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Critical Review

Role of Radiation Therapy in the Management of Diffuse Intrinsic Pontine Glioma: A Systematic Review

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Abstract

Purpose: Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary pediatric brain tumor, with <10% of children surviving 2 years. Radiation therapy (RT) remains the mainstay of treatment, but there is a great clinical need for improvements and advancements in treatment strategies. The aim of this systematic review was to identify all available studies in which RT was used to treat patients with DIPG.

Methods and Materials: A literature search for studies published up to March 10, 2018 was conducted using the PubMed database. We identified 384 articles using search items "diffuse intrinsic pontine glioma" and 221 articles using search items "diffuse brainstem glioma radiotherapy." Included studies were prospective and retrospective series that reported outcomes of DIPG treatment with RT.

Results: We identified 49 studies (1286 patients) using upfront conventionally fractionated RT, 5 studies (92 patients) using hypofractionated RT, and 8 studies (348 patients) using hyperfractionated RT. The mean median overall survival (OS) was 12.0 months, 10.2 months, and 7.9 months in patients who received conventional, hyperfractionated, and hypofractionated RT regimens, respectively. Patients undergoing radiosensitizing therapy had a mean median OS of 11.5 months, and patients who did not receive concomitant systemic therapy had an OS of 9.4 months. In patients who received salvage RT, the mean median OS from initial diagnosis was 16.3 months.

Conclusions: As one of the largest systematic reviews examining RT for DIPG, this report may serve as a useful tool to help clinicians choose the most appropriate treatment approach, while also providing a platform for future investigations into the utility of RT and systemic therapy.

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Introduction

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary brain tumor in children.[1] Although DIPG originates in the pons, it is an extensively invasive malignancy of the brainstem that commonly infiltrates other regions of the stem with little notable mass effect.[2] DIPG is almost exclusively seen in children, with a median age at diagnosis of 6 to 7 years.[3-6]

The diagnosis is typically made using a combination of clinical signs and symptoms of short latency (<3-6 months) and characteristic radiographic findings, either on magnetic resonance imaging or computed tomography. The clinical presentation of DIPG often comprises a triad of cerebellar signs, long tract signs, and cranial nerve palsies. Findings on MRI include an intrinsic, centrally located tumor involving >50% to 66% of the pons[7] with hypointensity on T1 images,[8] hyperintensity on T2 images[9] with indistinct tumor margins and engulfment of the basilar artery, and absence of cystic or exophytic components.[10-14]

Historically, biopsy has not been routinely performed as the standard of care unless a tissue analysis is required to identify a potential pharmacologic target. Although biopsy has not been shown to alter treatment outcomes,[10] recent advances in stereotactic neurosurgery have enabled surgeons to obtain reliable tissue for histologic and genomic analyses with morbidity of <4%.[1] Complete surgical resection of DIPG is hindered by the location and infiltrative nature of the tumor.[15]

A diagnosis of DIPG carries a dismal prognosis, with a 2-year survival rate of <10%, making DIPG one of the most fatal pediatric malignancies.[16] The mainstay of treatment for DIPG is conventionally fractionated radiation therapy (RT), delivered over a 6-week period.[17] However, upfront radiation appears to only provide transient relief of symptoms while offering minimal survival advantage. Studies examining the role of alternative fractionation regimens and/or addition of radiosensitizers have failed to demonstrate a survival benefit.[10,19-33] The median overall survival (OS) for this unique patient population remains approximately 10 months.[34]

In this systematic review, we identified 70 studies of both retrospective and prospective design with a total of 2028 patients with DIPG who were treated with RT with or without systemic radiosensitization.

Methods and Materials

A literature search for studies published up to March 10, 2018, was conducted using the PubMed database. The query identified 384 articles using search items "diffuse intrinsic pontine glioma" and 221 articles using search items "diffuse brainstem glioma radiotherapy." All titles and abstracts retrieved in the original search were screened to identify those addressing the use of RT in patients with DIPG. The details of the electronic search results are summarized in Figure E1 (available online at https://doi.org/10.1016/j.adro.2019.03.009). To account for variations in RT schedules between the studies, radiation doses were converted to a total biologically effective dose with an α/β ratio of 10. Major outcomes with regard to survival, control, and toxicity were extracted from each study. All figures were created using R studio, version 1.1, with the tidyverse and ggpubr software. Given the lack of granular data from individualized studies (including numbers at risk, standard errors, and confidence intervals), a formal meta-analysis was not possible.

