Patterns of failure after radiation therapy in primary spinal high-grade gliomas: A single institutional analysis

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Abstract

Background. Primary spinal high-grade gliomas (S-HGG) are rare aggressive tumors; radiation therapy (RT) often plays a dominant role in management. We conducted a single-institution retrospective review to study the clinicopathological features and management of S-HGGs.

Methods. Patients with biopsy-proven S-HGG who received RT from 2001 to 2020 were analyzed for patient, tumor, and treatment characteristics. Kaplan–Meier estimates were used for survival analyses.

Results. Twenty-nine patients were identified with a median age of 25.9 years (range 1–74 y). Four patients had GTR while 25 underwent subtotal resection or biopsy. All patients were IDH wildtype and MGMT-promoter unmethylated, where available. H3K27M mutation was present in 5 out of 10 patients tested, while one patient harbored p53 mutation. Median RT dose was 50.4 Gy (range 39.6–54 Gy) and 65% received concurrent chemotherapy, most commonly temozolomide. Twenty-three (79%) of patients had documented recurrence. Overall, 16 patients had documented recurrence. Median OS from diagnosis was 21.3 months and median PFS was 9.7 months. On univariate analysis, age, gender, GTR, grade, RT modality, RT dose and concurrent chemotherapy did not predict for survival. Patients with H3K27M mutation had a poorer PFS compared to those without mutation (10.1 m vs 45.1 m) but the difference did not reach statistical significance (P = .26).

Conclusions. The prognosis of patients with spinal HGGs remains poor with two-thirds of the patients developing distant recurrence despite chemoradiation. Survival outcomes were similar in patients ≤ 29 years compared to adults > 29 years. A better understanding of the molecular drivers of spinal HGGs is needed to develop more effective treatment options.
Primary spinal high-grade gliomas (HGG) are rare and aggressive tumors. In our single institutional cohort of 29 patients treated with definitive radiation therapy with or without chemotherapy, prognosis remains poor with median overall survival of 21.2 months, median progression-free survival of 9.7 months, 69.6% patients developing local recurrence and 65.2% patients developing distant recurrence. Survival outcomes were similar in children, adolescents, and young adults ≤ 29 years compared to adults > 29 years.

Materials and Methods

After Institutional Review Board approval, we retrospectively analyzed all patients with spinal cord tumors who received RT at our center from 2001 to 2020. Patients with a biopsy-proven high-grade glioma, WHO grade III or IV, primarily arising in the spinal cord were included. Pathologic grading was based on the 2016 World Health Organization classification of CNS tumors. Patients with biopsy proven grade 1–2 gliomas, presumed low-grade gliomas on imaging, and mixed gliomas which entails ganglioglioma, ganglioneuroma, neuroglial tumors and diffuse leptomeningeal glioneuronal tumors (DLGNT) were excluded. Patients who did not receive planned RT were also excluded. Patients were stratified according to their age ≤ 29 versus > 29 years of age to compare outcomes in children and young adults versus adults. An age cut-off of 29 years was used based on the Children’s Oncology Group (COG) trials definition for pediatric age group (0–14 years) and adolescent/young adults (AYA, 15–29 years). Pertinent demographic, clinical, radiologic and pathological characteristics as well as treatment and follow-up details were extracted from the electronic medical records.

