Abstract

1.1. Aims: The wave of SARS-CoV-2 is affecting every country in the world in a more or less homogeneous way and one wonders what is the best therapeutic option for the infected patient diagnosed with Glioblastoma Multiforme. Neurosurgeons are now called to balance the risks of the negative impact of the pandemic and those of cancer. Despite the infection, the treatment of neuro-oncological patients cannot be significantly delayed. For this reason, doctors face a challenge during the pandemic: finding the right balance between SARS-CoV-2 infection and treating the patient's own neuro-oncological status. Our aim is to analyze the experience of Neurosurgery department of the University of Campania "Luigi Vanvitelli" at the CTO Hospital of Naples, about surgical treatment and Stupp protocol of the patient, as in the pre-COVID-19 era.

1.2. Methods: Between March and May 2020 five patients with Glioblastoma Multiforme were surgically treated and all of them were diagnosed as being positive with SARS-CoV-2, following a nasopharyngeal swab.

1.3. Results: All the operated patients are still alive as of November 2020. The surgical intervention even allowed an improvement in the basic neuro-oncological clinical picture with a clear improvement in their quality of life and without even the need to resort to neurorehabilitation.

1.4. Conclusion: Where possible, continuing to guarantee surgical treatment in the COVID-19 era is mandatory to increase the overall survival of the neuro-oncological patient but also to improve their quality of life.

2. Introduction

The COVID-19 pandemic has disrupted all aspects of society globally. As healthcare resources had to be preserved for infected patients, and the risk of in-hospital procedures escalated for uninfected patients and staff, neurosurgeons around the world have had to postpone non-emergent procedures. Current guidelines of the treatment of high-grade gliomas (HGG) provide an evidence-based care framework that aims to prolong progression-free survival and overall survival (OS). However, during the pandemic, doctors face the challenge of finding a balance between the risks of COVID-19 in a vulnerable population and the potential for under-treatment of cancer patients. In addition, there is a societal need for the protection of healthcare workers and to avoid further secondary viral spread to patients [1]. Other Authors demonstrated that neuro-oncological surgery for urgent cases can be performed during the pandemic within similar time frames achieved in non-pandemic times [2]. We compare our aggressive surgical treatment followed by the Stupp protocol with a more conservative therapeutic strategy, deciding to postpone the intervention to a less critical phase of the pandemic. Based on the experience of the Neurosurgery of the University of Campania "Luigi Vanvitelli" of the CTO Hos-

pital of Naples, we analyze the therapeutic approach to COVID-19 patients with HGG to claim that neuro-oncological surgery can be continued safely during the respiratory disease pandemic if these infected patients are paucisymptomatic for both respiratory and neuro-oncological disease

3. Materials and Methods

Between March and May 2020, in full pandemic emergency, five patients with Glioblastoma Multiforme were surgically treated by the Neurosurgery department at the CTO of Naples. All five patients who were operated on, initially presented to the CTO Emergency Department where, after a careful physical examination and the execution of some instrumental tests such as a CT / MRI and a fundus eye due to the clinical implications that the tumor mass generally produces on the clinical picture of the patient, they were all diagnosed as being positive with SARS-CoV-2, following a nasopharyngeal swab.

The first patient, a 68-year-old male, presented himself to the

emergency room with persistent fever (37.5 °C), mild dyspnea, productive coughing and tachypnea (26 bpm). His past medical history showed hypertension and chronic kidney disease. Arterial blood gas analysis showed normal blood oxygen saturation (SO₂: 95.6%), hypoxemia (76.3 mmHg), hypocapnia (32.4 mmHg), respiratory alkalosis (pH 7.52) and PaO₂/FiO₂: 294 mmHg. Blood sample analysis documented only mild leukocytopenia (3.840 per mm³). Signs and symptoms typical of intracranial hypertension including progressive and worsening headache syndrome and mental disorders were objectified. Physical examination revealed right pyramidalism, sensory-motor aphasia. A compressive lesion (512 x 219 mm) at the level of the left Silvio fissure was confirmed with a shift of the midline of 5 mm, at first, by a CT scan (Figure 1) and, subsequently, by the execution of an MR. A left fronto-temporo-parietal craniotomy was thus planned which revealed a voluminous, richly vascularized lesion with dural afferents and the left middle meningeal artery.