Results

Epidemiology, clinical presentation, and diagnosis

In our review of 70 studies with a total 2028 patients with DIPG, the overall mean age at diagnosis was 7.1 years (47% male, 53% female). Radiographic and clinical findings were sufficient to make the diagnosis in most studies. The utility of biopsy was relevant in scenarios in which the diagnosis was questionable or a tumor exhibited exophytic components.[35,36] The morbidity data associated with stereotactic biopsy were largely not reported in the reviewed studies.

Given the tumor location and infiltrative characteristics, the role of surgical resection remains extremely limited. We identified a total of 14 studies that described outcomes after subtotal resection followed by definitive RT (Table E1; available online at https://doi.org/10.1016/j.adro.2019.03.009). The mean median OS was 11.2 months with and 11.5 months without subtotal resection.

Definitive radiation therapy

We reviewed a total of 61 studies with 1620 patients treated with upfront RT with or without systemic therapy. The mean median OS and progression-free survival (PFS) for all patients treated with upfront RT were 11.4 months and 7.7 months, respectively. The mean 1- and 2-year rates for OS were 45.0% and 16.9%, respective, whereas

Table 1 Survival outcomes for selected reviewed studies with definitive RT with or without systemic therapy

Reference	No. of patients	Total RT dose (Gy)	RT dose per fraction (Gy)	Biologically effective dose (Gy_{10})	Median OS (mo)
Conventional RT					
[25]	44	55.8	1.8	66	–
[95]	43	54	1.8	64	9.9
[48]	22	54	1.8	64	10.4
[27]	25	59.4	1.8	70	12.1
[96]	26	54	1.8	64	12
[39]	25	54	1.8	64	13.3
[97]	22	54-59.4	–	–	–
[44]	43	54	1.8	64	9.5
[69]	64	54	1.8	64	–
[98]	22	50-70	1.5	57-81	14.2
[47]	25	54	1.8	64	–
[56]	50	54	1.8-2	64-65	13
[99]	32	54.7	–	–	11.7
[49]	21	54	1.8	64	11.7
[40]	23	54	–	–	26.1
[100]	38	54	–	–	14.8
[50]	58	59.4	1.8	70	9.6
[46]	35	54	1.8	64	–
[73]	31	54	1.8	64	6.3
[64]	37	54	1.8	64	13.6
[55]	20	54	1.8	64	9.2
[57]	30	54	1.8	64	9
[28]	21	54	1.8-2	64-65	12
[71]	23	54	2	65	17
[37]	33	55.8	–	–	12
[45]	32	54	1.8	64	8.3
[65]	20	54	1.8	64	8
[51]	38	54	1.8	64	11
[101]	36	50-55	1.6-1.8	58-66	10
Hypofractionated RT					
[22]	7	25	5	38	6.6
[29]	14	45	3	59	7.6
[23]	9	39	3	51	8.6
Hyperfractionated RT					
[18]	34	72	1 (twice daily)	79	12
[30]	66	78	1 (twice daily)	86	–
[68]	53	72	1 (twice daily)	79	–
[21]	39	75.6	1.26 (twice daily)	85	10
[26]	32	66	1.1 (twice daily)	73	9
[20]	57	70	1.2 (twice daily)	78	10
[19]	34	66	1.1 (twice daily)	73	11

Abbreviations: OS = overall survival; RT = radiation therapy.

the mean 1-year PFS rate was 23.5%. Data on 2-year PFS were limited and only reported in 3 studies.[37-39] Table 1 includes a selected set of these studies. The comprehensive list can be found in Table E2 (available online at https://doi.org/10.1016/j.adro.2019.03.009).

Further examination of the studies on the role of definitive RT revealed that the median OS appears unchanged between 1988 and 2017 (Fig E2; available online at https://doi.org/10.1016/j.adro.2019.03.009). With regard to age at diagnosis and its association with prognosis, Yamasaki et al conducted a retrospective study of 19 patients with DIPG and observed the median OS to be 26.1 months in a cohort of patients with a median age at diagnosis of 13.5 years.[40] When stratified by age (<20 vs ≥ 20 years at diagnosis), the median OS was 11.8 versus 59.9 months ($P = .03$), suggesting that older age (≥20 years) may confer a survival benefit. In contrast, Broniscer et al reported on 10 patients with DIPG who had a median age at diagnosis of 2.2 years and found 3-year PFS and OS rates of 45% and 69%, respectively.[41] The authors hypothesized that children under the age of 3 years may have a biologically distinct

