A RETROSPECTIVE ANALYSIS OF EPIDEMIOLOGY AND CLINICAL OUTCOMES OF PATIENTS WITH ADULT GLIOMAS TREATED IN AIN SHAMS CLINICAL ONCOLOGY DEPARTMENT IN THE PERIOD FROM 2017 TILL 2020.

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ABSTRACT:

Background: *Gliomas are the most common malignant brain tumors in adults and comprise a wide array of varying biological aggressiveness. Though the data regarding the epidemiology of gliomas is presented in the literature, but they could vary according to other factors and consequently affecting the outcome.*

Aim of work: *To analyse retrospectively epidemiological and clinical outcomes of adult glioma patients treated in Ain Shams University hospitals (ASU) in Cairo, Egypt in the period from 2017 till 2020.*

Patients and methods: *Convenient sampling of 133 patients with adult brain glioma. The primary objective was to analyze the epidemiological and demographic data and to assess progression free survival (PFS) and overall survival (OS) of the study population. Secondary objectives included correlation between different clinic-pathological factors and outcome.*

Results: *One hundred thirty-three participants were included, with a median age of 53, with a male to female ratio of 1.5. Incidence was more common in urban than rural areas (71.9 vs 28.1). Glioblastoma represented sixty percent of the cases, followed by grade II (22.7) then grade III (17.3%). The most common presenting symptom was focal deficits, followed by symptoms of increased intracranial tension. Percentage of patients who underwent maximum safe resection (MSR) was 19%, and 41.4% underwent subtotal excision. Almost eighty six percent of the patients received radiotherapy, while two-thirds of the patients received chemotherapy. PFS was significantly higher in patients offered MSR. OS was significantly higher with Grade II, MSR and better performance. Temporal lobe tumors have the best median OS.*

Conclusion: *Progression free survival was significantly higher with initial MSR. Overall survival was significantly better with Grade II, MSR, better performance as well as temporal lobe tumors. Older age was significantly correlated with higher grade of gliomas.*

Keywords: *Glioma, epidemiology, risk factors.*

INTRODUCTION:

The term Glioma refers to tumors that have histologic features similar to normal glial cells (astrocytes and oligodendrocytes)[1].

The classification of glioma has developed over time. A new WHO classification was issued in mid-2021. The fifth WHO classification included changes in nomenclature; the use of the term “type” and “subtype” instead of “entity” and “variant” respectively and the use of the Arabic

numbers instead of the Roman numbers. Moreover, the change of the grading to grading within the type instead of a grade assigned to each entity[2].

Most primary CNS tumors have no identifiable risk factors other than some rare genetic disorders and ionizing radiation.

Surgery is the initial step in management of all suspected diffuse gliomas. The goal is to reach maximal safe resection. As in other diffuse gliomas, gross total resection is associated with improved outcomes but is not always possible based on the location or extent of the tumor. However, surgery is not curative, and radiotherapy and chemotherapy are ultimately required in all patients[3].

Though the data regarding the epidemiology of gliomas is presented in the literature, but they could vary according to other factors and consequently affecting the outcome.

AIM OF THE WORK:

We aimed at analysing retrospectively epidemiological and clinical outcomes of adult glioma patients treated in our center.

MATERIAL AND METHODS:

Data sources:

We obtained approval of Ain shams university research ethics committee to use the medical records collected in the clinical oncology department in the period from 2017 till 2020.

Study design:

We performed a retrospective cohort study, according to the guidelines of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statements) checklist[4].

Study population:

diagnosed between 2017 and 2020. We included all brain and spinal cord glioma patients who were diagnosed on the basis of histopathology or MRS. We also included only adult patients aged more than 18 years.

We obtained information on the following variables in included patients: age at diagnosis, sex, date of presentation, date of diagnosis, age at diagnosis, tumor site, tumor size, pathology and grade of each tumor type as defined by WHO classification for CNS tumors second edition, date of surgery, type of surgery, type of adjuvant treatment, radiotherapy data including start date, total dose, fractionation received and modality of radiotherapy. We also included chemotherapy data including type of chemotherapy received, its aim, start data and duration.

Data for a second treatment modality and steroid dependency,defined as: the failure to withdraw the corticosteroids after initiating it as part of those patient treatment as relapse of the increased intra-cranial tension symptoms occur were also included[5].

Outcomes:

Our main objective was to plot the descriptive epidemiological, clinical and personal data in the form of tables that included the mean, standard deviation and minimum and maximum values. Additionally, to calculate clinical outcomes including overall survival and progression free survival.

