



A comparative analysis of clinicopathological features and survival among early adolescents/young adults and children with low-grade glioma: a report from the Children's Oncology Group

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Abstract

Background For several types of cancer, biological differences and outcome disparities have been documented in adolescents/young adults (AYAs, 15–39 years old) versus children. This study compared clinicopathological features and survival between younger AYAs and children with low-grade glioma (LGG), a common brain tumor among AYAs.

Methods This was a secondary analysis of Children's Oncology Group legacy study CCG-9891/POG-9130, which enrolled participants 0–21 years of age with newly-diagnosed LGG treated with surgery alone. For analysis, participants were categorized as children (0–14 years old) or early AYAs (eAYAs, 15–21 years old) and compared on demographics, clinical presentation, tumor characteristics, surgical outcomes, progression-free survival (PFS) and overall survival (OS).

Results Among 468 children and 50 eAYAs, more eAYAs presented with seizures (34.0% vs. 19.2%; $p=0.015$), without other significant differences in clinicopathological features. 5-year PFS rates for children and eAYA were 80.2% (95% confidence interval [95% CI], 76.1–83.7) and 83.0% (95% CI 68.8–91.1), respectively; 5-year OS rates were 97.3% (95% CI 95.2–98.5) and 95.4% (95% CI 82.7–98.8), respectively. Multivariable analysis including all participants showed presence of residual tumor to be an independent predictor of PFS ($<1.5\text{ cm}^3$, hazard ratio [HR] 5.93 [95% CI 3.45–10.18]) and ($\geq 1.5\text{ cm}^3$, HR 8.38 [95% CI 4.75–14.79]) ($p<0.001$), while midline-chiasmatic location (HR 9.69 [95% CI 3.05–30.75], $p<0.001$) and non-pilocytic astrocytoma histology (HR 6.77 [95% CI 2.35–19.49], $p<0.001$) were independent predictors of OS.

Conclusion Unlike several other cancers, LGG has similar presenting features and survival for both eAYAs and children. This support continuing a unified treatment approach and enrollment of eAYAs in pediatric clinical trials for LGGs.

Keywords Glioma · Adolescent · Young adult · Children · Pathology · Signs and symptoms

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Introduction

Adolescents and young adults (AYA, 15–39 years of age) are a population recognized by the United States (US) National Cancer Institute as facing critical, age-related challenges in cancer care and research compared with children and older adults [1]. Inferior survival for AYAs compared with children has been reported for several cancer types, including acute lymphoblastic and myeloid leukemia, soft tissue sarcoma, osteosarcoma, and Ewing sarcoma [2–5]. Additionally, excess frequency and severity of treatment-related toxicity has been documented among AYAs [6, 7]. Although these disparities remain poorly understood, they are indicators of potential differences in cancer and host biology, receipt of appropriate therapy, and health behaviors among AYAs. Knowledge about these disparities is important for

improving clinical care and informing additional research in this at-risk population [8, 9].

Low-grade glioma (LGG) constitutes a heterogeneous group of tumors that occurs in all age groups. LGG has a peak incidence between the second and fourth decades of life and is one of the most common brain tumors among older adolescents [10]. However, little is known about the biology and clinical behavior of LGG among AYAs. In young children versus older adults, LGGs exhibit contrasting biological and clinical features [9]. Most pediatric LGG are characterized by *BRAF* and other RAS/RAF pathway alterations, are unlikely to transform to high-grade glioma, and are associated with excellent long-term overall survival (OS) [11]. In contrast, RAS/RAF pathway alterations are rare in adult LGG, which is typified by *IDH1/2* and *ATRX* mutations/alterations, a high incidence of malignant transformation, and a more guarded prognosis [9, 12, 13]. Whether LGG among AYAs has more in common with pediatric or adult LGG phenotype, or whether it is a third biological entity distinct from both, has not been established [14]. This question is of pressing clinical importance, as the therapeutic approaches for adult and pediatric LGGs are divergent, including the choice between chemotherapy and radiation therapy. Radiation therapy, in particular, is commonly used in adults but only rarely in children with LGG [10, 11].

