Objective: Diffuse intrinsic pontine gliomas (DIPGs) are highly aggressive tumors and have a poor prognosis. Nearly all patients experience disease progression after definitive treatment, accompanied by severe neurologic deficits and morbidity. Here, we report a series of patients treated with reirradiation for palliation of symptoms.

Methods: Six patients received reirradiation for progressive DIPG at MD Anderson Cancer Center from 2007 to 2009. Progression after initial chemoradiation and salvage chemotherapy had been confirmed clinically and by magnetic resonance imaging. Each case was discussed at a multidisciplinary conference before reirradiation.

Results: Interval between the initial radiation therapy and reirradiation was 8 to 28 months. The initial radiation therapy dose was 54 to 55.8 Gy. Time to initial progression was 4 to 18 months. All of the patients had further progression on salvage chemotherapy. Reirradiation was given with concurrent chemotherapy to a dose of 20 Gy (n=4) or 18 Gy (n=1); 1 patient withdrew care after a single 2-Gy fraction. Four patients had substantial clinical improvement in symptoms, with improvement in speech (n=3), ataxia (n=3), and swallowing (n=2). Three patients showed renewed ability to ambulate after reirradiation. Four patients had decreased tumor size on posttreatment magnetic resonance imaging. The median clinical progression-free survival time was 5 months. Acute radiation-related toxicities were fatigue (n=2), alopecia (n=2), and decreased appetite (n=1). No grade 3 or 4 toxicities were reported.

Conclusions: Reirradiation with chemotherapy may be feasible to improve symptoms and delay progression with minimal toxicity. Patients who are most likely to benefit may be those with prolonged response to initial therapy and a long interval since initial radiation.

Key Words: brainstem glioma, palliative radiation, pediatric brain tumors

(Diagnosis and treating outcomes could result in improved care.)

Palliative Reirradiation for Progressive Diffuse Intrinsic Pontine Glioma

Hiral P. Fontanilla, MD,* Chelsea C. Pinnix, MD, PhD,* Leena M. Ketonen, MD, PhD,‡ Shiao Y. Woo, MD,* Tribhawan S. Vats, MD,‡ Michael E. Ryting, MD,‡ Johannes E. Wolff, MD,‡ and Anita Mahajan, MD*

Diffuse intrinsic pontine gliomas (DIPGs) account for 70% to 80% of brainstem gliomas in children. They are highly aggressive tumors and have a poor prognosis. Patients often present with a brief history of severe neurologic deficits, including ataxia, long tract signs, and cranial nerve deficits. The standard treatment is focal radiation therapy (RT) at a dose of 54 Gy. Most patients experience a rapid clinical response to initial RT, with roughly 70% exhibiting improvements in neurologic symptoms. Nevertheless, the overall results of treatment are disappointing, with nearly all patients experiencing disease progression within 5 to 8 months after RT.1–5 Response to salvage chemotherapy is also unsatisfactory, and the median survival time is less than 1 year.5–6 Patients who show progressive disease with salvage chemotherapy often experience severe neurologic deficits and morbidity and have limited treatment options.

Reirradiation has been used for a variety of recurrent diseases in the brain.7–12 Given the lack of effective treatment options for recurrent DIPG, here we sought to evaluate the feasibility of repeat, modest-dose palliative RT to the brainstem for such patients, with the goals of improving symptoms and delaying further progression of disease. To our knowledge, this report describes the first series of patients receiving reirradiation to the brainstem for recurrent DIPG.

MATERIALS AND METHODS

This retrospective case review of children with DIPG who received repeat RT at The University of Texas MD Anderson Cancer Center from 2007 to 2009 was approved by the appropriate institutional review board. Detailed chemotherapy and RT records were thoroughly reviewed. Progression of disease after initial treatment was defined as clinical worsening of symptoms and increase in tumor size or progressive contrast enhancement by magnetic resonance imaging (MRI). The modified Macdonald criteria were used to follow tumor growth on MRI.13,14 We used the 2-dimensional linear measurement of the maximum tumor diameter on T2 images, with the largest perpendicular diameter measured on the same image. All the images were reviewed by a single neuroradiologist experienced in brainstem gliomas.

Six patients were identified as having undergone reirradiation for progressive DIPG at MD Anderson Cancer Center from 2007 to 2009. The median age at the time of diagnosis was 4 years (range, 3 to 11 y). There were 4 girls and 2 boys. Each case was discussed at a multidisciplinary conference before reirradiation. Reirradiation was offered to those patients who had shown clinical and radiographic evidence of disease progression during salvage chemotherapy and for whom other treatment options were limited. Risks of treatment were explained and consent for treatment was obtained in all cases. Computed tomography (CT)-based treatment simulations were done while the patients were in a supine position. Thermoplastic masks were used for head immobilization. Anesthesia was used for patients who were unable to follow instructions and remain immobile during simulation and treatment. Diagnostic MR images were fused with the planning CT scans for target delineation. The target for reirradiation was individualized and included all areas of the gross tumor visible on MRI.

From the Departments of *Radiation Oncology; ‡Pediatric Neuro-oncology; and †Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX.

The authors declare no conflicts of interest.

Reprints: Hiral P. Fontanilla, MD, Department of Radiation Oncology, Box 97, MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030. E-mail: hpatel1@mdanderson.org.

Copyright © 2011 by Lippincott Williams & Wilkins

ISSN: 0277-3732/12/3501-0051

DOI: 10.1097/COC.0b013e318201a2b7

American Journal of Clinical Oncology • Volume 35, Number 1, February 2012 www.amjclinicaloncology.com | 51
as seen on the T1 contrast, T2, and fluid attenuated inversion recovery MRI sequences. RT was delivered with an intensity-modulated radiotherapy technique, with 6-MV photons, with a planned dose of 18 to 20 Gy in 2-Gy daily fractions prescribed to the target volume. Retreatment plans were individualized for each patient based on the earlier RT plan, the interval between treatments, and the clinical judgment of the treating radiation oncologist. Normal structures including the optic chiasm, optic nerves, optic lens, cochlea, and pituitary were contoured, and the dose to those structures was minimized. The brainstem received nearly the full prescription dose during both initial RT and reirradiation. Concurrent chemotherapy was planned during the reirradiation for all the patients as determined by the treating neuro-oncologist. Serial MRI scans were obtained after the completion of therapy to evaluate the treatment response. Radiographic evidence of progression was defined according to the modified Macdonald criteria with T2-weighted images. Progressive signal abnormality on T2-weighted image and progressive contrast enhancement were also recorded as part of progressive disease. Clinical evidence of progression was determined by the treating oncologists as worsening of symptoms. Detailed records were kept and extracted with regard to clinical symptoms and treatment-related toxicity.

Patient characteristics at the time of diagnosis and aspects of the initial treatment are shown in Table 1. Initial presenting symptoms included ataxia in all the patients and cranial nerve deficits in 4 patients. Initial RT was given at a dose of 54 to 55.8 Gy with concurrent chemotherapy (Fig. 1A). The concurrent chemotherapy regimens varied and included cisplatin, etoposide, vincristine, topotecan, temozolomide, vandetanib, and ifosfamide. Four patients received initial treatment on prospective protocols investigating the effectiveness of concurrent chemotherapy.

Time to first progression after initial RT ranged from 4 to 18 months, as confirmed by clinical progression and on MRI (Fig. 2). All the patients were treated with additional chemotherapy at first progression, with regimens including irinotecan, bevacizumab, alemtuzumab, nimotuzumab, vandetanib, temozolomide, and vincristine. All patients had experienced further clinical and radiographic progression after salvage chemotherapy and before reirradiation.

### RESULTS

Details regarding each patient’s reirradiation are listed in Table 2. The time from the initial course of RT to reirradiation ranged from 8 to 28 months. Median age at the time of reirradiation was 5 years (range, 5 to 12 y). The patients’ Lansky play scores were between 40 and 80 before the reirradiation. The planned reirradiation was 20 Gy in 10 fractions for 5 patients and 18 Gy in 10 fractions for 1 patient. Concurrent chemotherapy was planned for all the patients, with the regimen determined by the treating neurooncologist. Bevacizumab and irinotecan were administered concurrently to 3 patients. Other regimens included temozolomide, etoposide, and cisplatin, given alone or in combination. Patients 1, 2, and 4 had earlier progression on the chemotherapy regimen that was given concurrently with reirradiation, and the rationale for treatment was possible therapeutic interaction of this regimen with radiation. Treatment was withdrawn for patient 6 after a single 2-Gy fraction because of the patient’s deteriorating condition. That patient developed respiratory distress owing to continued aspiration and was transferred to supportive care. The planned treatment for that patient had been 20 Gy in 10 fractions with concurrent bevacizumab and irinotecan, but the patient did not receive this therapy.

All the patients tolerated the treatment well without any severe (grade ≥3) acute symptoms. Acute toxicities reported were fatigue (n=2), alopecia (n=2), decreased appetite (n=1), nausea (n=1), and headache (n=1). No grade 3 or 4 toxicities were reported. Four of the five patients who completed treatment experienced significant clinical improvement in symptoms, which lasted for a median of 5 months (range, 0

---

### TABLE 1. Individual Patient Details of Diagnosis and Initial Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Time of Diagnosis (y)</th>
<th>Symptoms at Presentation</th>
<th>Initial RT*</th>
<th>Initial Chemotherapy</th>
<th>Time to Progression (mo)</th>
<th>Chemotherapy After Initial Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Ataxia, change in speech and personality, R foot drop, L gaze palsy, R CN VII</td>
<td>54 Gy/30 fx</td>
<td>Cisplatin, etoposide, vincristine</td>
<td>18</td>
<td>Nimotuzumab, bevacizumab, irinotecan</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>Ataxia, R strabismus, difficulty in walking</td>
<td>55.8 Gy/31 fx</td>
<td>Topotecan</td>
<td>4</td>
<td>Vincristine, temozolomide, irinotecan</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>CN VI, frequent falls</td>
<td>54 Gy/30 fx</td>
<td>Vandetanib</td>
<td>9</td>
<td>Vandetanib, nimotuzumab, bevacizumab</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Ataxia, tremors, seizures, horizontal gaze palsy, difficulty in swallowing</td>
<td>54 Gy/30 fx</td>
<td>Temozolomide</td>
<td>7</td>
<td>Nimotuzumab, bevacizumab, irinotecan</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>Ataxia, double vision</td>
<td>54 Gy/30 fx</td>
<td>Methotrexate (neoadjuvant), cisplatin, etoposide, ifosfamide, vincristine</td>
<td>13</td>
<td>Vincristine, lomustine, alemtuzumab</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>Ataxia, facial weakness, difficulty in swallowing, slurred speech</td>
<td>54 Gy/30 fx</td>
<td>Cisplatin, etoposide, temozolomide</td>
<td>9</td>
<td>Bevacizumab, irinotecan, etoposide, valproic acid, nimotuzumab</td>
</tr>
</tbody>
</table>

*All patients had concurrent chemotherapy with initial radiation therapy (RT).*
to 7 mo) (Table 2). Improvement was noted in speech (n=3), ataxia (n=3), and swallowing (n=2). Three patients who had not been walking before reirradiation could walk after the treatment. Two patients had improvement in Lansky score, and other 3 had stable scores, after the treatment. One patient was alive with disease progression at 5 months’ follow-up; median survival time for the other 5 patients was 6 months after the completion of reirradiation.

Four of the five patients who completed the treatment had decreases in tumor size on follow-up MRI (as determined by an experienced neuroradiologist) (Fig. 2). The median time to progression by MRI was 4 months (range, 0 to 6 mo). One patient (patient 2) showed decreased tumor size but increased abnormal enhancement on follow-up MRI. Subsequent MRI showed progression, and the patient died 4 months after reirradiation.

**DISCUSSION**

DIPGs are highly aggressive tumors and are fatal in nearly all patients. Initial RT produces responses in approximately 70% of patients, but unfortunately, the typical time to progression after initial treatment is 5 to 8 months. As the disease progresses, patients commonly develop severe neurologic deficits that adversely affect their quality of life. Although DIPG is not considered curable at this time, reirradiation therapy with a modest total dose, requiring a short overall treatment time, may be a reasonable option for palliation of symptoms. Our experience with reirradiation, given with concurrent chemotherapy, showed appreciable symptomatic improvement and radiographic response in patients who completed the planned treatment. The treatment was well tolerated, with minimal toxicity from radiation and concurrent chemotherapy.

Three patients who were unable to ambulate before reirradiation could do so on its completion. Some patients also experienced noticeable improvements in speech, swallowing, and Lansky scores, all of which would be expected to enhance the patients’ quality of life. Posttreatment MRI also showed decrease in contrast enhancement, improvement in T2 signal abnormality, and decreases in tumor size, although the extent of the decrease in size was small and variable.

As the reirradiation was given with concurrent systemic therapy in all the cases, it is admittedly difficult to determine the relative contribution of each modality to the results. Nevertheless, we believe that radiation played a major role, because all patients had experienced disease progression despite multiple courses of chemotherapy before. Three patients had earlier progression on the regimen that was used concurrently with reirradiation. All patients had received concurrent chemotherapy, usually in the context of investigational studies, with initial RT, although some patients did not receive this treatment at our institution. The role of concurrent chemotherapy is not well established in this disease, but because of the poor prognosis, efforts are continuing to escalate therapy with the addition of various systemic treatments. After initial progression, all patients in this series were also treated with various different chemotherapy regimens that were thought to be promising and had variable response. Although the effectiveness of chemotherapy regimens continues to be studied, our series does suggest the safety of combining low-dose reirradiation with systemic treatment. The ideal combination and relative effectiveness of chemotherapy in this setting is unknown.

Our experience, although based on a small number of patients who all experienced disease progression eventually, suggests characteristics that may help to identify those who are most—or least—likely to benefit. In this series, the patient who derived the least benefit, both radiographically and clinically, had shown disease progression within 3 months after the initial therapy and had a relatively short (8 mo) interval between courses of RT. Another patient who did not complete the treatment was acutely ill and was not likely to be an ideal candidate for reirradiation at that time. Offering reirradiation earlier, before the acute deterioration, may have been beneficial in this case. In contrast, the patients who may benefit most from reirradiation are those with a prolonged response to initial RT, a long interval since initial therapy, and...
FIGURE 2. Axial magnetic resonance images (MRI) for a 5-year-old boy with progressive brainstem glioma. A, T2-weighted image obtained at initial diagnosis shows diffuse brainstem enlargement by a diffuse intrinsic pontine glioma, with marked hyperintensity of the pons, compression of the fourth ventricle, and characteristic engulfment of the basilar artery by the tumor. B, Postcontrast T1-weighted image at initial diagnosis shows thin rim of enhancement on right (arrow). C, Axial T2-weighted image obtained 13 months later, after initial radiation and chemotherapy, before reirradiation, shows significant improvement after initial radiation and chemotherapy but progression compared with a previous magnetic resonance images (not shown); (D) postcontrast T1-weighted image obtained at the same time shows progressive enhancement on left with a cavitary focus (arrow) with the resolution of the right-sided enhancement. E, Axial T2-weighted image obtained 2 months later, after reirradiation, shows the improvement of the T2 hyperintensity; (F) postcontrast T1-weighted image obtained at the same time also shows the improvement in enhancement and the reduction in size of the cavitary focus with margin enhancement (arrow).
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Reirradiation (y)</th>
<th>Reirradiation</th>
<th>Time Since Initial RT (mo)</th>
<th>Concurrent Chemotherapy With Reirradiation</th>
<th>Lansky Score at Reirradiation</th>
<th>Symptoms at Reirradiation</th>
<th>Response to Reirradiation</th>
<th>MRI Findings</th>
<th>Lansky Score After Reirradiation</th>
<th>Time to Further Progression</th>
<th>Acute Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>20 Gy/10 fx</td>
<td>28</td>
<td>Bevacizumab, irinotecan</td>
<td>40</td>
<td>Not walking, ataxia, CN VII, VI, speech difficulty</td>
<td>Clinical improvement in walking, speech, mood</td>
<td>Decreased size of primary</td>
<td>90</td>
<td>Progression by MRI at 6 mo, clinical progression at 7 mo, deceased at 9 mo</td>
<td>Alopecia</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>20 Gy/10 fx</td>
<td>8</td>
<td>Temozolomide</td>
<td>80</td>
<td>Ataxia, CN VII, R strabismus, diplopia, L hemiparesis, difficulty in swallowing, on steroids</td>
<td>Brief clinical improvement with swallowing, speech, vision</td>
<td>Decreased size but increased enhancement</td>
<td>80</td>
<td>Progression at 2 mo, deceased at 4 mo</td>
<td>Fatigue, somnolence</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>20 Gy/10 fx</td>
<td>13</td>
<td>Cisplatin, etoposide, temozolomide</td>
<td>60</td>
<td>Not walking, CN VII, VI, III, speech, R hemiparesis, ataxia, on steroids</td>
<td>Walking with walker, smile and speech improved, off steroids</td>
<td>Decreased size, decreased enhancement</td>
<td>60</td>
<td>Progression by MRI at 3 mo, clinical progression at 5 mo</td>
<td>Alopecia</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>20 Gy/10 fx</td>
<td>13</td>
<td>Bevacizumab, irinotecan</td>
<td>70</td>
<td>Not walking, ataxia, speech, hearing loss, night terrors</td>
<td>Clinical improvement, walking with ataxia, swallowing and speech improved, continued hearing problems</td>
<td>Decreased size, decreased enhancement</td>
<td>80</td>
<td>Progression at 5 mo, deceased at 6 mo</td>
<td>Fatigue</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>18 Gy/10 fx</td>
<td>23</td>
<td>Bevacizumab, irinotecan</td>
<td>50</td>
<td>Difficulty with swallowing, speech, vomiting, urinary hesitancy, on steroids</td>
<td>Stable clinical course, improved urinary hesitancy</td>
<td>Decreased size of primary</td>
<td>50</td>
<td>Progression at &gt;4 mo, deceased at 10 mo</td>
<td>Decreased appetite, nausea, headache</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2 Gy/1 fx*</td>
<td>12</td>
<td>Bevacizumab, irinotecan*</td>
<td>40</td>
<td>Difficulty with speech, aspiration, not walking</td>
<td>--</td>
<td>--</td>
<td>Deceased within 1 wk of withdrawal of care</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

*The patient’s parents declined further treatment after a single 2-Gy fraction (and no chemotherapy); the planned treatment had been 20 Gy/10 fractions with concurrent chemotherapy. MRI indicates magnetic resonance imaging; RT, radiation therapy.
good performance status. Interval from earlier radiation is also an important consideration for limiting toxicity. The interval for most of the patients in this study was 1 year, except for 1 patient who was treated at 8 months; we generally, use several combinations of chemotherapy to delay reirradiation as long as possible.

