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Effect of Time from Diagnosis to Start of Radiotherapy on Children with Diffuse Intrinsic Pontine Glioma

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Abstract

Background—Children with diffuse intrinsic pontine glioma (DIPG) continue to have poor outcomes, and radiotherapy (RT) is the only temporarily effective treatment. In this retrospective analysis, we studied the effect of time from diagnosis to start of RT on event-free survival (EFS) and overall survival (OS) in children with DIPG.

Methods—Records of children (*n*=95) with DIPG treated with RT at a single institution between April 1999 and September 2009 were analyzed. RT was delivered at doses of 54.0–55.8 Gy at 1.8 Gy per fraction, and children were followed prospectively. The effect of gender, race, interruption during treatment course, age at diagnosis, duration of symptoms prior to diagnosis, use of protocol-based chemotherapy, and time from diagnosis to initiation of RT on EFS and OS was assessed by the Cox proportional hazards model.

Results—Time as a continuous variable from diagnosis to start of RT did not affect outcome. Time dichotomized to ≤14 days significantly affected OS [hazard ratio [HR]=1.70, *P*=0.014) and race other than white or black affected EFS [HR=2.32, *P*=0.017). The 95 patients had a 6-month EFS and OS of 60%±5% and 94.7%±2.3%, respectively, and a 12-month EFS and OS of 11.6% ±3.1% and 49.5%±5%, respectively.

Conclusions—Time as a continuous variable did not affect OS or EFS in our cohort; however, children treated within 2 weeks of diagnosis had poor outcomes. Although rapid initiation of RT is desirable, our findings do not support intensive efforts aimed at shortening delays from diagnosis to start of RT.

Keywords

Diffuse intrinsic pontine glioma; radiotherapy; timing; outcomes

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Conflict of Interest Statement

None of the authors have any actual or potential conflicts of interest.

Introduction

Diffuse intrinsic pontine glioma (DIPG) represents approximately 80% of the malignant brainstem tumors occurring in children. Despite numerous clinical trials, the outcome of children with DIPG continues to remain dismal, with a median survival of 9–12 months and a 2-year overall survival (OS) rate of less than 10% [1]. This failure of improvement in outcomes reflects the lack of success of recent investigational agents in the standard management of this disease [2–16]. The diffuse nature and high-risk location of these tumors have resulted in rare tissue acquisition via upfront brainstem biopsy, and therefore little is known about the biological factors involved in the development of these tumors. Conventional chemotherapy continues to be investigational, and radiation therapy (RT) is the standard treatment modality, although it offers limited benefit only [17]. Although RT has been successful in improving initial symptoms and imaging shows improved control of tumor growth in most patients, disease progression is common within 1 year of patients receiving irradiation [16]. Dose escalation trials and altered fractionation schemes have not led to improvement in outcomes, and the typical treatment course is 54–55.8 Gy at 1.8 Gy per fraction [6,11]. Because of the dismal outcomes of DIPG, few studies have focused on standardizing the radiotherapeutic approach taken for this aggressive tumor, despite biological mechanisms being more actively investigated via model systems, and, more recently, by autopsy-based or biopsy-based tissue acquisition [18–23].

Although attempts to initiate irradiation within 30 days of diagnosis have been made in clinical trials, no studies have evaluated the impact of time from diagnosis to the start of radiation treatment on the outcome of children with DIPG. RT is often initiated as soon as possible after diagnosis, even with less established, nonconformal methods in some cases. Hypofractionated RT has been administered in recent clinical investigations, but has not led to a significant change in overall outcome [24].

In this retrospective study, we studied the effect of time from diagnosis to start of RT as well as the effect of gender, race, interruptions during the treatment course, age at diagnosis, duration of symptoms prior to diagnosis, and protocol-based chemotherapy on event-free-survival (EFS) and OS in children with DIPG.

Methods

Study Population

Ninety-five patients (aged 1.5 to 16.5 years) with DIPG were identified and included in this study. Children enrolled on unreported frontline studies were excluded from analysis. The diagnosis of DIPG was made on the basis of findings from magnetic resonance imaging (MRI) in all patients treated at St. Jude Children’s Research Hospital with RT with or without protocol-based chemotherapy between April 1999 and September 2009. The study was approved by the institutional review board. Patient data were de-identified after imaging assessment to ensure anonymity for the solitary surviving patient at the time of analysis.

