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Radiotherapy for high grade glioma: Experience of Radiation Oncology Department of Mohammed VI University Hospital

THESIS

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BY

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Born in August 4th, 1997 in Beni Mellal

TO OBTAIN THE DEGREE OF MEDICAL DOCTOR

KEYWORDS

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JURY

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بسم الله الرحمن الرحيم

"رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ
عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحاً
تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ."

صدق الله العظيم

سورة النمل الآية 19

Hippocratic Oath

I swear to fulfil, to the best of my ability and judgment, this covenant: I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow. I will apply, for the benefit of the sick, all measures [that] are required, avoiding those twin traps of over treatment and therapeutic nihilism. I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug. I will not be ashamed to say "I know not, "nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery. I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. If it is given me to save a life, all thanks. But it may also be within my power to take a life; this awesome responsibility must be faced with great humbleness and awareness of my own frailty. Above all, I must not play at God. I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick. I will prevent disease whenever I can, for prevention is preferable to cure. I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.

.

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Liste arrêtée le 26/09/2022

Dedications

In the memory of my mother:

Rabiaa Tamoun.

Life has not been the same ever since you left us for a better place,
I wish I could go back and spend more time with you.
If it wasn't for you, I wouldn't be where I am today.
Your life was a blessing, every moment with you were irreplaceable and every memory is a treasure that I wish to honor.
I love you beyond words and miss you beyond measure. I will hold you in my heart until we meet again.

To my
dear Father Mohammed Tahiri
and
Fatiha Lamsaadi.

No dedication can express my respect, my eternal love and my consideration for the efforts you have made for my education and my well-being. Today I dedicate to you the fruit of years of work and continuous efforts, and I wish that it brings you joy and pride seeing your hopes come to fruition.
May Allah grant you health and long life so that I can render you even a small part of you have done for me.

To my brother Issam Tahiri, Siham Ouflah and Julia Tahiri.

***Issam**, you were always my mentor ever since I was little, I am so proud to be your little brother, you always been there for me and I wish to make you honored with this dedication.*
***Siham**, thank you for all the moments we shared over the last two years and thank you both for welcoming me into your home. I'm so happy to have witnessed Julia's first year growing up, may she forever be the happy, charming ray of sunshine she is now.*

To my sister Fatima Ezzahra, Ahmad Ettabaa and Reda, Abir and Nour Ettabaa.

Dear sister, you always were the light that guided my path, you always showed me the bright side of everything, you we were there with me in every step of the way, even with the distance, you were always right here in my heart, I love you and I miss you. I wish your small family all the health and joy in the world, I can't wait to see you all again.

To my brother Hassan Tahiri, Rahma Hdouch and Sami Tahiri.

I'm so grateful to have you as a brother, thank you for all the sweet memories.
***Rahma**, you took care of me ever since we lost my mother, and for that I am forever in your debt.*
***Sami,** I am so proud of you and I hope that you make us all proud. I wish you all the good luck and success in your lives*

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Thank you for all the memories we made, it was an amazing journey that we shared. I shall also thank you for putting up with me all these years. I will miss all the laughs, all the beautiful moments, all the highs and all the lows. I could never have hoped for better friends. I am so grateful to have you all as my friends, but even more proud to call you family.

To Ilham Faouzi.

It is truly a blessing to have someone as brilliant as you in my life. You inspire me to be the best version of myself, you help me overcome all the challenges. I will do everything in my power to pave the way for you and assist you in your endeavors. I hope to make you proud and I hope for a bright future ahead. I would also like to thank your sisters Loubna and ElHossna for all the sweet memories and I wish your parents all the health and joy in the world.

To Professor Mouna DARFAOUI,

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To my Grandparents.

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To my Aunts and Uncles.

Thank you for all the sweet memories, you all were always there to lend a helping hand. Thank you for the guidance and the kindness you've shown me throughout the years.

To my Cousins.

We all grew up together not as cousins but as brothers, we share the most amazing memories that I cherish deeply. I wish you all the luck and success in the world. I hope to make you all proud.

To my Family and friends.

To my family members and friends that I care about immensely. I dedicate this modest work to you all, wishing you health, peace of mind and a long life where we would share a lot of moments of pure happiness.

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Professor K. ANIBA,

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Professor M. KHOUCHANI,

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Professor A. BELBACHIR,

You do us a great honor to judge this thesis. Your competence and your sense of duty have deeply impressed us. May this work be the expression of our deep respect and our gratitude.

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LIST OF ABREVIATIONS

18-DFG-2: Fluoro-2-Deoxy-D-Glucose

ADC: Apparent Diffusion Coefficient

AKT: Protein Kinase

ARF: ADP Ribosylation Factor

CBTRUS: Central Brain Tumor Registry of the United States

CP: Contrast product

CDK4: Cycline Dependant Kinase 4

CDKN2A: Cycline Dependent kinase Inhibitor 2A

CHO: Choline

Cr: Creatine

CTH: Chimiothérapie

DNOR: Danish Neuro-Oncoloy Registry

DNA: Deoxyribonucleic acid

E2F: Transcription

EGFR: Epidermal growth factor receptor

EORTC: European Organization for Research and Treatment of Cancer

GFAP: Glial Fibrillary Acid Protein

GBM: Glioblastoma

H3K27M: Histone mutation k27

HGG: High grade Glioma

HPS: Hématoxyline Phloxine Safran

HR : Hazard Ratio

ICHT : Intracranial hypertension

IDH : Isocitrate Déshydrogénase

IHC: Immunohistochemistry

STB: Stereotactic Biopsy

MRI: Magnetic Resonance Imaging

KPSS: Karnofsky Performance Statuts Scale

LAC: Lactate

MAP: Microtubule-associated protein

MDM2: Murine Double Minute 2

MGMT : O6-Méthylguanine-ADN Méthyltransférase

MI: Myo Inositol

MMS : Mini Mental State

NAA: N-acétylaspartate

OR: Odds Ratio

p53 : Protéine 53

PAS : Périodique Acide Sciff.

PCV: Procarbazine, lomustine et Vincristine

PDGFR: Platelet growth factor receptor

PDT: Photo dynamic therapy

PI3: Phosphoinositide 3 kinase

Prb: Retinoblastoma protein

Pten: Phosphatase and tensin homolog

RECRAB: Cancer Registry of Rabat

RB: Retinoblastoma

RNA: Ribonucleic acid

RPA: Recursive Partitioning Analysis

RR: Relative risk

RT: Radiotherapy

SEER: Surveillance Epidemiology and End Results

SNC: Central Nervous System

SR: Sex-Ratio

SRM: Magnetic Resonance Spectroscopy

SV-40: Simian Virus 40

CT scan: Computed Tomography scan

TEP: Positron Emission Tomography

TERT : Telomerase Reverse Transcriptase

TMZ : Témozolamide

Summary

INTRODUCTION

Glioblastomas (GBM) (Astrocytoma of grade IV according to the WHO classification) are by far the most common and malignant kind of brain tumour. Their malignity is locoregional and their systematic metastasis is exceptional.

They can be primary (primary GBM) or may result from the transformation of pre-existing low-grade astrocytoma (secondary GBM).

The main clinical manifestations are intracranial hypertension, convulsive crisis and/or neurological deficits. They vary depending on the localisation and size of the tumour.

From a diagnostic point of view, it has advanced considerably with the development of the precision of paraclinical examinations, the CT-scan and more particularly magnetic resonance imaging (MRI).

Some factors seem to have a more or less impact on the prognosis of these tumours namely the age, the Karnofsky index, presence of cognitive disorders, the residual volume. The classification of patients depending on these factors determines the prognosis group and guides the therapeutical strategy.

Their prognosis remains poor, and therapeutic arsenal only aims to slow down the evolution of the disease.

From the therapeutic perspective, glioblastomas seem to cause many handicaps and presents a real challenge for neu-oncologists. Their diffuse and infiltrative nature makes their complete resection illusory. Nevertheless, the quality of the procedure influences survival, but the post-operative recurrence is still the rule.

Glioblastomas are characterized by their chemo resistance and radio resistance, which relatively explains the poor impact of treatment on survival. Focused radiotherapy postoperatively increases the median survival [1] .For chemotherapy, the most studied active molecules are alkylating agents, in particular nitrourea and temozolomide.

METHODOLOGY

I. Type of the study:

This is a retrospective study of a consecutive series of 33 patients with glioblastoma.

II. Place and span of the study:

This study was conducted over a period of 5 years, spread between January 2017 and December 2021 in the department of oncology-radiotherapy at the University Hospital Med VI Marrakech.

III. Target population:

Using the inclusion and exclusion criteria, our patients were selected from an initial sample of 48 cases admitted in the oncology-radiotherapy department at the University Hospital Med VI Marrakech.

1. Criteria of inclusion:

- All glioblastomas histologically confirmed ;
- No age limits ;
- All patients that underwent radiotherapy.

2. Criteria of exclusion:

- Patients with incomplete or unexploitable medical files.

IV. Methodology:

All the patients were identified from the department's register and the files were collected from the Oncology department's archives.

All the epidemiological, clinical, paraclinical, therapeutical and evolutive data were registered in a preestablished operating sheet (appendix 1), then collected from the medical records. From which several results were grouped and calculated.

V. Statistical data analysis:

We used Microsoft Excel 2016 for the preparation of the database and for the elaboration of the graphs. The text entry was done on Microsoft Word 2016.

VI. Ethical considerations:

The collection of data was done taking into consideration the global rules of ethics relating to the respect of confidentiality and the protection of the patients' own

RESULTS

I. General information:

1. Epidemiological characteristics:

a.Age

The average age of the patients was 51.60 years with extremes ranging from 29 to 74 years old .

The distribution of patients according to age showed a high frequency, estimated at 60.60% in adults aged between 41 and 60%. On the other hand, the paediatric population was not represented in our study.

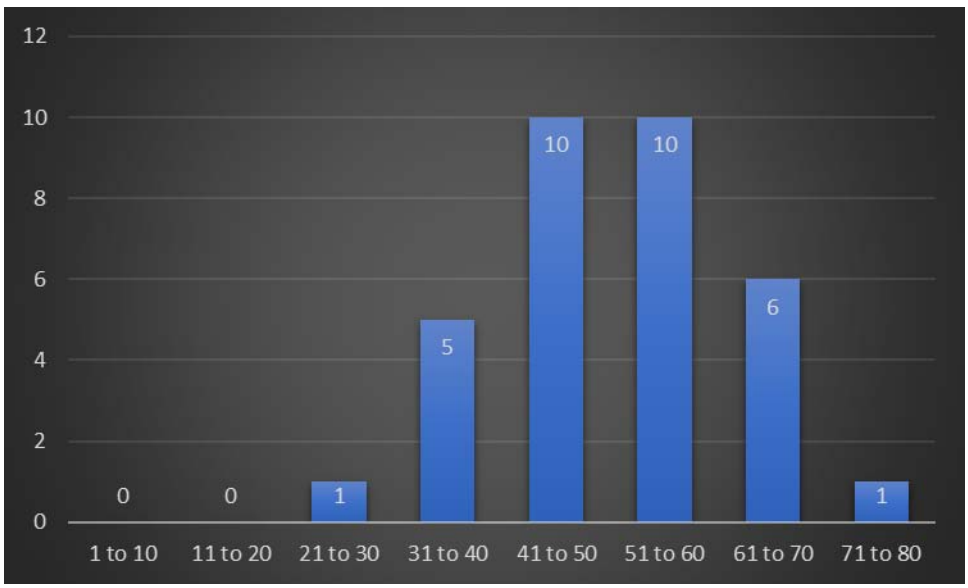

Figure 1: Distribution of patients by age group

b.Gender:

In our study, 20 cases were men (60,6%) and 13 cases were women (39,4%) with a gender ratio of 2:1.

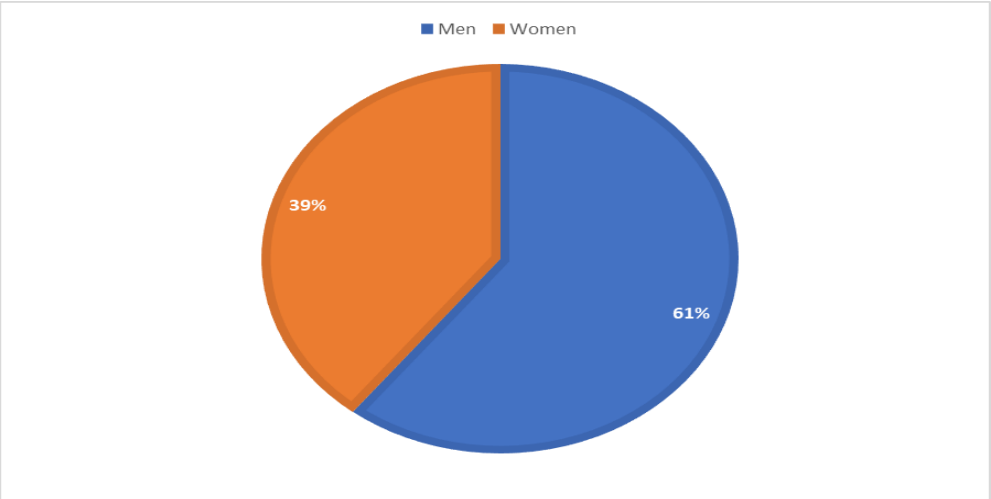

Figure 2:Distribution of patients by gender

c.Origin:

The majority of our patients originated from urban areas (85%) while the remaining (15%) originated from rural areas.

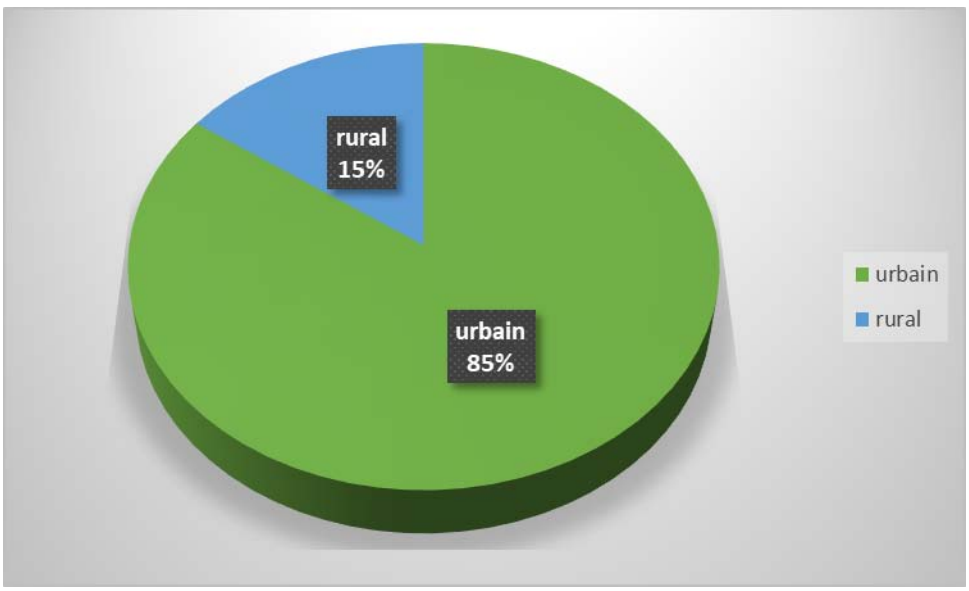

Figure 3:Distribution of patients by urban or rural origin

Most of our patients were from the region of Marrakech-Safi (70%), followed by the region of Beni Mellal-Khenifra (12%) then the region of Draa-Tafilalet (9%)

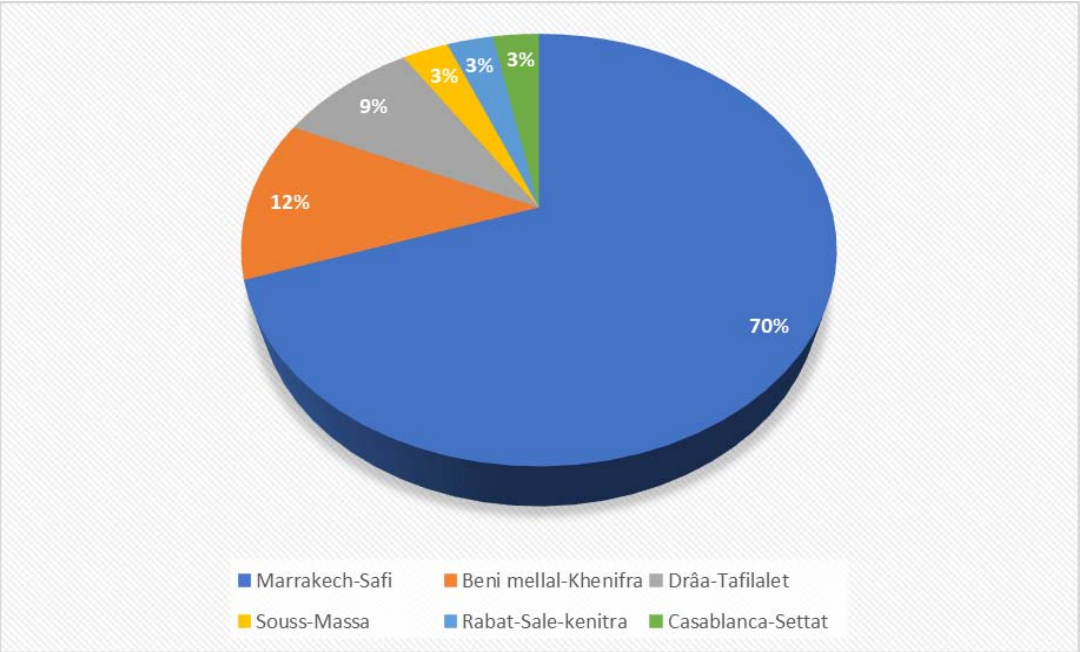

Figure 4:Distribution of patients by region

2. Medical history

Five of our patients, i.e. 15% of our cases, had associated chronic diseases. The most frequent antecedents were high blood pressure (9%) and diabetes (6%).

As for the surgical history, one patient was operated for cholecystitis and one patient was operated for a cataract.

Regarding toxic history, no patient reported exposure to lead. Pesticide exposure was difficult to determine. However, 8 patients or 24.24% of cases were smokers, all male, while 2 of them also consumed cannabis.

Our patients reported no family history of glioblastoma or other cancers.

II. Clinical Data:

1. The time of evolution:

The time to diagnosis in our study ranged from one week to two years with a mean time of 25 weeks.

2. Reason of consultation:

The reason for consultation was mainly represented by motor deficits in 51% of the cases, followed by intracranial hypertension in 48% of the cases, and higher functions deficit in 18%

3. Clinical signs:

a.Intracranial hypertension syndrome:

16 cases in our study (48%) presented an intracranial hypertension syndrome made of headache in helmet, vomiting and visual disorder.

b.Isolated headaches:

12 of our patients (36%) presented headaches that were resistant to analgesic treatment.

c.Motor deficits:

16 patients (48%) presented motor deficits,10 of them (30%) presented a hemiparesis, 6 of them (18%) had a hemiplegia, while 1 patient (3%) presented limb trembling.

d.Sensitive deficits:

Only one patient (3%) reported a sensitive disorder.

e.Seizures:

Seizures were reported in 3 cases (9%)

f.Higher functions deficits:

6 patients (18%) presented higher functions deficits. 3 of these patients (50%) presented language problems, 2 patients (33.3%) presented memory issues, and one patient (16.6%) presented behavioural problems.

g.Vestibular syndrome:

Only one patient (3%) presented with a vestibular syndrome.

h.Cranial pairs problems:

3 patients (9%) presented a facial paralysis, 1 patient (3%) presented a divergent strabismus, 1 patient (3%) presented a hypoacusis.

i.Karnofsky score:

In our cohort, 12 patients scored 100%, 14 scored 80%, 5 scored 60%, and 2 scored 40%.

Table I: Distribution of patients by symptoms

Symptoms	Number	Percentage
Motor deficits	16	48%
Intracranial hypertension	16	48%
Isolated headaches	12	36%
Higher functions disorders	6	18%
Deterioration in general status	7	21%
Seizures	3	9%
Sensitive deficit	1	3%
Vertigo	1	3%

III. Paraclinical data:

1. Topography:

The tumour location was predominantly parietal (36%), followed by temporal (15%), front-parietal (15%), frontal (12%), temporo-parietal (12%), cerebral trunk (3%), thalamus (3%), then axial (3%).

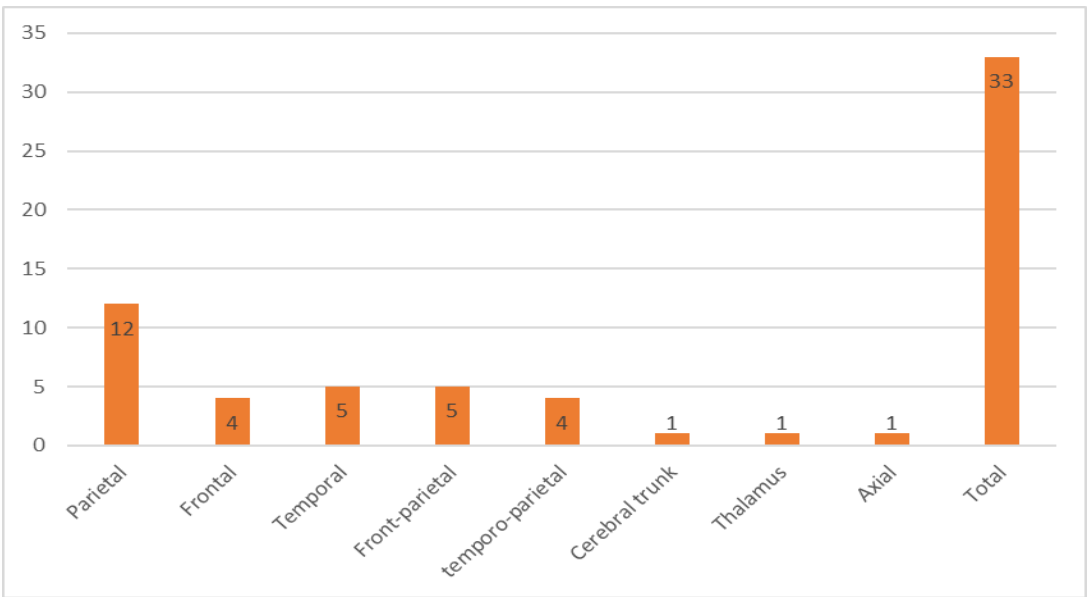

Figure 5: Distribution of patients by tumour topography:

2. CT-scan:

CT scan was performed for 21 patients; it showed a hypodense heterogeneous tumour in 90%. The tumour was badly limited in 52%. Necrosis was noted in 23%. Haemorrhage was present in 4%. Perilesional oedema responsible for mass effect was noted in 85%. After injection of iodinated contrast medium, the enhancement is heterogeneous, variable both in shape and intensity.

The tumour size in the greater axis was between 2.9 cm and 7 cm with an average of 5 cm.

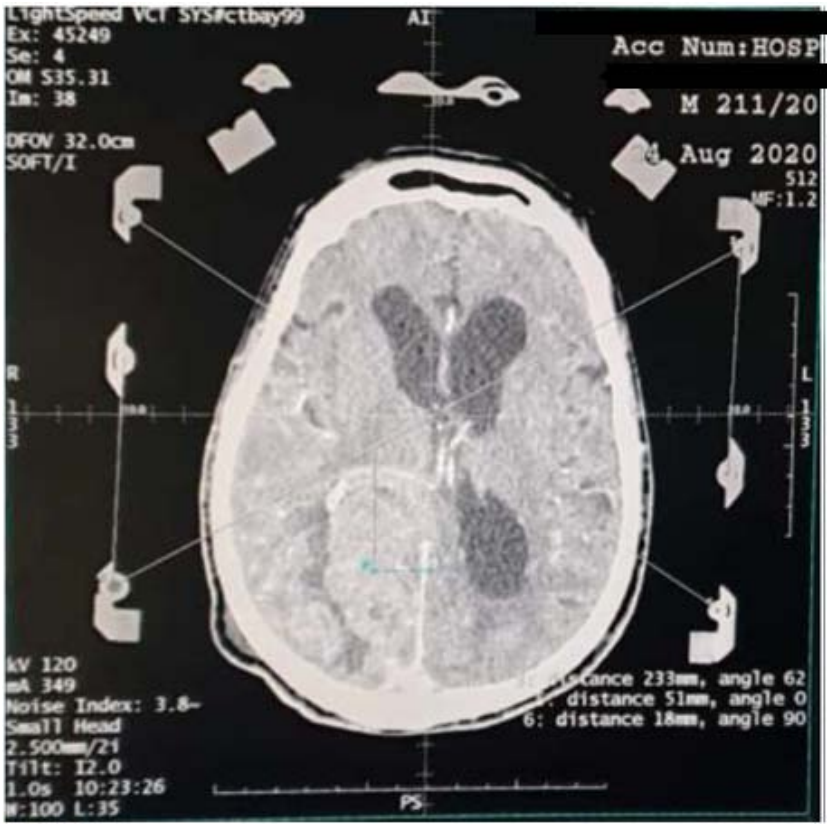

Figure 6: Axial section CT image showing a poorly defined hypodense right occipital tumour process that enhances after contrast injection

3. MRI :

MRI was performed in 24 patients in our series. In T1 weighting, it was hypodense in 83% of cases. In T2-weighted and FLAIR, it appeared as a hyper signal in 87.5% of cases and a hypo signal in 12.5% of cases.

Necrosis was present in 33.3% of cases, haemorrhage was observed in 12% of cases and peri-lesion oedema in 91.6% of cases. Boundaries were irregular in 62.5% of cases.

Spectro MRI was performed for 10 patients 30% and it showed an elevated choline peak and a wavy NAA peak.

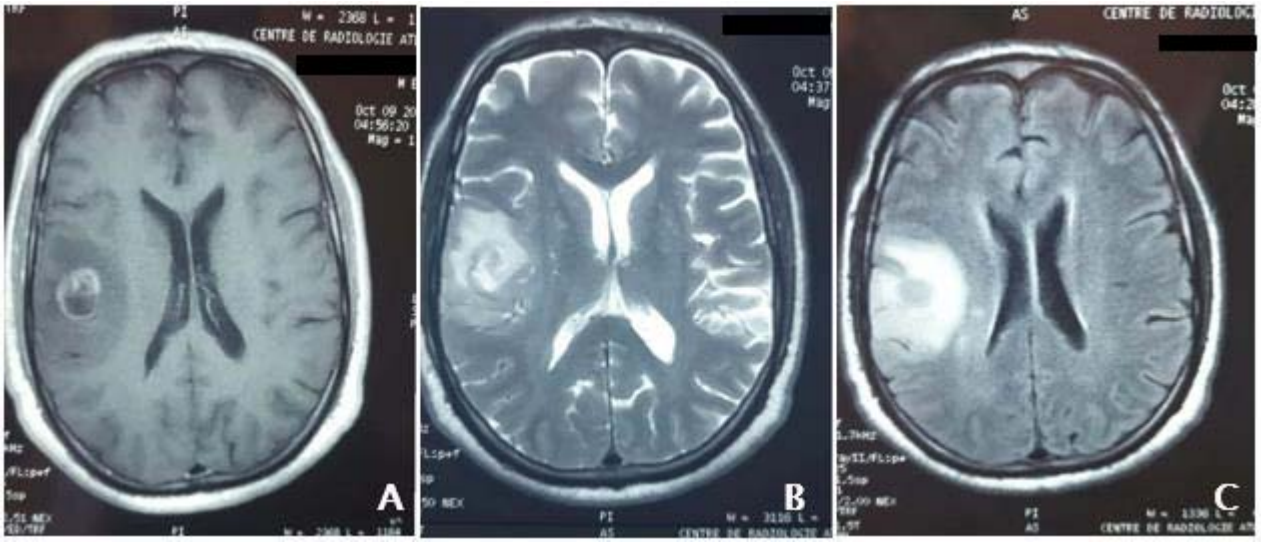

Figure 7: Aspect of a high-grade glioblastoma in injected T1 (A), injected T2 (B), and flair sequence (C).

