Original Article

Early Radiotherapy Preserves Vision in Sporadic Optic Pathway Glioma

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BACKGROUND: Sporadic optic pathway/hypothalamic gliomas represent a unique entity within pediatric low-grade glioma. Despite favorable survival, location makes treatment difficult and local progression debilitating. This study is a longitudinal assessment of visual acuity (VA) among children treated within the last 2 decades. **METHODS:** Clinical characteristics were abstracted for patients treated from 2000 to 2018 at Texas Children's Cancer Center in Houston. Ophthalmologic data taken at 3- to 6-month intervals were examined with age-appropriate VA metrics converted to the LogMAR (logarithm of the minimum angle of resolution) scale. Kaplan-Meier blindness-free survival (BFS) curves, calculated as time-to-bilateral functional blindness (LogMAR ≥0.8 in both eyes), were calculated for patients receiving early radiation therapy (RT; upfront or as first-line salvage treatment) or chemotherapy (CT) and evaluated using the log-rank test. **RESULTS:** Thirty-eight patients with a median follow-up of 8.5 years (range, 2-17 years) were identified. Median age at diagnosis was 3 years (interquartile range, <1-6 years). Early RT was administered in 11 patients (29%). Twenty-seven patients (71%) were treated primarily with CT, initiated at a median age of 3.5 years (range, <1-11 years). Eight patients in the CT group did eventually require RT secondary to VA loss and following multiple lines of CT. Median age at RT for all patients was 11 years (range, 3-17 years). BFS rates were 81% at 5 years and 60% at 8 years for CT and 100% at 5 and 8 years for early RT ($P = .017$). **CONCLUSIONS:** In a contemporary cohort, early RT, defined as initial or first-line salvage therapy, was found to have superior BFS for appropriately selected patients with sporadic optic pathway/hypothalamic gliomas. ***Cancer* 2021;0:1-10**. © *2021 American Cancer Society*.

LAY SUMMARY:

- Children with low-grade brain tumors of the optic pathway generally have excellent long-term survival; however, given the location of these tumors, there can commonly be threatened vision if the tumor grows.
- Although radiation is generally deferred in children on the basis of legitimate concerns regarding the effects on the developing brain, it may represent a vision-preserving therapy for well-selected older patients.

KEYWORDS: blindness-free survival, early radiation therapy, optic pathway hypothalamic glioma, proton beam therapy, visual acuity.

INTRODUCTION

Optic pathway/hypothalamic gliomas (OP/HGs) are a unique entity within pediatric low-grade gliomas (LGGs), with favorable outcomes measured in standard end points including overall survival (90%-100% at 5 years); however, these tumors carry significant risk of visual impairment.[1,2] As 50% to 70% of cases are associated with neurofibromatosis type 1 (NF1), decision-making is not clear in sporadic variants.[3]

Chemotherapy (CT) is typically the initial approach for younger patients with OP/HGs to delay definitive radiation therapy (RT).[4-6] However, recent studies have not found successful visual preservation with CT, and most children (>60%) have persistent progression, which requires salvage treatment.[7,8] The natural history of OP/HGs ranges widely, from indolence to rapid progression.[9] Appropriately timing salvage initiation is critical, leading to close surveillance of patients with serial magnetic resonance imaging and ophthalmologic examinations.[10,11] Tumors can progress with stable vision; conversely, vision can also decline despite radiographic stability.[12] Generally, treatment is only initiated once tumor growth is established by radiologic or clinical findings. Given the possible late effects of RT—neurocognitive decline, endocrinopathies, cerebral vasculopathy, and secondary malignancies—most centers adopt a chemotherapy-first approach, attempting to delay and even omit RT. However, most children will progress after their initial CT regimen, and questions regarding the appropriate time to initiate RT are often posed, presenting serious decision-making challenges for pediatric and radiation oncologists.

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Given the long-term survival of most of these patients, a major concern is how delaying definitive RT may cause loss of functional vision, substantially burdening the patient, family, and society.[3] We propose using a meaningful end point, blindness-free survival (BFS) for future clinical trials. Using the BFS end point, we investigated the temporal effect of RT on long-term visual outcomes in children with OP/HGs.

MATERIALS AND METHODS

Patient Selection

Following institutional review board approval, comprehensive clinical characteristics and ophthalmologic data of children (<18 years old) with sporadic optic pathway/hypothalamic glioma diagnosed during an 18-year period (2000-2018) at a high-volume pediatric cancer center (Texas Children's Cancer Center in Houston) were acquired. However, before the construction of a proton center in 2006, some patients at our institution were treated with photon beam therapy at affiliated hospitals, but those patients were diagnosed before the year 2000; therefore, all patients included in our study received proton beam therapy (PBT). A retrospective, longitudinal, observational study was conducted of those patients without NF. A minimum follow-up of 5 years from diagnosis was required unless the patient underwent definitive therapy (RT or surgery) upfront and had at least 2 years of follow-up, given that these modalities represent curative therapy (late tumor progression/visual acuity [VA] decline unlikely). Given the sensitive tumor location, biopsies were not required for study inclusion. Tumor characteristics including grade, location, and posterior extent of disease (Dodge classification[13]) were captured. Information regarding the treatment paradigm at our institution is provided in the supporting information).