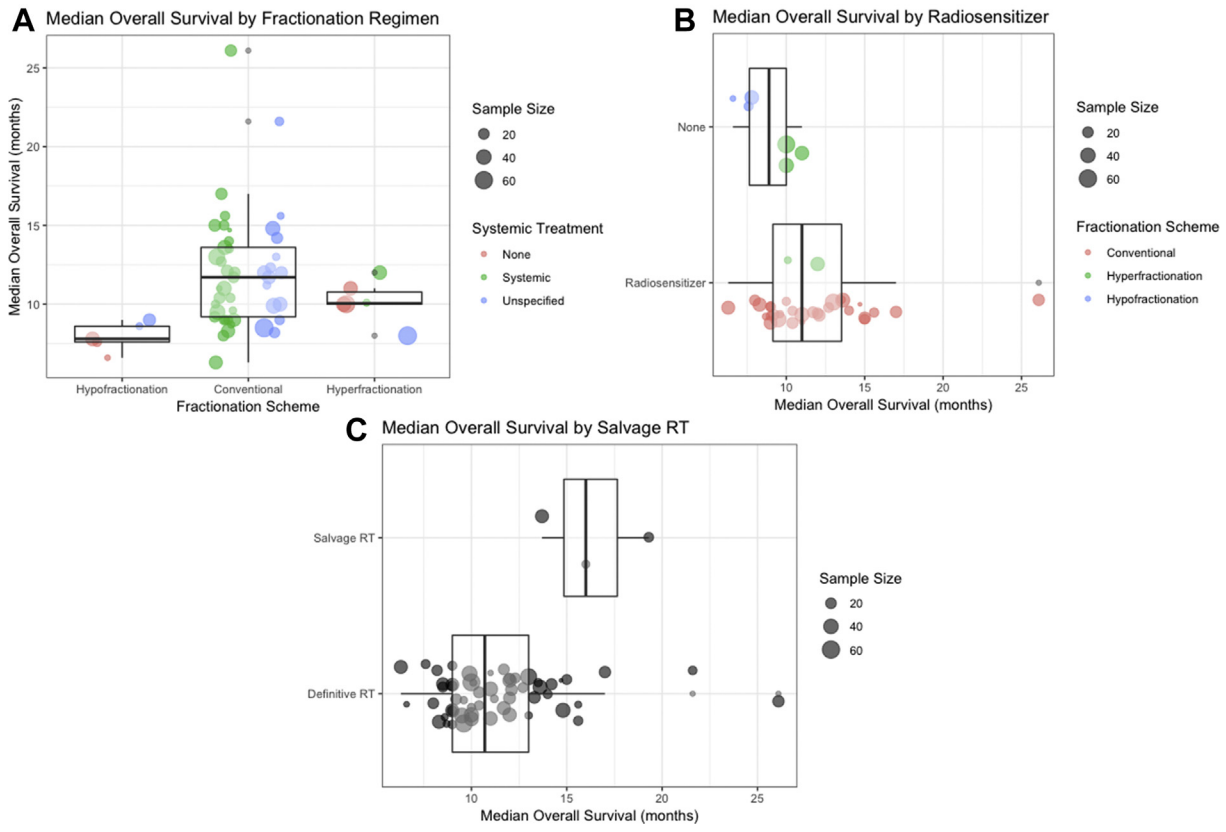

Figure 1 Box and whisker plots. (A) Median overall survival (OS; in months) plotted based on fractionation regimen. Mean median OS was 12.0 months for patients receiving conventional radiation therapy (RT), 10.2 months for hyperfractionated RT, and 7.9 months for hypofractionated RT. (B) Median OS (in months) plotted based on the use of radiosensitization therapy. Patients who received radiosensitizing therapy had a mean median OS of 11.5 months versus 9.4 months. (C) Median OS (in months) plotted based on the use of salvage RT; patients undergoing salvage RT had a mean median OS of 16.3 months from the initial date of diagnosis.

form of DIPG with a potentially better prognosis than DIPG in older children. Thus, the association between age at diagnosis and survival outcome remains unclear and requires further investigation in large-scale prospective analyses.

Fractionation and dose

We identified 49 studies (1286 patients) in which upfront conventionally fractionated RT regimens were used to treat DIPG. The mean median OS and PFS for all patients treated with upfront conventional RT were 12.0 months and 9.3 months, respectively. The mean 1- and 2-year rates for OS were 47.1% and 16.3%, respectively, whereas the mean 1-year PFS rate was 23.5%.

