



Molecular features and clinical outcomes in surgically treated low-grade diffuse gliomas in patients over the age of 60

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Abstract

Purpose WHO grade II gliomas are uncommon in patients over the age of 60, and there is a lack in consensus regarding their management. We present molecular tumor characteristics as well as clinical outcomes in patients over the age of 60 undergoing surgical resection of a WHO grade II glioma.

Methods After receiving IRB approval, patients were identified through the UCSF Brain Tumor Center. Pathologic diagnosis was completed using WHO 2016 grading criteria.

Results Twenty-six patients with a mean age of 66 years met inclusion criteria with a median follow-up of 5.2 years. Diagnoses included diffuse astrocytoma *IDH*-mutant (19.2%), diffuse astrocytoma *IDH*-wildtype (26.9%), Oligodendroglioma *IDH*-mutant and 1p/19q-codeleted (50%), and a rare case of mixed oligoastrocytoma (3.9%). 66% of astrocytoma *IDH*-wildtype tumors possessed TERT mutation. Median extent of resection was 75.4%. Progression-free (PFS) and overall survival (OS) were 23.5 and 62.6 months, respectively. Shorter PFS was associated with the astrocytoma *IDH*-wildtype subtype despite similar extent of resection and adjuvant treatment rates compared to the other subtypes. OS did not differ between subtypes. Malignant transformation and death were associated with larger preoperative and residual tumor volume.

Conclusions Older patients with diffuse gliomas may safely undergo aggressive treatment with surgical resection and adjuvant therapy. Elderly patients with low grade gliomas have worse clinical outcomes compared to their younger counterparts. This may be due to an increased frequency of diffuse astrocytoma *IDH*-wildtype tumors in this age group.

Keywords Low-grade glioma · Surgical resection · Elderly · Old age

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Introduction

Low grade oligodendrogliomas and astrocytomas, grade II per World Health Organization (WHO) Classification of Central Nervous System Tumours, occur in a younger age group compared to WHO grade III and IV gliomas. The mean age of diagnosis for WHO grade II gliomas is in the late third or early fourth decade of life [1, 2]. However, only about 10–18% of low-grade gliomas occur in patients at least 60 years-of-age or older, and there is a lack of consensus regarding the optimal management strategy and molecular differences in older patients [2, 3].

The molecular profiles of these tumors have more recently been defined [2, 4], although the number of older patients within these cohorts are limited. The Cancer Genome Atlas Research Network performed a genome-wide analysis on 293 grade II/III gliomas and defined three separate glioma subgroups based on *IDH*, 1p/19q, and TP53 status. Within

the cohort of grade II gliomas, there were 13 *IDH*-wildtype (9.5%), 48 *IDH*-mutant and 1p/19q-codeleted (35.3%), and 75 *IDH*-mutant and 1p/19q-intact (55.1%) tumors. However, only 14 patients had grade II tumors and were 60 years of age or older (2 *IDH*-wildtype, 2 *IDH*-mutant and 1p/19q-codeleted, and 4 *IDH*-mutant and 1p/19q-intact) [4]. Eckel-Passow et al. reported on 615 patients with grade II/III gliomas and defined 5 glioma subgroups based on *IDH*, 1p/19q and *TERT* status. Within the group of grade II tumors, there were 26 *IDH*-wildtype (8.5%), 111 *IDH*-mutant and 1p/19q-codeleted (36.1%), and 170 *IDH*-mutant and 1p/19q-intact (55.4%) tumors. Interestingly, *TERT* promoter mutation-only tumors tended to occur more frequently in older patients with an average age of 59 with the second oldest subgroup being triple negative tumors [2]. While prior reports have examined outcomes in older patients with low grade gliomas, no prior reports to our knowledge have specifically examined such a cohort based on this newer molecular characterization.

Within the context of grade II glioma, older age often results in worse overall and progression free survival and more aggressive clinical behavior which may be related to a combination of patient, treatment, and tumor characteristics [5–10]. Older patients have been reported to have higher rates of neurological deficits on presentation, increased tumor burden and a higher incidence of contrast-enhancing features on imaging on retrospective analyses [11, 12]. Analysis of preoperative variables for overall survival has also demonstrated older age as a poor prognostic factor [7, 13]. Chang et al. reported on a pre-operative scoring system for low-grade gliomas in adults who were undergoing first-time resection using an institutional series of 281 patients. On multivariate analysis, eloquent location, KPS score, age > 50, and tumor diameter > 4 cm allowed for a 4-point scoring system predicting both OS and PFS with more points correlating with worse outcomes. Worse outcomes with age was believed to be secondary to a more malignant underlying biology as well as patient specific factors including natural life expectancy, higher rates of medical comorbidities, and increased vulnerability to illness post-operatively [7].

