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Clinical Investigation

Hypofractionation vs Conventional Radiation Therapy for Newly Diagnosed Diffuse Intrinsic Pontine Glioma: A Matched-Cohort Analysis

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Summary

Despite conventional radiation therapy (30 fractions in 6 weeks), most children with diffuse intrinsic pontine glioma will die within 1 year after diagnosis. To reduce patient burden, we investigated the role of hypofractionation radiation therapy (13 or 16 fractions in 3 to 4 weeks). A 1:1 matched-cohort analysis demonstrates a similar

Purpose: Despite conventional radiation therapy, 54 Gy in single doses of 1.8 Gy (54/1.8 Gy) over 6 weeks, most children with diffuse intrinsic pontine glioma (DIPG) will die within 1 year after diagnosis. To reduce patient burden, we investigated the role of hypofractionation radiation therapy given over 3 to 4 weeks. A 1:1 matched-cohort analysis with conventional radiation therapy was performed to assess response and survival.

Methods and Materials: Twenty-seven children, aged 3 to 14, were treated according to 1 of 2 hypofractionation regimens over 3 to 4 weeks (39/3 Gy, n = 16 or 44.8/2.8 Gy, n = 11). All patients had symptoms for $\leq$3 months, $\geq$2 signs of the neurologic triad (cranial nerve deficit, ataxia, long tract signs), and characteristic features of DIPG on magnetic resonance imaging. Twenty-seven patients fulfilling the same diagnostic criteria and receiving at least 50/1.8 to 2.0 Gy were eligible for the matched-cohort analysis.

Results: With hypofractionation radiation therapy, the overall survival at 6, 9, and 12 months was 74%, 44%, and 22%, respectively. Progression-free survival at 3, 6, and 9 months was 77%, 43%, and 12%, respectively. Temporary discontinuation of steroids was observed in 21 of 27 (78%) patients. No significant difference in median overall survival (9.0 vs 9.4 months;

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overall survival rate with a hypofractionation regimen compared with a conventional radiation therapy regimen. Outside clinical trials, this low-burden regimen could be considered as an alternative to protracted regimens.

$P = .84$) and time to progression (5.0 vs 7.6 months; $P = .24$) was observed between hypofractionation vs conventional radiation therapy, respectively.

Conclusions: For patients with newly diagnosed DIPG, a hypofractionation regimen, given over 3 to 4 weeks, offers equal overall survival with less treatment burden compared with a conventional regimen of 6 weeks.

Introduction

Despite exhaustive clinical research to improve outcome, survival in children and adolescents with diffuse intrinsic pontine glioma (DIPG) has remained unchanged over the past 3 decades (1). For a patient with newly diagnosed DIPG, the current standard treatment consists of conventionally fractionated external beam radiation therapy up to a dose of 54 Gy in 30 fractions of 1.8 Gy over 6 weeks (1, 2). This usually results in a transitory improvement of neurologic signs and symptoms; however, most patients will die within 1 year after diagnosis because of tumor progression within the irradiated area.

Unlike new protocols attempting to improve outcome by intensified regimens, associated with increased toxicity, numerous outpatient visits, and prolonged hospital stays, we aimed to reduce treatment burden by offering a hypofractionation radiation therapy schedule for patients with newly diagnosed DIPG (1, 3, 4). We recently demonstrated the feasibility and compliance of 39 Gy given in 13 fractions of 3.0 Gy over 3 weeks (4). Although the number of patients was limited to 9, the median overall survival of 8.6 months was within the range of 7 to 14 months published in 2 recent critical reviews (1, 3). Especially for children with poor compliance and performance status or parents who refuse a more intensive regimen, the hypofractionation regimen may reduce the burden of treatment without compromising survival.

We report the results in a large group of patients with newly diagnosed DIPG treated by 2 hypofractionation regimens: 39 Gy in 13 fractions or 44.8 Gy in 16 fractions. A 1:1 matched-cohort analysis was performed, including patients with similar diagnostic features, receiving a conventionally fractionated radiation therapy dose of at least 50 Gy in 6 weeks.

