Neuroscience and Neurosurgery

Glioblastoma Therapeutic Modalities And Proposed Management Protocol

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Abstract

Glioblastomas are the most common brain tumors in adults. They generally affect adults between the ages of 45 and 65. Treatment of these tumors involves a combination of surgery, radiotherapy and chemotherapy. The prognosis for these processes is usually poor; however, in recent years we have seen advances in the field of clinical research and molecular biology in particular, which give us a glimpse of a glimmer of hope. Prognostic factors have been identified and they make it possible to set up a therapeutic strategy as well as to have an idea of the response to treatment. We report the results of a prospective series of 500 patients operated on by the same surgical team and attempt to propose a management protocol that can serve as a basis for multi-center studies.

Keywords: Glioblastoma, Surgery, Stupp Protocol, Prognostic factors.

Introduction

Glioblastomas represent a major problem in neuro-oncology due to their frequency, severity and difficulty of treatment [3, 37]. The annual incidence is around 1.56 to 3.69/100,000 inhabitants; the latter presents an upward slope until the 80s then a plateau phase from the 90s. 14, 16]. The stages of diagnosis are well established [1, 2, 27, 31, 34]. The new methods of immunohistochemistry and molecular biology reveal the inadequacies of morphological aspects alone in favor of cellular oncogenesis criteria [5, 12, 15, 38, 41]. The relationship between the

degree of extension of the resection and the survival time is well established and optimal surgery aided by new technologies has become the essential time of initial treatment and sometimes that of recurrence [1, 3]. Advances in the field of radiotherapy have allowed a considerable reduction in the iatrogenic effects of irradiation, better ballistic precision and an optimization of the therapeutic choice. Despite all this progress, the results obtained are still modest and above all transitory [22, 29].

The contribution of chemotherapy is mediocre due to the pharmacokinetic obstacles, the low number of available molecules and the innate or acquired capacities of the chemoresistance and alkylating lesion repair systems; there is still hope that chemosensitive subgroups can be identified [35, 42].

Finally, several phase I and II immunotherapy and targeted therapy trials are underway; they may be able to bridge the gap between the knowledge acquired in basic research and current clinical results [17, 30, 43].

Patients And Methods

We report a prospective series of 500 adult patients operated on during the period from January 2011 to January 2022. All these patients were operated on by the same surgical team. The average follow-up varies between 12 and 120 months.

All patients were evaluated clinically with research of the geographical origin of the patient, neurological and somatic examination as well as the Karnofsky index. Consciousness was assessed using the Glasgow Coma Score (GCS).

Brain MRI was performed in all patients. Some of them also benefited from spectroscopy.

In terms of surgery, each time we aimed for maximum excision and we systematically performed closure of the dura mater by enlargement plasty. Some patients with impaired consciousness (GCS less than 8) had a craniectomy.

The postoperative control CT was performed within 72 hours.

All pathological examinations were performed by the same pathologist. The adjuvant oncological treatment consisted of a Stupp regimen comprising radiotherapy with a dose of 60 Gy and chemotherapy based on oral temodal concomitantly and in consolidation.

The monitoring protocol was based on a calendar with a consultation every month for the first 6 months and then every 3 months. MRIs were performed at 1 month and then every 3 months. The survival analysis was made by Kaplan Meier curve.

Results

-Origin Of Patients

A quarter of our patients were from the south. Another quarter of agricultural regions . The rest of the other patients came from the center and other wilayas.

-Age And Sex

The average age of patients is 48.5 years with a maximum of patients aged 45 to 65 years. Those under 20 represent 5% of patients. In terms of sex ratio, there is a clear male predominance since 76% of patients were men.

-Clinical

The average time between the appearance of the first clinical signs and the diagnosis is 30 days with extremes ranging from 10 to 60 days. Eight (28) patients had impaired consciousness on admission with a GCS less than 8. The intracranial hypertension syndrome was present in 62% of cases. A motor deficit was objectified in 56% and secondary epilepsy in 30%. The functional score assessed by the Karnofsky index was greater than 80 in half of the patients, between 80 and 50 in a quarter and finally less than 50 in the remaining quarter.

-Imagery

MRI allowed us to make a presumptive diagnosis and localize the lesion. The latter was frontal in half of the cases and temporal in a quarter of the cases. The parietal, occipital and deep localizations were found in the remaining quarter.

Spectroscopy performed in 25% of cases (degenerating low-grade gliomas) revealed an increase in choline as well as a peak in lactate-lipids.

-Surgery

Neuronavigation was used in 42 cases of deep localization. We performed total macroscopic resection in 67% of cases (Fig. 1), subtotal and partial in 33%.

Operative mortality (D0 to D30) was nil and we noted the installation of a motor deficit in 26 patients. 68 other patients saw their preoperative deficit worsened.

