

# Radiotherapy Outcomes in Adults with H3K27M-Altered Midline Gliomas and Poor Performance Status

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## ABSTRACT

**Objective:** Treatment of H3K27M-altered midline gliomas is a significant challenge. This study aims to assess the efficacy of radiotherapy for these patients.

**Materials and Methods:** Thirteen patients with histologically confirmed H3K27M-altered midline glioma, treated with radiotherapy +/- temozolomide between 2019 and 2021, were retrospectively analyzed. Clinical and radiological responses, survival times, and prognostic factors were evaluated. All patients were treated with hypofractionated radiotherapy, with a dose of 25-40 Gy.

**Results:** The median age was 42 years (ranging from 19 to 55). Karnofsky Performance Status scores ranged from 50 to 70, with a median score of 50. Hypofractionated radiotherapy was administered to all patients, with 25 Gy given in 5 fractions to 7 patients (53.8%), 39 Gy in 13 fractions to 3 patients (23.1%), and 40 Gy in 15 fractions to 3 patients (23.1%). Clinically, two patients (15.4%) showed symptomatic improvement, five patients (38.8%) remained stable, and six patients (46.2%) had neurological deterioration. Radiologically, one patient had a partial response, six patients (46.2%) had stable disease, and radiological progression occurred in three patients (23.1%). The median progression-free survival and median overall survival time were 123 and 154 days, respectively. Karnofsky Performance Status 50 was associated with a worse prognosis.

**Conclusion:** These results suggest that the efficacy of radiotherapy might be limited for adults with H3K27M-altered midline gliomas with poor performance status. New studies are necessary for a more comprehensive understanding of effective therapeutic strategies.

**Keywords:** Diffuse midline glioma, DMG, H3K27M-altered, high grade glioma, poor performance status, radiotherapy

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## INTRODUCTION

Diffuse midline glioma (DMG) with H3K27M mutation was first included as a distinct entity in the 2016 World Health Organization (WHO) classification of tumors of the central nervous system and has gained increasing recognition.<sup>[1]</sup> In the fifth edition of this classification, published in 2021, it was revised from 'DMG, H3K27M-mutant' to 'DMG, H3K27M-altered' to include additional alterations that can characterize this entity. H3K27M-altered glioma is defined by a specific genetic mutation that plays a crucial role in packaging DNA within cells. It primarily affects children but can also occur in adults. It exhibits a diffuse growth pattern and typically develop in midline structures of the brain, including the brain-

stem, thalamus, and spinal cord.<sup>[2]</sup> Regardless of histological features, it is classified as a WHO grade 4 due to its aggressive behavior and unfavorable prognosis.

The management of H3K27M-altered midline gliomas presents a significant challenge. While surgery is the mainstay of the treatment, only a small percentage of patients are eligible for complete surgical resection due to the complex anatomy of the affected structures and the aggressive nature of tumor. Radiotherapy, with or without chemotherapy, is frequently the only effective option for patients with unresected or partially resected tumors,<sup>[3]</sup> with reported median survival times ranging between 8.76 and 22.8 months in the literature.<sup>[4,5]</sup>



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We retrospectively evaluated the results of radiotherapy with or without temozolomide for adult patients with H3K27M-altered midline gliomas.

## MATERIALS and METHODS

### Patient Selection and Follow-up

In this study, adult patients diagnosed with H3K27M-altered midline gliomas who underwent radiotherapy, with or without temozolomide were retrospectively reviewed. The inclusion criteria of the study were as follows: patients aged 18 or older, histologically confirmed glioma with H3K27M-altered, received radiation therapy; stereotactic biopsy or tumor resection was allowed. All patients underwent preoperative Magnetic Resonance Imaging (MRI) for surgical decision, and postoperative MRI was also obtained for those who underwent tumor resection. Clinical and radiological evaluation was done 3 months after completion of radiotherapy, according to Response assessment in neuro-oncology criteria (RANO).

### Treatment Specifications

All patients were immobilized using a thermoplastic mask. The simulation computed tomography (CT) was obtained with a slice thickness of at least 2.5 mm. Following the rigid registration of pre-operative MRIs (T2 flair and T1 with contrast) and CT, the gross tumor volume (GTV) was defined as a contrast-enhancing lesion on T1 and/or a high-intensity lesion on T2 flair images. The clinical target volume (CTV) margin of 1.5 cm was added to GTV in all dimensions cropping from anatomical barriers such as bone and tentorium. The planning target volume (PTV) margin of 0.5 cm was added to CTV in all dimensions. Three different hypofractionated radiotherapy schedules were applied to PTV including doses of 25 Gy in 5 fractions, 39 Gy in 13 fractions, or 40 Gy in 15 fractions.