The Children's Oncology Group (COG) legacy study CCG9891/POG9130 was a prospective observational cohort study of patients aged 0–21 years with newly-diagnosed LGG treated only with surgical resection. This study design afforded a unique opportunity to explore potential differences in the biological behavior of LGG across the age spectrum of infancy to young adulthood. The primary aim of this secondary analysis was to compare the clinicopathological features and survival of early adolescents and young adults (eAYA, 15–21 years old) and children (0–14 years old) who participated in the original clinical trial.

Methods

CCG-9891/POG-9130

CCG-9891/POG-9130 was a prospective cohort study conducted by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) from October 1991 to August 1996 at participating sites in the US and Canada. The study design has been previously described [15]. Key eligibility criteria included age 0–21 years, newly-diagnosed and pathologically-confirmed LGG (WHO grade I or II), and treatment consisting only of surgical resection followed by observation. Eligible patients were enrolled after tumor biopsy/resection and followed until they met off-study criteria (entry onto another CCG/POG therapeutic study, confirmation of

being lost to follow-up, or death). Participants could have tumors in any intracranial location except intrinsic brainstem tumors (medulla, pons, midbrain) or isolated optic nerve tumors without involvement of the chiasm.

Exclusion criteria included neuro-ocular-cutaneous syndromes other than neurofibromatosis, multiple sites of disease within the central nervous system (CNS), other major progressive illness, other cancers, or having been previously treated for cancer. Gross total resection was defined as absence of residual tumor by operative report and postoperative imaging. Those with residual tumor were further classified as having $< 1.5 \text{ cm}^3$ (near-total resection) or $\geq 1.5 \text{ cm}^3$ (subtotal resection) of residual tumor.

Current study

The current study is a retrospective analysis of the CCG9891/POG9130 dataset. All participants eligible for the primary study were included in this analysis. For the purposes of this study, participants were categorized as children (age 0–14 years) or eAYA (age 15–21 years) at the time of study entry. The following parameters were compared: sex, race/ethnicity, histopathological features, tumor location, seizure at presentation, level of consciousness at presentation, extent of resection, surgical complication, progression-free survival (PFS) and OS.

Statistical methods

Pearson Chi square test was performed to compare the proportional frequency of clinicopathological features between children and eAYAs. The primary endpoints for analysis of treatment efficacy were PFS and OS, as defined in the original protocol [15]. PFS was measured from the time of enrollment to first disease relapse or progression, death from any cause, or until last follow-up if no progression occurred, whichever occurred first. OS was measured from the time of enrollment to date of death. Patients not experiencing progression of disease or death were censored at the time of last follow-up. Nonparametric PFS and OS survival distributions were estimated by using the Kaplan–Meier method [16]. Point estimates of PFS and OS were reported with 95% confidence intervals (95% CI). The equality of survival functions between eAYAs and children were assessed by the log-rank test.

Associations between risk of progression/death and prognostic factors were assessed using multivariable Cox regression analysis. Based on published results of the multivariable analysis from the primary study (CCG9891/POG9130), an a priori model was used to generate a Cox regression model, with the age variable modified to be < 15 versus 15–21 years, consistent with the aims of this secondary analysis. This is in contrast with the original analysis,

which used <5 and ≥ 5 as the age variable [15]. Results of this analysis were validated using a backward selection multivariable model, where univariate Cox regression was used to estimate the main effect of each potential prognostic factor. Variables with p value <0.2 from univariate models were considered for inclusion in the multivariable model. Backwards selection with likelihood ratio test was used to generate a Cox regression model with a threshold p value of 0.05 for inclusion in the final model (Supplemental Table 2). A variation of this approach was also used where the age variable <15 versus 15–21 years was preferentially kept in the model until the final stage.

For all statistical tests, all p values were two-sided with <0.05 considered significant. All statistical computations were performed using SAS version 9.4 and STATA version 14.