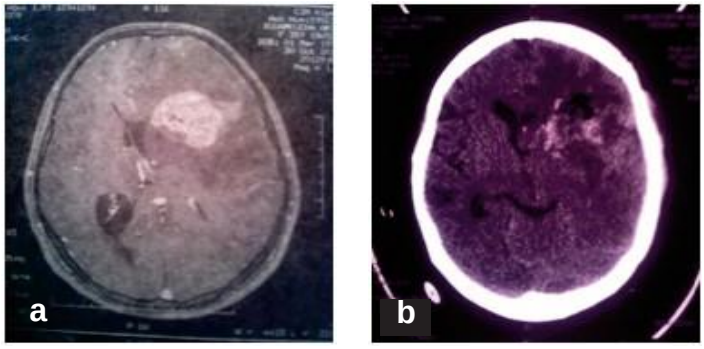


Fig. 1:

A. Frontal glioblastoma T1 MRI with gadolinium

B. Postoperative CT scan at 24 h demonstrating total resection

-Histology

Neuropathological examination revealed primary or de novo glioblastoma in 70% of cases (Fig. 2). Secondary glioblastomas or glioblastomas with an oligo-dendroglial contingent were objectified in 25%, giant cell glioblastomas in 4% and finally gliosarcomas in 1%.

-Adjuvant Treatment

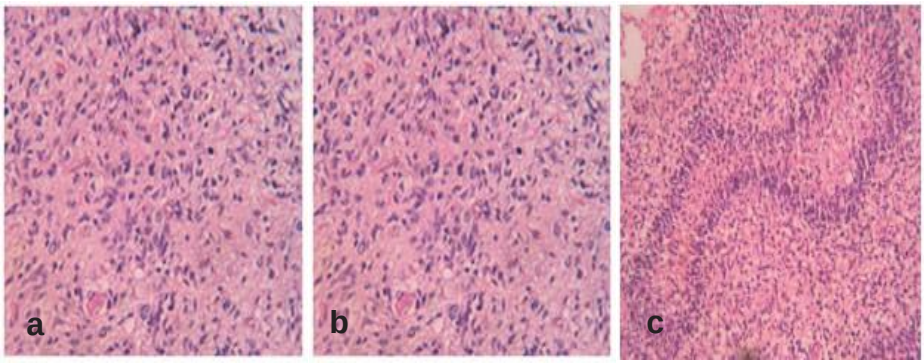
All patients were treated according to the Stupp protocol (as mentioned in the patients and methods section); however 20% of them did not have a concomitant temodal (due to a stock shortage) they only received it as a consolidation regimen. The mean time between surgery and the start of radiotherapy was 49.7 days or 7 weeks.

-Survival

-The average overall survival is 32.8 months and the median survival is 14.8 months. 46% of patients were alive at 2 years, 21% at 3 years and 12% at 5 years (population of long survivors).

-Recidivism

We observed a recurrence in all our patients, however with variable delays. 10% of patients relapsed within 6 months after surgery, while the majority of patients (75%) presented a recurrence between 6 and 12 months. Finally, we observed a recurrence beyond 12 months in 15% of patients (Fig. 3).



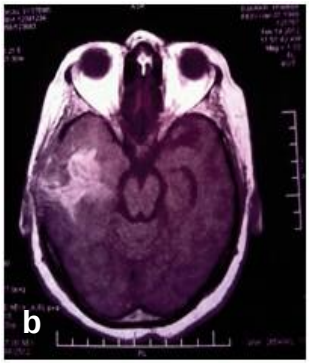


Fig. 2: Typical histological appearance of a glioblastoma (HE staining).

A, cell polymorphism; B endothelio-capillary proliferation; C palisade necrosis

Fig. 3: A Temporal glioblastoma; B Postoperative MRI at 1 month showing gliosis; C Recurrence at 15 months

Discussion

Glioblastoma is the most common brain tumor in adults. The incidence of this pathology is clearly increasing with an annual increase of 1%; it is 1.56 to 3.69/100,000 inhabitants [8, 10, 14.16]. This incidence seems to be influenced by certain factors; in fact, there is a reduction in the risk of occurrence of around 30 to 60% in the presence of allergic conditions [32] and the regular intake of non-steroidal anti-inflammatory drugs [39]. On the other hand, it seems that the risk is increased by 30% with the use of pesticides [37] and by around 500% after anterior brain radiotherapy [35]. As far as our patients are concerned, we have no information on a possible allergic condition and the taking of non-steroidal anti-inflammatory drugs. None of our patients underwent radiotherapy; however a large number of our patients come from an agricultural region which could suggest a potential influence of pesticides. The peak frequency is between 45 and 65 years old, however the age group between 70 and 75 years old is increasingly concerned with the increase in life expectancy [8, 10]. Most of our patients were

between 45 and 65 years old. The male predominance reported in the literature with a sex ratio of 1.5 to 1.8:1 [10] is also found in our series.

