Successful Treatment of Metastatic Relapse of Medulloblastoma in Childhood With Single Session Stereotactic Radiosurgery: A Report of 3 Cases

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Summary: Stereotactic radiosurgery (SRS) is an increasingly used treatment modality in adults, but its use and effectiveness in pediatric brain tumors is still uncertain. We describe 3 patients with metastatic relapse of medulloblastoma, who were treated with SRS, and achieved prolonged, progression-free survival. Tolerability of the treatment was excellent with no adverse effects reported. This work adds to the growing evidence that SRS may have an important role to play in the treatment of pediatric brain tumors.

Key Words: metastatic relapse, medulloblastoma, stereotactic radiosurgery, pediatric

M edulloblastoma is the most common malignant brain tumor in childhood.¹ Multimodal treatment of localized disease, comprising complete surgical resection, radiotherapy, and chemotherapy can result in 5-year event-free survival of up to 81%.² Metastatic disease at presentation is associated with a less favorable prognosis, with a 5-year survival rate of around 70%.³ Patients with metastatic relapse or disease progression are unlikely to be cured, but may achieve good remission with additional treatment. Reported approaches include second look surgery,⁴ further radiotherapy, and intensive chemotherapy regimens with or without hemopoietic stem cell rescue.⁵⁶ Stereotactic radiosurgery (SRS) is a relatively novel technique for the management of pediatric brain tumors and their metastases. Precise cross-sectional localization, is achieved using fixation in a head frame and multiple intersecting beams are used to deliver a large single fraction of radiation to a discrete area of tumor. There is increasing evidence it may successfully treat pediatric brain tumors with isolated reports of its use in metastatic relapse of medulloblastoma.⁸–¹⁰ We describe prolonged progression-free survival in a series of 3 patients with metastatic relapse of medulloblastoma treated with SRS.

MATERIALS AND METHODS

Patient Cohort

Three children between the ages of 10 and 16 were treated at our center with SRS after metastatic relapse of medulloblastoma.

Patient characteristics are detailed in Table 1. Patient 1 developed spinal cord compression shortly after surgery and required urgent focal radiotherapy, followed by intensive chemotherapy and craniospinal radiotherapy. Histopathology demonstrated desmoplastic medulloblastoma with areas of advanced neurocytic differentiation. Patients 2 and 3 were both diagnosed with classical medulloblastoma, enrolled on the hyperfractionated radiotherapy trial (ClinicalTrials.gov: NCT00276666) and treated with surgical resection, hyperfractionated radiotherapy, and intensive chemotherapy. Stains for β-catenin were not in use at time of diagnosis.

SRS was offered after small volume disease relapse was detected on routine surveillance magnetic resonance imaging (MRI). Patients 1 and 3 had no treatment other than SRS for their disease recurrence. Patient 2 received oral etoposide while awaiting approval for SRS.

Treatment by SRS

The decision to administer SRS was made by a pediatric neuro-oncology multidisciplinary team. Patient 1 was treated under local anesthetic in a head frame. Patients 2 and 3 were treated under general anesthetic. Planning for all cases was performed on DICOM MR images using Leksell GammaPlan software (Elektra AB, Stockholm, Sweden). Individual lesions measured from 8.5 to 92 mm³, with a total disease volume of 92, 32.4, and 39.3 mm³ in patients 1, 2, and 3, respectively. Therapy was delivered using a Leksell Gamma Knife (Elektra AB) in a single session in all cases, with total “beam on” times of 17.8 to 51.2 minutes.

RESULTS

Response to SRS

The treatment was administered to all 3 patients as planned. Response to treatment was monitored by serial MRI and clinical review. Figure 1 shows the imaging for patient 1 at initial diagnosis of disease relapse, immediately before SRS and then at 3 and 12 months after SRS.