Results

Participant characteristics

A total of 518 participants were assessed (468 children and 50 eAYAs). Participant characteristics are summarized in Table 1. Between the two age groups, there were no differences by sex, race/ethnicity, pathological subtype, tumor location, extent of resection, preoperative level of consciousness, or occurrence of surgical complications. However, seizures at presentation were significantly more common among eAYAs than children (17/50, 34% vs. 90/468, 19%; $p=0.015$).

Survival

Median follow-up period for participants who were progression-free was 7.4 years. In total, there were 104 progressions (95 children, 9 eAYA) and 16 deaths (13 children, 3 eAYA). As shown in Fig. 1a, b, there was no difference in PFS or OS between the two age groups. When the groups were further stratified by age (0–4, 5–9, 10–14, and 15–21 years), there was still no significant difference in PFS or OS (Fig. 1c, d). Among participants with pilocytic astrocytoma (PA) histology ($n=358$ children and 36 eAYAs), there was no difference by age group in PFS and OS (log rank $p=0.27$ and 0.64, respectively). The 5-year PFS for children and eAYA was 80.2% (95% CI 76.1–83.7) and 83.0% (95% CI 68.8–91.1), respectively; while the 5-year OS for the groups was 97.3% (95% CI 95.2–98.5) and 95.4% (95% CI 82.7–98.8), respectively.

Results of Cox regression analysis on PFS for all participants combined are summarized in Table 2 and Supplemental Table 1. In univariate analysis, race/ethnicity, history of seizures, level of consciousness at presentation

and presence/absence of surgical complications were not associated with PFS. In multivariable analysis, residual tumor was the only independent predictor of PFS. Patients with residual tumor <1.5 cm³ had almost sixfold, and those with ≥ 1.5 cm³ over eightfold, greater likelihood of disease progression than patients who had no visible tumor on post-operative imaging (Table 2).

Results of Cox regression analysis on OS for all participants combined are summarized in Table 2 and Supplemental Table 1. In univariate analysis, non-White participants had poorer OS when compared to White participants. History of seizures, level of consciousness at presentation and presence/absence of surgical complications were not associated with OS. In multivariable analysis, pathology type and tumor location were independent prognostic factors for OS. In the adjusted analysis, patients with non-PA patients were 6.77 times more likely to die than those with PA. Patients with midline-chiasmatic patients were 9.69 times more likely to die than those with non-midline-chiasmatic tumors (Table 2).

Discussion

In this comparative analysis of children and eAYAs with LGG, we found no significant differences in clinicopathological features or outcomes. To our knowledge, this is the first study of LGG to compare the clinical presentation, tumor location, extent of resection, histopathological characteristics, and survival between these two age groups. The possibility of age-related differences for LGG is an important question because outcome disparities affecting AYAs have been documented for several forms of cancer [2–5]. Our finding that this is not true for LGG is clinically significant because it supports continued enrollment of eAYAs in pediatric clinical trials for LGGs.

Of approximately 70,000 AYAs diagnosed with cancer annually in the United States, approximately 13,000 have a brain tumor [17, 18]. According to the Central Brain Tumor Registry of the United States (CBTRUS), between 2009 and 2013 a total of 16,653 and 6869 CNS tumors were diagnosed among children aged 0–14 and eAYA aged 15–19 years, respectively [19]. Yet, there remains a paucity of published studies regarding these eAYAs. Here, we explored potential age-related differences between pediatric patients and eAYA patients with LGGs. Of the several variables examined in our study, seizures occurring more commonly amongst eAYAs was the only significant difference. Both tumor location and tumor type are known to influence risk for seizures. Tumors involving the cerebral rather than cerebellar hemispheres, especially the temporal, frontal and parietal lobes, are more associated with seizures. Glioneuronal tumors such as gangliogliomas have also been associated with increased seizure