4. Other:

All of our patients had a preoperative workup that included :

- A blood grouping ;
- A haemostasis exam ;
- Electrolyte exam ;
- Blood counts.

IV. Histological exam:

All patients in our patients underwent histological exams. The anatomopathological diagnosis of glioblastomas was established after a biopsy for 6 patients (i.e., 18% of the patients) and after surgical excision for 27 patients (i.e., 81% of the patients).

The anatomopathological aspect of glioblastoma is presented by a heterogeneous tumour

proliferation made of a cellular atypia with a high cytonuclear ratio, hyper chromatic nuclei of variable sizes and shapes, multiple mitoses, high cellular density and cellular necrosis (40%) with numerous haemorrhagic foci and important vascular neogenesis. The Immunohistochemistry was realised for 20 patients (60%), and confirmed the diagnosis of grade IV glioblastoma in all of them.

V. Treatment:

1. Symptomatic treatment:

All patients received medical treatment with the goal of:

- Relieve pain ;
- Medical treatment of ICHT ;
- Prepare patients for surgery.

Pre and postoperative corticotherapy based on methylprednisolone, at a dose of 1mg/kg/day and prophylactic antibiotic therapy was prescribed for all patients in our series.

Sodium valproate-based anti-convulsive treatment was indicated for patients presenting with comitiality or at risk of it.

Postoperative analgesic treatment was systematically prescribed in all cases.

2. Specific treatment:

a.Surgical treatment:

All patients in our series underwent surgical treatment. The resection was macroscopically total in 12 patients (36%), partial in 15 cases (45%), and a simple biopsy was performed in 6 cases (18%).

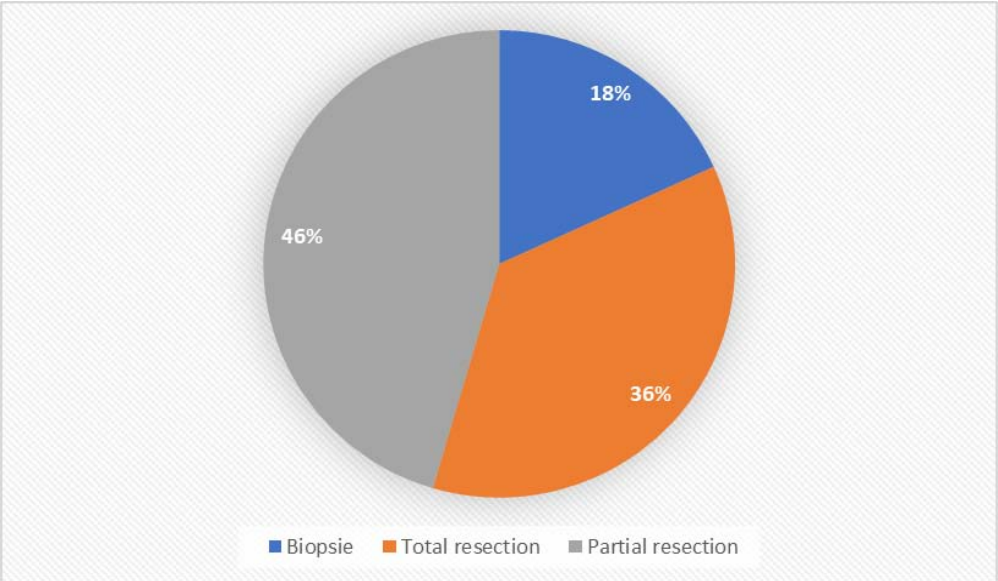

Figure 8: Distribution of patients according to type of surgery.

b.Radiotherapy:

All our patients received a complementary radiotherapy treatment.

1.Delay between surgery and radiotherapy:

The delay between the surgery and the radiotherapy ranged from 1 month to 7 months with an average of 1.9 months.

2.Indications and objectives of radiotherapy:

Radiotherapy's main goal is to kill the cancer cell using beams of intense energy which helps reduce to tumor size. This is why it became a primordial part of the therapeutical arsenal for glioblastoma alongside surgery and chemotherapy.

3.Preparation:

Before starting the radiotherapy:

- The indication is discussed in the neuro-oncology multidisciplinary team meeting.

- Consider early post-operative MRI to define the extent of residue and to differentiate the post-surgical changes. The patient may also require another MRI closer to starting radiation therapy planning.
- Radiotherapy may commence as soon as practically possible, ideally within 6 weeks.

We used a thermoplastic mask for all our patients.

4.Delineation of targets:

Currently, 2 identical techniques in terms of power are recognized for the delivery of 60Gy. The RTOG (Radiation Therapy Oncology group) recommends a first phase of 46Gy at large volume including the edema, then a second phase with the remaining 14Gy (the boost) focusing on the resection cavity.

The EORTC (European Organisation for Research and Treatment of Cancer) recommends a single phase. Currently in Europe, only one phase of radiation is used as gold standard.

The contouring is based on delineation of 3 different targets:

- GTV: Gross tumor volume,
- CTV: Clinical target volume,
- PTV: Previsionnal target volume.

These volumes were contoured using the dosimetric scan after fusion if MRI was available.

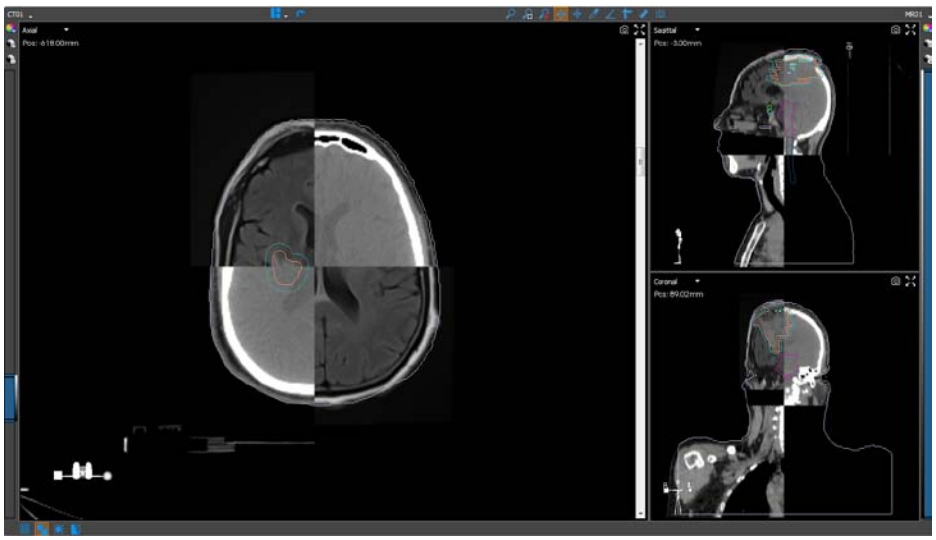

Figure 9: The delineation of a glioblastoma with MRI

5.Dosimetry scan:

It is performed using a dosimetry scanner. Apart from medical emergencies, it usually takes several days, depending on the complexity of the technique, the type of tumor and any previous radiotherapy treatments that must be taken into account.

It consists in choosing the irradiation technique best adapted to the anatomical area to be treated. This area is carefully delimited on the dosimetry scanner by the radiation oncologist, who uses all the results of the examinations previously carried out. It also helps in deciding on the technique (3D radiotherapy, with intensity modulation, in stereotactic conditions, with respiratory servo control, etc.), the dose and the number of sessions. Based on these indications, the team of dosimetrists and medical physicists will position the radiation beams and specify their technical characteristics.

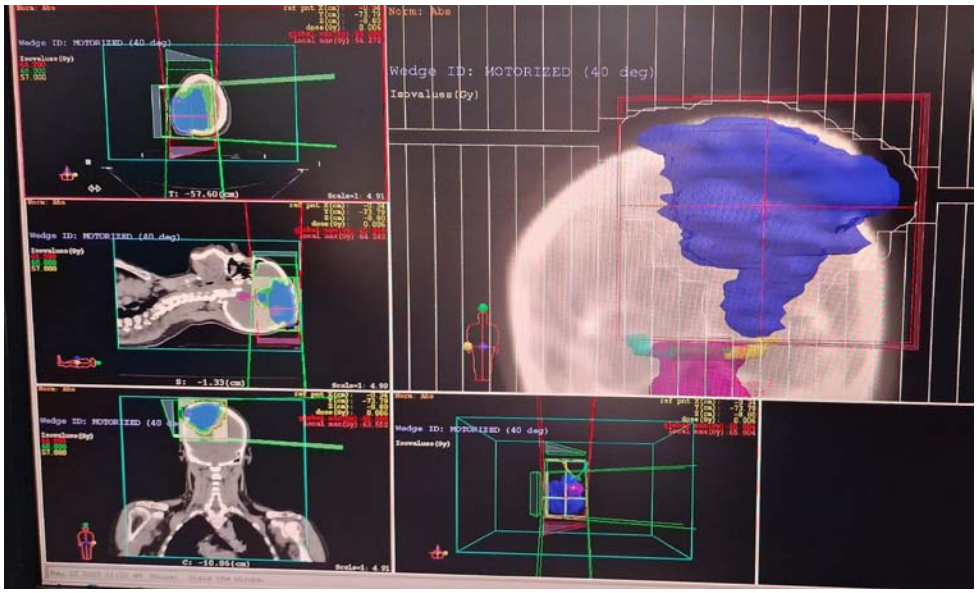

Figure 10 : Dosimetric analysis for glioblastoma

6.Dosage and fraction:

Table II: Patients' distribution by radiotherapy plan

Number of patients	Spreading	Total dosage (Gy)	Fraction	Dose per Fraction (Gy)
25	6 weeks	6000	30	200
8	3 weeks	4000	15	267

7.Quality control:

Radiotherapy for glioblastomas comes with various risks mainly due to the anatomical area. Many organs can be at risk mainly the optic nerve, the optic chiasma, the eyes, the lenses, the brain stem. Some organs can be considered as potentially at risk: The chochlea, the lacrimal glans and the pituitary gland.

In our study, 6 cases had side effects, the radiotherapy was interrupted prematurely due to worsening of oedema in 2 cases (6%), technical issues in 2 cases (6%) and death in 2 cases (6%).

c.Chemotherapy :

27 of our patients (81%) underwent a neoadjuvant chemotherapy. The molecule used in 26 cases (96%) was Temozolomide 75mg / m^2 taken once a day orally during radiotherapy treatment.

The treatment was interrupted in 13 cases (39%) , in 6 cases (18%) it was due to toxicity mainly low platelets count, in 5 cases (15%) it was to lack of availability in the department, in 2 cases (6%) it was to patient's death.

Adjuvant chemotherapy, based on 6 cycles of Temozolomide 150 to 200mg/m^2 on days 1 to 5 of each 28-day cycle, was taken only by 12 patients due to lack of availability or bad tolerance and complications. The median number of achieved cycles was 2.2

VI. Evolution:

1. Short term:

25 patients (75%) did a post-operation MRI, in 2 cases (8%) there was no report provided.

19 of our patients (57%) suffered post-operation oedema, haemorrhage in 2 cases (6%) and a focal deficit in 2 cases (6%).

These patients received antiedematous treatments and surgical treatment.

2. Long term:

We lost contact we the majority of these patients, from the available data; 2 patients (6%) died during chemotherapy, 7 patients (21%) had a sort of aggravation, progression or recidivism was in 8 cases (24%), 6 patients (18%) have been stabilised.

DISCUSSION

I. Epidemiology:

1. Frequency and incidence:

Gliomas represent 26% of all primary brain tumours and other CNS tumours and 81% of malignant tumours [2]. Glioblastoma represents the most frequent tumour with a percentage of 56.6% according to CBTRUS [3], 20.3% according to Dutertre[4] and 69.5% according to DNOR (Danish neuro-oncoloy registry)[5].

The incidence varies according to geography, for glioblastoma it is 3.19/100000 in the United States; 2.05/100000 in England; 3.69/100000 in Greece; 3.40/100000 in Australia; 0.59/100000 in Korea[6].

In Morocco, the cancer registry cited the frequency of brain tumors in relation to all cancers, it presents 2.4% according to the register of Rabat (RECRAB) with an incidence of glioblastoma of 1.4/100000 [7] , and according to the register of Casablanca with an incidence of 2,4/100000 [8]

2. Age:

Glioblastomas can occur at any age with a median age of 46 to 64 years [9], [10]. In our study, the average age was 51.60 which is consistent with the literature

Table III: Age of onset of glioblastoma in the literature.

Authors	Number	Extreme age	Median age	Most affected age group
Delion [10]	94	22-81	64,5	----
Bauchet [6]	952	-----	63,9	----
Mineo [11]	340	16-81	55	----
Bartolomei [12]	73	29-77	52	----
Malkoun [13]	46	40-77	61	----
Lonjon [14]	20	19-64	52	----
Rogger stupp 2005 [15]	573	18-70	56	----
Hiroaki shimizi [16]	26	24-79	46	----
Elfane [17]	55	11-84	59	50-69
Our cohort	33	29-74	51,60	41-60

3. Gender:

In the majority of studies, there is a male predominance with a sex ratio (SR) M/F varying from 1.2 to 3.2 and this is the case in our series with 60.6% for males and 39.4% for females with a sex ratio of 2

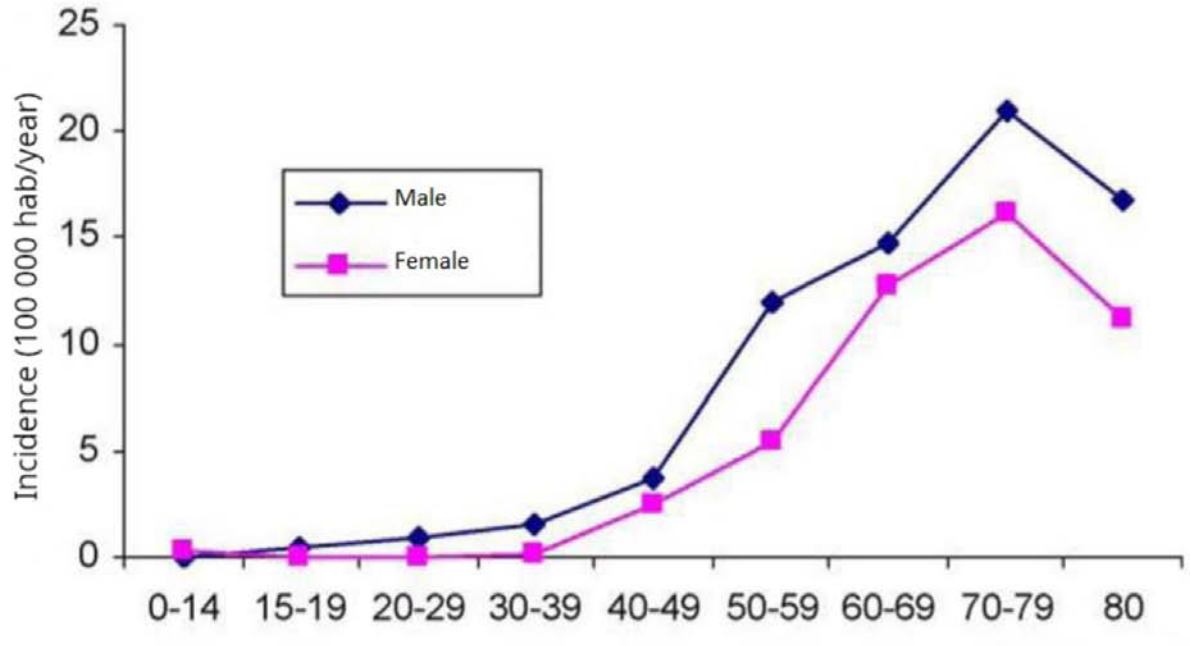

Figure 11: Incidence of glioblastoma by age and sex (Gironde Registry) [10].

4. Risk factors:

a. Genetic predisposition:

Some genetic syndromes are known to predispose individuals to cancers related to identified abnormalities: Li Fraumeni syndrome, mutation on the p53 gene, Turcot syndrome, NF1 neurofibromatosis[18], Gardner syndrome, Lynch syndrome [19], but this concerns only 1% of gliomas [20].

In our series, no history of glioblastoma or other cancers in the family was noted.

Table IV: Major genetic predisposition syndromes. [21]

Illness/Syndrome	Transmission	Gene	Localisation	Incidence	Protein
NF type 1 Von Recklinghausen	AD P 100 % E variable	NF1	17q11.2	1 pour 4000	Neurofibromine
NF type 2	AD P 100 % E High	NF2	22q12	1/40 000 à 1/100 000	Merline
Li-Fraumeni	AD	TP53	17p13	315 familles	p53
Turcot type 1	AD P low	hMLH1 hPMS2 hMSH2	3p21.3 7p22 2p16	-	-
Sd Gardner	AD P high	APC	5q21-22	1 /14,000	Papc
von Hippel-Lindau	AD P high E variable	VHL	3p25-26	1/40 000	pVHL

b.Ionizing radiation:

Ionizing radiation damages DNA by inducing both single and double breaks in these strands, which subsequently leads to modifications and genetic alterations leading to cancer [22]. The existence of ionizing radiation, even at a low dose, in the brain (treatment of skin or scalp lesions, repeated X-ray examinations for odontological purposes, previous irradiation of tumor lesions) is a well-established risk factor according to the literature[19], [23], [24].

c.Professional environment:

The risk of chemical carcinogenesis related to the occupational environment: rubber workers, workers in industries using lead [50], agricultural workers with frequent exposure to pesticides, have been targeted in studies conducted in these occupational sectors [19], as

risk factors to be taken into account [19].

In our series, there was no notion of exposure to lead or pesticides.

d.Allergy and atopic disorders:

It has been reported that allergies protect against several types of cancer, including glioma[22], and it has been suggested that this effect may be due to increased surveillance by the innate immune system in allergy sufferers, but this potential mechanism has not been definitively proven. In addition, although the majority of reports have found an association between allergies and atopic diseases (e.g. eczema, psoriasis, asthma, hay fever) with a reduced risk of glioma [25], [26], some studies have identified the opposite effect [6] . According to scheurer et al the lack of asthma or history of allergy combined with<10 years of anti-inflammatory drug use was found to have the greatest protective effect for GBM, whereas antihistamine use for ≥10 years increased the risk of anaplastic glioma regardless of asthma or allergy history [24], [27].

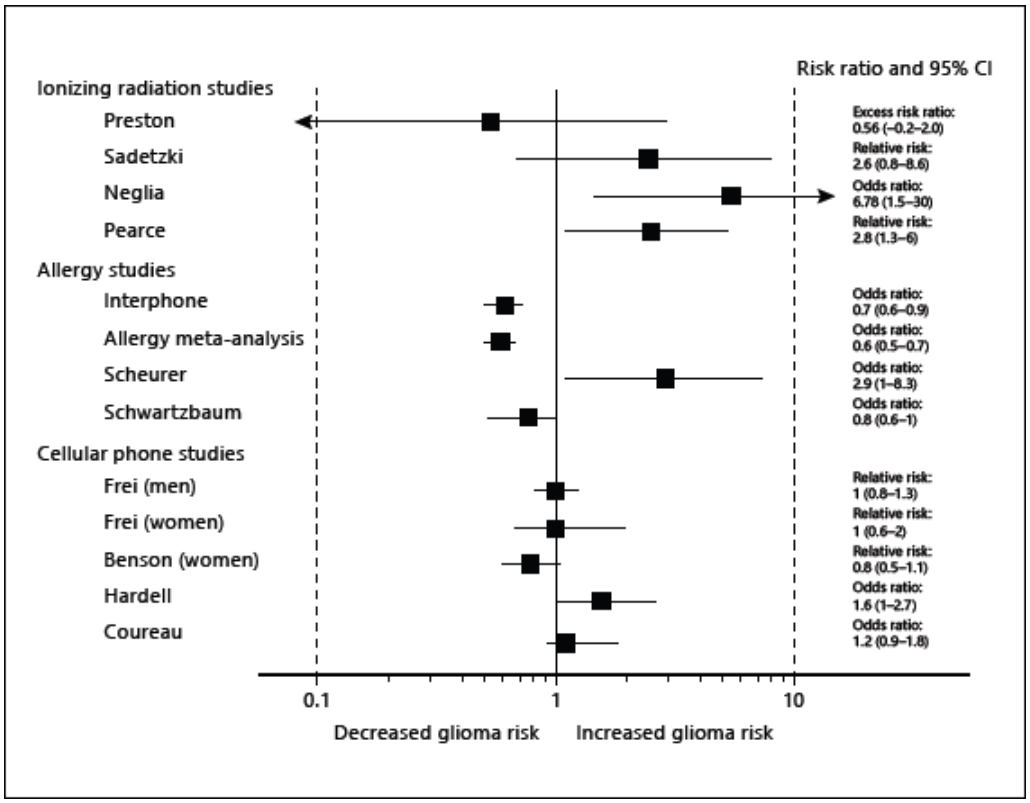

Figure 12: Results of some recent analyses of potential risk factors for gliomas[24].

e.Ethnicity

There is a different distribution of high-grade glioblastoma by ethnicity. For example, the relative risk of developing glioma is 1.7 (95% CI: 1.1-2.6) in Caucasian whites compared with non-Caucasians; in America the incidence is 6.84/100,000 in whites and 3.48/100,000 in blacks, whereas in Japan the incidence of occurrence of these primary brain tumors is lower[28].

f.Nitro compounds, dietary habits:

Some nitro compounds have been classified as probable human carcinogens by the International Agency for Research on Cancer [29]. A meta-analysis found that consumption of smoked meats during pregnancy increased the risk of brain tumors in the child (RR: 1.68;

95% CI: 1.30- 2.17) [30] . Another study conducted in Israel identified vegetable oils in the diet (OR: 1.36; 95% CI: 1.06-1.73) and potassium intake during pregnancy (OR: 1.44; 95% CI: 1.04-1.99) as risk factors for brain tumors in children[31].

Of note, consumption of carotene, certain dietary fibers, and some phytoestrogens [32] would reduce the risk (OR: 0.4-0.5; CI95%: 0.2-0.9) [33].

g.Tobacco:

Smoking is considered a risk factor due to the presence of nitrosated compounds in cigarette smoke, which are considered carcinogenic and likely to induce high-grade gliomas[29]; consumption of more than two packs of cigarettes per day increases the risk of occurrence (RR: 2.3; CI95 % : 1,2-4,5)[34]. This risk remains higher even in relapsed smokers (HR 1.51; 95% CI 0.97-2.34). However, the duration of smoking cessation seems to be beneficial, and subjects who have stopped smoking for more than ten years have a reduced risk of developing a glioma compared to those who have stopped for less than ten years (HR: 0.55; CI95%: 0.29-1.07)[35] .

In our study, the percentage of smokers was 24%.

h.Infections:

Infections, especially viral ones, have a special place in the identification of risk factors. Indeed, DNA sequences of different polyomaviruses (JC, BK and SV-40 viruses, simian virus-40) exist in many human brain tumors [36]. The T-antigen (tumor antigen) of these viruses has the property of being able to form a complex with p53 and pRb and to render them inactive. The genes encoding these two proteins belong to the tumor suppressor gene family [36].

Results have shown that there is an inverse relationship between the occurrence of

high-grade glioma and infections related to varicella-zoster virus in particular and other herpes (OR : 0.41; CI95%: 0.24-0.70)[37]-[39], an international population-based study had reported a significant reduction in the risk of the occurrence of glioma in patients with influenza and/or colds (RR: 0.72; CI95%: 0.61-0.85) [22].

II. Oncogenesis:

High-grade gliomas (grade III and IV) are defined by the type of tumor cell they contain and by their histological grade. They can be classified as astrocytomas, oligodendrogliomas or anaplastic oligo-astrocytomas; they may arise de novo or as a result of the progression (anaplastic transformation) of diffuse grade II gliomas.

The understanding of the oncogenesis of glial tumors requires the study of gene alterations (oncogenes, tumor suppressor genes), involved in cell division. A large number of recurrent genetic alterations have been identified in gliomas (fig.11). These multiple genetic alterations result in the activation of molecular pathways (receptor tyrosine kinase pathway, P53 pathway, Rb gene pathway) which are currently relatively well known in gliomas and which lead to uncontrolled cell proliferation.

Gliomagenesis involves molecular alterations such as amplifications, mutations, rearrangements or chromosomal deletions. These chromosomal alterations affect different proto-oncogenes (Egfr, Pdgfr, Mdm2...) and tumor suppressor genes (p16, p53, Rb, Pten...). The sequence of these genetic alterations is at the origin of tumor progression, some genes being altered early on, others later in the course of evolution.

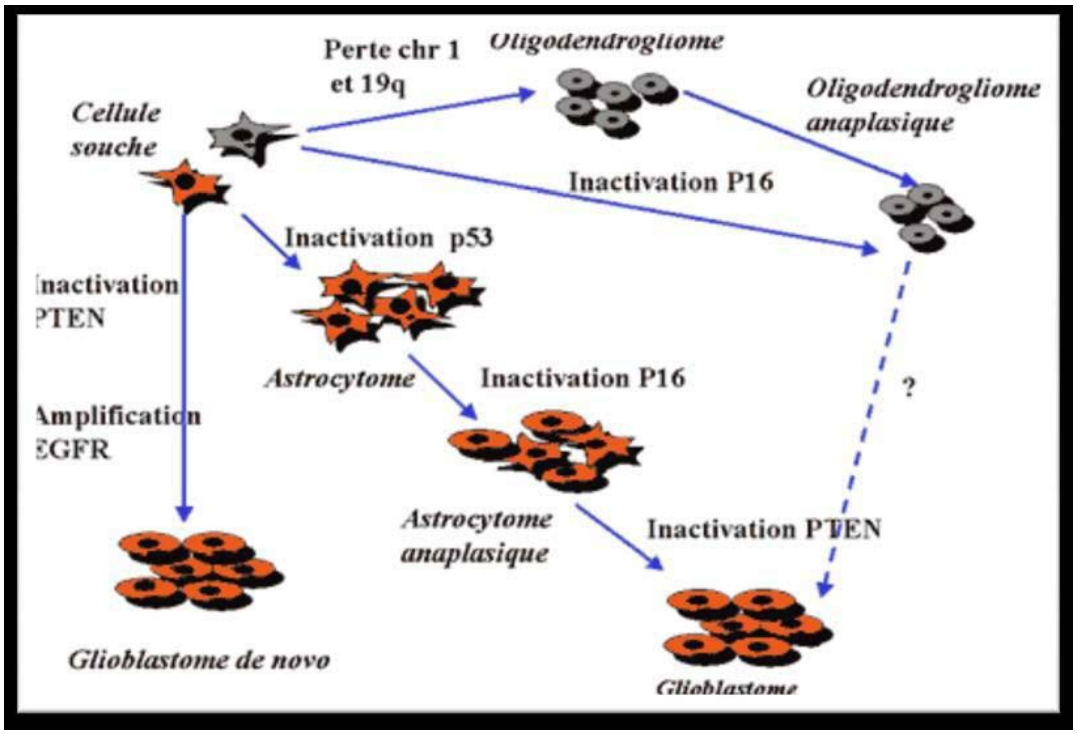

Figure 13: Hypothetical model of glioma histogenesis and the recurrent molecular alterations observed.