All patients underwent gadolinium-enhanced MRI of the entire neuroaxis. All patients underwent initial surgical intervention followed by adjuvant radiation therapy. All pathology specimens were reviewed at our center, and mutational status and tumor genomics were reviewed where available. RT was planned and delivered using 3D conformal RT, intensity modulated radiation therapy (IMRT), or passive scatter proton therapy using conventional fractionation with a daily dose of 1.8–2 Gy per fraction. Patients were simulated supine or prone with a vacuum bag for immobilization. Anesthesia was utilized for patients too young or unable to tolerate simulation or RT treatments. Simulation CT scans were acquired using a Philips simulator with 1.5–2.5 mm slices. Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) was used to develop proton-based radiation treatment plans and Pinnacle treatment planning system (Koninklijke Philips N.V., Amsterdam, Netherlands) or Raystation treatment planning system (Raysearch Laboratories AB, Stockholm, Sweden) for photon-based planning. The target volumes and RT dose were at the discretion of the treating physician and were guided by the extent of the
Results
A total of 29 patients were identified with a median age at diagnosis of 25.9 years (range 1–74 years). Patient characteristics and treatment details are described and compared between the two age groups in Table 1. Patients ≤ 29 years and > 29 years were similar in all clinical characteristics. The most common presenting symptoms were bilateral or unilateral extremity weakness, back pain, neck pain and urinary incontinence. Only 4 patients underwent a gross total resection (GTR), 14 patients had a subtotal resection (STR), and 11 underwent biopsy alone. Five patients had multiple resections before RT. A median spinal cord length of 4 vertebral bodies were involved (range, 1–14). Sixteen out of 29 patients had disease localized to one site in the spine, 8 patients had contiguous involvement of multiple spinal regions and 5 patients had disease disseminated to a distant site in the spine (n = 4), or CSF with leptomeningeal disease (n = 1). None of the patients had intracranial involvement at presentation.

Pathology and Molecular Profiling
All patients had a histologically confirmed diagnosis of HGG. Nineteen patients had a WHO grade IV tumor and 10 had WHO grade III tumor (Table 1).

Molecular information was available for a limited number of patients. IDH1 mutation and MGMT promoter methylation were analyzed in 14 and four patients, respectively; all patients were IDH wildtype by immunohistochemistry and MGMT-promoter unmethylated. H3K27M mutation was present in five out of 10 patients tested. Other less commonly seen mutations were MAPK, NMYC and NOTCH in 1 patient each. All of these tumor mutations occurred in patients younger than 29 years. One of the patients was also found to have Li-Fraumeni syndrome and harbored a p53 mutation, in association with NMYC. No other patients had p53 mutation. Among 5 patients ≤ 29 years who had H3K27M mutation tested, 4 had the mutation (80%), while only 1 out of 5 patients > 29 years of age had the mutation (20%) (Figure 1). This patient’s age was 57 years at diagnosis.

Radiation Treatment
Twenty-two patients received photon-based radiation and 7 received proton therapy. Median RT dose was 50.4 Gy (range 39.6–54 Gy) with 79% receiving >45 Gy. RT dose was guided by the extent of disease and number of vertebral levels involved. Patients receiving < 45 Gy had at least 3 vertebral levels involved. About 65% of patients received concurrent chemotherapy, most commonly temozolomide (in 17 of 19 patients). One patient each received concurrent bevacizumab or temozolomide.

One patient who was under 29 years of age at diagnosis, underwent upfront craniospinal irradiation (CSI) for CSF positive leptomeningeal disease, with a CSI dose of 34 Gy in 17 fractions followed by spine boost of 9 Gy in 5 fractions. Another patient received focal spine RT to 54 Gy initially followed by modified CSI at relapse 3 months after completion of initial radiation, with previously treated spine carved out. One patient > 29 years of age underwent total spinal irradiation for disseminated disease involving multiple vertebral levels—with a whole spine dose of 39.6 Gy with 9 Gy boost.

RT was tolerated well with only one patient developing CTCR grade 3 radiation necrosis (suspected) at the end of radiation which improved with steroids, bevacizumab and hyperbaric oxygen therapy. One other patient had pseudoprogression at 3 months after RT, with imaging changes that improved on follow-up with no new or progressive symptoms. No other grade 3 or higher toxicities were seen.

Patterns of Failure
Table 2 describes the patterns of failure in detail. Median follow-up for all patients after end of RT was 14.8 months (range, 5.7–72.7 months). Twenty-three (79%) patients had a documented recurrence. Of these, 16 patients (55.2%) relapsed locally, 10 (22.2%) relapsed in the brain and 8
(27.6%) developed leptomeningeal disease; only 8 (35%) had isolated local relapse.