Patients treated with 13 or 15 fraction schemes were scheduled to undergo concomitant temozolomide treatment. For the adjuvant temozolomide decision, patients were assessed 3–4 weeks after completing radiotherapy, and the treatment was planned with a dose of 150–200 mg/m<sup>2</sup> for five days every four weeks until progression for eligible patients.

### Statistical Evaluation

The Statistical Package for the Social Sciences (SPSS) program (version 16.0, SPSS Inc., Chicago, IL, USA) was used to analyse the data. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. The survival

rate was calculated with Kaplan Meier method. Univariate analysis is done with log-rank test. Multivariate was not performed due to small sample size. Frequency percentages were calculated for categorical variables.

The current study was approved by the institutional ethical committee (2022/135; 20.6.2022). The need to obtain informed patient consent was waived by the ethical committee due to its retrospective design. The study was performed in accordance to the Declaration of Helsinki.

## RESULTS

From February 2019 and May 2021, a total of thirteen adult patients with H3K27M-altered midline glioma who received radiotherapy were identified. Their ages ranged from 19 to 55, with a median age of 42 years. Of the patients, 10 were male and 3 were female, and their Karnofsky Performance Status (KPS) scores ranged from 50 to 70, with a median score of 50. Nine patients had the radiological appearance of a contrast-enhancing tumor, whereas four patients had the radiological appearance of a non-contrast-enhancing lesion. Nine patients had only biopsy-confirmed diagnosis, while four patients underwent subtotal resection. Initially, three patients (23.1%) had a morphological grade 2, two patients (15.4%) had a grade 3, and eight patients (61.5%) had a grade 4 tumor. However, after the presence of the H3K27M mutation, all patients were re-graded as grade 4. Hypofractionated radiotherapy was administered to all patients, with 25 Gy given in 5 fractions to 7 patients (53.8%), 39 Gy in 13 fractions to 3 patients (23.1%), and 40 Gy in 15 fractions to 3 patients (23.1%) (Table 1). Additionally, adjuvant temozolomide was given to 5 patients at a dose of 150–200 mg/m<sup>2</sup> for five days every four weeks until progression 3–4 weeks after completion of radiotherapy.

After the completion of radiotherapy, clinical and radiological evaluation was performed at 3 months. Only two patients (15.4%) had symptomatic improvement, 5 patients (38.8%) remained clinically stable, and 6 patients (46.2%) experienced neurological worsening. The radiological evaluation was performed on 10 patients according to RANO criteria. The results showed that only one patient had a partial response, while six patients (46.2%) had stable disease and three patients (23.1%) had radiological progression. However, the radiological evaluation could not be performed for three patients who died within 3 months after receiving radiotherapy due to neurological deterioration. These three patients had a KPS score of 50.

The median progression-free survival and median overall survival (Fig. 1) time were 123 days and 154 days, respectively. In the univariate analysis, the prognostic factors were evaluat-

Table 1. Patient characteristics

Patient number	Gender	Age	KPS	MRI contrast enhancement	Tumor location	Surgery	Radiotherapy dose/fraction	TMZ
1	F	36	60	+	T	STR	25/5	+
2	F	38	60	-	T	STR	40/15	+
3	F	32	50	+	T	STR	40/15	-
4	M	55	50	+	MB	B	25/5	-
5	M	50	60	-	T+MC	B	39/13	+
6	M	45	50	+	CC+MC	B	25/5	-
7	M	53	50	+	CC+MC	B	25/5	-
8	M	55	60	+	MB	B	39/13	+
9	M	53	60	+	MB	B	39/13	-
10	M	19	50	+	CC	B	25/5	-
11	M	30	50	+	MB	B	25/5	-
12	M	35	70	-	T+MC	B	40/15	+
13	M	42	50	-	T	STR	25/5	-

KPS: Karnofsky performance status; MRI: Magnetic resonance imaging; TMZ: Temozolomide; F: Female; M: Male; +: Present; -: Absent; STR: Subtotal resection; MB: Midbrain; T: Thalamus; MC: Mesencephalon; CC: Corpus callosum; B: Biopsy