All patients had an excellent radiological response to treatment. In patient 1, 2 months after radiosurgery the right frontal lesion showed changes suggestive of hemorrhage secondary to the treatment (Fig. 1). After 6 months
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Time of SRS</th>
<th>Initial Diagnosis</th>
<th>Initial Treatment</th>
<th>Disease Status at End of Treatment (Date)</th>
<th>Interval Between End of Treatment and SRS</th>
<th>Disease Status at Time of SRS</th>
<th>Dose Administered</th>
<th>Follow-up (SRS to Most Recent MRI)</th>
<th>Patient Status at Last Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>16 y</td>
<td>Medulloblastoma</td>
<td>Complete macroscopic resection of primary 12.6 Gy to T6 compressive lesion 33.8 Gy CSRT 21 Gy PFB</td>
<td>Complete Remission at primary site Residual abnormality in thoracic thecal sac (March 2006)</td>
<td>1 y 8 mo</td>
<td>Single 92 mm³ metastatic nodule in the right frontal lobe</td>
<td>25 Gy to metastatic nodule (50% isocontour)</td>
<td>4 y</td>
<td>Stable disease</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>14 y</td>
<td>Medulloblastoma</td>
<td>Complete macroscopic resection of primary HART and chemotherapy as per protocol Oral etoposide after cerebral metastatic recurrence</td>
<td>Complete Remission (March 2007)</td>
<td>2 y</td>
<td>Three recurrent nodules; 22 mm³ in right cerebellum, 8.5 mm³ in left side of the cerebellar peduncle, 8.8 mm³ in the left occipital lobe</td>
<td>20 Gy to lesion right cerebellum (60% isocontour) 15 Gy to lesion cerebellar peduncle (60% isocontour) 20 Gy to lesion right cerebellum (60% isocontour)</td>
<td>3 y 3 mo</td>
<td>Complete remission</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>10 y</td>
<td>Medulloblastoma</td>
<td>Complete macroscopic resection HART and chemotherapy as per protocol</td>
<td>Complete Remission (July 2008)</td>
<td>1 y 2 mo</td>
<td>Two recurrent nodules, 1 in each cerebellar hemisphere; 13.1 mm³ on left 19.3 mm³ on right</td>
<td>25 Gy to lesion right cerebellum (50% isocontour) 25 Gy to lesion left cerebellum (50% isocontour)</td>
<td>2 y 6 mo</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>

Packer chemotherapy (CCG A9961 arm A), lomustine 75 mg/m² PO D1, cisplatin 70 mg/m² IV D1, vincristine 1.5 mg/m² D1, D8, D15.
Total to primary, 62 Gy.
CSRT indicates craniospinal radiotherapy; HART, hyperfractionated radiotherapy—CSRT 39.68 Gy, PFB 22.32 Gy (all given as 1.24 Gy twice/d); MRI, magnetic resonance imaging; PFB, posterior fossa boost; SRS, stereotactic radiosurgery.
the lesion showed central necrosis with a tiny rim of enhancement and mild surrounding edema on T2 and fluid-attenuated inversion recovery imaging. One year after radiosurgery, imaging demonstrated stable disease with no abnormal enhancement in the frontal lesion. This was unchanged on most recent imaging 4 years after radiosurgery. Clinically the patient remains asymptomatic.

In patient 2, 3 months after SRS, MRI appeared to suggest an increase in size of the 2 lesions in the right cerebral hemisphere and left cerebellar peduncle. The left occipital lesion was not visible. On repeat imaging at 6 and 12 months it was apparent these were transient changes attributable to the radiosurgery. At most recent review, 2 years and 10 months after radiosurgery, the patient was clinically well and there was no radiological evidence of disease on imaging.

In patient 3, 3 months after SRS there had been a marked decrease in the size of both cerebellar lesions with only the left lesion being visible. No disease was apparent on imaging 12 months after radiosurgery and at most recent review, 2 years after SRS, there was no clinical or radiological evidence of recurrence.

**Adverse Effects**

The treatment was tolerated well in all cases, including patient 1 who had the frame fitted and the SRS administered under local anesthetic. At the time of publication no adverse effects attributed to radiosurgery are apparent.

