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Radiation Therapy of Glioblastoma: Experience of a Moroccan Center

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Abstract

Background: Glioblastomas are the most frequent and aggressive primary brain tumors. Their prognosis remains bleak, despite progress in management and understanding of the different biological mechanisms. Our objective is to highlight the impact of radiotherapy in improving the management of glioblastoma through the experience of the radiotherapy department at Hassan II University Hospital.

Materials and methods: This was a retrospective study analyzing the medical records of patients with glioblastoma over the period from August 2012 to January 2020. The data was analyzed using the epi-info software, therapeutic toxicities evaluated according to CTCAE V.4 scale, and overall survival estimated by the KEPLIN MEIER curves.

Results: 95 cases were collected. The median age was 57 years [18–85]. CT scan and MRI were performed on all our patients. The surgical procedure consisted of total resection in 46.32%. All patients received post-operative treatment; 30 radiotherapy alone, and 65 radiotherapy combined with chemotherapy according to the Stupp protocol. At the end, the median overall survival was 5.53 (± 0.8) months.

Conclusion: Our study highlights the crucial role of radiotherapy in the management of glioblastoma and emphasizes the clinician’s role in early diagnosis before functional decline. The prospects for precision medicine (immunotherapy, targeted therapies …) could improve these results.

1. Introduction

Gliomas are the most frequent primary brain tumors of the central nervous system, classified in grades ranging from I to IV according to their degree of differentiation, glioblastoma being grade IV. The 2004 Casablanca cancer registry reported a glioblastoma frequency of 2.8% among all cancers, with an incidence rate of 2.55 new cases per 100,000 inhabitants per year in men and 2.03 new cases per 100,000 inhabitants per year in women. However, comprehensive descriptive epidemiological data specifically for glioblastoma is limited.

The clinical presentation is variable and influenced by the location and size of the tumor [1]. Diagnostic confirmation is based on anatomo-pathological examination with immunohistochemical study of the specimen. Several molecular markers have been known for a long time in neuro-oncology and have been used as prognostic markers of survival or predictive of response to certain treatments (MGMT status) [2]. The therapeutic standard is currently defined by optimal surgical resection when possible, followed by the combination of radiotherapy and concomitant Temozolomide followed by adjuvant Temozolomide [3].

Radiotherapy plays a very important role and the advent of new techniques has improved the management of patients by allowing better coverage of the target volume and better sparing of organs at risk.

Despite the development of new imaging techniques, surgical techniques, new systemic treatments and new radiotherapy techniques, the prognosis remains poor.

The objective of our work is to highlight the impact of radiotherapy in the improvement of glioblastoma management by tracing the experience...
of the radiotherapy department of HASSAN II hospital.

2. Materials and Methods

This is a retrospective descriptive study carried out in the radiotherapy department of the Hassan II University Hospital in Fez, on the files of patients with glioblastoma. This study was spread over a period of 8 years from AUGUST 2012 to JANUARY 2020 and involved all patients over 18 years with histologically proven glioblastoma, in whom the theoretical indication of radiotherapy is indicated.

The different data were collected from the electronic patients' records HOSIX, and the treatment data on the ARIA software. The data was analyzed using the epi-info software, therapeutic toxicities evaluated according to CTCAE V.4 scale, and overall survival estimated by the KEPLEIN MEIER curves. Descriptive statistics were used to summarize baseline patient characteristics, with qualitative variables expressed as numbers and percentages and quantitative variables expressed as means ± standard deviations (SD). Categorical data were summarized using frequencies and percentages, while numerical data were summarized using medians and interquartile ranges or means and standard deviations depending on the distribution of the variables.

With regard to ethical considerations, data collection was carried out with respect to the anonymity of the patients and the confidentiality of their information.

3. Results

During our study period, a total of 95 patients were included. The age range of the patients spanned from 18 to 85 years, with a median age of 57 years. 57 were male (60%) and 38 female (40%), the sex ratio M/F is 1.5. The delay of consultation varied between one week and 18 months with an average delay of 31 weeks. The most frequent reason for consultation was intracranial hypertension syndrome in 73.68% of the cases, followed by motor deficit in 57.89%, then seizures in 24.21% of the cases. Among the patients included in the study, 6 had an ECOG/WHO Performance Status score of 0, 48 had a score of 1, 32 had a score of 2, 7 had a score of 3, and 2 had a score of 4. The involvement of the pathetic nerve was noted in only one patient (1.05%) responsible for strabismus. The pneumogastric nerve was affected in only one patient (1.05%) responsible for swallowing disorders.

