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# Nuclear Factor-Kappa B in Gliomas as a Predictive Factor for Tumor Recurrence – A Clinicopathological Study

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## Abstract

**BACKGROUND:** Glioma is the most common primary malignant brain tumor. Nuclear factor κB (NF-κB) has emerged as a regulator of the malignant phenotype in glioma, and in particular glioblastoma multiforme, with clear relation to tumor size, recurrence, and invasiveness.

**AIM:** The aim of the study was to study the analysis of NF-κB expression in gliomas of different histologic types and grades and its correlation with various clinicopathologic indicators.

**METHODS:** One hundred and ten paraffin blocks of glioma cases classified according to WHO classification into 14 (12.7%) cases of Grade I pilocytic astrocytoma, 27 (24.5%) cases of Grade II gliomas, 26 (23.6%) cases of Grade III gliomas, and 43 (39.1%) cases of Grade IV glioblastoma. The correlations between immunostainings and clinicopathological parameters were analyzed statistically.

**RESULTS:** Positive immunostaining for NF-κB was encountered in (64/110) 58.2% of gliomas. Statistical analysis revealed significant association between positive NF-κB expression and high histological grade ($p < 0.001$), recurrence of the tumors ($p = 0.001$), large tumor size (≥5 cm) ($p < 0.001$), histological subtypes (glioblastoma represented 51.6% of NF-κB positive cases, while pilocytic astrocytoma represented 1.6% of NF-κB positive cases) ($p < 0.001$) and age of the patient (≥40) ($p = 0.039$).

**CONCLUSIONS:** A strong direct relation between NF-κB expression and the grade of glioma was observed. NF-κB expression behaves as a negative independent prognostic factor for the risk of tumor recurrence. Hence, inhibition of NF-κB may be a new therapeutic strategy to prevent recurrence of gliomas, particularly the high-grade type.

## Introduction

The transcription factor NF-κB is highly expressed in almost all types of cells. NF-κB is involved in many complex biological processes, particularly those related to immunity. The activation of the NF-κB signaling pathway also proved to be in relation to many diseases as cancer, diabetes, neurological disorders, and even memory diseases. Under healthy physiological conditions, the NF-κB pathway promotes the growth of synapse and synaptic plasticity in neurons, while it can promote inflammatory responses to injury in glia. In addition, NF-κB promotes the maintenance and maturation of B cells regulating gene expression in a majority of diverse signaling pathways. Based on this, the NF-κB plays a major role in activating the mammalian immune system [1].

### *Targets of NF-kB in glioma*

NF-kB targets cell cycle regulatory genes, antiapoptotic genes, cell adhesion proteins, and inflammatory cytokines that regulate tumor growth and metastatic ability. The major NF-kB targets include the cell cycle regulatory protein cyclin D1, the anti-apoptotic protein XIAP1, and inflammatory proteins such as Interleukin-8 (IL)-6, IL-8, matrix metallopeptidase-9 (MMP)-9, MMP-13, and cyclooxygenase 2 (Cox2). The regulation of signal transduction pathways that cause proliferation, release of inflammatory cytokines, and expression of metalloproteinases in the tumor microenvironment by NF-kB activation promotes tumor growth. It is also important to note that there is an extensive crosstalk between NF-kB and oncogenic and tumor suppressor signaling pathways, including those active in glioblastoma multiforme (GBM) [2].

### *NF-kB and angiogenesis*

New blood vessel formation is critical for the maintenance of any growing tumor and vascular proliferation is a critical point to diagnose GBM histologically. Neovascularization in GBM is essentially driven by vascular endothelial growth factor (VEGF). Not only is VEGF an NF-kB target gene, but it is also induced by NF-kB-regulated factors such as IL-6. Another NF-kB target gene that promotes angiogenesis is IL8. While IL-8 levels are low in normal tissue, in GBM, the IL-8 level is high. This finding is related to loss of tumor suppression by tumor suppressor inhibitor of growth family member 4, and to the

presence of macrophages and microglia within the GBM microenvironment. These findings highlight that NF-kB is essential for angiogenesis in GBM and that it promotes this malignant feature [3].

