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# Correlation of IDH1, p53 and Ki-67 immunoexpression levels with morphological, clinical prognostic parameters and preoperative/postoperative radiological findings and response to treatment in high-grade glial tumor cases

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**Abstract**

In this study, we aimed to investigate the prognostic factors affecting survival in adult patients with high-grade glial tumors. The retrospective study included 79 consecutive patients who were referred to our clinic for adjuvant radiotherapy/radiochemotherapy between 2010 and 2017. The effect of proposed prognostic factors on overall survival (OS) and disease-free survival (DFS) was evaluated with univariate and multivariate analyses. Median age was 56.63 (range, 24-84) years and the median Karnofsky Performance Status (KPS) at diagnosis was 89% (range, 50-100%). Most the cases (n=69; 87.1%)were histologically diagnosed as World Health Organization (WHO) grade IV. At a median follow-up of 12 months, OS and DFS were 12 and 8 months, respectively. Although age, KPS, IDH1, p53 and Ki-67 status were found to be statistically significant among the prognostic factors affecting OS in univariate analyses, only KPS, p53 and Ki-67 were statistically significant in multivariate analysis.In contrast, age, KPS, IDH1, and Ki-67 were found to be significant factors for DFS in univariate analysis, while only KPS and Ki-67 were found to be significant factors for DFS in multivariate analysis. KPS was the most important prognostic factor for OS and DFS. In the evaluation of postoperative histopathological findings, p53 and Ki-67 were found to be prognostic for OS while only Ki-67 was prognostic for DFS. However, IDH1, which is known as an important prognostic factor, did not have a significant prognostic value, which could be due to the limited number of cases in our study.

**Keywords:** High-grade glial tumor, Karnofsky Performance Status, IDH1, p53, Ki-67

## Introduction

High-grade glial tumors (World Health Organization [WHO] grades III and IV) account for about half of primary brain tumors in adults. Although they can be seen at any age, they are one of the most common malignant tumors in late adults. Of these, glioblastoma (GBM), [WHO Grade IV]) constitutes 15-25% of primary central nervous system (CNS) tumors and 50-60% of adult high-grade glial tumors [1–3]. Despite advancements in the surgical and adjuvant treatment techniques used in the treatment of high-grade glial tumors, the median survival time has been reported to be less than 15 months in most cases [2,4]. Longer survival periods (three and five years) have been reported in 3-5% and 0.5% of GBM cases, respectively, and factors including age, Karnofsky Performance Status (KPS) at diagnosis, tumor size and localization, extent of necrosis in the tumor, and the width of surgical excision have been identified as important prognostic factors [5]. Similarly, Curren et al. reviewed three Radiation Therapy Oncology Group (RTOG) studies that evaluated a total of 1578 cases and found that age is the most important factor affecting survival, and KPS≥70 was the second most important prognostic factor in cases under 50 years of age [6].

Over the past 30 years, many molecules have been used in prognostic grading of various astrocytic tumors. Among these, p53 has emerged as an important molecular marker in

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glial tumors [3]. P53 is a tumor suppressor gene that plays an important role in promoting tumor cell apoptosis and is increased in many cancer types including GBM. However, the relationship between p53 immunoreactivity and the survival rates of cases of glial tumors remains controversial. This notion has been attributed to the fact that the extent of p53 expression in GBM could be associated with the methods used in the studies [2,3]. Ki-67, another immunohistochemical marker, is routinely used in clinical trials as a reliable indicator of cancer cell proliferation activity, mostly indicating a poor prognosis in cases with glial tumors [7]. In some studies, increased Ki-67 levels have been seen in high grades of these tumors and have been shown to be associated with poor prognosis, and cases with increased Ki-67 values have been reported to have shorter overall survival (OS) and disease-free survival (DFS) times [3,7,8]. Recently, various molecular markers have been shown to be associated with improved survival in some adult cases of glial tumors. Of note, isocitrate dehydrogenase (IDH) 1/2 mutations have been identified in approximately 80% of diffuse and anaplastic astrocytomas as in secondary GBMs. It has also been reported that IDH mutant tumors have distinctive genetic and clinical features and that cases with such mutations have a better prognosis than cases with IDH-wild-type [8–10].

