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Increased Subventricular Zone Radiation Dose Correlates With Survival in Glioblastoma Patients After Gross Total Resection

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Abstract

Purpose—Neural progenitor cells in the subventricular zone (SVZ) have a controversial role in glioblastoma multiforme (GBM) as potential tumor-initiating cells. The purpose of this study was to examine the relationship between radiation dose to the SVZ and survival in GBM patients.

Methods and Materials—The study included 116 patients with primary GBM treated at the Johns Hopkins Hospital between 2006 and 2009. All patients underwent surgical resection followed by adjuvant radiation therapy with intensity modulated radiation therapy (60 Gy/30 fractions) and concomitant temozolomide. Ipsilateral, contralateral, and bilateral SVZs were contoured on treatment plans by use of coregistered magnetic resonance imaging and computed tomography. Multivariate Cox regression was used to examine the relationship between mean SVZ dose and progression-free survival (PFS), as well as overall survival (OS). Age, Karnofsky Performance Status score, and extent of resection were used as covariates. The median age was 58 years (range, 29–80 years).

Results—Of the patients, 12% underwent biopsy, 53% had subtotal resection (STR), and 35% had gross total resection (GTR). The Karnofsky Performance Status score was less than 90 in 54 patients and was 90 or greater in 62 patients. The median ipsilateral, contralateral, and bilateral mean SVZ doses were 48.7 Gy, 34.4 Gy, and 41.5 Gy, respectively. Among patients who underwent GTR, a mean ipsilateral SVZ dose of 40 Gy or greater was associated with a

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significantly improved PFS compared with patients who received less than 40 Gy (15.1 months vs 10.3 months; $P=.028$; hazard ratio, 0.385 [95% confidence interval, 0.165–0.901]) but not in patients undergoing STR or biopsy. The subgroup of GTR patients who received an ipsilateral dose of 40 Gy or greater also had a significantly improved OS (17.5 months vs 15.6 months; $P=.027$; hazard ratio, 0.385 [95% confidence interval, 0.165–0.895]). No association was found between SVZ radiation dose and PFS and OS among patients who underwent STR or biopsy.

Conclusion—A mean radiation dose of 40 Gy or greater to the ipsilateral SVZ was associated with a significantly improved PFS and OS in patients with GBM after GTR.

Introduction

Glioblastoma multiforme (GBM) contains a subset of stem-like cells that are capable of self-renewal, tumor propagation, and differentiation into multiple lineages (1). Whether these glioma stem cells are the cell of origin of gliomas is unknown, but this population may play an important role in tumor recurrence because they are resistant to chemotherapy and radiation therapy and are capable of initiating tumors that recapitulate GBM histology (1, 2).

A putative source of glioma stem cells is the subventricular zone (SVZ), the largest area of neurogenesis in the adult human brain (3). Multipotent neural progenitor cells (NPCs) line the lateral wall of the lateral ventricles (LVs). These NPCs share many properties with glioma stem cells including their ability to migrate in humans (4). Furthermore, GBMs that contact the LVs have been associated with multifocal dissemination (5, 6) and worse overall survival (OS) than nonperiventricular GBMs (7, 8). Moreover, in mouse models, activation of oncogenes in SVZ NPCs leads to increased NPC proliferation, cell survival, and migration, as well as the development of infiltrating gliomas in the rodent cortex (9, 10). Given the evidence that suggests that cells from the SVZ potentially initiate or contribute to GBMs and worsen patient outcome, therapy that targets these cells may be potentially beneficial.

Two small retrospective series have shown that an increased adjuvant radiation dose to the SVZ was associated with improved progression-free survival (PFS) (11, 12). The first study examined a heterogeneous group of 55 World Health Organization grade 3 and grade 4 gliomas and found that a mean dose greater than 43 Gy to the bilateral SVZ significantly improved PFS (11). More recently, a second group reported that a mean dose greater than 58 Gy was prognostic for OS in 40 patients with GBM (12). However, given the small patient numbers, heterogeneous outcomes, and varying radiation dose stratifications, it is unclear whether inclusion of the SVZ in radiation treatment is beneficial for patient outcome.

The purpose of this study was to further examine the relationship between radiation dose to the SVZ and patient outcome in a large, homogeneous group of patients with primary GBM who were treated uniformly with surgical management followed by concomitant adjuvant temozolomide and radiation therapy at a single institution.