Table 1 Participant and disease characteristics

	Children (n = 468)	Early AYAs (n = 50)	p
Age (years)			–
Median	7.1	16.2	
Range	0.6–14.9	15.0–20.5	
	n (%)	n (%)	p
Sex			0.36
Male	249 (53.2)	30 (60.0)	
Female	219 (46.8)	20 (40.0)	
Race/ethnicity			0.74
White	375 (80.1)	42 (84.0)	
Hispanic	19 (4.1)	1 (2.0)	
African American	53 (11.3)	6 (12.0)	
Others/unknown	21 (4.5)	1 (2.0)	
Pathological subtype			0.66
Pilocytic astrocytoma	358 (76.5)	36 (72.0)	
Low-grade differentiated astrocytoma	30 (6.4)	3 (6.0)	
Ganglioglioma	33 (7.1)	6 (12.0)	
Other	47 (10.0)	5 (10.0)	
Tumor location			0.21
Cerebral hemisphere	107 (22.9)	18 (36.0)	
Cerebellar hemisphere	152 (32.5)	14 (28.0)	
Cerebellar vermis	117 (25.0)	13 (26.0)	
Midline	70 (15.0)	4 (8.0)	
Optic chiasm/hypothalamic	22 (4.7)	1 (2.0)	
Extent of resection			0.44
Gross total resection	299 (63.9)	33 (66.0)	
Residual tumor < 1.5 cm ³	92 (19.6)	12 (24.0)	
Residual tumor ≥ 1.5 cm ³	77 (16.5)	5 (10.0)	
Seizures (pre-surgical)			0.015*
Yes	90 (19.2)	17 (34.0)	
No	377 (80.6)	33 (66)	
Unknown	1 (0.2)	0	
Consciousness (pre-surgical)			0.125*
Normal	416 (88.9)	48(96.0)	
Abnormal	52 (10.9)	2 (4.0)	
Unknown	1 (0.2)	0	
Perioperative complications			0.89*
Yes	135 (28.9)	14 (28.0)	
No	333 (70.7)	36 (72.0)	
Unknown	2 (0.4)	0	

*Calculation for p value excludes unknown

frequency compared to glial-type tumors [20]. In this study, the eAYA group had a higher proportion of tumors that originated from the cerebral hemispheres (36.0% vs. 22.9%) and/or were gangliogliomas (12.0% vs. 7.1%). Even though these differences did not reach statistical significance due to the relatively small sample, the combination may explain the higher incidence of seizures among eAYAs. Importantly,

we found no other age-related differences in tumor location, histopathological characteristics, or survival.

When these patients were analyzed in aggregate, certain outcome predictors emerged. As reported in the primary study, tumors in the midline and chiasmatic region, non-PA tumors and the presence of residual tumor were associated with worse PFS and OS on univariate analysis [15]. As part of this secondary analysis, we expanded univariate