Reirradiation of the brainstem after the initial RT at a dose of 50 to 55 Gy can be associated with significant, possibly lethal, toxicity, and should be approached with care. Published data on the consequences of brainstem reirradiation with regard to incidence of necrosis are sparse, but some information may be extrapolated from the studies of reirradiation to other areas of the brain. Merchant et al reported a series of patients with recurrent ependymoma treated with reirradiation and noted necrosis, particularly after stereotactic radiation. Rates of necrosis seemed to be higher after the use of hypofractionated RT. Nieder et al, combining data from several studies, reported a 14% incidence of confirmed radionecrosis in 28 patients treated with cumulative doses of 86 Gy or more. The risk of late toxicity increases with higher cumulative dose, larger volume of reirradiated tissue, and short interval between treatments. As DIPG is also associated with significant tumor-related necrosis, radionecrosis may be difficult to identify in this setting.

Radiation necrosis is typically seen 6 months to several years after RT. Bauman et al found that 3 of 34 patients developed necrosis 7.5 to 33 months after reirradiation for various primary central nervous system tumors. For patients with DIPG, whose survival time is expected to be short, this may be an acceptable risk. Bevacizumab, an antibody against vascular endothelial growth factor, has also been reported to improve clinical symptoms in children with DIPG suffering from radiation necrosis. Increases in vascular endothelial growth factor are associated with capillary permeability related to tumor factors and radiation necrosis, and bevacizumab may also improve symptoms by reducing edema. Several studies have evaluated the antitumor effects of bevacizumab in high-grade glioma including DIPG, and the initial results have been conflicting. Three patients in our series were treated with concurrent bevacizumab during reirradiation. Additional studies are necessary to determine the therapeutic use of bevacizumab in the reirradiation setting.

Summary

Disease progression after the definitive treatment of DIPG is accompanied by severe neurologic deficits and morbidity. Given the lack of effective treatments for recurrent DIPG, quality of life must be given considerable priority, and the morbidity of salvage therapy should be limited. Low-dose reirradiation with concurrent systemic therapy may be a feasible option to improve symptoms and further delay disease progression with minimal toxicity. This option may be considered for select patients, particularly those with prolonged response to initial therapy and a long interval since initial RT.

REFERENCES

**Claudia N:**  
Paciente de 9 años, diagnosticada de glioma del tronco, cuya clínica se inició el 15 de octubre con vómitos e inestabilidad, no cefalea. Se siguió de desorientación y disminución del nivel de conciencia, por lo que es traida al Servicio de Urgencias e ingresada en UCI pediátrica. 
Ingresó el 16 de octubre de 2016, para cirugía, precisando drenaje externo, se realiza biopsia tumoral y colocación de derivación ventriculoperitoneal y pendiente de tratamiento radioterápico. 
Ha recibido tratamiento con dexametasona suspendida el día 10/11/16. 
La paciente es valorada en nuestra consulta presentando buen nivel de consciencia y de colaboración con los déficits descritos en la exploración respecto a parálisis de pares craneales, ataxia y dismetría mano derecha. 
La paciente es valorada en nuestra consulta presentando buen nivel de consciencia y de colaboración con los déficits descritos en la exploración respecto a parálisis de pares craneales, ataxia y dismetría mano derecha. 

**Exploración neurológica prerradioterapia:** 
Neurológico: Consciente, orientada y colaboradora. Lenguaje normal. Parálisis de III PC derecho, VI par izquierdo, VII par izquierdo (en mejoría, es capaz de ocluir por completo el ojo izquierdo) y hemiparesia derecha, con mejoría desde su ingreso siendo capaz actualmente de bipedestación. Ataxia. Dismetría especialmente con mano derecha.

**DIAGNÓSTICO AP:**
1 Y 2. - FRAGMENTOS CEREBRALES CON EDEMA Y HEMORRAGIA. AUSENCIA DE NEOPLASIA.  

**Tratamiento realizado:**
RT estereotaxica fraccionada cerebral sobre lesión tumoral concomitante con temozolamida 75mg/m2, con posterior aumento de la dosis a 150 mg/m2 el primer ciclo y 200 mg/m2 los siguientes hasta completar 6-12 ciclos. 
Volumen blanco: 
Dosis PTV1: 5600 Gy (T2 FLAIR y PTV2 T1 realizado con gadolinio) con exclusión aparato óptico a los 5400 cGy. Dosis en órganos críticos quiasma, tronco cerebral y ojos dentro de tolerancia. Se valoro subir dosis, pero no fue posible llegar a 60 Gy por tolerancia órganos críticos. Volumen tumoral toda la lesión en T1 con gadolinio y T2 FLAIR con margen de 10 mm asimétrico. 
Fraccionamiento y duración del tratamiento: 5 sesiones semanales de 180 cGy/sesión, en volumen 1 y 2. El tratamiento se inició el 21-11-16 hasta el 11-1-17. 
Tolerancia/incidencias: la tolerancia ha sido buena, sin incidencias. 

**RMN cerebral de mayo 2017 (máxima respuesta):** 
La masa descrita en protuberancia y hemimesencéfalo izquierdo ha disminuido de tamaño de forma muy significativa tras radio y quimioterapia, quedando únicamente un pequeño mesencefálico posterior izquierdo, de aproximadamente 8 mm de diámetro, que se realiza con contraste. 
Restos hemáticos evolucionados en lecho tumoral. 
Válvula de derivación con entrada frontal derecha y extremo en ventrículo ipsilateral. Asimetría en el tamaño ventricular con leve disminución de tamaño del asta frontal izquierda respecto al control de febrero. 
Cambios posquirúrgicos con craneietomía occipital. 
Conclusión: 
Disminución (>90%) de la masa tumoral de troncoencéfalo con respecto a estudio inicial. 

La paciente ha evolucionado bien, con tratamiento de temodal que ha tolerado bien y con mejora de los déficits de pares craneales, y hemiparesia, haciendo vida normal, solo precisando lentes correctoras que actualmente no necesita y vida escolar normal con excelente resultado académico.
Ante la progresión radiológica en marzo 2018, estando asintomática, nos proponen reirradiación.

NUEVA PROPUESTA 13-3-18:
posible progresión radiológica en RMN aunque clínicamente permanece estable, paraceuticamente asintomática. Solicitan valorar reirradiación.

Evolución:

- TC de cráneo 24.10.2016: Cambios postquirúrgicos de craniectomía occipital con lesión de tronco con sangrado evolucionado. Derivación ventricular con entrada frontal derecha y extremo del catéter en Monroe derecho.
- RM cráneo 22.02.2017: tumor de troncoencefalo ya conocido con leve disminución de tamaño con respecto a estudio previo de 2016.
- RM cráneo 17.05.2017. disminución >90% del tumor de troncoencefalo con respecto a estudio inicial.

RM cráneo 1-3-2018: Progresión.
Se observa aumento de tamaño de restos tumorales presentes en protuberancia con extensión a mesencéfalo posterior izquierdo y bulbo anterior izquierdo, que incluso en la actualidad cruza línea media hacia el lado derecho de la protuberancia. Restos hemáticos evolucionados en lecho tumoral.
Válvula de derivación con entrada frontal derecha y extremo en la parte más distal ventrículo ipsilateral. Persiste la asimetría en el tamaño ventricular, con leve mayor tamaño del izquierdo, sin cambios respecto a estudio previo. El IV ventrículo mantiene tamaño y morfología respecto a previo (h febrero 2017 se encontraba dilatado).
Cambios posquirúrgicos con craniectomía occipital.
Desarrollo de angioma cavernoso en corona radiada izquierda (se identifica desde agosto 2017). Se observa un engrosamiento mucoso de seno esfenoidal izquierdo y de senos maxilares en probable relación con sinusopatía.
Conclusión:
Crecimiento significativo del resto tumoral respecto a estudio previo de 15.11.2017. Hallazgos en relación con progresión tumoral.
Angioma cavernoso postradioterapia.

Evolución junio 2018:
Se nota un poco de afectación del equilibrio leve, aunque aguanta carga.
No atragantamientos. No cambios en la vision.
Neurológico: Imposibilidad de mirada a la izquierda, III par izquierdo.
Menor fuerza en mano derecha y mayor dismetría.
Marcha en tandem dificultosa. EMPEORAMIENTO LEVE DE PARES CRANEALES, TANTO OCULOMOTORES COMO DEL FACIAL.
Evolución del 29-6-18:En general se encuentra muy bien, mejor.


Al valorarla en consulta la exploración es igual e incluso algo mejor que la del junio 2018, bien orientada, ha terminado el curso escolar con excelentes notas, según la madre, esta muy bien.
Imágenes al diagnóstico (imagen de la derecha) y en marzo 2018 imagen izda).

Imagen recidiva en junio 2018.
Original Research

Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group

Geert O. Janssensa,*, Lorenza Gandolab, Stephanie Bollec, Henry Mandevilled, Monica Ramos-Albiac e, Karen van Beekf, Helen Benghiagt, Bianca Hobebeh, Andres Morales La Madrild, Rolf-Dieter Kortmann j, Darren Hargravek, Johan Mentenf, Emilia Pecorib, Veronica Biassonil, Andre O. von Bueren m,n, Dannis G. van Vuurden o, Maura Massimino l, Dominik Sturm p, Max Peters a, Christof M. Krammn

a Department of Radiation Oncology, University Medical Center Utrecht and Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands
b Pediatric Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
c Department of Radiotherapy, Gustave Roussy Cancer Campus, Villejuif Cedex, France
d Department of Clinical Oncology, The Royal Marsden NHS Foundation Trust, Sutton, UK
e Department of Radiation Oncology, Hospital Vall d’Hebron, Barcelona, Spain
f Department of Radiation Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium
g Department of Clinical Oncology, University Hospital Birmingham, Birmingham, UK
h Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands
i Department of Pediatric Hematology and Oncology, Hospital Sant Joan de Deu, Barcelona, Spain
j Department of Radiation Therapy, University Hospital Leipzig, Leipzig, Germany
k Pediatric Oncology Unit, Great Ormond Street Hospital, London, UK
l Pediatrics Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
m Department of Hematology & Oncology, University of Geneva, Geneva, Switzerland
n Department of Pediatric Hematology & Oncology, University Hospital Goettingen, Goettingen, Germany
o Department of Pediatric Oncology & Hematology, VU University Medical Center, Amsterdam, The Netherlands
p Division of Pediatric Neuro-oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Received 9 September 2016; received in revised form 25 November 2016; accepted 5 December 2016

* This study was presented at the 17th International Symposium on Pediatric Neuro-Oncology (ISPNO), Liverpool, UK, June 12–15, 2016.
* Corresponding author.
E-mail address: g.o.r.janssens@umcutrecht.nl (G.O. Janssens).

http://dx.doi.org/10.1016/j.ejca.2016.12.007
0959-8049/© 2017 Elsevier Ltd. All rights reserved.
Diffuse intrinsic pontine glioma (DIPG); Radiotherapy; Re-irradiation; Matched-cohort analysis; Survival prediction model

Abstract  Background: Overall survival (OS) of patients with diffuse intrinsic pontine glioma (DIPG) is poor. The purpose of this study is to analyse benefit and toxicity of re-irradiation at first progression.

Methods: At first progression, 31 children with DIPG, aged 2–16 years, underwent re-irradiation (dose 19.8–30.0 Gy) alone (n = 16) or combined with systemic therapy (n = 15). At initial presentation, all patients had typical symptoms and characteristic MRI features of DIPG, or biopsy-proven high-grade glioma. An interval of ≥3 months after upfront radiotherapy was required before re-irradiation. Thirty-nine patients fulfilling the same criteria receiving radiotherapy at diagnosis, followed by best supportive care (n = 20) or systemic therapy (n = 19) at progression but no re-irradiation, were eligible for a matched-cohort analysis.

Results: Median OS for patients undergoing re-irradiation was 13.7 months. For a similar median progression-free survival after upfront radiotherapy (8.2 versus 7.7 months; \( P = .58 \)), a significant benefit in median OS (13.7 versus 10.3 months; \( P = .04 \)) was observed in favour of patients undergoing re-irradiation. Survival benefit of re-irradiation increased with a longer interval between end-of-radiotherapy and first progression (3–6 months: 4.0 versus 2.7; \( P < .01 \); 6–12 months: 6.4 versus 3.3; \( P = .04 \)). Clinical improvement with re-irradiation was observed in 24/31 (77%) patients. No grade 4–5 toxicity was recorded. On multivariable analysis, interval to progression (corrected hazard ratio = 27–54; \( P < .01 \)) and re-irradiation (corrected hazard ratio = .18–.22; \( P < .01 \)) remained prognostic for survival. A risk score (RS), comprising 5 categories, was developed to predict survival from first progression (ROC: .79). Median survival ranges from 1.0 month (RS-1) to 6.7 months (RS-5).

Conclusions: The majority of patients with DIPG, responding to upfront radiotherapy, do benefit of re-irradiation with acceptable tolerability.

© 2017 Elsevier Ltd. All rights reserved.

1. 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 four decades [1,2]. For a newly-diagnosed patient with DIPG, the current standard of treatment consists of radiotherapy followed by best supportive care (BSC) [1–3]. This approach usually results in a transitory improvement of neurological signs and symptoms, however most patients will die within one year after the diagnosis due to local tumour progression and brainstem failure.

At the time of disease progression, various systemic regimens have been applied. Although partial remissions and stable diseases have been observed in a small number of patients, none of the tested agents have shown any survival benefit when compared with radiotherapy alone [4]. Unlike new agents attempting to improve outcome by intensified regimens, inevitably associated with increased toxicity, numerous outpatient visits or prolonged hospital stays, re-irradiation at progression has the potential to improve symptoms and overall survival (OS) with limited treatment burden [4–7]. In pilot studies that included 6 to 11 patients, up to 90% of the patients developed neurological improvement, whereas a survival benefit up to 4 months was observed for patients receiving re-irradiation [7].

The purpose of this study is to analyse the outcome of patients with DIPG undergoing re-irradiation at the first progression. A matched-cohort analysis, including patients with similar disease characteristics receiving no re-irradiation at progression, was performed and a survival prediction model was developed.