Secondary objectives included the following: assessing the survival outcomes in the study group to study the relationship between different variables on OS and PFS.

Ethical considerations:

The study was commenced after obtaining the approval of Ain Shams University research ethics committee,

Faculty of Medicine Ain Shams University. Obtained on 21st of February 2021.

Data confidentiality was maintained.

Statistical analysis: The following statistical methods were used: Description of continuous variables: mean and standard deviation or median and interquartile range, description of categorical variables: number and percentage, test for normal distribution of continuous variables: Shapiro-Wilk test, test the relationship between two categorical variables: Chi-squared test or Fisher's exact test. Survival analysis: Kaplan-Meier method and Comparison of survival curves: Logrank test, A p-value <0.5 was considered significant and Statistical analysis was done using MedCalc® Statistical Software version 20.009 (MedCalc Software Ltd, Ostend, Belgium; 2021.

RESULTS:

Patients' characteristics: A total of 133 patients with adult gliomas (more than 18 years) were reviewed. The median age at diagnosis was 53 years, ranging from 19 to 78 years**.** The incidence of glioma was more common in males that females; 60.3% and 39.7% respectively**.** The incidence of glioma was more in urban areas than rural areas**.** We have collected the Eastern Cooperative Oncology Group performance status (ECOG P.S) at presentation. Half of the patients presented had an ECOG P.S of 1**.**

Diagram 1 elucidates the distribution of gliomas in the study population. When analyzed according to the histological type, they were ordered as follows: 56.9% of the cases were glioblastoma, 15.6% of the cases were anaplastic astrocytoma, 14.7% were diffuse astrocytoma and 2% were oligodendroglioma. The study population only included 2 cases with spinal gliomas scoring the least in the terms of incidence.

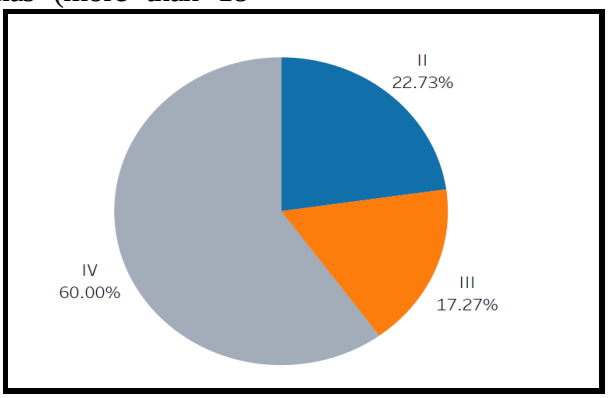

Diagram (1): Distribution of different grades of gliomas among the study population.

Regarding the initial diagnosis of glioma, most patients (86%) were diagnosed via a brain MRI with contrast, whereas only a few (14%) were diagnosed via an MRS.

Concerning the histopathological diagnosis, 85% of the study population obtained a tissue biopsy for confirmation. Histopathological diagnosis included: diagnosis after surgery that proceeded to maximal safe resection or subtotal excision, excision biopsy, stereotactic biopsy and open biopsy.

As for the surgical procedure, 19% only performed a maximal safe resection, while 41.4% did not proceed to completion surgery and 34.7% had a subtotal excision.

Adjuvant treatment varied among different types of gliomas. However, most patients received radiotherapy as a part of their treatment (85.9%) with 62.5% of the radiotherapy receivers group received it in the adjuvant setting, whereas 36.6% of the radiotherapy receivers group received radiotherapy without performing surgery;

either solely or in combination with Temozolomide as a radio-sensitizer. Most of the study population received conventional fractionation with only 15.7% receiving radiotherapy with hypofractionation technique.

The reported median duration of radiotherapy course is 6 weeks with a maximum of 12 weeks and a minimum of 2 weeks. During the COVID 19 pandemic, 2 patients received their course of radiotherapy in 12 weeks rather than 6 weeks as they have contracted COVID 19.

Correlation between different variables:

We used Chi-square test and found a significant correlation between the grade of glioma and age, using 50 years as a cutoff (P < 0.0001). Table 1 shows the correlation between age and glioma grade.

Table (1): Correlation between age and grade using 50 years of age as a cutoff.