The clinic is dominated by the syndrome of intracranial hypertension, motor deficit and epilepsy [1, 2, 34] and this was also found in our series. The determination of the Karnofsky score pre-operatively and post-operatively is crucial because it represents one of the prognostic factors (which will be detailed later).

MRI is the key examination for the diagnostic approach [1, 2, 27, 31] and spectroscopy can help to objectify the degeneration of a low-grade glioma [13]. It is routinely used today. All our patients were explored by CT and MRI while spectroscopy was only in 25%.

The treatment of glioblastomas involves surgery and radiotherapy. For several years, the addition of concomitant chemotherapy to radiotherapy and in consolidation (Stupp protocol) has proven its superiority compared to the surgery regimen associated with radiotherapy alone [35; 42]. Surgery is the crucial stage of treatment. It is important to perform the most complete excision possible because this improves the prognosis of patients. In this context, we performed total macroscopic resection in 67% of cases. This excision is optimized by the use of neuronavigation and intraoperative ultrasound [1-3]. As far as we are concerned, we only used neuronavigation in 42 cases of deep localization (perioperative ultrasound not being available). Regarding the adjuvant treatment, we opted for the Stupp protocol given its superiority. The protocol includes irradiation with doses of 60 Gy associated with Temodal during irradiation and in consolidation. However, 20% of our patients did not receive concomitant chemotherapy due to the unavailability of the product. The time between surgery and radiotherapy is significant; it should be as short as possible and not exceed 8 weeks [29]. In this series, we ensured an average delay of 7 weeks thanks to the multidisciplinary consultation meetings.

The anatomo-pathological examination uses morphology and immunohistochemistry. The morphology makes it possible to distinguish 4 types: glioblastoma multiforme; giant cell

glioblastoma; small cell glioblastoma and glioblastoma with an oligodendroglial component. All the specimens were studied on this plan. Immunohistochemistry is an important step because it allows the search for the TP53 mutation which is found in secondary glioblastomas and the amplification of the EGFR (endothelial growing factor receptor) which is objectified in primary glioblastomas [28]. We did not carry out in our patients the search for the TP53 mutation and the EGFR. The search for the IDH1 mutation has become systematic in the context of secondary glioblastomas. We performed this examination in 20% of cases (lack of this marker).

Several prognostic factors have emerged over the years. They are clinical and biological.

Age is an essential prognostic factor, in fact younger patients tend to survive longer; we observed an 18-month survival rate of around 64% for patients under 40 years old, while it was around 20% for patients between 40 and 60 years old and 8% for patients over 60 years old. This is confirmed for the 3-year survival since it was 25.8% for patients under 40 years old, 2.3% for patients between 40 and 60 years old and 0% for patients over 60 years.

The neurological state assessed by the Karnofsky score (KPS) also represents a very important element of the prognosis. In fact, the 18-month survival rate is 34% in patients with a KPS greater than 70, whereas it is only 13% for a KPS between 20 and 30 [19]. This is confirmed in our series since the median survival is 15.8 months for a KPS greater than 80; 12.6 months for a KPS between 80 and 50 and finally 4.3 months for a KPS less than 50. Tumor location is also a prognostic factor because it determines the extension of the resection. In this logic, deep localizations have a poor prognosis. It should be noted that the frontal location has a better prognosis in surgically accessible locations [19]. This relationship between frontal location and better prognosis is also observed in our study since the median survival in the frontal locations is 11.4 months whereas it is respectively 9.6 months and 9.1 months for the parietal and temporal.

The degree of extension of surgical resection is a key prognostic factor which is confirmed by most series in the literature with an 18-month survival of 34% in the event of total resection, 25% in the event of resection. partial and finally 15% in the case of biopsy [19]. This influence of the quality of excision on survival is also present in our patients since the median survival is 15.8 months in the event of total excision, 11.3 months in the event of partial excision and 7. 3 months in case of biopsy. This is also confirmed when we study survival as a function of the 2 parameters which are the quality of excision and the Stupp protocol. Indeed, the median survival is 16 months in case of total excision, 11.2 months in case of partial excision and finally 8.7 months in case of biopsy.

Histologically, it is recognized that secondary glioblastomas have a better prognosis than primary or “de novo” glioblastomas; In addition, variants with giant cells and with an oligodendroglial component also constitute elements of better prognosis [15, 24, 28].

Much progress has been made in recent years in molecular biology. The IDH1 mutation is one of the most interesting to look for because it is associated with a better prognosis in secondary glioblastomas indeed some studies have objectified median survival of 27 to 31 months in the presence of the mutation and median survival of 11 3 to 15 months in the absence of the latter [36, 47]. Other biological abnormalities may exist such as overexpression of EGFR, loss of P53 function and co-deletion 1p19q.