2. Material and methods

2.1. Eligibility

A multicenter retrospective analysis was performed across SIOP-E (Socié´ te´ International d’Oncologie Pédiatrique)—linked centres. Patients aged less than 18 years, and fulfilling the following criteria were eligible: (1) clinical and radiological signs of a typical DIPG at primary diagnosis¹ or a biopsy confirming high-grade glioma, (2) an interval of ≥3 months between the last

¹ Typical DIPG: onset of symptoms ≤3 months before diagnosis, ≥2 signs of the neurologic triad (cranial nerve deficit, ataxia, or long tract signs) combined with specific MR features (appearance of a poorly margined tumour with mass effect occupying ≥50% of the axial diameter of the pons, hypointensity on T1 and hyperintensity on T2 images. Additional radiological criteria include encasement of the basilar artery, extension into the mesencephalon and/or medulla oblongata and/or cerebellar peduncle as well as contrast enhancement (focal ring, peripheral, spotty or focal patchy) ± necrosis.
day of upfront radiotherapy and the start of fractionated re-irradiation. The combination of re-irradiation and systemic agents was allowed. Patients with leptomeningeal spread or multifocal disease on MRI at first progression, or patients undergoing more than one course of re-irradiation, as well as patients with systemic therapy as the third-line treatment were excluded from the analysis. Also children with a history of neurofibromatosis were excluded, because they belong to a subgroup expected to have a more favourable prognosis [8].

As a matching cohort, a validated group of 54 patients fulfilling the same inclusion criteria at initial presentation but no re-irradiation at progression was selected [3].

2.2. Radiotherapy

Both conventional (dose/fraction: 1.8–2.0 Gy) and hypo-fractionated (dose/fraction: >2.0 Gy) radiotherapy regimens were permitted during upfront radiotherapy. At first progression, a radiotherapy regimen consisting of at least ten fractions was required for analysis in this study. At progression, the clinical target volume included the tumour as defined by FLAIR (if available) or T2-weighted MR-images images with a margin of .0–1.0 cm. Margins were adjusted for bony structures and tentorium. An additional margin between .2 and .5 cm was added to create the planning target volume.

2.3. Assessment of progression

Before the onset of re-irradiation, a neurological and general clinical examination, performed by a paediatric neurologist or an experienced paediatric oncologist, was available for all patients. Disease progression was defined as a clinical (neurological) deterioration with need for steroid re-usage or dose-escalation, confirmed by MRI. During and after re-irradiation clinical re-evaluation by the radiation oncologist and/or paediatric oncologist/neurologist was performed according to the standard practice. Grade 3, 4 and 5 adverse events were registered using the CTC AE (Common Terminology Criteria for Adverse Effects), version 4.0.

2.4. End-points

The primary end-point was OS, measured from diagnosis to the date of death. Progression-free survival (PFS) was defined as the time to clinical (neurological) deterioration after upfront radiotherapy and measured from diagnosis. Patients were censored at the last follow-up.

2.5. Statistical analysis

Statistical analyses were performed using the R language environment. The Kaplan–Meier method was used to estimate survival for the entire group, for separate risk groups and for the groups which comprised the final risk score. The log-rank test statistic was adopted to assess statistical significance in survival estimates between groups. The chi-squared and Mann–Whitney U test were used to compare patient, tumour and treatment characteristics. To correct for multiple testing of baseline characteristics, the Holm’s Sequential Bonferroni procedure was used (18 tests).

For multivariable analysis Cox-proportional hazards regression was adopted to calculate the effect of the determinants (age; time to progression [categorised in <90 d, 90–180 d and >180 d]; upfront radiotherapy [conventional versus hypofractionation]; second-line therapy [categorised in RT + BSC, RT + systemic treatment, RT + re-irradiation and RT + re-irradiation/systemic treatment]) on survival, providing hazard ratio’s (HR’s) with 95% confidence intervals (CI’s). After univariable analysis, factors with a P-value ≤.10 were included in the multivariable analysis. With a backward stepwise approach the least significant predictors were excluded, starting with the full model. Models were compared at each step with the likelihood ratio test, with statistical significance set at P ≤ .05.

2.6. Prediction model

The C-statistic was used to quantify the discriminative ability of the final model [9]. Internal validation of the model was done using 2000 bootstrap resamples of the original data set, in which the model building steps were repeated. Subsequently, the C-statistic and the coefficients (β’s) from the original model were adjusted with the optimism calculated from the bootstrap resamples. The optimism-corrected β’s were used in further analyses (calibration, risk score creation). Calibration of the final adjusted model was done up to 9 months. No external validation was performed.

Individual survival proportions were calculated with the survival proportion formula $S(t) = S(0)^{\exp(\beta \text{predictor}_1 \times \text{predictor}_1 + \beta \text{predictor}_2 \times \text{predictor}_2 \ etc.)}$. The β’s correspond to the natural logarithm/ln of the HR’s after multivariable analysis (corrected for optimism) [10]. S(0) is the baseline survival proportion at a certain follow-up with the coefficients from multivariable analysis at 0. Risk scores (RSs) were calculated by multiplying the optimism-corrected coefficients by ten and rounding these to .5 precision. Afterwards, an individual RS was created by multiplying the contribution of the variables to the RS by the value of the variables themselves. This score was subdivided in 5 clinically relevant and statistically practical risk groups.

The R language environment (version 3.2.1; available at http://www.r-project.org/) was used for all statistical analyses (using the survival and rms packages http://CRAN.R-project.org/package=rms; http://CRAN.R-project.org/package=survival).
All analyses and reporting were performed in accordance with the TRIPOD statement [11].

3. Results

3.1. Patient groups and treatment

Between August 2011 and May 2015, 46 patients from seven countries across Europe underwent re-irradiation at progression after upfront treatment for DIPG. Fifteen out of 46 patients were excluded from this analysis for a number of reasons: systemic treatment at progression after re-irradiation (n = 6), onset of symptoms between 4 and 6 months before primary diagnosis (n = 3), neo-adjuvant chemotherapy before the first course of radiotherapy (n = 2), 3 courses of radiotherapy (n = 2), re-irradiation of the craniospinal axis (n = 1), death before onset of re-irradiation (n = 1). Thirty-one patients fulfilled the stringent inclusion criteria at the time of initial diagnosis and disease progression. The majority of patients (n = 25/31; 81%) was treated with a conventionally fractioned regimen up to a total dose of 18.0, 19.8 or 20.0 Gy in 1.8 or 2.0 Gy fractions. A total dose of 30.0 Gy in 3.0 Gy fractions was prescribed to six patients. Patient and treatment characteristics are listed in Table 1.

Re-irradiation started within one month after first progression in 23/31 (74%) patients. Sixteen out of 31 (52%) patients received re-irradiation alone, whereas 15/31 (48%) patients were re-irradiated combined with systemic agents, most frequently nimotuzumab plus vinorelbine (n = 9).

After applying eligibility criteria, 15 out of 54 patients from the cohort without re-irradiation were excluded due to early disease progression (<90 d). Thirty-nine patients were eligible for the matched-cohort analysis (Fig. 1. Flowchart). In this cohort, 20/39 (51%) patients received BSC, whereas 19/39 (49%) patients were treated with a systemic agent (ST) at the first progression.

3.2. Efficacy

Although no difference in median PFS after upfront radiotherapy (8.2 [95% CI: 7.2–9.2] versus 7.7 [95% CI: 7.1–8.5] months; P = .58) was observed for the cohort with or without re-irradiation, the analysis demonstrated a significant median OS benefit (13.7 [95% CI: 13.0–17.4] versus 10.3 [95% CI: 9.4–12.5] months; P = .04) in favour of patients undergoing re-irradiation (Fig. 2). OS at 6, 9, 12 and 18 months was 100 versus 95%, 87 versus 67%, 71 versus 33% and 23 versus 10% with re-irradiation compared with no re-irradiation, respectively.

On subgroup analysis, the survival benefit of re-irradiation increased with a longer interval between end of upfront radiotherapy and re-irradiation (3–6 months: 4.0 [95% CI: 2.7–NA] versus 2.7 [95% CI: 1.9–3.7] months; P < .01; 6–12 months: 6.4 [95% CI: 5.4–10.6] versus 3.3 [95% CI: 2.1–7.4] months; P = .04; Fig. 3A and B). No survival benefit of adding systemic therapy to re-irradiation versus re-irradiation alone was observed (6.1 [95% CI: 5.6–8.5] versus 5.4 [95% CI: 4.8–8.7] months, P = .38; Fig. 3C). Age, analysed as a categorical (cut-off value 10 years; Fig. 3D) or a continuous variable in the Cox model, did not influence survival (P = .18).

3.3. Clinical benefit from re-irradiation

All patients had severe neurological signs at the onset of re-irradiation. In 24/31 (77%) children clinical benefit, defined as any improvement of performance status (n = 16) or a neurological sign (ataxia, n = 11; cranial nerve, n = 11; long tract signs, n = 10; fatigue, n = 6; headache, n = 5) after re-irradiation was observed. No grade 3, 4 or 5 neurotoxicity related to radiotherapy was recorded.

3.4. Univariable and multivariable analysis

The impact of various common prognostic factors on survival is summarised in Table 2. On multivariable analysis, after correction for second-line therapy (BSC and ST), both re-irradiation and interval between upfront radiotherapy and re-irradiation remained independent prognostic factors for OS.

3.5. Prediction model

For the entire group of 85 patients, the Cox analysis yielded 5 predictive categories of which the coefficients as well as the use of re-irradiation were the major predictors for better outcome. The model, comprising 5 categories, can predict survival from the first progression (Fig. 4). With increasing RS, survival from the first progression improved significantly (RS-1: 1.0 [0.5–2.0] month; RS-2: 1.8 [1.5–3.5] months; RS-3: 3.6 [3.1–6.1] months; RS-4: 5.4 [4.8–9.8] months; RS-5: 6.7 [5.9–NA] months). The area under the receiver operating characteristic curve (optimism-corrected) was .79.

4. Discussion

Most children with diffuse intrinsic pontine glioma will die within one year after the diagnosis despite clinical response to upfront radiotherapy. The role of systemic agents at progression remains elusive. Given the clinical benefit observed after upfront radiotherapy, the role of re-irradiation at first progression was investigated. This matched-cohort analysis demonstrated a significant benefit in median OS of 3.4 months for patients with a
Table 1
Patient, tumour, and treatment characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No re-irradiation (n = 39)</th>
<th>Re-irradiation (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient and tumour characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4 to 14</td>
<td>2 to 16</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>27</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>1–2 months</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2–3 months</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Neurologic triad</td>
<td>.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial nerve deficit</td>
<td>39</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>34</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Long tract signs</td>
<td>25</td>
<td>19</td>
<td>.81</td>
</tr>
<tr>
<td><strong>Radiology features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass effect in the pons</td>
<td>39</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Poorly marginated</td>
<td>39</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>T1 hypo-, T2 hyperintensity</td>
<td>39</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>&gt;50% of axial diameter pons involved</td>
<td>39</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>&gt;67% of axial diameter pons involved</td>
<td>33</td>
<td>30</td>
<td>.12</td>
</tr>
<tr>
<td>Encasement of basilar artery</td>
<td>31</td>
<td>28</td>
<td>.32</td>
</tr>
<tr>
<td>Extension into mesencephalon, medulla</td>
<td>20</td>
<td>21</td>
<td>.17</td>
</tr>
<tr>
<td>Extension into cerebellar peduncle</td>
<td>21</td>
<td>24</td>
<td>.04</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>28</td>
<td>13 (24 available)</td>
<td>.01</td>
</tr>
<tr>
<td>Pathology-proven glioma</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First- and second-line treatment</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + BSC</td>
<td>20</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>RT + ST</td>
<td>19</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>RT + reRT</td>
<td>NA</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>RT + reRT/ST</td>
<td>NA</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>TTP from end of RT</td>
<td>.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–180 d</td>
<td>20</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>180–360 d</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>&gt;360 d</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>First-line RT regimen</td>
<td>.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>18</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hypofractionation</td>
<td>21</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>First-line ST regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide based</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nimotuzumab-vinorelbine based</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Second-line RT regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0 Gy (10 fr x 1.8 Gy)</td>
<td>NA</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>19.8 Gy (11 fr x 1.8 Gy)</td>
<td>NA</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>20.0 Gy (10 fr x 2.0 Gy)</td>
<td>NA</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>30.0 Gy (10 fr x 3.0 Gy)</td>
<td>NA</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Second-line ST regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temozolomide based</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nimotuzumab-Vinorelbine based</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Etoposide + cyclophosphamide + thalidomide</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fotemustine</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Valproic acid + celecoxib</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Valproic acid + temsirolimus + irinotecan</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Newly-diagnosed DIPG
Cohort without re-RT (n=54)
Cohort with re-RT (n=46)
(n=100 or 54+46)

Systemic therapy after re-RT (n=6)
Neoadjuvant chemotherapy before RT (n=2)
More than 2 courses of RT (n=2)
Re-RT of craniospinal axis re-RT (n=1)
Death before onset of re-RT (n=1)
(n=100-15=85 or 54 + 31)

Upfront RT
(n=85 or 54+31)

Progression from end of RT < 90 days (n=15)
(n=85-15=70 or 39+31)

Progression from end of upfront RT
≥ 90 days
(n=70 or 39+31)

BSC
(n=20)
ST
(n=19)
re-RT
(n=16)
re-RT + ST
(n=15)

BSC: Best Supportive Care; ST: Systemic Therapy; re-RT: re-irradiation

Fig. 1. Flowchart.

Fig. 2. Kaplan–Meier curves with progression-free survival (Fig. 2A) and overall survival (Fig. 2B) from diagnosis for patients with (n = 31) and without (n = 39) re-irradiation at first progression.
Fig. 3. Kaplan–Meier curves with survival measured from first progression, by interval duration between end of upfront radiotherapy and re-irradiation (Fig. 3A: 90–180 d; Fig. 3B: 180–360 d), treatment regimen (Fig. 3C; BSC, best supportive care; ST, systemic therapy; re-RT, re-irradiation), and age (Fig. 3D; cut-off: <10 versus >10 years).

Table 2
Survival from first progression: univariable and multivariable analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>$P$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 versus &lt;10</td>
<td>1.01 (0.95–1.08)</td>
<td>.75 NS</td>
</tr>
<tr>
<td>TTP (days from end upfront RT till progression)</td>
<td>0.18 (0.09–0.36)</td>
<td>&lt;.0001 .50 (0.24–1.05)</td>
</tr>
<tr>
<td>90–180 versus &lt;90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;180 versus &lt;90</td>
<td>0.07 (0.03–0.16)</td>
<td>&lt;.0001 .22 (0.10–0.51)</td>
</tr>
<tr>
<td>Upfront RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>0.88 (0.57–1.36)</td>
<td>.56 NS</td>
</tr>
<tr>
<td>versus hypofractionation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + ST versus RT + BSC</td>
<td>0.17 (0.09–0.33)</td>
<td>&lt;.0001 .24 (0.12–0.49)</td>
</tr>
<tr>
<td>RT + re-RT versus RT + BSC</td>
<td>0.13 (0.06–0.26)</td>
<td>&lt;.0001 .18 (0.08–0.38)</td>
</tr>
<tr>
<td>RT + re-RT + ST versus RT + BSC</td>
<td>0.10 (0.05–0.21)</td>
<td>&lt;.0001 .14 (0.07–0.31)</td>
</tr>
</tbody>
</table>

Abbreviations: BSC, best supportive care; CI, confidence interval.
typical disease course for DIPG, responding to upfront radiotherapy and undergoing re-irradiation. Symptom improvement was observed in nearly 80% of patients.

The benefit of re-irradiation in this SIOP-E cohort confirms earlier publications with small patient numbers [4–7]. Fontanilla et al. [5] first described the feasibility of re-irradiation in combination with different systemic agents in six patients with disease progression after upfront radiotherapy (54.0–55.8 Gy), and salvage chemotherapy. Clinical improvement in symptoms was observed in 4 out of 5 patients receiving the prescribed total dose of 18.0–20.0 Gy in 2.0 Gy daily fractions, given 8 to 28 (median 13) months after upfront radiotherapy. Wolff et al. [6] conducted a retrospective chart review of 31 patients with recurrent DIPG, including the patients described by Fontanilla et al. Patients were treated with various therapy elements in several combinations and treatment attempts. The most relevant clinical finding in this review was a partial response and a prolonged event-free survival of 3.9 months in four out of seven patients undergoing re-irradiation (P = .02). However, the results of the study of Wolff et al. should be interpreted with caution since the interval between upfront radiotherapy and re-irradiation was atypically long for DIPG, all therapies were combined, and no control group was available. In the study of Massimino et al. [7], eleven out of sixteen locally progressing patients underwent re-irradiation at the first progression (19.8/1.8 Gy) after initial radiotherapy (54.0/1.8 Gy) combined with nimotuzumab and vinorelbine. Median OS was 16 months compared with 12 months for the five children with local progression not undergoing re-irradiation (P = .03). Neurological improvement was seen in the majority of patients. More recently, Vanan et al. [4] published data on ten patients with progressive DIPG treated with re-irradiation (dose ranges between 21.6 and 36.0/1.8 Gy) across different centres in Canada. The median time from diagnosis to first progression of 12 months also suggests some patient selection. Nevertheless, neurological improvement was observed in all but one patient on re-irradiation.