In gliomas, the accepted oncogenetic hypothesis is the transformation of stem cells or progenitor cells that would have the capacity to self-renew and differentiate (pluri- or multipotent cells). They would therefore be able to generate the different morphological types of tumor cells within a tumor. The identification of IDH mutations in gliomas of grade II, III and secondary glioblastomas but not in de novo glioblastomas, has allowed to propose 2 pathways of gliomagenesis.

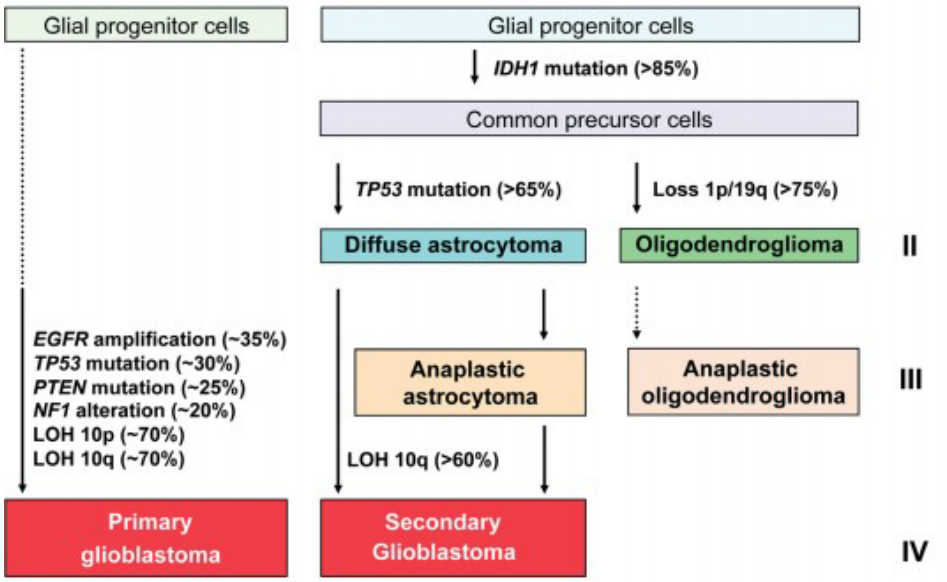

Figure 14: Histo-molecular classification and gliomagenesis.

1. Cell cycle deregulation, signal transduction activation and glial proliferation:

The inactivation of p53 that is associated with the astrocytic tumor phenotype is an early genetic alteration, persisting during secondary "anaplastic transformation." Conversely, mutually exclusive deletion of p16/CDKN2A, inactivation of RB1 at 13q, and amplification of CDK4 are more common in high-grade gliomas. PTEN inactivation at 10q and EGFR amplification are preferentially observed in glioblastomas.

These genetic alterations mainly affect 3 major pathways involved in cell cycle control and signal transduction: p53, RB1 (retinoblastoma pathway) and growth factor receptor tyrosine kinase. At the glioblastoma stage there is a joint alteration of these 3 major pathways[40] .

❖ The p53 pathway regulates the cellular response to DNA damage in hypoxia and

leads to cell cycle arrest with either apoptosis of the cell or the initiation of repair mechanisms. This pathway can be inactivated by the mutation of p53, or by the amplification of MDM2, or more rarely by that of MDM4 which leads to the degradation of p53, by the inactivation of p14/ARF (deletion or epigenetic inactivation) which inhibits MDM2 [41].

❖ The RB protein (product of the RB1 gene), is hypo-phosphorylated in quiescent cells and thus sequesters the transcription factor E2F. E2F when released induces transcription of genes that will promote advancement in the cell cycle. Phosphorylation of RB by the Cyclin D1/CDK4/CDK6 complex results in the release of E2F. The negative control on proliferation exerted by RB through its binding to E2F, can be abolished: either by inactivation of RB1 (deletion, mutation or methylation), or by amplification of CDK4 or more rarely CDK6 which lead to phosphorylation of RB, or by inactivation (deletion or methylation) of p16/CDKN2A which inhibits CDK4 [41], [42].

❖ Thus, the inhibition of p53 and RB results in the progression of the cell cycle from G1 to S phase and the removal of the inhibition exerted by p53 at the G1 and G2 phases.

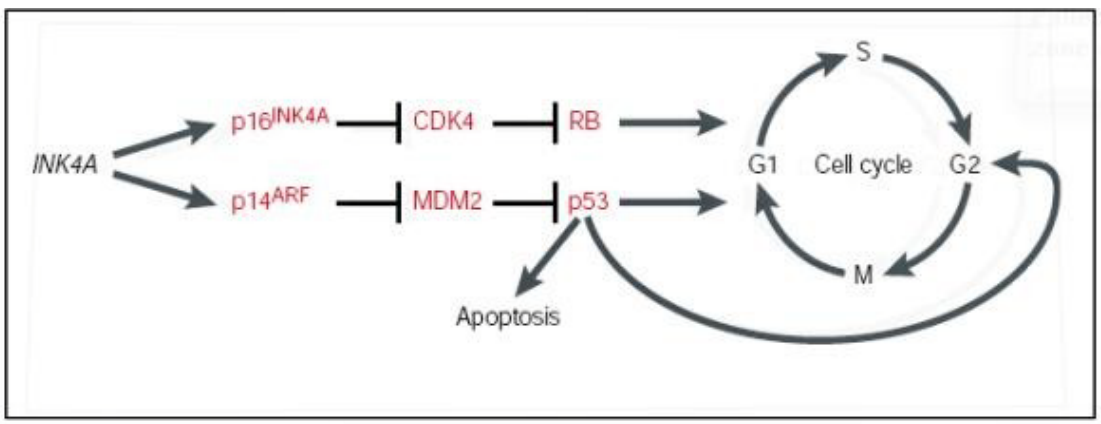

Figure 15: Cell cycle regulatory pathway controlled by INK4AR.

❖ The growth factor pathway can be activated in gliomas by several mechanisms that affect proliferation, differentiation, motility (infiltration) and apoptosis:

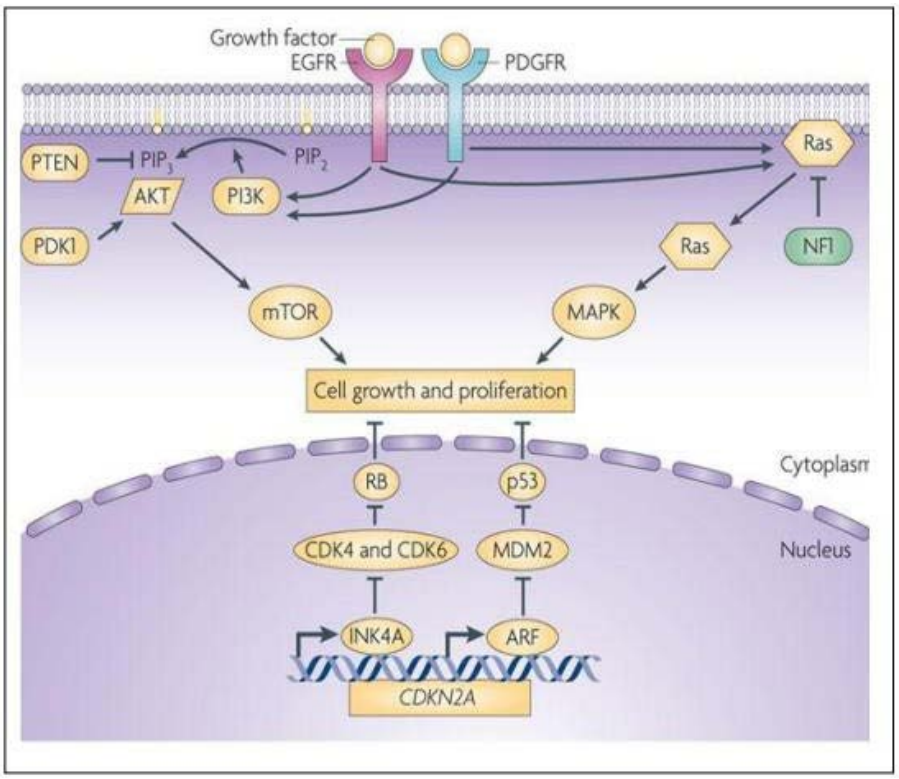

Figure 16: Signaling pathways involved in the process of glioma carcinogenesis RAS/ MAP kinase and PI3 kinase / AKT altered in gliomas.

- Overexpression of growth factor and its receptor, thus forming an autocrine loop (PDGF/PDGFR).

- Amplification or mutation of the growth factor, the most characteristic example of which is the EGFR, in particular its form EGFRvIII, which is a truncated form of the receptor that is self-activated in the absence of ligand, and which is essentially observed in primary glioblastomas [40], [42].

- Inactivation of PTEN which normally inhibits the PI3K/AKT signaling pathway

downstream of growth factor receptor tyrosine kinases [40], [41].

- The growth factor pathway mainly activates the oncogenic Ras/MAPK and PI3K/AKT signaling pathways [43]. Mutations in Ras are rare in gliomas and this signaling pathway is activated upstream due to receptor hyperactivation. On the other hand, activating mutations of PIK3CA, which activate the PI3K/AKT pathway, are very frequent[41], [43], it is activated by a multitude of receptor tyrosine kinases in glioblastoma, and this is why "single-target" targeted therapeutics have failed so far and suggests that "multi-target" therapeutics should be more effective [44].

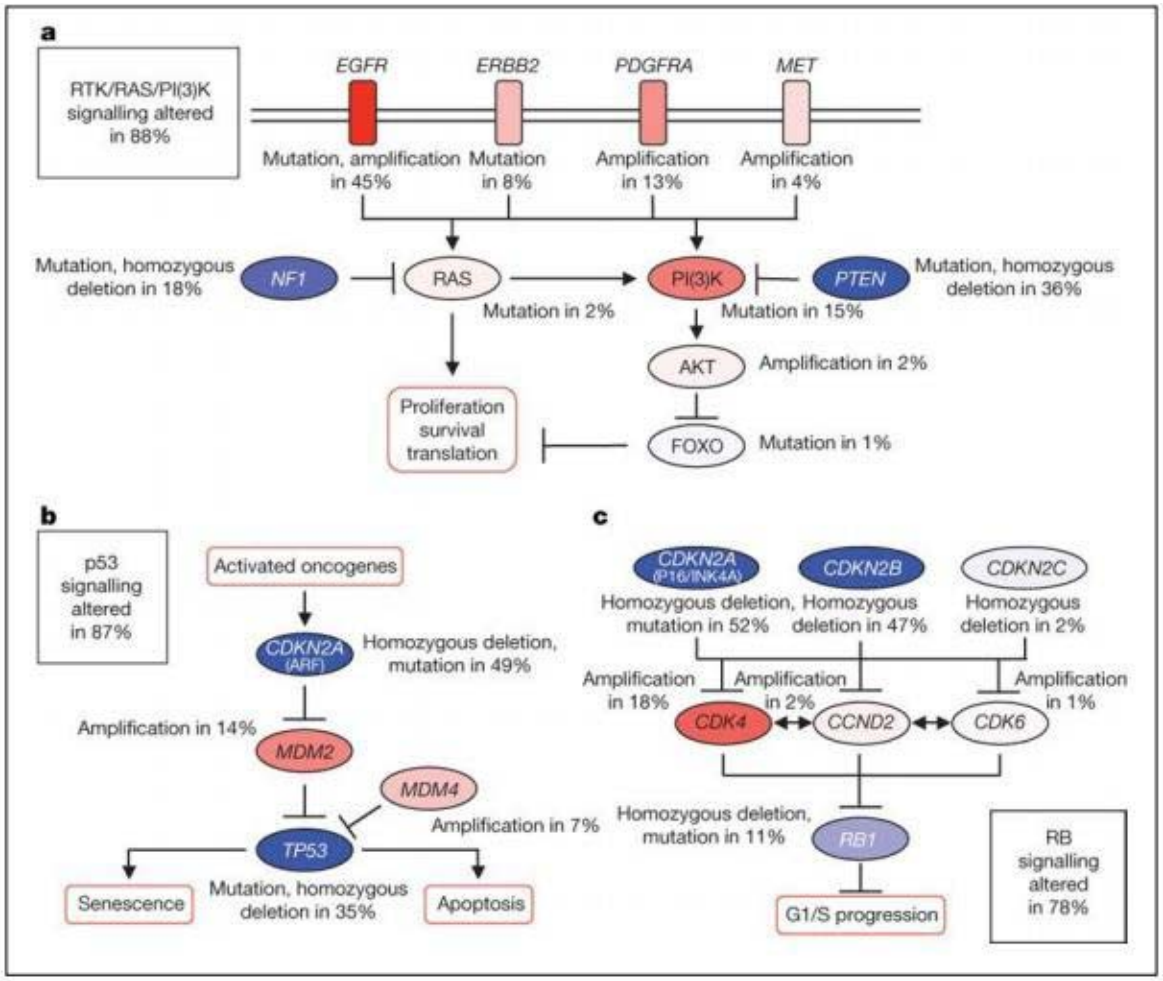

Figure 17: Most frequent genetic alterations in glioblastoma.

2. Role of micro-RNAs (miRNAs):

The miRNAS are small RNA molecules (16-29 nucleotides), highly conserved during evolution, which modulate gene expression at the post-transcriptional level. Recent data suggest that some miRNAs may be involved in the oncogenesis of gliomas (especially glioblastomas) by interfering with signaling pathways [45]. These include miR-26a-2 (overexpressed in 12% of glioblastomas, which represses PTEN expression [45], [46]), mir34-a, miR-21, miR7, miR-124 and miR-181.

III. Anatomo-pathology:

Gliomas are tumors that derive mainly from macroglia. According to their morphological characteristics, they are divided into several subcategories based on the cell type from which they arise. For each histopathological type, the WHO distinguishes four grades of increasing malignancy (I to IV).

1. WHO classification of 2007:

It is a classification based on a histogenic concept: the microscopic resemblance of tumor cells with a component of normal brain tissue and their degree of differentiation. This characterization is based on morphological criteria in standard staining (Hematoxylin-Eosin: HE), often completed by immunohistochemical studies (IHC), or even ultrastructural studies and the presence of anaplasia criteria: low differentiation, high cell density, nuclear atypia, mitotic activity, atypical mitoses, necrosis, vascular and endothelial proliferation, allowing to specify the grade [47].

Table V: 2007 WHO classification of diffuse glioma according to histology and grade.

Phenotype	Subtype	Grade
Astrocytic tumors	Pilocytic astrocytome	I
	Diffuse astrocytoma	II
	Anaplastic astrocytoma	III
	Glioblastoma	IV
Oligodendroglial tumors	Oligodendroglioma	II
	Anaplastic oligodendrioglioma	III
Oligoastrocytic tumors	Oligoastrocytoma	II
	Anaplastic oligoastrocytoma	III

However, this classification has certain limitations: lack of reproducibility due to the absence of specific markers and the subjectivity of the criteria with 30% inter-observer discordance between a grade II or III and between a tumor of astrocytic and oligodendroglial

origin [48], the lack of prognostic precision and of prediction of the therapeutic response.

2. WHO Classification 2016:

Following major advances in the field of molecular genetics, the 2016 WHO classification is no longer based solely on morphological criteria, but also on molecular parameters. Its aim is to define more homogeneous tumor groups in terms of prognosis and response to treatment.

This classification separates diffuse astrocytic or oligodendroglial tumors from other astrocytic types (pilocytic astrocytoma, pilomyxoid astrocytoma, ependymal giant cell astrocytoma, and pleomorphic xanthoastrocytomas). The definition of the histopronostic grade of tumors has also been modified, but not that of diffuse gliomas, which remains based on cellularity, number of mitoses, presence of abnormal vessels and necrotic foci [49].

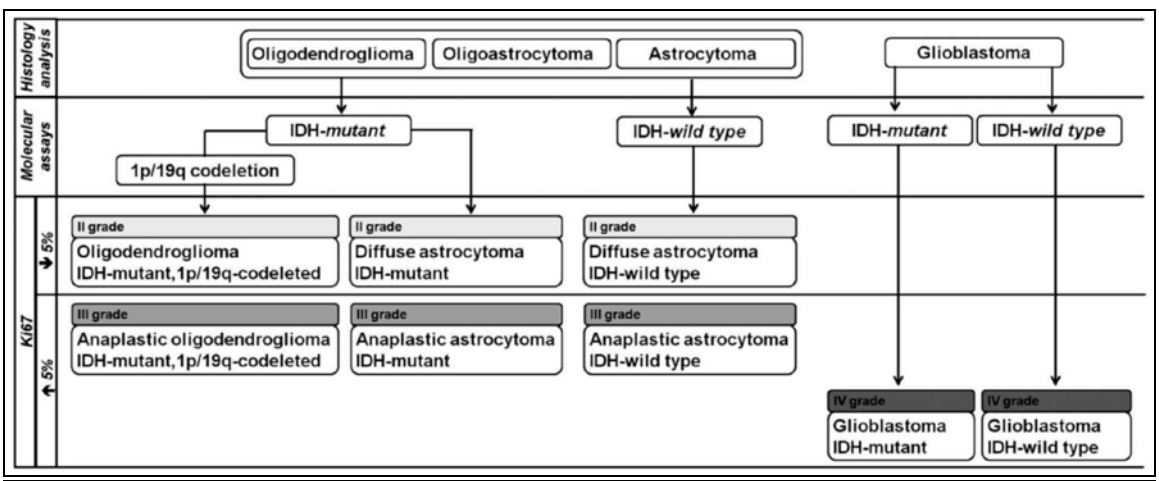

Figure 18: WHO classification 2016.

3. WHO Classification 2021:

The 2021 WHO classification of tumors of the central nervous system (CNS), 5th edition (WHO CNS 5) is built on the previous, revised 4th edition, published in 2016 (WHO2016CNS), which incorporated molecular information into the diagnosis of brain tumors for the first time, breaking with the century-old histogenetic classification. The basic concept underlying WHO2016CNS was rooted in the Haarlem Consensus Guidelines that aimed to establish instructions for incorporating molecular findings into the diagnosis of brain tumors and define diagnostic entities as narrowly as possible using molecular information. WHO CNS 5 also adopted a series of recommendations of "the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT)" that facilitates a consensus review of novel diagnostically relevant data and determines how such information can be fit into future CNS tumor classifications. However, the combination of histology and molecular information used to diagnose and grade CNS tumors remains at the center of tumor taxonomy.

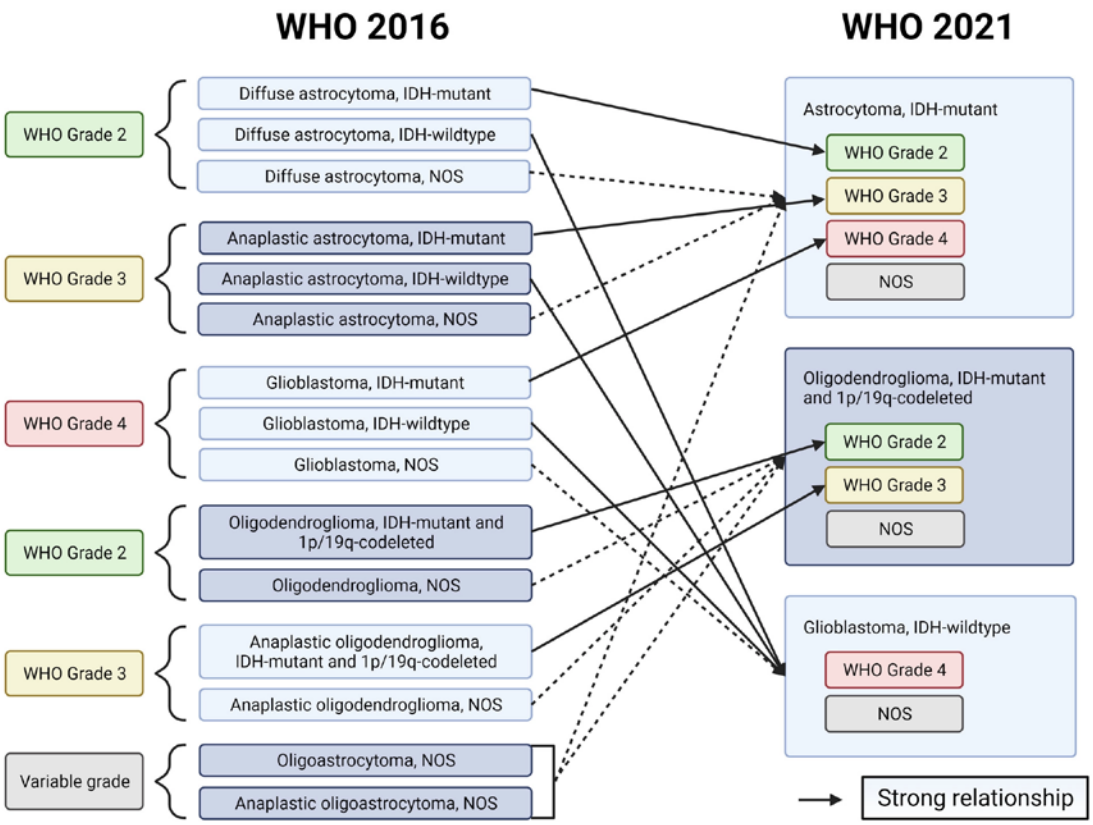

Figure 19 :WHO classification 2021

4. Anatomopathological aspect:

Glioblastoma multiforme (GBM, grade IV) is characterized by the presence of necrosis and microvascular proliferation (endotheliocapillary). The necrosis is typically map-like with peri-necrotic cell palisades or takes the form of large areas of ischemic necrosis . The mitoses are numerous.

The WHO distinguishes between small cell glioblastomas characterized by monomorphism, intense mitotic activity and low GFAP expression, glioblastomas with an oligodendroglial component that include typically "oligo-like" territories, multi-nucleated

giant cell glioblastomas (5% of GBMs), gemistocytic, granular cell glioblastomas (positive on PAS staining) or lipid cell glioblastomas depending on the majority contingent. Gliosarcomas are characterized by a biphasic, glial-mesenchymal architecture (2% of GBMs). The histology may mimic that of a lower grade if the sample was taken from the periphery of the tumor (CTI) or in a territory that does not take the contrast medium.

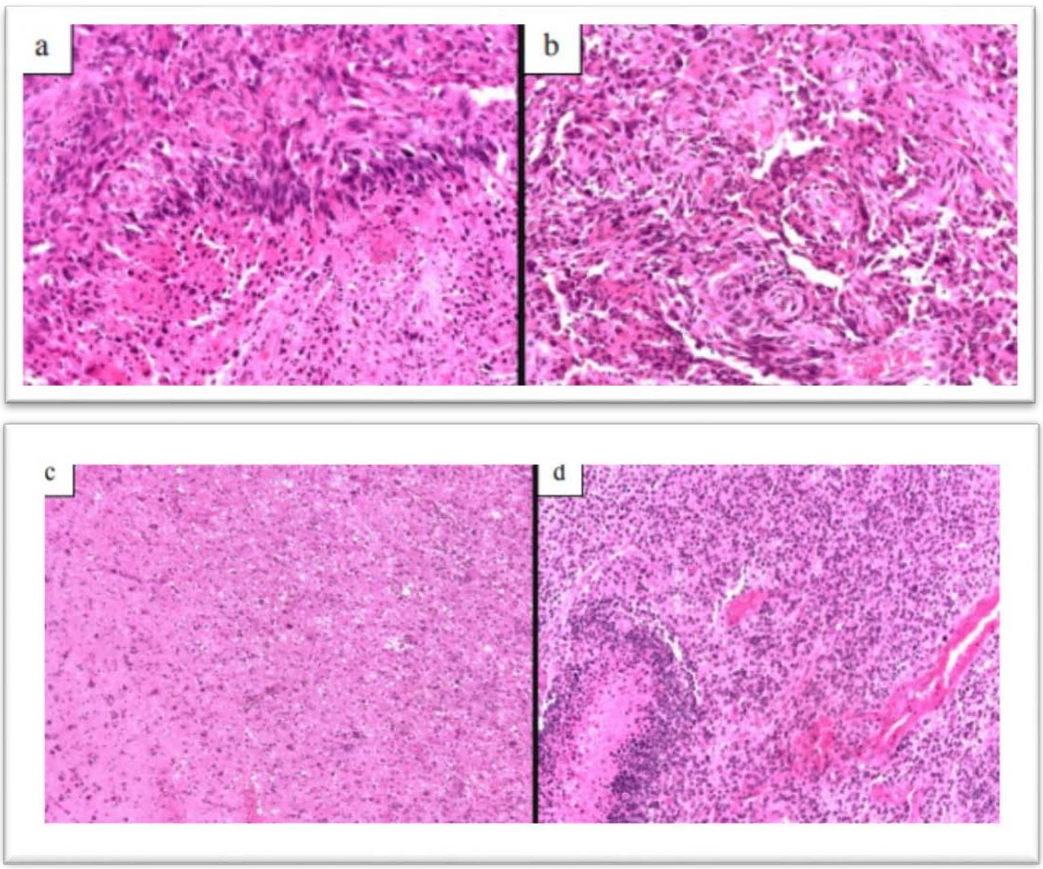

Figure 20: Glioblastoma multiforme : a) palisading necrosis (HPS, x200); b) glomeruloid neovascularization (HPS, x200); c) poorly limited invasion front (HPS, x100); d) palisading necrosis and "oligo-like" contingent in a glioblastoma with an oligodendroglial con.

Table VI: WHO 2007 grading of high-grade gliomas.

Type cellulaire	Différenciation	Densité cellulaire	Atypies nucléaires	Activité mitotique	Nécrose	Prolifération vasculaire
Astrocytome Grade III	moyennement	Augmentée	présentes	présente (≥ 2)	Non	Non
Astrocytome Grade IV	peu	Elevée	marquées	marquée	Oui	Oui
Oligodendrogliome Grade III	anaplasie focale ou diffuse	Augmentée	présentes	Nombreuses	Possible	possible, proéminente
Oligoastrocytomes Grade III	moyennement	Augmentée	présentes	Nombreuses	Non	Possible
Oligoastrocytomes Grade IV	peu	Elevée	marquées	Nombreuses	Oui	Oui

5. Anne's Hospital Classification:

The classification of the Hôpital Sainte-Anne is based on the study of systematic stereotactic biopsies along the biopsy tracts and on imaging. It distinguishes among adult gliomas, 3 histological categories: the oligodendrogliomas or oligo-astrocytomas of grade A or grade B, and glioblastomas [50].

The grading of oligodendrogliomas is based on contrast uptake and endothelial cell hyperplasia, defined by endothelial hyperplasia of all capillaries in at least one field at low magnification, and by the punctate presence of endothelial cell nuclei. A distinction is made between: grade A: absence of endothelial hyperplasia and contrast, grade B: presence of endothelial hyperplasia and/or contrast.

Glioblastoma multiforme is defined with the same basic criteria as WHO, defining GBM isolated tumor cells as undifferentiated, with little or no visible cytoplasm without GFAP expression, oblong nuclei, inconspicuous nuclear membrane, and generally lacking

chromatin clusters.