	Grade			
Age = 50y	**II**	**III**	**IV**	
No	20 37.7% RT 80.0% CT 18.3% GT	15 28.3% RT 78.9% CT 13.8% GT	18 34.0% RT 27.7% CT 16.5% GT	53 (48.6%)
Yes	5 8.9% RT 20.0% CT 4.6% GT	4 7.1% RT 21.1% CT 3.7% GT	47 83.9% RT 72.3% CT 43.1% GT	56 (51.4%)
	25 (22.9%)	19 (17.4%)	65 (59.6%)	109
Chi-squared			28.246	
Significance level			P < 0.0001	

Progression free survival after the first line treatment statistics:

The results showed that the median PFS after first line modality is 7 months.

A significant association was proven between the type of surgery performed (maximal safe resection versus subtotal excision versus none) and the PFS after 1st line modality. Maximal safe resection had better median PFS followed by subtotal excision followed by no surgery: 13 months (95% CI 8-19 months), 7 months (95% CI 4-12 months), and 4 months (95% CI 3-7 months) (P value= 0.0049), respectively. This highlights the importance of the extent of tumour resection in survival (Diagram 2).

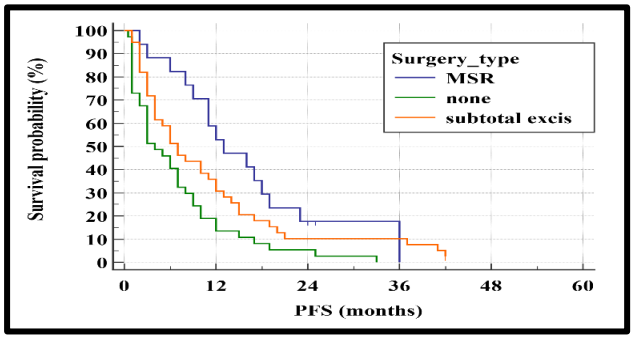

Diagram (2): Correlation between type of surgery and PFS after 1st line modality

Overall survival statistics:

In our study, the median overall survival for all gliomas was 8.83 months. Log rank Test was used to correlate the median overall survival with different variables. It showed a statistically significant correlation

between grade of glioma and OS (P value= 0.008). Grade II gliomas had a median overall survival of 17.2 months, grade III gliomas had a median overall survival of 16 months, while the median overall survival for grade IV was 8.15 months **(Diagram 3).**

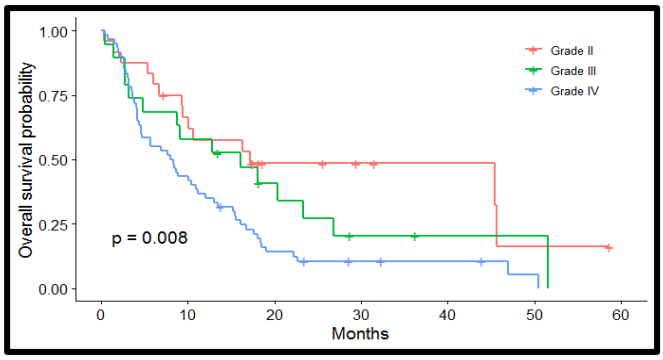

Diagram (3): Correlation between grade and median overall survival probability.

Type of surgery was also correlated with the median OS. It yielded statistically significant results, where the median OS for maximal safe resection, subtotal excision and no surgery was 18.5, 9.5 and 4.6 month respectively (P value= 0.003) (Diagram 4)

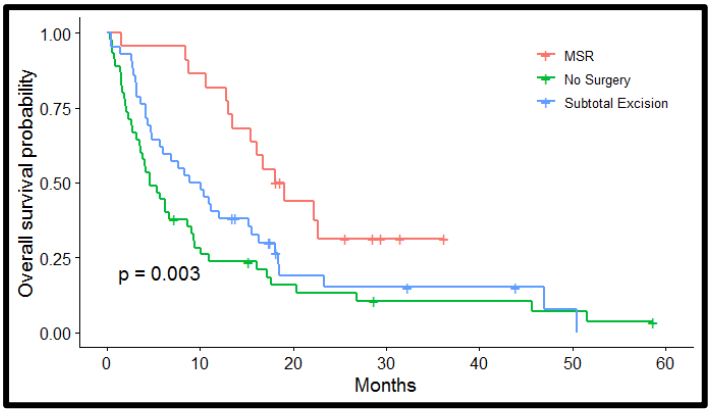

Diagram (4): Correlation between type of surgery and median overall survival.

ECOG P.S at presentation was also correlated with the OS. A statistically significant correlation was proven (P value= 0.014). The median OS for patients presented with ECOG P.S=1 was 15 months, while the median OS for patients presented with ECOG P.S=2, 3, 4 was 6.8, 6.3, 4 months respectively (Diagram 5).