Methods and Materials

Eligibility

Newly diagnosed patients with the clinical and radiologic suspicion of DIPG and treated by a hypofractionation regimen were eligible for this multicenter retrospective analysis. All patients, aged 3 to 21, were required to have had symptoms for less than 3 months and at least 2 findings of the neurologic triad: cranial nerve deficits, ataxia, or long tract signs. No performance status criteria were used. The availability of preradiation therapy magnetic resonance imaging (MRI) containing at least T1 images and T2 images and gadolinium administration was necessary for review. Patients in this analysis had to meet all major and at least 2 minor radiologic criteria for DIPG. The major criteria are the appearance of a poorly marginated tumor with mass effect occupying more than 50% of the axial diameter of the pons, hypointensity on T1 images, and hyperintensity on T2 images (5). Minor radiologic criteria include encasement of the basilar artery, extension into the mesencephalon and/or medulla oblongata and/or cerebellar peduncle, and contrast enhancement (focal ring, peripheral, spotty, or focal patchy) with or without necrosis (5, 6). Children with a history of neurofibromatosis were excluded because they belong to a subgroup expected to have a more favorable prognosis (7). In case of doubt, a biopsy was performed to confirm high-grade glioma.

As a matching cohort, we randomly selected patients from 6 different institutes with identical clinical and radiologic features who were receiving a conventional fractionated radiation therapy dose of at least 50/1.8 to 2.0 Gy on the pontine tumor.

No systemic treatment other than steroids was allowed in the neoadjuvant, concomitant, or adjuvant setting of both cohorts. In case of progression after radiation therapy, the use of systemic therapy was permitted in both cohorts.

Radiation therapy

Two hypofractionation regimens were investigated. The first regimen, used at the Radboud University Medical Centre Nijmegen and Academic Medical Center Amsterdam, delivered 39 Gy in 13 daily fractions of 3.0 Gy 4 times a week (overall treatment time: 3 weeks). The second regimen, used at Erasmus Medical Centre in Rotterdam, applied 44.8 Gy in 16 fractions of 2.8 Gy 4 times a week (overall treatment time: 4 weeks). In the matching cohort, patients received a median total dose of 54 Gy in 30 daily fractions of 1.8 Gy 5 times a week (overall treatment time: 6 weeks).

The majority of the patients in both cohorts were treated by 2 opposing lateral photon beams. The clinical target volume included the tumor as defined by the T2-weighted MR images with a margin of 1.5 to 2.0 cm. The margins were adjusted for bony structures and tentorium. An additional margin between 0.3 cm and 0.5 cm was added to create the planning target volume.

Assessment of response

A baseline neurologic and general clinical examination, performed by a pediatric neurologist or an experienced pediatric oncologist, was available for all patients. During radiation therapy, re-evaluation by the radiation oncologist and/or pediatric oncologist was performed routinely. In the group of patients treated with hypofractionation, the use of steroids and the Radiation Therapy Oncology Group grade 3 and 4 skin, ear, and central nervous system toxicity was scored. Because repeated MR imaging was not routinely performed during follow-up, disease

progression was defined as a clinical (neurologic) deterioration with need for steroid reuse or dose escalation.

Endpoints

The primary endpoint was overall survival, measured from diagnosis to the date of death. The secondary endpoint was time to progression, defined as the time to clinical (neurologic) deterioration with need for steroid dose escalation, measured from diagnosis. Data were censored at the last control visit.

Statistical analysis

Statistical analyses were performed with SPSS 16.0. Overall survival and time to progression were calculated with the Kaplan-Meier method, and all analyses were based on an intention-to-treat policy. The differences between the Kaplan-Meier curves were calculated with the log-rank test. The χ^2 test and Mann-Whitney U test were used to compare patient, tumor, and treatment characteristics, and the Kruskal-Wallis test was used to compare overall treatment times in both cohorts.

Results

Patient groups and treatment

Between December 2002 and August 2010, 27 patients from 3 centers in the Netherlands were treated with a hypofractionation regimen. All patients receiving the 13 × 3 Gy regimen met the inclusion criteria prospectively. The patients treated with the 16 × 2.8 Gy regimen fulfilled the stringent inclusion criteria on a retrospective basis. Twenty-seven of 35 patients from 6 centers in the United Kingdom, Canada, the Netherlands and Belgium were used as a matched-pair cohort. The group of patients receiving conventional radiation therapy was treated between July 1993 and October 2006. The baseline patient and tumor characteristics are shown in Table 1. Although all the stringent inclusion criteria are respected, a slight imbalance (fewer long tract signs and less extension into the cerebellar peduncle) in favor of the conventional regimen is observed.