### *NF-kB activation plays a role in the pathogenesis of GBM and in resistance to treatment*

NF-kB activation has been widely proved to be related to cancer and resistance to treatment. NF-kB activation may be the cause of resistance of glioblastoma cells to alkylating agents. Various studies involving glioma-derived cell lines and mouse models also clearly suggest a pathogenic role for NF-kB in the regulation of gliomagenesis. Studies of TNFa induced NF-kB in six glioma cell lines confirmed the presence of a p50/p65 heterodimer that controls cell cycle progression. NF-kB may affect proliferation and invasiveness of glioma cells in culture and in the maintenance of glioblastoma initiating stem-like cells [2].

### *Mesenchymal differentiation mediated by NF-κB promotes radiation resistance in glioblastoma*

NF-κB promotes mesenchymal differentiation in glioblastoma cells through stimulation of transcription factors. By correlating between MES composite metagene and progression following radiotherapy, they were considered as non-responders. A significant association between the expression of Phosphorylated p65, a transcriptionally active form of NF-κB, and the non-responders were detected compared to those with a good response to radiation. Patients with a MES signature belong to the group with poor prognosis and are resistant to standard lines of treatments and hence, they have high recurrence rate [4].

## Material and Methods

The material of this study consisted of 110 cases of glioma, collected as formalin fixed paraffin embedded tissue blocks. These were collected from archives of Pathology Department, Kasr AL-Ainy faculty of medicine, Cairo University in the period from January 2017 to December 2019.

The clinical data were obtained from the pathology reports of the patients. These data included age at time of diagnosis, sex, site, tumor size, and history of recurrence.

Each paraffin block was recut by rotatory microtome at 5 microns thickness then mounted on glass slides to be stained by hematoxylin and eosin for routine histopathological examination and on charged slides for immunostaining.

### *Histopathological findings included*

The cases were graded as I, II, III, and IV according to the WHO classification and the histological subtype was determined [5].

### *Immunohistochemical Staining for NFKB p65*

Immunostaining was done using BenchMark XT (Ventana) autostainer with the following steps:

- Deparaffinization by using the EZ-prep solution
- Cell conditioning (standard cell conditioning CC1) for 80 min
- Antigen retrieval using reaction buffer (PH 6.0).

The sections then were incubated with the primary antibody for 1 h at room temperature. The primary antibody was rabbit polyclonal antibody, NF-κB, p65 subunit, targets the N-terminus of RELA. Catalog No. abx033005, 80u obtained from Abbexa Ltd, Cambridge, UK. Application of diaminobenzidine (DAB) as a chromogen. (NexES iView DAB Detection Kit).Counterstaining with Hematoxylin II for 8 min. Post-counter staining with bluing reagent for 4 min. Slides were cleared in Xylene and then cover slips were applied.

A section of colonic adenocarcinoma was used as positive control according to the manufacturer recommendations (Figure 1).

### *Assessment of NFKB immunostaining*

Expression NFKB was identified as cytoplasmic staining in tumor cells. The immunohistochemical reactions were analyzed according to the pattern of staining [2]:

1. Tumor cell showing diffuse cytoplasmic ± scattered nuclear staining were considered positive
2. Tumor cell showing absent or weak staining for p65 as in normal brain was considered negative (Figure 1).

### *Statistical analysis*

Microsoft Excel 2019 was used for data entry and data were analyzed using win Statistical Package for the Social Science (SPSS), version 17 (SPSS Inc., Chicago, IL).