Of the 61 studies that examined the role of upfront RT, there were 8 reports in which a total of 348 patients with DIPG who were treated with a hyperfractionated regimen (Table E3; available online at https://doi.org/10.1016/j.adro.2019.03.009). The mean median OS for these patients was 10.2 months, mean 1-year OS rate was 38.7%, and mean 2-year OS rate was 14.0% (Fig 1A). Mandell et al compared conventional and hyperfractionated RT for diffuse intrinsic brainstem tumors using a 2-arm randomized study. A total of 66 patients received conventional fractionation with 54 Gy in 33 fractions once daily, and 64 patients received a hyperfractionated scheme with 70.2 Gy in 60 fractions twice daily. The investigators found no significant difference between standard versus hyperfractionated schedules with regard to 1-year survival rates (30.9% vs 27.0%) or median time to progression (6 vs 5 months).[42]

Freeman et al conducted a multiyear trial designed to assess the efficacy of sequentially escalated doses of hyperfractionated RT (66 Gy in 1.1 Gy fractions, 70.2 Gy in 1.17 Gy fractions, and 75.6 Gy in 1.26 Gy fractions; all twice daily in 60 fractions over 6 weeks).[19-21] The results of hyperfractionated treatment with 75.6 Gy in terms of PFS and OS were not significantly different ($P = .6$ and $P = .5$, respectively) from those obtained at the 2 previous dose levels, suggesting that higher doses of hyperfractionated RT do not improve outcomes in DIPG. Given the paucity of data in favor of hyperfractionation schemes for DIPG, the potentially higher risks of acute toxicities, and the significant treatment burden associated with this approach, it is prudent to avoid

Table 2 Survival outcomes after definitive hypofractionated RT

Author	Year	Number of patients	RT dose per fraction (Gy)	Total RT dose (Gy)	Biologically effective dose (Gy_{10})	Survival outcomes				Morbidity/toxicity		
						Median OS (mo)	1-year OS (%)	Median PFS (mo)	1-year PFS (%)	CTCAE 3	CTCAE 4	CTCAE 5
Hankinson[22]	2016	7	5	25	38	6.6	28	–	–	–	–	–
Zaghloul[33]	2014	35	3	39	51	7.8	36.4	6.3	22.5	None	None	None
Janssens[24]	2013	27	2.8-3	39-44.8	51-57	9	22	–	–	None	None	None
Negretti[29]	2011	14	3	45	59	7.6	–	5.7	–	Nausea (8)	None	Intracranial hypertension (1)
Janssens[23]	2009	9	3	39	51	8.6	–	–	–	None	None	None

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; OS = overall survival; PFS = progression-free survival; RT = radiation therapy.

hyperfractionation outside of a clinical trial for these patients.

Finally, we identified 5 investigations in which a total of 92 patients with DIPG received definitive RT using a hypofractionated regimen (Table 2). The mean median OS for these patients was 7.9 months, and the mean 1-year OS rate was 28.8% (Fig 1A). In the reviewed studies, radiation-induced toxicity was minimal. A 1:1 matched cohort analysis between hypofractionated and conventional RT was performed by Janssens et al; 27 patients were treated over 3 to 4 weeks with either 39 Gy in 3 Gy fractions (n = 16) or 44.8 Gy in 2.8 Gy fractions (n = 11).[24] A total of 27 patients who met the same diagnostic criteria and received at least 50 Gy in 1.8 to 2.0 Gy fractions were eligible for the matched-cohort analysis. No significant difference in median OS (9.0 vs 9.4 months; $P = .8$) and time to progression (5.0 vs 7.6 months; $P = .2$) was observed between hypofractionated versus conventional RT, respectively. All children in the hypofractionated group experienced faint-to-moderate erythema of the skin, but no grade 3 or 4 toxicities from RT were recorded.

Zaghloul et al conducted a randomized controlled trial comparing hypofractionated and conventionally fractionated RT for DIPG.[33] The median and 1-year OS were 7.8 months and 36.4% for the hypofractionated arm and 9.5 months and 26.2% for the conventional arm. The OS hazard ratio (HR) was 1.1 (95% confidence interval [CI], 0.7-1.9; $P = .6$). Thus, in this study, hypofractionated RT was not proven as statistically noninferior to conventional fractionation.

Indeed, hypofractionation presents an attractive alternative to standard fractionation for these often debilitated patients, and initial results show that hypofractionation is well tolerated with the advantage of decreasing the treatment burden on children and their families. More recent prospective randomized controlled data have begun to show hypofractionated regimens to be statistically noninferior to conventional RT with regard to OS.[43] Thus, further large-scale, multi-institutional explorations are needed to identify the optimal technique, total dose, and fractionation for definitive RT in DIPG.