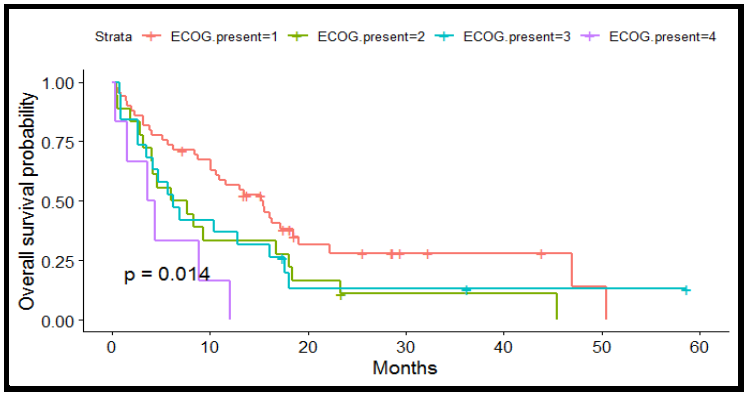

Diagram (5): Correlation between ECOG P.S and median OS.

The site of the tumor when it involved one lobe was correlated with median OS. It showed highly statistically significant results (P value< 0.0001). The median OS for temporal lobe tumors was 16.7 months, while the median OS for frontal lobe tumors was 9.3 months, and the median OS for parietal lobe tumors was 6.4 months (Diagram 6).

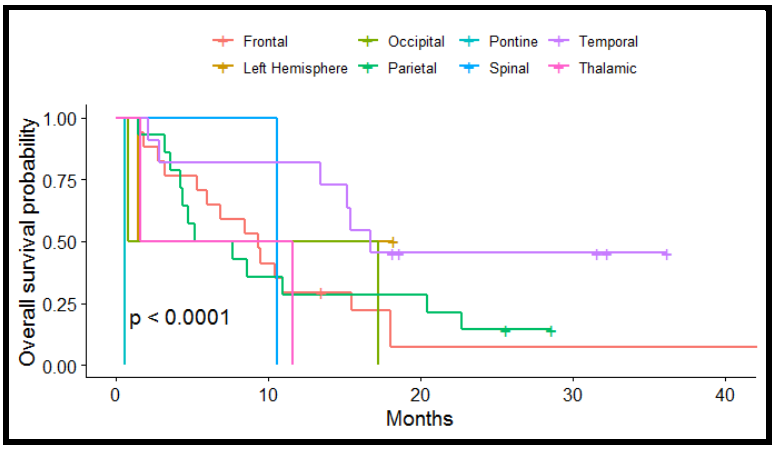

Diagram (6): Correlation between ECOG P.S and median OS

The pathology type was correlated with the median OS survival. The results were statistically significant (P value= 0.0013).

Sixty two patients who were diagnosed by surgery had a median OS of 15.4 months. The number of patients who underwent open biopsy was 16 patients and had a median OS of 16 months. Sixteen patients underwent stereotactic biopsy and had a median OS of 4.96 months. Fourteen patients did not undergo biopsy and had a median OS of 4.6 months**.**

Correlation between median OS and steroid dependence was not significant. Moreover, correlation between symptoms at presentation and steroid dependence was not significant as well.

DISCUSSION:

To our Knowledge, this is the most updated analysis of glioma patients treated in Ain Shams University hospitals. We have included 133 patients that attended Ain Shams University hospitals in the period from 2017 till 2020. In Egypt -according to Globocan 2020- Brain and nervous system tumors are the eighth most commonly diagnosed cancer with 4499 new cases in 2020. While, they are ranked the seventh in term of mortality with 3686 deaths in 2020

In our study, we found that the incidence of gliomas involved almost all age groups, with a median age of diagnosis of fifty years. The male to female ratio was 1.5. We have shown that the incidence of gliomas was two and half folds more common in urban than in rural areas.

In concordance with our findings, a Tunisian study found that the male to female ratio was 1.5 [6]**.**

Another two studies performed in Iran found that incidence of central nervous system tumors was more common in males than female, the male to female ratio was 1.48 in one study and 1.2 in another [7;8]**.**

Regarding the Western populations, in glial brain tumors the male to female ratio ranged from 1.3 for astrocytomas and 1.4 for oligodendrogliomas[9]**.** Another study found that the male to female ratio was 1.3[10] **.**

Concerning the age of incidence of gliomas in our population, the median age estimated at diagnosis was 53 years, whereas in the United states it was 59 years [9]. However, it was younger in Tunisian population which had a median age of

incidence of 49 years and even younger in the Iranian population that studied all central nervous system tumors and found the age of incidence to be 34 years.

