Reirradiation of Recurrent Medulloblastoma: Does Clinical Benefit Outweigh Risk for Toxicity?

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BACKGROUND: Patients with recurrent medulloblastoma (MB) have a dismal prognosis. There has been a reluctance to use radiation in the salvage therapy regimens for these patients because of concerns about toxicity and unknown efficacy. Comparing survival outcomes and toxicities in relapsed patients treated with and without radiation may help to define its role. METHODS: A retrospective review was conducted that included 38 patients with recurrent MB treated with similar risk-adapted therapy at initial diagnosis; reirradiation was a component of salvage therapy in 14. Overall survival (OS) and toxicity were evaluated according to the use of radiation, prior risk stratification, and other factors. RESULTS: For relapsed standard-risk patients, the use of additional irradiation resulted in a statistically significant improvement in OS from initial diagnosis (P = .036), with 5- and 10-year OS rates of 55% ± 14% and 33% ± 16% versus 46% ± 14% and 0% for reirradiated patients versus others, respectively. Similar improvement was observed in high-risk patients (P = .003). There was an association between the use of additional irradiation and an increased rate of necrosis as determined by neuroimaging (P = .0468). CONCLUSIONS: The use of irradiation as a component of salvage therapy for relapsed MB may prolong survival. The benefit appears to be greatest for relapsed standard-risk patients. Cancer 2014;120:3731-7. © 2014 American Cancer Society.

KEYWORDS: child, recurrent medulloblastoma, reirradiation, radiotherapy, pediatric brain tumor, necrosis, treatment outcome.

INTRODUCTION

Medulloblastoma (MB) is an embryonal tumor arising in the posterior fossa and the most common malignant brain tumor in children. Current therapy for patients ≥3 years consists of maximal surgical resection followed by craniospinal irradiation (CSI) with supplemental “boost” treatment of the postoperative tumor bed, followed by platinum-based chemotherapy. This contemporary treatment has resulted in 5-year progression-free survival of 80% for standard-risk (SR) patients, and more than 60% for patients with high-risk (HR) disease. The prognosis remains dismal for patients who experience disease progression. The expected 2-year overall survival (OS) after disease progression is less than 25%. Management of these patients has been a challenge as there is no standard approach to salvage therapy.

The present study drew from a cohort of 235 patients ≥3 years of age with MB who received postoperative risk-adapted CSI and postirradiation chemotherapy on 2 successive prospective multi-institution studies. Details regarding treatment after relapse were reviewed including the use of additional irradiation. Comparing survival outcomes and toxicities observed in patients with recurrent MB treated with or without additional irradiation may help to define its role in these patients. This represents the largest series reporting outcomes for patients with recurrent MB treated with additional irradiation.

MATERIALS AND METHODS

Patients

Thirty-eight patients treated at St. Jude Children’s Research Hospital who experienced disease progression after treatment for MB were identified among the cohort of 80 patients treated on the SJMB96 protocol (ClinicalTrials.gov: NCT00003211) from October 1996 to August 2003 and 155 patients treated on the SJMB03 (ClinicalTrials.gov: NCT00085202) protocol from January 2004 to May 2011. Treatment consisted of surgery, with the intent of gross total resection, and immediate postoperative radiation therapy and postirradiation chemotherapy. Tumor risk classification and details regarding treatment have been described previously. For purposes of analysis the following information was...
obtained from the medical record: date of completion of primary therapy, date of tumor progression, location of tumor progression (primary site vs neuraxis), therapy at time of progression including surgery, parameters associated with the second course of irradiation including toxicity, date of last follow-up, disease status, and date of death.

Initial Therapy
The SJMB96 and SJMB03 protocols were similar with the exception of clinical target volume for radiotherapy (RT) and vincristine dose. Until 2003, SR patients received CSI (23.4 Gy), posterior fossa RT (36 Gy), and primary-site RT (55.8 Gy) using a 2-cm clinical target volume (CTV) margin. After 2003, SR patients received CSI (23.4 Gy) and primary-site RT (55.8 Gy) using a 1-cm CTV. HR patients received CSI (36-39.6 Gy) followed by primary-site RT (55.8 Gy) using a 2-cm (pre-2003) or 1-cm (post-2003) CTV margin.

Following RT, there was a 6-week rest period followed by 4 cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, and vincristine) and stem cell or bone marrow rescue. After the patients completed protocol therapy, they underwent disease evaluation every 3 months for the first 18 months, every 6 months for 5 years, and then yearly.