Utility of radiosensitizers/systemic therapy

Of the 70 reviewed studies, 44 (1046 patients) had patients with DIPG who received concomitant systemic radiosensitizing therapy. The mean median OS and PFS were 11.5 months and 8.7 months, respectively. The mean 1- and 2-year rates for OS were 43.0% and 13.7%, respectively, and the mean 1-year PFS rate was 21.7%. The reviewed studies were categorized based on the agents administered concomitantly with upfront RT.[18,25,27,28,31,32,38-40,44-66] Several investigations used multiple chemotherapeutic agents and were therefore included in calculating outcomes for each applicable agent (Table 3). The mean median OS and PFS rates for the most commonly used agent (alkylating agent) were 13.4 months and 12.1 months, respectively. Furthermore, patients who received alkylating agents had mean 1- and 2-year OS rates of 48.0% and 15.9%, respectively, and a mean 1-year PFS rate of 27.1%.

In the 12 reviewed studies, a total of 397 patients with DIPG did not receive any systemic therapy.[19-22,29,30,33,56,58,67,68] The mean median OS and PFS in these patients were 9.4 months and 6.4 months, respectively. The mean 1- and 2-year rates for OS were 37.6% and 12.8%, respectively, and the mean 1-year PFS rate was 20.2%. Patients who received radiosensitizing therapy had a mean median OS of 11.5 months (Fig 1B). However, the heterogeneity of the reviewed studies, as well as selection and treatment bias, preclude us from making any meaningful conclusions with regard to the survival benefits of systemic therapy.

The recommendation to add a radiosensitizer should be balanced against the risks of significant medication-induced toxicities. Chemotherapeutic agents used with

Table 3 Survival outcomes and chemotherapy-related toxicities based on radiosensitizing agent

Agent	Total Number of Patients	Mean median OS (mo)	Mean 1-year OS (%)	Mean median PFS (mo)	Mean 1-year PFS (%)	Toxicities	
						CTCAE 3	CTCAE 4
Alkylating agent[28,31,38,40,44,49,50,55,56,59,62,64,66]	323	13.4	48.0	12.1	27.1	Nausea (5), neutropenia (2), leukopenia (2)	Leukopenia (2), thrombocytopenia (3), neutropenia (2)
						Lymphopenia (39), neutropenia (13), leukopenia (11), infection (4)	thrombocytopenia (16),
Topo-isomerase inhibitor[28,32,45,53,57,58,61,64-66]	237	11.2	40.6	6.0	21.0	Neutropenia (2), constipation (1), seizures (2), hematological side effects (2)	Neutropenia (7), anemia (11), hematological side effects (3), thrombocytopenia (3)
						Neutropenia (33), thrombocytopenia (5), anemia (9), nausea/vomiting (3), infection (7), leukopenia (8), lymphopenia (12), nausea (1)	
Anti-microtubular agent[28,31,39,40,52,53,56,57,60]	171	12.8	40.0	13.5	23.0	Hypokalemia (1), constipation (1), seizures (2)	Neutropenia (1)
						Anemia (9), neutropenia (14), nausea/vomiting (3), infection (7)	
Platinum agent[18,28,32,42,51,52,56,64,66]	285	11.7	37.2	6.7	21.0	Neutropenia (2), leukopenia (1), thrombocytopenia (2)	Neutropenia (6), thrombocytopenia (3)
						Thrombocytopenia (5)	
Anti-metabolic agent[25,28,63]	74	10.4	45.0	5.9	18.6	Lymphopenia (17), leukopenia (3), neutropenia (5), hepatotoxicity (2)	Lymphopenia (2), neutropenia (2)
EGFR inhibitor[27,39,48]	54	11.9	—	7.5	29.6	Anemia (2), neutropenia (6), lymphopenia (26), hepatotoxicity (5), hypokalemia (1)	
Blood vessel growth inhibitor[46,47,54]	75	10.4	44.8	8.2	—	Hepatotoxicity (2), lymphopenia (14), neutropenia (2)	Thrombocytopenia (2), neutropenia (2), lymphopenia (11)
						Anemia (5), neutropenia (5), thrombocytopenia (1)	
Other agents[69-74,102]	—	—	—	—	—	Lymphopenia (14), hepatotoxicity (7), hypertension (5), vomiting (2), motor neuropathy (2), constipation (2), rash (2), skin desquamation (1)	Pain syndrome (1), allergy (1), leukopenia (1), neutropenia (2), DVT/PE (1)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DVT = deep vein thrombosis; EGFR = epidermal growth factor receptor; OS = overall survival; PE = pulmonary embolism; PFS = progression-free survival; RT = radiation therapy.