CT scans were requested in 71 patients, and in most cases the lesion was heterogeneous and poorly defined, enhanced by contrast medium, with perilesional oedema (Fig. 1).

Magnetic resonance imaging was requested in all patients in our series.

The appearance was typically a large hemispherical mass of spontaneous heterogeneous density and signal with a spontaneously heterogeneous with significant perilesional edema. The heterogeneity is related to a necrotic component with sometimes hemorrhagic remodeling and an irregular wall (enhanced after contrast) that appears in T2 and FLAIR hypersignal (Fig. 2).

The most prevalent localization identified was temporo-parietal, observed in 22.10% of our patients. This was closely followed by temporal localization, present in 16.84% of cases. Other frequently encountered sites included frontal localization, accounting for 14% of cases, and fronto-temporal localization, also at 14%. Parietal localization was noted in 10% of cases, while occipital localization was found in 9%. Less common localizations included paragittal and corpus callosum.

The anatomopathological diagnosis of GBM was established after surgical excision in 76 patients (80% of patients) and biopsy in 19 patients (20%). In our series, the anatomopathological aspect of glioblastoma is globally presented by a cellular atypia with a high cytonuclear ratio, hyperchromatic nuclei of variable size and shape often nucleated, as well as mitoses of abnormal morphology and variable number (Fig. 3). The search for IDH1 mutation was not performed in all our patients due to its unavailability and the limited resources available for our patients. However, twenty cases were identified as IDH1-wildtype glioblastomas, while twelve case was classified as an IDH1-mutant glioblastoma.

All patients in our series received symptomatic treatment. Pre- and post-operative corticosteroid therapy based on methylprednisolone, at a dose varying between 60 mg/day and 120 mg/day associated with anticonvulsant treatment based on sodium valproate in patients presenting convulsive seizures, i.e. 24.2%.

Furthermore, all patients underwent a surgical intervention. The surgical approach involved macroscopically complete resection in 44 patients (46.32%), partial resection in 32 patients (33.68%). A biopsy alone was conducted in 19 patients (20%).

In our series, all 95 patients received radiotherapy after surgery. 3 patients died during radiotherapy due to their disease. All patients received 3D conformal radiotherapy with a high energy photon
linear accelerator. The dose received was 60 Gy in 88 patients, 40.5 Gy in 6 patients, 20 Gy in 1 patient. Hypofractionated treatment regimens were chosen by the attending physicians for patients with compromised general health status.

The acute complications of the treatment were graded according to the 4th version of the CTCAE: The majority of our patients presented with grade I alopecia, dizziness, and fatigue. No grade IV toxicity was reported.

The survival of our patients was estimated by the KEPLEIN MEIER curves. The median overall survival was 5.53 (± 0.8) months (Fig. 4).

4. Discussion

GLIOBLASTOMA is the most aggressive diffuse glioma of the astrocytic lineage and corresponds to grade IV according to the WHO classification. It is the most common malignant tumor of the brain and CNS, accounting for 45.2% of primary CNS malignancies, 54% of all gliomas and 16% of all primary CNS tumors [4,5]. According to the 2004 Casablanca cancer registry, the frequency (frequency in relation to all cancers) is 2.8% and the incidence is 2.55 new cases/100,000 inhabitants/year in men and 2.03 new cases/100,000 inhabitants/year in women [6]. There is currently no nationwide cancer registry, and regional registries lack comprehensive descriptive epidemiological data specifically for glioblastoma. However, based on findings from certain regional academic studies, glioblastoma represents 47.6% of malignant intracranial tumors, with an overall frequency of 0.94% (0.48% in 2016 and 1.37% in 2017) among all cancer cases [7].

The median age of diagnosis is 64 years. It is rare in children in whom it represents only about 3% of all reported brain and central nervous system tumors in 0–19 year olds. A higher incidence of GLIOBLASTOMA has been reported in males compared to females [1].

The time from the onset of symptomatology to diagnosis is usually short. It ranges from 3 months to 4 months depending on the study [8,9].

The role of radiologist in the management of glioblastoma is essential at all stages of treatment: at diagnosis, after surgery, for the planning of radiotherapy and in the post-treatment phase [10,11]. Indeed, in the presence of any HTIC syndrome or impairment of higher functions, imaging examinations are essential to:

- make the diagnosis of a brain tumor, and eliminate differential diagnoses.
- Specify the location of the tumor.
- Describe the morphological characteristics (structure, limit, volume, extension)
- guide the indication of the surgical procedure.
- To ensure post-therapeutic surveillance.