Currently the patient's age plays a significant role in determining the adjuvant treatment course. Based on results of RTOG 9802, a phase 3 randomized trial comparing adjuvant radiation with combination chemoradiation in "high risk" patients with low-grade gliomas, adjuvant therapy with chemoradiation is recommended for all patients older than 40 years [14]. RTOG 9802 highlighted the aggressive nature of low grade gliomas in older patients and the clear need for and benefit of aggressive adjuvant therapy in this cohort. However, there still exists a hesitation in pursuing aggressive treatment strategies in older patients. Clinically, some providers advocate for aggressive upfront treatment while others recommend a more conservative approach [11,

15, 16]. Older patients with gliomas tend to undergo lower rates of treatment with surgical resection and radiotherapy compared to younger cohorts of patients due to concern for high rates of treatment-related complications [11, 12, 17]. National Comprehensive Cancer Network (NCCN) guidelines do not distinguish whether to offer maximal safe resection vs biopsy based on patient age. Additionally, if biopsy is pursued rather than resection, a low grade diagnosis in this age group may represent under-sampling of a high grade glioma. In this report, we sought to determine postsurgical morbidity within older patients with low grade gliomas associated with aggressive resection, the molecular features within this cohort, as well as more long-term clinical outcomes based on treatment and molecular features.

Methods

Patient selection, data collection, and defining molecular grouping and outcomes

After obtaining approval from the UCSF institutional IRB (Study Number 15-17826), a search query was performed through UCSF Brain Tumor Center to include patients with a primary histologic diagnosis of WHO grade II glioma at least 60 years-of-age at the time of initial surgery that had undergone surgical resection more than biopsy alone. Patients were excluded if they had prior chemotherapy, radiation treatment, or surgical resection. This query identified 26 patients diagnosed between 1997 and 2017. Patient and tumor characteristics in addition to perioperative outcomes were collected retrospectively from operative, radiology, pathology, and scanned documents available through the UCSF electronic medical record. An integrated diagnosis based on the 2016 WHO classification scheme was utilized. *IDH* mutation and 1p/19q-codeletion status was determined for all cases. The study neuropathologist (M.P.) reviewed all cases to confirm diagnostic classification and grading based on WHO 2016 criteria. Contrast enhancement of tumors was determined by both review of the radiology report as well as direct review of preoperative post-contrast MRI scans by the authors. Adjuvant therapy was defined as treatment that was received after surgery but before progression. Recommendation of adjuvant therapy was based on discussion within the UCSF Tumor Board or by the direction of the patient's primary neuro-oncologist at UCSF and was based on pathologic diagnosis, age, patient preference, and availability of clinical trials. Progression-free survival (PFS) was defined as the time from the procedure date until the date of the first scan demonstrating unequivocal radiographic progression with confirmation based on the radiology report and clinic notes. Malignant progression was based on biopsy confirmation of a higher tumor grade or new enhancement

on imaging with the consensus opinion of the UCSF tumor board that the findings represented progression to a higher grade rather than treatment effect.

