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Risk stratification in pediatric low-grade glioma and glioneuronal tumor treated with radiation therapy: an integrated clinicopathologic and molecular analysis

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Abstract

Background. Management of unresectable pediatric low-grade glioma and glioneuronal tumor (LGG/LGGNT) is controversial. There are no validated prognostic features to guide use of radiation therapy (RT). Our study aimed to identify negative prognostic features in patients treated with RT using clinicopathologic and molecular data and validate these findings in an external dataset.

Methods. Children with non-metastatic, biopsy-proven unresectable LGG/LGGNT treated with RT at a single institution between 1997 and 2017 were identified. Recursive partitioning analysis (RPA) was used to stratify patients into low- and high-risk prognostic groups based on overall survival (OS). CNS9702 data were used for validation.

Results. One hundred and fifty patients met inclusion criteria. Median follow-up was 11.4 years. RPA yielded low- and high-risk groups with 10-year OS of 95.6% versus 76.4% (95% CI: 88.7%–98.4% vs 59.3%–87.1%, $P = 0.003$), respectively. These risk groups were validated using CNS9702 dataset ($n = 48$) (4-year OS: low-risk vs high-risk: 100% vs 64%, $P < 0.001$). High-risk tumors included diffuse astrocytoma or location within thalamus/midbrain. Low-risk tumors included pilocytic astrocytoma/ganglioglioma located outside of the thalamus/midbrain. In the subgroup with known *BRAF* status ($n = 49$), risk stratification remained prognostic independently of *BRAF* alteration (V600E or fusion). Within the high-risk group, delayed RT, defined as RT after at least one line of chemotherapy, was associated with a further decrement in overall survival ($P = 0.021$).

Conclusion. A high-risk subgroup of patients, defined by diffuse astrocytoma histology or midbrain/thalamus tumor location, have suboptimal long-term survival and might benefit from timely use of RT. These results require validation.

Key Points

1. Management of unresectable pediatric low-grade glioma is controversial.
2. We identify and validate a high-risk cohort with suboptimal long-term survival.
3. This high-risk cohort might benefit from timely use of radiation therapy.

Pediatric low-grade gliomas (LGGs) and glioneuronal tumors (LGGNTs) represent heterogeneous diseases with multiple treatment options and varied outcomes depending on clinicopathologic variables and treatment modality.[1] Several selection biases drive the choice of therapy. For tumors that can be totally resected, no adjuvant therapy is required and outcomes are usually excellent.[2,3] For unresectable tumors, optimal management is controversial.

Importance of the Study

There are no validated prognostic features to guide use of radiation therapy in unresectable pediatric low-grade gliomas and glioneuronal tumors. Optimal management of these tumors is controversial. Using clinicopathologic and molecular data from patients treated homogeneously with RT, we identified and validated low- and high-risk groups with significantly disparate 10-year OS. Risk stratification remained significant independently of BRAF alteration (V600E or fusion). Within the high-risk group, delayed RT, defined as RT administered after at least one line of chemotherapy, was associated with a further decrement in OS. High-risk tumors, defined by diffuse astrocytoma histology or thalamic/midbrain location, might benefit from timely use of RT.

Despite the efficacy of radiation therapy (RT) in locally controlling unresectable disease, concerns regarding RT-related adverse effects[4] in young children have resulted in a preference for initially administering chemotherapy or targeted therapy, both of which are associated with inferior progression-free survival (PFS) compared with RT.[5–9] RT is recommended for older children or for those whose tumors have progressed on systemic therapy. For patients who are candidates for RT, there are no validated criteria for risk stratification based on overall survival (OS), and the timing of RT remains controversial as it is assumed that all patients can be successfully salvaged with RT. As a result, patients might experience significant morbidity and mortality due to repeated tumor progressions prior to RT in an otherwise curable disease.[10] This highlights the need for a data-driven approach, incorporating both clinicopathologic and molecular data, to risk-stratify this patient population, with the goal of facilitating treatment decisions and thereby optimizing outcomes for these patients.

We used a cohort of patients who were uniformly treated with RT at St Jude Children's Research Hospital (St Jude) with a median follow-up of greater than 10 years to identify critical clinicopathologic and molecular variables associated with OS. Patients were treated either on an institutional phase II study, RT1 (ClinicalTrials.gov identifier: NCT00187226) or according to Children's Oncology Group Study ACNS0221 (ClinicalTrials.gov identifier: NCT00238264). *BRAF* status was available for some patients. Our focus was on OS, in order to identify high-risk patients who could not be successfully salvaged. We hypothesized that clinicopathologic features along with molecular data could be used to risk-stratify patients based on OS. We employed recursive partitioning analysis (RPA) to divide patients with LGG/LGGNT into 2 prognostic groups with clinical utility and subsequently validated the model using an external prospective dataset from the Children's Cancer and Leukemia Group's CNS9702 trial, which included patients who were treated in a similar manner to those at St Jude.