Ophthalmologic Functional Examination

Baseline ophthalmologic examination and subsequent changes in VA were recorded for all patients temporally and at a minimum of every 12 weeks while on treatment as is recommended for patients with OP/HG. Patients' better and worse eyes were identified at baseline and tracked individually. Given the pediatric population and as per consensus guidelines from the Response Evaluation in Neurofibromatosis and Schwannomatosis Visual Outcomes Committee (which also apply for sporadic OP/HGs), utilization of Teller Acuity Cards (Stereo Optical) in children younger than 2½ years old and an HOTV test (test involving identification of the letters H, O, T, and V) or logarithm of the minimum angle of resolution (LogMAR) charts for older children were used to evaluate VA.[14] All findings regardless of age-appropriate technique were then converted to a LogMAR scale for the purposes of comparison. A decline of 0.2 LogMAR from baseline was used to define worsening in vision with a follow-up visit confirming the decline as per recommended guidelines.[15] Presence of optic pallor, strabismus, nystagmus, and proptosis at diagnosis were noted.

Defining Blindness-Free Survival and Disease Progression

In choosing a cutoff to define blindness for our blindness-free survival (BFS) end point, we used the standard for legal blindness in most states (≥0.8 LogMAR, ie, 20/125 bilaterally), rather than complete blindness (1.3 LogMAR) or unilateral blindness, to better identify children who developed such serious vision loss that special accommodations and/or language tools (ie, Braille) could be necessary. Patients discovered to be blind at diagnosis (ie, before treatment) and who never developed functional vision were excluded from the primary end-point analysis to support a categorical analysis. BFS curves were further stratified to: 1) an early RT group that included patients receiving RT upfront or as first-line salvage treatment, or 2) a CT group in which RT, if delivered, was given after ≥2 chemotherapy regimens. We hypothesized that younger patients may do worse at diagnosis; therefore, an analysis of BFS curves based on age at diagnosis (<5 years or ≥5 years) was done to assess for differences. We also assessed the correlation between poor visual outcomes (≥0.8 LogMAR at last follow-up) and clinical risk factors at diagnosis. Finally, for patients in the early RT group, Humphrey visual field tests and confrontational visual fields were evaluated at last follow-up to further understand vision quality beyond VA. Visual fields were not assessed longitudinally, given the unreliability of visual field testing in young age. Disease progression was defined per the recommendations of the Response Assessment in Pediatric Neuro-Oncology Working Group[15] and is further detailed in the supporting information.

Toxicity Reporting

Clinically significant radiation therapy toxicities (grade ≥3) were also abstracted from the electronic health record using NCI Common Terminology Criteria for Adverse Events (CTCAE v5). For patients undergoing RT, the need for endocrine supplementation in follow-up was recorded. Those who underwent early RT generally had neuropsychiatric evaluations available for cognitive function (very superior, superior, high average, average,

borderline, extremely low, or inconsistent). Otherwise, educational level, social work notes, need for special schooling, and oncology notes provided supplementary information to classify patients' cognitive outcomes following PBT.

Statistical Analysis

Kaplan-Meier curves were calculated, stratified, and compared using the log-rank test in GraphPad Prism version 8.0.0 for Windows (GraphPad Software, Inc), and a heat map summarized each patient's long-term visual outcome in contrast to their VA at baseline. Summary statistics and nonparametric comparisons were performed with JMP software (version 14; SAS Institute, Inc). Clinical risk factors at diagnosis correlating with poor visual outcome were analyzed using a Fisher's exact test with a one-sided P value of <.05 considered statistically significant. Variables initially planned for analysis included: <12 months old at diagnosis, sex, presence of optic pallor at diagnosis, acute vision loss at presentation, blindness at presentation, hydrocephalus, and placement of a ventriculoperitoneal shunt. A Fisher's exact test compared final count of cases with preserved vision in 1 or both eyes. A Mann-Whitney test was used to compare RT target volumes between the early RT group and those receiving RT later in the CT group. The median was the preferred measure for reporting central tendency given nonnormal distributions and is provided along with the interquartile range (IQR) or absolute range when appropriate.