Molecular analysis

Of the 26 surgical specimens, *IDH* mutation status as well as 1p/19q co-deletion status were available for all specimens and allowed for categorization of subtype based on the 2016 WHO classification [18]. *IDH* mutation status was assessed by immunohistochemistry (IHC) using primary antibody specific to IDH1R132H mutant protein (H09, Dianova GmbH, Hamburg, Germany) using standard techniques, and all cases with positive IDH1R132H stain were classified as *IDH*-mutant. In cases with negative IHC results, Sanger sequencing of *IDH1* and *IDH2* genes covering exon 4 regions was performed and tumors were classified as mutant or wildtype accordingly. *ATRX* alterations were assessed by IHC (HPA001906, Sigma Aldrich, St. Louis, MO) using standard techniques, and loss of nuclear staining in the majority of the tumor cells in the presence of an internal positive control was interpreted as loss of *ATRX* expression, suggestive of *ATRX* alterations. *TP53* alterations were assessed by IHC (DO-7, Dako, Agilent, Santa Clara, CA) using standard techniques, and strong nuclear staining in more than 50% of tumor nuclei was interpreted as positive, and these cases were classified as *TP53*-mutant. A subset of cases was assessed by Sanger sequencing of *TP53* gene covering exons 4 through 8 and tumors were classified as mutant or wildtype according to sequencing results. Chromosome 1p and 19q deletions were separately assessed by fluorescence in situ hybridization using Vysis 1p36/19q13 Dual color Probe kit (Abbott Laboratories, Abbott Park, IL). Upon counting at least 50 non-overlapping cells, a 1p36:1q25 (or 19q13:19p13) ratio of 0.8 or less was accepted as deleted if > 15% of cells have an at least 2:1 ratio of target:reference probe. Cases with both 1p and 19q deletion were classified as 1p/19q-codeleted. *TERT* promoter mutation was assessed either by a single- or a 2-step PCR and Sanger sequencing of a 244 base-pair segment of *TERT* promoter region spanning the C228T and C250T mutations, and the cases were classified as *TERT*-mutant or *TERT*-wildtype accordingly.

Volumetric analysis and extent of resection quantification

Pre-operative and post-operative tumor volumes were quantified by using BrainLab Smartbrush software (Brainlab, Munich, Germany). Manual segmentation was performed with region-of-interest analysis based on fluid-attenuated inversion-recovery (FLAIR) sequences from pre- and post-operative MRI scans to quantify tumor volume. Extent of Resection (EOR) was calculated as: (pre-operative tumor

volume – post-operative tumor volume)/pre-operative tumor volume × 100%. Manual segmentations were performed by one operator (R.M.) with tumor volumetrics verified for accuracy after an initial training period (S.H.). Knowledge of clinical outcomes was withheld from participants involved in tumor volumetrics and perioperative outcomes data collection. Pre-operative MRI scans were obtained within 24 h prior to resection, and post-operative scans were all obtained within 48 h post-resection. All patients in the cohort had available preoperative and postoperative MRI scans for analysis. To ensure that post-operative FLAIR signal was not surgically induced edema or ischemia, FLAIR pre- and post-operative MRIs were carefully compared alongside DWI sequences prior to including each region in the volume segmentation. Post-contrast T1 weighted images were not used for EOR analysis because for many patients with enhancement, this was diffuse and patchy, making volumetric analysis unreliable. For the analysis, GTR, STR, and partial resection were defined as 100%, 70–99%, and < 70%, respectively.

Statistical analysis

Descriptive statistics were used to define the patient cohort, tumor locations and characteristics, treatment details, EOR, and neurological outcomes. One-way analysis of variance (ANOVA), χ^2 test, and Pearson linear correlation coefficient were performed for univariate analysis. Log-rank test was performed to assess differences in PFS and OS and included patients with at least 30 days of follow-up. The level of significance was 0.05 for all analyses. Statistical analysis was performed using JMP Pro 13 (SAS Institute, Cary, NC).

Results

Patient and tumor characteristics

Demographics and tumor characteristics are listed in Table 1. The mean age at the time of surgery was 66.2 years (range 60.3–76.7) with a median follow-up of 5.2 years (range 0.4–12.4 years). The majority of tumor involved the frontal lobe (38.5%) and were left-sided (57.7%). Pathologic diagnoses based on the updated 4th edition of WHO classification included five cases of diffuse astrocytoma, *IDH*-mutant, seven cases of diffuse astrocytoma, *IDH*-wildtype, and 15 cases of oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted. There was one case designated as a mixed oligoastrocytoma. For this case, histology demonstrated distinct regions of oligodendroglioma and astrocytoma morphology. The oligodendroglioma-like component showed IDH1 R132H mutation, 1p/19q-codeletion, retained *ATRX* expression