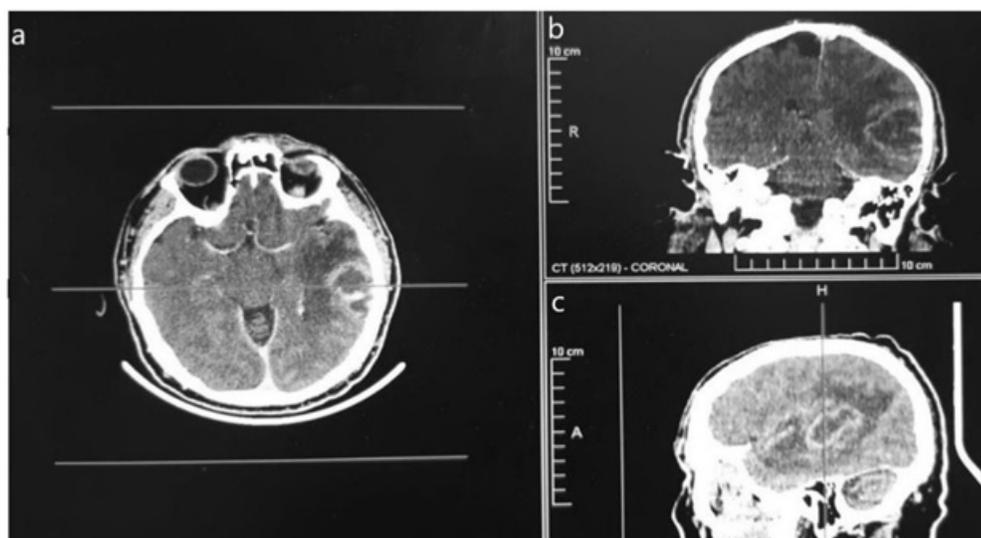


Figure 1: Patient CT scan acquired on the three planes (a) preoperative axial CT (b) preoperative coronal CT (c) preoperative sagittal CT

The second patient, a 52-year-old female patient presented herself to the emergency room with fever (38 °C), chills, shortness of breath (30 bpm), asthenia and diarrhea. Her past medical history showed hypertension as well as diabetes mellitus. Blood sample analysis documented mild leukocytopenia (3.780 per mm³), increased level of C-reactive protein (12 mg/L), ESR (> 265 U/L) and procalcitonin. Arterial blood gas analysis showed SO₂: 93.8%, PaO₂: 73.7 mmHg, PaCO₂: 31.9 mmHg, respiratory alkalosis (pH 7.49) and PaO₂/FiO₂: 292,6 mmHg. At neurological examination we observed short-term memory deficit, emotional indifference towards herself, others and her illness as the behavioural disinhibition syndrome. The instrumental examinations revealed left frontal mass with extension through the corpus callosum.

The third patient, a 72-year-old female patient, presented herself to

the emergency room without fever and dyspnea but with pharyngeal pain which gave her difficulty in eating, asthenia and myalgia and symptoms of intracranial hypertension syndrome. At neurological examination we observed a stasis papilla with lifting of the papilla margins and turgid venous vessels. Cerebral CT scan showed a mass in the right frontal region.