IV. Clinical examination:

1. The time of evolution:

This is the time between the onset of symptoms and the diagnosis. This delay is generally short. In several studies, it ranges from 1 to 3 months [1]. In our series, the time from onset ranged from 1 week to 2 years, with a mean time of 25 weeks.

2. The reason for consultation:

According to DNOR study, focal deficit was the most common symptom, reported in 64% of all affected patients, while seizures (31%), cognitive changes (43%) and headache (35%) were less frequent [1].

In our study the reason for consultation was mainly represented by motor deficit in 51% followed by intracranial hypertension 48% and disorders of higher functions in 18%.

3. Clinical signs:

The mode of expression of malignant glial tumors is that of any expansive process of the intracranial central nervous system that acts by two pathophysiological mechanisms: either direct suffering of cerebral structures giving rise to a lesional clinical expression, or an expansive syndrome secondary to the tumor volume itself, to the oedema that it induces, to venous vascular compressions or to the blockage of cerebrospinal fluid channels [19]. These two processes are responsible for the variability of the signs and symptoms presenting the tumor that can be classified under 3 headings:

- Symptoms of encephalic dysfunction.

- Symptoms related to the expansive nature of the lesion.
- Focal lesion syndroms [19].

a.General condition:

The Karnofsky Index is a patient performance status scale that was developed in 1948 by Dr. David A. Karnofsky, an American specialist in cancer chemotherapy, to provide an objective assessment of the functioning and survivability of patients hospitalized and followed for tumor pathology. The KPSS scale (appendix 2) ranges from 100: which implies full functional capacity to perform daily activities in a normal manner without symptoms or signs of disease, to zero: which implies death [51]. It is reasonably reliable in predicting very limited survival time when the score is low (<50) and especially in patients with advanced malignancy [51].

In our series the majority of patients had a satisfactory general condition (36%), this index varied between 20 and 100% with an average of 81.

Table VII: Karnofsky index according to studies.

Authors	Variation of the karnofsky index	Average index
Roy C Martin [52]	50---100	83
Reithmeier [53]	20---100	80
Chang [14]	----	79
Our cohort	20---100	81

The WHO score is a tool that allows for a global assessment of the patient's general condition and plays an essential role in the therapeutic decision.

The Mini-Mental State Examination or Folstein Mental State Examination was developed to screen people with major neurocognitive impairment, it is also used to monitor cognitive status and to measure the decline in cognitive function of patients with the disorder, which is a major prognostic factor. It is in the form of a short answer questionnaire. The persons evaluated must also perform some simple tasks. The items assessed are grouped into six subsections: orientation, registration, attention and calculation, memory retention, language and constructional praxis[54].

In our series, this examination was not used for patient evaluation.

b.Symptoms related to the expansive nature of the lesion

The ICHT syndrome is the consequence of the development of the tumor within a functional brain tissue contained in an inextensible cranial cavity.

The importance of the symptoms is therefore correlated to the tumor volume, to the importance of the associated oedema and to the tumor topography.

The ICHT associates bilateral throbbing headaches with paroxysmal reinforcement appearing when changing position, when coughing and sneezing, nausea and vomiting in jet as well as disorders of consciousness and vigilance, one can sometimes find a papillary oedema at the bottom of the eye and a diplopia by paralysis of the VI (abducens) without localizing value.

The ICHT syndrome was found in 59.6% of patients in A. ALENTORN ET AL [55] ; 26.7% in A. Vazquez [56]. In our series it was 48%.

i. **Headaches:**

Headache is a major reason for consultation in high-grade gliomas, whether isolated or associated with vomiting or disorder of consciousness, thus constituting an ICHT

syndrome.

In our series, isolated headache was present in 36% of cases compared with 8% in A. Vazquez [57] and 31.8% in Pfund et al [56].

ii. **Vomiting:**

Vomiting is characteristic of ICHT when it is easy to vomit, independent of meals and associated with headaches that can be calmed.

In our series, 30% of our patients presented vomiting.

iii. **Disturbances of consciousness**

They may develop rapidly or progressively depending on the size and location of the tumor. Its degree varies from drowsiness to deep coma with decerebrate rigidity and neurovegetative disorders related to involvement.

In our study, 12% of the patients presented consciousness disorders.

c.Focal lesion syndrome

i. **Motor and sensory deficits:**

These symptoms are the consequence of infiltration of the brain parenchyma by the high grade glial tumor and depend on the tumor topography. They may be hemiplegic motor deficits, hemiplegic sensory deficits of variable intensity ranging from hypoesthesia to anesthesia. These deficits progressively worsen with tumor progression.

In our series, motor deficits were present in 51% of cases, compared with 21.2% in Reithmeier [58] and 21% according to Korevaar [59]. Sensory deficit was present in 3% of our patients.

ii. **Coma seizures:**

An epileptic seizure is an abnormal electrical discharge of neurons. Tumor growth on the surface of the brain can irritate the surrounding cerebral cortex and subsequently disrupt the activity of the neurons by triggering seizures. A partial or generalized epileptic seizure is indicative in about 40% of brain tumors.

Table VIII: The frequency of comitial seizures according to studies.

Authors	Percentage
Reithmeier [58]	32%
Chang[52]	31.9%
Mineo [17]	22%
Our cohort	18%

iii. **Cranial nerve damage**

The involvement of the cranial nerves is not negligible, among the most affected nerves, we note the optic nerve, the facial nerve, and the cochleo-vestibular nerve, the pathetic nerve.

In our series, we noted the involvement of the pathetic nerve in 3 % with divergent strabismus, the facial nerve in 9% of our patients with facial palsy and the cochleo-vestibular nerve in 3% who presented with hypoacusis.

d.Symptoms of encephalic dysfunction

iv. **Higher Functions Disorder:**

It constitutes a major prognostic factor and includes: attention, executive functions, intellectual functions, visio-spatial functions, and language disorders [17].

In our series, 9% of our patients had aphasia, 6% had amnesia and 3% had a

behavioral disorder.

Table IX: The frequency of higher functions disorder according to studies.

Authors	Perrcentage
El fane [17]	20%
Lonjon [14]	10%
Delion [10]	24,4%
Chang [52]	36,2%
Our cohort	18%

V. Paraclinical data:

Imaging represents an essential step in the diagnostic approach of high-grade gliomas, and especially in the evaluation of the therapeutic possibilities and prognosis of these tumors. In the postoperative phase, it is used to evaluate the surgical procedure itself and to plan the associated treatments. In the follow-up, imaging is used to assess the responses and complications of these treatments.

CT is currently the most accessible examination and should be performed as a first line of defence. MRI is often necessary for a complete characterization of the lesion.

MRI is currently recognized as the examination of choice for diagnosis and also for follow-up. Diffusion and perfusion imaging techniques available on modern imagers are easily performed in clinical practice. They provide different and complementary information to that provided by morphological imaging, which is particularly interesting for diagnosis but also for follow-up.

The purpose of imaging is to:

- Make the diagnosis of a brain tumor and eliminate non-tumor lesions.
- Specify the location of this tumor in relation to the brain parenchyma (intra- or extra parenchymal, or intra ventricular).
- Describe the morphological and enhancement characteristics (structure, limits, volume, extension) of this lesion and its impact on the cerebral structures (mass effect, involvement, hydrocephalus).
- Evoke the nature and attempt to evaluate the degree of malignancy of the lesion.
- To guide the indication and planning of the surgical procedure or stereotactic biopsy.
- Ensure post-treatment follow-up [19].

1. The CT scan:

CT is a rapid, easy and sensitive exploration technique. It is the method of choice for the initial diagnosis of high-grade glial tumors and allows a precise topographic diagnosis. It also allows to specify the morphological characteristics of glial tumors: size, shape, boundaries, presence or absence of calcifications, density, homogeneity or not and the type of enhancement after injection of contrast. It also evaluates the extension, the contributions, the presence of other localizations and the impact on the ventricular system.

CT is still widely used because of these advantages:

- Its cost.
- Its greater availability.

- Its ease, rapid technique and feasible in case of contraindication to MRI or difficulties in its realization.
- Its clear superiority in the detection and characterization of calcifications, particularly those of small size not visible on MRI [19].

CT also has disadvantages compared to MRI:

- It is an irradiating technique.
- It is less efficient for the analysis of iso-dense tumors, for the evaluation of tumor extension and for proposing a more precise histological diagnosis [19].

Although CT is not the reference examination, when performed for a grade III glioma or glioblastoma, it shows a hypodense mass of heterogeneous appearance with irregular contours. The tumor is surrounded by a hypodensity corresponding to the peri-lesional edema. Calcifications may be present, indicating the age and malignant transformation of a benign glioma. A mass effect, responsible for cerebral involvement and hydrocephalus, is often visualized.

In case of injection of iodinated contrast, the contrast is heterogeneous. In case of central necrosis with annular contrast, the imaging is more often suggestive of a glioblastoma.

In our series, CT was requested in 21 patients and it allowed to evoke the diagnosis in all cases. The tumor size in the long axis was between 2.9 and 7 cm, with an average of 5 cm, with the presence of engagement in 20.68% of patients and perilesional oedema in 85%.

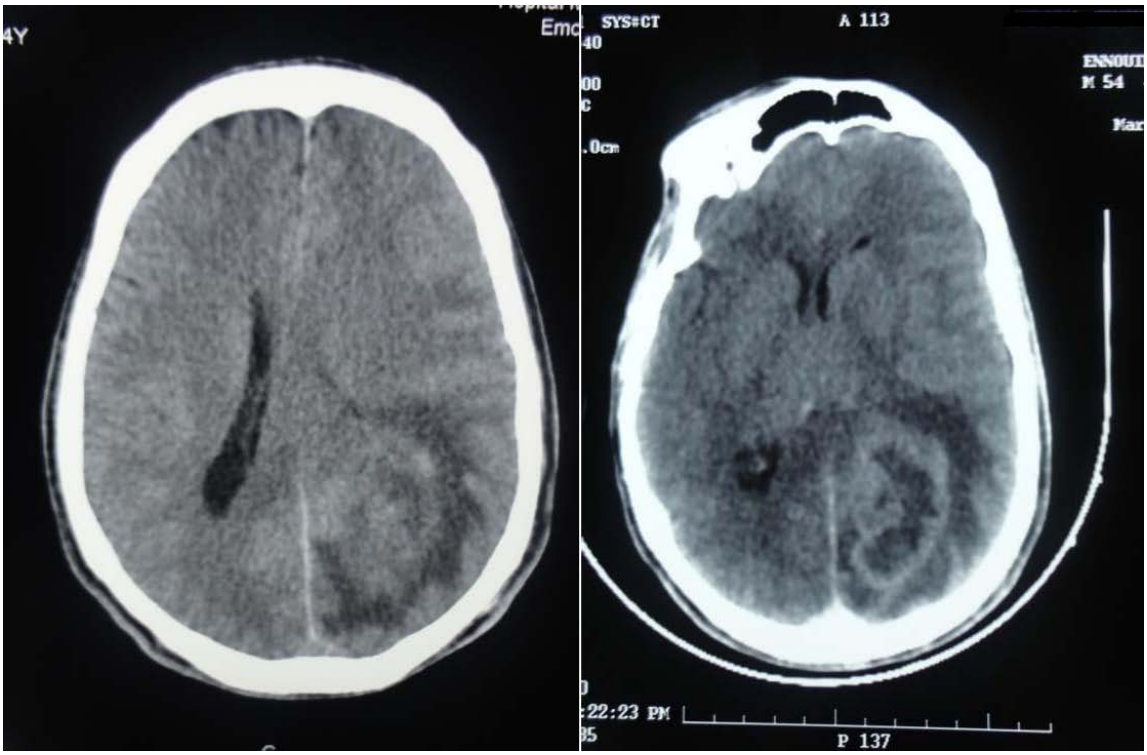

Figure 21: Axial section CT image of a heterogeneous poorly bounded occipital high-grade glial tumor before and after CP injection [17].

2. MRI:

a.MRI in conventional sequence:

It is a technique that does not use radiation and offers the hope of earlier diagnosis and, above all, the establishment of differential diagnoses. MRI allows to obtain slices in all planes of space, and its superior sensitivity in the evaluation of high-grade gliomas has been demonstrated. In addition, MRI allows exploration of the entire neuraxis, which is necessary to evaluate dissemination to the meninges [19].

It is performed without and with injection of the contrast medium: gadolinium chelate, and according to T1, T2 and FLAIR (fluid attenuated inversion recovery) weighted sequences which allows a better differentiation of the tumor, of the edema and a better

characterization of the cystic or necrotic portions of the tumor [53].

The high-grade glial tumor often has a heterogeneous appearance with irregular boundaries. Classically it has a T1 hypo signal and a T2 hyper signal. In the center of the tumor, a necrotic area can be seen. Around the lesion, there is a cerebral edema that is clearly visible on T2 and FLAIR sequences and which is now known to contain numerous tumor cells.

In our series, MRI was performed in 24 of our patients.

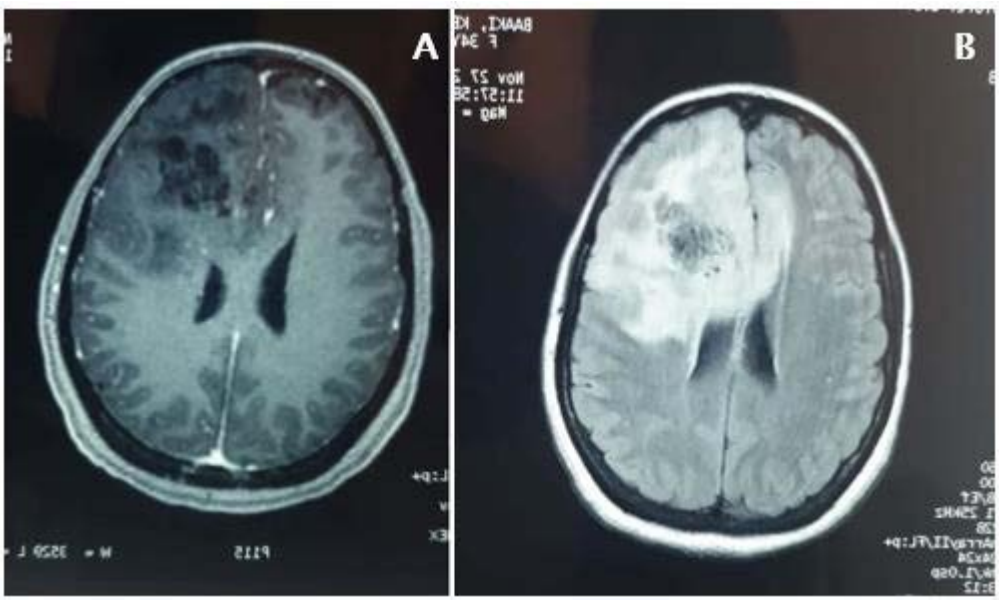

Figure 22: MRI appearance of a high-grade glial tumor in injected T1-weighted sequence (A), and in FLAIR sequence (B). [17]

b.MRI in diffusion sequence :

Diffusion MRI provides information on the malignancy of tumors; it allows the assessment of the mobility of water movements in a medium which is correlated to the apparent diffusion coefficient (ADC). When it is a dense cellular medium, water molecules in the interstitial (intercellular) tissue diffuse poorly: it is therefore a restricted diffusion

indicating the high grade of gliomas. Indeed, high grade glial tumors are characterized by a high cell density responsible for a restriction of diffusion with a decrease in ADC. Thus, diffusion imaging allows to approach the macroscopic composition of tumors and to participate in the discrimination of tissue, cystic, necrotic and edematous components and to guide stereotactic biopsies [53], [60].

Tractography or diffusion tensor imaging allows to assess the degree of organization and the direction of the myelinated fiber bundles by mapping the main white matter bundles. It then allows to clarify the anatomical limits of the tumor in relation to the bundles, an important element in the surgical management in order to reduce postoperative morbidity. It also allows to differentiate primary from secondary brain tumors, by distinguishing edema and peri-lesional infiltration [53], [60].

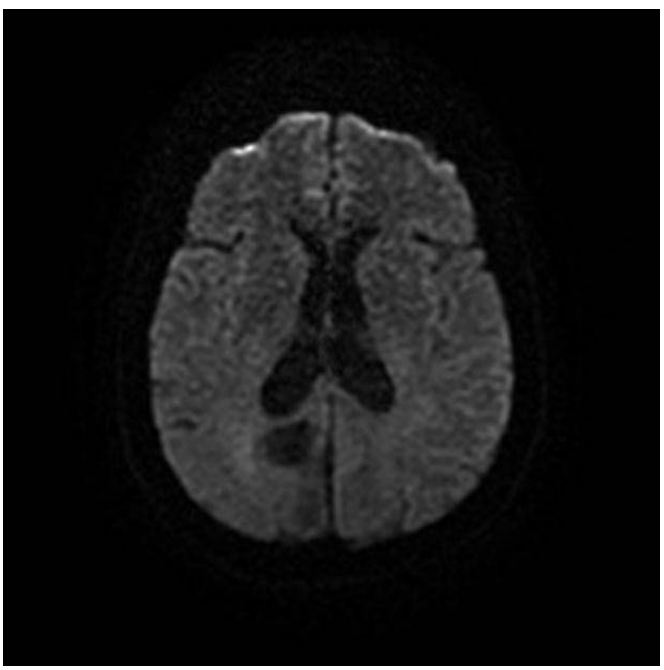

Figure 23: Diffusion sequence MRI, showing a hypointense right parietal tumor process.

c.MRI in perfusion sequence :

The perfusion sequence allows an estimation of the tissue perfusion by studying the variation of the signal intensity of the brain parenchyma during the first passage of a bolus of gadolinium in T2 gradient echo or spin echo sequence. It is always expressed as a relative value compared to the contralateral healthy tissue (white matter or gray matter). The study of tissue perfusion provides information on the density of circulating vessels within the tumor tissue, allowing the presence of tumor angiogenesis to be demonstrated, as reflected by tumor areas of increased perfusion. It also allows an approach of the tumor grade and the choice of biopsy sites. Perfusion values close to the gray matter generally correspond to WHO grade III [53]. In follow-up, the appearance of areas of increased perfusion reflects anaplastic transformation because it is rapidly followed by the appearance of contrast.

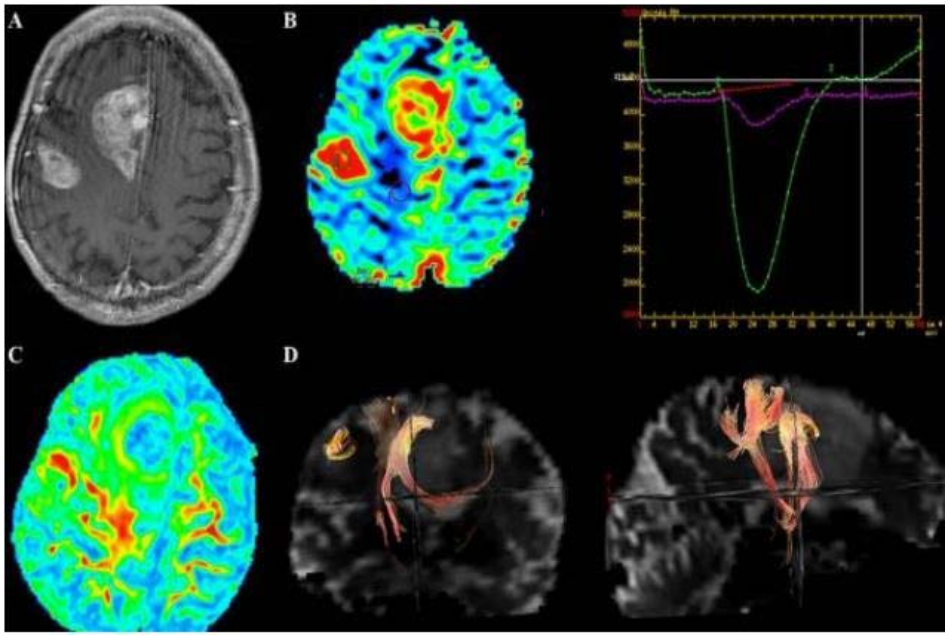

Figure 24: Right hemispheric glioblastoma, bifocally enhancing in T1 post-gadolinium (A); showing significant hyperperfusion (B). Anisotropy mapping analysis confirms the presence of a single lesion by showing a range of isovals (green) between the two areas of

enhancement (C). Tractography shows a homolateral corticospinal bundle reflow and invasion of the corpus callosum (D).

d.MRI in activation sequence

Activation imaging uses an echoplanar sequence sensitive to blood oxygen content. This technique is based on the existence of a disproportion between regional increase in cerebral blood flow and oxygen extraction from the blood in response to cortical activation. Mapping of regional cortical activity for patients with gliomas located in certain key functional areas could be part of the functional areas could be part of the pre-therapeutic evaluation. This technique would correlate well with preoperative evoked potentials. Combined with data from preoperative evoked potentials, activation imaging may help the surgeon to spare functional areas, especially in the resection of gliomas close to motor areas [19].

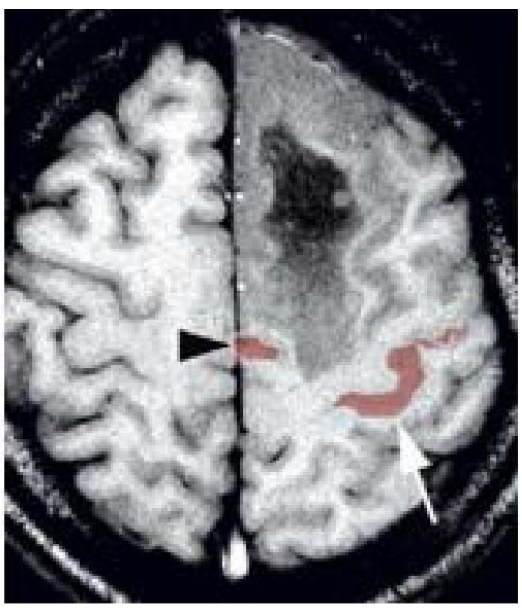

Figure 25: Activation imaging in a patient with a left frontal glioblastoma. Superposition of a mapping obtained during a finger tapping session (alternating periods of tapping movements of the right index finger and rest) and an axial section in spT1. The motor area of the hand (arrow) and part of the supplementary motor area (arrowhead) are localized and

their location with respect to the tumor infiltration allows to judge the possibilities of excision[19].

e.MRI in magnetic resonance spectroscopy sequence:

Magnetic resonance spectroscopy (MRS) allows a metabolic study of the brain parenchyma, which makes it possible to distinguish between tumoral and non-tumoral lesions, and to approach the histological type and grade of the glioma [61]. therapeutic planning when radiotherapy is envisaged, by specifying the limits of tumor extension and assessing the post-radiotherapy response.

Metabolites measured by proton spectroscopy on brain MRI are important elements of its cellular metabolism. We cite:

- N-acetylaspartate (NAA) is a marker of viability and axonal density in normal neurons. Decreased resonance reflects neuroaxonal damage or replacement by pathological tissue, in this case tumor.
- Choline (Cho) is of major interest in the exploration of brain tumors. It reflects membrane cell turnover and is therefore increased in all processes leading to hypercellularity.
- Creatine (Cr) is a marker of the energy pool of brain cells characterizing the overall physiological state of the brain tissue. The creatine peak is often used as a reference peak because it is stable over time.
- Myo-Inositol (mI) is a sugar, a marker of glial proliferation. It is particularly found in low grade glial tumors and in gliosis.
- Free lipids are present in cases of necrosis.
- Lactates (Lac), markers of anaerobiosis, witnesses of mitochondrial functional

alteration. They are not detectable in the normal brain, except in the CSF. They are increased in most pathological processes [9], [61], [62].

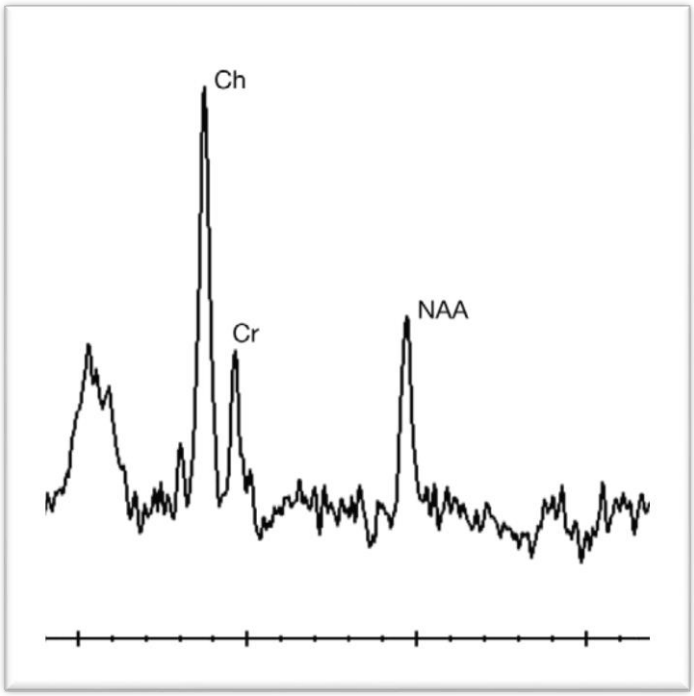

Figure 26: Grade III astrocytoma: nuclear magnetic resonance (NMR) spectrogram characteristic of an anaplastic glial tumor: collapse of the N-acetyl-aspartate peak, elevation of the choline peaks
[63].

3. Arteriography

It has lost much of its interest because of the information provided by CT and MRI. Nevertheless, in some cases, arteriography may be performed to clarify the relationship of the tumor with the arterial and venous vessels, and the degree of vascularization of the tumor, possibly accompanied by an interventional radiology procedure such as embolization before lumpectomy. It can show a repression of the normal vessels by the tumor, the presence of tumor neo-vessels and an arterio-venous shunt [4].

In our series, no patient benefited from this examination.

4. Positron emission tomography (PET)

This is a metabolic imaging technique that allows to follow the metabolism of a molecule of interest labeled by a radioactive isotope. Two tracers are mainly used: a fluorine-18-labeled glucose analog, 18-FDG 2-[18F]fluoro-2-deoxy-D-glucose or 18-FDG, and an amino acid, 11-carbon-labeled methionine, L-methyl-11C-methionine or 11C-MET, which is the reference tracer in neuro-oncology. The uptake increases with the tumor grade [64] and is inversely correlated with the prognosis [64], and it thus allows differentiation between low-grade and high-grade gliomas [64], [65]; it also allows better orientation of the stereotactic biopsy, clarification of the size of the post-surgical tumor residue, identification of progression from one grade to another during the course of the disease, and differentiation between a recurrence and a post-radiation lesional process [66], [67]. PET can, to some extent, predict response to radiotherapy and probably to chemotherapy [68].

This examination was not performed in our patients because it was not available in our hospital.