Table 1 Patient and tumor characteristics

Patients (#)	26
Mean age [range]	66.2 [60.3–76.7]
Sex (#, %)	
Male	13 (50%)
Female	13 (50%)
Mean preoperative tumor volume (cm ³) [range]	58.8 [0.5–359.3]
Tumor side (#, %)	
Right	11 (42.3%)
Left	15 (57.7%)
Tumor location (#, %)	
Frontal	10 (38.5%)
Temporal	7 (26.9%)
Parietal	3 (11.5%)
Insula	6 (23.1%)
Preoperative seizures (#, %)	18 (69.2%)
Tumor pathology (#, %)	
Diffuse astrocytoma, <i>IDH</i> -mutant	5 (19.2%)
Diffuse astrocytoma, <i>IDH</i> -wildtype	7 (26.9%)
Oligodendroglioma, <i>IDH</i> -mutant and 1p/19q-codeleted	13 (50.0%)
Mixed oligoastrocytoma ^a	1 (3.9%)
Enhancement on pre-op imaging (#, %)	5 (19.2%)
Median follow-up (years) [range]	5.2 [0.4–12.4]

IDH isocitrate dehydrogenase, *TMZ* temozolomide

^aPatient with *IDH* mutation and focal 1p/19q-codeletion but *TERT* wildtype. Reviewed by two neuropathologists at UCSF who agreed upon the diagnosis

and negative p53 staining, and astrocytoma-like component demonstrated *IDH1* R132H mutation, loss of *ATRX* expression, intact 1p/19q and wildtype *TERT* promoter. Further molecular characterization of the diffuse astrocytoma, *IDH*-wildtype tumors demonstrated that 66.7% harbored a *TERT* promoter mutation (Table 2). There were five cases (19.2%) with enhancement on preoperative imaging, which was not significantly associated with any particular subtype (see Table 2). Mean preoperative tumor volume was found to be 58.8 cm³.

Surgical treatment characteristics and adjuvant therapies

Treatment characteristics of the cohort are summarized in Table 3. As many of these lesions were located adjacent to eloquent cortex, 14 cases (53.8%) utilized either language or motor mapping. The median extent of resection (EOR) was 75.4% with 8 patients (30.8%) undergoing a GTR. The majority of patients underwent adjuvant treatment postoperatively (53.9%) and after evidence of progression (75%).

Perioperative outcomes

Perioperative outcomes are summarized in Table 3. In terms of complications (including persistent neurological deficit by 90 days), one patient developed a subdural hematoma requiring evacuation and five patients developed persistent neurological deficits. Neurological deficits included two cases of persistent mild speech hesitancy, one case of single extremity weakness (4/5 proximal and 1/5 distal strength), one case of combined facial droop and upper extremity weakness (4/5 strength), and one case of a persistent superior quadrantanopsia.

Long-term clinical outcomes

Long-term outcomes are summarized in Table 3. Median censored PFS and OS were found to be 23.5 and 62.6 months, respectively. Nine cases (34.6%) on follow-up demonstrated malignant transformation. Table 2 depicts treatment characteristics and differences in clinical outcomes between the glioma molecular subtypes. Although EOR and adjuvant therapy did not significantly differ between the three molecular subtypes, diffuse astrocytoma *IDH*-wildtype cases were associated with a significantly shorter PFS (Fig. 1a; Table 2). However, molecular subtype did not appear to significantly impact overall survival (Fig. 1b; Table 2). Univariate analysis of other patient, tumor, and treatment features associated with PFS and OS did not reveal any significant associations (Table 4). Larger preoperative tumor size and a greater amount of residual tumor on postoperative scans were associated with more frequent malignant progression and death (Table 5). Contrast enhancement was not associated with a difference in PFS, OS, or malignant transformation.

Discussion

The United States population is aging, and therefore, the management of elderly patients with gliomas involves numerous considerations including the expected longevity of these patients. In 2014, life expectancy in the US at age 65 and 75 was 19.3 and 12.2 years, respectively [19]. As the life expectancy of patients age 60–69 and 70–79 with low-grade gliomas were found to be about 6 and 1.3 years respectively, further therapeutic intervention has the potential to improve both overall survival and quality of life [20]. Differences already exist in the management of older and younger patients with malignant gliomas. Kaloshi et al. compared treatment and outcomes data between 62 patients at least 60 years-of-age and 704 patients <60 years-of-age with low-grade gliomas. The authors found that in elderly patients time-to-treatment was shorter (1.2 months), chemotherapy

Table 2 Differences in demographics, treatment regimens, and clinical outcomes between glioma subtypes