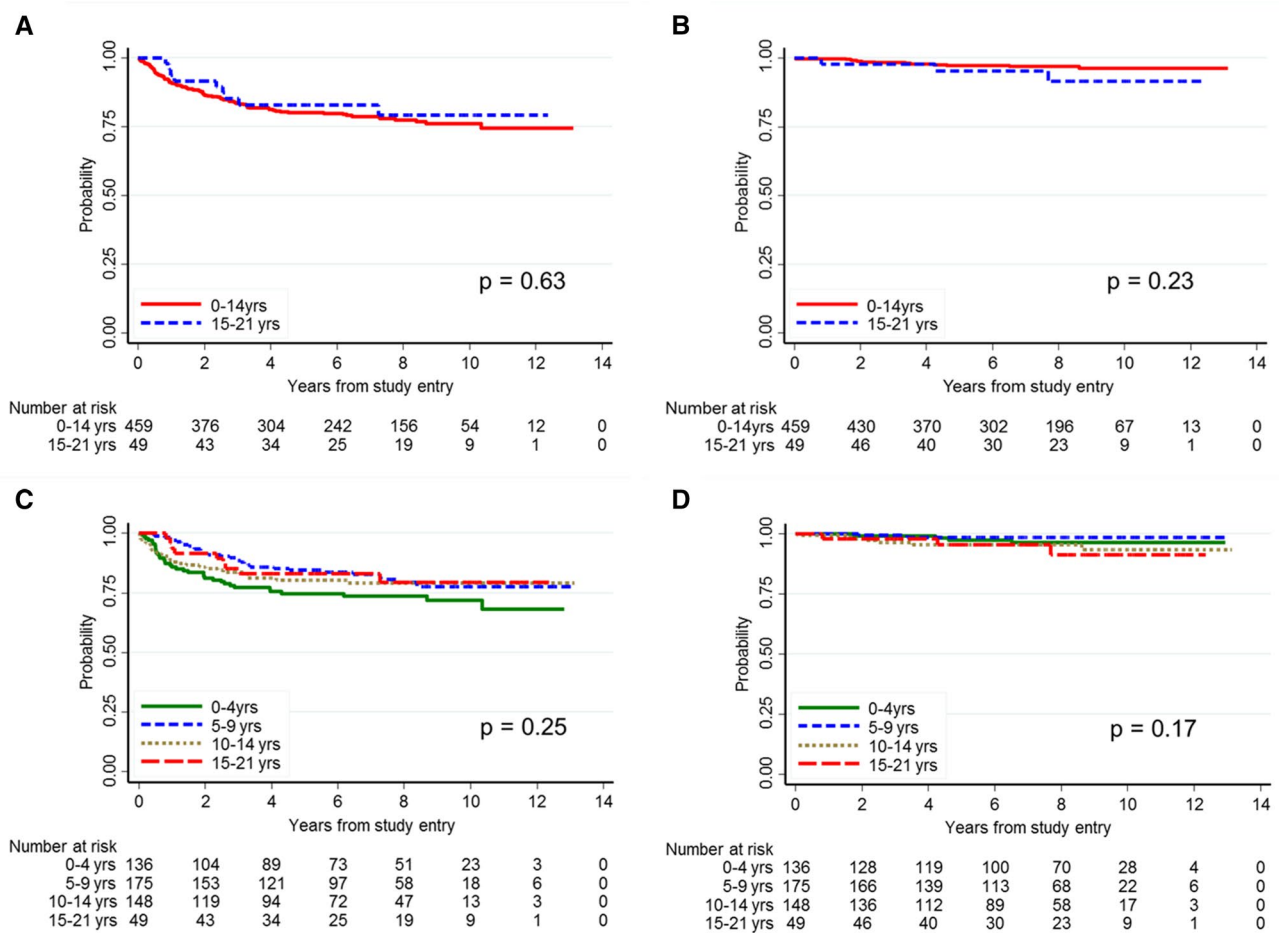


Fig. 1 Progression-free survival of patients aged **a** 0–14 and 15–21 years old, **c** 0–4, 5–9, 10–14 and 15–21 years old. Overall survival of patients aged **b** 0–14 and 15–21 years old, **d** 0–4, 5–9, 10–14 and 15–21 years old

Table 2 Multivariable analysis of progression-free and overall survival

Factor	Category	PFS		OS	
		HR (95% CI)	p	HR (95% CI)	p
Residual tumor	Gross total resection	1	<0.001	1	0.18
	Residual tumor < 1.5 cm ³	5.93 (3.45–10.18)		2.26 (0.53–9.65)	
	Residual tumor ≥ 1.5 cm ³	8.38 (4.75–14.79)		3.71 (0.87–15.87)	
Tumor location	Non-midline-chiasmatic	1	0.095	1	<0.001
	Midline-chiasmatic	1.47 (0.94–2.31)		9.69 (3.05–30.75)	
Pathology type	Pilocytic astrocytoma	1	0.085	1	<0.001
	Non-pilocytic astrocytoma	1.48 (0.96–2.28)		6.77 (2.35–19.49)	
Age (years)	0–14	1	0.755	1	0.27
	15–21	0.90 (0.45–1.79)		2.22 (0.59–8.38)	

A priori model

analysis to include race/ethnicity, history of seizures, level of consciousness at presentation and presence/absence of surgical complications. While most of these factors did not significantly affect PFS or OS, interestingly, race/ethnicity significantly affected OS. Here, non-White race was

significantly associated with poorer OS on univariate analysis, but not multivariable analysis. This finding is likely to be multifactorial, where impaired access to care and lower socioeconomic status could be relevant, as both have been associated with more advanced-stage disease in children

with CNS tumors, non-CNS solid tumors and melanoma [21–24]. Future epidemiology studies of LGG with larger and more diverse samples should investigate this potential association more definitively.