RESULTS

Patient, Disease, and Treatment Characteristics

Thirty-eight patients with median follow-up of 8.5 years (range, 2-17) were identified. The median age at diagnosis was 3 years (IQR, <1-6 years); 53% of patients were male. Patient and disease characteristics are provided in Table 1. Exactly half of patients presented with vision loss, and most (66%) presented with optic pallor. Nystagmus (45%), strabismus (32%), and hydrocephalus (29%) were also common. Seven patients had evidence of leptomeningeal dissemination at presentation. Patients were stratified for comparison as shown in Figure 1. Early RT was administered as initial therapy (n = 6) or first-line salvage (n = 5) in 11 patients (29%). For this group, the median age at initial diagnosis was 6 years (range, 2-16 years), and the median time to RT from diagnosis was 2.5 years (IQR, 0.3-9.5 years). Six patients (55%) underwent RT at 15 years of age or older; the remainder (n = 5, 45%) underwent RT at 10 years of age or younger (exact ages: 6, 7, 8, 10, and 10 years old). Twenty-seven patients (71%) were initiated on CT at a median age of 3.5 years (range, <1-11 years). Of these, 8 patients (30%) received RT following ≥2 systemic therapy regimens secondary to worsening VA at a median of 5 years from initial diagnosis (range, 2-12 years). Comprehensive treatment details are provided in Table 2. All patients received PBT to a median dose of 50.4 GyRBE (relative biological effectiveness; range, 45-54 GyRBE) in 1.8 GyRBE daily fractions. Across both groups, median age at RT initiation was 11 years (range, 3-17 years). The median clinical target volume (CTV) in the early RT group was 37 cc (IQR, 22-56 cc) compared with 80 cc (IQR, 53-155 cc) for patients who received RT later in the CT group ($P < 0.01$).

TABLE 1. Patient and Disease Characteristics (N = 38)

Factor	No. (%)
Age at diagnosis, y	
<1	11 (29)
1-2	5 (13)
2-5	9 (24)
5-9	11 (29)
≥10	2 (5)
Sex	
Female	20 (53)
Male	18 (47)
Race/ethnicity	
White (non-Hispanic)	22 (58)
White (Hispanic)	11 (29)
Black	3 (8)
Asian	2 (5)
Histology	
Pilocytic astrocytoma	24 (63)
Pilocytic astrocytoma with pilomyxoid features	3 (8)
Pilomyxoid astrocytoma	4 (11)
Unknown	7 (18)
Posterior extent of tumor	
Prechiasm/optic nerve	1 (3)
Postchiasm/hypothalamus	37 (97)
Clinical symptoms at diagnosis	
Optic pallor	25 (66)
Acute vision loss	19 (50)
Nystagmus	17 (45)
Esotropia/exotropia	12 (32)
Hydrocephalus	11 (29)
Papilledema	5 (13)
Macrocephaly	4 (11)
Proptosis	3 (8)
Diencephalic syndrome	2 (5)
Seizure	1 (3)
Precocious puberty	1 (3)
WHO grade	
Grade 1	27 (71)
Grade 2	4 (11)
Unknown	7 (18)
M stage	
Focal lesion only	31 (82)
Metastatic at presentation	7 (18)
BRAF mutation status known (n = 21, 56%)	
BRAF-KIAA1549 fusion	8 (38)
BRAFV600E	7 (33)
BRAF wt	6 (29)

Abbreviation: WHO, World Health Organization.

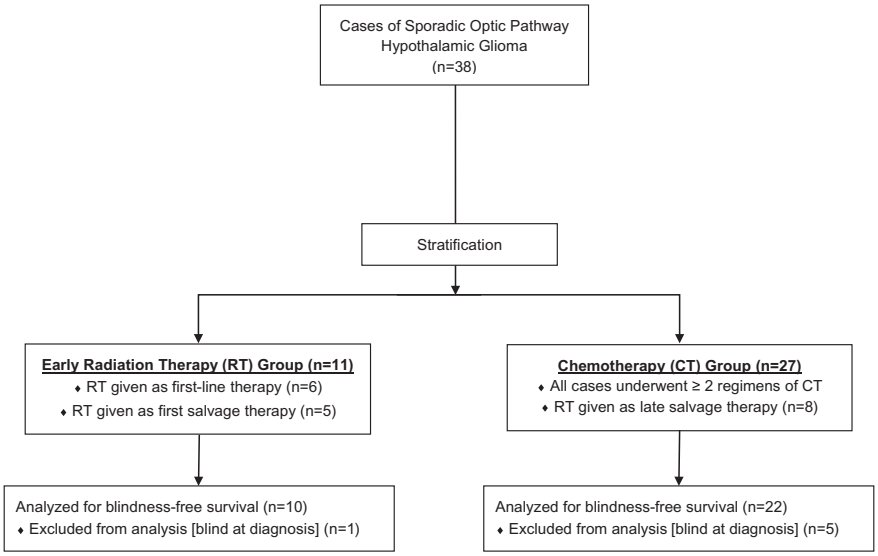

Figure 1. Stratification scheme of early radiation therapy (RT) versus chemotherapy (CT). Patients were stratified on the basis of whether they received early RT, defined as first-line therapy or first salvage therapy. Patients who never developed functional vision were excluded from the main analysis.

Apart from 1 patient in the CT group who underwent craniospinal irradiation after developing leptomeningeal disease, all patients received focal RT with a 5-mm expansion from the gross target volume to form the CTV.