**DISCUSSION**

In this case series of 3 patients we describe the experience of a single center in treating small volume metastatic recurrence of medulloblastoma with SRS. In 2 patients there is no evidence of disease recurrence after at least 2 years of follow-up. In the other patient, who had extensive craniospinal leptomeningeal metastases at presentation, the disease is stable 4 years after radiosurgery. Tolerability of the treatment was excellent with no apparent short-term or long-term adverse effects.

Conventional radiotherapy is one of the cornerstones of treatment in high-risk medulloblastoma and many other brain tumors, but concerns relate to its adverse effects. SRS involves irradiating only a small area of tissue with high-dose radiation and seems to have a better safety profile with regard to children's cognitive decline than whole-brain radiotherapy. There is therefore growing interest in assessing the use of SRS in pediatric brain tumors.

Although there is increasing evidence that SRS may have a role to play in the treatment of a number of different pediatric brain tumors its use is still mainly described within case series. As long ago as 1996, SRS was demonstrated to be effective in the treatment of surgically incurable benign brain tumors and a possible role in the treatment of malignant brain tumors was identified. It has subsequently shown to be an efficacious treatment in children with recurrent or residual intracranial ependymoma and juvenile pilocytic astrocytoma. In general few significant side effects have been reported although higher complication rates have been observed in adults.

There is much less experience with SRS for metastatic relapse of medulloblastoma in the pediatric population with only around 28 children in total having been described as receiving such treatment. Although we only have 3 patients in our cohort our experience is therefore still an important addition to the literature. We echo the findings of 2 other centers who reported that metastatic relapse of medulloblastoma can be treated solely by SRS with few significant side effects and may achieve a clinically relevant period of disease control. There is also some adult data supporting the use of SRS to treat foci of intracranial medulloblastoma relapse. Although most of the published
work on SRS in pediatric metastatic medulloblastoma is encouraging, there is 1 report in which the use of high dose chemotherapy and SRS in 8 children with metastatic relapse of medulloblastoma did not show an effect on survival. This group also reported that 1 child developed brain stem edema after SRS causing bulbar palsy and quadriaparesis.10

The optimal radiation dose for use in SRS for metastatic medulloblastoma remains uncertain. Clearly, when considering dose a balance must be struck between mitigating possible side effects whilst preserving therapeutic efficacy. The patients in our series had relatively large doses of radiation compared with similar patients described in the literature. For example, Milker-Zabel et al.8 used SRS with a mean dose of 15 Gy to treat patients with recurrent medulloblastoma and, in conjunction with fractionated stereotactic radiotherapy, reported an impressive effect on local control. SRS with doses of around 15 Gy have also been effective in treating ependymomas and pilocytic astrocytomas in children.15,16 Our patients typically received between 20 and 25 Gy during each treatment of SRS (Table 1). Although none of our patients appeared to have any significant acute side effects and all tolerated their treatment extremely well, it is possible that lower doses of radiation may be efficacious, with a corresponding reduction in the likelihood of significant side effects. However, it is only with more studies and longer follow-up that this will be proven.

One known difficulty with SRS is assessing response to treatment. Transient tumor edema has been described as mimicking disease progression in both adults19 and children on MRI.20 In our cohort one of our patients (patient 2), appeared to demonstrate disease progression soon after radiosurgery but this resolved on repeat imaging. A period of careful observation may therefore be warranted if imaging suggests disease progression after SRS, and no clinical symptoms are apparent. The literature suggests the MRI changes attributable to radiosurgery should resolve within 6 to 15 months in the majority of cases20 which is consistent with our experience.

A possible weakness of our study is that the lesions which were felt to represent metastatic recurrence were not biopsied. However, suspect lesions were followed on at least 2 short interval scans after detection to confirm progression. Imaging characteristics also matched the primary tumor. The clinical team in charge of the patients were therefore confident that all lesions represented metastatic recurrence and that the risks involved in obtaining formal histological confirmation could not be justified.

In conclusion, our case series demonstrates that, in carefully selected patients, SRS can achieve excellent disease control with minimal toxicity and short inpatient stay. It is now time for a larger collaborative study to investigate the efficacy of this treatment modality in pediatric patients with metastatic relapse of medulloblastoma.

REFERENCES