upfront RT for DIPG have the potential to impair the quality of life of this fragile patient population without offering a substantial clinical benefit. The most notable chemotherapy sequelae in the reviewed studies were Common Terminology Criteria for Adverse Events grade 3 to 4 hematologic toxicities as well as nausea and vomiting.[18,25,27,28,31,32,38-40,42,44-66,69-74] No Common Terminology Criteria for Adverse Events grade 5 toxicities were recorded (Table 3). Currently, because there is no established role for chemotherapy for DIPG in children (radiation is the standard treatment),[75] decisions with regard to the addition of radiosensitizers should be based on the clinical and practical matters of the case.

Salvage radiation therapy

In recent years, interest has been growing for the consideration of re-RT for refractory or progressive DIPG. We reviewed 4 studies in which a total of 64 patients with DIPG were treated with re-RT (Table E4;

available online at https://doi.org/10.1016/j.adro.2019.03.009). The mean median OS from initial diagnosis and from date of completion of re-RT was 16.3 months and 6.2 months, respectively (mean median OS from initial diagnosis was 11.4 months with definitive RT alone; Fig 1C).

Some of this apparent improvement may be due to selection bias. Lassaletta et al performed a multi-institutional retrospective review of 16 patients with progressive DIPG who were treated with re-RT.[76] The re-RT dose and fractionation varied between institutions from 21.6 to 36 Gy (median, 30.6 Gy), with 14 patients receiving focal RT and 2 patients receiving whole-brain irradiation for disseminated progression. Of these patients, 88% received conventional fractionation regimens and 12% received hypofractionated RT. All but 3 patients showed neurologic improvement. The median OS from diagnosis and re-RT was 19.3 months and 6.5 months, respectively. When compared with a historic cohort of 46 non-reirradiated patients, the median time from progression to death was 92 days in non-reirradiated patients versus 218 days in reirradiated patients ($P = .0001$). Notably, 1 patient developed pontine necrosis and subsequent quadriparesis after receiving 30 Gy of re-RT in 10 fractions.

Survival benefit also appears to increase with a longer interval between the end of upfront RT and re-RT, with recent studies recommending $\geq$3 months after upfront RT before re-RT.[77] In summary, re-RT may be an appropriate approach in the management of progressive DIPG for a well-selected group of patients given the apparent symptomatic and possible survival benefit; however, studies with larger cohorts of patients receiving re-RT are needed to more definitively elucidate these survival trends.

Ongoing clinical trials

As of March 23, 2018, there are 26 ongoing trials in the United States (including 24 trials actively recruiting patients) that aim to evaluate various systemic, surgical, and RT modalities for patients with DIPG in both newly diagnosed and progressive settings. Information about these studies has been retrieved from clinicaltrials.gov and is summarized in Table 4.

Diffuse Intrinsic Pontine Glioma Molecular Pathogenesis

Clues to the vulnerability of DIPG are beginning to emerge from molecular studies, which is an important advancement given the dismal prognosis of DIPG even when considering the incremental improvements provided by various RT regimens described in this review. The most striking discovery was that >80% of DIPG contain a lysine-to-methionine substitution at K27 on one of the histone H3 variants.[78] Dubbed K27M mutations, this subgroup of high-grade midline gliomas has a worse prognosis than its wild-type counterparts regardless of the tumor location, age, and intervention, including RT.[79] At a molecular level, K27M has a dominant-negative effect on polycomb repressive complex (PRC2) in such a way that its catalytic product, H3K27 methylation, is dramatically reduced and abnormally enriched at select loci.[47,80-83] In turn, the aberrant activity of PRC2 in K27M DIPG and resultant dysregulated epigenome is thought to drive its cancer stem cell properties, resistance to therapy, and oncogenic phenotype.[82-86] In fact, the discovery of large-scale alterations in the chromatin landscape and oncogenic transcriptional dependencies in K27M DIPG led to speculation that these could be viable therapeutic targets. As a result, numerous strategies have emerged (briefly reviewed in the following) with an emphasis on efforts that are now in clinical trials in combination with RT.