The treatment characteristics are listed in Table 2. Radiation therapy was started within 2 weeks from diagnosis in 20 of 27 (74%; median, 7 days; range, 0 to 40 days) children of the hypofractionation group and in 14 of 27 (52%; median, 14 days; range,

Table 1 Patient and tumor characteristics

Characteristic	Hypofractionation RT n	Conventional RT n	*P* value
No. of patients	27	27	-
Sex			.14*
M	12	17	
F	15	10	
Age (y)			
Median	7.5	7.3	.98†
Range	3.7-13.7	2.8-14.6	
Duration of symptoms			.57*
<1 mo	18	20	-
1-2 mo	6	6	-
2-3 mo	3	1	-
Neurologic triad			
Cranial nerve deficit	27	27	-
Ataxia	22	25	.21*
Long tract signs	22	15	.04*
No. of patients with complete triad	22	14	.02*
Radiology			
Mass effect in the pons	27	27	-
Poorly marginated	27	27	-
T1 hypointensity, T2 hyperintensity	27	27	-
>50% of axial diameter pons involved	27	27	-
>67% of axial diameter pons involved	23	25	.33*
Encasement of basilar artery	22	21	.50*
Extension into mesencephalon, medulla	15	15	.61*
Extension into cerebellar peduncle	18	8	.01*
Contrast enhancement	21	16	.19*
Pathology-proven glioma			.35*
WHO grade 3	2	3	-
WHO grade 4	4	1	-

Abbreviations: RT = radiation therapy; WHO = World Health Organization.
* χ^2 test.
† Mann-Whitney U test.

Table 2 Treatment characteristics

Characteristic	Hypofractionation RT n	Conventional RT n	*P* value
No. of patients	27	27	-
Radiation therapy dose prescribed			
39.0/3.0 Gy	16	-	-
44.8/2.8 Gy	11	-	-
≥50/1.8-2.0 Gy	-	27	-
Radiation therapy dose given			
39.0/3.0 Gy	16	-	-
44.8/2.8 Gy	10	-	-
≥50/1.8-2.0 Gy	-	25	-
Time from diagnosis to start of radiation therapy			.02*
Days	0-40	3-54	-
Median	7	14	-
Overall treatment time			<.01†
Days	7-34	30-50	-
Median	20	41	-

Abbreviation: RT = radiation therapy.
* Mann-Whitney U test.
† Kruskal-Wallis test.

3 to 54 days) children of the conventionally fractionated group. In the hypofractionation group, 11 of 27 patients received chemotherapy (temozolomide, n=11) after documented progression. In the conventional radiation therapy group, 9 of 27 patients received chemotherapy (temozolomide, n=3; etoposide, n=2; nimotuzumab, n=1; thalidomide + etoposide + cyclophosphamide, n=1; fotemustine, n=1; tamoxifen, n=1) for documented progression.

At the end of follow-up, 26 of 27 patients had died in the hypofractionation group. In 25 patients, death was due to local disease progression. One patient died of a central nervous system infection after proven tumor progression shown on MRI. At the time of this analysis 1 patient is still alive, 2.4 years from diagnosis, without disease progression. In the conventional group, all patients died of disease progression.

Efficacy

In the hypofractionation cohort, the median overall survival was 9.0 months (95% CI, 8.6-9.3 months) (Fig. 1A). The overall survival at 6, 9, and 12 months was 74%, 44%, and 22%, respectively. The median time to progression was 5.0 months (95% CI, 4.1-5.9 months), as illustrated in Fig. 1B. Progression-free survival at 3, 6, and 9 months was 77%, 43%, and 12%. In the hypofractionation group, all patients received steroids at the beginning of and during radiation therapy. In 21 of 27 (78%) patients, the use of steroids could be temporarily discontinued.

No significant difference in median overall survival was observed between hypofractionation and conventional radiation therapy: 9.0 months vs 9.4 months, respectively ($P=.84$) (Fig. 2A). There was no significant difference in median time to progression between hypofractionation and conventional radiation therapy: 5.0 months vs 7.6 months, respectively ($P=.24$) (Fig. 2B).