Materials and Methods

Study Population—St Jude Cohort

Patients with LGG/LGGNT treated with focal RT between 1997 and 2017 at St Jude were identified. Indications for RT included radiographic progression of disease, symptomatic disease, or deterioration in visual field/acuity. Patients could have been treated with chemotherapy prior to RT. Those who underwent RT between 1997 and 2010 were treated on a phase II institutional protocol, RT1 (ClinicalTrials.gov identifier: NCT00187226), and those who underwent RT after 2010 were treated according to Children's Oncology Group Study ACNS0221 (ClinicalTrials.gov identifier: NCT00238264). Exclusion criteria are shown in the CONSORT diagram (Fig. 1). A total of 150 patients were included for analysis. Tumors in relatively uncommon anatomic sites were excluded, such as the spinal cord (n = 3, two patients had metastatic disease) and cerebral cortex (n = 8, four were diagnosed as LGG not otherwise specified [NOS]). Also excluded were patients who did not undergo a biopsy (n = 19) or patients whose tumors were diagnosed as LGG NOS (n = 12) due to insufficient biopsy material. Additionally, patients with metastatic disease (n = 9) and prior malignancy (n = 1) were excluded due to the known poor prognosis in this subgroup, as were single patients with rare histological entities, such as angiocentric glioma (n = 1), neurocytoma (n = 1), and gangliocytoma (n = 1). The study was approved by the St Jude institutional review board (#Pro00009006).

Study Population—CNS9702 Cohort

The external validation dataset, CNS9702, was a population-based study that enrolled patients younger than 16 years of age with LGG/LGGNT across 22 treatment centers in the United Kingdom. Treatment strategy, methodology, and results for the entire study population have been previously reported.[11] The dataset we used for validation consisted of patients on CNS9702 who underwent RT as first line of therapy. The exclusion and inclusion criteria for the external validation dataset were identical to those of the St Jude dataset (Fig. 1). A total of 48 patients were included for analysis. As with the St Jude dataset, the most common reason for exclusion was lack of a biopsy (n = 12). Other reasons for exclusion included location (spinal cord: n = 9; cerebral cortex: n = 9), metastatic disease (n = 4), designation of LGG NOS (n = 2), and rare histologic entities represented by a single patient, such as dysembryoplastic neuroepithelial tumor (n = 1).

Histopathologic Review

For both study cohorts, histopathology was centrally reviewed by a single neuropathologist (D.W.E.). For

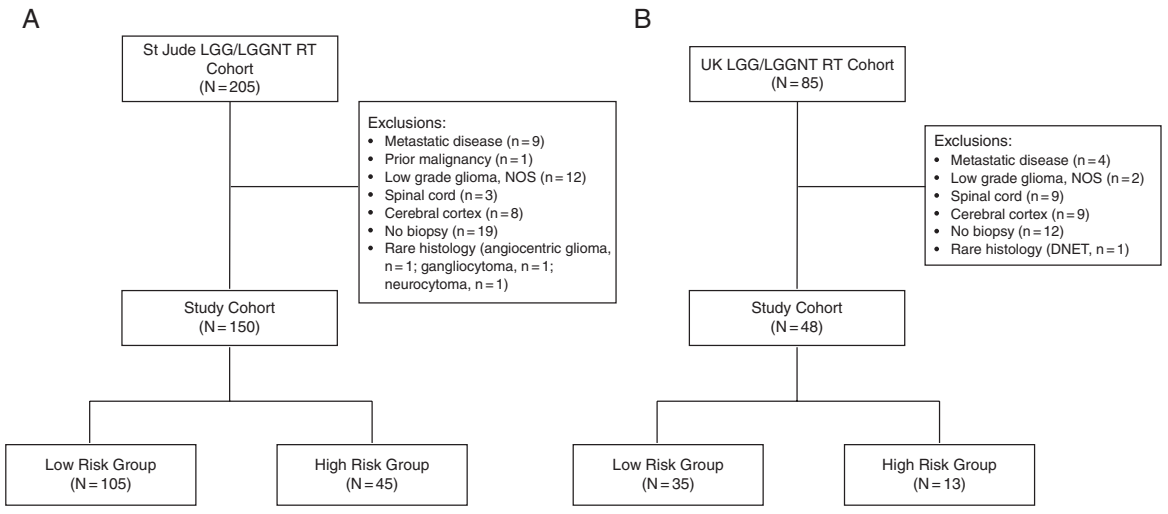

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram.

each case, standard hematoxylin and eosin–stained histopathologic preparations were supplemented by immunohistochemistry on 5 μm formalin-fixed paraffin-embedded tissue sections. For the St Jude cohort, *BRAF* alterations were identified when tissue was available. A mouse monoclonal antibody (Ventana #7990-4855; prediluted) was used to detect *BRAF* V600E-mutant protein.[12] Interphase fluorescence in situ hybridization was used to detect chromosome 7q34 duplication, a surrogate marker for *KIAA1549-BRAF* fusion, using a probe developed in-house.[13] The presence of the histone *H3K27M* mutation was also detected by immunohistochemistry.