Visual Outcomes and Blindness-Free Survival

In terms of primary end point for visual preservation, 6 patients were excluded (5 in the CT group and 1 in the early RT group) based on legal blindness at diagnosis and never developing functional vision (ie, advanced disease precluded BFS). For the 32 patients eligible for analysis, BFS rates were 81% at 5 years and 60% at 8 years for CT and 100% at both 5 and 8 years for early RT ($P = 0.017$; Fig. 2A). At time of last follow-up, 70% of early RT patients maintained normal to satisfactory VA (≤0.2 LogMAR) in a minimum of 1 eye and 60% maintained it in both eyes versus 36% and 18% in the CT group, respectively ($P = 0.03$, $P = .02$). Individual VA outcomes for each patient in both groups at last follow-up compared with diagnosis appear in Figure 4. In terms of visual field preservation among the early RT group at last follow-up, 2 patients had full visual fields bilaterally, 2 had mild, scattered losses bilaterally on Humphrey visual field testing but full on confrontational testing, 2 had hemifield deficits bilaterally, another 2 had full fields in their good eye (blind in the other), 1 patient had bitemporal loss, and 1 patient had lost all peripheral vision (central vision only). Of the patients receiving "late" RT in the setting of VA decline in the CT group (n = 7), RT was successful in reversing or preventing legally defined blindness (≥ 0.8 LogMAR bilaterally) in 2 cases. However, collectively for all patients who received RT (n = 19), regardless of timing and without a threshold to define subnormal vision, the absolute VA for patients' better and worse-acuity eye (classified before treatment) was stable or improved in 94% and 75%, respectively. In only 1 case did a patient's vision continue declining in both the better and worse eye following RT. In 3 cases, patients experienced visual decline in the worse eye but preservation or improvement in the better eye.

Age at diagnosis (<5 or ≥ 5 years old) did not significantly impact visual outcome in terms of BFS ($P = .67$; Fig. 2B). Furthermore, BFS was not significantly different within the CT group for patients receiving late RT versus those who never received RT ($P = .93$; Fig. 2C). For the 5 patients who were excluded from the categorical BFS analysis because they were blind at diagnosis, the 4 who received CT had no meaningful improvements in vision following treatment and the 1 who received early RT had some improvement in the better eye (LogMAR 1.2 at diagnosis to 0.9 at last follow-up). No patients who were blind at diagnosis had significant vision improvement (LogMAR ≤0.8). Finally, in an analysis of all patients (N = 38) for clinical risk factors at diagnosis associated with poor long-term visual outcomes, the only statistically significant factors were blindness at presentation ($P = .001$) and <12 months of age at diagnosis ($P = .04$).

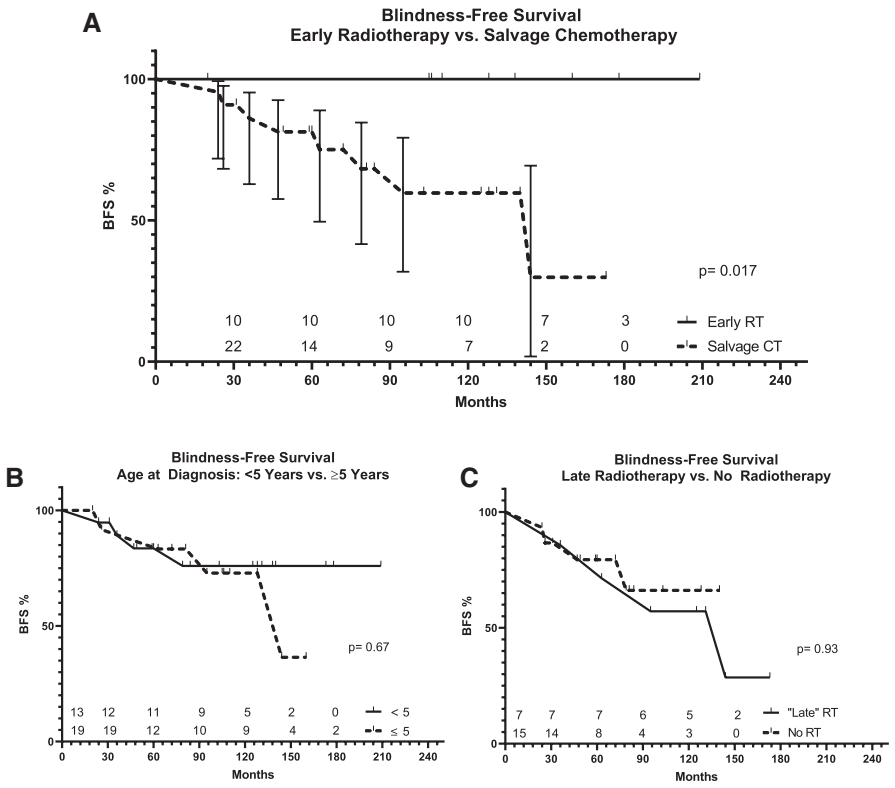

Figure 2. Blindness-free survival (BFS). (A) BFS stratified by whether the patient received early radiation therapy (RT), or salvage chemotherapy (CT) with error bars representing the 95% CI. (B) BFS stratified by age at diagnosis. (C) Comparison of patients who received late RT in the salvage CT group (ie, for acutely declining visual acuity) with patients who never received RT.