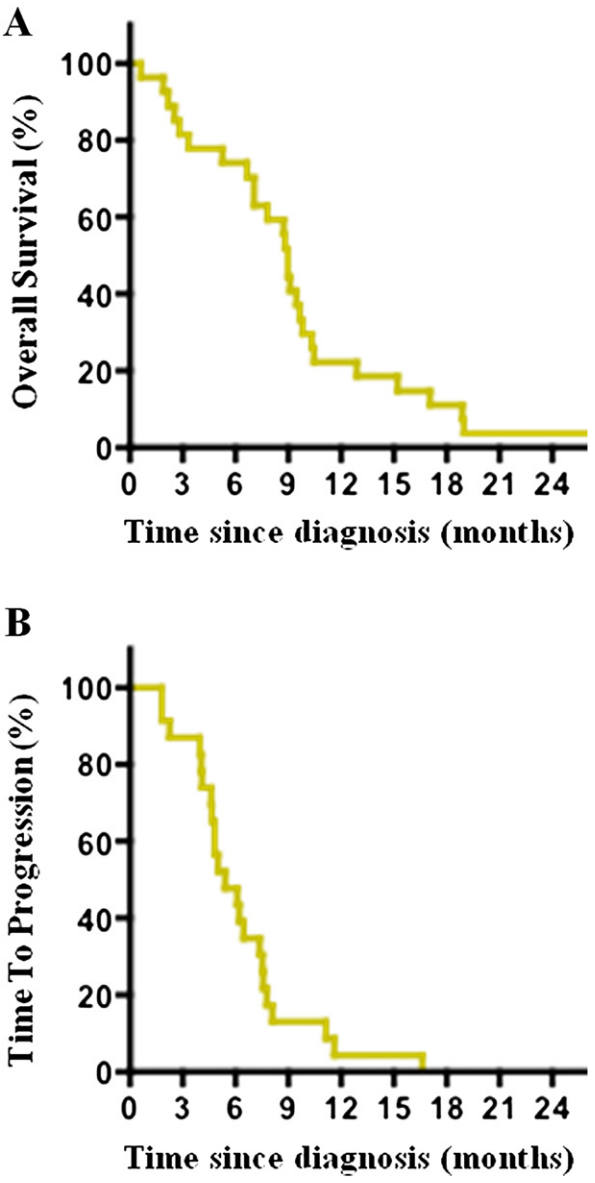

Fig. 1. Overall survival (1A) and time to progression (1B) for patients with newly diagnosed diffuse intrinsic pontine glioma after hypofractionation radiation therapy (39/3.0 Gy or 44.8/2.8 Gy, 4 fractions/week).

In subgroup analysis, no significant difference in overall survival or time to progression was observed with 44.8/2.8 Gy compared with 39.0/3.0 Gy (Fig. 3).

Toxicity and compliance to radiation therapy

Both hypofractionation regimens were well tolerated. A statistically significant difference in median overall treatment time was observed in favor of the hypofractionation regimens: 20 days (range, 16 to 22 days) for the 39/3.0 Gy regimen, 24 days (range, 7 to 34 days) for the 44.8 Gy regimen vs 41 days for the conventionally fractionated regimens (range, 30 to 50 days) (Table 2) ($P<.01$).

In the hypofractionation regimen, 1 treatment interruption was needed after 2 fractions because of brain edema, uncontrollable by

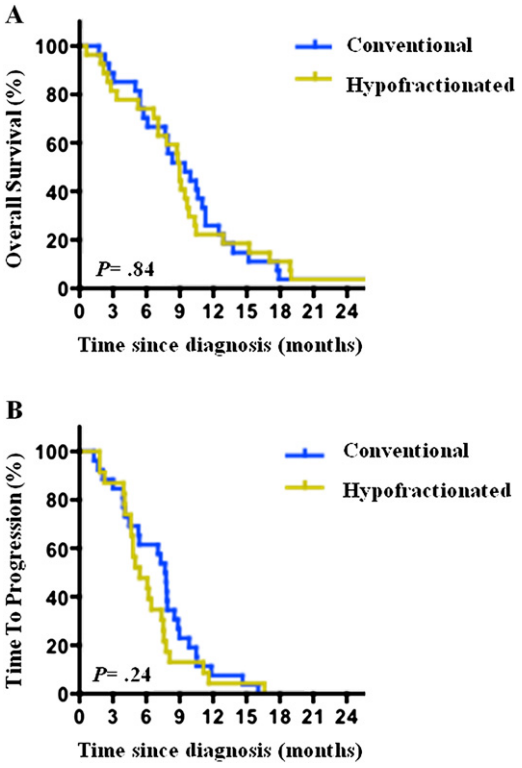

Fig. 2. Overall survival (2A) and time to progression (2B) for patients with newly diagnosed diffuse intrinsic pontine glioma after hypofractionation radiation therapy matched to a group receiving conventional radiation therapy.