Surgery

For the St Jude cohort, the extent of surgical resection was defined using postoperative MRI, along with clinical and operative data. Gross total resection (GTR) was defined as the removal of all tumor-related T1 enhancement and T2 fluid attenuated inversion recovery (FLAIR) abnormality, excluding signal change thought to be postsurgical. Subtotal resection (STR) was defined as presence of residual tumor–related T1 enhancement and/or T2 FLAIR abnormalities visible on postoperative MRI. Biopsy was defined as sampling rather than resection of tumor. For the CNS9702 cohort, primary surgical resection or biopsy was recommended for all patients except those with neurofibromatosis type 1 (NF1) and those with chiasmatic/hypothalamic tumors consistent with optic pathway glioma, as described previously.[11] Extent of resection was based on the local operative report and on the postoperative MRI following the recommendation of the Brain Tumor Subcommittee.[14] GTR was defined as without measurable disease. STR was defined as residual tumor of a measurable size.

Radiation Therapy

For the St Jude cohort, RT was delivered with a 3D conformal or intensity-modulated radiation technique to a total dose of 54 Gy *relative* biological effectiveness (RBE) in 1.8 GyRBE fractions over 6 weeks. The gross tumor volume (GTV) included both the cystic and solid components of the tumor and was defined by T2/FLAIR hyperintensity and T1 enhancement (if present). In patients who underwent surgery before RT, the GTV was defined as the surgical bed and any residual T2/FLAIR hyperintensity or T1 enhancement. The clinical target volume (CTV) margin was 1 cm for patients treated from 1997 to 2006. The CTV margin was 0.5 cm for patients treated after 2006. For patients treated with photon therapy, a planning target volume (PTV) margin of 0.5 or 0.3 cm was used. For patients treated with pencil-beam scanning proton therapy, scenario-based optimization was used with a 3-mm positional uncertainty and a 3% range uncertainty. For tumors involving or adjacent to the optic pathway that were treated with proton therapy, the total dose was reduced to 52.2 GyRBE to minimize risk of optic chiasm/nerve toxicity. For the CNS9702 cohort, similar focal RT was delivered to 54 GyRBE for children >5 years old and 50 GyRBE for children <5 years old, as described previously.[11] All tumors were treated with a CTV margin of 1–2 cm.

Radiographic Evaluation

For the St Jude cohort, all patients underwent brain MRI at baseline, every 3 months for the first 2 years, every 6 months through 5 years, and yearly thereafter. Radiographic response was categorized according to criteria of RECIST (Response Evaluation Criteria in Solid Tumors), with radiographic progression being defined as >25% tumor growth or the appearance of new lesions.[15] For the CNS9702 cohort, tumor progression was defined

by local radiologic report and/or symptomatic progression, as described previously.[11]

Outcome Measures and Variable Definitions

The primary outcome measure was OS. Secondary outcomes were PFS and cumulative incidence of secondary malignancies. Survival time was calculated from start of RT to death or last follow-up, whichever occurred first. Time to progression was calculated from start of RT to progression, death, or last follow-up, whichever occurred first. All outcome measures were calculated in an identical fashion for both cohorts. Tumor size, measured prior to RT, was defined as the largest tumor diameter, and was dichotomized as ≥6 cm and <6 cm, consistent with adult LGG studies.[16] Tumors involving the optic pathways and/or hypothalamus were grouped together, consistent with published data.[17] Tumors involving the thalamus and/or midbrain were grouped together, as were those involving the pons and/or medulla, as both structures were often involved. Delayed RT was defined as RT administered after at least one line of systemic therapy.

Statistical Analysis

Frequency distributions between groups were assessed with Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Survival analysis was computed using the Kaplan–Meier method, and the log-rank test was used to compare curves. Prognostic variables were identified via Cox proportional hazards. Variables significant on Cox univariate analysis ($P < 0.05$) were considered for multivariate analysis. Cumulative incidence of secondary malignancies was estimated using death as a competing risk. All statistical tests were 2-sided. Statistical analyses were performed with Stata software (2014 release).

RPA was used to devise high-risk and low-risk prognostic groups based on OS. RPA divides patients into homogeneous groups based on chosen covariates with respect to a predetermined outcome parameter, such as OS.[18] We employed classification and regression tree analysis (CART)[19] in Stata to generate statistically significant divisions ($P \leq 0.05$) with respect to OS, based on variables that were significant on Cox multivariate analysis with the exception of tumor size. CART in Stata is specifically for failure time data and uses the martingale residuals of a Cox model to approximate chi-square values for all variables.[20] Tumor size was not included because measurement methods varied across patients. Patients treated prior to 2000 were more likely to have CT-based measurements and patients treated in 2000 and onward were more likely to have MRI-based measurements. The minimum size for each subgroup was 10. The St Jude dataset was used to construct a risk-stratification model. The CNS9702 dataset from the United Kingdom was used for external validation of the resulting model.