Disease Control and Progression-Free Survival

At last follow-up, all patients were alive. Patients undergoing initial treatment with RT experienced no progression at any time interval (100% progression-free survival [PFS]), and all patients had over 8 years of follow-up (Fig. 3A). Furthermore, no cases of progression were reported with RT when used as first-line salvage (Fig. 3B). Two patients received MAPK/ERK kinase (MEK) inhibitors as first-line salvage and remain free from progression at 81 and 84 months. Three patients received temozolomide as first-line salvage with a median PFS of 19 months, whereas 20 patients received other chemotherapy (mostly vinblastine) with a median PFS of 9 months. Most progression overall was local; however, 4 patients in the CT group developed leptomeningeal disease during their disease course following repeated local failure. Of these, 3 patients were ≤1 year old at diagnosis and not ideal candidates for early RT because of young age, and 1 patient had received late salvage with RT after 2 regimens of CT and secondary to VA decline. Of the 3 that did not receive RT, 1 patient received 3 regimens of systemic therapy (including a MEK inhibitor), and the other 2 patients both received 5 different regimens of systemic therapy, all secondary to repeated local failures. Of the 19 patients eventually receiving RT, none progressed locally, and only the 1 above-mentioned patient progressed distantly, developing a new intracranial lesion months after treatment.

Toxicities From Radiation Therapy

All patients tolerated and completed RT as prescribed without acute complications. The median follow-up time following RT was 51 months (IQR, 19-106 months). As of last follow-up, 11 patients (58%) required post-RT hormonal supplementation. Of the 16 patients with long-term follow-up, 3 grade 3 toxicities were appreciated. One patient developed orbital edema and pain requiring surgical intervention; another 2 patients developed treatment-related vasculopathy (moyamoya disease) confirmed by angiography at 15 and 36 months from RT completion at 8 and 10 years old, respectively. In 1 of the 2 cases of vasculopathy, the patient presented with an internal carotid artery stroke and experienced transient hemiparesis. The patient had been heavily pretreated with 3 regimens of chemotherapy, including irinotecan/bevacizumab, and

TABLE 2. Treatment Details

Treatment	No. (%)
Initial surgery prior to oncologic Tx (N = 38)	
Biopsy only	27 (71)
Subtotal resection	3 (8)
Shunt only	1 (3)
No surgery	7 (19)
Initial therapy (N = 38)	
Chemotherapy	32 (84)
Radiotherapy	6 (16)
Initial salvage therapy (n = 32, 84%)	
Chemotherapy or targeted agent	26 (83)
Radiotherapy	5 (17)
Surgery	1 (3)
Radiation therapy details (n = 19, 50%)	
Chemotherapy regimens prior to RT, median (range)	1 (0-5)
Radiation as initial treatment	6 (32)
Radiation as 1st-line salvage	5 (26)
Radiation after ≥2 regimens of chemotherapy	8 (42)
Radiation implemented as response to decreased VA	8 (42)
Age at start of RT, median (range), y	10 (3.7-17)
RT dose in Gy RBE, median, range	50.4 (45-54)
Required surgery for cyst decompression after RT	4 (21)
Systemic therapy details (n = 32, 84%)	
Number of regimens received to date, median (range)	3 (1-6)
Vincristine + carboplatin	32 (100)
Vinblastine	19 (59)
Temozolomide	14 (44)
Bevacizumab + irinotecan	11 (34)
MEK inhibitor	7 (22)
BRAF inhibitor	3 (9)
Other	3 (9)
Secondary surgery details (n = 16, 39%)	
GTR	1 (6)
STR "debulking"	11 (69)
Cyst fenestration/decompression	4 (25)

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B1; GTR, gross total resection; MEK, MAPK/ERK kinase; RBE, relative biological effectiveness; RT, radiation therapy; STR, subtotal resection; Tx, treatment.

underwent a subsequent subtotal surgical resection before receiving RT. A baseline angiogram was not available for either case before RT to assess for tumor compression of the circle of Willis. Pseudoprogression was observed in 8 of 16 cases (50%), 4 cases were seen in the early RT group, and 4 cases were after late RT in the salvage CT group. Of the 8 cases of pseudoprogression, 50% (n = 4) required surgical decompression because of cystic expansion following RT.[16] In terms of cognitive function, in the early RT group (n = 11), classification was average to high average in 9 cases (82%), of which at the time of last follow-up, 1 patient was employed, another 2 were enrolled in college, and a fourth was in graduate school pursuing a doctoral degree. One patient of these 9, despite being high-functioning, expressed frustration about issues with transient short-term memory, but this did not impact their daily living activities (CTCAE grade 1). For the other 3 cases, 1 patient was classified as borderline with low to average IQ, and another patient was significantly impaired, ranking extremely low in several domains and requiring special schooling; however, this patient had already suffered from confusion and personality disorder before RT following a surgical procedure. No secondary malignancies were reported.