MRI remains the reference examination; only situations of contraindication to MRI can lead to limit the exploration to a CT scan without and with injection of contrast medium.

In glioblastomas, the cell density is high or moderate. The tumor proliferation is diffuse and invades the surrounding structures. The cells are polymorphic or on the contrary monomorphic and poorly differentiated, rounded or oval with cytonuclear atypia (high cytonuclear ratio, hyperchromatic
nuclei of variable size and shape, often nucleolated) [2,12]. In the new classification, gliomas mutated for IDH1 or IDH2 are grouped under the term “IDH-mutated”. These mutations are common in diffuse gliomas, occurring in 87% and 83% of grade II and III gliomas and 85% of secondary glioblastomas, respectively. IDH-mutated status is a better prognostic factor for grade II, III and IV gliomas [12,13].

Therapeutic management is guided by the WHO 2016 classification after discussion in a multidisciplinary consultation meeting which must include at least one neurosurgeon, one (neuro-)oncologist, one

Fig. 2. MRI sections showing a large right parieto-temporal intra-axial tumor process, roughly oval in shape, with irregular contours, described in heterogeneous T1 enhyposignal (A), in heterogeneous T2 hypersignal (B) and FLAIR (C), delimiting areas of central necrosis described in T1 hyposignal (A) and T2 hypersignal (B). The whole is surrounded by significant peri-injury edema described as T1(A) hyper T2(B) and FLAIR(C) (Radiology Department, Hassan II University Hospital).

Fig. 3. Histological aspect of glioblastoma. A: high cell density with pallissadic tumor necrosis (arrows) (HESx 100). B: High cell density, with cytonuclear atypia and mitosis (HESx 400).
radiation oncologist, and if possible a radiologist and an anatomopathologist. A personalized care plan must be explained and given to the patient or to the trusted person if the patient has a cognitive deficit. The patient's consent to care must always be sought. Supportive care including psychological support, social care, nutritional follow-up, rehabilitation (depending on the resources of the different centers) must be offered to the patient.

The therapeutic standard is currently defined by optimal surgical resection when possible and then the combination of radiotherapy and concomitant Temozolomide followed by adjuvant Temozolomide. This standard is based on the phase III trial (EORTC - NCIC trial) [3]and has been confirmed by population studies in different countries. All studies have shown a significant increase in median overall survival and in the rate of long-surviving patients [9,14]. Radiation therapy should be started within 2–6 weeks after the surgical excision procedure, provided that the scalp has healed. It can be started more rapidly as early as 2 weeks in case of simple biopsy. The influence of the time between surgery and the start of radiotherapy on survival is the subject of controversy. Too long a delay would be deleterious, or without influence, or even beneficial in some studies [15–17]. In combination with Temozolomide, the dose is 60 Gy in 30 fractions of 2 Gy per day, 5 days per week. In patients over 70 years of age, or with a WHO status <2, regardless of MGMT status several regimens can be proposed [3]. Recently, it was demonstrated in a randomized trial that the 25 Gy in 5 fractions regimen was non-inferior to the delivery of 40.5 Gy in 15 fractions.

Fig. 4. Overall survival estimated by KEPLIN MEIER curves. Overall survival evaluation based on the therapeutic protocol. 0 surgery alone. 1 radiotherapy after surgery. 2 surgery followed by radiochemotherapy.
However, this trial was performed for developing countries and its use in Europe is questionable [18].

4.1. Study limits

Limitations of this study include the retrospective and documentary nature of data collection, which may have led to the loss of important information not recorded in patient files. Additionally, the lack of a local molecular biology platform and limited financial resources restricted the collection of comprehensive molecular data.

5. Conclusion

Glioblastoma (GBM) is a highly aggressive brain tumor associated with various complications. However, limited access to healthcare services, absence of a local cancer registry, and the presence of other oncology centers prevent a comprehensive understanding of the local incidence of GBM. Treatment of GBM typically involves a multimodal approach, including surgical resection, radiotherapy, and chemotherapy. Molecular profiling holds potential for identifying new therapeutic options. Improving healthcare accessibility, reducing delays in treatment, and integrating palliative care can enhance patients’ quality of life. Early diagnosis and management at specialized centers by multidisciplinary teams are crucial. Clinicians play a vital role in diagnosing GBM, implementing multidisciplinary approaches, and supporting patients.

Conflict of interest

The authors declare no competing interests.

References