Results

Patient Characteristics—St Jude Cohort

Median follow-up was 11.4 years (Table 1). Median age at time of RT was 8 years. The following 4 anatomic sites were included in the analysis: optic pathway/hypothalamus, thalamus/midbrain, pons/medulla, and cerebellum. The following histologic diagnoses were included in the analysis: pilocytic astrocytoma, diffuse astrocytoma, and ganglioglioma. Forty percent of tumors involved the optic pathway or hypothalamus and 26% involved the thalamus or midbrain. The majority of tumors (81%) were pilocytic astrocytomas followed by diffuse astrocytomas (12%) and gangliogliomas (7%). Most patients underwent either a biopsy (53%) or STR (47%) prior to RT. Approximately a third of the patients (34%) received at least one course of chemotherapy prior to RT. The mean RT dose was 54 GyRBE and most patients were treated with photon therapy.

Prognostic Factors for Overall Survival and Progression-Free Survival—St Jude Cohort

The 10-year OS and PFS for the entire St Jude cohort was 90% (95% CI: 82.7–93.8) and 66% (95% CI: 56.6%–73.3%), respectively. On multivariate analysis, the following characteristics were associated with increased risk of mortality: thalamus/midbrain location versus optic pathway/hypothalamic location (hazard ratio [HR]: 6.02; 95% CI: 1.35–26.73; $P = 0.018$), diffuse astrocytoma versus pilocytic astrocytoma (HR: 3.76; 95% CI: 1.18–11.94; $P = 0.025$), tumor size ≥6 cm versus tumor size <6 cm (HR: 32.6; 95% CI: 7.72–137. 7; $P < 0.001$) (Table 2).

Inclusion of cerebral cortex tumors with a specific LGG histology ($n = 4$) did not change the results of our original multivariate analysis (Supplementary Table 1). Given that extent of resection may be correlated with tumor size and tumor location, we performed a subgroup analysis in patients who underwent biopsy alone and those who underwent STR. In the subgroup of patients who underwent a biopsy ($n = 80$), thalamus/midbrain location compared with optic pathway/hypothalamus location remained associated with an increased risk of mortality (HR: 15.6; 95% CI: 2.01–121.74; $P = 0.009$), and tumor size ≥6 cm compared with tumor size <6 cm also remained associated with an increased risk of mortality (HR: 7.38; 95% CI: 1.58–34.56, $P = 0.011$). Similarly, in the subgroup of patients who underwent an STR ($n = 70$), thalamus/midbrain location compared with optic pathway/hypothalamus location remained associated with an increased risk of mortality (HR: 5.77; 95% CI: 1.6–20.84, $P = 0.007$), and tumor size ≥6 cm compared with tumor size <6 cm also remained associated with an increased risk of mortality (HR: 11; 95% CI: 2.92–41.27, $P < 0.001$).

On multivariate analysis, the following characteristics were associated with increased risk of progression: tumor size ≥6 cm compared with <6 cm (HR: 2.84; 95%

Table 1 Patient and tumor characteristics of the St Jude cohort

Variable	*n*	*n* Patients with Molecular Data (*N* = 49)	*P* [α]
Median follow-up, y (range)	11.4 (0.24–29.4)	5.83 (0.24–20.6)	<0.01
Median age, y (range)	8 (1.2–20)	7.9 (2.2–18.4)	0.616
Sex (%)			0.384
Female	71 (47)	26 (53)	
Male	79 (53)	23 (50)	
Race (%)			0.416
White	114 (77)	35 (71)	
Black	28 (19)	12 (25)	
Other	8 (5)	2 (4)	
NF1 (%)			0.428
Yes	7 (5)	1 (2)	
No	143 (95)	48 (97)	
Tumor location (%)			0.029
OPG/hypothalamus	59 (40)	20 (41)	
Thalamus/midbrain	39 (26)	6 (12)	
Pons/medulla	34 (23)	15 (31)	
Cerebellum	18 (12)	8 (16)	
Histology (%)			0.181
Pilocytic astrocytoma	120 (81)	41 (84)	
Diffuse astrocytoma	19 (12)	3 (6)	
Ganglioglioma	11 (7)	5 (10)	
BRAF alteration (*N* = 49) (%)			
*BRAF*V600E	8 (16)	8 (16)	
BRAF fusion	29 (60)	29 (59)	
BRAF wildtype	12 (25)	12 (25)	
Tumor size before RT (%)			0.472
<6 cm	145 (97)	48 (98)	
≥6 cm	5 (3)	1 (2)	
Surgical extent (%)			0.002
Biopsy	80 (53)	16 (33)	
STR	70 (47)	33 (67)	
Number of surgeries before RT (%)			0.079
1	101 (69)	28 (57)	
2	38 (26)	18 (37)	
>2	8 (5)	3 (6)	
Chemotherapy before RT (%)			0.271
Yes	51 (34)	20 (41)	
No	99 (66)	29 (59)	
Radiation modality (%)			<0.001
3D CRT	114 (76)	23 (47)	
IMRT	28 (19)	19 (38)	
Proton therapy	8 (5)	7 (14)	
Mean radiation dose in GyRBE (range)	54 (48–55.8)	54 (50.4–54)	0.329