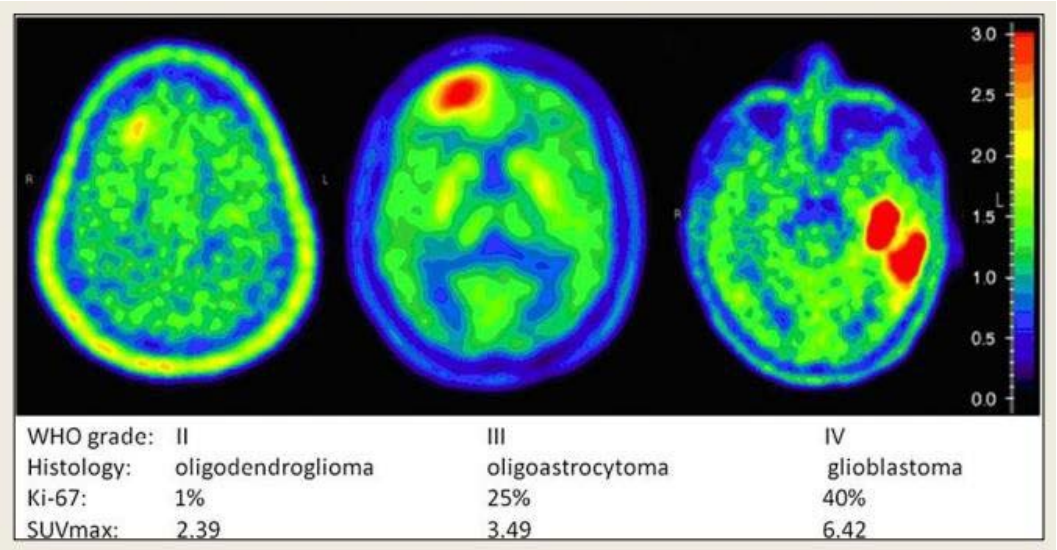

Figure 27: PET findings of different grades of glioma.

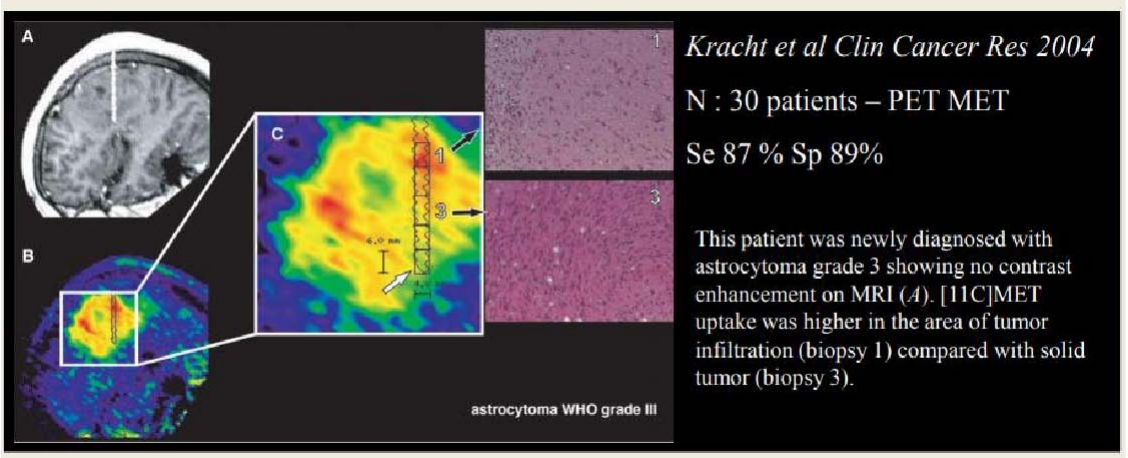

Figure 28: Interest of PET in the diagnosis of high grade glioma targeting biopsy.

VI. Tumor location:

Several classifications based on microscopic observation and histogenetic hypotheses have the defect of not taking into account the anatomical and surgical data which are however essential for the prognosis, especially since the diffusion of imaging methods allowing a very precise localization of most of the tumoral processes such as CT

and MRI. The location of the tumor is of considerable importance because lesions of the same histological nature can have a completely different evolution depending on their location.

High-grade gliomas develop mainly in the suprasensory region, most often in the white matter of the hemispheres, especially in the frontal, temporal and parietal lobes [69].

According to the results of the DNOR study, the preferential location of high-grade gliomas was frontal (33%) followed by temporal (30%), parietal (18%), occipital (10%) and cerebellar (0.6%) [9]. The same result is also noted in the study of Yi Yang with (32.8%) at the frontal frontal level and (26.9%) at the temporal level, (18.7%) located at the parietal level and only (4.4%) at the occipital level [69].

In our series in which we find that the tumor localization was predominantly parietal (36%), followed by temporal (15%), front-parietal (15%), frontal (12%), temporo-parietal (12%), cerebral trunk (3%), thalamus (3%), then axial (3%).

VII. Metastasis:

High-grade gliomas are infiltrating tumors preferentially affecting the cerebral hemispheres. These lesions rarely metastasize to other organs such as the liver or lungs, however, cases of metastasis to the neuraxis: intracranial cavity or distant intra-axial (intrarachid dissemination into the CSF) or peripheral nerves, have been described; according to Saito's series, intracranial metastases were more frequent than spinal dissemination with a reported incidence of 25% and 8.8%, respectively, but this remains exceptional [53].

According to the results of a study by M. Fourtasi, the metastases of 4 cases of

malignant glioma involved bone, bone marrow, liver, lung and kidney and appeared 3 to 13 months after the surgical procedure. The overall survival after the occurrence of systemic metastases was between 2 and 5 months in cases of glioblastoma, and 8 months in the case of anaplastic oligodendroglioma: the latter, carrying a Co-deletion of chromosomes 1p and 19q, had responded well to chemotherapy [70].

In our series, no case of metastasis was found.

VIII. Prognostic factors:

The prognosis for patients with high-grade glioma is often very poor, despite recent advances in the diagnosis and treatment of the disease, which makes the study of clinical features and prognostic factors, a crucial step in order to provide a more targeted approach and basis for the treatment and management of patients, and this by allowing the estimation, depending on their presence or absence, of life expectancy, and to determine the therapeutic project as well as the personal plans of the patient and Identify the predictive factors of the response to treatment.

1. Clinical prognostic factors

a. Age:

Age is the most frequently cited prognostic factor in most studies of high-grade gliomas. The age of the patient with high-grade glioma plays a crucial role in the prognosis and survival of the disease, it conditions the surgical management as well as the associated therapies (radio-chemotherapy), advanced age is associated with a decrease in the use of these three modalities and an increase in supportive care, due to the decrease in tolerance of the elderly to the operation because of their poor physical condition

Several studies have confirmed that the incidence of cancer has increased with age, especially after 65 years of age, due to the poorly adjusted immune system of the elderly and the function of the anti-tumor system as well as the low repair capacity of cells [69].

According to the SEER data, age greater than or equal to 65 is a poor prognostic factor for HGG with a decreased survival rate and a high death rate and a decreased chance of surgical resection of the tumor as well (Table XII).

In our series 5 cases (15%) of our patients were older than 65 years.

Table X : Results of survival rate, number of deaths and surgical resection of high-grade gliomas stratified by age [71]

Age groups	20-39 years	40-59 years	>65 years
Surgical resection	22,91	22,50	19,7
Survival	61,36	34,93	22,32
Death	37,01	62,09	73,12

b.Clinical and cognitive status

Cognitive status before surgery or oncologic treatment has been reported as a predictor of survival time independent of age and Karnofsky PS (KPS). Meyers reported that decline in cognitive performance over time preceded radiological evidence of HGG disease progression in 85% of cases and was accompanied by a five-fold increase in the risk of PD according to Armstrong and colleagues. Cognitive deterioration over time could thus

provide information on tumor activity during the course of the disease [59].

A Karnofsky score above 70 is correlated with long survival.

In our series, the median Karnofsky score was 81.

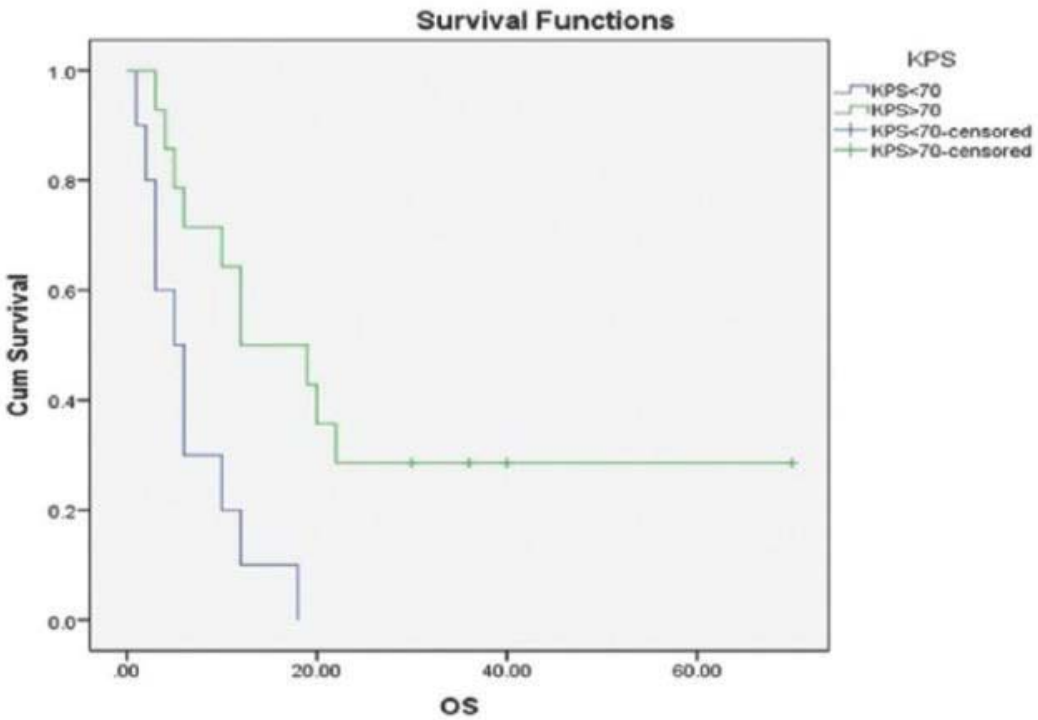

Figure 29: Kaplan Meier estimate of overall survival KPS <70 versus KPS >70. [72]

Revealing symptoms of the HGG tumor influence survival, which is significantly higher in patients with initial critical symptomatology compared with those who presented with HTIC or neurological deficit at diagnosis [73].

2. Histological prognostic factors:

The histological criteria retained as significantly correlated with outcome were the number of mitoses, necrosis, nuclear atypia, endothelial hyperplasia, and capillary network density, the median survival with or without endothelial hyperplasia was: 3.5 versus 11 years

and increased from 10 to 51 weeks if there were more than 70 microvessels per field (×200) [73], [74]. Histological grade has the greatest impact on survival cited in most studies for high-grade gliomas with a median survival of no more than two years.

3. Biological prognostic factors

The identification of certain molecular alterations allows to better define the tumor process and its prognosis. The major biomarkers that have been described for high grade gliomas are: 1p/19q deletion, O6-methylguanine-DNA methyl transferase (MGMT) promoter mutation, IDH1/IDH2 mutation.

4. Radiological prognostic factors

Prognostic factors Tumor location is considered a prognostic factor since frontal location correlates with a good prognosis, unlike temporal and parietal location [75], contrast enhancement is in favor of a high grade of malignancy and therefore considered a negative prognostic factor [76].

In our series, frontal localization was observed in only 4 patients (12%).

The tumor necrosis takes the aspect of a centro-tumoral lesion, irregular, hypo dense in CT, hypointense in T1 and hyperintense in T2 in MRI without enhancement after injection of CP, it is an important prognostic factor whatever its volume. Also considered as a factor affecting prognosis is a tumor larger than 6 cm, or exceeding the midline of the brain and the presence of major peri-tumor edema [77].

5. The extent of surgical resection

Surgical resection significantly influences both short-term and long-term outcomes. The extent of surgical resection assessed by early postoperative MRI is a major factor of

better prognosis [77].

In our series, the resection was total in 12 patients (6%), partial in 15 patients (5%), 6 (18%) patients had a biopsy.

a.Methylation of the promoter of the MGMT (O6MethylGuanineMethylTransferase)

The MGMT enzyme removes the alkyl groups at the O6 position of guanine and induces DNA repair, thus eliminating mutagenic and cytotoxic O6 alkylguanine lesions. High expression of MGMT then induces resistance to chemotherapy. Molecular analysis of MGMT promoter methylation status therefore represents a prognostic factor in glioblastoma and also has predictive value on therapeutic response [78]; promoter methylation inactivates this gene, it is then unable to repair the damage caused by alkylating chemotherapy such as temozolomide and thus makes this oncological treatment more effective.

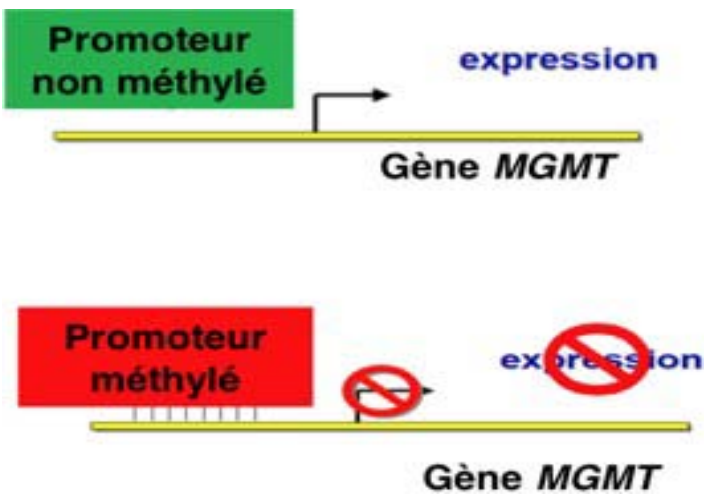

Figure 30: Mutation of the MGMT promoter. [79]

b.IDH1 and IDH2 (Isocitrate dehydrogenase) mutations:

IDH1 and IDH2 mutations have an important diagnostic value and are synonymous with diffuse gliomas with a prognostic value in terms of prolonged survival [79], [80].

Detection is performed by immunohistochemistry associated with the search for rare mutants in molecular biology if immunohistochemistry is negative.

It is almost always present in patients with a 1p-19q co-deletion, but is inconstant in non-co-deleted patients (32-35% of cases) [81]. When the IDH mutation is isolated, it seems to define within anaplastic gliomas an intermediate prognostic group, between the 1p-19q-IDH co-deleted patients having the best prognosis and the patients having neither co-deletion nor IDH mutation who constitute the worst group. This mutation is present in the majority of grade III gliomas (50-60% grade III, 5-10% of secondary glioblastomas).

c.Co-deletion 1p19q:

Co-deletion 1p19q is a factor in prolonged survival and chemosensitivity to PCV (procarbazine, lomustine and vincristine) and Temozolomide [82]. The discovery of a 1p-19q co-deletion in a patient managed for anaplastic glioma indicates a much better prognosis compared to tumors without this co-deletion with a 3-5 fold longer median survival [83].

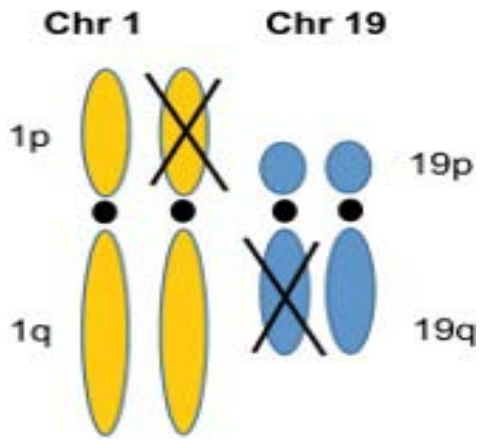

Figure 31: Co délétion 1p19q. [83]

d.Mutation of the promoter of the TERT (Telomerase reverse transcriptase) gene

This mutation affects 80% of glioblastomas and 95% of 1p19q co-deleted gliomas. The TERT promoter mutation induces telomere size maintenance and thus the absence of cellular senescence [84].

e.Histone H3K27M mutation

The H3K27M mutation affects about 5-10% of IDH Wild Type gliomas (unmutated) and 90% of unmethylated MGMTs, and is thus predictive of a poor prognosis [84].

f.Amplification of EGFR

EGFR amplification of variable intensity correlates with protein overexpression and poor prognosis [83], [84]. Most abnormalities result in the formation of a mutant transcript called EGFRvIII that is observed in high-grade gliomas. Tumors overexpressing EGFR show chemoresistance to the treatment used, PCV and/or Temozolomide [85], [86].

g.The TP53 mutation

The TP53 mutation corresponds to the loss of the tumor suppressor gene p53 which allows the arrest of the propagation of cells with an unstable genome by causing cell cycle arrest in G1 phase or by activating cell death via apoptosis [87]. The loss of this tumor suppressor gene is associated with genomic instability that favors the appearance of successive genetic mutations responsible for an increase leading to tumor progression [88].

IX. Therapeutic management

High-grade gliomas are very aggressive tumors, their management after histological confirmation is based on a therapeutic strategy combining surgical removal as complete as possible, followed by radiotherapy and chemotherapy, medical treatment to combat cerebral edema and ensure a good state of hydration.

1. Symptomatic treatment:

The goal is to create optimal conditions for craniotomy and tumor resection with minimal risk by acting on two factors: reduction of intracranial volume to lower intracranial pressure and cerebral protection to ensure tolerance to ischemia. Various treatments may be necessary.

a.Corticosteroid therapy

Corticosteroids (dexamethasone and methyl prednisolone) are systematically used preoperatively because of their efficacy on tumor edema [89] and lead to a spectacular neurological improvement. Their mechanism of action associates an inhibition of certain enzymes, in particular phospholipase A2 responsible for the release of arachidonic acid, a direct action on the tumor capillaries, and stabilization of the cell membranes. Thus it is used to reduce the permeability of the BBB [90]. Their reaction is rapid, within a few hours, particularly in tumors accompanied by significant edema.

Dexamethasone is used at a dose of 1 mg/kg or more if necessary, depending on the clinical condition, with the addition of a gastric protective H2-receptor blocker [91].

All our patients received methylprednisolone-based corticosteroid therapy at a dose of 120 mg pre- and postoperatively.

b.Osmotic diuretics

Mannitol improves cerebral compliance by reducing the water content of the cerebral parenchyma by creating a transcapillary osmotic gradient. Moreover, the decrease in viscosity that it causes improves the perfusion of ischemic cerebral areas. The effect of mannitol used in infusion at a dose of 0.25 to 1g/kg over 15 to 20 minutes, starts 5 minutes after the end of the administration with a maximum effect between the 30th and

40th minute and lasts for 2 to 3 hours [92]. Hypertonic saline is as effective as mannitol and seems particularly indicated in situations of hypovolemic shock with intracranial hypertension.

c.Anticonvulsants

Instituted in patients with epileptic seizures and also during surgery as a prophylactic measure [93]. The treatment lasts 2 to 3 months after surgery, levotiracetam is strongly recommended [91].

In our series, an anti-comitial treatment based on sodium valproate was indicated in patients with comitiality.

d.Analgesics

Analgesic treatment was prescribed for all our patients pre and postoperatively. It was generally administered according to WHO levels.

In association with the above-mentioned means, the global management of high-grade gliomas includes complementary support care such as a psychologist, a social worker, a dietician, physical rehabilitation with the help of a physiotherapist and psychomotrician, and speech therapy. The installation of devices in case of hearing loss or visual disorders as well as aids for home maintenance (medical bed, wheelchair, nurse and home help) are used according to the deficits presented by the patients. Anxiolytic and antidepressant treatments may also be prescribed.

2. Specific treatment

a.Surgical treatment

The therapeutic management of high-grade glioma is mainly based on surgery, whether it is surgical resection or simply a biopsy. It allows the histological diagnosis of the

tumor, to establish a therapeutic strategy, and to obtain an immediate symptomatic improvement by reducing the frequency of seizures, lowering intracranial pressure and eliminating the deficit related to tumor compression [94].

i. **The biopsy**

The biopsy must be performed each time a radical or subtotal surgical procedure is not envisaged, in any case each time before a complementary treatment by radiotherapy or chemotherapy is undertaken, we distinguish between open biopsies, and stereotactic biopsies with or without frame, it requires a strict anatomical location (cerebral scanner, angiography and cerebral MRI prior to it). Mortality is less than 1%, the main risk is intra-tumor hemorrhage.

The indications for biopsy depend on the characteristics of the lesion:

- Functional area (motor, language area, visual...).
- Deep location (basal ganglia).
- Invasion of the corpus callosum.
- Multifocal lesions [95].
- Simple surgical biopsies:

They are conceivable only in case of a sufficiently large tumor of superficial topography, in an accessible lobe (frontal or temporal), at a distance from a highly functional region. A simple circular craniotomy of 2 to 3 cm in diameter allows direct control of the biopsied area, cortical and subcortical hemostasis under visual control. Extemporaneous examination is essential and must confirm the presence of tumor cells in the specimens before closure. General anesthesia is preferable for reasons of comfort.

❖ Imaging-guided biopsies:

These are similar to image-guided excision techniques and include location imaging (3D MRI sequences, specific sequences, transferred to an image processing console) followed by the procedure itself, most often under general anesthesia. Neuronavigation instruments have the advantage of locating the projection point on the scalp of the tumor iso-center, its contours and the point of biopsy. The craniectomy is then reduced in diameter, from 2.5 to 3 cm, in order to limit unnecessary cortical exposure. Once the dura is opened, the samples are taken under visual control, and the same requirement for extemporaneous anatomopathological examination before closing the approach is necessary. The neuronavigation equipment allows to check the position of the biopsies in relation to the initial location.

❖ Stereotactic biopsies:

The biopsy allows to take a precise sample of the intracerebral lesion by trepanation after radiological location and with the help of a dedicated frame called "stereotaxis frame" in order to have it analyzed in the anatomopathology laboratory. The procedure is as follows:

- The use of a stereotactic frame that:
- Ensures reproducible restraint of the skull.
- Creates a three-dimensional operative space in which the patient's cerebral anatomical space is integrated.
- Centers the radiological sights for the operative controls.
- Serves as a fixation for different instruments and instrument holders.

Subsequently, the imaging allows the calculation and simulation of intracerebral

trajectories oriented according to the individual anatomy and the calculation of proportional coordinates of anatomical structures and brain lesions.

- Instrumental surgical approach through a small diameter craniotomy orifice.
- Interactive verification of the procedure performed with, first of all, radiological control of the position of the implanted intracranial instruments.
- In the case of glial brain tumor biopsies, it is the realization of staged biopsies according to a trajectory that interests the different components of this tumor. The topography of the trajectory and the number of biopsies must take into account the location of the tumor, particularly in relation to functional structures, and its extension as it appears on imaging. The biopsies must be in sufficient number and performed in the lesion and peri-lesion areas. The rate of non-contributing biopsies is 4 to 9%[81], [96].

The extemporaneous examination remains essential, cytological techniques (smear technique) have proven their reliability with a correlation rate of 80 to 90% between extemporaneous and definitive diagnosis [96], but it only provides a confirmation of the glial nature of the tumor. It is only the final anatomical examination that will determine the other data necessary for grading, those of molecular biology and those of cellular marking. It is worth remembering the interest of correlating anatomopathological data with imaging data, increasing the reliability of a necessarily limited biopsy sample [81], [96]. Cell labeling techniques allowed us to show the presence of isolated tumor cells in cycles beyond the tumor limits visible on conventional imaging, i.e. in T2 and FLAIR sequences. The very low proportion of cycling cells in these regions distant from the imaging anomalies makes them difficult to detect. Recent work on the use of H1 proton spectroscopy sequences in glial

tumors suggests that the limit of tissue spectral profile abnormalities lies beyond that of visible T2 or FLAIR abnormalities [97], [98].

In our series, 18% of cases had undergone biopsy.

Figure 32: Creation of a trepan hole in stereotactic condition. [17]

ii. **Surgery of exeresis**

Resection surgery remains a major option in the therapeutic management of high-grade gliomas and is considered a major prognostic factor. Tumor resection is also useful to reduce the mass effect and/or neurological deficit; it can also reduce the need for corticosteroid therapy, and it allows for a decrease in the dose of radiotherapy, increase the effect of chemotherapy, and limit the sampling error that can occur when a single sample biopsy is obtained [99].

Exceresis techniques vary from team to team and depend mainly on individual parameters: age, terrain, location, tumor volume, and grade assumed on imaging data or

previously identified by biopsy. The proximity or not of highly functional areas (motor, sensitive or language), which must be respected. They must be followed by a rigorous operative strategy involving the use of pre or peroperative location techniques (functional MRI, stereotaxis, neuronavigation, echography), as well as cortico-subcortical stimulation techniques, the objective of which is to minimize the functional risks while ensuring a good quality of excision.

Macroscopically complete resection can be defined by the surgeon's impression that all tumor tissue has been resected and that the resection margins have passed into macroscopically normal brain tissue [100]. Complete resection is defined by the disappearance of all contrast on immediate postoperative imaging (48 hours after), CT or more commonly MRI in T1 sequence with gadolinium injection [101].

❖ Stereotactic excision:

It allows :

- Oriented surgical planning that is mindful of individual anatomy.
- Choice of a trajectory and a surgical approach respectful of the functional regions and structures.
- Realization of a limited circular craniotomy and a minimal transcortical approach.
- Resection controlled by the coupling between preoperative imaging and surgical microscopy [102].

❖ Neuronavigated resection:

Used by a trained surgeon who is aware of its limitations, neuronavigation tools, pointers, microscopes are proving to be very useful in the resection of gliomas in functional

or subinsular regions. They are widely used during the resection of supratentorial gliomas, in particular at the beginning of the operation to perform a bone flap of reduced size adapted to the location and volume of the tumor, but also during and at the end of the resection where they support or correct the surgeon's judgment on the extent of the resection.

A recent study integrating functional MRI activation images in a neuronavigation environment has shown the usefulness in the resection of tumors in the vicinity or at the level of a functional region, allowing the prediction of the risk of neurological deterioration as a function of the distance between the lesion boundaries identified during surgery and the position of functional activation signals [103].

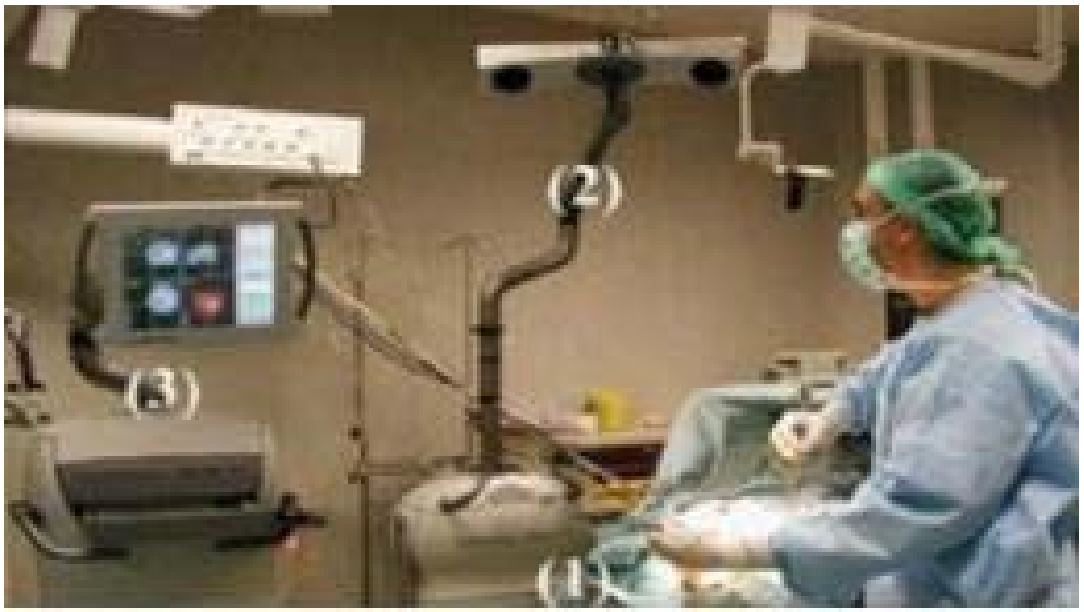

Figure 33: Neuronavigation is an interactive tool that allows the surgeon to indicate at any time the position of his instruments (1) and his microscope focus on the patient's three-plane MRI, which is itself displayed on a monitor (3). Infrared cameras (2) positioned in the operating room detect several times a second the millimetric positioning of each of the elements: patient's head, microscope focus, pointer, surgical instruments (Carpentier cliché). [104]

❖ Excision under intraoperative ultrasound:

Intraoperative ultrasound is an additional means of checking both the quality of the excision and the extent of cerebral displacement, which progressively distorts the neuronavigation data during the operation. In order to update the neuronavigation data, some teams have tried to match the neuronavigation images to the ultrasound images [105].