The current analysis demonstrates that a conventionally fractionated radiotherapy dose of 20.0 Gy at the time of progression is sufficient to observe a clinical response in the majority of patients responding to upfront radiotherapy. This is not surprising given the early clinical response frequently observed after a small number of fractions during upfront radiotherapy [1–3]. However, the observation demonstrates that, despite the aggressive nature of DIPG, the tumour remains sensitive for radiotherapy. The latter is of utmost importance in a disease like DIPG, since the selection of the lowest potential radiotherapy dose with a clinical effect equal to any higher dose, can offer options for future trials focussing on re-irradiation to improve OS.

No severe neurotoxicity related to re-irradiation was recorded in our study. Similar observations were made by other investigators [4–7]. Re-irradiation of the brainstem after initial high-dose radiotherapy can be associated with significant, potentially lethal, toxicity. The risk of radiation-induced necrosis of the brainstem and surrounding nervous tissue is related to the initial radiotherapy dose, the dose per fraction, the interval between both radiotherapy courses, the re-irradiation

Fig. 4. Survival prediction model. Based on the risk score (RS) 5 categories were identified. Increasing numbers correlate with better survival from first progression.
dose, the radiotherapy volume, as well as the combination with systemic agents [12–15]. Radiation necrosis after conventionally fractionated radiotherapy is typically observed three to twelve months after the treatment, but can occur up to several years after radiotherapy [15]. As our survival prediction model demonstrates, re-irradiation may be an acceptable risk for children with DIPG, whose survival time is expected to be short. Nevertheless, we recommend a total re-irradiation dose around 20.0 Gy in daily fractions of 1.8–2.0 Gy to the gross tumour volume with a small margin of .5 cm, delivered by a highly conformal technique to reduce the potential risk of brain necrosis.

Molecular profiling studies over the recent years have provided meaningful insight into DIPG biology, hallmarked by the discovery of histone 3 K27M-mutations as a pathognomonic feature of DIPG [16]. Given the presence of these mutations in high-grade gliomas occurring in other midline structures, this has led to a new diagnostic category of ‘diffuse midline glioma, H3 K27M-mutant’ in the revised 4th edition of the WHO classification of tumours of the central nervous system [17]. In the largest series of DIPG analysed for H3 K27-mutations so far, the specific type of mutation was suggested to define two subgroups of DIPG with different prognosis and phenotypes [18]. The age (and gender) distribution of the cohort presented here do not suggest an imbalance of H3 mutations between patients undergoing re-irradiation or not. However, the now well-established prospective assessment of H3 mutational status will facilitate to evaluate the role of re-irradiation in a subgroup-specific manner within biology-driven trials.

By using stringent eligibility criteria, resulting in a similar progression-free survival between both cohorts after upfront treatment, potential bias introduced by the retrospective character of this study has been reduced to a minimum. As demonstrated in the flowchart, fifteen patients with DIPG did not fulfil the eligibility criteria.Combining both 31 patients, fulfilling the eligible criteria, with 15 patients, excluded for a number of reasons, results in a median OS of 16.2 months. This observation demonstrates the importance of stringent eligibility criteria for DIPG in order not to overestimate the role of a new treatment, in particular re-irradiation (Figs. S1 and S2). However, the impact of pseudo-progression and steroid use on survival is more difficult to demonstrate. Pseudo-progression, advocated as a predictor of improved survival, especially when re-irradiation is performed in the window 3–6 months after upfront radiotherapy, cannot be excluded. Criteria for disease progression used in the cohort with/without re-irradiation were identical, implying a similar chance of pseudo-progression. In both cohorts median OS of patients, assumed to have disease progression between 4 and 6 months, is inferior compared with patients with progression 6–12 months after upfront radiotherapy.

Although pseudo-progression is not excluded based on this observation, its impact on outcome is probably reduced to a minimum. Concern about steroid use is inevitable in lack of guidelines. Clinicians, even within the same department and the same era, avoid or prefer steroids for many reasons, just like patients do. The latter is recently demonstrated by Veldhuijzen van Zanten et al. [19].

Stronger argumentation comes from the fact that re-irradiation remains an independent prognostic factor for OS even after correction for different approaches at disease progression. Attempts to establish a prospective randomised trial within the SIOP-E community failed due to ethical, political and financial reasons. Meanwhile, an international DIPG-registry was created recently to accomplish improved understanding of new approaches and biology. This tool will provide a database of demographic, clinical, radiologic, pathologic, and molecular data. More than ever before, quality-of-life should be monitored to determine whether the benefit of OS compensates for treatment-related burden.

5. Conclusion

This matched-cohort analysis demonstrates a significant benefit in median OS of 3.4 months for patients with DIPG, responding to upfront radiotherapy, and undergoing re-irradiation at the first progression. Symptom improvement was observed in nearly 80% of the patients. According to SIOP-E recommendations, re-irradiation of children with DIPG at the first progression can be considered when eligibility criteria are fulfilled and radio-necrosis after upfront radiotherapy is excluded.

Role of contributors

GJ, LG, CK participated in the concept and design of the study. GJ, LG, SB, HM, MRA, KB, HB, BH, AMM, RK, DH, JM, EP, VB, AB, DV, CK were responsible for the acquisition of data. Quality control of data and algorithms was done by GJ and MP. Statistical analysis was done by MP. GJ, LG, MM, DS, MP, CK participated in the analysis and interpretation of the data. Manuscript preparation and editing was done by GJ and GJ + MP, respectively. All authors reviewed and approved the final version of the report.

Conflict of interest statement

Henry Mandeville was supported by the National Institute of Health Research/Biomedical Research Centre at The Royal Marsden NHS Foundation Trust, Sutton. Darren Hargrave was supported by the National Institute for Health Research/Biomedical Research Centre at Great Ormond Street Hospital for Children, NHS Foundation Trust, and University
College London. The remaining authors have no conflicts of interest to disclose.

Funding

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.12.007.

References

Clinical Investigation

Reirradiation for Recurrent Pediatric Central Nervous System Malignancies: A Multi-institutional Review

Avani D. Rao, MD,* Arif S. Rashid, MD,* Qinyu Chen, MHS,* Rosangela C. Villar, MD,† Daria Kobyzeva, MD,‡ Kristina Nilsson, MD, PhD,§ Karin Dieckmann, MD,‖ Alexey Nechesnyuk, MD,‡ Ralph Ermoian, MD,‖ Sara Alcorn, MD,* Shannon M. MacDonald, MD,* Matthew M. Ladra, MD,* Eric C. Ford, PhD,¶ Brian A. Winey, PhD,# Maria Luís S. Figueiredo, MD,** Michael J. Chen, MD,** and Stephanie A. Terezakis, MD*

*Department of Radiation and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center Johns Hopkins School of Medicine; †Department of Radiation Oncology, Centro Infantil Boldrini, São Paulo, Brazil; ‡Department of Radiation Oncology, Federal Research and Clinical Centre of Pediatric Hematology, Oncology and Immunology, Moscow, Russia; §Department of Radiation Oncology, Uppsala University Hospital, Uppsala, Sweden; ¶Department of Radiation Oncology, Universität Klinik für Strahlentherapie und Strahlenbiologie, Wien, Germany; ‖Department of Radiation Oncology, University of Washington, Seattle, Washington; #Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts; and **Department of Radiation Oncology, Grupo de Apoio ao Adolescente e à Criança com Câncer, São Paulo, Brazil

Received Apr 1, 2017, and in revised form Jun 13, 2017. Accepted for publication Jul 22, 2017.

Summary
The treatment parameters, toxicity, and outcomes of pediatric central nervous system reirradiation were evaluated through a multinational, multi-institutional pediatric research consortium. Low rates of

Purpose: Reirradiation has been proposed as an effective modality for recurrent central nervous system (CNS) malignancies in adults. We evaluated the toxicity and outcomes of CNS reirradiation in pediatric patients.

Methods and Materials: The data from pediatric patients <21 years of age at the initial diagnosis who developed a recurrent CNS malignancy that received repeat radiation therapy (RT) across 5 facilities in an international pediatric research consortium were retrospectively reviewed.

Results: Sixty-seven pediatric patients underwent CNS reirradiation. The primary diagnoses included medulloblastoma/primitive neuroectodermal tumor (n = 20; 30%),

Reprint requests to: Stephanie A. Terezakis, MD, Department of Radiation and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, 401 N Broadway, Suite 1440, Baltimore, MD 21231-2410. Tel: (410) 287-7889; E-mail: sterezak@jhmi.edu

Drs. Rao and Rashid are co-first authors who contributed equally to design, data collection, and manuscript preparation for this work.

Conflict of interest: none.

0360-3016/$ see front matter © 2017 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ijrobp.2017.07.026
radiosensitive than are adults. Thus, this population merits
growth and development, children are inherently more
long-term side effects. Furthermore, given their ongoing
ancies and, thus, are more vulnerable to experiencing
for longer term survival with many pediatric CNS malig-
malignancies (6-10). Younger patients have the possibility
regarding reirradiation in children with recurrent CNS
patients (2-5); however, a paucity of data is available
diation in recurrent CNS malignancies for adult oncology
recurrent CNS disease in pediatric oncology patients.

Several studies have demonstrated the utility of reirra-
diation in recurrent CNS malignancies for adult oncology
patients (2-5); however, a paucity of data is available
regarding reirradiation in children with recurrent CNS
malignancies (6-10). Younger patients have the possibility
for longer term survival with many pediatric CNS malign-
nancies and, thus, are more vulnerable to experiencing
long-term side effects. Furthermore, given their ongoing
growth and development, children are inherently more
radiosensitive than are adults. Thus, this population merits

distinct and careful consideration for toxicity concerns and
efficacy of CNS reirradiation.

Currently, few studies have investigated the main factors
determining tolerance to CNS reirradiation in the pediatric
population, such as total dose, volume of brain reirradiated,
fraction size, use of chemotherapy, and patient age at
reirradiation (11). The present study is a unique study that
evaluated the treatment parameters, toxicity, and outcomes
of pediatric CNS reirradiation through a multinational,
multi-institutional pediatric research consortium to aid in
the determination of whether the potential benefits
outweigh the potential toxicities of repeat RT.

Methods and Materials

Patient selection

Sixty-seven pediatric patients with primary CNS malign-
nancies diagnosed at age <21 years had been treated
initially with definitive intent by surgery and RT. These
patients had developed recurrent CNS disease and had
undergone repeat RT after progression in or near the site
of initial RT and were identified for an institutional review
board-approved retrospective study. The patients had come
from 5 RT facilities with expertise in pediatric oncology.
The RT data were gathered for analysis as a part of a
multinational, multi-institutional pediatric research con-
sortium. The initial RT had been delivered as early as 1993,
with the most recent patient receiving repeat RT in 2016.

The review of patient information included date of birth,
diagnosis, location of mass, performance status at the first
treatment, extent of initial surgical resection, initial RT

Introduction

Nearly 8000 cases of pediatric cancers are diagnosed in the
United States every year, and approximately 20% of child-
hood malignancies are primary brain tumors (1). Radiation
therapy (RT) has been the mainstay of treatment, along, and
often in combination, with surgery and chemotherapy.
However, 30% to 40% of children with primary brain tumors
will develop recurrence in the central nervous system (CNS).
Because of the fear of cumulative CNS toxicity, in particular,
concerns of the effects after cranial irradiation in the pediatric
population, salvage surgery and chemotherapy are the most
frequently preferred initial treatment options.

Frequently, recurrent CNS malignancies are difficult to
fully treat with surgery alone given the presence of micro-
scopic tumor spread. Moreover, chemotherapy alone is also
unable to adequately control most childhood brain tumors
(1). With modern developments in RT delivery, more precise
radiation techniques, including stereotactic radiosurgery
(SRS) and intensity modulated RT (IMRT), have provided
the potential for reirradiation to be reasonably considered for
recurrent CNS disease in pediatric oncology patients.

Several studies have demonstrated the utility of reirradi-
ation in recurrent CNS malignancies for adult oncology
patients (2-5); however, a paucity of data is available
regarding reirradiation in children with recurrent CNS
malignancies (6-10). Younger patients have the possibility
for longer term survival with many pediatric CNS malign-
nancies and, thus, are more vulnerable to experiencing
long-term side effects. Furthermore, given their ongoing
growth and development, children are inherently more
radiosensitive than are adults. Thus, this population merits

Conclusions: CNS reirradiation in pediatric patients could be a reasonable treatment
option, with moderate survival noted after repeat RT. However, prospective data
characterizing the rates of local control and toxicity are needed. © 2017 Published
by Elsevier Inc.
timing, dose, and technical parameters, chemotherapy details, late toxicities due to initial RT, date of imaging confirmation of CNS progression, extent of second surgical resection, salvage chemotherapy details, performance status at recurrence, reirradiation timing, dose, and technical parameters, late toxicities due to reirradiation, and survival and recurrence outcomes. Data were collected separately at the respective treating institutions and analyzed centrally. First progression in the present series was defined by radiographic progression in or near the site of initial RT, including the detection of secondary neoplasms in the 5 patients found to have pathologically distinct tumors from their initial diagnosis that were treated with a second RT course.

### Treatment techniques

The initial treatment approaches were driven by the standard of care of the treatment era and the experience and resources available at each site. The patients were followed up for symptoms. Surveillance imaging such as computed tomography or magnetic resonance imaging was obtained at the discretion of the individual treatment teams at each participating institution.

After radiographic evidence of recurrent CNS malignancy, the patients were offered surgical resection at the discretion of the participating institution’s expert neurosurgeon’s assessment of feasibility and utility. All patients in the study subsequently underwent reirradiation using 2-dimensional (2D) RT, 3-dimensional conformal RT (3D-CRT), IMRT, SRS, or proton therapy. Proton therapy, however, was only available at 1 center participating in the present study.

### Statistical analysis

Statistical analysis included descriptive statistics and Kaplan-Meier overall survival (OS) and local progression-free survival (LPFS) statistics, using log-rank tests to assess for differences between groups. OS was calculated from the initial diagnosis and from the end of the last fraction of repeat RT until death from any cause. If a patient did not die, the patient was censored at the last follow-up visit. LPFS after repeat RT was calculated from the end of the last fraction of repeat RT until evidence of second CNS progression in or near the site of repeat RT. Patients who did not experience second CNS progression or death were censored at the last follow-up visit.

### Results

### Patient characteristics

The patient characteristics for the entire cohort are listed in Table 1. Sixty-seven pediatric patients were treated with CNS reirradiation. Their median age at the initial diagnosis was 7.6 years (range 0.2-19.3). Of the 67 patients, 43 (64%) were male. The primary diagnoses included medulloblastoma/primitive neuroectodermal tumor (PNET) (n=20; 30%), ependymoma (n=19; 28%), germ cell tumor (n=8; 12%), high-grade III/IV glioma (n=9; 13%), low-grade II/III glioma (n=5; 7%), and other (n=6; 9%). The most common location for the primary CNS malignancy was the cerebellum (n=27; 40%). The median age at the first RT course and at repeat RT was 8.5 years (range 0.5-19.5) and 12.3 years (range 3.3-30.2), respectively.