The bivariate relationship was displayed in cross-tabulations and comparison of proportions was performed using the Chi-square test. The significance of the results was assessed by determining the probability factor “p” value using the Chi-square test. Furthermore in some situations, other statistical tests were used, Pearson correlation, Mann–Whitney test (non-parametric t-test) for independent samples, and Kruskal–Wallis

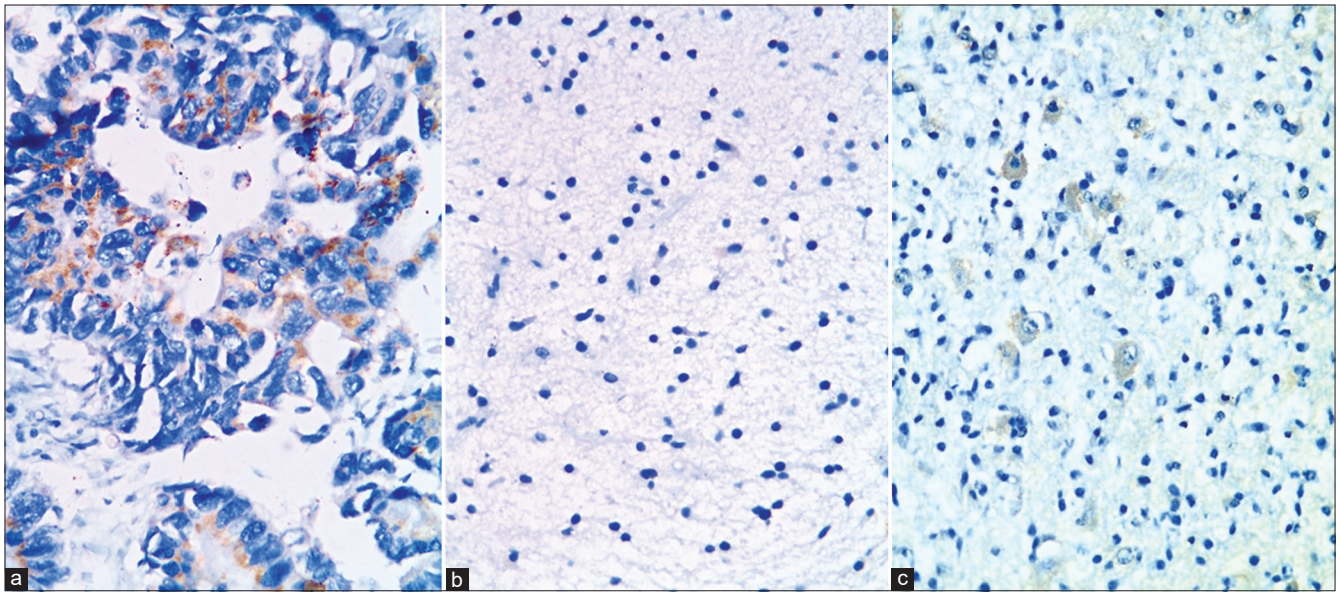


*Figure 1: Photomicrographs showing (a) positive control: colonic adenocarcinoma; positive cytoplasmic immunostaining for NFKB (Immunoperoxidase, DAB ×400 original magnification). (b) Diffuse astrocytoma (G II); negative for NFKB (Immunoperoxidase, DAB ×400 original magnification). (c) Anaplastic astrocytoma (G III); focal positive NFKB cytoplasmic immunoreaction (Immunoperoxidase, DAB × 400 original magnification)*

test (non-parametric ANOVA). $p < 0.05$ is considered statistically significant.

Data were statistically described in terms of mean ± standard deviation or frequencies (number of cases) and percentages when appropriate. Confidence interval for the mean and the mean differences was also calculated to assess sample size and significance.

### *Capturing of microscopic photos*

Microscopic photos were captured using a digital camera attached to an Olympus microscope model BX 51.

## Results

This study included 110 patients with mean age of 38.923 ± 16.0050 years; range 0.5–70. Fifty-nine (53.6%) were younger than 40 years old and 51 (46.4%) were 40 years old and older. Sixty-three (57.3%) cases were males and 47 (42.7%) were females. According to the patients' records, only 18 (16.4%) cases had history of recurrence. In addition, the patients' records showed that 59 (53.6%) cases had small gliomas (<5 cm) and 51 (46.4%) had large gliomas (>5 cm). Most of the studied cases (95 cases, 86.4%) were in the cerebral cortex.