Until 2016, CNS tumors were classified according to their tissue/cellular characteristics and glial tumors were classified into four grades (I, II, III, and IV). In the 2016 report on the reclassification of CNS tumors published by WHO [11], it was emphasized that investigating the genetic infrastructure causing high-grade glial tumor biology based on the molecular changes causing cancer cell formation as well as mutations specific to tumor type, molecular parameters, and chromosomal anomalies in the classification is of paramount importance for determining tumor types, prognosis, and sensitivity to treatment.

The aim of this study was to investigate the prognostic factors affecting survival in adult patients with high-grade glial tumors (WHO III and IV).

## Material and Methods

The retrospective study included 79 consecutive patients who were referred to Manisa State Hospital Radiation Oncology Clinic for adjuvant radiotherapy/radiochemotherapy and were diagnosed with high-grade glial tumor (WHO III and IV) in the Medical Pathology Laboratory of Manisa State Hospital and Manisa Celal Bayar University Hospital between October 2010 and December 2017.

Following surgical resection, all the patients were treated with standard radiotherapy (60 Gy/3D conformal or intensity-modulated radiation therapy [IMRT]) or radiochemotherapy (60 Gy/3D conformal or IMRT + concurrent oral temozolomide 75mg/m2/day), followed by maintenance adjuvant temozolomide chemotherapy (200 mg/m$^2$/day, 5 days/every 28 days). Prior to data collection and analysis, an ethics approval was obtained from Manisa Celal Bayar University Scientific Research Ethics Committee (Date: 07.02.2018; No: 20478486-050.04.04) and Manisa Provincial Secretariat of General Public Hospitals Union - Education Department (Date: 11.10.2018; No: 76379986-604.02). Demographic and clinical characteristics including age, gender, KPS at diagnosis, surgical resection type, tumor locationand size, pathological subtype/grade, immunohistochemical scores, adjuvant radiotherapy/radiochemotherapy and maintenance systemic therapy, time to relapse or progression, treatment of recurrence, and final status of the patients were retrieved from patient files and the hospital database.

### Inclusion criteria for the study

Patients aged 18 years or older who were histologically diagnosed with high-grade glial tumors (WHO III and IV) and had a KPS ≥50 at the time of first surgical resection were included in the study.

Computed tomography (CT) and magnetic resonance imaging (MRI) examinations were performed both preoperatively and every three months postoperatively, and the images were evaluated by an experienced radiologist in terms of tumor size and location and presence of necrosis. In all patients, preoperative MRI images were compared with the images obtained within 48 hours after surgery in terms of the presence of volumetric residue. The extent of surgical resection was divided into three categories based on the surgeon's intraoperative observations and postoperative radiological images: (i) biopsy (<10% resection), (ii) subtotal resection (10-90% resection), and (iii) gross total resection (greater than 90% resection).

The hematoxylin-eosin, p53 (clone DO7), and Ki-67 (Clone MIB-1) stained histological sections of all cases were retrieved from the archive and re-evaluated. Three to five micron thick sections were obtained from the formalin-fixed paraffin-embedded (FFPE) tissue specimens and were automatically stained on a LeicaBondMax immunohistochemistry device using IDH1 (Clone R132H) antibody. The percentage and intensity of p53 staining was assessed based on a total manual count of 1000 cells, with 200 cells in five fields with different staining intensities, and was categorized as negative (<50% staining) and positive (≥50% staining). The percentage of Ki-67 staining was calculated based on a total manual count of nuclear-stained 1000 cells in the area with the highest staining intensity. Presence of strong granular and cytoplasmic staining in IDH1-stained sections was accepted as positive staining. Adjuvant and maintenance treatments and post-treatment follow-ups of all patients were performed in our clinic.

### Statistical analysis

Data were analyzed using SPSS for Windows version 23.0 (Armonk, NY: IBM Corp.). Descriptives were presented as mean, standard deviation (SD), median, and minimum and maximum values for continuous variables and as frequencies (n) and percentages (%) for categorical variables. Normal distribution of data was assessed using visual (histograms) and analytical methods (KolmogorovSmirnov and ShapiroWilk tests). The P53 and Ki-67 cut-off values were calculated using Received Operator Characteristic (ROC) curve analysis. The cut-off values of Ki-67 and p53 were on ROC analysis were 15.5

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and 50, respectively. Curves of OS and DFS were obtained using Kaplan-Meier Analysis. The effects of variables on patients' survival time were analyzed using univariate and multivariate Cox regression analyses. A p value of <0.05 was considered significant.