Methods and Materials

Patient selection and characteristics

One hundred sixteen patients with primary histopathologically diagnosed GBM treated at the Johns Hopkins Hospital between 2006 and 2009 were included in the analysis under institutional review board approval. All included patients underwent surgical management (gross total resection [GTR]/subtotal resection [STR]/biopsy) followed by adjuvant radiation therapy with intensity modulated radiation therapy (60 Gy/30 fractions) and concomitant temozolomide. All patients were aged greater than 18 years and had a minimum follow-up of 7 months after completion of radiation therapy treatment. Only patients with complete treatment plan dosimetry data were included in the analysis. Dates of patients' deaths were collected from their medical records and the Social Security Death Index.

Contouring and dosimetry data collection

GBM tumor target volumes were defined at the time of original treatment planning by the radiation oncologist. Gross tumor volume 1 (GTV1) was defined on a T1-weighted magnetic resonance imaging (MRI) sequence after gadolinium plus a T2 fluid-attenuated inversion recovery (FLAIR) sequence MRI. This initial treatment volume plus a 1- to 1.5-cm margin was defined as planning target volume 1 (PTV1) and treated to 46 Gy in 23 fractions. Gross tumor volume 2 (GTV2) was defined on a T1-weighted MRI sequence after gadolinium. This cone-down volume plus an approximately 1- to 1.5-cm margin was defined as planning target volume 2 (PTV2) and treated to an additional 14 Gy in 7 fractions. A portion of the SVZ was only included in the planning target volume if it overlapped with the GTV1, GTV2, PTV1, or PTV2 criteria and was not purposefully included or excluded by the treating radiation oncologist.

Ipsilateral, contralateral, and bilateral SVZs were retrospectively contoured on treatment plans by use of coregistered MRI and computed tomography. The SVZ was defined as a 5-mm margin along the lateral wall of the LVs (Fig. 1). This SVZ contour definition was in accordance with operational definitions of the SVZ as a 3- to 5-mm periventricular region on the lateral wall of the LV, as well as by the protocol used by Evers et al (11) in 2010 and Gupta et al (12) in 2012, as outlined by Barani et al in 2007 (13). Dose-volume histograms were calculated, and mean doses were extracted for ipsilateral, contralateral, and bilateral SVZ regions of interest, as well as GTV1, GTV2, PTV1, and PTV2.

Statistical analysis

Data analysis and statistical tests were completed with SPSS software (version 20; SPSS, Chicago, IL). The PFS endpoint was defined as the date of radiologic evidence of recurrence and concomitant acknowledgment of disease progression and a change in treatment plan by the treating neuro-oncologist or patient death if this occurred before there was radiologic evidence of disease progression.

Univariate Cox proportional hazards analysis was used to identify prognostic factors for PFS and OS. Patient age was stratified as younger than 70 years versus 70 years or older. Karnofsky Performance Status (KPS) score at diagnosis was stratified as less than 90 versus

90 or greater. Surgical management was categorized as stereotactic biopsy, STR, and GTR. Extent of resection was categorized as GTR in which there was no residual contrast enhancement on MRI; STR was defined as resection with residual contrast enhancement. Patients lost to follow-up or those who were alive and had not progressed at the time of analysis were censored at the time of last follow-up when we examined PFS. Patients lost to follow-up or those who were alive at the time of analysis were censored at the time of last follow-up when we examined OS.

Multivariate Cox proportional hazards analysis was used to examine the relationship between mean SVZ dose and PFS, as well as OS. Age, KPS score, and extent of resection were used as covariates based on univariate prognostic analysis and inclusion of factors known to affect GBM patient outcome. During analysis, mean ipsilateral, bilateral, and contralateral SVZ doses were stratified into a high-dose or low-dose arm at the 25th, 50th, and 75th percentiles. Kaplan-Meier plots of survival and hazards were generated. This analysis was completed for all patients as well as the resection subgroup of STR and GTR patients and the GTR-only subgroup.