### Details of initial therapy after diagnosis

The initial treatment details are summarized in Table 2. Of the 67 patients, 56 (84%) underwent surgical resection after the initial diagnosis. Resection included gross total resection in 24 patients (36%), subtotal resection in 26 patients (39%), and biopsy only in 6 patients (9%). All patients underwent RT as a part of their initial treatment paradigm. The median radiation dose in equivalent 2-Gy fractions (EQD2) was 63.7 Gy (range 27.6-74.8). The initial RT course was typically delivered using 3D-CRT (n=21; 31%) or IMRT or volumetric modulated arc therapy (VMAT) (n=27; 40%). The remaining RT courses were delivered using 2D conventional RT (n=10; 15%),

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>67</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td>7.6 (0.2-19.3)</td>
</tr>
<tr>
<td>Initial RT course</td>
<td>8.5 (0.5-19.5)</td>
</tr>
<tr>
<td>Repeat RT course</td>
<td>12.3 (3.3-30.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (36)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (64)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma/PNET</td>
<td>20 (30)</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>19 (28)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Grade II/III glioma</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Grade III/IV glioma</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Primary location</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Pineal gland</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Thalamus/hypothalamus</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Hippocampus/amygadala</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Meninges</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Orbit</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Abbreviations: PNET = primitive neuroectodermal tumor; RT = radiation therapy.
Table 2  Treatment details: initial therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%) or Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT technique</td>
<td></td>
</tr>
<tr>
<td>2D, conventional</td>
<td>10 (15)</td>
</tr>
<tr>
<td>3D, conformal</td>
<td>21 (31)</td>
</tr>
<tr>
<td>IMRT or VMAT</td>
<td>27 (40)</td>
</tr>
<tr>
<td>SRS</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Proton</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mixed modality</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (9)</td>
</tr>
<tr>
<td>RT prescription (Gy)</td>
<td></td>
</tr>
<tr>
<td>EQD2</td>
<td>63.7 (27.6-74.8)</td>
</tr>
<tr>
<td>Total dose</td>
<td></td>
</tr>
<tr>
<td># receiving &lt; 54 Gy</td>
<td>14 (21)</td>
</tr>
<tr>
<td># receiving ≥ 54 Gy</td>
<td>53 (79)</td>
</tr>
<tr>
<td>Dose/fraction</td>
<td>1.8 (1.0-20)</td>
</tr>
<tr>
<td>Total fractions</td>
<td>30 (1-68)</td>
</tr>
<tr>
<td>Chemotherapy status</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Pre- and post-RT only</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Post-RT only</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Pre-RT only</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Pre-RT and concurrent only</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Concurrent only</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Concurrent and post-RT</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Pre-RT, concurrent, and post-RT</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Craniospinal RT</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42 (63)</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (37)</td>
</tr>
<tr>
<td>Anesthesia required for immobilization</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43 (64)</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (36)</td>
</tr>
</tbody>
</table>

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; EQD2 = equivalent dose in 2-Gy fractions; IMRT = intensity modulated radiation therapy; RT = radiation therapy; VMAT = volumetric modulated arc therapy; SRS = stereotactic radiosurgery.

Mixed modality (n = 2; 3%), SRS (n = 1; 1%; 20 Gy × 1). The initial RT technique was unknown for 6 patients (9%). Thirty-four patients (51%) received concurrent chemotherapy with initial RT. Further details of chemotherapy sequencing are included in Table 2.

Details of repeat therapy after CNS recurrence

The median interval from initial RT to imaging evidence of CNS recurrence was 1.7 years (range 0.1-16.0). The median interval from initial RT to repeat RT was 2.0 years (range 0.3-16.5). The relapse location was infield in 52 patients (78%) and surrounding initial RT field in 15 patients (22%). The treatment intent was defined as radical or curative for 51 patients (76%). Forty-five patients (67%) underwent surgical resection after CNS recurrence, with 17 patients (25%) undergoing gross total resection, 22 patients (33%) subtotal resection, and 6 patients (9%) undergoing biopsy only.

The median prescription dose in EQD2 at reirradiation was 53.1 Gy (range 18.6-70.1). IMRT/VMAT (n = 46; 69%) was used in a larger proportion of repeat RT courses. Fewer patients were treated with 2D-CRT (n = 1; 1%) at reirradiation than at the initial RT course. Proton therapy was used for 4 cases (6%) of repeat RT. The SRS doses were 12 to 13 Gy × 1 or 5 Gy × 5. Thirty-four patients (51%) received concurrent chemotherapy with repeat RT. Further details of chemotherapy sequencing are included in Table 3.

Toxicity of initial and repeat CNS RT

Radiation necrosis was detected in 2 cases (3%) after the first RT course and 1 additional patient (1%) after reirradiation (Table 4). The 2 patients with radionecrosis after initial RT had both been diagnosed with an ependymoma, treated to 54 Gy and 55.8 Gy in 1.8-Gy fractions, respectively. The first patient was fully asymptomatic from this

Table 3  Treatment details: second radiation therapy course

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%) or Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT technique</td>
<td></td>
</tr>
<tr>
<td>2D, conventional</td>
<td>1 (1)</td>
</tr>
<tr>
<td>3D, conformal</td>
<td>9 (13)</td>
</tr>
<tr>
<td>IMRT or VMAT</td>
<td>46 (69)</td>
</tr>
<tr>
<td>SRS</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Proton</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Mixed modality</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>RT prescription (Gy)</td>
<td></td>
</tr>
<tr>
<td>EQD2</td>
<td>53.1 (18.6-70.1)</td>
</tr>
<tr>
<td>Total dose (Gy)</td>
<td>45 (12-59.4)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td># receiving &lt; 54 Gy</td>
<td>46 (69)</td>
</tr>
<tr>
<td># receiving ≥ 54 Gy</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Dose/fraction (Gy)</td>
<td>1.8 (1.5-13)</td>
</tr>
<tr>
<td>Total fractions</td>
<td>25 (1-33)</td>
</tr>
<tr>
<td>Chemotherapy status</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Pre- and post-RT only</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Post-RT only</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Pre-RT only</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Pre-RT and concurrent only</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Concurrent only</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Concurrent and post-RT</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Pre-RT, concurrent, and post-RT</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Craniospinal RT</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53 (79)</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Anesthesia required for immobilization</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61 (91)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; EQD2 = equivalent dose in 2-Gy fractions; IMRT = intensity modulated radiation therapy; RT = radiation therapy; VMAT = volumetric modulated arc therapy; SRS = stereotactic radiosurgery.
radiographic diagnosis of radionecrosis 3 months after initial RT; however, the tumor appeared slightly enlarged and more heterogeneous, suggestive of necrosis. The patient did not receive any additional medical therapy for this radiographic finding. Three years after the initial RT, the patient required repeat RT to 54 Gy for frank tumor progression. The second patient had developed eye strabismus at the time of diagnosis of radionecrosis 5 months after initial RT. The tumor appeared slightly more enlarged and more heterogeneous, suggestive of necrosis. The patient was treated with a course of high-dose steroids with improvement; however, 2.7 years after initial RT, the patient required repeat RT to 54 Gy for tumor progression. The 1 patient who developed radionecrosis after repeat RT was initially treated to 54 Gy and then received stereotactic body RT to 25 Gy in 5 fractions and developed concerning radiographic changes, seizures, edema, and somnolence. Two months after treatment, the patient developed progressive disease throughout the brainstem; therefore, the diagnosis of progression versus radionecrosis was unclear but was considered radionecrosis for the purposes of the present study. This patient received high-dose steroids for management but died 6 months later of tumor progression.

Six patients (9%) developed secondary neoplasms after initial RT; including 1 patient who developed a hematologic malignancy and 5 who developed second intracranial neoplasms. Of the 5 intracranial neoplasms, 1 was a benign meningioma and 4 were malignant tumors, including 1 aggressive fibrosarcoma, 2 high-grade gliomas, and 1 ethmoid sinus/orbital wall osteosarcoma in a patient with hereditary bilateral retinoblastoma. One patient developed a secondary malignancy identified shortly after the second RT course after initial treatment of biopsy proven PNET requiring repeat RT 7 years later for biopsy-confirmed progression of PNET. However, 3 months after reirradiation, the patient developed progression in the radiation bed, with biopsy showing astrocytoma, and the findings from autopsy pathology review suggesting this was a secondary malignancy from the initial RT course.

One patient experienced leukoencephalopathy after reirradiation. Endocrine dysfunction requiring replacement therapy was noted in 15 patients (22%) after initial RT and an additional 3 patients (4%) after repeat RT.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>After initial RT n (%)</th>
<th>After repeat RT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radionecrosis</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
<td>15 (22)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Secondary neoplasm</td>
<td>6 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infield Intracranial solid tumor</td>
<td>5 (7)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Abbreviation: RT = radiation therapy.

Discussion

The prognosis of recurrent pediatric CNS tumors is poor, and the options for treatment are limited. Reirradiation in pediatric patients has not been well-studied given the heterogeneity of the patient population and concerns for late toxicity. Recent advancements in radiation technique yielding IMRT and SRS now allow for improved sparing of normal tissues and, subsequently, reduce toxicities, opening avenues for reirradiation. The present study combined the experience of 5 centers as part of a multinational consortium with expertise in pediatric radiation oncology, aggregating the experience of CNS reirradiation to better delineate the toxicities, feasibility, and potential efficacy of repeat RT for recurrent pediatric CNS malignancies.

Studies are emerging of the adult population demonstrating the potential utility of reirradiation of CNS tumors. In a study by Fogh et al. (12), high-grade gliomas were effectively treated with hypofractionated SRS, with evidence of a survival benefit when controlled for resection and chemotherapy use, with acceptable tolerability. These promising data from the adult population argue for the need for further prospective studies and clinical trials to explore the value of pediatric CNS reirradiation.

The principle concern with CNS reirradiation is the risk of radiation necrosis. As an irreversible delayed reaction, it is potentially fatal (13). Radiation necrosis rates were found to be low in our cohort, with a total of 3 cases observed, 2 after the initial RT course and 1 after repeat RT, for a crude rate of radionecrosis of 4.5% overall and 1.5% after reirradiation. Although these data are roughly in-line with rates measured from other studies of radionecrosis, one
Fig. 1. Survival curves for pediatric patients treated with repeat central nervous system radiation therapy. Kaplan-Meier curves demonstrating the median overall survival for the entire cohort from (A) initial diagnosis (96.4 months, 95% confidence interval [CI] 62.0-130.8) and (B) end of repeat radiation therapy (12.8 months, 95% CI 2.7-22.9). (C) Overall survival from end of repeat radiation therapy was stratified according to dose of repeat radiation therapy as equivalent 2-Gy fractions (EQD2) <53.1 Gy or >53.1 Gy (9.0 months, 95% CI 2.4-15.5, vs 14.2 months, 95% CI 0.6-27.8; \( P = .023 \)). Overall survival of the subgroups of patients with (D) medulloblastoma (8.4 months, 95% CI 0-18.1) and (E) ependymoma (20.5 months, 95% CI 6.0-35.0) and (F) local progression-free survival of the whole cohort (7.9 months, 95% CI 5.1-10.7) from end of repeat radiation therapy are shown.

The limitation of the present study was the lack of central radiology review owing to logistic limitations given the multinational, multi-institutional nature of the present study. Ruben et al. (14) reviewed the data from 426 patients who underwent conventional cranial RT, 56 of whom required a second RT course (51 with SRT), for a crude rate of 4.9%, an actuarial incidence of 13.3% after 3 years. The total dose, fraction size, and chemotherapy type were significant factors in the development of necrosis (14). Although the study was one of the largest to characterize these factors associated with the development of radionecrosis, the investigators concluded that the low incidence hindered the development of a robust predictive model for radionecrosis development.

In our study, highly conformal radiation techniques were frequently used in the reirradiation setting. Although IMRT/VMAT and SRS were used in fewer than one half of the initial RT cases, IMRT and SRS were used in a significant majority (75%) of reirradiation cases, likely owing to the clinicians’ desire to limit the irradiated volume of normal tissues. Laboratory and clinical investigation have provided some idea regarding dose and volume effects in the CNS. Studies investigating radiation tolerance and recovery with respect to myelopathy and occult injury in rhesus monkey spinal cords have suggested an intrinsic ability for CNS tissue to recover a significant amount within 2 years (15, 16). This was the same interval as the median interval from initial RT to repeat RT in our study. However, the extrapolation of this observed tissue recovery in animal models to clinical treatment scenarios is not well defined. Mayer and Sminia (4) reported 21 brain reirradiation studies and normalized the findings using the biologically effective dose. The present study found that highly conformal techniques allowed for treatment of smaller reirradiation volumes to higher doses compared with conventional RT techniques without an increase in radionecrosis rates. No correlation was found between the interval between the initial and reirradiation course and the incidence of radionecrosis. They concluded that radionecrosis occurs at cumulative doses >100 Gy when the total dose is normalized in 2-Gy fractions. However, occurrence is detected only in cases of even greater cumulative doses when highly conformal RT was used. In our study, patients requiring repeat RT were more likely to receive highly conformal techniques, and the median EQD2 dose at reirradiation was less compared with the median
dose at initial RT. Given the data by Mayer and Sminia (4) suggesting that it might be possible to deliver higher radiation doses with fractionated SRS without a significantly increased risk of radionecrosis, it is possible that some of our subjects could have been treated more aggressively to high doses at reirradiation without increased toxicity. Further investigation is needed into precisely defining normal tissue tolerances in the case of reirradiation. This will require more studies with composite dosimetry from initial and repeat RT courses to assess for associations between complications and spatial and dose-volume histogram dosimetry data. Albeit small numbers, our data suggest that patients receiving higher doses at repeat RT had improved survival. It is, thus, important to determine these dose thresholds, given the desire to minimize the risk profile but deliver higher doses at repeat RT.

Our collaborative study of combined histologic findings is comparable to a single-institutional study by Bauman et al. (5). They retrospectively reviewed the data from 34 patients with primary brain tumors retreated with fractionated external beam irradiation from 1977 to 1993. Their study reported only modest palliative and survival benefits with progression-free survival of 3.3 months, OS of 8.3 months, and a crude radionecrosis rate of 9% after repeat RT for recurrent CNS malignancies (5). Our results compare favorably across all metrics with previously published data, possibly because of improving radiation techniques and patient selection. Furthermore, our cohort featured a considerable proportion of ependymomas with a known favorable prognosis compared with other common CNS tumors. A smaller, more recent study by Chojnacka et al. (7) reported a series of 8 patients treated from 2008 to 2009 with repeat RT to a dose of 40 Gy, conventionally fractionated, delivered using 3D-CRT. The OS and progression-free survival were 17.5 and 6.5 months, respectively, without long-term complications. Although a smaller series, the favorable numbers and lower rate of toxicity are encouraging and likely reflect improvements in technique.

Subgroup analysis of our cohort demonstrated that repeat RT might be particularly beneficial in patients with recurrent ependymomas. We found an OS from end of repeat RT of 20.5 months in patients with recurrent ependymomas compared with 8.4 months in patients with recurrent medulloblastoma. Previous studies have suggested a benefit to repeat RT for recurrent ependymomas. Merchant et al. (10) reported durable tumor control after reirradiation in patients with locally recurrent ependymoma undergoing focal fractionated reirradiation. Bouffet et al. (8) retrospectively reviewed 47 patients with recurrent ependymomas treated with full-dose reirradiation, for an OS rate at 3 years of 81% without significant toxicity. The investigators concluded that reirradiation could dramatically alter the natural history of recurrent ependymomas. The study also noted differences in γH2AX expression that correlated with differences in survival. Recent series have shown promising results in reirradiation of recurrent medulloblastoma. Bakst et al. (9) reported an institutional series of 13 patients treated with reirradiation, 44% of whom received aggressive multimodality therapy, including high-dose chemotherapy and autologous stem cell transplantation. Of the patients, 46% were long-term survivors without evidence of disease >5 years after treatment. Similar promising outcomes have been reported in a study by Wetmore et al. (17) in which significant improvement was found in OS in both relapsed standard-risk and high-risk medulloblastoma patients treated with reirradiation compared with those who did not receive repeat RT.

Our findings should be considered in comparison with other salvage therapy options for relapsed pediatric brain tumors. Systemic therapy regimens have been used with varying success. Gururangan et al. (18) reviewed their experience treating 30 patients with recurrent medulloblastoma with high-dose chemotherapy with or without RT or standard salvage chemotherapy. The investigators reported poor outcomes in the standard salvage chemotherapy cohort, although it is likely that patients with a worse prognosis were selected for the standard regimens. A Children’s Oncology Group (19) study investigating myeloablative chemotherapy in recurrent malignant astrocytoma demonstrated cases of durable remission; however, these cases were more likely to have undergone surgical debulking. Nineteen percent of patients died of toxicity from the regimen. It is likely that future investigations will consider systemic therapy and RT and their possible synergistic and/or cumulative effects and toxicity profiles in tailoring multimodality therapy for recurrent pediatric brain tumors.

The limitations of the present study included its retrospective nature, which hindered our ability to obtain detailed previous RT records, including Digital Imaging and Communications in Medicine data. The latter would have been useful for reporting the total dose to areas of overlap and any associations between the dose and areas of radionecrosis or secondary malignancy development after the first or second RT courses. Additionally, given the limited number of patients in the present study, we are unable to identify the clinical benefit for particular subgroups. Future studies should prospectively outline enrollment of specific histologic diagnoses to create a more homogenous study group to better understand which patients would benefit from reirradiation. Repeat RT should also be separately investigated as part of multimodality therapy. Diligent efforts to spatially resolve the dose distributions to critical structures such as the brainstem and optic apparatus on initial and repeat RT courses will be instrumental in better defining the tolerance of these structures to reirradiation.

Conclusion

CNS reirradiation in pediatric patients could be a reasonable considered as a treatment option with reasonable survival rates to justify its use. Prospective data are warranted
for this group of patients with a poor prognosis to validate the clinical outcomes and to assess the risks for serious toxicities or futility of treatment.