Histological tumor diagnosis was performed according to the WHO criteria [5]. Fourteen patients had Grade I glioma (pilocytic astrocytoma). Twenty-six patients had Grade II (diffuse) glioma including 16 diffuse astrocytoma and 10 oligodendroglioma. Twenty-seven patients had Grade III (anaplastic) glioma including 23 anaplastic astrocytoma and four anaplastic oligodendroglioma. Forty-three patients had Grade IV gliomas including 40 glioblastoma and three gliosarcomas (Table 1).

**Table 1: Grouping of cases according to the histological grade**

| Grade | Number of cases | Percentage |
|---|---|---|
| Grade I | 14 | 12.7 |
| Grade II | 27 | 24.5 |
| Grade III | 26 | 23.6 |
| Grade IV | 43 | 39.1 |
| Total | 110 | 100 |

Grade IV shows the highest frequency compared to the other grades.

### *NF-κB expression*

NF-κB immunohistochemical expression was encountered in the neoplastic cells of 64/110 (58.2%) cases. Among the positive gliomas, Grade IV glioblastomas represented 51.6% of the cases.

### *According to the NF-κB expression in relation to the different grades of glioma*

Among Grade I cases, 13 (92.8%) cases were negative (Figure 1), and 1 (7.2%) case was positive. In Grade II cases, 16 (61.5%) cases were negative, and 10 (38.5%) cases were positive. In Grade III, 20 (74%) cases showed positive cytoplasmic expression and 7 (26%) cases were negative. Thirty-three (76.7%) Grade IV cases showed positive cytoplasmic expression of NF-κB

(Figure 2), while the remaining 10 (23.3%) cases were negative (Table 2).

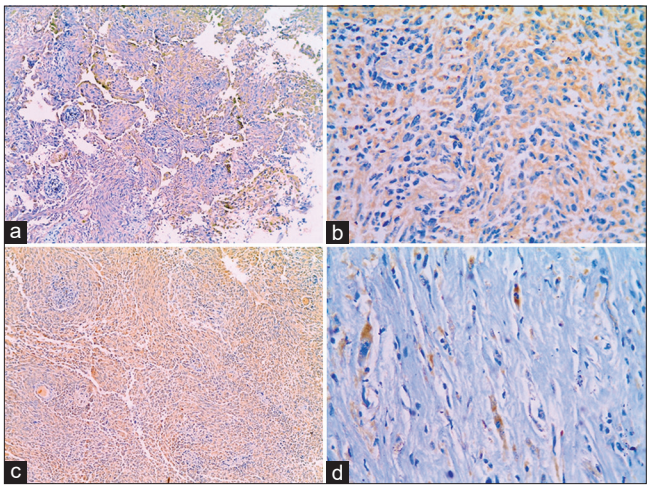


*Figure 2: Photomicrographs showing (a) glioblastoma (G IV); positive cytoplasmic NFKB immunoreaction (Immunoperoxidase, DAB ×100 original magnification). (b) Glioblastoma higher power (×200 original magnification). (c) Gliosarcoma (G IV); positive cytoplasmic NFKB immunoreaction (Immunoperoxidase, DAB ×100 original magnification). (d) Gliosarcoma higher power (400 original magnification)*

### *With reference to the histological subtype*

All (100%) cases of gliosarcoma as well as anaplastic oligodendroglioma showed positive cytoplasmic expression of NF-κB (Figure 2), followed by the rest of glioblastomas (75%) and anaplastic astrocytoma (69.6%) subtypes.