The fourth patient, a 70-year-old male, presented himself to the emergency room with persistent fever (37.7°C), dyspnea, dry coughing, tachypnea (28 bpm), conjunctivitis and rhinorrhea. The patient had a past medical history for hypertension, hypertriglyceridemia, hypercholesterolemia and second grade obesity (BMI: 38). Arterial blood gas analysis showed SO₂: 92.5%, PaO₂: 72.3 mmHg, PaCO₂: 30.5 mmHg, respiratory alkalosis (pH 7.56) and PaO₂/FiO₂: 287 mmHg. Blood sample analysis documented lym-

phocytopenia (1.324 per mm^3). A behavioural alteration syndrome characterized by a deficit of attention was highlighted with short-term memory, alternating moments of depression with moments of euphoria. The instrumental tests revealed left frontal mass.

The fifth patient, a 60-year-old female, presented herself to the emergency room without fever or dyspnea but with loss of taste and smell, myalgia, asthenia and productive coughing. The patient had a past medical history for hyperthyroidism and right bundle branch block. Arterial blood gas analysis showed no alteration. Blood sample analysis documented lymphocytopenia (1.424 per mm^3). Neurological examination showed right pyramidalism and motor dysphasia Cerebral CT scan revealed left frontal mass.

4. Results

All patients remained in the intensive care unit for one day after surgery and, after being discharged, we decided to treat them by radio-chemotherapy according to the Stupp protocol. After the operation, first patient presented a transitional motor dysphasia and his pyramid syndrome disappeared (Figure 2).

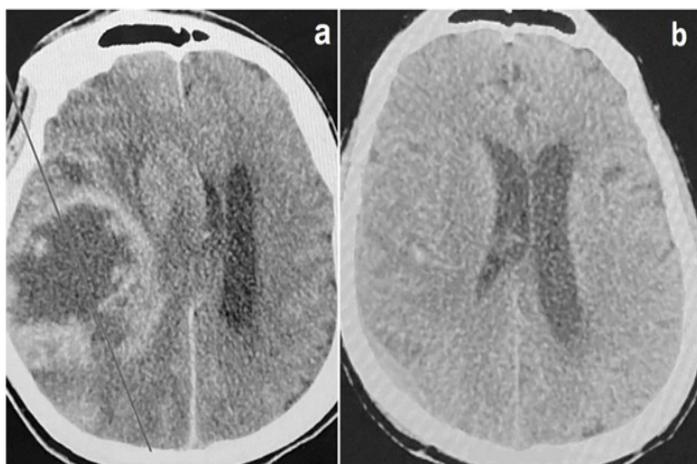


Figure 2: CT scan acquired on the axial plane of the first patient (a) preoperative axial CT (b) postoperative axial CT

About second patient, the behavioural syndrome disappeared; third patient showed headache and vision improvement; regarding the fourth patient, we observed improvement of the behavioural syndrome; the fifth patient also improved the aphasia and pyramidalism. Postoperative CT showed gross total removal of tumor. The histological examination revealed in all cases HGG. At the follow-up, we have used the electronic clinical control with good results. All the operated patients are still alive. The surgical intervention not only allowed an improvement in the outcome measured in terms of overall survival of the patient after treatment, but also in the neuro-oncological status with a clear improvement in their quality of life.

5. Discussion and Conclusion

Close collaboration between the various structures belonging to

the same health company appears essential to guarantee hospitalization and neurosurgical treatment of the patients. Specifically, the decision not to make the CTO a COVID center made it possible to keep the beds of its intensive care free, allowing neuro-oncological patients to be operated on and this was only possible due to the close collaboration with the reference COVID center. The coordination between health facilities therefore constitutes one of the reasons that led us to provide a health service similar to that which would have been given in the pre-COVID-19 era. In this regard, it is essential to remember that the neuro-oncological patient must be transferred post-operation to intensive care and remain here for at least one day and that the saturation of the beds, consequent to the increase in territorial infections, has the inevitable consequence of the reduction of the surgical option. Nevertheless, we must in any case emphasize that the highly stringent Italian health policies have certainly contributed to limit the spread of infections and, consequently, to allow the CTO hospital not to be converted into a COVID center to cope with any worsening of the pandemic crisis.