References

Junio 2018 – REIRRADIACIÓN TUMOR INTRÍNSECO DE TRONCO DIPG

1.- DESCRIPCIÓN DEL CASO

Paciente de 9 años con diagnóstico, en octubre del 2016, de tumor intrínseco de tronco (DIPG) tras biopsia, con resultado de glioma difuso alto grado H3F3A K27M+. Fue tratado con RT con dos volúmenes: uno más amplio intentando abarcar la lesión en T2/FLAIR con margen hasta 54 Gy y luego la zona captante a la que solo se pudo llegar a 56 Gy (previsto 60 Gy) + Temodal concomitante que finaliza en enero 2017 y adyuvante, que continua hasta el momento actual (junio 2018).

Tiene una respuesta clínica casi completa con desaparición de los déficits pretratamiento, excepto la parálisis de los óculo-motores y radiológica con reducción del tumor más del 90% (máxima respuesta en mayo 2017) y luego estabilización.

Ha realizado vida normal incluso con excelente resultado escolar. A finales de marzo de 2018 se objetiva progresión radiológica sin progresión clínica y nos planteamos reirradiación, decidiéndose no realizarla ante la no progresión clínica (comente el caso con el Dr. Giralt).

Actualmente, leve progresión clínica (hace vida normal y según la madre esta como siempre) y en RMN progresión radiológica.

2.- DUDA CONSULTADA

Las preguntas son:

• Ante la progresión radiológica, en RMN, si nos planteamos reirradiar, supongo que estás de acuerdo en no confirmar la progresión por otras pruebas tipo PET, etc, al bastar con la progresión radiológica.

• Por otro lado si nos planteamos reirradiar, incluir toda la zona de T2/Flair que ha aumentado y la mínima zona captante, o solo la captante. La propuesta de dosis es 20 (máximo 24 Gy) con fraccionamiento de 1,8 Gy.

• Finalmente, ante la mínima progresión clínica, tratamos ya o esperamos a mayor progresión clínica (la madre es consciente del riesgo de reirradiación y le da miedo los efectos secundarios al ver tan bien a su hija).
3.- RESPUESTAS

➢ Nosotros reirradiamos los DIPG, si han pasado más de 6 meses desde la primera RT, si hubo beneficio sintomático y radiológico y si el paciente tiene síntomas. Utilizamos fraccionamiento convencional y le damos 30,6 Gy en sesiones de 1,8 Gy. Yo creo que en tu caso la decisión difícil es decidir si irradiar ahora o cuando empiece a tener síntomas. En mi opinión (y no se basa en nada científico), esperaría a tener síntomas que mejorar. Y el volumen, incluiría lo que el neuroradiólogo define como tumor, aunque el volumen sea amplio. Tratar dejando zonas fuera, me parece poco lógico, cuando ya has decidido tratar y asumir las complicaciones. Os adjunto bibliografía. (Dra. Carmen González)

➢ Esperaría a reirradiar ante una progresión clínica más evidente que la que describes. Es muy probable que este planteamiento no afecte a la supervivencia. Mientras intentaría contactar con Oncohematología Pediátrica (Lasaleta por ejemplo en el Niño Jesús de Madrid) por si pudieran ofrecer algo más. (Dr. Raúl Matute)

➢ Esperaría para la reirradiación a una progresión clínica clara. Nosotros en nuestro centro reirradiamos (20 Gy en 10 fr) cuando hay clínica y si ha tenido respuesta a la primera RT con una duración de al menos 6 meses. En los casos que hemos tratado no hemos observado de momento complicaciones de la reirradiación y lo que se puede obtener de beneficio es una mejoría sintomática paliativa, por eso pienso que tiene más sentido asumir el riesgo cuando hay síntomas de nueva aparición. Respecto al volumen de reirradiación, yo haría únicamente el GTV (lo que en RM sea definido como tumor) + el margen del PTV claro. (Dra. Mónica Albiach)

➢ Esperaría como el resto de compañeros a que la niña progresara clínicamente para reirradiar. También como ha comentado otro compañero hablaría con Oncología Pediátrica para buscar otra posible alternativa. Nosotros tratamos hace ya algunos años un
niño con Nimotuzumab asociado a Temozolamida tras progresión a RT, con buena respuesta inicial clínica y radiológica. (Dra. Sonia García)

➢ N prominentemente esperamos a la progresión clínica para reirradiar (Dra. Patricia Cabrera)

4.- CONCLUSIÓN

La reirradiación en el DIPG puede ser factible para mejorar los síntomas y retrasar la progresión con toxicidad mínima.

Los pacientes que tienen más probabilidades de beneficiarse son aquellos con Respuesta al tratamiento inicial y un largo intervalo desde la radiación inicial.

La decisión de la reirradiación sería cuando el paciente tiene empeoramiento clínico evidente y no solo cuando hay empeoramiento radiológico, puesto que el objetivo principal de este tratamiento es sintomático. En este sentido la serie de 31 pacientes del Grupo de trabajo DIPG de la SIOP-E (European Journal of Cancer 73 (2017) 38-47) consideran progresión de la enfermedad como un deterioro clínico (neurológico) con necesidad de reutilización de esteroides o aumento de la dosis, confirmado por resonancia magnética.

En cuanto a las pruebas radiológicas, en la bibliografía el crecimiento y el diseño de los volúmenes de tratamiento se basan en la RNM (T2, Flair) con el consejo de que se recurra para el diseño a un neuroradiólogo experto. No habla en ningún caso de otras pruebas como el PET TAC.

Respecto al intervalo libre de progresión para considerar la reirradiación hay variación según las series. En el grupo del M D Anderson, que es la primera serie publicada (Am J Clin Oncol 2012;35:51–57) con 6 pacientes, el intervalo fue mayor de 8 meses. En el Grupo Europeo de la SIOP incluyen a pacientes con recaída precoz, a partir de 3 meses y en el grupo Canadiense (Pediatr Blood Cancer. 2018;e26988) de 4 meses.

En nuestro medio la mayoría de los Centros valoran la reirradiación cuando el intervalo es mayor de 6 meses.
El fraccionamiento aconsejado es el estándar entre 1,8 y 2 Gy. En el grupo Canadiense usan en algún caso el fraccionamiento de 3 Gy, pero recomiendan el estándar.

La dosis total varía entre 18 - 36 Gy. El grupo del MD Anderson se queda en 18 - 20 Gy. La SIOP-E entre 18 y 30 Gy, aunque en sus conclusiones aconsejan 20 Gy. Y el grupo canadiense es el que llega a dosis más altas 21.6 a 36 Gy (dosis media 30.6 Gy).

Por tanto se debería realizar con un fraccionamiento de 1,8 – 2 Gy una dosis de 20 - 30,6 Gy

Respecto a los resultados en todas las series se encuentra una mejora de síntomas neurológicos (>80%) e incluso beneficio en la Supervivencia Global (3,4 meses en el grupo Europeo respecto a los no radiados) con toxicidades solo Grado 1 y 2.

Como conclusión : se puede valorar la reirradiación de un DIPG cuando el paciente tenga progresión clínica y radiológica por RNM, con mejores resultados si el intervalo desde la primera radiación es mayor de 6 meses , a dosis de 20- 30,5 Gy con fraccionamiento estándar esperando conseguir una mejora de la sintomatología neurológica y con toxicidad aguda no muy importante.

5.- BIBLIOGRAFÍA
Reirradiation in patients with diffuse intrinsic pontine gliomas: The Canadian experience

Alvaro Lassaletta1 | Douglas Strother2 | Normand Laperriere3 | Juliette Hukin4 | Magimairajan Issai Vanan5 | Karen Goddard4 | Lucie Lafay-Cousin2 | Donna L. Johnston6 | Shayna Zelcer7 | Michal Zapotocky1 | Revathi Rajagopal1 | Vijay Ramaswamy1 | Cynthia Hawkins1 | Uri Tabori1 | Annie Huang1 | Ute Bartels1 | Eric Bouffet1

1 The Hospital for Sick Children, Toronto, Ontario, Canada
2 Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
3 Princess Margaret Cancer Centre, Toronto, Ontario, Canada
4 British Columbia Children’s Hospital, Vancouver, British Columbia, Canada
5 Cancer Care Manitoba, Winnipeg, Manitoba, Canada
6 Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada
7 Children’s Hospital of Western Ontario, London, Ontario, Canada

Correspondence
Eric Bouffet, The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8.
Email: eric.bouffet@sickkids.ca

Funding information
Meagan’s Walk Fellowship in Pediatric Neuro-Oncology

Abstract
Objective: Clinical trials have failed to demonstrate a survival benefit of adjuvant chemotherapy in diffuse intrinsic pontine gliomas (DIPG). Radiation therapy (RT) is the only effective treatment thus far and reirradiation (rRT) has become an option at the time of progression. The aim of this study was to review the Canadian experience of DIPG rRT with a focus on the safety and possible efficacy of this approach.

Method: We retrospectively reviewed the demographic, clinical, and RT data of patients with DIPG treated in Canada with rRT.

Results: Since January 2011, we identified 16 patients with progressive DIPG who received rRT. Median time from diagnosis to progression was 10.5 months (range, 4–37 months). rRT was given focally in 14 patients at a dose ranging from 21.6 to 36 Gy. rRT was well tolerated by all children but one. All but three patients showed neurological improvement. With a median follow-up from original diagnosis of 19.2 months, all patients died, with a median time from rRT to death of 6.48 months (range, 3.83–13.26 months). When compared to a historic cohort of 46 consecutive patients, the median time from progression to death was 92 days in the non-reirradiated patients versus 218 days in the reirradiated ones (P = 0.0001).

Conclusion: In this limited experience, rRT was safe and feasible in patients with progressive DIPG, providing neurological improvement and a prolonged life span in most patients. Prospective Canadian rRT protocols are ongoing to further assess the benefit of this approach, including quality of life assessment.

KEYWORDS
children, DIPG, glioma, pontine, reirradiation

1 INTRODUCTION

More than 90% of the children diagnosed with diffuse intrinsic pontine gliomas (DIPG) will succumb to their disease within 2 years of diagnosis. Despite numerous clinical trials of chemotherapy, radiosensitizers, and biological modifiers, survival has remained unchanged over the last three decades and DIPG has become the leading cause of death from CNS malignancies in the pediatric population. To date, the median survival from diagnosis of DIPG continues to be less than 1 year. There is no known effective therapy for recurrent disease and the time from progressive disease following radiation therapy (RT) to death is approximately 3 months. New understanding of the biology in DIPG in recent years has led to the design of new targeted therapy drugs that are currently under evaluation in phase 1 and 2 trials for patients with newly diagnosed and recurrent disease.
With the lack of agents known to be active in newly diagnosed DIPG,\(^2\) with inconsistent access to experimental therapies, with the knowledge that RT is the only treatment modality that has been shown to lengthen life after diagnosis of DIPG,\(^3\) and with increasing evidence of the safety of reirradiation (rRT) in other pediatric brain tumors,\(^{10,11}\) there is growing interest in considering rRT for refractory or progressive DIPG. We report the Canadian experience of rRT of children with DIPG at the time of disease progression.

## 2 | METHODS

Multicenter retrospective data collection was performed across Canada. All patients under 18 years who received rRT after progression of DIPG were included. Disease progression was defined as neurological deterioration confirmed by magnetic resonance imaging (MRI). No restrictions were made in terms of therapy received before or after rRT. Any regimen of conventional RT at progression was permitted. Clinical information was extracted from patient medical records.

The primary aim of the study was to analyze the time from progression to death (measured from date of progression to date of death) and overall survival (measured from date of first diagnosis to date of death) of the group. The reirradiated group was compared to a historic cohort of 46 consecutive patients with DIPG treated without rRT at the Hospital for Sick Children from 2000 to 2011.

Descriptive statistics were used to summarize patient and treatment characteristics, along with outcomes. The Kaplan–Meier method was used to determine distribution of survival. The log-rank test was used to explore for differences in survival between groups. Statistical analysis was performed using SPSS, version 20 (SPSS Inc., Chicago, IL). This study was approved by the Institutional Review Board of each participating institution.

## 3 | RESULTS

Between January 2011 and February 2016, 16 patients with progressive DIPG received rRT at six institutions across Canada. Median age at diagnosis was 5.87 years (range, 2.25–13 years). Median time from diagnosis to progression was 10.5 months (range, 4–37 months). Fourteen patients had local progression, one local + disseminated progression, and one disseminated progression. rRT started with a median of 26.5 days (range, 7–120) after first progression. Median time from diagnosis to rRT was 13 months (range, 4.7–38.9 months). Patient and treatment characteristics are listed in Table 1.

rRT total dose and fractionation varied between institutions from 21.6 to 36 Gy (median dose 30.6 Gy). rRT was given focally in 88% of the patients. Two patients received whole brain rRT with 30.6 Gy due to disseminated progression. One patient who was reirradiated focally with 30.6 Gy had a second relapse 6 months after rRT and received a third course of rRT with 21.6 Gy. One patient had treatment for first progression with bevacizumab and irinotecan for 4 months before starting rRT. Only one patient received concomitant therapy during rRT (bevacizumab). Seven patients received chemotherapy after rRT including temozolomide, valproic acid, nimotuzumab, and bevacizumab or a combination of these.

All patients had neurological symptoms at progression. In 13 patients (81%), these neurological symptoms improved after rRT; in six patients, the recovery was full. An evaluation of dexamethasone use showed that six patients used none, nine were started on dexamethasone at progression and were either weaned by the end of rRT (n = 4) or were continued after rRT (n = 5), and there was no information in one patient. Ten patients had an MRI after rRT to assess tumor response. In eight patients, a radiological improvement was seen. One of the patients who had progression on MRI showed increase in size with evidence of necrosis within the tumor and survived 6 months after rRT. rRT was well tolerated by all children with the exception of one. There were no side effects in 10 patients. Five had transient tiredness and decreased appetite during treatment. One patient developed right-sided weakness and brain stem dysfunction (left pontine necrosis) and progressed to cerebellar dysfunction and quadraparesis after receiving 30 Gy in 10 fractions.

With a median follow-up from diagnosis of 19.2 months, all patients died, with a median time from rRT to death of 6.48 months (range, 3.83–13.26 months). When we compared those who first progressed at less than or greater than 10 months after diagnosis, there was a significant difference in median time to death from diagnosis: 14.76 months (range, 9.12–37.2 months) versus 23.4 months (range, 17.88–45.6 months), respectively (P = 0.019). When compared to a historic cohort of 46 consecutive patients with DIPG who did not receive rRT at progression, median time from progression to death was 92 days (range, 2–335 days) in the non-rRT patients versus 218 days (range, 117–422 days) in the rRT group (P = 0.0001). Median time from initial diagnosis to death was 11.27 months (range, 3–36.5 months) in the non-rRT patients versus 19.26 months (range, 9.12–45.7 months) in the rRT group (P = 0.0002).