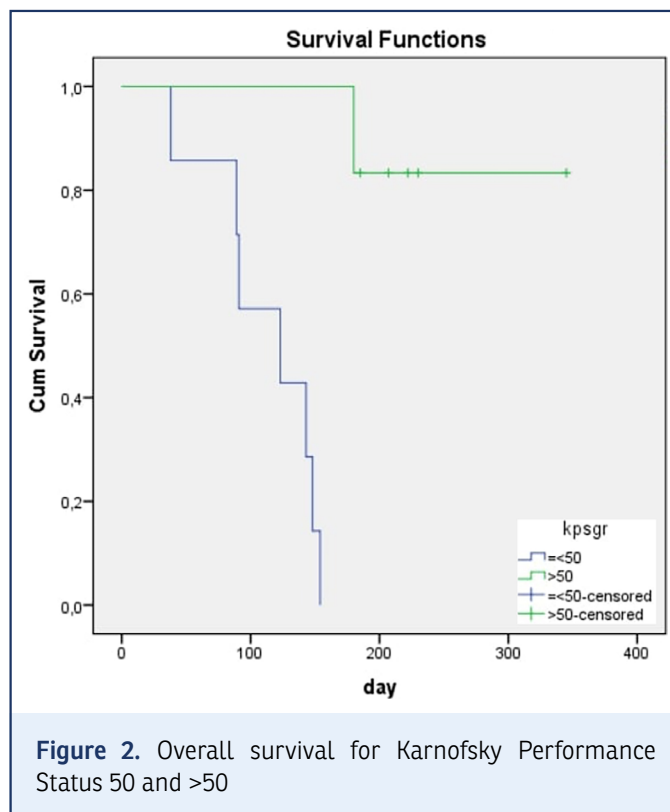
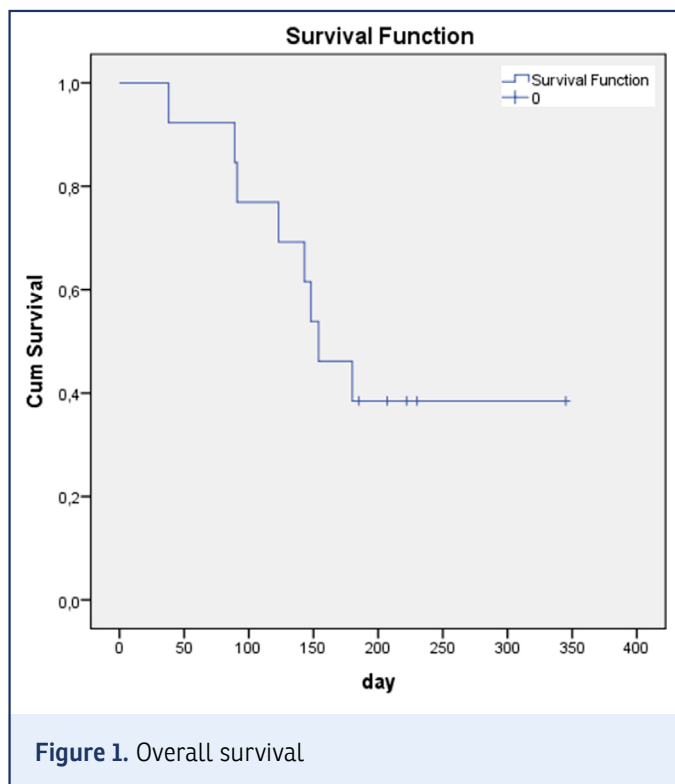
ed including age ( $\leq 40$  years versus  $> 40$  years), KPS score (50 versus  $> 50$ ), and the extent of surgery (biopsy versus subtotal resection). The results of the analysis showed that patients with a KPS score of 50 were associated with a worse prognosis, with a median survival time of 123 days (Fig. 2). The median survival time for patients with a KPS score  $> 50$  was 215 days.

## DISCUSSION

The role of radiotherapy is well-established in gliomas. The standard practice for high-grade glioma is the combination of radiotherapy and temozolomide.<sup>[6,7]</sup> However, the decision regarding treatment for elderly and/or frail patients is particularly challenging, as their life expectancy is limited to a few months, and they are generally excluded from clinical trials. Several studies have investigated hypofractionated radiotherapy compared to the standard fractionation of 60 Gy in 6 weeks or temozolomide, and the results of these studies concluded that shorter schedules of radiotherapy (40 Gy in 15 fractions, 25 Gy in 5 fractions), temozolomide or combination of these treatments, could be a treatment option in elderly and/or frail high-grade glioma patients.<sup>[8-12]</sup> Hypofractionated radiotherapy schemes have also been shown to be non-inferior in cases with diffuse intrinsic pontine glioma (DIPG) in children, 80% of which are H3K27M mutant.<sup>[13]</sup> The presence of the H3K27M mutation can also be seen in adults. The majority of patients' survival time is less than 1 year after diagnosis.<sup>[14]</sup> A systemic review showed that radiotherapy was