The first two have no prognostic value [11, 20, 26, 46]; however, co-deletion 1p19q is associated with a good prognosis since it is associated with a better response to temodal [7].

The time elapsed between surgery and radiotherapy is considered a prognostic factor since the risk of death would increase by 2% per day of waiting [29]. We tried to shorten it as much as possible and were able to obtain an average delay of 7 weeks, which corresponds to the recommended delays of 4 to 8 weeks.

It also seems that Stupp's protocol is also a good prognostic factor [35, 42].

All the prognostic factors mentioned have even more weight when they are associated in the same patient. It is important to evaluate them in order to have an estimate of survival and therefore adapt the therapeutic management [19]. The latter will be all the more aggressive as the good prognostic factors are present.

Recurrence is the rule, as observed in our series. In these cases the determination of a 2nd line protocol is necessary. Surgery may have its place when the recurrence occurs beyond 6 months in a young patient whose KPS is greater than or equal to 70 and with an accessible location [169]; the same is true for anti-angiogenic treatments such as Bevacizumab [21, 44]. Reoperation rates vary from 9 to 31% in the literature; ours was 29%.

Proposal for a management protocol

The establishment of a management protocol in the various neurosurgery departments can make it possible to assess the incidence, therapeutic progress, survival and financial impact of this pathology.

1 - Establish Initial Treatment Once The Diagnosis Is Posed:

An anti-oedema treatment based on methylprednisolone at a rate of 2mg/Kg/24h and/or glycerol in syrup A gastric bandage.

An anticonvulsant treatment in case of confirmed convulsions and prophylaxis in epileptogenic localizations.

A thromboembolic treatment based on Lovenox at an isocoagulant dose of 0.4 mg / 24 h subcutaneously in bedridden patients.

Antidepressant treatment. This treatment should be maintained until surgery.

2 - Evaluate The Radio-Clinical Prognostic Factors: age, Karnofsky index and location of the lesion.

3 - Define The Type Of Surgery To Be Proposed According To Clinical And Radiological Data

-Age / Karnofsky and accessible location

-Patient under 40 years old with KPS greater than 70: total excision with dural plasty.

-Patient under 40 years old with KPS less than 70: subtotal excision with dural plasty.

- Patient aged 40 to 70 with KPS greater than 70: total excision with dural plasty.

-Patient aged between 70 and 75 years old with a KPS greater than 70 excision as wide as possible with dural plasty.

-state of consciousness

In patients whose GCS is less than or equal to 8, we recommend craniectomy with lost bone with excision as wide as possible and dural plasty.

- Seat of the lesion

Deep localizations should benefit from a biopsy.

4-Systematic Extemporanate Examination (Preferentially Smear Technical)

to speed up post-operative care

5 - Address The Entire Sample In Anatomo-Pathology.

The search for the IDH1 mutation and the VEGF assay are strongly recommended because it has prognostic value.

6- Control Mri Or Ct With And Without Contrast Product a maximum of 72 hours after surgery in order to assess any postoperative residue.

7- Minimize The Duration Of Hospitalization in order to reduce the risk of occurrence of complications such as infections (immunocompromised character of the patient).

8-Readjustment Of Medical Treatment

To The Output. The latter must be continued until the start of radiotherapy.

9-Shortening The Time Between Surgery And Radiotherapy; the ideal

being 4 to 6 weeks. This highlights the major interest of multidisciplinary consultation meetings (RCP).

10-Apply A Stupp Protocol As Adjuvant Therapy.

11-Readjustment Of Medical Treatment Before And After Radiotherapy.

12-Clinical And Radiological Control At 1 Month.

Imaging should preferably be MRI, but failing that, high-resolution CT can be performed. excision, the existence or not of edema and the response to treatment according to Mac Donald's criteria. The following checks will be carried out every 3 months.

13-Recidence Management.

If the latter occurs before 6 months, the indication for surgery is not appropriate and the temodal will have to be continued with the medical treatment. Recurrences of accessible locations occurring after 6 months must be reoperated and benefit from temodal and bevacizumab.

14-Accompaniment Of The Patient with his family by explaining the different stages of the treatment.

Conclusion

The glioblastoma management protocol requires the determination of prognostic factors. All therapeutic efforts are made to increase the median survival and thus maintain a correct quality of life allowing the patient and his family to make the most of this period. Recurrence is the rule and justifies a change in therapy and the definition of a 2nd line strategy in which surgery may have its place as well as anti-angiogenic treatments such as Bevacizumab.

Glioblastoma remains a therapeutic challenge but the situation has changed: the clinical results remain modest but very real and the means of action have become numerous. Progress comes from fundamental research in molecular biology, the imaging industry, clinical and neuropathological research, but also cooperative actions and the bringing together of learned societies in the general movement of cancer.

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