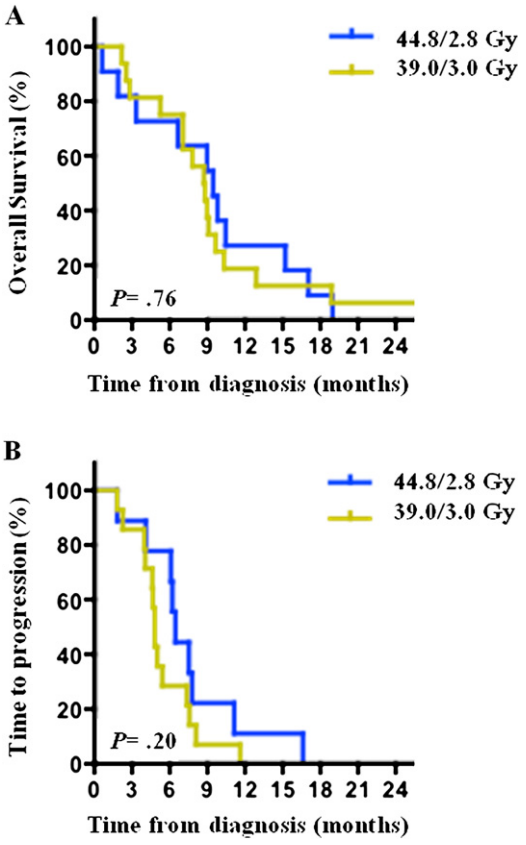

Fig. 3. Overall survival (3A) and time to progression (3B) after 39/3.0 Gy vs 44.8/2.8 Gy for patients with newly diagnosed diffuse intrinsic pontine glioma.

steroids. The treatment was resumed after 4 days. Radiation therapy was interrupted after 5 fractions in 1 patient because of progressive disease during treatment. In the conventional group, 2 patients did not receive a total dose of 50 Gy because of disease progression after 22 and 26 fractions.

All children in the hypofractionation group experienced faint to moderate erythema of the skin followed by dry desquamation. A minority had moist desquamation confined to the skin folds of the auricle. No grade 3 or 4 acute toxicity from radiation therapy was recorded. Two children experienced recurrent central nervous system infections caused by bacterial colonization of a ventricular-peritoneal drain, put in place for obstructive hydrocephalus.

Discussion

The results of this matched-cohort analysis reveal a similar overall survival with a hypofractionation regimen (13 or 16 fractions in 3 to 4 weeks) compared with a conventional radiation therapy regimen (30 fractions in 6 weeks) for patients with newly diagnosed DIPG. A nonsignificant difference in median time to progression was observed in favor of the conventional radiation therapy regimen.

According to Hargrave et al (1), the overall survival of 9 months with hypofractionation radiation therapy in this study is within the range of 8 to 11 months observed in studies using more stringent inclusion criteria and is better than the 7.6 months overall survival observed in a recent hypofractionation study reported by Negretti et al (8). The outcome in our cohort confirms the results of our previous pilot study on hypofractionation (4). Similar outcome results, even in the presence of an imbalance of neurologic symptoms in favor of the conventional regimen, further support the efficacy of hypofractionated radiation therapy for DIPG. After decades of several types of intensive regimens in clinical trials, this is the first time a low-burden protocol has demonstrated similar outcome compared with conventional radiation therapy in a larger group of patients fulfilling several stringent inclusion criteria (1, 3, 4). Hargrave et al clearly demonstrated that the range in median overall survival shifted from 7 to 16 months toward 8 to 11 months when the clinical and radiologic eligibility criteria were specified and respected (1). The combination of short symptom duration ($\leq$3 months), a minimum of 2 signs of the neurologic triad, the presence of predefined MRI characteristics, and a biopsy result positive for high-grade glioma in case of doubt (22%) enabled us to avoid higher fraction doses to the normal brain for a potentially indolent or curative disease course in all but 1 patient (4%).