**Table 2: NF-κB expression in relation to different grades of gliomas in the studied cases**

| NF-κB expression grade | Positive (%) | Negative (%) | Total (%) |
|---|---|---|---|
| Grade I | 1 (1.6) | 13 (28.3) | 14 (12.7) |
| Grade II | 10 (15.6) | 16 (34.8) | 26 (23.6) |
| Grade III | 20 (31.2) | 7 (15.2) | 27 (24.5) |
| Grade IV | 33 (51.6) | 10 (21.7) | 43 (39.1) |
| Total | 64 (100) | 46 (100) | 110 (100) |

(p<0.001).

On the other hand, almost all cases of pilocytic astrocytoma 13/14 (92.8%) showed negative NF-κB expression; Table 3.

**Table 3: NF-κB expression in different histologic subtypes of gliomas in the studied cases**

| Histological type | NF-κB expression | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Pilocytic astrocytoma | 1 | 13 | 14 |
| | 1.6% | 28.3% | 12.7% |
| Diffuse astrocytoma | 8 | 8 | 16 |
| | 12.5% | 17.4% | 14.6% |
| Anaplastic astrocytoma | 16 | 7 | 23 |
| | 25.0% | 15.2% | 20.9% |
| Glioblastoma | 30 | 10 | 40 |
| | 46.9% | 21.7% | 36.4% |
| Oligodendroglioma | 2 | 8 | 10 |
| | 3.1% | 17.4% | 9.1% |
| Anaplastic oligodendroglioma | 4 | 0 | 4 |
| | 6.3% | 0.0% | 3.6% |
| Gliosarcoma | 3 | 0 | 3 |
| | 4.6% | 0.0% | 2.7% |
| Total | 64 | 46 | 110 |
| | 100.0% | 100.0% | 100.0% |

(p < 0.001).

### *With reference to the histological subtype according to pattern of growth and behavior*

Diffuse astrocytic tumors including Grade (II, III, and IV) showed positive NF-κB expression in 57/82 (69.5%) of the cases, whereas the studied localized pilocytic astrocytomas showed negative NF-κB expression in 13/14 (92.8%) of cases; Table 4.

**Table 4: NF-κB expression in localized and diffuse subtypes of gliomas in the studied cases**

| Histological type | NF-κB expression | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Localized (pilocytic) | 1 | 13 | 14 |
| | 1.6% | 28.3% | 12.7% |
| Diffuse astrocytic type (Grade II and III) | 24 | 15 | 39 |
| | 37.5% | 32.6% | 35.5% |
| Diffuse oligodendroglioma (Grade II and III) | 6 | 8 | 14 |
| | 9.4% | 17.4% | 12.7% |
| Glioblastoma | 33 | 10 | 43 |
| | 51.6% | 21.7% | 39.1% |
| Total | 64 | 46 | 110 |
| | 100.0% | 100.0% | 100.0% |

(p < 0.001).

Most of the studied Grade III and Grade IV cases showed positive NF-κB expression in comparison with Grade I and Grade II. These results are statistically significant.

All cases of gliosarcoma and anaplastic oligodendroglioma showed positive NF-κB expression followed by glioblastoma and anaplastic astrocytoma subtypes. On the other hand, most of pilocytic astrocytoma cases showed negative NF-κB expression, statistically significant.

Diffuse astrocytic tumors including both Grade II and III astrocytomas together with Grade IV glioblastomas represent nearly 90% of NF-κB positive cases: Showing a statistically significant relation.

### *Association of NF-κB expression with different clinicopathological criteria*

#### *Recurrence*

It was found that most of the recurrent cases (94.4%) showed positive NF-κB expression, whereas the other cases presented with primary lesion showed positive NF-κB expression in 51% of the cases, showing a significant relationship between positive NF-κB expression and recurrence in glioma (p = 0.001); Tables 5 and 6.

**Table 5: NF-κB expression in recurrent and non-recurrent cases of gliomas**

| Recurrence | NF-κB expression | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Recurrent | 17 | 1 | 18 |
| | 26.6% | 2.2% | 16.4% |
| No recurrence | 47 | 45 | 92 |
| | 73.4% | 97.8% | 83.6% |
| Total | 64 | 46 | 110 |
| | 100.0% | 100.0% | 100.0% |

(p = 0.001).