Results

Patient characteristics

The median age of patients in this study was 58 years (range, 29–80 years). Of the patients, 12% underwent biopsy, 53% had STR, and 35% had GTR. The KPS score was less than 90 in 54 patients and was 90 or greater in 62 patients. Ipsilateral, contralateral, and bilateral contoured volume averages were 7.05 cm³, 7.91 cm³, and 14.8 cm³, respectively. The median ipsilateral, contralateral, and bilateral mean SVZ doses were 48.7 Gy (range, 1.98–60.0 Gy), 34.4 Gy (range, 1.59–60.0 Gy), and 41.5 Gy (range, 1.77–60 Gy), respectively. Patient characteristics and quartile doses are listed in Table 1.

Prognostic factors on univariate analysis

On univariate analysis of all 116 patients, age younger than 70 years trended as a beneficial prognostic factor for OS ($P=.155$; hazard ratio [HR], 0.645 [95% confidence interval (CI), 0.352–1.18]) when compared with age of 70 years or older. A KPS score of less than 90 trended ($P=.191$) as a negative prognostic factor for OS ($P=.191$; HR, 1.29 [95% CI, 0.88–1.89]) compared with a KPS score of 90 or greater. Finally, biopsy had a statistically significantly worse PFS compared with resection with GTR or STR ($P=.006$; HR, 2.29 [95% CI, 1.26–4.15]). Biopsy trended toward worse OS ($P=.191$; HR, 1.48 [95% CI, 0.823–2.64]). Direct contact of the tumor with the LV was not prognostic for PFS or OS, with tumor boundaries defined by edge of contrast enhancement. Univariate analysis for patients who underwent STR and GTR resection, as well as GTR-only patients, was also completed (Table 1).

Multivariate analysis

We conducted multivariate analysis to determine whether SVZ dose was associated with patient survival using age, surgical resection, and KPS score as covariates. Although not all covariates were statistically significant, these factors were included in the multivariate

analysis on the basis of being known prognostic factors for GBM patient survival. In the subgroup of GTR patients, a mean ipsilateral SVZ dose of 40 Gy or greater had a significantly improved PFS of 15.1 months compared with 10.3 months in patients who received less than 40 Gy ($P=.028$; HR, 0.385 [95% CI, 0.165–0.901]) (Fig. 2, Table 2). Moreover, in patients who underwent GTR, a dose of 40 Gy or greater was associated with a significantly improved OS (17.5 months vs 15.6 months; $P=.027$; HR, 0.385 [95% CI, 0.165–0.895]) when compared with those who received less than 40 Gy (Fig. 3, Table 2). Although a higher ipsilateral SVZ radiation dose significantly improved PFS and OS in the GTR subgroup, this result was not significant when all patients were included or in the subgroup that included both STR and GTR resections. The association of bilateral and contralateral SVZ doses with PFS and OS was also evaluated and was not found to be statistically significant when patients were stratified at the 25th, 50th, or 75th dose percentiles.

Correlation between ipsilateral SVZ dose and KPS score

Of 116 patients, 23 received an ipsilateral SVZ dose of less than 40 Gy and 93 received an ipsilateral SVZ dose of 40 Gy or greater. Of the 23 patients who received less than 40 Gy, 7 had a decrease in KPS score of 10 or greater when we compared KPS before radiation treatment and KPS at the end of radiation treatment. Of the 93 patients who received 40 Gy or greater, 22 had a decrease in KPS score of 10 or greater. This difference was not significant by the Fisher exact test ($P=.592$), and radiation dose to the ipsilateral SVZ did not correlate with changes in KPS score (Table 3).

Discussion

The SVZ is a large source of neurogenesis in the LVs of the adult human brain. Whether SVZ NPCs have a functional role or contribute to tumor initiation and recurrence is controversial, and radiation oncologists have proposed sparing the SVZ in treatment plans (13, 14). Although in humans the functional role of NPCs is unclear, in rodents NPCs have been shown to migrate and replace endogenous cells after cortical injury, after stroke, and in epilepsy (15). Moreover, in numerous animal studies, NPCs have exhibited tropism to gliomas, and in some studies NPCs have exerted an antitumor effect that improved survival in animal models (16–19).

In contrast, NPCs are also hypothesized to be the origin of gliomas and to contribute to recurrence. Glioma stem cells and NPCs share many properties including self-renewal and an undifferentiated state. However, in glioma stem cells, proliferation and differentiation are dysregulated, and they have the capacity for tumor propagation. This dysregulation can be achieved in NPCs through induced activation of oncogenes in rodents, which results in gliomas (9, 10). In addition, factors released by glioma cells are hypothesized to recruit NPCs in close proximity and potentially induce NPC malignant transformation (20). Thus the potential for NPCs to be recruited to tumors and undergo malignant transformation represents a risk for cells within the SVZ to contribute to GBMs or potentially give rise to tumors.