With regard to abnormal PRC2 activity in K27M DIPG, early studies suggested that recovering some H3K27 trimethylation (K27me3) by inhibiting the KDM6 family of demethylases could decrease proliferation in patient-derived K27M DIPG cell lines and increase survival in mouse xenografts.[87] Conversely, because K27M DIPG shows not only decreased PRC2 activity but also gains of K27me3 and transcriptional repression of select cell-cycle regulators,[80,82,83,85] some groups have taken the stance that further inhibiting the activity of PRC2 itself may be a viable therapeutic intervention for K27M DIPG. This showed promise in preclinical models[82,83]; however, the effects of PRC2 inhibition on K27M DIPG are not always consistent,[88] and the reactivation of these cell cycle regulators may not be a direct consequence of PRC2 inhibition itself.[89]

Currently in clinical trials for K27M DIPG are therapeutics that target histone acetylation. This strategy emerged from both functional screens[90] and the observation that K27M DIPG consistently showed elevated histone acetylation levels in numerous studies,[81,83,86,90,91] most notably H3K27 acetylation. Recent studies revealed that targeting the histone acetylation–interacting domains of bromodomain proteins has therapeutic efficacy in vitro and in xenograft models.[83,86,92] Alternate methods to target histone acetylation focused on histone deacetylase inhibition (HDACi), further revealing another tractable preclinical vulnerability in K27M DIPG.[86,90,93] However, this should be met with cautious optimism given the high HDACi doses required to decrease tumor burden.[93]

Interestingly, some synergy has been observed between not only HDACi and bromodomain protein inhibition but also the CDK7 inhibitor THZ1, leading to the hypothesis that there is a transcriptional dependency in K27M DIPG that is vulnerable to epigenetic intervention.[86] Data on the preclinical efficacy of combining molecular therapy with upfront RT for DIPG

Table 4 Ongoing clinical trials evaluating various treatment modalities in the management of newly diagnosed and progressive DIPG

Identifier	Phase	Summary	Agent/intervention
New disease			
NCT02960230	1	H3.3K27M Peptide Vaccine for Children with Newly Diagnosed DIPG	H3.3K27M Peptide Vaccine
NCT03330197	1	Ad-RTS-hIL-12 + Veledimex in Pediatric Subjects with Brain Tumors or DIPG	Ad-RTS-hIL-12 + Veledimex
NCT03178032	1	Oncolytic Adenovirus, DNX-2401, for Naive DIPG	Oncolytic Adenovirus
NCT03396575	1	Brain Stem Gliomas Treated with Adoptive Cellular Therapy During Focal RT Alone or with Dose-intensified TMZ	Dendritic Cell Vaccine + TMZ
NCT03355794	1	Ribociclib and Everolimus Following RT in Children with Newly Diagnosed DIPG and RB+ Biopsied DIPG	Ribociclib + Everolimus
NCT02992015	1	Gemcitabine in Newly-Diagnosed DIPG	Gemcitabine
NCT03086616	1	Convection Enhanced Delivery with Irinotecan Liposome Injection Using Real Time Imaging in Children With DIPG	Nanoliposomal Irinotecan
NCT01922076	1	WEE1 Inhibitor AZD1775 and Local RT in Treating Children with Newly Diagnosed DIPG	WEE1 inhibitor AZD1775
NCT02758366	2	Prolonged Exposure to Doxorubicin in Patients with GBM and DIPG	TMZ + Doxorubicin
NCT03243461	3	International Cooperative Trial of the HIT-HGG Study Group	Valproic acid or Chloroquine + TMZ
Progressive disease			
NCT02717455	1	Panobinostat in Children with DIPG	Panobinostat
NCT02444546	1	Wild-Type Reovirus in Combination with Sargramostim in Treating Patients with High-Grade Refractory Brain Tumors	Sargramostim + Wild-type Reovirus
NCT02502708	1	IDO Pathway Inhibitor, Indoximod, and Temozolomide for Pediatric Patients with Progressive Primary Malignant Brain Tumors	Indoximod + TMZ
NCT02359565	1	Pembrolizumab in Treating Younger Patients with Recurrent, Progressive, or Refractory DIPG	Pembrolizumab
NCT01884740	1/2	Intraarterial Infusion of Erbitux and Bevacizumab for Relapsed/Refractory Intracranial Glioma	Mannitol + Cetuximab + Bevacizumab
NCT03387020	1	Ribociclib and Everolimus in Treating Children with Recurrent or Refractory Malignant Brain Tumors	Ribociclib + Everolimus
NCT03126266	2	Re-Irradiation of Progressive or Recurrent DIPG	30.6-36 Gy of re-RT over 17-20 days
NCT02644291	1	Mebendazole Therapy for Recurrent/Progressive Pediatric Brain Tumors	Mebendazole
All patients			
NCT02420613	1	Suberoylanilide Hydroxamic Acid with Temsirolimus in Children With DIPG	Vorinostat + Temsirolimus
NCT03389802	1	APX005M in Pediatric CNS Tumors	humanized IgG APX005M to CD40
NCT02343406	2	ABT-414 in Children with High Grade Gliomas	Depatuxizumab
NCT01837862	1/2	Mebendazole for the Treatment of Pediatric Gliomas	Bevacizumab + Irinotecan + Mebendazole
NCT02233049	2	Biological Medicine for DIPG eradication	Erlotinib, Everolimus, or Dasatinib
NCT02644460	1	Abemaciclib in Children with DIPG	Abemaciclib
NCT01502917	1	Convection-Enhanced Delivery of 124I-8H9 for Patients with Non-Progressive DIPG Previously Treated with External Beam Radiation Therapy	Monoclonal Antibody 124I-8H9
NCT03416530	1	ONC201 in Pediatric H3 K27M Gliomas	ONC201 (dopamine receptor D2 antagonist)