Patients were divided as (i) aged below 45 and (ii) above 45 years, as (i) KPS<70 and (ii) KPS≥70, as (i) <50 mm and (ii) ≥50 mm according to tumor size, as (i) gross total resection and (ii) others (biopsy and subtotal resection), as (i) Ki-67<15.5 and (ii) Ki-67≥15.5, as (i) p53<50 and (ii) p53 ≥50, and as patients with side effects of (i) chemotherapy and (ii) radiochemotherapy. Groups were compared with regard to OS and DFS. OS was defined from the date of surgical resection to the date of death and DFS was defined from the date of the first craniotomy to the time of diagnosis of imaging-based progression or to the time of tumor-related death. Survival time curves were compared using the logrank test. The effect of proposed prognostic factors on survival was evaluated with univariate and multivariate analyses.

## Results

The 79 patients comprised 45 (57%) men and 34 (43%) women with a mean age of 56.63±1.58 (range, 24-84) years. Of these, 16 (20.3%) were aged below 45 years and 63 (79.7%) were aged 45 years or older. KPS at diagnosis was ≥70 and in the majority of the cases (n=62; 78.5%) and headache was the most common presenting symptom (31.6%). Among the locations of primary tumors, frontal and parietal lobes were the most common locations, which had equal rates (20.3%). Mean tumor size was 49.43±14.204 (range, 15-78) mm, also the primary tumor size was >50 mm in 46 (58.2%) and ≥50 mm in 33 (41.8%) cases. Gross total resection was the most common surgical resection type (n=52; 65.8%), followed by subtotal resection or biopsy only (n=27; 34.2%). According to histological examination performed after surgery, most the cases (n=69; 87.1%) were diagnosed as WHO grade IV. During the study, IDH1 was evaluated in 45 (57%), p53 in 61 (77%), and Ki-67 in 65 (82%) cases due to the insufficient material in the immunohistochemical examination (Table 1).

Median follow-up was 12 months and OS and DFS times were 12 (Confidence Interval [CI]: 8.54-15.46) and 8 (CI: 0-40.659) months, respectively. Age, KPS, IDH1, p53, and Ki-67 were found to be significant prognostic factors for OS in univariate analyses, whereas only KPS, p53, and Ki-67 were found to be significant prognostic factors for OS in multivariate analyses (Table 2).

Mean OS time was 16 months in patients with KPS ≥70 (CI: 13.2-18.7) as opposed to 6 months in patients with KPS <70 (CI: 5.12-6.8, p=0.001), 12 months in patients with p53<50 (CI: 8.57-15.46) as opposed to 18 months in patients with p53 ≥50 (CI: 0-40.65, p=0.049), and 17 months in patients with Ki-67 <15.5 (CI: 9.16-24.84) as opposed to 11 months in patients with Ki-67 ≥15.5 (CI: 8.12-13.87, p=0.021) (Figure 1).

In terms of DFS, factors including age, KPS at diagnosis, IDH1, and Ki-67 were found to be significant prognostic factors in univariate analysis, while only KPS and Ki-67 were found to be significant prognostic factors for DFS in multivariate analysis (Table 3). The median DFS time was 9 months in patients with KPS≥70 (CI 7.24-10.76) as opposed to 4 months in patients with KPS<70 (CI 3.26-4.72, p=0.005) and it was 13 months in patients with Ki-67<15.5 (CI 9.1-16.88) as opposed to 7 months in patients with a Ki-67 ≥15.5 (CI 5.8-8.1, p=0.002) (Figure 2).