DISCUSSION

In this first longitudinal study, we used a BFS end point for children with OP/HGs and evaluated the timing of RT. Our main finding is that patients qualifying for early RT, defined as RT for initial or first-line salvage therapy, maintain their long-term VA. Over 2 decades, most pediatric cancer centers have shifted from using RT as definitive or early salvage to administering multiple lines of systemic chemotherapy. Although this has allowed a certain percentage of patients to forgo the toxicity of early RT, some patients risk losing sight in addition to the morbidity of subsequent primary progressions. Despite excellent 5-year–survival rates, progression remains the leading long-term cause of morbidity for patients with LGGs.[17,18] For nonoperable gliomas, the question remains, "How late is soon enough?" for RT.[19] As highlighted by Bitterman et al, broad avoidance of RT for fear of toxicity may dismiss an optimal salvage therapy and may place certain patients at high risk of subsequent tumor progression.[20] Given our change in practice, enough patients with long-term follow-up were available to stratify based on the timing of RT and subsequent effect on visual outcomes and clinical progression. Our findings suggest that early RT improves visual preservation (BFS) while providing durable, curative treatment in well-selected patients.

Visual outcomes in patients with sporadic OP/HGs are suboptimal. Campagna et al published on visual outcomes in OP/HGs in children without NF1 and ultimately found their visual prognosis "unsatisfactory." Unsurprisingly, they also found that older children treated with RT seemed to have better visual outcomes than younger children.[21] Shofty et al published their experience with visual outcomes following CT and found the overwhelming majority of patients who received CT for progressive OP/HGs developed a decline in vision.[12] Finally, Awdeh et al from St. Jude Children's Hospital found patients treated initially with CT before receiving RT had decreased VA compared with those who received primary RT.[22] This group has also recently published on visual outcomes, noting a 5-year, low cumulative incidence of VA decline for patients undergoing RT.[23] Finally, their most recent data established RT's ability to provide long-term disease control in terms of 10-year event-free

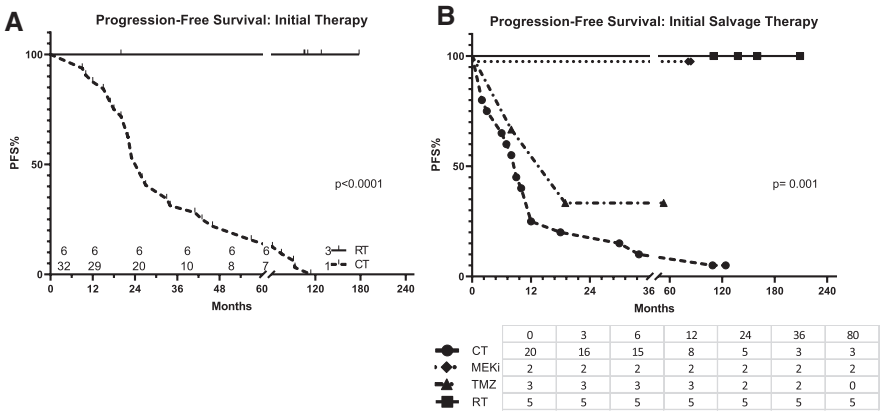

Figure 3. Progression-free survival (PFS). (A,B) PFS depending on choice of therapy initially and for first salvage, respectively. CT indicates chemotherapy; MEKi, MEK inhibitor; RT, radiation therapy; TMZ, temozolomide.

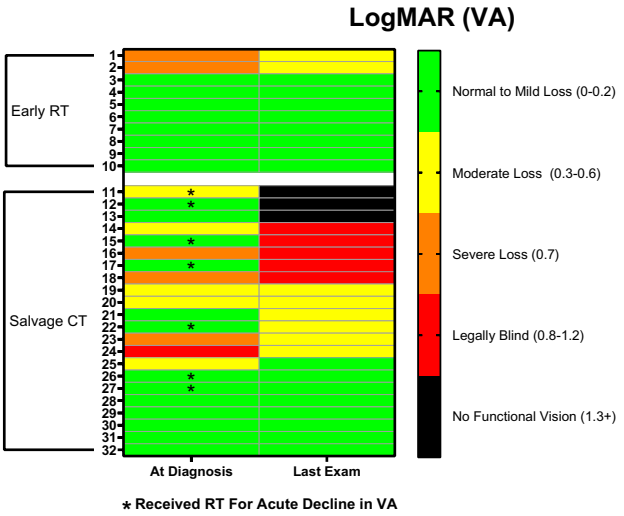

Figure 4. Degree of visual acuity (VA) loss (early radiation therapy [RT] vs chemotherapy [CT]). Each patient's individual VA outcome in their best eye is quantified at diagnosis and at last follow-up using a heat map. Green represents normal to only mild loss of VA (logarithm of the minimum angle of resolution [LogMAR] ≤0.2), yellow represents moderate loss (LogMAR 0.3-0.6), orange is severe (LogMAR 0.7), red indicates legal blindness (LogMAR 0.8-1.2), and black (LogMAR ≥1.3) represents near or complete blindness. Patients in the salvage CT group who received RT for acute decline in VA are noted.