Abbreviations: CNS = central nervous system; DIPG = diffuse intrinsic pontine glioma; GBM = glioblastoma; RB = retinoblastoma; RT = radiation therapy; TMZ = temozolomide.

are limited,[92] but an exciting possibility is that these approaches may have synergistic effects that can reduce dosing and therefore toxicity while providing therapeutic benefit.

Future Directions

Ongoing molecular characterizations of DIPG and the potential use of targeted therapy depends on the ability to obtain adequate tissue samples for histopathologic analysis. However, a dismal prognosis irrespective of histologic grading and typical neuroradiologic features has been the main reason to avoid tissue sampling in children with DIPG for the past 20 years. We remain hopeful that with ongoing advancements in stereotactic neurosurgical procedures, the number of DIPG biopsy samples will continue to increase to help further characterize these tumors at the molecular level.

Additionally, all of the reviewed studies used photon beam RT. Although advanced radiation delivery techniques, such as 3-dimensional conformal RT and intensity modulated RT, have improved treatment precision, there remains undesired exposure of normal tissues to low-intermediate doses of radiation, causing increased radiation-induced toxicities. With proton therapy, physicians can deliver radiation more precisely and preserve normal tissues without compromising radiation dose to the tumor, possibly reducing radiation toxicities. Traditionally, proton therapy has been reserved for patients with potentially curable brain tumors because the poor prognosis of high-grade lesions, such as DIPG, mitigates the potential reduction in long-term toxicities.[94] However, further trials investigating the role of proton RT in the treatment of DIPG may be warranted.

Conclusions

Despite advancements in radiation and systemic strategies as well as developments in oncologic research, survival outcomes for children with DIPG have not changed significantly over the past 20 years. The present review of the aggregate data from >2000 patients in 70 studies has revealed a median survival of approximately 11 months for patients treated with definitive RT. Of note, given the heterogeneity and poor quality of the reporting of some of the data from the studies used in this review, sufficient granular information on variability surrounding each measure of OS could not be obtained, limiting us from performing a rigorous meta-analysis. Although recent prospective and retrospective studies have challenged the potential survival benefit of hypofractionated RT compared with conventional RT, this is not meant to imply that standard fractionation should remain the standard of care for children with DIPG. In fact, in clinical scenarios in which patients are unlikely to tolerate prolonged courses of RT, consideration should be given to these hypofractionated regimens.

Minimal potential survival benefit with conventional RT should be weighed against the psychosocial and treatment burden on children and their families, as well as potential risks of early radiation toxicities and often daily anesthesia. On the other hand, as several randomized controlled trials have shown, a hyperfractionated regimen does not seem to offer a survival benefit and remains significantly inconvenient for children, their families, and radiation staff. The addition of radiosensitizing therapy to upfront RT comes at the expense of chemotherapy-associated toxicities that may have a deleterious effect on the quality of life of children during their final months. Furthermore, given the promising retrospective data suggesting a survival benefit with re-RT, this approach should be a strong consideration for patients who are eligible, but the potential for radiation-induced toxicities should be considered.

With recent molecular discoveries making way for clinical trials, we remain hopeful that novel targeted therapies will one day produce a therapeutic benefit for this challenging disease. Until then, pediatric patients with newly diagnosed DIPG who are candidates for radiation should receive definitive RT and be considered for enrollment in a clinical trial with systemic therapy.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.03.009.

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