**Table 6: Correlation between NF-κB expression and tumor recurrence using the odds ratio**

| NF-κB expression | Odds ratio | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower | Upper |
| Odds ratio for recurrence (Yes/No) | 16.277 | 2.079 | 127.425 |

*Tumor size*

Positive NF-κB expression by the tumor cells was detected in 39/51 (76.5%) of large glioma cases (>5 cm in largest dimension), whereas small gliomas (<5 cm) showed negative NF-κB expression in 57.6% of the case and positive NF-κB expression in 42.4% of the cases. Reaching the conclusion that NF-κB expression is significantly related to the tumor size $p < 0.001$; Tables 7 and 8.

**Table 7: NF-κB expression in glioma cases in relation to tumor size (largest dimension)**

| Tumor size | NF-κB expression | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Small (<5 cm) | 25 | 34 | 59 |
| | 39.1% | 73.9% | 53.6% |
| Large (>5 cm) | 39 | 12 | 51 |
| | 60.9% | 26.1% | 46.4% |
| Total | 64 | 46 | 110 |
| | 100.0% | 100.0% | 100.0% |

($p < 0.001$).

**Table 8: Correlation between NF-κB expression and tumor size using the odds ratio**

| NF-κB expression | Odds ratio | 95% confidence interval | |
|---|---|---|---|
| | | Lower | Upper |
| Odds ratio for tumor size (Equal or more than 5/<5) | 4.420 | 1.932 | 10.114 |

*Site*

Six cases (67%) of deeply seated gliomas showed positive NF-κB expression followed by cortical gliomas showing positive NF-κB expression in 61% of the cases, whereas all cerebellar gliomas showed negative NF-κB expression showing a significant relationship between positive NF-κB expression and cerebral gliomas ($p = 0.011$); Table 9.

**Table 9: NF-κB expression in glioma cases in relation to tumor location**

| Tumor location | NF-κB expression | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Cortical | 58 | 37 | 95 |
| | 90.6% | 80.4% | 86.4% |
| Cerebellar | 0 | 6 | 6 |
| | 0.0% | 13.0% | 5.5% |
| Deep | 6 | 3 | 9 |
| | 9.4% | 6.5% | 8.2% |
| Total | 64 | 46 | 110 |
| | 100.0% | 100.0% | 100.0% |

($p = 0.011$).

Most of the recurrent cases showed positive NF-κB expression.

Both (Tables 5 and 6) show that positive NF-κB expression in recurrent cases of glioma is higher than that in primary (non-recurrent) cases. This relationship is statistically significant.

Positive NF-κB expression is higher in glioma cases with large tumor size (>5 cm). These results are statistically significant.

Both (Tables 6 and 7) show significant relation between positive NF-κB expression and large sized tumors.

All cerebellar gliomas showed negative NF-κB expression whereas, all the NF-κB positive cases were located within the cerebral hemispheres. These results are statistically significant.

## Discussion

Gliomas represent about 81% of malignant primary brain tumors. Although they are considered rare, they cause significant mortality and morbidity. The most common gliomas histology is glioblastoma, which makes up around 45% of all gliomas. This type has a 5-year relative survival rate of about 5% [6].

The classification of gliomas was significantly reorganized in the 2016 WHO update, with great respect to Grade II–IV gliomas (astrocytoma, oligodendroglioma, glioblastoma), referred to as infiltrating gliomas to differentiate them from well-circumscribed WHO Grade I brain tumors as pilocytic astrocytoma [7].

Activation of NF-κB affects various faces of cancer biology including cell survival and treatment resistance. Considerable evidence suggests a role for NF-κB in the pathogenesis of GBM and its resistance to treatment, pointing to that NF-κB pathways might be useful treatment targets [2].