	Diffuse astrocytoma, <i>IDH</i> mut (N = 5)	Diffuse astrocytoma, <i>IDH</i> wt (N = 7)	Oligodendroglioma, <i>IDH</i> mut and 1p/19q-codel (N = 13)	p-value
Molecular markers (#, %)				
<i>TERT</i> Mutation ^a	1 (20%)	4 (66.7%)	13 (100%)	0.0008
Loss of <i>ATRX</i> ^b	2 (50%)	0 (0%)	0 (0%)	0.02
<i>TP53</i> Mutation ^c	2 (66.7%)	2 (28.6%)	1 (7.7%)	0.09
Mean age	64.0 [60.0–68.1]	68.7 [65.3–72.2]	65.4 [62.9–68.0]	0.17
Male sex (#, %)	2 (40%)	4 (57.1%)	6 (46.2%)	0.83
Left sided tumor (#, %)	5 (100%)	4 (57.1%)	6 (46.2%)	0.046
Tumor site (#, %)				0.0006
Frontal	2 (40%)	0 (0%)	8 (61.5%)	
Temporal	2 (40%)	5 (71.4%)	0 (0%)	
Parietal	0 (0%)	2 (28.6%)	1 (7.7%)	
Insula	1 (20%)	0 (0%)	4 (30.8%)	
Enhancement (#, %)	1 (20%)	0 (0%)	4 (30.8%)	0.14
Mean pre-op tumor volume (cm ³ , std error)	25.0 ± 35.4	42.7 ± 29.9	82.1 ± 22.0	0.21
Mean residual tumor volume (cm ³ , std error)	7.2 ± 23.8	17.0 ± 20.1	38.2 ± 14.8	0.48
Mean EOR (% , std error)	86.8 ± 11.4	78.2 ± 9.6	67.6 ± 7.1	0.34
Adjuvant therapy (#, %) ^d				0.37
None	3 (60%)	4 (57.1%)	3 (23.1%)	
TMZ	1 (20%)	2 (28.6%)	7 (53.9%)	
TMZ + RT	1 (20%)	1 (14.3%)	1 (7.7%)	
Malignant transformation (#, %)	1 (20%)	4 (57.1%)	4 (30.8%)	0.36
Progression (#, %)	1 (20%)	5 (71.4%)	7 (53.9%)	0.19
Death (#, %)	0 (0%)	3 (42.9%)	4 (30.8%)	0.13
PFS (months)	55.9 [32.7–79.1]	16.2 [0–35.8]	37.3 [22.9–51.7]	0.04
OS (months)	72.5 [40.9–104.1]	40.7 [14.1–67.4]	67.3 [47.7–86.9]	0.21

EOR extent of resection, *PFS* progression free survival, *OS* overall survival, *TMZ* temozolomide, *RT* radiotherapy. [] denotes 95% confidence interval. The one case of mixed oligoastrocytoma was excluded for this analysis

^aData not available for one patient

^bData not available for one patient

^cData not available for two patients

^dAdjuvant therapy defined as treatment prior to first progression. Two oligodendroglioma patients lost-to-follow-up

was more often used as first line treatment (60%), and tumor resection was done at a lower rate with only 27% undergoing partial or total resection compared to 61% in the younger cohort [11]. This difference in treatment paradigm may come from prior reports demonstrating increased risk of perioperative complications and worse outcomes in older patients with malignant gliomas [7, 14]. However, patients in this age group with glioblastoma often undergo aggressive resection with acceptable perioperative outcomes, and thus, it seems counterintuitive that such an intervention would be withheld for older patients in which there is still much to be gained in terms of life expectancy.

There are a limited number of reports that have examined outcomes specifically in older patients with low-grade glioma, and most of these studies did not include a cohort of patients undergoing aggressive surgical intervention as

were included in the current cohort. Schomas et al. examined outcomes in 32 patients with low-grade gliomas who were at least 55 years of age. While a greater extent of resection did not correlate with improved outcome, only two patients underwent gross or near gross total resection, precluding meaningful statistical analysis. A greater percentage of patients also received post-operative radiotherapy (72%) with 97% receiving no chemotherapy. The only factor found to be associated with shorter PFS was enhancement on CT [12]. Chi and Batchelor reported on 16 patients with low-grade gliomas who were at least 55 years of age with 7 patients undergoing biopsy and 9 undergoing at least a partial resection. Ten patients were given adjuvant treatment with various regimens of radiation, temozolomide, or PCV. Longer PFS correlated with a histologic diagnosis of oligodendroglioma and a MIB-1 index of 5% or higher [21]. In