**Table 1.** Demographic, clinical and pathological characteristics

| Parameter | | | n (%) |
|---|---|---|---|
| Gender | Female | | 34 (43%) |
| | Male | | 57 (57%) |
| Age (years) | <45 | | 16 (20.3%) |
| | ≥45 | | 63 (79.7%) |
| KPS | <70 | | 17 (21.5%) |
| | ≥70 | | 62 (78.5%) |
| Presenting symptom | Headache | | 25 (31.6%) |
| | Epilepsy | | 18 (22.8%) |
| | Hemiparesis/hemiplegia | | 14 (17.7%) |
| | Speech disorder | | 12 (15.2%) |
| | Nausea – vomiting | | 6 (7.6%) |
| | Facial paralysis | | 4 (5.1%) |
| Tumor location | Frontal | | 16 (20.3%) |
| | Parietal | | 16 (20.3%) |
| | Temporal | | 15 (19%) |
| | Temporoparietal | | 10 (12.7%) |
| | Parieto-occipital | | 9 (11.4%) |
| | Frontotemporal | | 7 (8.9%) |
| | Occipital | | 3 (3.8%) |
| | Corpus Callosum | | 3 (3.8%) |
| Resection type | Gross total resection | | 52 (65.8%) |
| | Subtotal resectionorbiopsy | | 27 (34.2%) |
| Tumor size | <50 mm | | 46 (58.2%) |
| | ≥50 mm | | 33 (41.8%) |
| Histological grading | WHO III | | 7 (8.9%) |
| | WHO IV | | 69 (87.3%) |
| | Not evaluated | | 3 (3.8%) |
| IDH1 | Positive | | 6 (7.6%) |
| | Negative | | 39 (49.4%) |
| | Not evaluated | | 34 (43%) |
| Ki-67 | <15.5 | | 16 (20.3%) |
| | ≥15.5 | | 49 (62%) |
| | Not evaluated | | 14 (17.7%) |
| P53 | <50 | | 50 (63.3%) |
| | ≥50 | | 11 (13.9%) |
| | Not evaluated | | 18 (22.8%) |
| Treatment side effects | Radiochemotherapy | Yes | 8 (10.1%) |
| | | No | 71 (89.9%) |
| | Adjuvant Temozolomide | Yes | 18 (22.8%) |
| | | No | 61 (77.2%) |

KPS: Karnofsky Performance Status, IDH1: Isocitrate dehydrogenase 1

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**Table 2.** Effects of factors on overall survival

| | Univariate analysis (HR, 95% CI) | p | Multivariate analysis (HR, 95% CI) | p |
|---|---|---|---|---|
| **Gender** | 1.02 (0.63-1.65) | 0.97 | 1.68 (0.73-3.86) | 0.2 |
| **Age (years)** | 2.29 (1.19-4.42) | 0.013 | 0.64 (0.14-2.93) | 0.57 |
| **KPS** | 3.5 (1.9-6.4) | 0.001 | 7.2 (2.1-24.47) | 0.001 |
| **Resection type** | 1.5 (0.9-2.6) | 0.69 | 1.5 (0.58-3.88) | 0.38 |
| **Tumor size** | 1.7 (1.05-2.81) | 0.31 | 2.6 (1.04-6.49) | 0.4 |
| **Histological grading** | 1.48 (0.86-2.46) | 0.16 | 1.28 (0.2-8.04) | 0.81 |
| **IDH1** | 4.02 (0.95-16.8) | 0.045 | 0.64 (0.12-3.2) | 0.59 |
| **P53** | 1.6 (0.9-4.15) | 0.049 | 2.2 (0.6-7.9) | 0.049 |
| **Ki-67** | 2.2 (1.12-4.5) | 0.021 | 3.6 (1.19-18.37) | 0.027 |
| **Concurrent chemotherapy side effects** | 0.9 (0.42-2.06) | 0.86 | 1.28 (0.2-8.04) | 0.79 |
| **Adjuvant temozolomideside effects** | 0.89 (0.51-1.57) | 0.7 | 1.25 (0.32-4.81) | 0.73 |

KPS: Karnofsky Performance Status, IDH1: Isocitrate dehydrogenase 1

**Table 3. Effects of factors on disease-free survival**

| | Univariate analysis (HR, 95% CI) | p | Multivariate analysis (HR, 95% CI) | p |
|---|---|---|---|---|
| **Gender** | 1.10 (0.74-1.93) | 0.46 | 1.46 (0.79-2.74) | 0.22 |
| **Age (years)** | 2.15 (1.12-4.13) | 0.021 | 1.97 (0.39-9.8) | 0.4 |
| **KPS** | 2.34 (1.3-4.2) | 0.005 | 3.08 (1.19-7.95) | 0.02 |
| **Resection type** | 1.34 (0.81-2.22) | 0.24 | 1.8 (0.86-3.78) | 0.12 |
| **Tumor size** | 1.35 (0.83-2.19) | 0.22 | 2.19 (1.06-4.5) | 0.33 |
| **Histological grading** | 3.215 (1.005-10279) | 0.049 | 1.88 (0.37-9.56) | 0.44 |
| **IDH1** | 4.56 (1.08-19.199 | 0.038 | 1.73 (0.35-8.53) | 0.5 |
| **P53** | 1.08 (0.5-2.17) | 0.81 | 2.07 (0.6-5.8) | 0.198 |
| **Ki-67** | 2.92 (1.45-5.88) | 0.002 | 6.13 (1.45-25.87) | 0.013 |
| **Concurrent chemotherapy side effects** | 1.19 (0.54-2.6) | 0.66 | 1.17 (0.49-2.79) | 0.7 |
| **Adjuvant temozolomideside effects** | 1.08 | 0.7 | 1.55 (0.41-5.83) | 0.5 |