associated with survival benefits in H3K27M-altered DMGs, with the median overall survival and progression-free survival at 10 and 7 months, respectively.<sup>[15]</sup> Palmisciano et al.<sup>[3]</sup> reviewed the results of 617 patients with thalamic gliomas, of whom 82 were H3K27M mutant. The median survival for the entire cohort was 12.1 months, despite a median KPS was 80 after surgery. Adjuvant temozolomide and radiation therapy demonstrated a positive impact on survival for the entire cohort; however, subgroup analysis was not performed to assess its validity for H3K27M mutant tumors. In our study, hypofractionated radiotherapy schemes were preferred for all patients due to their short life expectancy.

The Karnofsky Performance Status is an important prognostic factor in gliomas. Several studies have demonstrated a significant association between both preoperative and post-operative KPS and survival in gliomas. A retrospective study has shown that a low KPS ( $< 85$ ) increased the risk of mortality by 2.3 times in glioma patients.<sup>[16]</sup> There is emerging data in the literature with better outcomes in H3K27M patients with higher KPS scores. In the series of Park et al.,<sup>[17]</sup> where 70% of the patient group consisted of patients with KPS 80 and above, the median overall survival was 21.8 months. In accordance with Park's findings, Osada et al.<sup>[4]</sup> published the results of 12 H3K27M-mutant glioma patients, where 58.3% of the patients with KPS 80 and above, with a median OS of 22.8 months. Our analysis has demonstrated that patients with a KPS score of 50 are associated with a worse prognosis



compared to higher KPS scores. In our series of 13 patients, 8 patients died within 6 months. Median survival time for all patients was less than 5 months and only 3 months for those with KPS 50. Although there is limited available data in the literature regarding the effect of KPS score on survival for H3K27M tumors, in light of these studies, the contribution of a high KPS score to overall survival is obvious. Further large-scale studies in this field are indicated.

Another issue is the palliative effect of treatment in other words symptom control. Stabilizing or improving health-related quality of life should also be essential in this disease which has a short life expectancy. In the present series following the completion of radiotherapy, 8 patients died without any symptom control, of the living 5 patients only 2 who had KPS scores of 60 and 70 showed neurological improvement. Therefore, not even palliation is achieved in patients with a KPS score of 50.

Post-operative radiotherapy is the standard treatment for patients with H3K27M-altered glioma. Even though hypofractionated radiotherapy is the most preferred radiotherapy scheme in low-performing patients, due to the limited symptom palliation detected in our study, it might be questioned whether the positive effects of the treatment outweigh the time spent in the hospital for this population. As Daily<sup>[18]</sup> addressed the toxicity of time in her paper, Gupta et al.<sup>[19]</sup>

questioned the time spent in hospitals for cancer treatment as opposed to the time that a particular patient gains from treatment. We anticipate an increased focus on and discussion of the reduction in hospital visits and time toxicity in the future. Therefore, clinicians should consider every aspect, including patient age, performance status, extent of surgery, and molecular subtype as well as the patient’s preference to receive radiotherapy in this difficult clinical situation without compromising survival. Due to short overall survival and limited symptom relief, we apply radiotherapy to this patient group with the shortest possible fractionation scheme.

The current study has several limitations. Firstly, the retrospective nature of the study and the limited sample size challenges the reliability of statistical analyses. Additionally, the absence of a comparison group, such as H3K27M wild gliomas, further limits the scope of our findings.

## CONCLUSION

Our results suggest that the efficacy of radiotherapy might be limited for adults with H3K27M-altered midline gliomas with poor performance status. There is a high probability that these patients cannot achieve the reported best-expected survival times. Clinical trials are needed to gain a better understanding of the molecular responses to radiotherapy and to identify specific patient subgroups that could benefit from this treatment.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (No: 2022/135, Date: 20/06/2022).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions:** Concept: E.K.U., Ö.U.; Design: E.K.U.; Supervision: E.K.U., Ö.U.; Materials: E.K.U., M.B.K.; Data Collection or Processing: E.K.U., M.B.K.; Analysis or Interpretation: E.K.U., M.B.K., M.K.B., Ö.U.; Literature Search: M.B.K., M.F., M.K.B.; Writing: E.K.U., M.B.K., M.F., M.K.B.; Critical review: Ö.U.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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