Abbreviations: OPG, optic pathway glioma; CRT, conformal radiation therapy; IMRT, intensity-modulated radiation therapy.
[α]*P*-value for frequency distributions based on Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Table 2 Univariate and multivariate analysis of OS in the St Jude cohort

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex				
Male	1			
Female	0.77 (0.30–1.97)	0.590		
Race				
Caucasian	1			
Black	1.23 (0.35–4.33)	0.743		
Other	2.58 (0.71–9.35)	0.148		
Age at RT	0.99 (0.89–1.10)	0.853		
Location				
OPG/hypothalamus	1			
Thalamus/midbrain	4.0 (1.40–11.35)	0.009	6.02 (1.35–26.73)	0.018
Pons/medulla	1.38 (0.33–5.81)	0.661	3.14 (0.54–18.0)	0.199
Cerebellum	No events	–	No events	
Histology				
Pilocytic astrocytoma	1			
Diffuse astrocytoma	7.49 (2.91–19.23)	<0.001	3.76 (1.18–11.94)	0.025
Ganglioglioma	3.25 (0.70–15.0)	0.131	4.93 (1–24.1)	0.051
Tumor size before RT				
<6 cm	1			
≥6 cm	10.58 (3.67–30.52)	<0.001	32.6 (7.72–137.7)	<0.001
BRAF alteration (*N* = 49)				
BRAF fusion	1			
*BRAF*WT	No events			
*BRAF*V600E	8.83 (0.79–98.71)	0.077		
Chemotherapy before RT				
No	1			
Yes	2.68 (1.11–6.48)	0.028	–	Not significant
RT dose (GyRBE)	1 (0.99–1)	0.804		
NF1				
No	1			
Yes	1.07 (0.14–8.13)	0.945		
Surgery				
Biopsy	1			
STR	0.94 (0.31–2.88)	0.912		
No surgery	0.86 (0.11–6.61)	0.885		
Number of surgeries before RT				
1	1			
2	0.93 (0.31–2.88)	0.912		
>2	0.86 (0.11–6.61)	0.885		

Abbreviations: OPG, optic pathway glioma; CRT, conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

CI: 1.1–7.32; $P = 0.031$) and delayed RT (HR: 2.53; 95% CI: 1.44–4.44; $P = 0.001$) (Table 3). Delayed RT was defined as RT administered after at least one line of chemotherapy. Larger tumor size was correlated with delayed RT ($P = 0.002$).

Risk Groups Derived from RPA Independently Predict Survival—St Jude Cohort

All patients from St Jude ($n = 150$) were used for RPA modeling. Only variables significant on multivariate analysis with the exception of tumor size were included as input

Table 3 Variables significant on univariate analysis of PFS in the St Jude cohort

	Univariate Analysis		Multivariate Analysis	
Variable[a]	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at RT	0.91 (0.85–0.98)	0.014	–	Not significant
Tumor size before RT				
≥6 cm	1			
<6 cm	3.89 (1.54–9.86)	0.004	2.84 (1.1–7.32)	0.031
Delayed RT[b]				
No	1			
Yes	2.73 (1.57–4.74)	<0.001	2.53 (1.44–4.44)	0.001

[a]Delayed RT is defined as RT after at least one line of chemotherapy.
[b]Only variables that were significant on univariate analysis are listed.

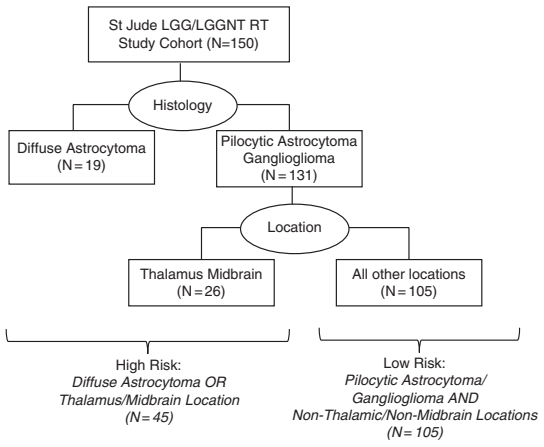

Fig. 2 Results of RPA of St Jude cohort.

elements for the RPA. The resulting model had 2 splits and 3 terminal nodes, which were simplified into 2 risk groups (Fig. 2) with statistically significant differences in OS rates (Fig. 3A). The high-risk group consisted of tumors with diffuse astrocytoma histology or location within the thalamus/midbrain. The low-risk group consisted of tumors located outside of the thalamus/midbrain with either pilocytic astrocytoma or ganglioglioma histology. The 10-year OS for the low-risk (n = 105) and high-risk groups (n = 45) was 95.6% versus 76.4% (95% CI: 88.7%–98.4% vs 59.3%–87.1%; P = 0.003), respectively. The difference in OS between low-risk and high-risk groups increased over time with a 7% absolute difference at 5 years (5-year OS: 90.5% vs 97%) and a 19.2% absolute difference at 10 years. Within the high-risk group, patients who underwent delayed RT had a significantly worse OS compared with those who underwent RT as first-line therapy (P = 0.021; Fig. 3D). In the low-risk group, timing of RT did not influence survival (P = 0.061; Fig. 3E). The risk groups remained independently prognostic for OS after adjusting for other variables such as tumor size and delayed RT (high-risk vs low-risk HR: 10.37, 95% CI: 3.5–30.76; P < 0.001) (Supplementary Table 2).