Reirradiation
Of the 38 patients with recurrent disease, 14 were reirradiated between August 2000 and June 2011. The use of irradiation was not systematic and was based on symptoms, the extent of disease at the time of relapse, the use and response to other treatments administered at the time of relapse including surgery and chemotherapy, prior treatment history and interval from initial treatment, and the goals set by the patient, his or her family, and caregivers.

The reirradiation course followed chemotherapy and/or surgery in all patients. Among the 6 patients (HR, 1; SR, 5) first treated with surgery, 2 (SR) patients did not receive chemotherapy prior to irradiation. Among the 8 patients (HR, 2; SR, 6) who did not undergo surgery at the time of relapse, all received chemotherapy prior to irradiation. The second course of irradiation consisted of CSI in 8 patients (57.2%), spinal only in 3 patients (21.4%), and primary site only in 3 patients (21.4%). Craniospinal irradiation was administered using standard beam’s eye-view treatment planning techniques. Boost treatment was administered using 3-D conformal radiation therapy methods. Conventional fractionation (1.5-2.0 Gy) was used in all CSI cases. One patient treated with a second course of CSI and focal irradiation did not complete the focal phase of the treatment because of symptomatic cerebellar edema. The median dose for the second treatment was 36 Gy (range, 18-54 Gy). The median total maximum cumulative dose was 91.9 Gy (range, 73.8 to 109.8 Gy). The median overall treatment time was 19 days (range, 9 to 44 days) for the second course of irradiation. By contrast, among the 24 un-irradiated patients, 7 (HR, 6; SR, 1) were initially treated with surgery; only 1 HR patient did not receive chemotherapy. The remaining 17 unirradiated patients (HR, 12; SR, 5) were not treated with surgery and received chemotherapy as their only therapy.

Analysis
Associations between different categorical variables were investigated by Fisher’s exact test. OS was defined between the time of diagnosis and death for patients who failed and between diagnosis and date of last follow-up for patients who were alive. Survival distributions were estimated using the Kaplan-Meier method and compared between 2 or more groups by the exact log-rank test. Patients were considered to have progressive disease if there were tumor cells detected on examinations of cerebrospinal fluid and/or evidence of new lesions, growth of existing lesions or new leptomeningeal disease on MRI. If there was any doubt about whether the lesion represented recurrent MB, surgical biopsy/excision and histologic confirmation of recurrent disease were obtained. If radiation necrosis was suspected, additional imaging was performed to determine whether the region was metabolically active with hypometabolic FDG PET activity considered consistent with therapy-induced necrosis. Treatment plans were reviewed to determine the association between the imaging changes and the distribution of RT dose. The median follow-up for the 6 patients who are still alive was 12.1 years (range, 7.2-14.6 years).

RESULTS
Study Cohort
A total of 38 patients (29 males and 9 females) with a median age at diagnosis of 8.19 years (range, 3.13-20.10 years) were included in this study. Initial risk classification was SR in 17 (45%) and HR in 21 (55%). The median time from diagnosis to first progression was 1.26 years (range, 0.18-8.74 years). Thirteen patients were treated with surgery at the time of recurrence. Extent of resection ranged from biopsy to gross total resection. Six of the 13 surgery patients were irradiated after surgery.
Reirradiation Cohort

CoHorts of patients who underwent re-RT and those that were treated without re-RT were not substantially different, other than the HR patients with more disease burden were generally not treated with re-RT. Characteristics of the 14 patients who received a second course of RT and their treatment at the time of initial diagnosis and recurrence are described in Tables 1 and 2. The reirradiation cohort included 11 SR patients with a median age of 15.4 years (range, 7.35-25.63 years) and 3 HR patients with a median age of 12.32 years (range, 8.5-21.95 years). SR patients were more likely to receive reirradiation in our cohort (P = .0022). The median time from first progression to reirradiation was 3.08 months (range, 0.67-48.33 months). Nine patients had at least 1 course of chemotherapy after reirradiation (Table 1).

Among the 11 reirradiated SR patients, disease progression was observed in 5 within 5 years of diagnosis, and a sixth patient progressed within 10 years. SR patients were more likely to receive reirradiation in our cohort (P = .0022). The median time from first progression to reirradiation was 3.08 months (range, 0.67-48.33 months). Nine patients had at least 1 course of chemotherapy after reirradiation (Table 1).