All patients showed evidence of diffusely infiltrative pontine lesions consistent with DIPG on MRI. The clinical diagnosis for each patient was made in a consensus-based manner by

an interdisciplinary team comprising specialists in neuroradiology, radiation oncology, neurooncology, neuropathology, neurology, and neurosurgery. Eighty-seven patients were enrolled in 1 of 6 chemotherapy-based protocols (SJBG07, PBTC-06, PBTC-07, PBTC-14, ACNS0126, and SJHG-98) as adjunctive treatment for DIPG along with RT [3,5,8,15,25,26]. All protocols are currently closed and have not demonstrated a clinically translatable benefit of chemotherapy in DIPG. The remaining 8 patients received RT as single-modality therapy for their disease, as they were not eligible for enrollment on prospective studies.

Radiotherapy

Three-dimensional imaging-based planning was used for all patients, including 3-dimensional conformal radiotherapy (3DCRT; $n = 77$), forward-planned intensity-modulated radiotherapy (IMRT; $n = 2$), and inversely planned IMRT ($n = 6$). Doses ranged from 54 to 55.8 Gy at 1.8 Gy per fraction. For 23 patients, a brief initial phase with 2D-planning via an opposed lateral approach was used (median dose = 9 Gy; range, 1.8 to 28.8 Gy), and a conformal approach was used subsequently in order to provide time for more elegant planning. The goal was to initiate therapy as quickly as possible, but this practice was discontinued for patients enrolled later as technological advancements improved planning speed. Because of the increased use of steroidal therapy for its anti-inflammatory effects, particularly during initiation of RT, 4 children were re-simulated when the thermoplastic mask fit could no longer be accommodated via mask modification. Immobilization and tumor targeting procedures for patients assessed during 2008 and 2009 have been previously described [27].

Volume Determination

The gross tumor volume (GTV) was determined on the basis of combined T1-weighted (post-contrast), T2-weighted, and fluid attenuated inversion abnormalities identified from the imaging done immediately before beginning RT. The clinical target volume (CTV) included the GTV with an anatomically confined margin of 10–20 mm expanded in 3 dimensions. The planning target volume included the CTV with an added geometric margin of 0.3–0.5 cm expanded in 3 dimensions. Treatment planning was performed using PLUNC (University of North Carolina, Chapel Hill, North Carolina) and KonRad (MRC Systems, Heidelberg, Germany) treatment planning systems.

Statistical Analyses

EFS was calculated from the date of RT initiation to the date of disease progression or death. Imaging evidence of progression was confirmed on subsequent imaging or the date of last follow-up. OS was calculated from the date of diagnosis to the date of death or the date of last follow-up. EFS and OS were estimated by the Kaplan-Meier method. The influence of gender, race, interruption during treatment course, age at diagnosis, duration of symptoms prior to diagnosis, protocol-based chemotherapy, and time from diagnosis to initiation of irradiation was determined on EFS and OS. The Cox proportional hazard model was used to determine the associations of covariates with EFS and OS. The primary objective was to determine the effect of time as a continuous variable as measured from time of diagnosis to

initiation of RT, and various dichotomizations of this variable were studied in the model (≤14 days vs. >14 days, ≤21 days vs. >21 days, and ≤28 days vs. >28 days). The duration of symptoms prior to diagnosis was analyzed in a similar manner as both a continuous variable and with dichotomized intervals of <14 days, 15–30 days, and > 30 days. The associations of these time intervals to both time to RT initiation and duration of symptoms prior to diagnosis were assessed by backward elimination Cox regression models with regard to EFS and OS.

Results

Of the 95 children with DIPG treated at St. Jude during the study period, 94 experienced a failure event at the time of data analysis and 94 patients died of disease. Tables 1 and 2 give demographic data for patients.

Considering a median time to failure of 12 months, time as a continuous variable from time of diagnosis to initiation of RT had no effect on EFS or OS. The 95 patients had a 6-month EFS and OS of 60% ± 5% and 94.7% ± 2.3%, respectively, and a 12-month EFS and OS of 11.6% ± 3.1% and 49.5% ± 5%, respectively (Fig. 1). Duration of symptoms prior to diagnosis did not affect EFS or OS either as a continuous variable or in dichotomized intervals. Gender, race, interruption during treatment course, age at diagnosis, and use of protocol-based chemotherapy did not significantly affect EFS or OS (Fig. 2a & 2b). The only variable significantly affecting EFS was race other than black or white, with a model estimate of 0.842 (SE = 0.352) and hazard ratio of 2.32 (CI 1.16–4.63, $P = 0.0167$). However, this variable did not significantly affect OS.