Given that the role of neural stem cells in glioma is highly controversial, the findings in this retrospective study support the hypothesis that cells within the SVZ may contribute to glioma recurrence and worsen patient survival. Interestingly, the finding that an ipsilateral SVZ dose of 40 Gy or greater was an independent predictor for PFS and OS was only restricted to those patients who had undergone GTR. One hypothesis for this finding might be that although NPCs in the SVZ seem to play a significant role in recurrence in patients who have undergone extensive resection, residual tumor mass outgrowth may be largely responsible for recurrence in patients with subtotal or biopsy. Notably, an ipsilateral SVZ dose of 40 Gy or greater did not correlate with worsened patient KPS score at the end of radiation treatment. Given the findings that higher radiation dose to the ipsilateral SVZ positively impacted patient survival without impairing short-term functional status in this cohort, further investigation through multi-institutional validation sets is warranted to account for biases inherent in the current retrospective literature.

As a retrospective study, our study is limited by several factors. Although we used age, KPS score, and extent of surgical resection as covariates in our multivariate analysis, multiple alternative factors may confound our results. Tumor location and relationship to the LVs, for instance, represent a confounding variable because tumors in contact with the SVZ inherently receive a higher radiation dose. Thus it is difficult to retrospectively determine whether radiation to the SVZ correlates with improved PFS and OS in tumors located farther from the SVZ. Moreover, deep-seated tumors that contact or are near the SVZ pose technical challenges for extensive surgical resection and represent a further bias in our survival analysis.

In addition, contact with the LVs has been previously associated with worse OS and multifocal disease in a retrospective cohort-matched study of 52 patients and another retrospective study of 91 patients (7, 8). However, contrast-enhancing LV contact was not significant in our cohort of 116 patients with multivariate analysis. Tumor contact with the SVZ may be negatively prognostic because it is hypothesized that cells in the SVZ contribute to the tumor. Conversely, higher radiation doses to the SVZ may target cells within the SVZ that potentially worsen patient outcome. Therefore these represent 2 potentially competing factors that influence patient outcome, and we hypothesize that patient PFS and OS are benefited by the irradiation of SVZ cells, causing elimination of cells that contribute to tumor progression.

Multivariate analysis for survival including both tumor LV contact and SVZ radiation dose as simultaneous covariates was not evaluated because of variable multicollinearity. SVZ radiation dose and tumor contact are highly correlated factors because the SVZ of GBMs contacting the LV inherently receive greater radiation dose. Furthermore, to be consistent with prior studies, the relationship between tumor contact to the LV and survival was defined on the T1 post-contrast MRI study (5, 7, 8). However, this definition does not account for tumor infiltration beyond contrast enhancement. Moreover, evaluation of additional patients would allow for a more robust multivariate analysis to account for additional confounding factors, particularly because our survival findings were limited to a subgroup of patients who underwent GTR and these findings were not significant in less extensive resections.

Moreover, although dichotomizing our patients at 70 years for age was most prognostic for our retrospective dataset, this may not be the best prognostic stratification universally. Finally, although patients included in this series received uniform first-line therapy with surgical resection, intensity modulated radiation therapy, and temozolomide chemotherapy at a single institution, upon recurrence, patients were treated with differing salvage therapies. These reinterventions consisted of re-resection, Gliadel (Eisai Inc, Woodcliff Lake, NJ) wafers, and additional chemotherapy regimens for recurrent GBM and represent an additional confounding factor in our survival data.

To conclude, we present a large, uniform patient cohort and show an impact on progression and survival through multivariate analysis accounting for age, extent of resection, and KPS score as confounding variables. Our results are in congruence with other groups who have also found a correlation between increased mean radiation dose to the SVZ and improved patient outcomes in 2 smaller independent series (11, 12). We showed that a higher radiation dose to the ipsilateral SVZ was associated with improved PFS and OS in GBM patients who underwent GTR without negatively impacting KPS. Further evaluation through additional multi-institutional validation sets, or prospective clinical trials, would be critical in determining whether inclusion of the SVZ in radiation treatment fields reduces GBM recurrence and improves patient survival.