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Risk</th>
<th>Extent of Disease at Relapse</th>
<th>Surgery Prior to Re-RT</th>
<th>Chemo Prior to Re-RT</th>
<th>Re-RT Volume</th>
<th>Chemotherapy After Re-RT</th>
<th>Additional Therapy After Re-RT (Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Average</td>
<td>PF</td>
<td>Y, GTR</td>
<td>Thio, Topo, Carbo</td>
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<td>N</td>
</tr>
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<td>PF, LS</td>
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<td>Topo, Oxal, VP16</td>
<td>Spinal</td>
<td>Lonafarnib</td>
<td>N</td>
</tr>
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<td>Average</td>
<td>Ventricle</td>
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<td>VP16</td>
<td>CSI</td>
<td>None</td>
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<td>PF</td>
<td>Y, GTR</td>
<td>NONE</td>
<td>CSI</td>
<td>GDC-0449</td>
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<td>CPX, topo, erlotinib</td>
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</tr>
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<td>Y, STR</td>
<td>GDC-0449</td>
<td>PF</td>
<td>Tarceva</td>
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<td>9</td>
<td>Average</td>
<td>LS</td>
<td>N</td>
<td>ICE</td>
<td>CSI</td>
<td>GDC-0449, Topo, SAHA, isoretinoin</td>
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<td>Average</td>
<td>LS</td>
<td>N</td>
<td>Erlotinib</td>
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<td>N</td>
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<tr>
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<td>Y, STR</td>
<td>Vismodegib, Carbo, VP16, GDA</td>
<td>CSI</td>
<td>CRA, Topo, CPX</td>
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<td>Average</td>
<td>LS</td>
<td>N</td>
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<td>CSI</td>
<td>SAHA, CRA, VP-16</td>
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<td>Average</td>
<td>LS</td>
<td>N</td>
<td>Topo/CPX/tarceva</td>
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<td>High</td>
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<td>VP16</td>
<td>Focal</td>
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</tr>
</tbody>
</table>

Abbreviations: PF, posterior fossa; LS, leptomeningeal spread; SC, spinal cord; STR, subtotal resection; GK, gamma knife; GTR, gross total resection; Topo, topotecan; Carbo, carboplatin; Oxal, oxaliplatin; VP16 etoposide; CPX, cyclophosphamide; Temo, temozolomide; Thio, thiotepa; ICE, ifosfamide, Carboplatin, etoposide; CRA, cis-retinoic acid; CSI, craniospinal irradiation; GDC-0449, vismodegib; Y, yes; N, no.

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Toxicity

Intratumoral hemorrhage documented by neuroimaging was the most common toxicity observed in this cohort. A
total of 24 patients (63%) had asymptomatic neuroimaging evidence of intratumoral hemorrhage (CTCAE version 4.03, grade 1), and 9 were irradiated. The observed rate of hemorrhage was similar ($P = 1.00$) between the irradiated patients (9 of 14; 64.3%) and the unirradiated patients (15 of 24; 62.5%). There was no difference in hemorrhage rates between 10 of 17 SR patients (59%) and 14 of 21 HR patients ($P = .7396$).

Sixteen patients were noted to have subclinical neuroimaging evidence of necrosis (CTCAE grade 1 or 2). The proportion of patients with necrosis according to risk classification was 10 of 17 (59%) for SR patients compared with 6 of 21 (29%) for HR patients ($P = .0990$). The proportion of patients with necrosis was 9 of 14 (64%) for irradiated patients compared with 7 of 24 (29%) for patients treated with other modalities ($P = .0468$). The patients did not receive additional therapy to treat the subclinical necrosis.

Other toxicities included hypopituitarism in 16 patients, 8 of whom received additional RT, and hypothyroidism in 14 patients, 7 of whom received re-RT. Thus, 8 of 14 patients (57%) in the irradiated cohort experienced hypopituitarism compared with 8 of 24 patients (33%) in the cohort that did not receive a second course of RT ($P = .187$), and 7 of 14 patients (50%) in the irradiated cohort experienced hypothyroidism compared with 7 of 24 patients (29%) in the unirradiated cohort ($P = .298$). Although our data did not suggest an