Time from diagnosis to initiation of RT as a continuous variable did not significantly affect OS or EFS. Dichotomization into intervals of ≤14 days vs.>14 days, ≤21 days vs. >21 days, and ≤28 days vs. >28 days did not affect EFS and was significant only for OS at the 14-day interval. Patients treated earliest (≤14 days) had a higher hazard rate (more deaths) than those treated later, with a model estimate of 0.528 (SE = 0.215) and a hazard ratio of 1.70 (CI = 1.11–2.59, $P = 0.0141$).

Discussion

DIPG is a highly aggressive brainstem tumor that remains uniformly fatal despite numerous clinical trials on investigational agents. RT is the only treatment modality that has proven transiently effective for the disease course of DIPG, with up to 70% of children receiving RT showing short-term neurologic improvement [4]. In most cases, RT is initiated as soon as possible after diagnosis, which sometimes comes at the cost of trying more tailored treatment. Although there are no previous studies on the effect of time to RT in DIPG, several studies have been performed on analogous adult tumors, including high-grade astrocytic tumors of the brain [28–30]. However, results from these studies are conflicting, showing improved outcome with short delays [24,29], increased risk of death with delay [28,31], or no effect on OS [31].

Our study found that time from diagnosis to initiation of RT as a continuous variable did not significantly affect OS or EFS in our study cohort. Further dichotomization of the variable

showed that patients treated earliest (≤14 days) had higher hazard rates than those treated later. This is contradictory to what we had expected, and caution should be used when interpreting the results of such a dichotomization. If this dichotomized variable predicts decreased OS, it is possible that patients treated earlier after diagnosis may have appeared more severely impaired than other patients with DIPG, prompting more expeditious treatment. These patients were possibly diagnosed at a more advanced stage, intrinsically conferring a worse outcome. These results are consistent with those from adults with glioblastoma multiforme [24].

Data from all patients with DIPG who were treated during the study period were included in this retrospective analysis. One patient was alive at the time of data analysis, at 47 months post-diagnosis. Another review of this patient's imaging data showed a pontine lesion hyperintense on T1 imaging, which is not typical for DIPG. However, the scan showed a diffuse T2 hyperintensity suggestive of DIPG. This is the only patient who has not experienced an event to date, likely because of having a low-grade tumor with diffuse imaging characteristics. Rare instances of long-term survivorship is consistent with findings from another study of clinically diagnosed long-term survivors of DIPG [32].

Gender or race did not significantly affect OS, but there was a significant association of race other than black or white with EFS. This is likely due to the small number of patients included in this study. There was no significant difference in outcomes of patients who had an interruption in their RT course, suggesting that small changes in treatment protocol may not have a significant effect on OS. Also, age at time of diagnosis or at time of RT, except for time as a dichotomized variable ≤14 days, did not significantly affect outcomes. This suggests that age at diagnosis does not reflect tumor aggressiveness, clinical course, or patient survival. Previous studies, including one assessing 10 children under the age of 3 years showed that younger patients with DIPG may have better outcomes than older patients do, suggesting a biologically distinct tumor in this age group [32]. However, almost all patients in our cohort were older than 3 years.

One limitation of our study is the retrospective nature of data acquisition. However, the relatively large sample size with otherwise uniform outcomes suggests that these numbers are sufficient to justify this analysis. Follow-up imaging was routinely performed every 2–3 months after completion of RT, allowing frequent serial surveillance for first signs of progression via MRI.

Although RT remains the only form of treatment for DIPG that is temporarily effective during the disease course, the mortality rates associated with DIPG continue to be among the highest for all pediatric cancers and no other form of therapy has been efficacious. While protocol-driven investigation of novel methods and agents to address this disease remains critical, this cohort fails to validate a clear benefit to immediate initiation of radiotherapy, despite recent technological advances in treatment planning throughput and dose conformality. It is common practice to expeditiously treat patients with DIPG shortly after diagnosis; however, our findings highlight the paradox that while rapid implementation of radiotherapy appears desirable, this may not improve outcome. Our study demonstrates that there is no relationship between the time from diagnosis to the time to treatment on EFS and

OS. Caution must be exercised to avoid overinterpretation of results from this dataset, as the results may be swayed in favor of starting RT sooner after diagnosis in patients with more aggressive clinical findings. As more treatment-related data become available for patients with DIPG, our findings can be confirmed in a larger series.