Seventeen patients (58.6%) were deceased at last follow-up; all deaths were attributable to tumor progression. Median OS from diagnosis was 21.2 months and median PFS after RT was 9.7 months. Kaplan–Meier survival curves for OS and PFS stratified by age and grade are presented in Figures 2 and 3 respectively. Overall, 2-year PFS and OS were 17.6% and 48.5%, respectively.

On univariate analysis, gender, age at diagnosis, extent of resection, grade, RT dose, RT modality, CSI, concurrent
chemotherapy and LMD did not correlate with OS or PFS (Table 3). Patients with H3K27M mutation tended to have a worse median PFS after RT compared to those without the mutation (10.1 m vs 45.1 m) but the difference did not reach statistical significance ($P = .26$).

**Treatment at Relapse**

Ten patients underwent reirradiation with a median dose of 20 Gy (range 20–40 Gy). This was limited to the site of recurrence in six patients, while four underwent CSI. One patient received radiation to the brain for isolated intracranial recurrence. Reirradiation was tolerated well with no grade 3 or higher side-effects. Bevacizumab was the most common systemic treatment at recurrence (4 patients). Other chemotherapeutic agents used were lomustine, temozolamide, intrathecal topotecan, and irinotecan. Sorafenib, olaparib, and imatinib were used on one patient each.

**Discussion**

Our analysis of 29 patients represents the largest single institution cohort to date reporting outcomes with surgery.
and RT in patients with primary spinal HGGs. This cohort had a median PFS of 9.7 months after RT and median OS of 21.2 months from diagnosis.

Most of the existing literature that has reviewed spinal gliomas has included low-grade gliomas. Patients with low-grade tumors have prolonged survival compared to patients with high-grade tumors. Previous studies have reported a correlation between the length of symptoms prior to diagnosis and outcomes, with an improved survival in patients with greater than 6 months of symptoms before diagnosis, consistent with the indolent course of low-grade gliomas. There have been fewer than 200 cases of spinal HGGs reported in the literature. In a study by Yanamadala et al. in 6 patients with spinal HGGs treated with surgery and RT, the 1-year OS was 100% with a mean follow-up of 1.5 years. The 1-year OS in our cohort was approximately 80%.

Maximal safe resection is associated with improved survival in intracranial HGGs. This is more challenging for spinal HGGs given the location of these tumors. Only 14% of our patients underwent GTR; 86% of patients had gross disease at the time of RT. Also, the median dose of RT was only 50.4 Gy, less than the standard of care 60 Gy for intracranial GBMs. Despite this, the rate of local failure was only 55% compared to over 80% for intracranial GBMs in the landmark Stupp trial. Notably, over one-third of our patients had a distant failure in the brain, which is a higher distant brain failure rate than seen in intracranial GBMs. The median PFS and OS for intracranial GBMs is 7 months and 15–20 months, respectively, which is lower than what we observed in our cohort of spinal HGGs.

The most common tumor location for our patients was thoracic followed by cervical spinal cord. This is consistent with prior observations that astrocytomas are most common in the cervical or thoracic spine, while ependymomas are more commonly seen in the lumbar or sacral region. This differential distribution of tumor locations often allows for higher radiation doses to be delivered to ependymomas that occur below the termination of the spinal cord. In our cohort, the radiation dose was often dependent on the length of spinal cord involved, with patients with at least 3 vertebral levels of spinal cord involved receiving less than 45 Gy.

Post-operative radiotherapy has been shown to improve survival in patients with WHO grade 2–4 infiltrative astrocytomas. The optimal RT dose for these tumors is not well defined. The median dose in our cohort was 50.4 Gy; a median dose of 45 Gy has previously been reported. There was no clear association of survival with radiation dose. Per the QUANTEC guidelines, the risk of myelopathy is <1% with a maximal cord dose up to 54 Gy, while it jumps to <10% for a point dose maximum of 61 Gy when using conventional fractionation of 1.8–2 Gy per fraction.