As regard the age of the presented cases in the study, patients' age ranged between (6 months and 70 years) with the mean age of 38.923 ± 16 years. In this study, the number of male patients exceeded the number of female patients, 63 and 47, respectively, with male to female ratio of 1.34:1.

These results were close to the results of Barakat *et al*., study which included 434 patients with pathologically proven HGGs presented to the Department of Clinical Oncology and Nuclear Medicine, faculty of medicine, Alexandria University between 2003 and 2012, the age of patients ranged between (21 and 83) years with the mean age of 50 years. The same study included 261 male patients and 17 female patients, with male to female ratio of 1.5:1. Another study conducted by Touati *et al*., included 333 patients, the mean age was 48.07 years, and men were 1.87 times more frequent than women. This is also close to surveillance, epidemiology, and end result program, where 44.8% of glioma cases were reported in middle-aged patient group (40–62 years) and male-to-female ratios of approximately 1.3:1 was observed in all histology subgroups [7], [8], [9].

The male gender predominance was also reported by central brain tumor Registry of the United States 2018 which stated that the incidence was higher in males for most glial tumors. Different from the present study, Rasmussen *et al*., study included 1930 patients with overall male to female ratio was 3:2; however, the mean age at onset was 60 years [10].

Histological tumor diagnosis and grading were performed according to the WHO criteria [4]. Fourteen patients (12.7%) had Grade I glioma. Twenty-six patients (24.5%) had Grade II (diffuse) glioma. Twenty-seven patients (23.6%) had Grade III (anaplastic) glioma. Forty-three patients (39.1%) had Grade IV gliomas. Highest frequency of Grade IV gliomas is compatible with studies of Rasmussen *et al*., 2017) who examined 1930 patients registered in the danish neuro-oncology registry from 2009 to 2014, and included 1364 (71%) Grade IV Glioblastoma cases, meanwhile Grade II and Grade III cases presented in the same study were 247 (12.8%) and 279 (14.5%) cases, respectively, with 40 (2.1%) Grade I cases, as well as the studies of Touati *et al*., who examined the 333 biopsies of gliomas and included 183 (55%) Grade IV cases, meanwhile Grade II and Grade III cases presented in the same study were 65 (19.5%) and 72 (21.6%) cases, respectively, with 13 (4%) Grade I cases [8], [10].

Based on histopathologic aspect with no further molecular testing, gliomas in this study were classified as following: Diffuse astrocytic and oligodendroglial tumors included 16 diffuse astrocytoma WHO Grade II (14.5%), 23 anaplastic astrocytoma WHO Grade III (20.9%), 40 glioblastoma WHO Grade VI (36.4%); representing the most common type, three gliosarcoma WHO Grade VI (2.7%), 10 oligodendroglioma WHO Grade II (9.1%), and four anaplastic oligodendroglioma WHO Grade III (3.6%). Other astrocytic tumors included 14 pilocytic astrocytoma WHO Grade I representing (12.7%) of cases.

In agreement with the present study, Hewedi *et al*., study included 996 cases of primary CNS neoplasms, gliomas represented (35%) of all tumors included in this study, classified as diffuse astrocytoma WHO Grade II (16.9%), anaplastic astrocytoma WHO Grade III (8%), glioblastoma WHO Grade VI (44.1%); representing the most common type, gliosarcoma WHO Grade VI (0.9%), oligodendroglioma WHO Grade II (1.4%), anaplastic oligodendroglioma WHO Grade III (0.6%), oligoastrocytoma WHO Grade II (3.2%), and pilocytic astrocytoma WHO Grade I representing (11.2%) of cases. Furthermore, Natukka *et al*., (2019) reported that 2284 out of 4730 glioma patients were glioblastomas (48.3%), followed by diffuse astrocytoma (12.1%) and anaplastic astrocytoma (10.2%), meanwhile oligodendroglioma and anaplastic oligodendroglioma cases represented (4.5%) and (2.9%) respectively. Keeping with the same findings, both Touati *et al*., and Barakat *et al*., reported glioblastoma cases predominance representing (55%) and (80.2%) of their total cases, respectively [7], [8], [10], [11].