At the follow-up level, with regard to clinical controls and in relation to the evolution of cases, we tried to use two strategies: that of carrying out the controls according to the standard procedures and that of preferring an approach that did not expose the patient to a possible contagion; in this case, the aid of electronic control is very important [3]. The CTO Hospital, in fact, has activated a telematic organization system that has allowed the specialists of the various departments, through telephone and video call support, to keep in touch with patients, especially regarding the management of therapy from home and the management of patients complications. We suggest aggressive surgical approach in the oligosymptomatic patient affected by clinical infectious disease and tumor. For this reason, beyond the quarantine to which patients were subjected before entering the Neurosurgery ward, the patient was guaranteed the same performance that he/she would have received in the pre-COVID-19 era and succeeding in preserving essential supplies, such as ventilators and other medical supplies for non COVID patients [4-6]. A higher post-operative mortality was highlighted in those patients with a particularly complex and severe neurological clinical picture and / or in which vital parameters are particularly compromised. In fact, the absolute contraindication to surgery for this type of patient was also present in the guidelines and protocols in force in the pre-COVID-19 era. For this reason, following the pandemic and the potential risks resulting from a SARS-CoV-2 infection, our experience could only reinforce this evidence. In fact, unconscious, hemodynamically unstable and strongly dyspneic patients continue to be treated in an alternative and less aggressive way. Consequently, all patients surgically treated were conscious with $\text{GCS} \geq 14$, $\text{SpO}_2 \geq 90\%$, body temperature $\geq 37^\circ\text{C}$, tachypnea ($21\text{-}30 \text{ bpm}$), $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$ but $> 200 \text{ mmHg}$ and a relatively stable neuro-oncological status. The overall assessment

of the patient's clinical and neurological status led us to provide a health service similar to that which would have been given in the pre-COVID-19 era. For patients with newly diagnosed or recurrent high-grade gliomas, urgent surgery should be performed with 1-2 weeks of diagnosis followed by adjuvant chemotherapy and radiation therapies per established standards. In cases where hypofractionated radiotherapy could be used to limit patient exposure in the hospital, this should be considered [5]. On the other hand, the planning of surgical operation for patients with Glioblastoma during the pandemic is not always possible, in fact, the neurosurgeons of Mount Sinai Hospital in New York decided to postpone surgery, proceeding with radiotherapy alone and using high doses of steroids. The results were the negative repercussions on patients' overall survival, as well as on the worsening of the neuro-oncological clinical status [7]. This type of decision, in fact, probably did not depend solely on a purely medical choice, but also on the organization of the hospital itself which led to the adoption of a more cautious attitude. Other Authors affirmed that patients with brain tumor who have acquired COVID-19 infection will pose new challenges for neuro-oncologists. For patients symptomatic for COVID-19, it seems prudent to withhold any systemic chemotherapy, unless entirely non-immunosuppressive, and to challenge the need for steroids until patients have fully recovered from COVID-19. More complicated is the situation of patients with brain tumor tested for COVID-19 as part of a screen who come back positive but are asymptomatic for COVID-19. Here, a careful evaluation of risk and benefit is necessary, and moderate delays of systemic chemotherapy may be a preferred option [8]. We closely collaborated with the Cotugno COVID Hospital, therefore the oligosymptomatic COVID patients were treated at the COVID Center and after two negative swabs, they returned to the Neurosurgery department for treatment with gross total removal of the glioblastoma and subsequent radio-chemotherapy according to the Stupp protocol, as in pre-COVID era. We chose this therapeutic strategy exclusively for the five patients who, after two negative swabs, had returned to neurosurgery. Continuing to guarantee surgical treatment is important both to increase the overall survival of patient affected by glioblastomas and to improve their quality of life. In our case, we have chosen this therapeutic strategy only for respiratory and neurological oligosymptomatic patients. Therefore, we preferred the surgical choice over any type of more conservative treatment, also in COVID era.

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