Our data showed that 60% of the cases were Grade IV, followed by grade II then by grade III. When they were analyzed according to the histological group, Glioblastoma was the most common subtype followed by astrocytoma then oligodendrogliomas. These findings are similar to the findings of a study based on the American population [10] and another in the English population [11]**.** Similar trends were observed in the new brain and central nervous system tumor statistics [12]**.**

We have also correlated the age of incidence with the development of different grades of gliomas, using the cutoff value of 50 years. The results showed a strong association between glioblastoma and older age (> 50 years) and grade II and III gliomas and younger age (≤ 50 years).

This results were in consistence with a Tunisian study that used 40 years of age as a cutoff and they included the pediatric population as well [6]**.** Miller et al have also shown that glioblastoma and astrocytoma occur in older population, while oligodendroglioma occurs in a relatively younger population aged 40-64 years [12]**.**

Unfortunately, we found that maximum safe resection was not the most common surgical procedure performed in our study, though it is the preferred one. This could be attributed to tumors that were located in eloquent areas especially in cases of glioblastoma and anaplastic astrocytoma and hence were deemed inoperable or due to cases of grade II glioma who did not perform surgery.

In our study, the adjuvant treatment after surgery for glioblastoma was chemo-radiation with Temozolomide followed by adjuvant 6 cycles of Temozolomide. In the cases of grade II tumors the adjuvant treatment consisted of either keeping the patient on follow up or adjuvant radiotherapy. However in grade III most patients were treated as glioblastoma but some received adjuvant radiotherapy followed by 6 cycles of Temozolomide.

The results showed that the median PFS for different grades of glioma after first line modality is 7 months. A significant correlation was shown between the type of surgery and a longer PFS after 1st line modality. MSR scoring highest median PFS at 13 months, followed by subtotal excision at 7 months and lastly the median PFS for no surgery was 4 months.

In agreement with the findings, two large meta-analyses that associated the type of surgery for either low grade or high grade glioma and better PFS [13;14]**.**

The median OS survival of all gliomas was 8.83 months. A significant correlation was proven between grade and median OS. Median survival from grade II and III was 17.2 months and 16 months respectively, however the survival of grade IV was much worse with median OS equals 8.15 months.

This median OS for cases of glioblastoma was also lower than reported median OS when compared with other studies: European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) study showed that GBM patients who received concurrent chemo-radiation had a median OS of 14.6 months. Another study that was assessing the median OS survival in MGMT methylated versus non methylated glioblastoma showed better survival in MGMT methylated group receiving radiotherapy and Temozolomide equals 21.7 months v.s 12.7 months in the MGMT non-methylated group [15;16]**.**

This could be attributed to the unknown status of MGMT promotor methylation. Moreover, owing to the retrospective nature of the study and molecular facilities for

diagnosis that were not available at the time these data were obtained, some of grade III gliomas could actually be cases of GBM but were subjected to misdiagnosis. Another explanation is that the majority of GBM patients are elderly who are in need of special and extra care from their families and continuous follow up with geriatric oncology subspecialty; issues that could be deficient for many cases. Multifocality of the tumor could represent additional contributing factor in our study population.

In agreement with the findings of two large meta-analyses that associated the type of surgery for either low grade or high grade glioma and better OS [13;14], the extent of surgery played a substantial role in survival in our study. The median OS survival months in patients who underwent MSR was almost double that of patients who underwent subtotal excision and 4 times those who did not perform surgery at all.

The correlation between OS and pathology type in the a former study by *Tsitlakidis and colleagues* [17], showed that patients diagnosed by surgery has a substantially better survival than patients who underwent biopsy only (15.4 v.s 5.8 months for excisional biopsy) highlighting the importance of gross total resection in survival.

Temporal lobe tumors had better survival than frontal lobe and parietal lobe tumors. This is contradicting the results of a study that showed that frontal lobe tumors had better survival than temporal lobe tumors [18], but agreeing with another study on GBM (constituting the majority of our study population where temporal, occipital, or parietal primary tumor sites are suggestive of positive survival outcomes [19]. It is worth to mention that the authors found also the race to be a factor significantly affecting OS. Improved survival with temporal lobe tumors seems logical as the symptoms associated with this are (visual, auditory and verbal disturbances) makes the patient seek medical advice earlier so diagnosed in earlier stage.