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Summary

We aimed to examine the relationship between radiation dose to the sub-ventricular zone and progression-free survival, as well as overall survival, for glioblastoma patients. Survival and dosimetry data were retrospectively collected from 116 patients with primary glioblastoma who were uniformly treated. A mean radiation dose of 40 Gy or greater to the ipsilateral subventricular zone was associated with significantly improved progression-free and overall survival for patients with glioblastoma after gross total resection.

Fig. 1.

Representative 2-dimensional subventricular zone (SVZ) contouring. The periventricular region contours were the ipsilateral SVZ and contralateral SVZ. The tumor treatment area contours were gross tumor volume 1 (GTV1), gross tumor volume 2 (GTV2), planning target volume 1 (PTV1), and planning target volume 2 (PTV2). Periventricular contours (green) and tumor treatment contours comprised GTV1 (blue) and PTV1 (teal) shown on computed tomography (A), T1 after gadolinium (B), and fluid-attenuated inversion recovery (FLAIR) sequences (C).

Fig. 2.

Progression-free survival (PFS) by ipsilateral sub-ventricular dose in gross total resection patients (n=41). PFS in patients whose ipsilateral subventricular zone (SVZ) received less than 40 Gy was significantly different from that in those who received a dose of 40 Gy or greater as measured by median survival of 10.3 months versus 15.1 months (95% confidence interval, 7.4–13.2 months) and log-rank test ($P=.023$), as well as adjusted hazard ratio for PFS (2.60) ($P=.028$).

Fig. 3.

Overall survival (OS) by ipsilateral subventricular dose in gross total resection patients (n=41). OS in patients whose ipsilateral subventricular zone (SVZ) received less than 40 Gy was significantly different from that in those who received a dose of 40 Gy or greater as measured by median survival of 15.6 months versus 17.5 months (95% confidence interval, 11.3–19.9 months) and adjusted hazard ratio for progression-free survival (2.60) ($P=.027$).

Table 1

Patient demographics, disease, and treatment characteristics

Characteristic	All patients (N=116)	STR and GTR subgroup (n=102)	GTR subgroup (n=41)
Sex			
Male	70 (60%)	61 (60%)	25 (61%)
Female	46 (40%)	41 (40%)	16 (39%)
Age			
Median (y)	58 (29–80)	59 (29–78)	58 (29–77)
<70 y	103 (89%)	90 (88%)	37 (90%)
70 y	13 (11%)	12 (12%)	4 (10%)
Karnofsky Performance Status score			
<90	54 (46%)	45 (44%)	13 (32%)
90	62 (54%)	57 (56%)	28 (68%)
Extent of resection			
Biopsy	14 (12%)	0	0
STR	61 (53%)	61 (60%)	0
GTR	41 (35%)	41 (40%)	41 (100%)
Tumor lateral ventricle contact			
Contact	58 (50%)	52 (51%)	22 (54%)
No contact	58 (50%)	50 (49%)	19 (46%)
FLAIR volume (cm ³)	99.4	102	96.0
T1 post-gadolinium volume (cm ³)	54.0	54.1	47.4
Ipsilateral subventricular zone			
Contoured volume (cm ³)	7.05 (2.99–14.2)	7.01 (3.00–14.2)	6.55 (3.00–12.0)
Mean dose (Gy)	48.7 (1.96–60)	48.3 (1.96–60.0)	46.7 (3.48–60.0)
Quartiles (25th, 50th, 75th)	42.9, 52.9, 58.3	41.3, 52.4, 58.2	40.1, 49.8, 57.3
Contralateral subventricular zone			
Contoured volume (cm ³)	7.91 (4.18–14.6)	7.98 (4.18–14.6)	7.35 (4.23–12.2)
Mean dose (Gy)	34.4 (1.59–60)	33.9 (1.59–60.0)	31.9 (1.87–59.1)
Quartiles (25th, 50th, 75th)	34.39, 42, 50.81	24.2, 34.1, 45.5	18.5, 33.7, 41.5
Bilateral subventricular zone			
Contoured volume (cm ³)	14.76 (5.37–28.3)	14.9 (5.37–28.3)	14.0 (7.91–24.0)
Mean dose (Gy)	41.5 (1.77–60)	40.8 (1.78–60.0)	39.2 (2.53–60.0)
Quartiles (25th, 50th, 75th)	34.39, 42, 50.81	33.2, 41.5, 50.0	30.4, 41.9, 47.9

Abbreviations: FLAIR = fluid-attenuated inversion recovery; GTR = gross total resection; STR = subtotal resection.