## 4 | DISCUSSION

Diffuse intrinsic pontine glioma continues to be a devastating disease with a fatal outcome.\(^12\) Despite extensive research including recent genomic studies leading to the development of targeted trials, thus far no improvement in survival has been achieved. RT is the only treatment that has shown benefit in these patients, although it is essentially considered as palliative, since long-term survival is a rarity.\(^13\) At the time of progression, most patients die within weeks or months with a progressive neurological decline and poor quality of life due to increasing disability. rRT, which has been safely used with evidence of survival benefit in other pediatric brain tumors such as ependymoma and medulloblastoma,\(^10,11\) has been recently proposed as a potential approach in children with progressive DIPG.\(^14\)

Three previous reports have described the outcome of patients whose treatment of recurrent disease included rRT.\(^14–16\) In the first, from MD Anderson Cancer Center, five patients were treated with rRT using either 18 Gy in 10 fractions (one patient) or 20 Gy in 10
<table>
<thead>
<tr>
<th>Number</th>
<th>Age at Dx</th>
<th>Time from diagnosis to first progression (months)</th>
<th>Time from first progression to start rRT (days)</th>
<th>Dose of rRT Gy (fraction)</th>
<th>MRI improved after rRT</th>
<th>DEX/Weaned by end of rRT</th>
<th>Clinical improvement after rRT/extent</th>
<th>Side effects from rRT</th>
<th>Time from rRT to progression (months)</th>
<th>Outcome (OS: years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 y 5 m</td>
<td>14</td>
<td>20</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/PR</td>
<td>Tiredness, insomnia</td>
<td>6</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>10 y 3 m</td>
<td>4</td>
<td>12</td>
<td>30.6 (1.8)</td>
<td>Not done</td>
<td>Yes/No</td>
<td>No</td>
<td>Vomiting, tiredness</td>
<td>5</td>
<td>0.76</td>
</tr>
<tr>
<td>3</td>
<td>5 y</td>
<td>9</td>
<td>14</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>1.23</td>
</tr>
<tr>
<td>4</td>
<td>13 y</td>
<td>9</td>
<td>24</td>
<td>30.6 (1.8) WBR</td>
<td>Yes</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>4 y 9 m</td>
<td>32</td>
<td>75</td>
<td>30.6 (1.8) WBR</td>
<td>Yes</td>
<td>No</td>
<td>Yes/FR</td>
<td>Tiredness, ↓ Appetite</td>
<td>7</td>
<td>3.81</td>
</tr>
<tr>
<td>6</td>
<td>2 y 3 m</td>
<td>13</td>
<td>40</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>No</td>
<td>Yes/PR</td>
<td>None</td>
<td>3</td>
<td>1.63</td>
</tr>
<tr>
<td>7</td>
<td>5 y</td>
<td>36</td>
<td>30</td>
<td>36 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/PR</td>
<td>None</td>
<td>3</td>
<td>3.51</td>
</tr>
<tr>
<td>8</td>
<td>9 y</td>
<td>12</td>
<td>30</td>
<td>36 (1.8)</td>
<td>Not done</td>
<td>Yes/No</td>
<td>Yes/FR</td>
<td>Tiredness</td>
<td>9</td>
<td>1.95</td>
</tr>
<tr>
<td>9</td>
<td>5 y</td>
<td>10</td>
<td>60</td>
<td>21.6 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>6</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>4 y 6 m</td>
<td>6</td>
<td>15</td>
<td>21.6 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>4</td>
<td>1.06</td>
</tr>
<tr>
<td>11</td>
<td>4 y 9 m</td>
<td>10</td>
<td>12</td>
<td>21.6 (1.8)</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Yes/PR</td>
<td>None</td>
<td>4</td>
<td>1.49</td>
</tr>
<tr>
<td>12</td>
<td>6 y 1 m</td>
<td>11</td>
<td>120</td>
<td>300 (3.0)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>1.58</td>
</tr>
<tr>
<td>13</td>
<td>8 y 2 m</td>
<td>12</td>
<td>7</td>
<td>300 (3.0)</td>
<td>Yes</td>
<td>Yes/No</td>
<td>No</td>
<td>Left pontine necrosis</td>
<td>5</td>
<td>1.65</td>
</tr>
<tr>
<td>14</td>
<td>5 y 8 m</td>
<td>8</td>
<td>50</td>
<td>27.6 (1.8)</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes/PR</td>
<td>None</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>15</td>
<td>11 y 7 m</td>
<td>8</td>
<td>13</td>
<td>30.6 (1.8)</td>
<td>Not done</td>
<td>Yes/No</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>0.94</td>
</tr>
<tr>
<td>16</td>
<td>11 y 3 m</td>
<td>8</td>
<td>37</td>
<td>30.6 (1.8)</td>
<td>No</td>
<td>Unknown</td>
<td>No</td>
<td>Fatigue, mild nausea</td>
<td>5</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Dx, diagnosis; Y, years; M, months; DEX, dexamethasone; rRT, reirradiation; WBR, whole brain radiation; FR, fully recovered; PR, partial recovered; OS, overall survival.
Median time to progression after rRT was 5 months. In the second of five patients and remained stable in the other three patients. Grade 2 (moderate) in severity. Lansky performance scores increased side effects in five patients were minimal and none were greater than 

fractions (four patients), and concurrent chemotherapy after a second or subsequent progression following initial treatment. Acute adverse side effects in five patients were minimal and none were greater than Grade 2 (moderate) in severity. Lansky performance scores increased in two of five patients and remained stable in the other three patients. Median time to progression after rRT was 5 months. In the second report by investigators from Italy, rRT was built into a phase II study of radiation plus nimotuzumab and vinorelbine for newly diagnosed DIPG patients. rRT was offered at the time of tumor progression. Of 25 evaluable patients, 20 had progressive disease including 16 with local progression only. Of these 16, 11 were treated with focal 19.8 Gy rRT (1.8 Gy daily fractions). Of five patients who experienced disseminated progression, four received rRT to metastatic disease. No patients had unexpected side effects or neurologic worsening during rRT. For the entire group, median survival after rRT was 6 months (range, 6 weeks–14 months). The 1-year progression-free survival rate in this study was 30% (±10%) in keeping with the results of previous DIPG experiences; however, the median survival in this cohort was 15 months, which compares favorably with all DIPG trials reported to date. From these two reports, one can conclude that rRT at doses of ∼20 Gy is safe and well tolerated. The recent retrospective review of cases collected by investigators from the European Pediatric Oncology International Society (SIOP-E) includes most patients from the Milan cohort described above. In this review, 31 patients with DIPG received rRT alone or in combination with systemic therapy. rRT started 3 or more months from completion of RT for initial diagnosis. Doses varied between 18 and 30 Gy in fractions ranging from 1.8 to 3 Gy. Almost 80% of the patients had clinical improvement after rRT. A historical comparison with a matched cohort of patients who did not receive rRT suggested a significant benefit in overall survival associated with this approach. Interval of diagnosis to progression and rRT remained prognostic for survival in the multivariate analysis.

In our experience, clinical improvement was observed in all but three patients. These results confirm the benefit of this approach in a palliative setting. Interestingly, steroids were completely avoided in six patients and were discontinued in four patients by the end of the rRT. Data on steroid usage are not available in all other reports, although this represents a major aspect of the benefit associated with rRT in this population. Similarly, evaluation of quality of life was lacking in these early reports. Quality of life data should be prospectively assessed when using this strategy since this information may be critical for parents confronted with a decision to proceed to rRT or supportive care.

Several aspects of DIPG rRT remain to be determined, including the optimal radiation dose and fractionation, and the minimal interval between the two courses of radiation. In our experience, no rRT was given if the interval between diagnosis and progression was less than 4 months. This may have excluded patients with more aggressive tumors. In the European experience, some patients were treated as early as 3 months after completion of initial radiation treatment, with no Grade 4–5 toxicity reported. In early report of rRT, most patients received relatively low doses in the range of 20 Gy with evidence of clinical improvement. In our experience, higher doses were used with no significant side effects when using 1.8 Gy fractionation, and 11 patients received more than 27 Gy in 1.8 Gy fractions with no evidence of increased toxicity. One patient received a second course of rRT that was well tolerated as previously reported. The good tolerance of this technique maybe related to the relatively low-dose delivered per fraction (1.8 Gy) in most patients. Of our 16 patients, two received 30 Gy in 10 fractions. One suffered pontine necrosis with brainstem dysfunction and quadriaparesis. This severe toxicity may have been related to the higher fraction size given in this case (3 Gy) and it is our recommendation that fraction sizes in the 1.8–2.0 Gy range should be used when delivering rRT in this context.

Diffuse intrinsic pontine glioma continues to be an incurable disease. As research continues to look for new treatment options, efforts should be made to find an effective treatment strategy in balance with quality of life after diagnosis. rRT may be an option for patients with relapse after conventional treatment. The tolerance of rRT combined with improvement in neurologic function suggests an acceptable quality of life, at least temporarily. Acknowledging the small number of patients in our study, in our experience, a dose of 30.6 Gy in 1.8 Gy fractions was well tolerated. It is unclear if additional chemotherapy adds benefit to these patients. However, the rationale for using chemother-
apy is weak, since no chemotherapeutic agent has ever demonstrated a benefit in newly diagnosed patients. Future clinical trials of rRT should further assess the optimal dose, fractionation, the interval between courses of RT, and the quality of life associated with this strategy. Prospective Canadian rRT protocols are in progress to address these questions.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ORCID
Alvaro Lassaletta http://orcid.org/0000-0003-2881-1473
Lucie Lafay-Cousin http://orcid.org/0000-0003-4569-3499
Donna L. Johnston http://orcid.org/0000-0001-6145-9809
Michal Zapotocky http://orcid.org/0000-0002-9013-2546
Revathi Rajagopal http://orcid.org/0000-0003-4380-4124
Vijay Ramaswamy http://orcid.org/0000-0002-6557-895X

REFERENCES

Junio 2018 – REIRRADIACIÓN TUMOR INTRÍNSECO DE TRONCO DIPG

1.- DESCRIPCIÓN DEL CASO

Paciente de 9 años con diagnóstico, en octubre del 2016, de tumor intrínseco de tronco (DIPG) tras biopsia, con resultado de glioma difuso alto grado H3F3A K27M+. Fue tratado con RT con dos volúmenes: uno más amplio intentando abarcar la lesión en T2/FLAIR con margen hasta 54 Gy y luego la zona captante a la que solo se pudo llegar a 56 Gy (previsto 60 Gy) + Temodal concomitante que yinaliza en enero 2017 y adyuvante, que continua hasta el momento actual (junio 2018).

Tiene una respuesta clínica casi completa con desaparición de los déficits pretratamiento, excepto la parálisis de los óculo-motores y radiológica con reducción del tumor más del 90% (máxima respuesta en mayo 2017) y luego estabilización.

Ha realizado vida normal incluso con excelente resultado escolar.

A finales de marzo de 2018 se objetiva progresión radiológica sin progresión clínica y nos planteamos reirradiación, decidiéndose no realizarla ante la no progresión clínica (comente el caso con el Dr. Giralt).

Actualmente, leve progresión clínica (hace vida normal y según la madre esta como siempre) y en RMN progresión radiológica.

2.- DUDA CONSULTADA

Las preguntas son:

- Ante la progresión radiológica, en RMN, si nos planteamos reirradiar, supongo que estáis de acuerdo en no confirmar la progresión por otras pruebas tipo PET, etc, al bastar con la progresión radiológica.

- Por otro lado si nos planteamos reirradiar, incluir toda la zona de T2/Flair que ha aumentado y la mínima zona captante, o solo la captante. La propuesta de dosis es 20 (máximo 24 Gy) con fraccionamiento de 1,8 Gy.

- Finalmente, ante la mínima progresión clínica, tratamos ya o esperamos a mayor progresión clínica (la madre es consciente del riesgo de reirradiación y le da miedo los efectos secundarios al ver tan bien a su hija).
3.- RESPUESTAS

➢ Nosotros reirradiamos los DIPG, si han pasado más de 6 meses desde la primera RT, si hubo beneficio sintomático y radiológico y si el paciente tiene síntomas. Utilizamos fraccionamiento convencional y le damos 30,6 Gy en sesiones de 1,8 Gy. Yo creo que en tu caso la decisión difícil es decidir si irradiar ahora o cuando empiece a tener síntomas. En mi opinión (y no se basa en nada científico), esperaría a tener síntomas que mejorar. Y el volumen, incluiría lo que el neuroradiólogo defina como tumor, aunque el volumen sea amplio. Tratar dejando zonas fuera, me parece poco lógico, cuando ya has decidido tratar y asumir las complicaciones. Os adjunto bibliografía. (Dra. Carmen González)

➢ Esperaría a reirradiar ante una progresión clínica más evidente que la que describes. Es muy probable que este planteamiento no afecte a la supervivencia. Mientras intentaría contactar con Oncohematología Pediátrica (Lasaleta por ejemplo en el Niño Jesús de Madrid) por si pudieran ofrecer algo más. (Dr. Raúl Matute)

➢ Esperaría para la reirradiación a una progresión clínica clara. Nosotros en nuestro centro reirradiamos (20 Gy en 10 fr) cuando hay clínica y si ha tenido respuesta a la primera RT con una duración de al menos 6 meses. En los casos que hemos tratado no hemos observado de momento complicaciones de la reirradiación y lo que se puede obtener de beneficio es una mejoría sintomática paliativa, por eso pienso que tiene más sentido asumir el riesgo cuando hay síntomas de nueva aparición. Respecto al volumen de reirradiación, yo haría únicamente el GTV (lo que en RM sea definido como tumor) + el margen del PTV claro. (Dra. Mónica Albiach)

➢ Esperaría como el resto de compañeros a que la niña progresara clínicamente para reirradiar. También como ha comentado otro compañero hablaría con Oncología Pediátrica para buscar otra posible alternativa. Nosotros tratamos hace ya algunos años un
niño con Nimotuzumab asociado a Temozolamida tras progresión a RT, con buena respuesta inicial clínica y radiológica. (Dra. Sonia García)

➢ Nosotros habitualmente esperamos a la progresión clínica para reirradiar (Dra. Patricia Cabrera)

4.- CONCLUSIÓN

La reirradiación en el DIPG puede ser factible para mejorar los síntomas y retrasar la progresión con toxicidad mínima.

Los pacientes que tienen más probabilidades de beneficiarse son aquellos con Respuesta al tratamiento inicial y un largo intervalo desde la radiación inicial.

La decisión de la reirradiación sería cuando el paciente tiene empeoramiento clínico evidente y no solo cuando hay empeoramiento radiológico, puesto que el objetivo principal de este tratamiento es sintomático. En este sentido la serie de 31 pacientes del Grupo de trabajo DIPG de la SIOP-E (European Journal of Cancer 73 (2017) 38-47) consideran progresión de la enfermedad como un deterioro clínico (neurológico) con necesidad de reutilización de esteroides o aumento de la dosis, confirmado por resonancia magnética.

En cuanto a las pruebas radiológicas, en la bibliografía el crecimiento y el diseño de los volúmenes de tratamiento se basan en la RNM (T2, Flair) con el consejo de que se recurra para el diseño a un neuroradiologo experto. No habla en ningún caso de otras pruebas como el PET TAC.

Respecto al intervalo libre de progresión para considerar la reirradiación hay variación según las series. En el grupo del M D Anderson, que es la primería serie publicada (Am J Clin Oncol 2012;35:51–57) con 6 pacientes, el intervalo fue mayor de 8 meses. En el Grupo Europeo de la SIOP incluyen a pacientes con recaída precoz, a partir de 3 meses y en el grupo Canadiense (Pediatr Blood Cancer. 2018;e26988) de 4 meses.

En nuestro medio la mayoría de los Centros valoran la reirradiación cuando el intervalo es mayor de 6 meses.
El fraccionamiento aconsejado es el estándar entre 1,8 y 2 Gy. En el grupo Canadiense usan en algún caso el fraccionamiento de 3 Gy, pero recomiendan el estándar.

La dosis total varía entre 18 - 36 Gy. El grupo del MD Anderson se queda en 18 - 20 Gy. La SIOP-E entre 18 y 30 Gy, aunque en sus conclusiones aconsejan 20 Gy. Y el grupo canadiense es el que llega a dosis más altas 21.6 a 36 Gy (dosis media 30.6 Gy).

Por tanto se debería realizar con un fraccionamiento de 1,8 – 2 Gy una dosis de 20 - 30,6 Gy.

Respecto a los resultados en todas las series se encuentra una mejoría de síntomas neurológicos (>80%) e incluso beneficio en la Supervivencia Global (3,4 meses en el grupo Europeo respecto a los no radiados) con toxicidades solo Grado 1 y 2.

Como conclusión: se puede valorar la reirradiación de un DIPG cuando el paciente tenga progresión clínica y radiológica por RNM, con mejores resultados si el intervalo desde la primera radiación es mayor de 6 meses, a dosis de 20- 30,5 Gy con fraccionamiento estándar esperando conseguir una mejora de la sintomatología neurológica y con toxicidad aguda no muy importante.

5.- BIBLIOGRAFÍA
Reirradiation in patients with diffuse intrinsic pontine gliomas: The Canadian experience

Alvaro Lassaletta1 | Douglas Strother2 | Normand Laperriere3 | Juliette Hukin4 | Magimairajan Issai Vanan5 | Karen Goddard4 | Lucie Lafay-Cousin2 | Donna L. Johnston6 | Shayna Zelcer7 | Michal Zapotocky1 | Revathi Rajagopal1 | Vijay Ramaswamy1 | Cynthia Hawkins1 | Uri Tabori1 | Annie Huang1 | Ute Bartels1 | Eric Bouffet1

1 The Hospital for Sick Children, Toronto, Ontario, Canada
2 Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
3 Princess Margaret Cancer Centre, Toronto, Ontario, Canada
4 British Columbia Children’s Hospital, Vancouver, British Columbia, Canada
5 Cancer Care Manitoba, Winnipeg, Manitoba, Canada
6 Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada
7 Children’s Hospital of Western Ontario, London, Ontario, Canada

Correspondence
Eric Bouffet, The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada MSG 1X8.
Email: eric.bouffet@sickkids.ca

Funding information
Meagan’s Walk Fellowship in Pediatric Neuro-Oncology

Abstract

Objective: Clinical trials have failed to demonstrate a survival benefit of adjuvant chemotherapy in diffuse intrinsic pontine gliomas (DIPG). Radiation therapy (RT) is the only effective treatment thus far and reirradiation (rRT) has become an option at the time of progression. The aim of this study was to review the Canadian experience of DIPG rRT with a focus on the safety and possible efficacy of this approach.