There are limited data on systemic therapy for these patients. There was no impact of concurrent chemotherapy on survival in our cohort of patients. The most common agent used was temozolomide, although there is limited evidence of benefit. Both temozolomide and bevacizumab have been shown to improve survival in retrospective series, especially in the recurrent setting. Bevacizumab is thought to be particularly suitable as it decreases peritumoral edema and mass effect. In a study evaluating the role of Bevacizumab for recurrent spinal HGGs, two out of six patients demonstrated a partial response, whereas five out of six patients had improvement in quality of life.

From the limited molecular data available for these patients, there were no tumors with MGMT methylation or IDH-1 mutation. This finding is similar to Yanamadala.
et al., who observed 0% MGMT methylation or IDH-1 mutation. Interestingly, we saw H3K27M mutation in 50% of patients with such data available. H3K27M mutation is one of several identified histone H3 gene mutations associated with midline gliomas. We observed H3K27M mutation more commonly in patients ≤ 29 years of age. Although not statistically significant, there was a suggestion of poorer PFS for patients with this mutation compared to those without the mutation (10.1 m vs 45.1 m). Although H3K27M mutant gliomas have been clearly associated with an extremely aggressive behavior in pediatric brainstem gliomas, there has been a heterogeneity in their prognostic impact on adult spinal HGGs in the existing literature. 17–20 Alvi et al. analyzed the molecular profile of 13 patients with spinal HGGs and found the presence of H3K27M mutation in 6 out of 13 cases by immunohistochemistry. 17 They also observed TERT promoter mutation in 3 patients and TP53 mutation in 5 patients. The median survival for patients with H3K27M mutation was 48.5 months compared to 77 months in H3K27M-wildtype tumors; however, the difference was not statistically significant (P = .45). They also reported that H3K27M-mutant tumors appeared to affect younger patients, a finding which was seen in our population as well wherein H3K27M mutation was seen in 80% patients < 29 years of age and only 20% patients > 29 years of age. Similarly, Gessi et al. identified the H3K27M mutation in 16 of 30 spinal HGGs, with a lower mean age of patients with H3K27M mutation (34 years) versus patients with wild-type tumors (53 years). 18 Karremann et al. suggested that H3K27M is a poor prognostic factor for HGGs in all regions of CNS. 21 In a meta-analysis of 6 studies by Lu et al., H3K27M was associated with worse prognosis and a poorer OS by 2.3 years. 22 Picca et al. reported 5 of 8 spinal cord gliomas in adults were positive for H3K27M and found no survival difference between H3K27M-mutant versus wild-type tumors when including all midline locations. 19 In contrast, Yi et al. found that the presence of the H3K27M mutation (detected among 20 of 25 WHO grade 4 spinal gliomas) was associated with significantly longer overall and disease-free survival (40 months). 20 Presence of H3K27M mutation has been given a separate classification in the most recent 2016 WHO classification of CNS tumors, namely “Diffuse Midline Glioma, H3K27M mutant” based on histological and molecular characterization. 3,20 Solomon et al. reported the incidence of H3K27M mutation in various midline CNS tumors including spinal cord, and found the incidence of mutations to be 53% in infiltrative gliomas, similar to the findings of our study. 23 Preclinical studies provide some evidence of improved outcomes with HDAC inhibitors (sodium valproate) in patients with H3K27M mutations. 24 Notably, there is a case report of a patient with a cervical cord GBM with H3K27M mutation treated with valproic acid who survived for 31 months, 25 suggesting potential therapies for these patients. TERT promoter mutation has been shown to portend significantly worse survival in spinal HGG patients; however, it was not assessed in our population. 17,19

We must acknowledge the limitations of this study, the most pertinent of which is the retrospective design. Given the rarity of these tumors, designing prospective studies is difficult. Also due to the small numbers of patients and events overall, it is difficult to determine statistically significant predictors of outcome. It is clear that the molecular data on these patients will provide a path for understanding of prognosis and ultimately, new therapies.
To conclude, the prognosis of patients with spinal HGGs remains poor despite maximal safe resection and adjuvant chemoradiation. H3K27M mutation are often seen more commonly in younger patients, and may portend worse survival. A better understanding of the molecular drivers of spinal HGGs is needed to develop more effective treatment options and is the subject of ongoing efforts.