Risk Groups Retain Prognostic Significance Among Tumors with Molecular Data—St Jude Cohort

Of the 49 tumors that were tested for *BRAF* alterations, 59% harbored a *BRAF* fusion, most commonly *KIAA1549-BRAF*, and 16% harbored a BRAF *V600E* mutation (Table 1). Patients with tumors for which molecular data were available had been treated more recently and therefore had shorter follow-up (median: 5.8 y) (P < 0.01) and were treated with more advanced RT techniques (P < 0.001) compared with the entire cohort. High-risk group was the only variable predictive of OS (HR: 15.38, 95% CI: 1.36–173.87; P = 0.027) (Supplementary Table 3). The 6-year OS rates for low-risk (n = 42) and high-risk groups (n = 7) were 97.6% versus 41.7% (95% CI: 84.3%–99.6% vs 1.12%–84.2%, P = 0.003), respectively (Fig. 3B). Tumors harboring *BRAF* V600E were not associated with worse OS or PFS compared with tumors harboring BRAF fusions (Supplementary Table 4). None of the tested thalamic or midbrain tumors (n = 26) harbored H3 K27M.

Risk Groups Are Externally Validated Using CNS9702 Cohort

A total of 48 patients from CNS9702 met inclusion criteria. Median follow up was 3.8 years from start of RT. A table of patient and tumor characteristics from CNS9702 can be found in Supplementary Table 5. Thirty-one percent of tumors involved the optic pathway/hypothalamus, 17% involved the thalamus/midbrain, 38% involved the pons/medulla and 15% involved in the cerebellum. The 2 histologies represented in the dataset were pilocytic astrocytoma (85%) and diffuse astrocytoma (15%). The 4-year OS for the low-risk group (n = 35) was 100%, and that for the high-risk group (n = 13) was 64.17% (95% CI: 30.2%–84.3%; P < 0001) (Fig. 3C).