and overall survival with low risk of late toxicity in older children without NF1.[24]

These studies suggest that RT can not only prevent acute visual decline but can establish visual stabilization and long-term disease control. However, quantifiable short-term vision improvement after RT treatment may not result in a practical or functional benefit to the patient if the vision has already become severely impaired (ie, improvements occur below a certain subnormal threshold). Therefore, to determine if RT treatment is impactful for visual morbidity, we defined a threshold of legal blindness, despite correction, to generate a longitudinal, time-based end point that better describes a patient's functional outcome. A recently published workshop on optic pathway glioma for NF1 patients by Azizi et al, recommends tracking patients VA (LogMAR) for each eye and classifying by World Health Organization category. We believe these recommendations should also be applied to patients with sporadic optic pathway glioma.[25] We tracked all patients' visual outcomes based on VA in both the better and worse eye. However, looking at fixed time intervals, especially when assessing vision soon after treatment with RT or CT, one could mistakenly conclude that treatment has improved long-term visual outcome, when in fact, VA was only temporarily improved. For this reason, we picked a categorical, simple end point and tabulated VA at all available time points for longitudinal analysis. Our observations support that patients who develop functional blindness in the CT group and then are initiated on RT secondarily, rarely recover functional vision, even though their objective and subjective vision may temporarily improve or stabilize. Thus, RT likely provides maximum benefit when used to preserve vision, rather than to restore it, making the end point of visual preservation in the form of BFS especially relevant.

Applied to practice, at the very minimum our findings further enforce the importance of regular interval evaluation of VA, ideally by a pediatric neuro-ophthalmologist at an interval at least as often as surveillance magnetic resonance imaging. Any decline in VA of 0.2 LogMAR or greater, regardless of the patient's gross visual ability,

should yield a high suspicion for progression. Testing should be repeated in a timely manner to confirm the result because VA can vary day-to-day based on extraneous factors, such as the child's cooperation. Once a drop of this magnitude has been confirmed, a multidisciplinary discussion and referral to radiation oncology to evaluate the patient and their candidacy for RT would be prudent. Our experience suggests that once vision is lost, it is rarely recovered; therefore, a low threshold for visual decline should be employed by the pediatric oncologist. Certain risk factors have been suggested as predictors of symptomatic progression of OPGs, including age (young age), tumor location (hypothalamic/chiasmatic, intraconal, or postchiasm), tumor structure changes (enlarged cystic component), and optic pallor at diagnosis; however, a paucity of data exists connecting outcomes with tumor characteristics,[11,26,27] and data are lacking regarding factors associated with vision loss in OP/HGs. When examining our cohort based on VA at last follow-up, we found that diagnosis in an infant (<12 months) correlated with poor visual outcome, in line with what has been previously reported.[27] However, in our longitudinal visual outcome analysis, which excluded children who were functionally blind at diagnosis and never developed significant vision (n = 6), we found no significant difference in BFS when stratified by age (<5 years or ≥5 years old) suggesting that even younger children, assuming they have preserved vision at diagnosis, may not necessarily have a worse visual outcome than older children. Almost all our patients had disease extension posteriorly beyond the chiasm, precluding assessment of this factor. Sex was not significant, starkly contrasting to the 5- to 10-times–increased risk of VA decline for females seen in NF1-mediated optic pathway glioma.[28] Finally, optic pallor at diagnosis did not predict a poor visual outcome using our BFS definition, though it has proved significant in prior reports.[1]

Although not the primary aim of this study, we must highlight the excellent long-term disease control achieved with today's RT, with no cases of local progression identified. RT is a definitive therapy: In well-selected patients, it represents curative treatment, decreasing the burden of chronic disease. We have previously reported on the use of a conformal 5-mm CTV margin.[29] A recent analysis of the results of the Children's Oncology Group phase 2 study ACNS0221 found that a 5-mm margin provides acceptable disease control.[30] In terms of dose, whereas 54 Gy is an accepted standard for pediatric LGGs, we have previously reported that with photon beam therapy,[31] and show in this report with PBT, that 50.4 Gy and even doses <50 Gy (sometimes used for younger age and/or larger volumes) provide a high rate of local control. We reported pseudoprogression in half of the cases undergoing RT, and of those, 4 cases of cystic expansion that required surgical decompression/cyst fenestration but in follow-up did not show true disease progression. This should not be surprising, as it known that patients with pilocytic astrocytoma histology (as seen in many cases of OP/HG) have greater than fivefold odds of developing pseudoprogression compared with other LGGs undergoing photon RT (29%) and this may be further increased by the use of PBT.[16,32] Clinical data supporting the neurocognitive outcomes of PBT versus photon beam therapy are emerging; children treated with focal PBT may have few differences in this domain compared with those who do not receive RT.[33-35] Although we have focused on visual outcomes in this study, long-term quality of life and cognitive outcomes are a critical next step of study in the OP/HG population treated early or late with PBT. Promising neurocognitive outcomes may encourage earlier RT referral.