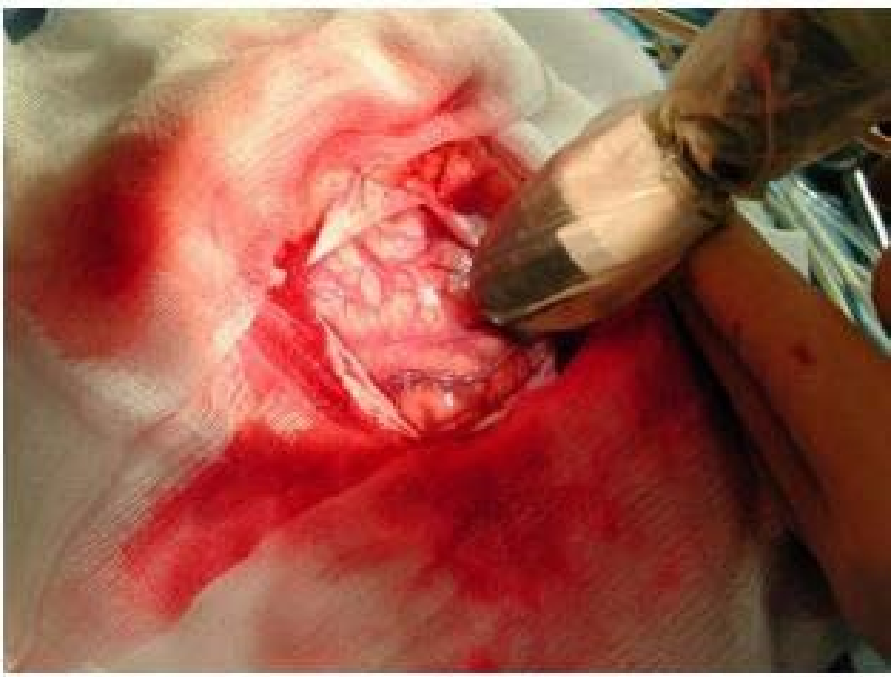

Figure 34: Intraoperative ultrasound is an additional means of checking both the quality of the exeresis (many tumors are hyper echogenic) and the extent of the cerebral displacement progressively distorting the neuronavigation data during the operation (Carpentier photograph) [104].

❖ Excision under operative MRI:

The removal of the tumor under operative MRI allows to control the quality of a tumor removal and to overcome the problem of cerebral displacement during the operation. during the operation. However, it comes up against numerous technical and economic

constraints, which limit its use in neurosurgical operating rooms. A distinction is made between high-field MR imagers (1.5 T), installed in an operating room of sufficient size, and compact low-field imagers (0.15 T), which are mobile and open, and are integrated into the operating field.

Low field imagers are sufficient for the evaluation of the quality of excision in the majority of cases [72], at least in the case of tumors that take contrast on MRI. Nimsky et al. recently reported their experience in 47 patients with a glial tumor resected under high-field operative MRI. They showed that in a team trained in tumor surgery, operative MRI prompted complete resection on imaging in nearly 40% of cases of low- or high-grade tumor, without additional morbidity [106].

Figure 35: Preoperative MRI.

❖ Excision in the functional zone: direct cortical stimulation techniques (awake surgery):

This intraoperative electrophysiology can concern either the motor regions (on sleeping patients), or the sensory, visual or language regions (on awake patients). It is based on the principle of bipolar electrical stimulations on the cortex or on the path of subcortical fibers [106], [107], inducing a peripheral response. A cortical and subcortical somatotopy is

thus defined for each patient and is materialized by numbered bookmarks. These data are continuously compared to the preoperative functional MRI data. A precise preoperative cognitive assessment quantifying the possible neurological deficits of the patient is essential in order to know perfectly his clinical state, indeed, a motor mapping is not reliable if the patient cannot fight against gravity and is infeasible if the patient is completely deficient. Similarly, intraoperative mapping of language areas is not reliable if the patient has an error rate of more than 25% in the object naming test. The use of corticosteroid therapy before the operation may improve the deficit and allow intraoperative mapping.

Technically, the operative conditions allowing cerebral mapping require the maintenance of normothermia (heating blanket), the absence of curare, local anesthesia of the subcutaneous and dura mater (for awake patients) and antibiotic prophylaxis when the procedure lasts two hours or more. The Ojeman bipolar stimulator, applied directly to the cerebral parenchyma (cortex or fibers) for two to five seconds, sends a continuous train of pulses of 0.1 to 1.5ms each, of adjustable intensity (from 2 to 12mA) at a rate of 20 to 60Hz (60Hz = 60 pulses per minute). It is usually recognized that a 10mA stimulation spreads over a 5mm radius around each of the two stimulator pads. Thus, the tumor resection must be stopped as soon as the stimulation of the faces and the edges of the operating cavity generates a motor or sensitive response [108]. At the end of the operation, a new mapping is performed since it allows to predict the potential of neurological recovery in the postoperative days. The stimulation of the language areas uses the same parameters. In order to explore the primary functions of language as much as possible, at least two cognitive tests must be performed: naming of objects presented every four seconds "this is a...", counting test (counting from 0 to 50). In order to ensure a lower risk of postoperative aphasia, it is recognized that a 10 mm safety margin of apparently non-functional cortex

should be left around the eloquent areas (which is not the case for the motor areas).

In our series, 12 cases (36%) had total resection and 15 cases (45%) had partial resection.

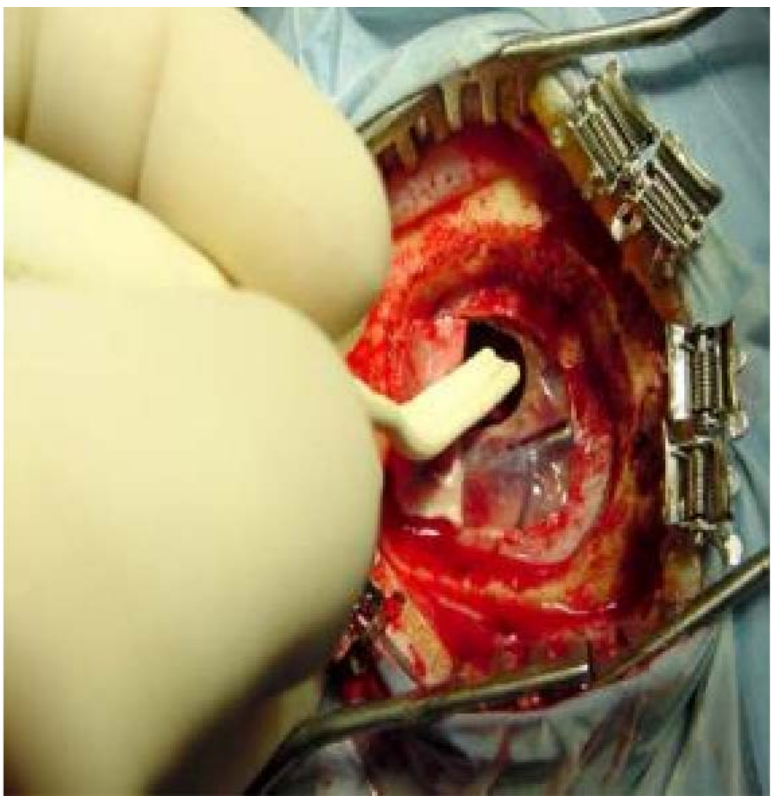

Figure 36: Intraoperative direct cortical and subcortical stimulation by the Ojeman bipolar stimulator (Carpentier photograph). [104]

iii. **Therapies associated with the surgical procedure**

❖ Fluorescence microscopy:

Fluorescence microscopy is based on the use of a hemoglobin precursor that allows the accumulation of fluorescent porphyrins in high grade gliomas. The detection of this fluorescence in the operating room via the microscope allows the visualization of certain persistent tumor islands and therefore, in theory, their better resection. The landmark

clinical trial on this technique was published by the ALA-Glioma Study Group in 2006[94], in which 161 patients with malignant glioma received a dose of 5-aminolevulinic acid in drinking water (Gliolan), the precursor that leads to the accumulation of fluorescent porphyrins in the tumors. At the same time, 161 other patients underwent conventional surgery. After a follow-up of more than 35 months, the authors explain that resection was considered complete in 65% of patients in the fluorescence group compared to 36% in the reference group ($p < 0.0001$). The six-month progression-free survival rate was 41% in the 5-aminolevulinic acid group and 21% in the other group. Despite all the inevitable biases of this study, there would seem to be an increase in progression-free survival compared with conventional microsurgery.

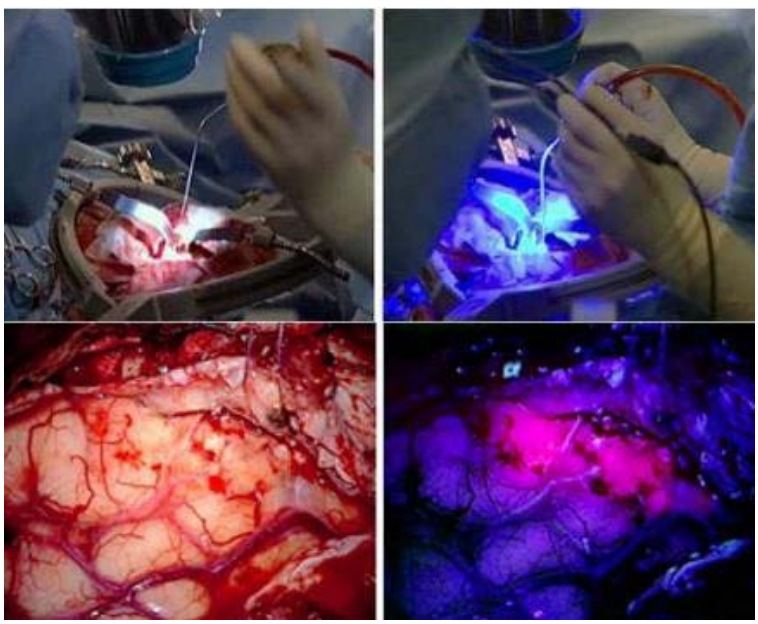

Figure 37: High-grade glioma optimization of fluorescence resection; operative view in white light and red fluorescence in blue light (400nm), specific accumulation(x200).

❖ Photodynamic therapy:

Photodynamic therapy (PDT) is a two-step treatment involving the intravenous administration of a photosensitive agent followed by its activation at a specific light

wavelength to target tumor cells; this sensitizer induces, via molecular oxygen-dependent mechanisms, cell death by oxidation. Thus, persistent tumor islands at the edge of the resection cavity and invisible under the operating microscope can be destroyed. PDT remains a promising therapeutic approach that requires further study in HGG [109].

❖ Immunotoxin:

It combines a ligand known to bind to molecules expressed on the surface of glial tumor cells (EGFR, TNFR...) and a toxin derived from bacteria. The The particularity of these molecules is that they require administration by micro-perfusion through catheters placed in the surgical site and connected to an external pump [110].

iv. **Complications of surgery**

Operative complications are rarely reported in the literature, and vary according to the surgical procedure. We speak of transient morbidity (infections, hematomas, hydrocephalus, regressive deficits) and permanent morbidity (permanent deficits).

The overall rate of post biopsy complications in the literature varies between 0.6 and 7.2%; these are mainly seizures, hematomas, cerebral edema, and infections [97], [110].

In our series, the patients who underwent STB were previously prepared (with anticonvulsants and corticosteroids), and the procedure was performed under good aseptic conditions. Also, we do not note any post-biopsy complications.

In the case of excisional surgery, the reported complication rates are in the range of 6 to 21% and can reach 28%. Mortality rates are 0 to 5%. In a large review of 400 craniotomies for brain tumors, Sawaya et al. [111] reported an overall transient morbidity rate of 19% and a permanent morbidity rate of 13%, and an overall mortality rate of 1.7% [90], [111]–[114]. reported an overall transient morbidity rate of 19% and a permanent

morbidity rate of 13%, and an overall mortality rate of 1.7% [124][125][126][127].

In our series, there was no operative mortality. The rate of infections was 3.4% (Pneumopathy), and the rate of aggravated or additional deficits was 6.84%. The rate of postoperative hematoma and fistula was 3.44% and postoperative edema was 13.79%. However, we lack data to estimate the actual rate of permanent or transient morbidity given the number of patients lost to follow-up.

Table XI: Postoperative morbidity and mortality in different series in the literature.

Series	Number of patients	Surgical Mortality (%)	Infectious complications (%)	Added Déficit (%)
Ciric et al. [114]	42	0	2	7
Ammirati et al. [113]	31	0	3	6
Celli et al.[86]	105	9,4	0,3	_
Devaux et al. [115]	263	1,1	_	1,1
Our cohort	33	0	3,4%	6,89

b.Radiotherapy:

Radiotherapy has a central place in the treatment of high-grade gliomas, and its adjuvant treatment after surgery is currently the standard treatment. Given the often infiltrative character of high-grade gliomas, either the surgical excision as large, can not be considered as carcinologically complete. Therefore, radiotherapy has been widely used postoperatively with the theoretical aim of sterilizing possible tumor lesions and prolonging the duration of postoperative remission. All the available data seem to show a beneficial

effect of radiotherapy in the treatment of high grade gliomas.

The dose delivered will depend on several factors such as the age and general condition of the patient. A dose/efficacy analysis confirmed that in malignant gliomas, the delivery of a dose of 60 grays in 1.8 to 2 grays fractions is associated with better survival compared with lower doses of radiotherapy [116]130]. The volume of radiotherapy must take into account the tumor infiltration visible on T2 or FLAIR weighted sequences, and the risk of side effects associated with a large volume of irradiation.

❖ Toxicity of radiotherapy:

- **Acute**: Several acute side effects have been described: asthenia, increased peri-tumor edema, skin erythema, and seizures, especially in cases of previous coma in the history of the disease[117] .
- **Chronic** : Late toxicity is important to consider since patient survival has been significantly prolonged. Hypopituitarism, mood change, memory impairment, dementia, coordination and/or balance disorders, and postradial necrosis are the main complications described. Postradiation necrosis classically occurs 6 months to 5 years after cerebral radiotherapy and may mimic a tumor recurrence. MRI spectroscopy, perfusion MRI and especially PET scans can help in the diagnosis [118].

A study by Emami & al, IJROBP [119] showed that the probability of developing a brain complication increases when the dose exceeds 60Gy.

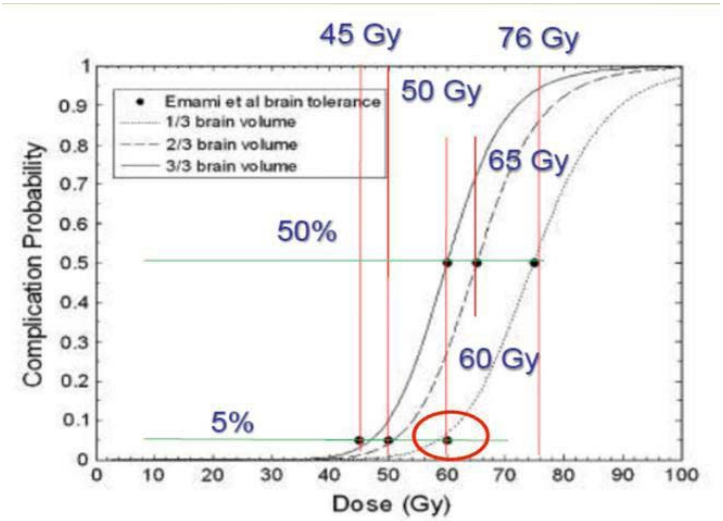

Figure 38: The probability of the occurrence of complications. [119]

c.Chemotherapy:

Chemotherapy has entered the therapeutic arsenal of high-grade gliomas to improve the prognosis because of its success in other cancerous pathologies. Its interest lies in the reduction of volumes and doses delivered, thus improving the quality of survival and the cure rate. This chemotherapy can be delivered pre-, per- or post-radiotherapy. The route of administration can be intravenous, intra-arterial or directly to the tumor at the time of surgical resection or via stereotactic procedures.

The median survival of HGG from series is 52 weeks, the percentage of survivors at 18 months is about 20%. The strategy varies according to the timing of treatment in relation to surgery and radiotherapy: neoadjuvant chemotherapy (after biopsy), adjuvant (after complete excision or radiotherapy), or at recurrence. The evaluation criteria are clinical (free interval, objective survival response rate) and radiological, in practice measured by contrast uptake (complete response, partial response, stabilization).

Combined with surgery and radiotherapy, chemotherapy increases median survival to

12 months for glioblasts and to 2-3 years for anaplastic astrocytomas. A significant improvement in median survival was observed for oligodendrogliomas and anaplastic astrocytomas with PCV (Procarbazine, Lomustine, and Vincristine) [120], and with the combination of fotemustine, cisplatin, and etoposide for nonoperable high-grade gliomas [121]. For recurrence, temozolomide [122], [123], a methylating agent close to dacarbazine, and fotemustine have received marketing authorization in France for glioblastoma after failure of standard treatments. The EORTC trial [124] defined a new standard for glioblastoma, based on the administration of temozolomide, which is an exclusive oral chemotherapy concomitantly with and following the conventional radiotherapy regimen (stupp protocol). In a population of 573 randomized patients, this regimen increased the median survival from 12.1 to 14.6 months and the 2-year survival rate from 8 to 26%, compared with exclusive radiotherapy. Temozolomide, also effective in anaplastic oligodendrogliomas, is generally preferred over PCV for its ease of administration, better tolerability and proven efficacy. It is generally administered at a dose of 150-200 mg/m2 from day 1 to day 5 for 4 weeks.

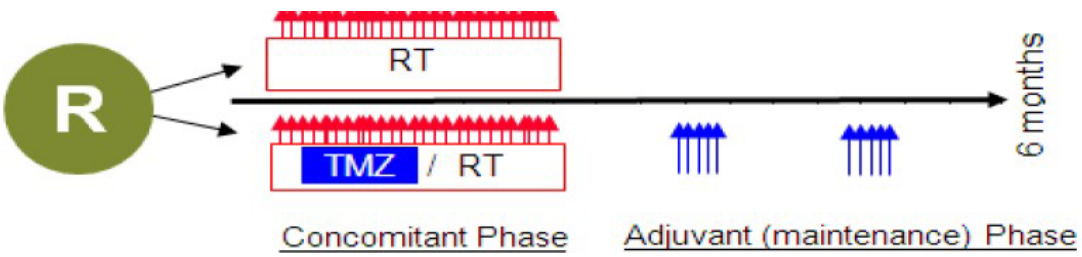

Figure 39: Therapeutic scheme of Temozolamide concomitantly with radiotherapy and in adjuvant "Stupp's scheme".

❖ Chemotherapy Toxicity:

VCP-based chemotherapy has multiple side effects such as nausea, vomiting, anorexia, fatigue, rash, numbness or paresthesia, abdominal pain, constipation, hepatotoxicity, encephalopathy, seizures, intracranial hemorrhages, infections, neutropenia,

and thrombocytopenia. Temozolomide has a rate of hematotoxicity between 8 and 23% [92], [124], which is lower than the rate of PCV [125]. Temozolomide does not exhibit cumulative toxicity, unlike PCV [126], which allows for prolonged administration.

d.Tumor-Treating Fields (TTFs)

Tumor-treating fields are a newly approved physical treatment that uses transducer arrays applied directly to the scalp to give low-intensity (1–3 V/cm), intermediate-frequency (200 kHz) alternating electric fields to treat newly diagnosed or recurring GB. TTFs generate selective toxicity in quickly dividing cells by causing neuronal depolarization and disrupting microtubule formation during mitosis. Since 2015, the FDA has approved this treatment technique as an adjunct therapy for recurrent gliomas [127], [128].

A phase III trial conducted by Stupp et al. reported a PFS improvement of 6.7 months for the maintenance TMZ + TTF group versus 4.0 months for the maintenance TMZ-alone group (HR, 0.63; 95 percent CI, 0.53–0.76 [$p < 0.001$]) and an OS benefit of 20.9 months vs 16.0 months for the maintenance TMZ-alone group (HR, 0.63; 95 percent CI, 0.53–0.76 [$p < 0.001$] (HR, 0.65; 95% CI, 0.53–0.76 [$p < 0.001$]) [127], [128].

TTFs have been tested in phase II and III trials in both first-time treated and recurring GB patients. PFS, OS outcomes, and objective responses improved as a result of the study. However, disagreements over study design, execution, and data interpretation have raised questions about the current evidence. Furthermore, the cost of completing the therapy is a further impediment to TTFs being used regularly [127], [129], [130].

There is plenty of evidence generated in the last years about the benefits of TTFs in GB. This therapy currently represents a potential alternative for the management of newly diagnosed and recurrent GB patients. However, despite the advances, the debate remains

open about the limitations of this novel technique, the costs of which, together with its poor accessibility, have limited its regular application in most neuro-oncologic centers.

e.Bevacizumab

GBs are highly vascularized tumors characterized by overexpression of vascular endothelial growth factor (VEGF), a key regulator of tumor-associated angiogenesis. VEGF is a major target recently explored in most therapeutic trials. Bevacizumab (BEV) is a humanized monoclonal antibody against VEGF that has proven a prolonged PFS (3–4 months) but not OS benefit at several phase II and III clinical trials in newly diagnosed and recurrent GB[130]–[132].

Particularly in the recurrence setting, BEV presented response rates of approximately 30% in uncontrolled phase II trials [43]. About co-adjuvant chemotherapy with BEV, a randomized phase III trial tested the combination of BEV + lomustine versus lomustine alone, and results showed an improvement in PFS without OS changes in the combination group [133]–[135].

Another common combination for recurrences is BEV + re-irradiation. Two phase III trials found that BEV + RT-TMZ combination therapy increased PFS but not OS, as in practically every clinical trial. On the other hand, re-irradiation plus BEV was studied by Kulinich et al. The results showed a significant OS improvement but no significant PFS benefit [46]. Remarkably, patients who had previously been irradiated and were given BEV presented a reduced incidence of radio-necrosis. These findings show that the efficacy of RT with BEV is highly variable. As a result, the usefulness of this combination is still up for debate, and more randomized studies will be needed to determine the benefit [131], [136]–[138]. However, neither combination therapy had demonstrated OS benefit, and the mentioned regimens are only recommended after failure of bevacizumab alone [127], [139].

Based on high radiological response rates and the optimistic PFS outcomes described, bevacizumab achieved FDA approval for recurrent GB in many parts of the world, such as the USA, Canada, and Switzerland, but its effects on tumor biology and growth dynamics remain controversial [20,32]. Its failure, in clinical trials, to demonstrate an OS benefit has either stopped approval of BEV therapy for newly diagnosed GB management or has slowed down the approval process, as has happened in many regions, such as the European Union, where it remains not approved, even in the recurrence setting [130].

A relevant aspect of BEV is how it affects patients' cognitive abilities, symptoms, and quality of life. There is strong evidence that patients using BEV had worse scores on objective tests of neurocognitive function and reported cognitive function compared to placebo, implying either undiscovered tumor progression or BEV-related neurotoxicity. Furthermore, among patients who did not have tumor development on imaging investigations, those initially treated with BEV reported a worsening in the severity of their symptoms, as measured by both patient-reported outcomes and symptom-related interference with daily activities [140]. On the other hand, some research suggests that BEV patients have a considerably longer deterioration-free life than placebo patients after a year of treatment. When examining cognitive functioning, emotional functioning, role functioning, weariness, visual dysfunction, weakness in both legs, hair loss, bladder control, and financial difficulties, patients in the BEV group have a considerably longer time before deterioration [132]. Thus, more data is necessary to determine the real impact of BEV on patients' symptoms and quality of life.

As far as evidence suggests, BEV has recently been included among the main systemic treatment options for GB progression or recurrence after its approval by the FDA as a viable therapeutic alternative. This anti-angiogenic therapy has been subjected to different trials combined with novel immunological therapies presented further in the text.

3. Indications:

a.Surgery:

When the patient's clinical performance is satisfactory and the tumor is operable, tumor resection is the gold standard of first line. It allows the removal of the tumor and thus improves the neurological function of the patient and prolongs survival. When one of the conditions is absent, a biopsy will be performed to determine the histological type of the tumor which can be open or stereotactic.

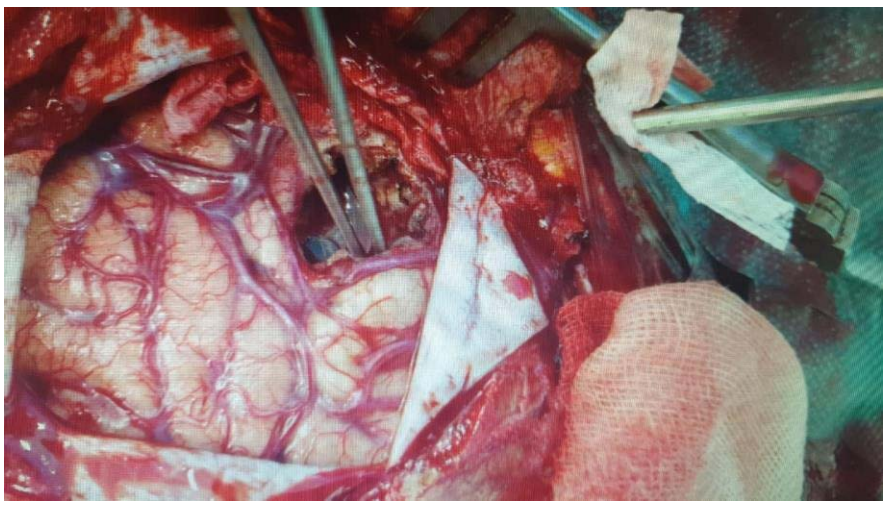

Figure 40: Intraoperative image of a surgical removal of a high-grade glioma

b.Radio-Chemotherapy

In glioblastoma, patients are grouped into prognostic classes according to the RPA (Recursive Partitioning Analysis) score, which is used to select the therapeutic protocol [141]. This classification is based on age, Karnofsky score, Mini Mental State (MMS) and operative report [142].

Table XII: RPA score.

Class	Description	Therapeutic protocol
III	Age <50 years, KPS 90-100, OMS = 0	Stupp treatment protocol
IV	Age <50 years and KPS<90 WHO 1-2 or age >50 years and complete or partial surgery and MMS > 27.	Stupp treatment protocol
V	Age≥ 50 years and MMS <27 or biopsy with radiation dose >54.4 Gy and KPS ≥ 70, WHO 1-2 Where Age ≥ 50 years, KPS <70, MMS normal.	Fractionated radiotherapy Classic or hypo-fractionated Marginal benefit of association with chemotherapy
VI	Age≥ 50 years and KPS ≥ 70, WHO 3- 4 biopsy with dose Of radiation therapy ≤ 54.4 Gy where. Age ≥ 50, KPS <70, abnormal MMS.	Palliative care

CONCLUSION

High-grade gliomas are primary brain tumors representing a heterogeneous group of malignant tumors with a variable clinical picture and a poor prognosis. The most common histological type is anaplastic astrocytoma grade VI "glioblastoma".