KPS: Karnofsky Performance Status, IDH1: Isocitrate dehydrogenase 1

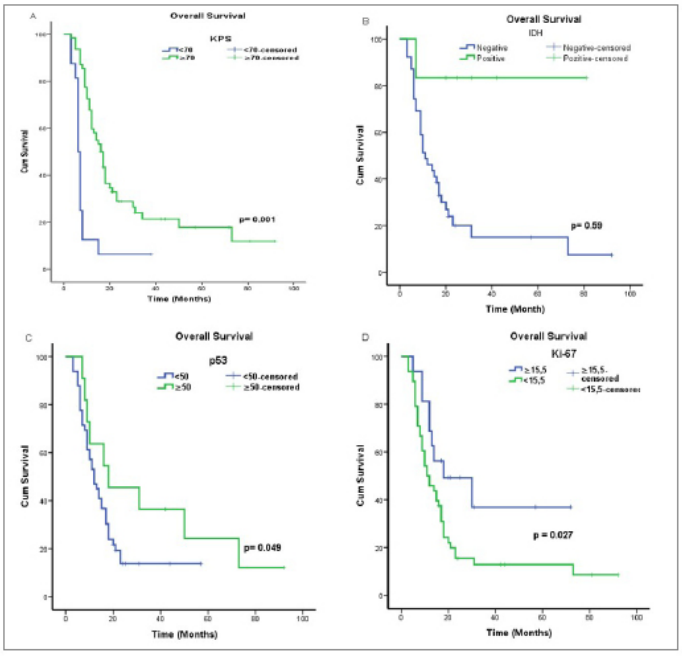


**Figure 1.** Kaplan-Meire Curves, Show Overall Survival (A; KPS, B; IDH1, C; p53, D; Ki-67)

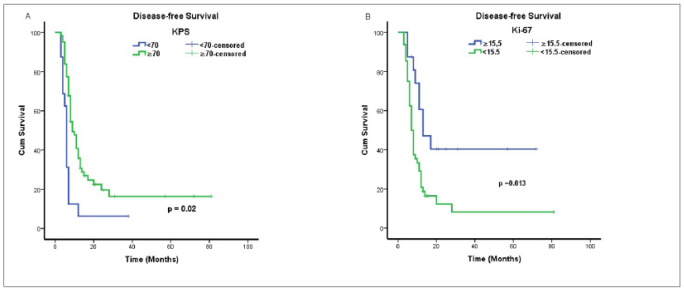


**Figure 2.** Kaplan-Meire Curves, Show Disease-free Survival (A; KPS and B; Ki-67)

## Discussion

Considering the results of our study, KPS was the most important determinat affecting OS and DFS in cases with high-grade glial tumors, in terms of immunohistochemical markers, p53 and Ki-67 were identified as significant prognostic factors in term of OS, while only Ki-67 was significant prognostic factor in DFS.

Numerous studies have shown that age and KPS are important prognostic markers in patients with high-grade glial tumors, but the poor prognosis in elderly patients is associated with the comorbidities caused by advanced age rather than the advanced

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age itself, and also with the effects of limited surgery and limited adjuvant treatments performed in these cases [12,13]. However, it has been reported that the OS time in elderly patients may be extended by 2.2 months in those receiving supportive treatment only, by 4.4 months in those undergoing surgery, and up to 15 months in those receiving additional radiochemotherapy [14]. These findings implicate that KPS at diagnosis, regardless of age, is an important prognostic factor for OS and DFS. In addition, Watanabe et al. [15] reported that high KPS (≥70) was the best predictor of response to radiotherapy in patients with GBM. In our study, in line with the literature, mean OS time was 16 months in patients with KPS ≥70 as opposed to 6 months in patients with KPS <70 (p=0.001) and the median DFS time was 9 months in patients with KPS≥70 as opposed to 4 months in patients with KPS <70 (p=0.005).