**Keywords**

high-grade glioma | proton therapy | radiation | spinal glioma

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**Table 3**  
Univariate Analysis of Factors Affecting Overall Survival (OS) and Progression-free Survival (PFS) (Cox Proportional Hazard Regression)

| Characteristics       | Median OS (months) | Univariable HR (95% CI) | P * | Median PFS (months) | Univariable HR (95% CI) | P * |
|-----------------------|--------------------|-------------------------|-----|--------------------|-------------------------|-----|
| Gender                |                    |                         |     |                    |                         |     |
| Females               | 14.4               | 0.80 (0.29-2.22)        | .67 | 10.0               | 0.72 (0.28-1.80)        | .48 |
| Males                 | 21.3               | Ref                     |     | 9.7                | Ref                     |     |
| Age at diagnosis      |                    |                         |     |                    |                         |     |
| ≤29                   | 18.2               | Ref                     | .93 | 8.4                | Ref                     | .98 |
| >29                   | 21.2               | 1.04 (0.39-2.82)        |     | 20.4               | 1.94 (0.78-4.85)        |     |
| Extent of resection   |                    |                         |     |                    |                         |     |
| GTR                   | 35.1               | Ref                     | .46 | 10.0               | Ref                     | .86 |
| Biopsy or STR         | 21.3               | 1.76 (0.39-7.89)        |     | 8.8                | 1.10 (0.36-3.29)        |     |
| RT dose               |                    |                         |     |                    |                         |     |
| ≤45 Gy                | 35.1               | Ref                     | .36 | 16.7               | Ref                     | .37 |
| >45 Gy                | 18.2               | 1.81 (0.50-6.49)        |     | 8.4                | 1.64 (0.54-4.93)        |     |
| CSI                   |                    |                         |     |                    |                         |     |
| No                    | 25.9               | Ref                     | .59 | 9.7                | Ref                     |     |
| Yes                   | 14.4               | 1.53 (0.33-6.98)        |     | 5.9                | 2.84 (0.80-10.11)       |     |
| Modality              |                    |                         |     |                    |                         |     |
| Photons               | 21.2               | Ref                     | .47 | 10.0               | Ref                     | .93 |
| Protons               | 14.4               | 0.62 (0.18-2.22)        |     | 5.9                | 0.95 (0.34-2.69)        |     |
| Histology type        |                    |                         |     |                    |                         |     |
| GBM                   | 28.9               | Ref                     | .30 | 8.4                | Ref                     | .20 |
| Non-GBM               | 25.8               | 0.45 (0.09-2.09)        |     | 9.7                | 0.44 (0.12-1.57)        |     |
| Grade                 |                    |                         |     |                    |                         |     |
| Grade 3               | 21.3               | Ref                     | .78 | 9.7                | Ref                     | .26 |
| Grade 4               | 28.9               | 1.16 (0.40-3.34)        |     | 8.4                | 1.79 (0.64-4.93)        |     |
| H3K27M mutation       |                    |                         |     |                    |                         |     |
| No                    | NR                 | Ref                     | .50 | 45.1               | Ref                     | .26 |
| Yes                   | NR                 | 0.02 (0–1919)           |     | 10.1               | 2.66 (0.47–15.10)       |     |
| Concurrent Chemo-therapy |                |                         |     |                    |                         |     |
| No                    | 18.2               | Ref                     | .24 | 10.9               | Ref                     | .12 |
| Yes                   | 21.2               | 2.12 (0.60-7.45)        |     | 8.8                | 2.23 (0.81-6.14)        |     |
| LMD                   |                    |                         |     |                    |                         |     |
| No                    | 25.8               | Ref                     | .75 | 9.7                | Ref                     | .33 |
| Yes                   | 21.3               | 1.17 (0.43–3.20)        |     | 7.4                | 1.54 (0.64–3.67)        |     |

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