The clinical symptomatology is dominated by the association of an intracranial hypertension syndrome and a neurological deficit. Their diagnosis has been facilitated by advances in neuroradiology, where MRI is the most effective morphological examination for the study of this type of tumor. However, clinical and radiological suspicion must be confirmed by histology completed by molecular marker analysis.

Current advances in the field of molecular biology and the study of the different molecular and cellular mechanisms of these tumors have offered a more targeted approach to this pathology citing as examples the methylation of the MGMT promoter of glioblastoma, IDH-mutated gliomas associated with a better prognosis.

Several risk factors have been incriminated, the most important being ionizing radiation and genetic predisposition. The main prognostic factors related to the patient are age, performance status (Karnofsky) and the presence of neurological deficits.

The management is based on a multimodal treatment defined during a discussion by a multidisciplinary team composed of neurosurgeon radiologist, anatomopathologist, oncologist. Technical aids (functional MRI, ultrasonic aspirator, operating microscope, neuronavigation, intraoperative mapping, 5-amino-levulinic acid (5-LA) fluorescent marker) can optimize this management by allowing a better intraoperative tumor identification, with an increase in resection rate and survival.

The prognosis of patients with high-grade gliomas is complex, due to profound changes in neurocognitive functioning, with fatigue and toxicities induced by treatments. As the evolution of

these tumors is rapidly unfavorable, disorders set in early with a major impact on the quality of life of patients and their families.

A close follow-up of the clinical and psychic state of the patients, complications and toxicity induced by the treatment (radio-chemotherapy) is necessary in order to preserve a better state of life.

ABSTRACT

Abstract

High-grade gliomas represent the most frequent and aggressive primary malignancies of the central nervous system. Magnetic resonance imaging (MRI) remains the current standard for the diagnosis and follow-up of these tumors. The diagnosis and classification of these tumors are largely based on their histopathological characteristics.

Our work consisted of a retrospective study of 33 patients collected between January 1, 2017 and December 31, 2021 in the department of oncology-radiotherapy at the University hospital Med VI Marrakech. The aim of this study is to highlight the epidemiological, clinical, paraclinical and therapeutic particularities of high grade gliomas. The age of our patients ranged from 29 to 74 years with a median age of 51 years, the age group 41-60 years was the most affected with a male predominance of 60.6% and a sex ratio of 2:1. The mean time to diagnosis was 25 weeks. The tumor manifested itself as intracranial hypertension syndrome in 48%, motor deficit in 51%, seizures in 9%, and higher function disorders in 18%. Computed tomography (CT) and magnetic resonance imaging (MRI) were requested in all of our patients, the most frequent location was parietal 36%. The average tumor size was 5 cm. The surgical procedure consisted of partial removal in 45%, total removal in 36% and biopsy in 18%. Anatomopathological examination allowed the diagnosis of the most frequent histological type was glioblastoma. Postoperative follow-up was simple in 23 patients (81% of cases), while in 6 patients (18% of cases) it was marked by various complications.

Key words: High-grade gliomas, MRI, WHO 2016 classification, Surgery.

Résumé

Les gliomes de haut grade représentent les tumeurs malignes primaires les plus fréquentes et les plus agressives du système nerveux central. L'imagerie par résonance magnétique (IRM) reste la norme actuelle pour le diagnostic et le suivi de ces tumeurs. Le diagnostic et la classification de ces tumeurs sont largement basés sur leurs caractéristiques histopathologiques.

Notre travail a consisté en une étude rétrospective de 33 patients colligés entre le 1er janvier 2017 et le 31 décembre 2021 au service d'oncologie-radiothérapie du CHU Med VI Marrakech. L'objectif de cette étude est de mettre en évidence les particularités épidémiologiques, cliniques, paracliniques et thérapeutiques des gliomes de haut grade. L'âge de nos patients variait de 29 à 74 ans avec un âge médian de 51 ans, la tranche d'âge 41-60 ans était la plus touchée avec une prédominance masculine de 60,6% et un sex-ratio de 2:1. Le délai moyen de diagnostic était de 25 semaines. La tumeur s'est manifestée par un syndrome d'hypertension intracrânienne dans 48 % des cas, un déficit moteur dans 51 % des cas, des crises d'épilepsie dans 9 % des cas et des troubles des fonctions supérieures dans 18 % des cas. La tomodensitométrie (CT) et l'imagerie par résonance magnétique (IRM) ont été demandées chez tous nos patients, la localisation la plus fréquente étant pariétale 36%. La taille moyenne de la tumeur était de 5 cm. La procédure chirurgicale a consisté en une exérèse partielle dans 45%, une exérèse totale dans 36% et une biopsie dans 18%. L'examen anatomopathologique a permis de diagnostiquer le type histologique le plus fréquent : le glioblastome. Les suites opératoires ont été simples chez 23 patients (81% des cas), alors que chez 6 patients (18% des cas) elles ont été marquées par diverses complications.

Mots clés : Gliomes de haut grade, IRM, Classification OMS 2016, Chirurgie.

ملخص

تمثل الأورام الدبقية عالية الجودة الأورام الخبيثة الأولية الأكثر شيوعًا وعدوانية في الجهاز العصبي المركزي. يظل تصنيف وتشخيص ومتابعة هذه الأورام. يعتمد التصوير بالرنين المغناطيسي (MRI) هو المعيار الحالي لتشخيص الأورام إلى حد كبير على خصائصها النسيجية المرضية.

في الفترة ما بين 1 يناير 2017 و 31 ديسمبر 2021 تم جمع 33 مريضًا لدراسة بأثر رجعي لـ نتائج العلاج الأورام بالأشعة في مستشفى محمد السادس الجامعي. الهدف من هذه الدراسة هو تسليط الضوء على الخصائص الوبائية ، السريرية والعلاجية للأورام الدبقية عالية الدرجة. تراوحت أعمار مرضانا بين 29 و 74 عامًا بمتوسط عمر 51 عامًا ، كانت الفئة العمرية 41-60 عامًا هي الأكثر تضررًا مع غلبة الذكور 60.6٪ ونسبة الجنس 2: 1. كان متوسط الوقت اللازم للتشخيص 25 يومًا. تجلى الورم في تمالزمة ارتفاع ضغط الدم داخل الجمجمة 48٪ ، بنسبة 18٪. تم طلب التصوير بالرنين المغناطيسي (MRI) في جميع مرضانا ، وكان الموقع الأكثر شيوعًا هو 36٪ المقطعي المحوسب (CT) والتصوير بالرنين المغناطيسي (MRI) في 9٪ ، واضطرابات وظيفية أعلى في 51٪ ، وعجز حركي في 36٪ ، وخزعة الجداري. كان متوسط حجم الورم 5 سم. يتكون الإجراء الجراحي من إزالة جزئية في 45٪ ، وإزالة كلية في 36٪ ، سمح الفحص التشريحي المرضي بتشخيص النوع النسيجي الأكثر شيوعًا وهو الورم الأرومي الدبقي. كانت في 18٪. تمت المتابعة بعد العملية الجراحية بسيطة في 23 مريضًا (81٪ من الحالات) ، بينما في 6 مرضى (18٪ من الحالات) تميزت بمضاعفات مختلفة.

الكلمات الأساسية: الأورام الدبقية عالية الجودة ، التصوير بالرنين المغناطيسي ، تصنيف منظمة الصحة العالمية ، الجراح 2016 ،

APPENDIX

Appendix 1 : Operating sheet:

File number:

1.Identity:

- First name:
- Last name:
- Age:
- Matrimonial status:
- Health coverage (Mutuel):
- Origins: Rural □, Urbain □
- Profession:
- Phone Number:
- Adress:

2.Medical History

a.Personal:

i.Medical:

- Diabetes:
- High blood pressure:
- Bone disease:
- Heart disease:

- Liver disease:
- Kidney disease:
- Other:

ii.Surgical:

iii.Toxic-Allergic:

b.Family:

- Glioblastoma
- Other:

3.Clinical examination

- Delay between symptoms and consultation:
- Date of consultation:
- Intracranial hypertension: Yes □ No □

  If yes: Headaches □, Nausea □, Vomiting□, Visual problems □
- Higher functions problems: Yes □ No □

  If yes: Language □, Memory □, Behaviour □
- Motor disorders: Yes □ No □,

  If yes: what type? ……..
- Sensitive disorders: Yes □ No □,

  If yes: what type? ……..
- Comitial crisis: Yes □ No □

• Deterioration in general status: Yes □ No □, ……...

4.Clinical examination at admission:

❖ Glasgow score:

❖ Kornofsky score:

❖ Motor disorders: Monoplegia □, Monoparesis □ , Paraplegia □, Paraparesis □, Tetraplegia □, Tetraparesis □, Hemiplegia □, Hemiparesis□(what side? …….)

❖ Reflex disorders: Yes □ No □

If yes, what type? …….

❖ Sensitive disorders: Yes □ No □

If yes, what type? …….

❖ Impairment of cranial pairs: Yes □ No □

If yes, what type? …….

❖ Higher functions disorders: Yes □ No □

If yes, what type? …….

❖ Cerebellar syndrome: Yes □ No □

5.Imagery

a.Topography:

❖ Right side □, Left side □

❖ Frontal: □ Fronto-parietal□, Parietal □

❖ Temporal: □ Fronto-temporal□, temporo-parietal□

❖ Occipital : □ Occipito-temporal □, occipio-parietal□

b.CT-scan:

❖ Yes □, No □

❖ Tumoral size:

Heterogenic□

❖ Badly limited □

❖ Tumoral necrosis □

❖ Haemorrhage □

❖ Oedema□

❖ Enhancement with contrast product: □

❖ Hydrocephalus□

❖ Signs of engagement □

c.MRI-scan:

❖ Yes □, No □

❖ T1 sequence: Hypo-intense image □, heterogenic □, Necrosis □, badly limited □

❖ T2 sequence: Hyperintense image □, heterogenic□

6.Histology:

❖ Yes □, No □

❖ Type of sampling: Stereo biopsy □, Surgical excision □

❖ Confirmed Glioblastoma: Gliosarcoma □, Giant cell glioblastoma □, Endothelial hyperplasia □,

Necrosis □

❖ Hystological type : Non mutant □, IDH □

❖ Cell proliferation index:

❖ Immuno-histochemistry:

7.Treatment:

a.Urgent:

❖ Corticosteroid therapy: Yes □ No □

❖ Mannitol: Yes □ No □

❖ Ventricular draining: Yes □, No □

b.Deferred

❖ Surgery:

Total resection: □

Partial resection: □

Biopsy: □

❖ Complications:

Focal deficit □

Infectious complications: □

Haemorrhagic complications: □

Post-op Oedema □

❖ Post-op CT-scan:

c.Radiotherapy:

❖ Yes □, No □

❖ Delay between surgery and radiotherapy:

❖ Dose:

❖ Fraction:

❖ Spreading: RTH 2D □, 3D □, Stereotaxic □

❖ Duration

❖ Intteruption : Transient interruption □, Definitive interruption □

❖ Dose at interruption

❖ Cause of interruption: Severe infection □, Worsening of oedema □, Death □, Other ……

d.Chemotherapy:

❖ Neoadjuvant CTH: Yes □ No □

❖ Concommittal CTH: Yes □ No □

❖ Molecule:

❖ Dose:

❖ Number of cycles: less than 3 □, 3 cycles□, More than 3 □, 6 Cycles□

❖ If interrupted: Cause : Aggravation □, toxicity □, Death□

❖ If no CTH, why? -Deterioration of general status □, Patient's refusal □, Toxicity□, Death□, Financial reasons □

❖ Toxicity of CTH:

Hematogenic: - Anaemia □, Neutropenia □, Leukopenia □, Low plaquets □

Non hematogenic: Pneumocystis□ , Severe infection □

e.Symptomatic treatment:

❖ Corticosteroid therapy: Yes □ No □

❖ Antiemetics: Yes □ No □

❖ Anticonvulsants Yes □ No □

❖ Pneumocystis prophylaxis Yes □ No □

❖ Re-education Yes □ No □

8.Evolution

❖ Total remission: □

❖ Progression or recidivism □

❖ Stabilisation □

❖ Aggravation □

❖ Death □

Appendix 2: KPSS scale:

Functional Evaluation		Karnofsky Scale
Functionally independent.	100	Normal; no complaints; no evidence of disease.
Able to carry on normal activity and to work; no special care needed.	90	Able to carry on normal activity; minor signs or symptoms of disease.
Comprehensive dental care can do rehabilitation and reconstruction.	80	Normal activity with effort; some signs or symptoms of disease.
Frail.	70	Cares for self; unable to carry on normal activity or to do active work.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. Limited treatment.	60	Requires occasional assistance, but is able to care for most of his personal needs.
Basic restorative as well as maintenance and monitoring.	50	Requires considerable assistance and frequent medical care.
Functionally dependent.	40	Disabled; requires special care and assistance.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
Emergency care. Pain and infection control.	20	Very sick; hospital admission necessary; active supportive treatment necessary.
No treatment.	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

Appendix 3 : WHO score

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self care. Totally confined to bed or chair

Appendix 3: The mini-mental state examination test:

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

BIBLIOGRAPHY

[1] **B. K. Rasmussen *et al.*,**
"Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the the Danish Neuro-Oncology Registry," *J Neurooncol*, vol. 135, no. 3, pp. 571–579, Dec. 2017, doi: 10.1007/s11060-017-2607-5.

[2] **Q. T. Ostrom *et al.*,**
"CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012," *Neuro Oncol*, vol. 17 Suppl 4, no. Suppl 4, pp. iv1–iv62, Oct. 2015, doi: 10.1093/neuonc/nov189.

[3] **"CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015**
- PubMed." https://pubmed.ncbi.nlm.nih.gov/30445539/ (accessed Apr. 12, 2023).

[4] **E. Masson,**
"Tumeurs intracrâniennes de l'adulte," *EM-Consulte*. https://www.em-consulte.com/article/237750/tumeurs-intracraniennes-de-l-adulte (accessed Apr. 12, 2023).

[5] **S. Hansen,**
"The Danish Neuro-Oncology Registry," *Clin Epidemiol*, vol. 8, pp. 629–632, Oct. 2016, doi: 10.2147/CLEP.S99459.

[6] **Q. T. Ostrom *et al.*,**
"The epidemiology of glioma in adults: a 'state of the science' review," *Neuro Oncol*, vol. 16, no. 7, pp. 896–913, Jul. 2014, doi: 10.1093/neuonc/nou087.

[7] **A. Benider, K. Bendahhou, S. Afghar, B. Charrat, and I. K. Ahmadaye,**
"Registre Des Cancers de La Région Du Grand Casablanca Pour La Période 2008-2012." Casablanca), Foundation Lalla Salma, 2016."

[8] **"Registre de cancer du grand Casablanca 2013-2017." [Online].**
Available:https://contrelecancer.ma/site_media/uploaded_files/Registre_des_Cancers_de_la_Region_du_Grand_Casablanca_2013-2017.pdf

[9] **C. Majós *et al.*,**
"Proton magnetic resonance spectroscopy ((1)H MRS) of human brain tumours: assessment of differences between tumour types and its applicability in brain tumour categorization," *Eur Radiol*, vol. 13, no. 3, pp. 582–591, Mar. 2003, doi: 10.1007/s00330-002-1547-3.

[10] **M. Delion, C. Moraru, F. Almayrac, D. Von Langsdorff, P. Paquis, and P. Menei,**
"Études des glioblastomes incidents de mai 2006 à mai 2007, Angers-Nice," *Neurochirurgie*, vol. 56, no. 6, pp. 499–502, Dec. 2010, doi: 10.1016/j.neuchi.2010.07.006.

[11] **D. F. 17. Ducreux D, Bidault F, Bruna A, Parker F, Roujeau T, et al.,**
"Impact of new functional imaging modalities on radiation therapy regimen for glioblastoma." Bull Cancer 2005 ; 92 (4) : 333-42.

[12] **M. Bartolomei *et al.*,**
"Combined treatment of glioblastoma patients with locoregional pre-targeted 90Y-biotin radioimmunotherapy and temozolomide," *Q J Nucl Med Mol Imaging*, vol. 48, no. 3, pp. 220–228, Sep. 2004.

[13] **N. Malkoun *et al.*,**
"Intérêt d'un traitement d'entretien prolongé par témozolomide dans la prise en charge des patients atteints d'un glioblastome," *Cancer/Radiothérapie*, vol. 15, no. 3, pp. 202–207, Jun. 2011, doi: 10.1016/j.canrad.2010.11.015.

[14] **N. Lonjon *et al.*,**
"[Second surgery for glioblastoma. A 4-year retrospective study conducted in both the Montpellier and Nice Departments of Neurosurgery. A literature review]," *Neurochirurgie*, vol. 56, no. 1, pp. 36–42, Feb. 2010, doi: 10.1016/j.neuchi.2009.11.013.

[15] **R. Stupp *et al.*,**
"Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma," *N Engl J Med*, vol. 352, no. 10, pp. 987–996, Mar. 2005, doi: 10.1056/NEJMoa043330.

[16] **H. Shimizu, T. Kumabe, R. Shirane, and T. Yoshimoto,**
"Correlation between choline level measured by proton MR spectroscopy and Ki-67 labeling index in gliomas," *AJNR Am J Neuroradiol*, vol. 21, no. 4, pp. 659–665, Apr. 2000.

[17] J.-F. MINEO, I. Quintin-Roue, B. Lucas, V. BUBURUSAN, and G. Besson, "Les glioblastomes (A propos de 55 cas)." https://toubkal.imist.ma/xmlui77/handle/123456789/4315 (accessed Apr. 12, 2023).

[18] **J.-S. Guillamo *et al.*,**
"Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients," *Brain*, vol. 126, no. Pt 1, pp. 152–160, Jan. 2003, doi: 10.1093/brain/awg016.

[19] **S. Chanalet, C. Lebrun-Frenay, M. Frenay, M. Lonjon, and M. Chatel,**
"Symptomatologie clinique et diagnostic neuroradiologique des tumeurs intracrâniennes," *EMC - Neurologie*, vol. 1, no. 1, pp. 91–122, Jan. 2004, doi: 10.1016/j.emcn.2003.10.001.

[20] **R. T. Baldwin and S. Preston-Martin,**
"Epidemiology of brain tumors in childhood--a review," *Toxicol Appl Pharmacol*, vol. 199, no. 2, pp. 118–131, Sep. 2004, doi: 10.1016/j.taap.2003.12.029.

[21] **D. Provost *et al.*,**
"Brain tumours and exposure to pesticides: a case-control study in southwestern France," *Occup Environ Med*, vol. 64, no. 8, pp. 509–514, Aug. 2007, doi: 10.1136/oem.2006.028100.

[22] **L.-E. Wang *et al.*,**
"Polymorphisms of DNA repair genes and risk of glioma," *Cancer Res*, vol. 64, no. 16, pp. 5560–5563, Aug. 2004, doi: 10.1158/0008-5472.CAN-03-2181.

[23] **J. P. Neglia *et al.*,**
"New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study," *J Natl Cancer Inst*, vol. 98, no. 21, pp. 1528–1537, Nov. 2006, doi: 10.1093/jnci/djj411.

[24] **Q. T. Ostrom, H. Gittleman, L. Stetson, S. Virk, and J. S. Barnholtz-Sloan,**
"Epidemiology of Intracranial Gliomas," *Prog Neurol Surg*, vol. 30, pp. 1–11, 2018, doi: 10.1159/000464374.

[25] **"Role of medical history in brain tumour development. Results from the international adult brain tumour study - PubMed."**

https://pubmed.ncbi.nlm.nih.gov/10389745/ (accessed Apr. 12, 2023).

[26] **M. Wrensch, Y. Minn, T. Chew, M. Bondy, and M. S. Berger,**
"Epidemiology of primary brain tumors: current concepts and review of the literature," *Neuro Oncol*, vol. 4, no. 4, pp. 278–299, Oct. 2002, doi: 10.1093/neuonc/4.4.278.

[27] **"Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies**
– Scheurer – 2011 – International Journal of Cancer – Wiley Online Library."
https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.25883 (accessed Apr. 12, 2023).

[28] **K. Saika and Y. Hirabayashi,**
"Comparison of Time Trends in Brain Central Nervous System Cancer Incidence (1973–97) in East Asia, Europe and USA, from Cancer Incidence in Five Continents Vols IV–VIII," *Japanese Journal of Clinical Oncology*, vol. 38, no. 9, pp. 650–652, Sep. 2008, doi: 10.1093/jjco/hyn092.

[29] **H. Loiseau, A. Huchet, and I. Baldi,**
"Épidémiologie des tumeurs cérébrales primitives," *Neurologie.com*, vol. 2, no. 4, pp. 83–86, Jun. 2010, doi: 10.1684/nro.2009.0147.

[30] **M. Huncharek and B. Kupelnick,**
"A Meta-Analysis of Maternal Cured Meat Consumption during Pregnancy and the Risk of Childhood Brain Tumors," *NED*, vol. 23, no. 1–2, pp. 78–84, 2004, doi: 10.1159/000073979.

[31] **F. Lubin *et al.*,**
"The role of nutritional habits during gestation and child life in pediatric brain tumor etiology," *Int J Cancer*, vol. 86, no. 1, pp. 139–143, Apr. 2000, doi: 10.1002/(sici)1097-0215(20000401)86:1<139::aid-ijc22>3.0.co;2-c.

[32] **N. Tedeschi-Blok, M. Lee, J. D. Sison, R. Miike, and M. Wrensch,**
"Inverse association of antioxidant and phytoestrogen nutrient intake with adult glioma in the San Francisco Bay Area: a case-control study," *BMC Cancer*, vol. 6, no. 1, p. 148, Jun. 2006, doi: 10.1186/1471-2407-6-148.

[33] **H. Chen *et al.*,**
"Diet and risk of adult glioma in eastern Nebraska, United States," *Cancer Causes Control*, vol. 13, no. 7, pp. 647–655, Sep. 2002, doi: 10.1023/a:1019527225197.

[34] **J. T. Efird *et al.*,**
"The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors," *J Neurooncol*, vol. 68, no. 1, pp. 57–69, May 2004, doi: 10.1023/b:neon.0000024746.87666.ed.

[35] **S. A. N. Silvera, A. B. Miller, and T. E. Rohan,**
"Cigarette smoking and risk of glioma: A prospective cohort study," *International Journal of Cancer*, vol. 118, no. 7, pp. 1848–1851, 2006, doi: 10.1002/ijc.21569.

[36] **K. V. Shah,**
"SV40 and human cancer: A review of recent data," *International Journal of Cancer*, vol. 120, no. 2, pp. 215–223, 2007, doi: 10.1002/ijc.22425.

[37] **M. Wrensch *et al.*,**
"Does Prior Infection with Varicella-Zoster Virus Influence Risk of Adult Glioma?," *American Journal of Epidemiology*, vol. 145, no. 7, pp. 594–597, Apr. 1997, doi: 10.1093/oxfordjournals.aje.a009155.

[38] **M. Wrensch, A. Weinberg, J. Wiencke, R. Miike, G. Barger, and K. Kelsey,**
"Prevalence of antibodies to four herpesviruses among adults with glioma and controls," *Am J Epidemiol*, vol. 154, no. 2, pp. 161–165, Jul. 2001, doi: 10.1093/aje/154.2.161.

[39] **M. Wrensch *et al.*,**
"History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls," *Am J Epidemiol*, vol. 161, no. 10, pp. 929–938, May 2005, doi: 10.1093/aje/kwi119.

[40] **D. W. Parsons *et al.*,**
"An integrated genomic analysis of human glioblastoma multiforme," *Science*, vol. 321, no. 5897, pp. 1807–1812, Sep. 2008, doi: 10.1126/science.1164382.

[41] **F. B. Furnari *et al.*,**
"Malignant astrocytic glioma: genetics, biology, and paths to treatment," *Genes Dev*, vol. 21, no. 21, pp. 2683–2710, Nov. 2007, doi: 10.1101/gad.1596707.

[42] **M. Sanson, J. Thillet, and K. Hoang-Xuan,**
"Molecular changes in gliomas," *Curr Opin Oncol*, vol. 16, no. 6, pp. 607–613, Nov. 2004, doi: 10.1097/01.cco.0000142485.81849.cc.

[43] **A. Lièvre and P. Laurent-Puig,**
"La voie de signalisation RAS/MAPK," *Cancérodig.*, vol. II, no. 1, 2010, doi: 10.4267/2042/30747.

[44] **"Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies - PubMed."** https://pubmed.ncbi.nlm.nih.gov/17872411/ (accessed Apr. 12, 2023).

[45] **Y. Li *et al.*,**
"MicroRNA-34a inhibits glioblastoma growth by targeting multiple oncogenes," *Cancer Res*, vol. 69, no. 19, pp. 7569–7576, Oct. 2009, doi: 10.1158/0008-5472.CAN-09-0529.

[46] **J. T. Huse *et al.*,**
"The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo," *Genes Dev*, vol. 23, no. 11, pp. 1327–1337, Jun. 2009, doi: 10.1101/gad.1777409.

[47] **E. Masson,**
"Référentiel gliomes diffus de l'adulte de grade OMS II, III et IV : anatomie pathologique et biologie," *EM-Consulte*. https://www.em-consulte.com/article/765811/referentiel-gliomes-diffus-de-ladulte-de-grade-oms (accessed Apr. 12, 2023).

[48] **M. J. van den Bent,**
"Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective," *Acta Neuropathol*, vol. 120, no. 3, pp. 297–304, 2010, doi: 10.1007/s00401-010-0725-7.

[49] **J. P. Brouland and A. F. Hottinger,**
"Nouvelle classification OMS 2016 des gliomes : quels changements ?," *Rev Med Suisse*, vol. 579, pp. 1805–1809, Oct. 2017.

[50] **C. Daumas-Duport, F. Beuvon, P. Varlet, and C. Fallet-Bianco,**
"Gliomes: classifications de l'OMS et de l'Hôpital Sainte-Anne.," *Ann Pathol*, vol. 20, no. 5, pp. 413–28, Oct. 2000.

[51] **V. Mor, L. Laliberte, J. N. Morris, and M. Wiemann,**
"The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting," *Cancer*, vol. 53, no. 9, pp. 2002–2007, May 1984, doi: 10.1002/1097-0142(19840501)53:9<2002::aid-cncr2820530933>3.0.co;2-w.

[52] **S. M. Chang *et al.*,**
"Patterns of care for adults with newly diagnosed malignant glioma," *JAMA*, vol. 293, no. 5, pp. 557–564, Feb. 2005, doi: 10.1001/jama.293.5.557.

[53] **W. H. Ng, T. T. Yeo, and A. H. Kaye,**
"Spinal and extracranial metastatic dissemination of malignant glioma," *Journal of Clinical Neuroscience*, vol. 12, no. 4, pp. 379–382, May 2005, doi: 10.1016/j.jocn.2004.11.004.

[54] **S. A. Grimm and M. C. Chamberlain,**
"Anaplastic astrocytoma," *CNS Oncol*, vol. 5, no. 3, pp. 145–157, Jul. 2016, doi: 10.2217/cns-2016-0002.