Limitations:

One of the most prominent limitations is the retrospective nature of collection of data through hospital records. This has the potential for incomplete data collection due to missing data in the records. Also, lack of standardization of laboratory and imaging investigations due to variability of laboratory and personal evaluation.

Secondly, this is a single center study and it might be argued that the results couldn't be generalized to the entire local population. However, our hospital is a major tertiary care center treating patients from all over the country; we can speculate our results are representative of our population.

Conclusion:

Epidemiological and clinical outcomes data on glioma are rather deficient, especially in the developing countries. We have also elucidated several risk factors incorporated in the development of glioma and multiple prognostic factors for their survival. PFS after first line modality of treatment for gliomas was significantly higher with MSR. OS for gliomas was significantly better with Grade II, MSR, better performance and temporal lobe tumors. Older age was significantly correlated with higher grade of gliomas.

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النتائج السريرية لمرضى الأورام الدبقية لدى البالغين الذين تم علاجهم في قسم الأورام في عين شمس في الفترة من 2017 حتى2020

هدير هشام محمد ، غادة رفعت مكاوي ، أحمد سعيد إبراهيم ، مى عز الدين ، لبنى راشد عز العرب
قسم علاج الأورام والطب النووي-
كلية الطب - جامعة عين شمس

المقدمة :الأورام الدبقية هي أكثر أورام الدماغ الخبيثة شيوعًا لدى البالغين وتتألف من مجموعة واسعة من الاورام المختلفة فى عدائيتها .على الرغم من أن البيانات المتعلقة بوبائيات الأورام الدبقية معروضة في بحوث علمية سابقة ، إلا أنها قد تختلف وفقًا لعوامل أخرى وبالتالي تؤثر على النتيجة.

هدف العمل :تحليل النتائج الوبائية والسريرية بأثر رجعي لمرضى الورم الدبقي البالغين الذين تم علاجهم في مستشفيات جامعة عين شمس) ASU (في القاهرة ، مصر في الفترة من 2017 حتى. 2020

المرضى والطرق :أخذت العينات من 133 مريضًا يعانون من ورم دبقي في المخ لدى البالغين .كان الهدف الأساسي هو تحليل البيانات الوبائية والديموغرافية وتقييم البقاء على قيد الحياة بدون تقدم للمرض) PFS (والبقاء على قيد الحياة) OS (للمشتركين بالرسالة .تضمنت الأهداف الثانوية الارتباط بين مختلف العوامل المرضية والنتائج.

النتائج :تم تضمين مائة وثلاثة وثلاثين مشاركًا ، بمتوسط عمر 53 عامًا ، ونسبة ذكر إلى أنثى . 1.5 كانت الإصابة أكثر شيوعًا في المناطق الحضرية منها في المناطق الريفية 71.9 (مقابل .) 28.1 يمثل الورم الأرومي الدبقي 60 ٪ من الحالات ، يليه الدرجة الثانية) 22.7 (ثم الدرجة الثالثة 17.3 (٪ .)كان أكثر أعراض التقديم شيوعًا هو العجز البؤري ، تليها أعراض زيادة الضغط داخل الجمجمة .كانت النسبة المئوية للمرضى الذين خضعوا لأقصى استئصال آمن 19 (MSR) ٪ ، وخضع 41.4 ٪ للاستئصال جزئى .تلقى ما يقرب من ستة وثمانين في المائة من المرضى العلاج الإشعاعي ، بينما تلقى ثلثا المرضى العلاج الكيميائي .كان PFS أعلى بشكل ملحوظ في المرضى الذين قاموا بعمل . MSR كان البقاء على قسد الحياة أعلى بشكل ملحوظ مع Grade II و MSR والأداء الأفضل. أورام الفص الصدغي لديها نسبة متوسط البقاء على قيد الحياة.

الاستنتاج :كان PFS بعد طريقة الخط الأول لعلاج الأورام الدبقية أعلى بشكل ملحوظ مع . MSR كان متوسط البقاء على قيد الحياة للأورام الدبقية أفضل بشكل ملحوظ مع الدرجة الثانية ، MSR ، أداء أفضل وأورام الفص الصدغي .كان التقدم في العمر مرتبطا بارتفاع درجة الأورام الدبقية.

الكلمات المفتاحية :الورم الدبقي ، علم الأوبئة ، عوامل الخطر