Table 3 Treatment characteristics and clinical outcomes

Surgical approach (#, %)	
Motor mapping	13 (50%)
Speech mapping	8 (30.8%)
Awake craniotomy	9 (34.6%)
Median EOR (range)	75.4% (18.2–100%)
GTR (#, %)	8 (30.8%)
STR (#, %)	7 (26.9%)
Partial resection (#, %)	11 (42.3%)
Median post-operative tumor volume (cm ³) [range]	7.6 [0–250.4]
Adjuvant therapy (#, %) ^a	
None	10 (38.5%)
TMZ	10 (38.5%)
TMZ+RT	4 (15.4%)
Treatment after progression (#, %) ^b	
None	3 (23.1%)
RT alone	1 (7.7%)
TMZ alone	1 (7.7%)
TMZ+RT	5 (38.5%)
Surgery+TMZ	1 (7.7%)
SRS+CCNU	1 (7.7%)
Postoperative complications (#, %)	
None	21 (80.8%)
Persistent neurological deficit	5 (19.2%)
Subdural hematoma	1 (3.8%)
Persistent neurological deficits (#, %) ^c	
None	21 (80.8%)
Speech hesitancy	2 (7.8%)
Single extremity weakness	1 (3.8%)
Facial droop and upper extremity weakness	1 (3.8%)
Superior quadrantanopsia	1 (3.8%)
Median PFS (mo) [range]	23.5 [3–96]
Malignant transformation observed (#, %)	9 (34.6%)
Median OS (mo) [range]	62.6 [4.9–150.5]
Death (#, %)	8 (30.8%)
Lost to follow-up (#, %)	2 (7.7%)

TMZ temozolomide, RT radiotherapy, SRS stereotactic radiosurgery, CCNU lomustine, PFS progression free survival, OS overall survival

^aDefined as adjuvant treatment prior to any progression. Two patients with unknown postoperative treatment

^bTreatment after first progression. 1 of the 13 patients demonstrating progression was lost to follow-up

^cDefined as new postoperative deficits by 90 days

a separate report, Pouratian et al. analyzed the outcomes of 20 patients at least 60 years of age with low-grade gliomas. 75% of patients were treated with biopsy alone with only one patient undergoing gross total resection. Interestingly, multivariate analysis demonstrated that, even within the cohort of older individuals, younger age was associated with better outcomes [20]. Interestingly, these studies demonstrate

differing distributions of histological diagnoses with Pouratian et al., Kaloshi et al., and Chi and Batchelor suggesting that oligodendrogliomas occur more frequently [11, 20, 21] while Schomas et al. found astrocytoma to be the most common diagnosis in the older population [12].

Results from this report provide additional insights into molecular features and treatment outcomes for older patients with low grade gliomas. First, we demonstrate that extensive resection may still be achieved in most cases with acceptable rates of long-term neurological morbidity. The complication rates encountered are similar to those described in larger cohorts of patients with low grade glioma inclusive of all age groups [13]. Although the treatment paradigm varied during the study period, the majority of patients received adjuvant therapy after resection. However, 38.5% of patients did not undergo adjuvant therapy, in most cases due to patient preference. The most frequent diagnosis in the cohort was oligodendroglioma which is in line with some but not all prior reports in older patients [11, 12, 20, 21]. We report a median PFS of 23.5 months (1.9 years), similar to prior reports, and a median OS of 62.6 months (5.2 years), longer than prior reports in a similar age group. This could be in part due to more extensive resection as most patients in prior studies focusing on this older age group underwent biopsy alone with adjuvant therapy [11, 12, 20].

However, these PFS and OS times are still shorter when compared to younger cohorts of low-grade glioma patients [11]. For example, in a phase III clinical trial comparing treatment with PCV after radiation compared to radiation alone in patient with grade II gliomas who had undergone surgical resection or biopsy. Median PFS and OS in the radiation only control arm were 4.0 and 7.8 years, respectively, higher than that noted in our study [14]. Similarly, prior data from our group in a surgical cohort of low grade glioma patients demonstrated a median PFS of 5.5 years [22]. Time to malignant transformation also appears to be shorter for older patients. Murphy et al. identified the incidence of malignant transformation to be 21% in a cohort of 599 patients with low-grade glioma in which the average age was 36 years. Median time to malignant transformation was 56.4 months, and on multivariate analysis, older age, extent of resection, and male sex were significant predictors of malignant transformation [23].