From the 110 studied cases, 18 (16.4%) cases had history of tumor recurrence. These results were close to the results displayed by Silvaggi *et al*., which included 16 (13.9%) cases having history of recurrence out of 115 living Grade II and Grade III glioma cases. Higher recurrence rate was reported by Kurdi *et al*., (2021) as 225 (54.5%) out of 663 glioma cases had history of recurrence stating that the most recurrent tumors were classical glioblastoma (63.5%), followed by glioblastoma with primitive neuronal components and gliosarcoma. The recurrence rate was close to 0% in cases of pilocytic/pilomyxoid astrocytoma [12], [13].

The studied cases were classified according to the tumor size into small gliomas (<5 cm) and large gliomas (>5 cm) as it has been previously described that tumor size of gliomas/glioblastomas >5 cm is a relevant prognostic factor affecting patient overall survival rate.

Fifty-one cases (46.4%) were large gliomas (>5 cm in largest dimension) while 59 (53.6%) were small gliomas (<5 cm), showing that large gliomas are less common than small gliomas. Alimohammadi *et al*., (2020) classified glioblastomas according to size into 45 (29.4%) 5 cm and above and 108 (70.6%) <5 cm, showing that large glioblastomas (>5 cm) are less common than smaller ones. Different from the present study Wang *et al*., classified gliomas according to size into 116 (62.4%) >5 cm and 70 (37.6%) <5 cm, showing that large gliomas (≥5 cm) are more common, making the surgical recession very challenging even under microscopy, resulting in complications and high recurrence. However, Yang *et al*., used another cutoff point selected by the X-tile program for optimal cutoff points of tumor size. The results were 27 mm and 44 mm and classified gliomas into 855 (13.4%) <26 mm, 2144 (33.5%) 27–44 mm and 3396 (53.1%) >44 mm, reaching the same conclusion that large gliomas >44 mm are more common than smaller ones [14], [15], [16].

Regarding tumor location, 95 (86.4%) of the studied cases of gliomas were in the cerebral cortex (frontal, parietal, temporal, and occipital), 6 (5.5%) were located within the cerebellum, and 9 (8.2%) were deep (fourth ventricle, corpus callosum, thalamus, and insular).

Keeping with the current results, Rasmussen *et al*. recorded that gliomas were primarily localized in the frontotemporal region (65%) and only 26 (1%) were in the cerebellum. In correlation between the histological type and tumor location, Kurdi *et al*., (2021) reported that the frontoparietal area was the most predominant location for glioblastoma (70–87%), oligodendroglioma was predominantly observed in the frontal lobe (21/34 cases: 61.8%) and pilocytic astrocytoma (83.3%. n = 60) was mainly found in the posterior fossa. Furthermore, in a study conducted by Hewedi *et al*., (96.6%) of gliomas were in the brain, and only (3.4%) in the spinal cord [10], [13], [17].

## Conclusion

There is a strong relation between NF-κB expression and the grade of gliomas and it is directly

proportional to the histological grade of glioma. Therefore, it may be used as a prognostic marker.

NF-κB expression behaves as a negative independent prognostic factor for the risk of tumor recurrence.

The differential expressions of NF-κB according to the histological subtypes appear to be involved in biologic behavior and clinical outcome of the diversity of glioma subtypes.

Mesenchymal differentiation in glioblastoma is strongly related to NF-κB expression.

NF-κB can be an attractive therapeutic target to prevent post-operative recurrence and resistance to radiotherapy, particularly those of high grade.

Pharmacological inhibition of NF-κB may be of therapeutic benefit by inhibiting the tumor growth and proliferation in recurrent, large size, or inoperable gliomas.

### *Suggested further studies*

The role of NF-κB is an independent predictor of both overall survival and malignant progression-free survival in both low- and high-grade glioma patients.

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