### TABLE 2. Parameters of Irradiation and Outcomes for Patients With Relapsed Medulloblastoma

<table>
<thead>
<tr>
<th>Interval Between RT Courses (mo)</th>
<th>Second-Course Dose (Gy)</th>
<th>Cumulative Dose</th>
<th>Current Disease Status</th>
<th>Overall Survival (From Date of Relapse [y])</th>
<th>Overall Survival (From Date of Diagnosis [y])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>50.4</td>
<td>106.2</td>
<td>NED</td>
<td>11.9</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>24</td>
<td>79.8</td>
<td>DOD</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>18</td>
<td>73.8</td>
<td>NED</td>
<td>10.6</td>
</tr>
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<td>78</td>
<td>27</td>
<td>82.8</td>
<td>DOD</td>
<td>6.7</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>22.5</td>
<td>78.3</td>
<td>NED</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>107</td>
<td>54</td>
<td>109.8</td>
<td>NED</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>54</td>
<td>109.8</td>
<td>NED</td>
<td>4.7</td>
</tr>
<tr>
<td>8</td>
<td>95</td>
<td>37.5</td>
<td>93.3</td>
<td>DOD</td>
<td>4.9</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>50.4</td>
<td>106.2</td>
<td>DOD</td>
<td>5.4</td>
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<tr>
<td>10</td>
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<td>24</td>
<td>79.8</td>
<td>DOD</td>
<td>0.3</td>
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<tr>
<td>11</td>
<td>42</td>
<td>48</td>
<td>103.8</td>
<td>DOD</td>
<td>1.1</td>
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<tr>
<td>12</td>
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</tr>
<tr>
<td>14</td>
<td>36</td>
<td>54</td>
<td>109.8</td>
<td>NED</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Abbreviations: NED, no evidence of disease; DOD, died of disease.

### Figure 1.
Overall survival according to the use of irradiation (re-RT) in patients with relapsed standard-risk medulloblastoma. Exact log-rank test: $P = .0364$.

### Figure 2.
Overall survival according to the use of irradiation (re-RT) in patients with relapsed high-risk medulloblastoma. Exact log-rank test: $P = .0030$. 
TABLE 3. Major Toxicities Observed in Relapsed Medulloblastoma Patients According to the Use of Irradiation

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Nonirradiated Patients and Toxity (%)</th>
<th>Irradiated Patients and Toxity (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (grade 1)</td>
<td>15/24 (62.5%)</td>
<td>9/14 (64.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>8/24 (33.3%)</td>
<td>8/14 (57.1%)</td>
<td>.187</td>
</tr>
<tr>
<td>Necrosis (grades 1, 2)</td>
<td>7/24 (29.2%)</td>
<td>9/14 (64.3%)</td>
<td>.047</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7/24 (29.2%)</td>
<td>7/14 (50.0%)</td>
<td>.298</td>
</tr>
</tbody>
</table>

increased incidence of pituitary or thyroid dysfunction in the patients treated with re-RT compared with those treated with other salvage therapies (Table 3), the lack of significance may be attributable to the relatively small sample size. As part of the analysis of the prevalence of these 4 toxicities, we assessed whether the patients who had received a second course of RT had a larger number of toxicities based on a trend test. There appears to be some evidence suggesting that patients who received additional RT were more likely to experience a larger number of these toxicities (P = .0124).

DISCUSSION

There is no standard approach to the management of children with recurrent medulloblastoma. The prognosis for these patients remains dismal, and there are few long-term survivors. Treatment options include surgery, different methods of irradiation, and a variety of chemotherapy regimens. Although radiation therapy is an essential component of multimodality therapy in the treatment of newly diagnosed MB, there has been much debate about the use of irradiation at the time of progression because of the potential for toxicity and uncertainty about its ability to improve overall survival. The purpose of our study was to evaluate the impact of irradiation on the patient, use of chemotherapy, volume of brain irradiation, and intensified chemotherapy could lead to clinically significant complications and should be carefully monitored.

Ionizing radiation induces more damage to the immature or developing brain and is associated with histopathologic changes and cognitive decline. Age of the patient, use of chemotherapy, volume of brain irradiated, fraction size, and total dose are the key factors when determining tolerance of the CNS to irradiation. Exposure of brain parenchyma to therapeutic doses of RT is associated with areas of demyelination and vasculopathy, which contribute to thrombosis and may eventually lead to therapy-induced necrosis.

Characteristics common to those patients doing well clinically after re-RT include response to initial RT, length between re-RT courses, and intensified chemotherapy could lead to clinically significant complications and should be carefully monitored.

The use of irradiation in our series was not systematic and was based mainly on clinical factors, including symptomatology, and the risk for potential side effects. Clearly, patients with asymptomatic progression at the primary site have more options than those with symptomatic neuraxis metastases, and similarly those initially treated for SR medulloblastoma have more options than those treated for HR medulloblastoma. Based on the results presented here, the use of radiation therapy at the time of first failure should be considered as a component of therapy, and comprehensive irradiation in dose and volume should be presented as an option to those with limited disease burden and limited prior treatment history. The effectiveness of irradiation must be balanced against the risk of potential side effects, most notably the risk of central nervous system (CNS) necrosis, which may affect quality of life or lead to fatal complications. Fortunately, in our small series, CNS necrosis was a subclinical observation and transient; however, with the goal of intensifying therapy in these patients to improve outcomes, the additive effects of aggressive surgery, radiation therapy, and intensified chemotherapy could lead to clinically significant complications and should be carefully monitored.