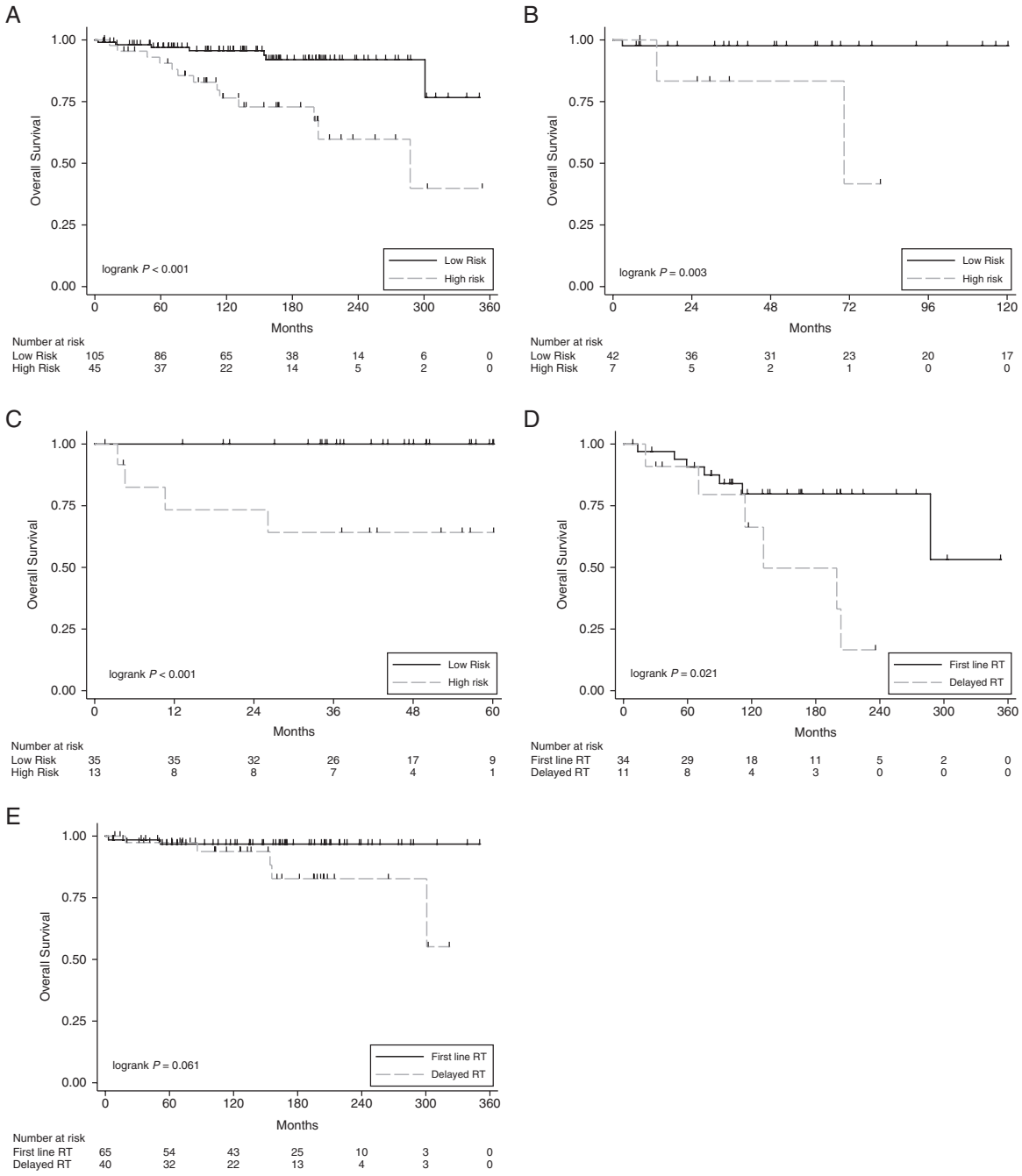

Fig. 3 Overall survival stratified by risk group for: (A) the entire St Jude cohort, (B) the patients in the St Jude cohort with molecular data stratified by risk group, and (C) the external validation dataset (the CNS9702 cohort). Overall survival stratified by timing of RT in: (D) high-risk group and (E) low-risk group. Delayed RT is defined as RT after at least one line of chemotherapy.

Secondary Malignancies—St Jude Cohort

There were 13 subsequent malignancies, 11 of which occurred within the radiation field. Secondary malignancies within the RT field occurred a median of 9.05 years after the start of RT and included the following histologic diagnoses: anaplastic astrocytoma, gliosarcoma, mucoepidermoid carcinoma of the parotid gland, glioblastoma, and meningioma. The 15-year cumulative incidence of second malignancies was 7.03% (95% CI: 3.2%–12.7%). One patient with a secondary malignancy had a known underlying genetic cancer predisposition syndrome (NF1). At last follow-up, 3 of the 11 patients with secondary malignancies were alive.

Discussion

The current management paradigm for unresectable LGG/LGGNT supports an approach of initially administering chemotherapy or targeted therapy and reserving RT for subsequent progressions with the assumption that disease outcome will not be affected by delaying RT. While this strategy is appropriate in certain patients, others might benefit from earlier initiation of RT. Currently, there are no validated criteria to guide use of RT. Our risk-stratification scheme addresses this significant gap in knowledge. We demonstrate that children in the high-risk group with diffuse astrocytoma or thalamic/midbrain tumors have significantly worse OS compared with the low-risk group, and delaying RT in high-risk patients is associated with a further decrement in OS. This decrease in OS was not apparent until after approximately 8 years of follow-up, highlighting the necessity of reporting long-term outcomes in this patient population and the need to validate these results in a larger cohort. RT timing did not influence survival in the low-risk patients. Delayed RT was also associated with worse PFS. We validated this risk stratification in an external dataset and showed that risk groups retained prognostic significance independently of *BRAF* status. Our findings have important implications for unresectable LGG/LGGNTs and challenge the current treatment paradigm.

It is difficult to compare our results to existing literature due to possible differences in reporting of histopathology and tumor location, as well as lack of long-term follow-up and adequate patient numbers. Interobserver agreement on histopathology can vary.[21,22] Therefore, central review by an experienced neuropathologist is critical and highlights a strength of our study. Although a large number of patients were treated on RT1, the initial report of RT1 did not analyze tumor histopathology or location with respect to OS or PFS.[7] ACNS0221 demonstrated inferior OS in patients with non-pilocytic phenotype with a median follow-up of 5 years; however, diffuse astrocytoma was not analyzed as a separate covariate.[23] Tumor location was also not analyzed with respect to OS or PFS. Indelicato et al published outcomes after proton therapy in 174 patients with a median follow-up of 4 years.[24] Only age was associated with improved OS. Lower RT dose, as well as brainstem location, was associated with lower PFS on univariable analysis. However, since brainstem tumors were uniformly treated to a lower dose, collinearity of these 2 variables did not permit a multivariable analysis. Furthermore, thalamic/midbrain tumors were not categorized separately. Other studies reporting outcomes after proton or photon therapy represent small and heterogeneous patient populations, limiting useful comparisons.[25–27] However, outcomes in children treated with chemotherapy have shown that supratentorial midline tumors[28] and thalamic tumors[5] are associated with worse outcomes. Diffuse astrocytoma has also been associated with worse PFS in the initial report of CNS9702, which included patients who were observed after surgery or treated with either chemotherapy or RT.[11]