Multivariable analysis using the AYA age variable (< 15 vs. 15–21 years) was consistent with results of the primary study previously published by Wisoff et al. (which used age variable < 5 vs. ≥ 5), showing extent of resection to be an independent predictor of PFS. This finding is consistent with previous reports in both children and adults, and one that supports gross total resection as the primary therapeutic goal for pediatric LGGs, when this can be achieved with acceptable functional outcome [15, 25, 26]. Multivariable analysis also showed tumor in the midline and chiasmatic region to be independent predictors of OS. These findings suggest that while the lower resectability of midline and chiasmatic tumors likely contributes to worse PFS, the extent of resectability alone does not completely account for the difference in OS outcomes in these tumors [27, 28]. Lastly, PA histopathology was found to be an independent predictor of OS, consistent with the known biological behaviors of these tumors [11].

Interestingly, eAYA were underrepresented in this study, as evidenced by the almost 10:1 ratio between children and eAYA who participated. Based on the CBTRUS data and incidence of LGGs, this ratio should be closer to 5:1 [19]. This discrepancy exemplifies the pernicious problem of low AYA participation in cancer clinical trials, which likely results from a complex combination of factors operating at the national-, site-, provider-, and patient/family-levels [29]. As our understanding of the biology and treatment of pediatric CNS tumors continues to evolve through molecular testing and development of targeted therapy, poor participation of AYA in clinical trials and resulting lack of biologic specimens may prove to be a significant obstacle in advancing the management of LGGs and other brain tumors in AYAs.

This secondary analysis of legacy COG study has several strengths with some limitations. An important strength is the prospective observational cohort design that followed patients after surgical resection alone, without the addition of adjuvant therapy such as chemotherapy or radiation therapy that could alter outcomes. This provided a unique opportunity to characterize the natural history of LGG across a spectrum of ages. Other notable strengths of this study include the relatively large sample in aggregate, good generalizability of a multicenter cooperative group trial, relatively long follow-up period, and central pathology review of all cases. Limitations of this study include the fact that CCG9891/POG9130 was completed over 20 years ago. Advances in surgical and laboratory techniques could alter diagnostic classification and outcomes. In particular, given that molecular analysis is now widely performed for risk stratification and therapeutic decision making, we would

have ideally analyzed all tumor tissues for specific genetic aberrations [30]. However, tumor tissues were not collected as part of the study and therefore unavailable for analysis. Additionally, it is noteworthy that the majority of participants in both age groups were diagnosed with PA, which could be due to the fact that PA has a higher incidence compared to other types of pediatric LGGs and because patients who received only surgical resection were considered evaluable for the study; this may have influenced the survival analysis.

Lastly, because AYAs aged 22–39 are not included in this analysis, our results cannot be readily generalized to that older age group. This would be an important study to replicate among older AYAs because some studies suggest that a significant proportion of older AYA may have adult-type LGGs. One example is seen with diffuse astrocytoma (WHO grade II), which frequently bears an *IDH* mutation in adults. Interestingly, almost half of the patients diagnosed with *IDH*-mutant diffuse astrocytoma are between 22 and 39 years of age. In contrast, the *IDH* mutation is rare in pediatric LGGs (age 0–21), reported to range from 0 to 17% [31, 32]. OS rates for patients aged 22–39 with *IDH*-mutant diffuse astrocytoma are similar to patients over 39 years of age [33]. This supports the notion that some older AYA have adult-type LGGs and are likely better treated on adult-focused therapeutic protocols. This also emphasizes the importance of further research of biological specimens and molecular genetics, as these studies will be imperative to fully characterize the biological differences between LGGs in the pediatric, AYA and older adult populations.

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Compliance with ethical standards

Disclosure The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCTN or NIH.

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