Bakst et al reported on a cohort of 13 recurrent MB patients who underwent at least 1 course of re-RT (intensity-modulated radiation therapy was used in 54% of cases) following resection and chemotherapy. The median RT dose and cumulative maximal doses of the second course of RT in this study were of 30 and 84, respectively. Six of these patients had no evidence of disease (NED) at the time of first failure should be considered as a component of therapy, and comprehensive irradiation in dose and volume should be presented as an option to those with limited disease burden and limited prior treatment history. The effectiveness of irradiation must be balanced against the risk of potential side effects, most notably the risk of central nervous system (CNS) necrosis, which may affect quality of life or lead to fatal complications. Fortunately, in our small series, CNS necrosis was a subclinical observation and transient; however, with the goal of intensifying therapy in these patients to improve outcomes, the additive effects of aggressive surgery, radiation therapy, and intensified chemotherapy could lead to clinically significant complications and should be carefully monitored.

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years after their initial recurrence. Most patients in this study (12 of 13 patients) were SR at initial diagnosis and underwent surgical resection of gross residual disease, and 69% also received initial chemotherapy before additional RT. Of note, the majority of these patients had focal recurrences and did not have M+ disease or leptomeningeal spread.

High-dose chemotherapy with peripheral blood stem cell support is not a reliable curative option for patients who have received optimal prior therapy of RT and platinum-containing chemotherapy. Massamino et al had 10 patients who all underwent induction chemotherapy followed by myeloablative therapy and finally additional RT. Seven patients had an additional RT dose of 20.2 Gy to the entire CNS whereas 3 patients had additional local RT exceeding 50 Gy. Three-year event-free survival (EFS) and overall survival (OS) were 19% and 56% respectively. One patient, however, was alive at 93 months (median survival, 41 months). Dunkel et al administered carboplatin, thiopeta, and etoposide to 23 patients who had recurrent MB, and 7 patients maintained EFS for a median of 54 months after autologous stem cell rescue. The EFS and OS were 34% and 46%, respectively. However, this study included younger patients originally treated only with chemotherapy who did not receive RT at the time of initial treatment. An expanded follow-up series including only those recurrent MB patients who were irradiated as part of their initial therapy reported that patients who received additional RT as part of their retrieval therapy had a trend toward better EFS.

Another study had administered high-dose cyclophosphamide to 7 recurrent MB patients who had all received prior RT. All 7 patients had a response during the treatment, but following completion, relapses occurred (median, 11.5 months) in all except 2 patients. They concluded that although cyclophosphamide can induce a high response rate, it cannot achieve long-term control, and MB patients who had both RT and chemotherapy had a better survival period than those who had chemotherapy alone. A third study treated 49 patients with recurrent or poor prognosis CNS malignancies with high-dose chemotherapy regimens followed by autologous stem cell rescue. Nineteen patients had MB, 4 of whom remain disease free. It is important to note that those 4 patients all had focal recurrences. All patients with widespread recurrence suffered disease progression.

Generally, the patients with single site of recurrence and minimal residual disease appear to have the greatest survival benefit after retreatment, irrespective of the modality. Our study suggests that average-risk patients who received a second course of RT may have better OS than their counterparts who were treated otherwise. However, this observation is based on a single variable analysis that does not take into consideration other factors such as other salvage therapies, pathology, and molecular subtype, which are known to affect survival. Five SR patients are currently alive, and all have NED. Although the OS was improved in our cohort of recurrent high-risk MB patients treated with a second course of RT, there were only 3 patients who received re-RT and only one-third were alive 7 years after diagnosis. It is not possible to determine whether CSI contributed to longer survival in this cohort, as all but 1 of the average-risk patients and none of the HR patients received CSI. There were limitations in providing a second course of CSI to HR patients, as they had already received near the maximal tolerated dose of radiation at the time of diagnosis.

There were no differences in the incidence of hemorrhage, pituitary, or thyroid dysfunction between patients who did and did not receive a second course of RT; however, our data suggested an association between RT and a higher rate of necrosis (P = .047). We also observed larger cumulative numbers of these toxicities in patients who were treated with RT.

Our data suggest that undergoing a second course of RT may have contributed to better OS in patients with recurrent MB. Based on our relatively small cohort of patients with medulloblastoma who received similar initial treatment, a second course of RT may be considered a reasonable salvage treatment option in select patients who have minimal residual disease at the time of recurrence.

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