The reason for the prognostic differences based on age in patients with low grade glioma is not well understood. The majority of astrocytomas in our cohort were *IDH*-wildtype (approximately 27% of the total cohort), which has been previously shown to portend similar overall survival to a diagnosis of glioblastoma [1]. Furthermore, two-thirds of *IDH*-wildtype astrocytomas also harbored *TERT* promoter mutation which portends an even worse prognosis within this low grade glioma subtype, and current recommendation includes reporting of these cases as “with molecular

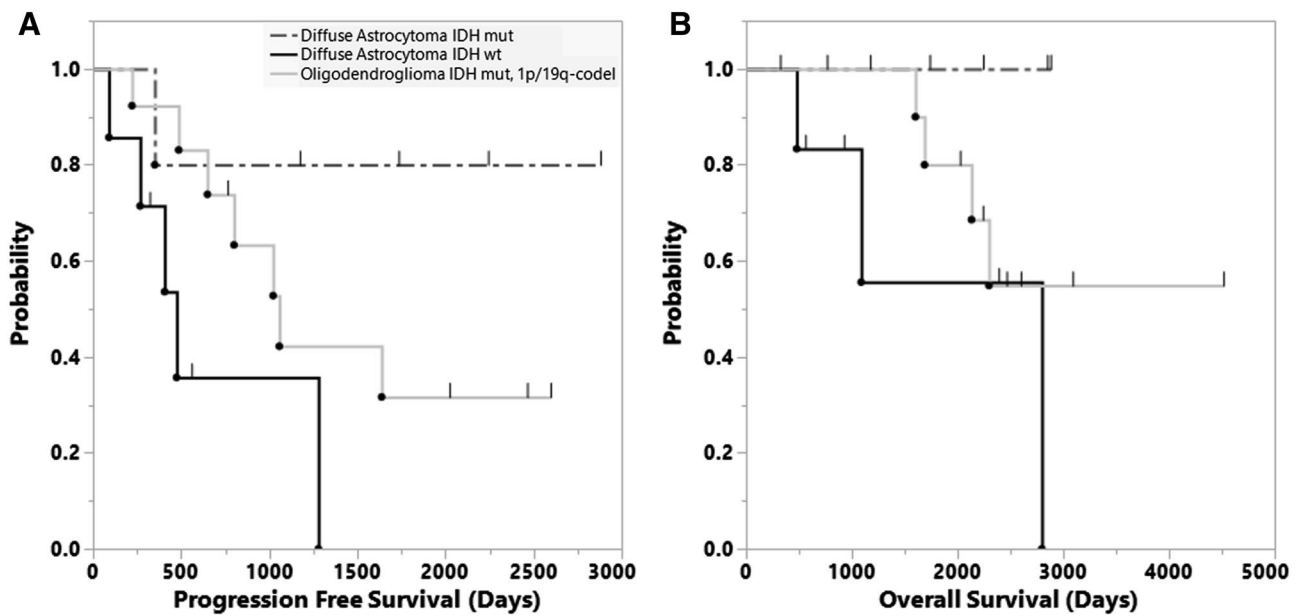


Fig. 1 Kaplan–Meier analysis of progression free and overall survival. **a** Glioma subtype versus PFS (log-rank: p-value=0.03). **b** Glioma subtype versus OS (log-rank: p-value=0.12). Circles represent event-of-interest and tick marks represent censored event

Table 4 Patient, tumor, and treatment characteristics associated with PFS and OS

Variable	PFS (months)	p-value	OS (months)	p-value
Age ^a	-0.32	0.11	-0.21	0.31
Sex		0.33		0.50
Male	29.0 [12.4–45.5]		57.3 [36.0–78.6]	
Female	40.8 [24.9–56.7]		64.2 [43.8–84.7]	
Tumor site		0.83		0.67
Frontal	36.1 [16.8–55.5]		70.2 [46.7–93.8]	
Temporal	32.8 [9.6–55.9]		50.5 [22.3–78.6]	
Parietal	28.7 [0–64.1]		44.8 [1.8–87.9]	
Insula	40.1 [12.7–67.5]		66.5 [33.1–99.8]	
Tumor side		0.62		0.28
Left	38.5 [23.5–53.4]		67.0 [48.3–85.8]	
Right	30.1 [11.7–48.4]		51.7 [28.9–74.6]	
Pre-op tumor volume ^a	-0.23	0.28	-0.15	0.47
Residual tumor volume ^a	-0.19	0.35	0.03	0.89
EOR ^a	0.21	0.29	0.11	0.58
Adjuvant therapy		0.16		0.25
Yes	36.3 [20.7–51.9]		50.0 [32.5–67.4]	
No	28.4 [10.6–46.2]		63.6 [43.7–83.5]	
Enhancement on imaging		0.29		0.23
Yes	27.2 [1.2–53.1]		73.9 [41.4–106.5]	
No	37.1 [24.1–50.1]		57.6 [41.4–73.9]	