Many studies evaluating the effect of tumor localization and surgical resection in association with age and KPS in high-grade glial tumors have shown that deeply located tumors adjacent to the corpus callosum or ventricles may have a poor prognosis while cases located in the frontal lobe have a better prognosis [16–18], and it has also been reported that survival rates can be improved as the size of tumor resection increases [18–21]. In our study, tumor localization or resection type did not have a significant prognostic value in high-grade glial tumors both in univariate and multivariate analyses.

Some recent studies investigated the histopathological markers in high-grade glial tumors and reported that the presence of IDH mutation was associated with longer survival times compared to IDH-wild-type (OS, 1410 days vs. 461 days, respectively, p<0.0001) [22]. In our study, IDH1 status was found to be a significant factor for OS and DFS in univariate analysis (p=0.045 and p=0.038, respectively), whereas it was not revealed as a significant factor in multivariate analysis (p=0.59 and p=0.5, respectively).

Literature indicates that Ki-67 overexpression may be associated with poor prognosis in high-grade glial tumors [9,23]. Identically, Zeng et al. divided the patients into three categories in terms of the extent of Ki-67 expression (low, moderate, and high) and reported that increased Ki-67 expression was significantly associated with lower OS time (1593, 619, and 381 days, respectively, p<0.0001) [22]. Similarly, our study indicated that increased Ki-67 expression was a predictor of poor prognosis in terms of both OS (17 months in Ki-67 <15.5 and 11 months in Ki-67≥15.5; p=0.021) and DFS (13 months in Ki-67<15.5 and 7 months in Ki-67≥15.5; p=0.002) in univariate and multivariate analyses.

In the literature, contradictory results have been reported in numerous studies regarding the effect of p53 expression on prognosis in high-grade glial tumors [24]. Some studies have shown that p53 overexpression is an indicator of poor prognosis in glial tumors, while others have not found any association between p53 mutation or immune-reactivity and survival in glial tumors [25–28]. On the other hand, p53 overexpression has been described as a good prognostic factor in some other studies [29,30]. In the study by Birner et al., a higher rate of cell proliferation was found in patients with p53 positive tumors and it was reported that these patients, who had p53 overexpression and received adjuvant radiotherapy and chemotherapy, had significantly better OS rates. The authors attributed this finding to patients' increased sensitivity to adjuvant therapy [29]. Umeshet al. found that p53 overexpression in adult GBM cases was associated with poor prognosis in multivariate analysis, while this association was not established in univariate analysis [24]. In our study, although patients with high p53 values had a poor prognosis in terms of OS in both univariate and multivariate analyses (18 months and 12 months, respectively; p=0.049), no significant relationship was found in terms of DFS.

## Conclusion

KPS at diagnosis has an important prognostic value in high-grade glial tumors, and immunohistochemical findings including IDH1, Ki-67, and p53 may play a significant role in predicting survival depending on the surgical procedure and ensuing histological examination.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

**Financial Disclosure**
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**Ethical Approval**
*Prior to data collection and analysis, an ethics approval was obtained from Manisa Celal Bayar University Scientific Research Ethics Committee (Date: 07.02.2018; No: 20478486-050.04.04) and Manisa Provincial Secretariat of General Public Hospitals Union - Education Department (Date: 11.10.2018; No: 76379986-604.02).*

## References

1. Perez CA, Brady LW, Primary Intracranial Neoplasms. In: Princ. Pract. Radiat. Oncol. Seventh Ed., 2018;799-837.
2. Chaudhry NS, Shah AH, Ferraro N, et al. Predictors of long-term survival in patients with glioblastoma multiforme: advancements from the last quarter century. Cancer Invest. 2013;31:287-308.
3. Alimohammadi E, Bagheri SR, Sadeghsalehi A, et al. Prognostic factors in patients with glioblastoma multiforme: focus on the pathologic variants. Acta Neurol Belg. 2020;120:1341-50.
4. Harat M, Blok M, Harat A, Soszyńska K. The impact of adjuvant radiotherapy on molecular prognostic markers in gliomas. Onco Targets Ther. 20196;12:2215-24.
5. Myung JK, Cho HJ, Kim H, et al. Prognosis of glioblastoma with oligodendroglioma component is associated with the IDH1 mutation and mgmt methylation status. Transl Oncol. 2014;7:712-9.
6. Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst. 1993;85:704-10.
7. Jin Q, Zhang W, Qiu XG, et al. Gene expression profiling reveals Ki-67 associated proliferation signature in human glioblastoma. Chin Med J (Engl). 2011;124:2584-8.