Although some may debate the use of initial treatment with RT in patients ≥10 years, most would initiate treatment with first-line CT in younger children. Furthermore, for patients with a BRAF mutation or those eligible for clinical trial or compassionate use of MEK inhibitor, the decision can become even more complicated. Indeed, several patients in our cohort benefited from long periods of disease control with these targeted agents. Recent prospective findings from a phase 2 trial of selumetinib suggest not only disease control but stabilization and improvement of VA in BRAF or NF1-associated cases.[36] In terms of endocrine dysfunction, given the location of OP/HGs many children may require endocrine supplementation regardless of RT; further delaying RT may lead to worse neuroendocrine function over time.[37] Finally, development of leptomeningeal disease may be a competing risk factor when delaying definitive therapy, though further study is needed. In our cohort, 3 patients who were treated with multiple courses of systemic therapy following repeated local recurrences, eventually developed metastatic disease. Unfortunately, this is particularly devastating because definitive RT must then either be forgone for continued systemic therapy, potentially impacting BFS, or the patient may need craniospinal irradiation leading to much greater long-term toxicity.

We appreciate that comparing patients who qualify for RT with those receiving CT is inherently biased, secondary to the differing patient populations, with younger patients, who are known to have worse outcomes and a different natural history of disease, more likely to be receiving CT. The purpose of this study was not to compare

the use of RT with CT; the benefit of CT, especially in younger patients as first-line therapy is clear, but rather to understand the optimal timing to initiate RT in the appropriately selected patient with respect to preserving vision. This study is limited by a modest sample size and retrospective nature. Whereas many patients who were managed primarily on systemic therapies were treated in the latter half of the study window and had access to targeted therapies as lines of salvage, we cannot thoroughly evaluate BFS with respect to targeted therapies when used earlier in a patient's treatment course. RT's role in the era of BRAF and MEK also requires further study. Long-term data regarding late toxicities of today's RT (conformal photon therapy and proton therapy) in this population are needed. In terms of VA, especially for younger patients, testing can be unreliable and therefore VA at baseline (Fig. 4) should be interpreted with some caution. Furthermore, whereas VA is generally the primary metric examined, in some cases, only central vision may be preserved (as seen in 1 of our patients in the early RT group). Therefore, the morbidity of visual field loss should be noted and requires further study. Additionally, the sequelae of PBT may not be well captured given that many patients will, fortunately, live decades beyond their original diagnosis. Although we have reported major toxicity in terms of vasculopathy, endocrine dysfunction, and neurocognition, further comprehensive study of the long-term effects is needed. Finally, this study represents the experience at 1 institution, which may not be generalizable. The decision to undergo RT for a patient with LGG should always include multidisciplinary discussion and shared decision-making with the patient's family. Strengths of this study include the longitudinal, multidisciplinary, median follow-up of 8.5 years and the use of a functionally meaningful end point to assess long-term visual outcomes.

In summary, our findings suggest that early RT, delivered as initial or first-line salvage therapy, preserves functional vision in the appropriately selected, older patient and should be considered following significant decline in VA (≥0.2 LogMAR). Furthermore, we defined the value of a new, functional end point (BFS) to evaluate for meaningful visual outcomes in patients with sporadic OP/HGs, which may be valuable for future prospective trials. Finally, whereas RT provides exceptional disease control, patients remain at risk for morbidity secondary to cystic evolution of their disease, vasculopathy, and endocrine and neurocognitive dysfunction; they therefore require careful and continued care with a multidisciplinary team.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Alexander N. Hanania: Study design/inception, data collection, statistical analysis, initial interpretation of findings, writing–original draft, and writing–review and editing. **Arnold C. Paulino:** Study design/inception, initial interpretation of findings, writing–original draft, and writing–review and editing. **Ethan B. Ludmir:** Data collection, writing–original draft, and writing–review and editing. **Veeral S. Shah:** Data collection, writing–original draft, and writing–review and editing. **Jack M. Su:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **Susan L. McGovern:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **Patricia A. Baxter:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **Mary Frances McAleer:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **David R. Grosshans:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **M. Fatih Okcu:** Initial interpretation of findings, writing–original draft, and writing–review and editing. **Murali M. Chintagumpala:** Study design/inception, data collection, initial interpretation of findings, writing–original draft, and writing–review and editing.

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