EOR extent of resection, PFS progression free survival, OS overall survival. [] denotes 95% confidence interval

^aCorrelation coefficient reported

Table 5 Factors associated with malignant progression and death

	Malignant progression (N=9)	No malignant progression (N=17)	p-value	Death (N=8)	Alive at last follow-up (N=18)	p-value
Mean age	66.9 [63.7–70.0]	65.9 [63.6–68.2]	0.77	66.3 [62.9–69.6]	66.2 [64.0–68.4]	0.91
Pre-op tumor volume (cm ³)	119.3 [74.4–164.3]	26.7 [0–59.4]	0.004	129.6 [83.7–175.5]	27.3 [0–57.8]	0.002
EOR (%)	65.4[48.3–82.6]	78.4[65.9–90.8]	0.16	60.6 [43.0–78.1]	79.8 [68.1–91.5]	0.07
Residual tumor volume (cm ³)	58.7 [26.8–90.6]	8.1 [0–31.3]	0.03	65.9 [33.3–98.5]	7.7 [0–29.5]	0.01
Enhancement (#, %)	2 (40%)	3 (60%)	0.78	1 (20%)	4 (80%)	0.55
Adjuvant therapy (#, %)	5 (35.7%)	9 (64.3%)	0.83	6 (42.9%)	8 (57.1%)	0.23

EOR extent of resection

[] denotes 95% confidence interval

features of glioblastoma, WHO grade IV” [1, 24]. Although we did not observe a difference in overall survival between molecular subtypes in the current study, this may be due to small sample size rather than a lack of prognostic utility of these markers in older patients. Another reason for the age-associated prognostic difference may be in part due to worse functional status at presentation. KPS scores in older patients with low-grade gliomas were previously found to be lower than their younger counterparts [11], and lower preoperative KPS is known to be a poor prognosticator [7]. Finally, although the median EOR was 75.4% in this cohort, this is still lower than previously reported in a younger cohort of patients [22]. As greater EOR is associated with longer PFS and OS in the context of low grade glioma, this may be another key factor associated with the differences in outcomes observed between older and younger patient cohorts [25, 26].

Given the retrospective nature of this study, there are expected limitations in the interpretation of the results. As several patients elected to transition care to non-affiliated institutions, there were two patients lost-to-follow-up. However, to the best of our knowledge this was due to patients selecting to have care closer to home rather than due to the aggressiveness of their disease per se. Additionally, the cohort included for analysis is relatively small, despite being at a referral center, which reflects the low frequency of WHO grade II tumors in this age group. Finally, although all patients had undergone at least a partial resection, we cannot completely rule-out under-sampling of a higher-grade lesion.

Conclusion

This study demonstrates that older patients with diffuse gliomas may safely undergo aggressive treatment with surgical resection and adjuvant therapy. Shorter PFS was associated with a diagnosis of diffuse astrocytoma *IDH*-wildtype which occurred with a higher frequency than has been previously

reported in younger cohorts. Differences in OS based on the glioma subtype were not observed in this cohort. Despite aggressive treatment, PFS and OS were shorter than in prior reports examining outcomes in younger patients with grade II glioma. Decreased residual tumor volume was associated with lower rates of malignant transformation, and thus, maximum safe resection should be recommended for these tumors regardless of age. Further population-based studies are needed to examine the frequency of low grade molecular subtypes within this age group. Additional studies are also needed to determine the impact of specific treatment regimens in older patients with low grade gliomas to understand the poorer clinical outcomes observed.

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Author contributions All authors have contributed significantly to the experimental design, analyses, interpretation of the data and writing of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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