Table 2

Univariate Cox regression analysis for associations between patient characteristics and survival

Prognostic factor	PFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<70 y vs ≥70 y)				
Biopsy, STR, and GTR	1.03 (0.562–1.88)	.928	0.645 (0.352–1.18)	.155
STR and GTR	0.924 (0.491–1.74)	.809	0.409 (0.215–0.778)	.006
GTR only	1.21 (0.423–3.47)	.720	0.278 (0.095–0.813)	.019
KPS score (<90 vs ≥90)				
Biopsy, STR, and GTR	1.13 (0.771–1.66)	.53	1.29 (0.88–1.89)	.191
STR and GTR	1.15 (0.761–1.73)	.514	1.26 (0.835–1.89)	.274
GTR only	0.965 (0.481–1.94)	.92	1.13 (0.568–2.26)	.724
Extent of resection				
Biopsy vs craniotomy	2.29 (1.260–4.15)	.006	1.48 (0.823–2.64)	.191
STR vs GTR	1.17 (0.78–1.78)	.440	1.16 (0.767–1.75)	.481
Tumor LV contact (no contact vs contact)				
Biopsy, STR, and GTR	1.11 (0.795–1.71)	.429	0.904 (0.618–1.32)	.605
STR and GTR	1.16 (0.772–1.75)	.467	0.972 (0.648–1.46)	.893
GTR only	1.45 (0.765–2.77)	.253	1.25 (0.666–2.35)	.487
Ipsilateral dose (<40 Gy vs ≥40 Gy)				
Biopsy, STR, and GTR	0.824 (0.506–1.34)	.434	0.926 (0.570–1.50)	.754
STR and GTR	0.771 (0.464–1.28)	.314	0.929 (0.562–1.54)	.775
GTR only	0.471 (0.209–1.06)	.070	0.607 (0.280–1.32)	.207

Abbreviations: CI = confidence interval; GTR = gross total resection; HR = hazard ratio; KPS = Karnofsky Performance Status; LV = lateral ventricle; OS = overall survival; PFS = progression-free survival; STR = subtotal resection.

Table 3

Multivariate Cox regression analysis for associations between ipsilateral subventricular dose and survival

Prognostic factor	PFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
GTR, STR, and biopsy patients				
Dose (40 Gy vs <40 Gy)	0.749 (0.453–1.24)	.259	0.827 (0.502–1.36)	.455
Age (<70 y vs 70 y)	1.04 (0.556–1.93)	.911	0.727 (0.376–1.41)	.342
KPS score (<90 vs 90)	1.03 (0.689–1.55)	.875	1.25 (0.846–1.85)	.262
Resection (biopsy vs craniotomy)	2.40 (1.28–4.51)	.006	1.34 (0.713–2.52)	.363
GTR and STR patients				
Dose (40 Gy vs <40 Gy)	0.761 (0.464–1.71)	.292	0.845 (0.505–1.42)	.523
Age (<70 y vs 70 y)	0.892 (0.464–1.71)	.731	0.400 (0.206–0.778)	.007
KPS score (<90 vs 90)	1.13 (0.735–1.73)	.579	1.25 (0.811–1.91)	.316
Resection (STR vs GTR)	1.15 (0.75–1.75)	.527	1.05 (0.681–1.61)	.834
GTR patients				
Dose (40 Gy vs <40 Gy)	0.385 (0.165–0.901)	.028	0.385 (0.165–0.895)	.027
Age (<70 y vs 70 y)	1.14 (0.378–3.43)	.819	0.205 (0.066–0.634)	.006
KPS score (<90 vs 90)	1.23 (0.571–2.67)	.592	1.51 (0.705–3.23)	.289

Abbreviations: CI = confidence interval; GTR = gross total resection; HR = hazard ratio; KPS = Karnofsky Performance Status; OS = overall survival; PFS = progression-free survival; STR = subtotal resection.