None of the above studies has incorporated molecular data on *BRAF* alterations. There is a known association between pilocytic astrocytoma and *KIAA1549-BRAF* fusion, as approximately 70% of pilocytic astrocytomas harbor this fusion.[29] It is unclear whether the fusion is associated with improved prognosis independently of tumor type, as the two are highly correlated. *BRAF V600E* mutation has been reported across multiple tumor types, including pilocytic astrocytoma, (pediatric-type) diffuse astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma.[13,30,31] Whether this mutation is associated with independent prognostic significance is controversial. Lassaletta et al reported inferior PFS in *BRAF* V600E mutant tumors in a heterogeneous patient population treated with surgery alone, chemotherapy, or RT.[32] Tumor location and histopathology were not included in the analysis as covariates, questioning the independent prognostic significance of *BRAF V600E*.[33] Our data shed some light on this topic, as we included both molecular and clinicopathologic data in our analysis. Furthermore, all patients were treated in a consistent fashion with RT, eliminating confounding effects from treatment heterogeneity. We did not find that *BRAF* V600E mutation was significantly associated with worse PFS or OS compared with BRAF fusion in the subset of patients with molecular data ($n = 49$). More importantly, our risk stratification scheme was able to demonstrate a significant difference in OS between low- and high-risk groups in this subset of patients with molecular data, suggesting that tumor location and histopathology likely prevail over *BRAF* alteration for LGG/LGGNT treated with RT.

Although OS was the primary outcome measure, we also analyzed PFS. We found that tumor size and delayed RT were associated with worse PFS. Tumor size has been correlated with outcomes in prior studies and was also correlated with OS in our analysis.[5,23] The association between delayed RT and worse PFS might be explained through 2 mechanisms. First, tumors treated with chemotherapy prior to RT tended to be larger at the time of RT, and large tumor size is associated with worse PFS. However, even after accounting for tumor size, delayed RT remained independently associated with worse PFS. Therefore, a second explanation might be that pretreated tumors have shorter PFS compared with tumors that have not been pretreated. Pretreated tumors might be inherently more aggressive and have acquired additional deleterious mutations over time. The phenomenon of temporal genomic heterogeneity has been described in the context of pediatric gliomas.[34,35]

The rationale for delaying or avoiding RT in young children is to reduce the risk of late effects, such as cerebral vasculopathy, neurocognitive impairment, endocrine deficiencies, and secondary malignancies. In the context of pediatric brain tumors, the reported cumulative incidence of a second malignancy is approximately 6–8% at 20 to 30 years, which is comparable to our result of 7% at 15 years.[36,37] In the setting of LGG, distinction between a secondary malignancy and transformation can be challenging—approximately 3% of pediatric LGG may transform to a secondary high-grade glioma.[38] Some patients with LGG may also harbor cancer predisposition syndromes, such as NF1, and be more susceptible to develop a subsequent malignancy. Along with young age, region and volume of brain being irradiated are significant risk factors for vasculopathy, neurocognitive effects, and endocrine deficiencies. Irradiation of optic pathway gliomas,

adjacent to the circle of Willis, can result in vasculopathy,[39] irradiation of the hippocampus can impair memory and learning,[40] and irradiation of the pituitary-hypothalamic axis can result in endocrine deficiencies.[41]

There are several limitations to our analysis. *BRAF* alterations were only determined in a subset of St Jude patients ($n = 49$). Similarly, absence of H3 K27M mutation was confirmed in a subset of patients with thalamic/midbrain tumors for whom data were available ($n = 26$). Additionally, the validation cohort from CNS9702 did not contain any molecular data. Although we did not find any statistically significant difference in outcome by *BRAF* alteration, our subset with molecular data was limited. Therefore, we cannot exclude the possibility that *BRAF* alterations might be associated with a difference in outcome. With additional molecular data, as well as MRI-based tumor measurements, further refinement of the risk stratification scheme might be possible. There is some difficulty in interpreting tumor size over a two-decade timespan with evolving imaging technologies from CT to high-resolution MRI. Secondly, although RPA is a clinically useful tool to divide patients into prognostic groups, the results can be highly dependent on patient population and input variables. Therefore, it is reassuring that we can reproduce statistically significant differences in the low-risk and high-risk groups using an independent dataset. Finally, application of our risk stratification scheme should be limited to unresectable LGG/LGGNT treated with RT. The validity of this risk scheme in other clinical contexts is unknown.

We have identified a high-risk group of patients with diffuse astrocytoma or thalamic/midbrain tumors associated with inferior survival and validate these results using an external dataset. Risk grouping retained prognostic significance independently of BRAF alteration. In this high-risk group, delayed RT was associated with a reduction in OS, suggesting that these patients might benefit from timely RT.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

pediatric low-grade glioma | radiation | risk stratification | survival

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