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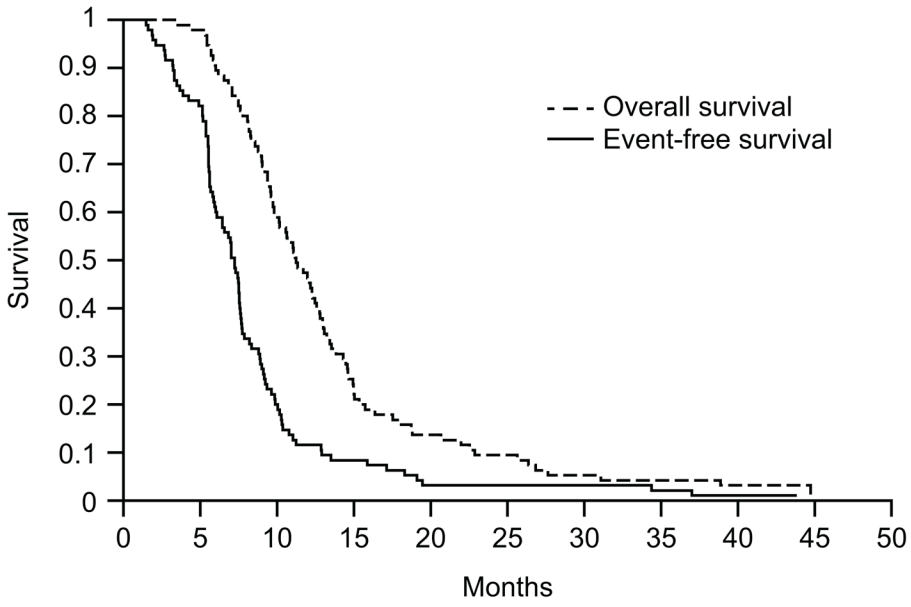

Figure 1.
Event-free survival and overall survival of patients (*n* = 95).

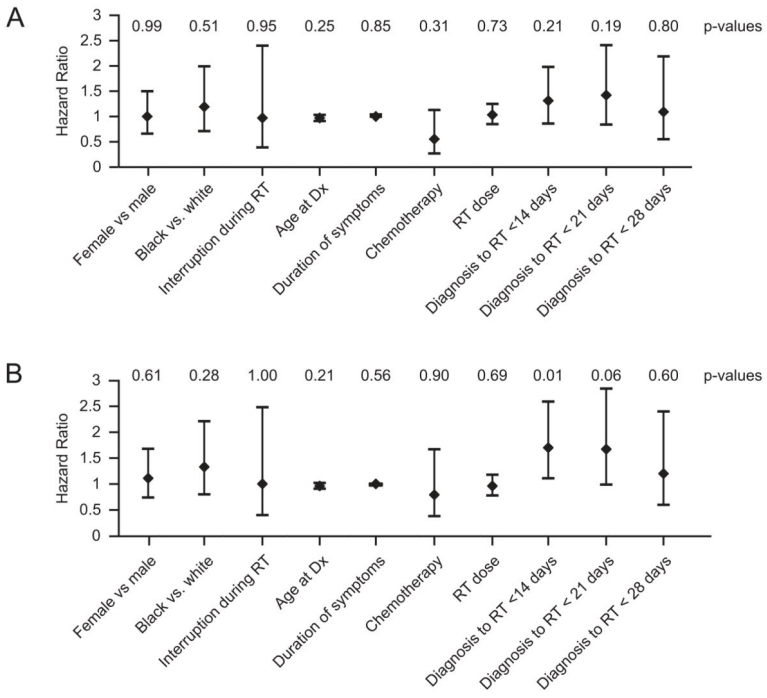

Figure 2.

Figure 2A & 2B. Hazard ratio with 95% confidence interval showing effect of gender, race, interruption during radiotherapy, age at diagnosis, duration of symptoms prior to diagnosis, use of protocol-based chemotherapy, radiotherapy (RT) dose, and time intervals from diagnosis to RT on (A) event-free and (B) overall survival. Relevant p-values are shown above each variable.

Table 1

Distribution of Categorical Variables of Interest (n = 95)

	N	%
Gender		
Male	44	46.32
Female	51	53.68
Race		
Black	20	20.05
White	65	68.42
Other	10	10.53
Interruption during RT		
No	90	94.74
Yes	5	5.26

Table 2

Descriptive Statistics of Continuous Variables of Interest (n = 95)

	Mean	SD	Median	Min	Max
Age at diagnosis (years)	7.05	3.36	6.25	1.44	16.39
Age at start of RT (years)	7.10	3.37	6.30	1.48	16.45
Days from diagnosis to start of RT	18.40	11.51	15.00	5.00	64.00
RT dose	55.06	1.00	55.80	54.00	59.40