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8. Cai J, Yang P, Zhang C, et al. ATRX mRNA expression combined with IDH1/2 mutational status and Ki-67 expression refines the molecular classification of astrocytic tumors: evidence from the whole transcriptome sequencing of 169 samples samples. Oncotarget. 2014;5:2551-61.

9. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765-73.

10. D'Alessio A, Proietti G, Sica G, Scicchitano BM. Pathological and Molecular Features of Glioblastoma and Its Peritumoral Tissue. Cancers (Basel). 2019;11:469.

11. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-20.

12. Barnholtz-Sloan JS, Williams VL, Maldonado JL, et al. Patterns of care and outcomes among elderly individuals with primary malignant astrocytoma. J Neurosurg. 2008;108:642-8.

13. Barker FG, Prados MD, Chang SM, et al. Bromodeoxyuridine labeling index in glioblastoma multiforme: relation to radiation response, age, and survival. Int J Radiat Oncol Biol Phys. 1996;34:803-8.

14. Ewelt C, Goeppert M, Rapp M, et al. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. J Neurooncol. 2011;103:611-8.

15. Watanabe T, Katayama Y, Yoshino A, et al. Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. J Neurooncol. 2005;72:57-62.

16. Paravati AJ, Heron DE, Landsittel D, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma and anaplastic astrocytoma: validation of Radiation Therapy Oncology Group-Recursive Partitioning Analysis in the IMRT and temozolomide era. J Neurooncol. 2011;104:339-49.

17. Coffey RJ, Lunsford LD, Taylor FH. Survival after stereotactic biopsy of malignant gliomas. Neurosurgery. 1988;22:465-73.

18. Randolph DM 2nd, McTyre ER, Paulsson AK, et al. Impact of timing of radiotherapy in patients with newly diagnosed glioblastoma. Clin Neurol Neurosurg. 2016;151:73-8.

19. Ammirati M, Vick N, Liao YL, et al. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. Neurosurgery. 1987;21:201-6.

20. Jeremic B, Milicic B, Grujicic D, et al. Multivariate analysis of clinical prognostic factors in patients with glioblastoma multiforme treated with a combined modality approach. J Cancer Res Clin Oncol. 2003;129:477-84.

21. Laws ER, Parney IF, Huang W, et al. Glioma Outcomes Investigators. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg. 2003;99:467-73.

22. Zeng A, Hu Q, Liu Y, et al. IDH1/2 mutation status combined with Ki-67 labeling index defines distinct prognostic groups in glioma. Oncotarget. 2015;6:30232-8.

23. Liu Y, Tang K, Yan W, et al. Identifying Ki-67 specific miRNA-mRNA interactions in malignant astrocytomas. Neurosci Lett. 2013;546:36-41.

24. Umesh S, Tandon A, Santosh V, et al. Clinical and immunohistochemical prognostic factors in adult glioblastoma patients. Clin Neuropathol. 2009;28:362-72.

25. Jaros E, Perry RH, Adam L, et al. Prognostic implications of p53 protein, epidermal growth factor receptor, and Ki-67 labelling in brain tumours. Br J Cancer. 1992;66:373-85.

26. Korkolopoulou P, Christodoulou P, Kouzelis K, et al. MDM2 and p53 expression in gliomas: a multivariate survival analysis including proliferation markers and epidermal growth factor receptor. Br J Cancer. 1997;75:1269-78.

27. Baxendine-Jones J, Campbell I, Ellison D. p53 status has no prognostic significance in glioblastomas treated with radiotherapy. Clin Neuropathol. 1997;16:332-6.

28. Kyritsis AP, Bondy ML, Hess KR, et al. Prognostic significance of p53 immunoreactivity in patients with glioma. Clin Cancer Res. 1995;1:1617-22.

29. Birner P, Piribauer M, Fischer I, et al. Prognostic relevance of p53 protein expression in glioblastoma. Oncol Rep. 2002;9:703-7.

30. Burton E, Lamborn K, Forsyth P, et al. Aberrant p53, mdm2, and Proliferation differ in glioblastomas from long-term compared with typical survivors. Clin Cancer Res. 2002;8:180-7.