[55] **A. Alentorn, K. Hoang-Xuan, and T. Mikkelsen,**
"Presenting signs and symptoms in brain tumors," *Handb Clin Neurol*, vol. 134, pp. 19–26, 2016, doi: 10.1016/B978-0-12-802997-8.00002-5.

[56] **Z. Pfund, L. Szapáry, O. Jászberényi, F. Nagy, and J. Czopf,**
"Headache in intracranial tumors," *Cephalalgia*, vol. 19, no. 9, pp. 787–790, 1999, doi: 10.1046/j.1468-2982.1999.1909787.x.

[57] **A. Vázquez-Barquero, F. Ibáñez, S. Herrera, J. Izquierdo, J. Berciano, and J. Pascual,**
"Isolated headache as the presenting clinical manifestation of intracranial tumors: a prospective study," *Cephalalgia*, vol. 14, no. 4, pp. 270–271, 1994, doi: 10.1046/j.1468-2982.1994.1404270.x.

[58] **T. Reithmeier, A. Kuzeawu, B. Hentschel, M. Loeffler, M. Trippel, and G. Nikkhah,**
"Retrospective analysis of 104 histologically proven adult brainstem gliomas: clinical symptoms, therapeutic approaches and prognostic factors," *BMC Cancer*, vol. 14, no. 1, p. 115, Feb. 2014, doi: 10.1186/1471-2407-14-115.

[59] **E. Butterbrod *et al.*,**
"Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment," *J Neurooncol*, vol. 144, no. 3, pp. 511–518, Sep. 2019, doi: 10.1007/s11060-019-03249-1.

[60] **M. Hamon, O. Coskun, P. Courthéoux, J. Théron, and X. Leclerc,**
"IRM de diffusion du système nerveux central : applications cliniques," *Journal de Radiologie*, vol. 86, no. 4, pp. 369–385, Apr. 2005, doi: 10.1016/S0221-0363(05)81368-X.

[61] **N. Fayed, H. Morales, P. J. Modrego, and M. A. Pina,**
"Contrast/Noise ratio on conventional MRI and choline/creatine ratio on proton MRI spectroscopy accurately discriminate low-grade from high-grade cerebral gliomas," *Acad Radiol*, vol. 13, no. 6, pp. 728–737, Jun. 2006, doi: 10.1016/j.acra.2006.01.047.

[62] **E. Masson,**
"Imagerie multimodale par résonance magnétique des tumeurs cérébrales," *EM-Consulte*. https://www.em-consulte.com/article/651308/imagerie-multimodale-par-resonance-magnetique-des- (accessed Apr. 12, 2023).

[63] **M. Chatel, M. Frenay, C. Lebrun, V. Bourg, and F. Fauchon,**
"Gliomes de haut grade : astrocytomes anaplasiques et glioblastomes," *EMC - Neurologie*, vol. 2, no. 3, pp. 257–278, Aug. 2005, doi: 10.1016/j.emcn.2004.12.002.

[64] **S. Kim *et al.*,**
"11C-methionine PET as a prognostic marker in patients with glioma: comparison with 18F-FDG PET," *Eur J Nucl Med Mol Imaging*, vol. 32, no. 1, pp. 52–59, Jan. 2005, doi: 10.1007/s00259-004-1598-6.

[65] **"Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas - PubMed."**
https://pubmed.ncbi.nlm.nih.gov/9083161/ (accessed Apr. 12, 2023).

[66] **L. Bauchet *et al.*,**
"Assessment and treatment relevance in elderly glioblastoma patients," *Neuro Oncol*, vol. 16, no. 11, pp. 1459–1468, Nov. 2014, doi: 10.1093/neuonc/nou063.

[67] **E. Masson,**
"Tumeurs cranioencéphaliques. Techniques d'imagerie et sémiologie," *EM-Consulte*. https://www.em-consulte.com/article/28379/tumeurs-cranioencephaliques-techniques-d-imagerie- (accessed Apr. 12, 2023).

[68] **F.-X. Roux and F. Nataf,**
"Cerebral oligodendrogliomas in adults and children. Current data and perspectives," *Neurochirurgie*, vol. 51, no. 3–4 Pt 2, pp. 410–414, Sep. 2005.

[69] **Y. Yang *et al.*,**
"Prognostic Nomograms for Primary High-Grade Glioma Patients in Adult: A Retrospective Study Based on the SEER Database," *Biomed Res Int*, vol. 2020, p. 1346340, Jul. 2020, doi: 10.1155/2020/1346340.

[70] **M. Fourtassi, D. Psimaras, F. Ducray, and M. Sanson,**
"Métastases systémiques des gliomes malins," *Bulletin du Cancer*, vol. 95, no. 5, pp. 522–525, May 2008, doi: 10.1684/bdc.2008.0627.

[71] **Y. Sun, Z.-Y. Xiong, P.-F. Yan, L.-L. Jiang, C.-S. Nie, and X. Wang,**
"Characteristics and prognostic factors of age-stratified high-grade intracranial glioma patients: A population-based analysis," *Bosn J Basic Med Sci*, vol. 19, no. 4, pp. 375–383, Nov. 2019, doi: 10.17305/bjbms.2019.4213.

[72] **M. Gupta, S. Bansal, D. S. Pruthi, M. Saini, N. Shirazi, and M. Ahmad,**
"Prognostic Factors in Elderly Patients with High-grade Gliomas: A Retrospective Analysis of 24 Cases," *J Neurosci Rural Pract*, vol. 9, no. 3, pp. 312–316, 2018, doi: 10.4103/jnrp.jnrp_576_17.

[73] **E. R. Laws *et al.*,**
"Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project," *J Neurosurg*, vol. 99, no. 3, pp. 467–473, Sep. 2003, doi: 10.3171/jns.2003.99.3.0467.

[74] **C. Daumas-Duport *et al.*,**
"Oligodendrogliomas. Part II: A new grading system based on morphological and imaging criteria," *J Neurooncol*, vol. 34, no. 1, pp. 61–78, Aug. 1997, doi: 10.1023/a:1005759220434.

[75] **A. Allam, A. Radwi, A. El Weshi, and M. Hassounah,**
"Oligodendroglioma: an analysis of prognostic factors and treatment results," *Am J Clin Oncol*, vol. 23, no. 2, pp. 170–175, Apr. 2000, doi: 10.1097/00000421-200004000-00013.

[76] **J. R. Perry, D. N. Louis, and J. G. Cairncross,**
"Current Treatment of Oligodendrogliomas," *Archives of Neurology*, vol. 56, no. 4, pp. 434–436, Apr. 1999, doi: 10.1001/archneur.56.4.434.

[77] **J. F. de Groot,**
"High-grade gliomas," *Continuum (Minneap Minn)*, vol. 21, no. 2 Neuro-oncology, pp. 332–344, Apr. 2015, doi: 10.1212/01.CON.0000464173.58262.d9.

[78] **M. J. van den Bent *et al.*,**
"MGMT promoter methylation is prognostic but not predictive for outcome to adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors: a report from EORTC Brain Tumor Group Study 26951," *J Clin Oncol*, vol. 27, no. 35, pp. 5881–5886, Dec. 2009, doi: 10.1200/JCO.2009.24.1034.

[79] **S. Turcan *et al.*,**
"IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype," *Nature*, vol. 483, no. 7390, pp. 479–483, Feb. 2012, doi: 10.1038/nature10866.

[80] **C. Hartmann *et al.*,**
"Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas," *Acta Neuropathol*, vol. 118, no. 4, pp. 469–474, Oct. 2009, doi: 10.1007/s00401-009-0561-9.

[81] **T. Revesz, F. Scaravilli, L. Coutinho, H. Cockburn, P. Sacares, and D. G. Thomas,**
"Reliability of histological diagnosis including grading in gliomas biopsied by image-guided stereotactic technique," *Brain*, vol. 116 (Pt 4), pp. 781–793, Aug. 1993, doi: 10.1093/brain/116.4.781.

[82] **M. J. Riemenschneider and G. Reifenberger,**
"Molecular neuropathology of gliomas," *Int J Mol Sci*, vol. 10, no. 1, pp. 184–212, Jan. 2009, doi: 10.3390/ijms10010184.

[83] **M. J. van den Bent and J. E. C. Bromberg,**
"Chapter 31 - Anaplastic oligodendroglial tumors," in *Handbook of Clinical Neurology*, W. Grisold and R. Soffietti, Eds., in Neuro-Oncology Part II, vol. 105. Elsevier, 2012, pp. 467–484. doi: 10.1016/B978-0-444-53502-3.00003-3.

[84] **H. Orliac,**
"Gliomes de haut grade traités par radiothérapie conformationnelle tridimensionnelle versus arcthérapie dynamique : étude prospective bicentrique de la tolérance aiguë, des fonctions neurocognitives et de la qualité de vie = High-grade gliomas treated by three-dimensional conformal radiotherapy versus dynamic arctherapy : a bicentric prospective study of acute tolerance, neurocognitive functions and quality of life," Limoges, 2018. Accessed: Apr. 12, 2023. [Online]. Available: http://aurore.unilim.fr/ori-oai-search/notice/view/unilim-ori-82672

[85] **S. Yip, A. J. Iafrate, and D. N. Louis,**
"Molecular diagnostic testing in malignant gliomas: a practical update on predictive markers," *J Neuropathol Exp Neurol*, vol. 67, no. 1, pp. 1–15, Jan. 2008, doi: 10.1097/nen.0b013e31815f65fb.

[86] **J. G. Cairncross *et al.*,**
"Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas," *J Natl Cancer Inst*, vol. 90, no. 19, pp. 1473–1479, Oct. 1998, doi: 10.1093/jnci/90.19.1473.

[87] **K. H. Vousden and X. Lu,**
"Live or let die: the cell's response to p53," *Nat Rev Cancer*, vol. 2, no. 8, pp. 594–604, Aug. 2002, doi: 10.1038/nrc864.

[88] **S. Shiraishi *et al.*,**
"Influence of p53 mutations on prognosis of patients with glioblastoma," *Cancer*, vol. 95, no. 2, pp. 249–257, 2002, doi: 10.1002/cncr.10677.

[89] **J. Skjoeth and P. K. Bjerre,**
"Effect of glucocorticoids on ICP in patients with a cerebral tumour," *Acta Neurol Scand*, vol. 96, no. 3, pp. 167–170, Sep. 1997, doi: 10.1111/j.1600-0404.1997.tb00261.x.

[90] **J. H. Philippon, S. H. Clemenceau, F. H. Fauchon, and J. F. Foncin,**
"Supratentorial low-grade astrocytomas in adults," *Neurosurgery*, vol. 32, no. 4, pp. 554–559, Apr. 1993, doi: 10.1227/00006123-199304000-00010.

[91] **P. Paquis and P. Menei,**
"Conclusions - Les glioblastomes. Standards, options, recommandations," *Neurochirurgie*, vol. 56, no. 6, pp. 503–507, Dec. 2010, doi: 10.1016/j.neuchi.2010.07.017.

[92] **"Stratégie thérapeutique initiale des accidents vasculaires cérébraux - Urgences-Online."**
https://urgences-serveur.fr/strategie-therapeutique-initiale.html (accessed Apr. 12, 2023).

[93] **K. Hoang-Xuan *et al.*,**
"Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions," *J Clin Oncol*, vol. 22, no. 15, pp. 3133–3138, Aug. 2004, doi: 10.1200/JCO.2004.10.169.

[94] **N. Sanai, Z. Mirzadeh, and M. S. Berger,**
"Functional outcome after language mapping for glioma resection," *N Engl J Med*, vol. 358, no. 1, pp. 18–27, Jan. 2008, doi: 10.1056/NEJMoa067819.

[95] **C. Balaña *et al.*,**
"Clinical course of high-grade glioma patients with a 'biopsy-only' surgical approach: a need for individualised treatment," *Clin Transl Oncol*, vol. 9, no. 12, pp. 797–803, Dec. 2007, doi: 10.1007/s12094-007-0142-0.

[96] **K. S. Firlik, A. J. Martinez, and L. D. Lunsford,**
"Use of cytological preparations for the intraoperative diagnosis of stereotactically obtained brain biopsies: a 19-year experience and survey of neuropathologists," *J Neurosurg*, vol. 91, no. 3, pp. 454–458, Sep. 1999, doi: 10.3171/jns.1999.91.3.0454.

[97] **J. Vaquero, R. Martínez, and M. Manrique,**
"Stereotactic biopsy for brain tumors: is it always necessary?," *Surg Neurol*, vol. 53, no. 5, pp. 432–437; discussion 437–438, May 2000, doi: 10.1016/s0090-3019(00)00213-5.

[98] **A. Pirzkall *et al.*,**
"Metabolic imaging of low-grade gliomas with three-dimensional magnetic resonance spectroscopy," *Int J Radiat Oncol Biol Phys*, vol. 53, no. 5, pp. 1254–1264, Aug. 2002, doi: 10.1016/s0360-3016(02)02869-9.

[99] **H. H. E. and D. G. G.**
"The blood-brain barrier: structure, function, and response to neoplasia," in *The gliomas*,

[100] **P. Menei and P. Metellus,**
"Traitement chirurgical des glioblastomes," *Neurochirurgie*, vol. 56, no. 6, pp. 477–482, Dec. 2010, doi: 10.1016/j.neuchi.2010.07.015.

[101] **P. Menei *et al.*,**
"Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of malignant glioma: a randomized phase II trial," *Neurosurgery*, vol. 56, no. 2, pp. 242–248; discussion 242–248, Feb. 2005, doi: 10.1227/01.neu.0000144982.82068.a2.

[102] **P. J. Kelly,**
"Role of stereotaxis in the management of low-grade intracranial gliomas," in *Gliomas*,

[103] **R. Krishnan *et al.*,**
"Functional magnetic resonance imaging-integrated neuronavigation: correlation between lesion-to-motor cortex distance and outcome," *Neurosurgery*, vol. 55, no. 4, pp. 904–914; discusssion 914–915, Oct. 2004, doi: 10.1227/01.neu.0000137331.35014.5c.

[104] **A. Carpentier, S. Lehericy, H. Duffau, P. Cornu, A. Krainik, and L. Hertz-Pannier,**
"Méthodes modernes d'aide à la chirurgie tumorale." Tumeurs cérébrales. Paris: Éditions Masson, pp. 51–64, 2004.

[105] **C. Giorgi and D. S. Casolino,**
"Preliminary clinical experience with intraoperative stereotactic ultrasound imaging," *Stereotact Funct Neurosurg*, vol. 68, no. 1–4 Pt 1, pp. 54–58, 1997, doi: 10.1159/000099903.

[106] **C. Nimsky, A. Fujita, O. Ganslandt, B. Von Keller, and R. Fahlbusch,**

"Volumetric assessment of glioma removal by intraoperative high-field magnetic resonance imaging," *Neurosurgery*, vol. 55, no. 2, pp. 358–370; discussion 370–371, Aug. 2004, doi: 10.1227/01.neu.0000129694.64671.91.

[107] **H. Duffau *et al.*,**
"Intra-operative direct electrical stimulations of the central nervous system: the Salpêtrière experience with 60 patients," *Acta Neurochir (Wien)*, vol. 141, no. 11, pp. 1157–1167, 1999, doi: 10.1007/s007010050413.

[108] **H. Duffau,**
"Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping," *J Neurol Neurosurg Psychiatry*, vol. 70, no. 4, pp. 506–513, Apr. 2001, doi: 10.1136/jnnp.70.4.506.

[109] **K. Mahmoudi *et al.*,**
"5-aminolevulinic acid photodynamic therapy for the treatment of high-grade gliomas," *J Neurooncol*, vol. 141, no. 3, pp. 595–607, Feb. 2019, doi: 10.1007/s11060-019-03103-4.

[110] **D. S. Bidros, J. K. Liu, and M. A. Vogelbaum,**
"Future of convection-enhanced delivery in the treatment of brain tumors," *Future Oncol*, vol. 6, no. 1, pp. 117–125, Jan. 2010, doi: 10.2217/fon.09.135.

[111] **R. Sawaya,**
"Extent of resection in glioblastoma – Where to draw the line?," *International Journal of Neurooncology*, vol. 1, no. 1, p. 11, Jan. 2018, doi: 10.4103/IJNO.IJNO_9_18.

[112] **F. Mundinger,**
"CT stereotactic biopsy for optimizing the therapy of intracranial processes," *Acta Neurochir Suppl (Wien)*, vol. 35, pp. 70–74, 1985, doi: 10.1007/978-3-7091-8813-2_10.

[113] **M. Ammirati, N. Vick, Y. L. Liao, I. Ciric, and M. Mikhael,**
"Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas," *Neurosurgery*, vol. 21, no. 2, pp. 201–206, Aug. 1987, doi: 10.1227/00006123-198708000-00012.

[114] **I. Ciric, M. Ammirati, N. Vick, and M. Mikhael,**
"Supratentorial gliomas: surgical considerations and immediate postoperative results. Gross total resection versus partial resection," *Neurosurgery*, vol. 21, no. 1, pp. 21–26, Jul. 1987, doi: 10.1227/00006123-198707000-00005.

[115] **B. C. Devaux, J. R. O'Fallon, and P. J. Kelly,**
"Resection, biopsy, and survival in malignant glial neoplasms. A retrospective study of clinical parameters, therapy, and outcome," *J Neurosurg*, vol. 78, no. 5, pp. 767–775, May 1993, doi: 10.3171/jns.1993.78.5.0767.

[116] **S. A. Leibel, C. B. Scott, and J. S. Loeffler,**
"Contemporary approaches to the treatment of malignant gliomas with radiation therapy," *Semin Oncol*, vol. 21, no. 2, pp. 198–219, Apr. 1994.

[117] **E. Masson,**
"Gliomes cérébraux," *EM-Consulte*. https://www.em-consulte.com/article/274358/gliomes-cerebraux (accessed Apr. 12, 2023).

[118] **D. Psimaras and J.-Y. Delattre,**
"[Perspectives in diagnosis and management of malignant gliomas]," *Cancer Radiother*, vol. 12, no. 6–7, pp. 695–700, Nov. 2008, doi: 10.1016/j.canrad.2008.09.006.

[119] **B. Emami *et al.*,**
"Tolerance of normal tissue to therapeutic irradiation," *Int J Radiat Oncol Biol Phys*, vol. 21, no. 1, pp. 109–122, May 1991, doi: 10.1016/0360-3016(91)90171-y.

[120] **D. R. Macdonald, L. E. Gaspar, and J. G. Cairncross,**
"Successful chemotherapy for newly diagnosed aggressive oligodendroglioma," *Ann Neurol*, vol. 27, no. 5, pp. 573–574, May 1990, doi: 10.1002/ana.410270519.

[121] **M. Frenay, C. Lebrun, M. Lonjon, P. Y. Bondiau, and M. Chatel,**
"Up-front chemotherapy with fotemustine (F) / cisplatin (CDDP) / etoposide (VP16) regimen in the treatment of 33 non-removable glioblastomas," *Eur J Cancer*, vol. 36, no. 8, pp. 1026–1031, May 2000, doi: 10.1016/s0959-8049(00)00048-4.

[122] **M. Brada *et al.*,**
"Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse," *Ann Oncol*, vol. 12, no. 2, pp. 259–266, Feb. 2001, doi: 10.1023/a:1008382516636.

[123] **M. J. van den Bent *et al.*,**
"Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972," *Ann Oncol*, vol. 14, no. 4, pp. 599–602, Apr. 2003, doi: 10.1093/annonc/mdg157.

[124] **O. Chinot,**
"Nouvelle place de la chimiothérapie des gliomes," *Bulletin du Cancer*, vol. 92, no. 4, pp. 343–354, Apr. 2005.

[125] **L. Kim *et al.*,**
"Procarbazine, lomustine, and vincristine (PCV) chemotherapy for grade III and grade IV oligoastrocytomas," *J Neurosurg*, vol. 85, no. 4, pp. 602–607, Oct. 1996, doi: 10.3171/jns.1996.85.4.0602.

[126] **"Temozolomide As Initial Treatment for Adults With Low-Grade Oligodendrogliomas or Oligoastrocytomas and Correlation With Chromosome 1p Deletions**
| Journal of Clinical Oncology." https://ascopubs.org/doi/10.1200/JCO.2004.10.169 (accessed Apr. 12, 2023).

[127] **A. C. Tan, D. M. Ashley, G. Y. López, M. Malinzak, H. S. Friedman, and M. Khasraw,**
"Management of glioblastoma: State of the art and future directions," *CA Cancer J Clin*, vol. 70, no. 4, pp. 299–312, Jul. 2020, doi: 10.3322/caac.21613.

[128] **R. Stupp *et al.*,**
"Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial," *JAMA*, vol. 318, no. 23, pp. 2306–2316, Dec. 2017, doi: 10.1001/jama.2017.18718.

[129] **D. B. Altshuler *et al.*,**
"Prospects of biological and synthetic pharmacotherapies for glioblastoma," *Expert Opin Biol Ther*, vol. 20, no. 3, pp. 305–317, Mar. 2020, doi: 10.1080/14712598.2020.1713085.

[130] **M. Weller *et al.*,**
"EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood," *Nat Rev Clin Oncol*, vol. 18, no. 3, Art. no. 3, Mar. 2021, doi: 10.1038/s41571-020-00447-z.

[131] **E. Le Rhun *et al.*,**
"Molecular targeted therapy of glioblastoma," *Cancer Treatment Reviews*, vol. 80, p. 101896, Sep. 2019, doi: 10.1016/j.ctrv.2019.101896.

[132] **O. L. Chinot *et al.*,**
"Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma," *N Engl J Med*, vol. 370, no. 8, pp. 709–722, Feb. 2014, doi: 10.1056/NEJMoa1308345.

[133] **B. Detti *et al.*,**
"Bevacizumab in recurrent high-grade glioma: a single institution retrospective analysis on 92 patients," *Radiol med*, vol. 126, no. 9, pp. 1249–1254, Sep. 2021, doi: 10.1007/s11547-021-01381-5.

[134] **O. L. Chinot *et al.*,**
"AT-17RE-ANALYSIS OF PFS/RESPONSE USING ORIGINAL MACDONALD CRITERIA AND RESPONSE EVALUATION CRITERIA IN SOLID TUMORS IN THE PHASE III AVAGLIO STUDY OF BEVACIZUMAB PLUS RADIOTHERAPY AND TEMOZOLOMIDE IN NEWLY DIAGNOSED GLIOBLASTOMA," *Neuro-Oncology*, vol. 16, no. suppl_5, p. v12, Nov. 2014, doi: 10.1093/neuonc/nou237.17.

[135] **D. P. Kulinich *et al.*,**
"Radiotherapy versus combination radiotherapy-bevacizumab for the treatment of recurrent high-grade glioma: a systematic review," *Acta Neurochir (Wien)*, vol. 163, no. 7, pp. 1921–1934, Jul. 2021, doi: 10.1007/s00701-021-04794-3.

[136] **M. Davis *et al.*,**
"ML309: A potent inhibitor of R132H mutant IDH1 capable of reducing 2-hydroxyglutarate production in U87 MG glioblastoma cells," in *Probe Reports from the NIH Molecular Libraries Program*, Bethesda (MD): National Center for Biotechnology Information (US), 2010. Accessed: Apr. 12, 2023. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK153220/

[137] **V. Mattei *et al.*,**
"The Importance of Tumor Stem Cells in Glioblastoma Resistance to Therapy," *Int J Mol Sci*, vol. 22, no. 8, p. 3863, Apr. 2021, doi: 10.3390/ijms22083863.

[138] **N. A. O. Bush, S. M. Chang, and M. S. Berger,**
"Current and future strategies for treatment of glioma," *Neurosurg Rev*, vol. 40, no. 1, pp. 1–14, Jan. 2017, doi: 10.1007/s10143-016-0709-8.

[139] **G. Frosina,**
"Radiotherapy of High-Grade Gliomas: First Half of 2021 Update with Special Reference to Radiosensitization Studies," *Int J Mol Sci*, vol. 22, no. 16, p. 8942, Aug. 2021, doi: 10.3390/ijms22168942.

[140] **M. R. Gilbert *et al.*,**
"A randomized trial of bevacizumab for newly diagnosed glioblastoma," *N Engl J Med*, vol. 370, no. 8, pp. 699–708, Feb. 2014, doi: 10.1056/NEJMoa1308573.

[141] **D. K. T. Tran and R. L. Jensen,**
"Treatment-related brain tumor imaging changes: So-called 'pseudoprogression' vs. tumor progression: Review and future research opportunities," *Surg Neurol Int*, vol. 4, no. Suppl 3, pp. S129–S135, Apr. 2013, doi: 10.4103/2152-7806.110661.

[142] **K. L. Chaichana *et al.*,**
"Supratentorial glioblastoma multiforme: the role of surgical resection versus biopsy among older patients," *Ann Surg Oncol*, vol. 18, no. 1, pp. 239–245, Jan. 2011, doi: 10.1245/s10434-010-1242-6.

بسم الله الرحمن الرحيم

قسم الطبيب

أقسمُ باللَّهِ العَظيم
أنْ أُراقِبَ اللَّهَ في مِهْنَتي
وأنْ أصُونَ حياةَ الإنْسانِ في كافَّةِ أطْوارِها؛ في كُلِّ الظُّروفِ والأحْوالِ، باذِلاً وُسْعِي في إسْتِنْقاذِها مِنَ الهَلاكِ والمَرَضِ والألَمِ والقَلَقِ.
وأنْ أحْفَظَ للنَّاسِ كَرامَتَهُمْ وأسْتُرَ عَوْرَتَهُمْ وأكْتُمَ سِرَّهُمْ،
وأنْ أكُونَ عَلَى الدَّوامِ مِنْ وَسائِلِ رَحْمَةِ اللَّهِ، باذِلاً رِعايَتِي الصِّحِّيَّةَ لِلقَريبِ والبَعيدِ، للصَّالِحِ والطَّالِحِ، والصَّديقِ والعَدُوِّ
وأنْ أثابِرَ عَلَى طَلَبِ العِلْمِ أسَخِّرُهُ لِنَفْعِ الإنْسانِ لا لأذاهُ
وأنْ أوَقِّرَ مَنْ عَلَّمَنِي، وأعَلِّمَ مَنْ يَصْغُرُنِي، وأكُونَ أخًا لِكُلِّ زَميلٍ في المِهْنَةِ الطِّبِّيَّةِ، مُتَعاوِنِينَ عَلَى البِرِّ والتَّقْوَى
وأنْ تَكُونَ حَياتِي مِصْداقَ إيمانِي في سِرِّي وعَلانِيَتِي نَقِيَّةً مِمَّا يُشِينُها تِجاهَ اللَّهِ ورَسُولِهِ والمُؤمِنِينَ
واللَّهُ عَلَى مَا أقُولُ شَهِيدٌ

كليـــــــة الطب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
جامعة القاضي عياض
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العلاج الإشعاعي للورم الدبقي عالي الدرجة: تجربة قسم العلاج بالأشعة بالمستشفى الجامعي محمد السادس مراكش

الأطروحة

قدمت ونوقشت علانية يوم **2023/04/17**

من طرف

السيد ياسر الطاهري
المزداد في 04 تشغ1997 ببني ملال

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:
الورم الدبقي – الأنكولوجيا – العلاج بالأشعة – التشخيص – العلاج - التتبع

اللجنة

السيد	خ. عنيبة أستاذ في جراحة الدماغ والأعصاب	الرئيس
السيدة	م. خوشاني أستاذة في العلاج بالأشعة	المشرف
السيد	أ. بلبشير أستاذ في علم التشريح المرضي	الحكم