Method: We retrospectively reviewed the demographic, clinical, and RT data of patients with DIPG treated in Canada with rRT.

Results: Since January 2011, we identified 16 patients with progressive DIPG who received rRT. Median time from diagnosis to progression was 10.5 months (range, 4–37 months). rRT was given focally in 14 patients at a dose ranging from 21.6 to 36 Gy. rRT was well tolerated by all children but one. All but three patients showed neurological improvement. With a median follow-up from original diagnosis of 19.2 months, all patients died, with a median time from rRT to death of 6.48 months (range, 3.83–13.26 months). When compared to a historic cohort of 46 consecutive patients, the median time from progression to death was 92 days in the non-reirradiated patients versus 218 days in the reirradiated ones (P = 0.0001).

Conclusion: In this limited experience, rRT was safe and feasible in patients with progressive DIPG, providing neurological improvement and a prolonged life span in most patients. Prospective Canadian rRT protocols are ongoing to further assess the benefit of this approach, including quality of life assessment.

KEYWORDS
children, DIPG, glioma, pontine, reirradiation

1 INTRODUCTION

More than 90% of the children diagnosed with diffuse intrinsic pontine gliomas (DIPG) will succumb to their disease within 2 years of diagnosis.1 Despite numerous clinical trials of chemotherapy, radiosensitizers, and biological modifiers, survival has remained unchanged over the last three decades and DIPG has become the leading cause of death from CNS malignancies in the pediatric population.2 To date, the median survival from diagnosis of DIPG continues to be less than 1 year. There is no known effective therapy for recurrent disease and the time from progressive disease following radiation therapy (RT) to death is approximately 3 months.3 New understanding of the biology in DIPG in recent years has led to the design of new targeted therapy drugs that are currently under evaluation in phase 1 and 2 trials for patients with newly diagnosed and recurrent disease.4–9

Abbreviations: DIPG, diffuse intrinsic pontine glioma; MRI, magnetic resonance imaging; rRT, reirradiation; RT, radiation therapy
With the lack of agents known to be active in newly diagnosed DIPG,\textsuperscript{2} with inconsistent access to experimental therapies, with the knowledge that RT is the only treatment modality that has been shown to lengthen life after diagnosis of DIPG,\textsuperscript{3} and with increasing evidence of the safety of reirradiation (rRT) in other pediatric brain tumors,\textsuperscript{10,11} there is growing interest in considering rRT for refractory or progressive DIPG. We report the Canadian experience of rRT of children with DIPG at the time of disease progression.

2 METHODS

Multicenter retrospective data collection was performed across Canada. All patients under 18 years who received rRT after progression of DIPG were included. Disease progression was defined as neurological deterioration confirmed by magnetic resonance imaging (MRI). No restrictions were made in terms of therapy received before or after rRT. Any regimen of conventional RT at progression was permitted. Clinical information was extracted from patient medical records.

The primary aim of the study was to analyze the time from progression to death (measured from date of progression to date of death) and overall survival (measured from date of first diagnosis to date of death) of the group. The reirradiated group was compared to a historic cohort of 46 consecutive patients with DIPG treated without rRT at the Hospital for Sick Children from 2000 to 2011.

Descriptive statistics were used to summarize patient and treatment characteristics, along with outcomes. The Kaplan–Meier method was used to determine distribution of survival. The log-rank test was used to explore for differences in survival between groups. Statistical analysis was performed using SPSS, version 20 (SPSS Inc., Chicago, IL). This study was approved by the Institutional Review Board of each participating institution.

3 RESULTS

Between January 2011 and February 2016, 16 patients with progressive DIPG received rRT at six institutions across Canada. Median age at diagnosis was 5.87 years (range, 2.25–13 years). Median time from diagnosis to progression was 10.5 months (range, 4–37 months). Fourteen patients had local progression, one local + disseminated progression, and one disseminated progression. rRT started with a median of 26.5 days (range, 7–120) after first progression. Median time from diagnosis to rRT was 13 months (range, 4.7–38.9 months). Patient and treatment characteristics are listed in Table 1.

rRT total dose and fractionation varied between institutions from 21.6 to 36 Gy (median dose 30.6 Gy). rRT was given focally in 88% of the patients. Two patients received whole brain rRT with 30.6 Gy due to disseminated progression. One patient who was reirradiated focally with 30.6 Gy had a second relapse 6 months after rRT and received a third course of rRT with 21.6 Gy. One patient had treatment for first progression with bevacizumab and irinotecan for 4 months before starting rRT. Only one patient received concomitant therapy during rRT (bevacizumab). Seven patients received chemotherapy after rRT including temozolomide, valproic acid, nimotuzumab, and bevacizumab or a combination of these.

All patients had neurological symptoms at progression. In 13 patients (81%), these neurological symptoms improved after rRT; in six patients, the recovery was full. An evaluation of dexamethasone use showed that six patients used none, nine were started on dexamethasone at progression and were either weaned by the end of rRT (n = 4) or were continued after rRT (n = 5), and there was no information in one patient. Ten patients had an MRI after rRT to assess tumor response. In eight patients, a radiological improvement was seen. One of the patients who had progression on MRI showed increase in size with evidence of necrosis within the tumor and survived 6 months after rRT. rRT was well tolerated by all children with the exception of one. There were no side effects in 10 patients. Five had transient tiredness and decreased appetite during treatment. One patient developed right-sided weakness and brainstem dysfunction (left pontine necrosis) and progressed to cerebellar dysfunction and quadraparesis after receiving 30 Gy in 10 fractions.

With a median follow-up from diagnosis of 19.2 months, all patients died, with a median time from rRT to death of 6.48 months (range, 3.83–13.26 months). When we compared those who first progressed at less than or greater than 10 months after diagnosis, there was a significant difference in median time to death from diagnosis: 14.76 months (range, 9.12–37.2 months) versus 23.4 months (range, 17.88–45.6 months), respectively (P = 0.019). When compared to a historic cohort of 46 consecutive patients with DIPG who did not receive rRT at progression, median time from progression to death was 92 days (range, 2–335 days) in the non-rRT patients versus 218 days (range, 117–422 days) in the rRT group (P = 0.0001). Median time from initial diagnosis to death was 11.27 months (range, 3–36.5 months) in the non-rRT patients versus 19.26 months (range, 9.12–45.7 months) in the rRT group (P = 0.0002).

4 DISCUSSION

Diffuse intrinsic pontine glioma continues to be a devastating disease with a fatal outcome.\textsuperscript{12} Despite extensive research including recent genomic studies leading to the development of targeted trials, thus far no improvement in survival has been achieved. RT is the only treatment that has shown benefit in these patients, although it is essentially considered as palliative, since long-term survival is a rarity.\textsuperscript{13} At the time of progression, most patients die within weeks or months with a progressive neurological decline and poor quality of life due to increasing disability. rRT, which has been safely used with evidence of survival benefit in other pediatric brain tumors such as ependymoma and medulloblastoma,\textsuperscript{10,11} has been recently proposed as a potential approach in children with progressive DIPG.\textsuperscript{14}

Three previous reports have described the outcome of patients whose treatment of recurrent disease included rRT.\textsuperscript{14–16} In the first, from MD Anderson Cancer Center, five patients were treated with rRT using either 18 Gy in 10 fractions (one patient) or 20 Gy in 10
**TABLE 1**  Patient and treatment characteristics

<table>
<thead>
<tr>
<th>Number</th>
<th>Age at Dx</th>
<th>Time from diagnosis to first progression (months)</th>
<th>Time from first progression to start rRT (days)</th>
<th>Dose of rRT Gy (fraction)</th>
<th>MRI improved after rRT</th>
<th>DEX/Weaned by end of rRT</th>
<th>Clinical improvement after rRT/extent</th>
<th>Side effects from rRT</th>
<th>Time from rRT to progression (months)</th>
<th>Outcome (OS: years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 y 5 m</td>
<td>14</td>
<td>20</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/PR</td>
<td>Tiredness, insomnia</td>
<td>6</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>10 y 3 m</td>
<td>4</td>
<td>12</td>
<td>30.6 (1.8)</td>
<td>Not done</td>
<td>Yes/No</td>
<td>No</td>
<td>Vomiting, tiredness</td>
<td>5</td>
<td>0.76</td>
</tr>
<tr>
<td>3</td>
<td>5 y</td>
<td>9</td>
<td>14</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>1.23</td>
</tr>
<tr>
<td>4</td>
<td>13 y</td>
<td>9</td>
<td>24</td>
<td>30.6 (1.8) WBR</td>
<td>Yes</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>4 y 9 m</td>
<td>32</td>
<td>75</td>
<td>30.6 (1.8) WBR</td>
<td>Yes</td>
<td>No</td>
<td>Yes/FR</td>
<td>Tiredness, ↓ Appetite</td>
<td>7</td>
<td>3.81</td>
</tr>
<tr>
<td>6</td>
<td>2 y 3 m</td>
<td>13</td>
<td>40</td>
<td>30.6 (1.8)</td>
<td>Yes</td>
<td>No</td>
<td>Yes/PR</td>
<td>None</td>
<td>3</td>
<td>1.63</td>
</tr>
<tr>
<td>7</td>
<td>5 y</td>
<td>36</td>
<td>30</td>
<td>36 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>3.51</td>
</tr>
<tr>
<td>8</td>
<td>9 y</td>
<td>12</td>
<td>30</td>
<td>36 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>9</td>
<td>1.95</td>
</tr>
<tr>
<td>9</td>
<td>5 y</td>
<td>10</td>
<td>60</td>
<td>216 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>Tiredness</td>
<td>6</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>4 y 6 m</td>
<td>6</td>
<td>15</td>
<td>216 (1.8)</td>
<td>Not done</td>
<td>No</td>
<td>Yes/FR</td>
<td>None</td>
<td>4</td>
<td>1.06</td>
</tr>
<tr>
<td>11</td>
<td>4 y 9 m</td>
<td>10</td>
<td>12</td>
<td>216 (1.8)</td>
<td>No</td>
<td>Yes/Yes</td>
<td>Yes/FR</td>
<td>None</td>
<td>4</td>
<td>1.49</td>
</tr>
<tr>
<td>12</td>
<td>6 y 1 m</td>
<td>11</td>
<td>120</td>
<td>300 (3.0)</td>
<td>Yes</td>
<td>Yes/Yes</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>1.58</td>
</tr>
<tr>
<td>13</td>
<td>8 y 2 m</td>
<td>12</td>
<td>7</td>
<td>300 (3.0)</td>
<td>Yes</td>
<td>Yes/No</td>
<td>No</td>
<td>Left pontine necrosis</td>
<td>5</td>
<td>1.65</td>
</tr>
<tr>
<td>14</td>
<td>5 y 8 m</td>
<td>8</td>
<td>50</td>
<td>27.6 (1.8)</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes/PR</td>
<td>None</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>15</td>
<td>11 y 7 m</td>
<td>8</td>
<td>13</td>
<td>30.6 (1.8)</td>
<td>Not done</td>
<td>Yes/No</td>
<td>Yes/FR</td>
<td>None</td>
<td>3</td>
<td>0.94</td>
</tr>
<tr>
<td>16</td>
<td>11 y 3 m</td>
<td>8</td>
<td>37</td>
<td>30.6 (1.8)</td>
<td>No</td>
<td>Unknown</td>
<td>No</td>
<td>Fatigue, mild nausea</td>
<td>5</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Dx, diagnosis; Y, years; M, months; DEX, dexamethasone; rRT, reirradiation; WBR, whole brain radiation; FR, fully recovered; PR, partial recovered; OS, overall survival.
Median time to progression after rRT was 5 months. In the second of five patients and remained stable in the other three patients. Grade 2 (moderate) in severity. Lansky performance scores increased side effects in five patients were minimal and none were greater than or subsequent progression following initial treatment. Acute adverse fractions (four patients), and concurrent chemotherapy after a second or subsequent progression following initial treatment. Acute adverse side effects in five patients were minimal and none were greater than Grade 2 (moderate) in severity. Lansky performance scores increased in two of five patients and remained stable in the other three patients. Median time to progression after rRT was 5 months. In the second report by investigators from Italy, rRT was built into a phase II study of radiation plus nimotuzumab and vinorelbine for newly diagnosed DIPG patients. rRT was offered at the time of tumor progression. Of 25 evaluable patients, 20 had progressive disease including 16 with local progression only. Of these 16, 11 were treated with focal 19.8 Gy rRT (1.8 Gy daily fractions). Of five patients who experienced disseminated progression, four received rRT to metastatic disease. No patients had unexpected side effects or neurologic worsening during rRT. For the entire group, median survival after rRT was 6 months (range, 6 weeks–14 months). The 1-year progression-free survival rate in this study was 30% (±10%) in keeping with the results of previous DIPG experiences; however, the median survival in this cohort was 15 months, which compares favorably with all DIPG trials reported to date. From these two reports, one can conclude that rRT at doses of ~20 Gy is safe and well tolerated. The recent retrospective review of cases collected by investigators from the European Pediatric Oncology International Society (SIOP-E) includes most patients from the Milan cohort described above. In this review, 31 patients with DIPG received rRT alone or in combination with systemic therapy. rRT started 3 or more months from completion of RT for initial diagnosis. Doses varied between 18 and 30 Gy in fractions ranging from 1.8 to 3 Gy. Almost 80% of the patients had clinical improvement after rRT. A historical comparison with a matched cohort of patients who did not receive rRT suggested a significant benefit in overall survival associated with this approach. Interval of diagnosis to progression and rRT remained prognostic for survival in the multivariate analysis.

In our experience, clinical improvement was observed in all but three patients. These results confirm the benefit of this approach in a palliative setting. Interestingly, steroids were completely avoided in six patients and were discontinued in four patients by the end of the rRT. Data on steroid usage are not available in all other reports, although this represents a major aspect of the benefit associated with rRT in this population. Similarly, evaluation of quality of life was lacking in these early reports. Quality of life data should be prospectively assessed when using this strategy since this information may be critical for parents confronted with a decision to proceed to rRT or supportive care.

Several aspects of DIPG rRT remain to be determined, including the optimal radiation dose and fractionation, and the minimal interval between the two courses of radiation. In our experience, no rRT was given if the interval between diagnosis and progression was less than 4 months. This may have excluded patients with more aggressive tumors. In the European experience, some patients were treated as early as 3 months after completion of initial radiation treatment, with no Grade 4–5 toxicity reported. In early report of rRT, most patients received relatively low doses in the range of 20 Gy with evidence of clinical improvement. In our experience, higher doses were used with no significant side effects when using 1.8 Gy fractionation, and 11 patients received more than 27 Gy in 1.8 Gy fractions with no evidence of increased toxicity. One patient received a second course of rRT that was well tolerated as previously reported. The good tolerance of this technique maybe related to the relatively low-dose delivered per fraction (1.8 Gy) in most patients. Of our 16 patients, two received 30 Gy in 10 fractions. One suffered pontine necrosis with brainstem dysfunction and quadriplegia. This severe toxicity may have been related to the higher fraction size given in this case (3 Gy) and it is our recommendation that fraction sizes in the 1.8–2.0 Gy range should be used when delivering rRT in this context.

Diffuse intrinsic pontine glioma continues to be an incurable disease. As research continues to look for new treatment options, efforts should be made to find an effective treatment strategy in balance with quality of life after diagnosis. rRT may be an option for patients with relapse after conventional treatment. The tolerance of rRT combined with improvement in neurologic function suggests an acceptable quality of life, at least temporarily. Acknowledging the small number of patients in our study, in our experience, a dose of 30.6 Gy in 1.8 Gy fractions was well tolerated. It is unclear if additional chemotherapy adds benefit to these patients. However, the rationale for using chemother-

**FIGURE 1** (A) Time from progression to death in patients who received reirradiation (green) versus patients who did not receive reirradiation (blue) ($P = 0.0001$). (B) Overall survival in patients who received reirradiation (green) versus patients who did not receive reirradiation (blue) ($P = 0.0002$)
apy is weak, since no chemotherapeutic agent has ever demonstrated a benefit in newly diagnosed patients. Future clinical trials of rRT should further assess the optimal dose, fractionation, the interval between courses of RT, and the quality of life associated with this strategy. Prospective Canadian rRT protocols are in progress to address these questions.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

ORCID
Alvaro Lassaletta http://orcid.org/0000-0003-2881-1473
Lucie Lafay-Cousin http://orcid.org/0000-0003-4569-3499
Donna L. Johnston http://orcid.org/0000-0001-6145-9809
Michal Zapotocky http://orcid.org/0000-0002-9013-2546
Revathi Rajagopal http://orcid.org/0000-0003-4380-4124
Vijay Ramaswamy http://orcid.org/0000-0002-6557-895X

REFERENCES