An interesting finding is the difference (although nonsignificant) in time to progression of 5.0 vs 7.6 months in favor of the conventionally fractionated regimen. A reasonable explanation for this can be obtained by comparing tumor and treatment-related characteristics and the use of MRI. Although all patients in both cohorts met the stringent inclusion criteria, a higher incidence of long tract signs and tumor extension into the cerebellar peduncle was observed in the hypofractionation group. Both features potentially contribute to an earlier detection of neurologic deterioration. Compared with the conventional regimen, radiotherapy in the hypofractionation cohort started 1 week and ended 3 weeks earlier. This means that a correction of 4 weeks should be

used to evaluate the real contribution of the radiotherapy regimen in terms of delaying disease progression, inasmuch as it is now calculated from the time of diagnosis. Repeated MRI was not routinely performed during follow-up in the hypofractionation cohort. Disease progression was defined as a clinical (neurologic) deterioration with need for steroid reuse or dose escalation. Progression according to this definition might be different from that according to a clinical-radiologic definition, particularly because of the lack of clear-cut MRI criteria for disease progression in brainstem tumors (1). When all the potential subjective factors in this rapidly progressive disease are considered, it is clear that overall survival seems to provide the most reliable information in the absence of standardized and validated criteria for disease progression (1).

The main reason why we treat patients 4 days per week instead of 5 is patient burden. Taking into account all radiation therapy-related publications on DIPG, it is unlikely that a difference in overall treatment time of 3 to 4 days will influence the final outcome (1). It is unclear whether or not 5 fractions of 2.8 to 3.0 Gy per week could result in a higher incidence of treatment interruptions (eg, brainstem edema) despite systematic steroid use. In the absence of any difference in overall survival time between 13 fractions of 3 Gy and 16 fractions of 2.8 Gy, the lower dose and shorter regimen can be defended. The selection of the lowest radiation dose with equal effect may become particularly interesting, especially in the context of reirradiation at the time of progression. For a disease with a course like DIPG, this approach can be justified and can offer potential options for future reirradiation trials. In 6 highly selected patients, preliminary experience of reirradiation of the brainstem, after an initial dose of 54 to 55.8 Gy, still demonstrated some improvement of symptoms with minimal toxicity with a dose of 18 to 20 Gy in 2.0-Gy fractions (9).

As we embark on the long-awaited molecular era for pediatric DIPG, it is probable that many new studies combining 1 or more small molecules with conventional radiation therapy will be tested in the next decade to come (10-12). Although it is clear that we should encourage the development of such new agents, it is our experience that a significant proportion of parents and patients, when properly informed, may prefer the option of a low-burden radiation therapy regimen with emphasis on quality of life. Hypofractionation radiation therapy offers a treatment course that is completed in 3 to 4 weeks. Assuming a median overall survival time of 9 months, the child and his or her parents will have to spend only 10% of the remaining survival time for in-hospital treatment. Protracted regimens using conventional fractionation double the radiation therapy overall treatment time, and when systemic combinations are used in addition to radiation, children may spend more than half of the remaining survival time under treatment (1, 3, 13, 14). This is the reason for us to start a phase II prospective trial on hypofractionation with emphasis on quality of life. Ideally, a randomized noninferiority study should be the method of choice to confirm our results. However, when conventional radiation therapy provides the well-known palliation of 8.5 months, the rationale becomes practically very difficult, especially in a rare tumor type and a myriad of other clinical trials (1, 2, 10, 11, 13). When outcome is confirmed in a prospective trial, the current hypofractionation regimen can serve as a potential base for combined treatment approaches in future trials. However, if uncertainty exists about the potential radiosensitizing effects of novel agents, a cautious approach is recommended, because with a higher dose per fraction the radiosensitizing effect can be larger, with the consequence of increased risk of toxicity. It is clear that such combinations can be tested only in the context of well-designed trials with emphasis on the precise monitoring of toxicity.

Conclusion

The results of this matched-cohort analysis demonstrate a similar overall survival rate with a hypofractionation regimen (13 or 16 fractions in 3 to 4 weeks) compared with a conventional radiation therapy regimen (30 fractions in 6 weeks) for patients with newly diagnosed DIPG. Outside clinical trials, this low-burden regimen could be considered as a good alternative to protracted regimens.

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