Patterns of Failure in Patients With Adult Medulloblastoma Presenting Without Extraneural Metastasis

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**Objectives:** The objective of this study is to evaluate long-term outcomes, specifically patterns of tumor recurrence, in patients with adult medulloblastoma treated with radiotherapy.

**Methods:** We recorded outcomes of 28 (median age, 25.5 y) patients 18 years old or above with M0 to M3 medulloblastoma treated between 1971 and 2012. Among them, 61% had standard-risk disease. All received craniospinal irradiation with a posterior fossa boost. Median dose to the craniospinal axis was 36 Gy. Median total dose to the primary site was 55.9 Gy and 46% received chemotherapy.

**Results:** Median follow-up among survivors was 14.2 years. At 5 and 10 years, local control was 80% and 73%, overall survival was 71% and 59%, cause-specific survival was 71% and 63%, and freedom from progression was 68% and 59%. Tumors recurred in 11 patients (39%); median time to recurrence was 2.4 years, and 82% of recurrences developed in patients with standard-risk disease. Of the recurrences, 55% involved the primary site; 36% were bone metastases without neural axis recurrence. There were no isolated recurrences in the spinal canal or ventricular system outside of the posterior fossa.

**Conclusion:** The primary site is the main site of medulloblastoma recurrence, with isolated bone metastases more common in adults than children. Our results prompt us to consider 4 modifications to our treatment approach with adults who present with medulloblastoma: (1) initial staging to include PET or bone scan; (2) radiotherapy dose to the primary site of 59.4 Gy; (3) chemotherapy during and/or following initial staging to include PET or bone scan twice a year for 3 years.

**Key Words:** radiation oncology, craniospinal irradiation, radiation therapy, medulloblastoma

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Only 10% of medulloblastomas present in adults but most treatment recommendations are extrapolated from the experience in pediatric patients. The purpose of our study is to evaluate long-term outcomes in patients treated with radiation therapy for medulloblastoma that was diagnosed in the adult age range with particular focus on pattern of tumor recurrence.

**METHODS**

Under institutional review board approval, we recorded outcomes in all patients that met our inclusion criteria: M0 to M3 medulloblastoma diagnosed at age 18 years or above and radiation therapy treatment in our department between January 1, 1971, and December 31, 2012. Our study population is 28 patients. Initial staging included computed tomography or magnetic resonance scan of the brain and entire spine. In the absence of radiographic evidence of tumor in the spinal canal, lumbar puncture was performed to evaluate tumor cytology in the craniospinal fluid (CSF).

Two patients had visible drop metastasis in the spinal canal (M3) and 3 patients had positive CSF cytology without radiographic evidence of drop metastasis.

Table 1 summarizes the main patient and tumor characteristics. Stage and risk stratification were based on the modified Chang stage.

All patients were treated with maximal surgical resection and craniospinal irradiation followed by a boost to the entire posterior fossa. Tables 2 and 3 summarize details of radiotherapy for each risk group. Fifty-four percent (15/28) of the patients were treated with radiation once-a-day with 1.8 Gy and 46% (13/28) were treated twice-a-day with 1.2 Gy per treatment.

The whole brain was treated using lateral opposed fields and the spine with 1 or 2 posterior fields, depending on length. The posterior fossa was boosted in all patients through either lateral opposed fields or more conformal plans. In 2 patients with visible drop metastasis to the spine, the area of visible disease was boosted through a posterior field.

The use of chemotherapy was at the discretion of the managing physicians and there were no specific guidelines over this time period. Almost half (46%, 13/28) of the patients received chemotherapy. Nine patients received chemotherapy only after completion of radiotherapy (cisplatinum, VP16, and cytoxan). Two patients received concurrent chemotherapy (vincristine and RT, and 2 other patients received concurrent vincristine) and adjuvant (vincristine and lomustine or cisplatinum, VP16, and cytoxan) chemotherapy.

**Statistical Methods**

In the overall survival analysis, an event is death from any cause. In the cause-specific survival analysis, an event is death from medulloblastoma. In the progression-free survival analysis, an event is medulloblastoma recurrence. It was not possible to determine toxicity from treatment or late complications from treatment with an acceptable degree of accuracy. The only potential complication from treatment that we were able to evaluate was second tumor development. SAS and JMP software were utilized for statistical analyses (SAS Institute, Cary, NC). The Kaplan-Meier product limit method provided outcome estimates.

**RESULTS**

**Tumor Recurrence**

The median follow-up among survivors was 14.2 years (range, 4.4 to 30.8 y). The 10-year actuarial local control rate...
was 73%. The 10-year progression free survival was 59%. The median time to recurrence of 2.4 years (range, 0.4 to 7.3 y). All but 1 of these 11 patients with recurrence eventually died from progression of medulloblastoma. One patient with recurrence was cured with salvage therapy. This patient had an isolated posterior fossa recurrence approximately 1 year after initial treatment, underwent repeat surgery, repeat radiotherapy, and additional chemotherapy and was without evidence of disease at last follow-up 26 years later.

Survival

The 10-year cause-specific survival and overall survival rates were 63% and 59%, respectively. The median survival after radiotherapy was 3.1 years (range, 0.5 to 9.1 y). One patient died 5.5 years after radiotherapy of causes unrelated to medulloblastoma or treatment. Figure 1 shows Kaplan-Meier estimates of freedom from selected endpoints.

Pattern of Recurrence

Table 4 shows the pattern of recurrence in the 11 patients who developed recurrent medulloblastoma. Of the patients developing a recurrence, 9 had standard-risk disease at diagnosis, and the other 2 had high-risk disease. In the 9 standard-risk patients, 4 developed primary site recurrences, 4 developed extraneural recurrences, and 1 patient had an unknown recurrence site. We classify 1 patient’s site of recurrence as "unknown" because multiple sources document recurrence of medulloblastoma but we are unable to confirm status at the primary site.

Both high-risk patients who recurred did so at the primary site and all of these patients were initially classified as being high-risk because of > 1.5 cm² residual at the primary site.

Given the limitations of the imaging studies used over the study period, all primary site recurrences were classified as being at the resection site (rather than distant from the resection site in the posterior fossa).

All 4 patients with isolated extraneural recurrence had bone metastases without disease in other organs. All of these 4 patients were standard-risk. None of these patients had a bone marrow biopsy during initial staging and none received chemotherapy as part of the initial treatment program.

Multivariate analysis is not meaningful with only 28 patients and multiple prognostic factors. We performed a univariate analysis of factors that could be related to the primary site recurrence. We do not present p values because of the limitations of these comparisons in the absence of control for confounding.

Table 5 shows the pattern of recurrence in the 11 patients who developed recurrent medulloblastoma. Of the patients developing a recurrence, 9 had standard-risk disease at diagnosis, and the other 2 had high-risk disease. In the 9 standard-risk patients, 4 developed primary site recurrences, 4 developed extraneural recurrences, and 1 patient had an unknown recurrence site. We classify 1 patient’s site of recurrence as "unknown" because multiple sources document recurrence of medulloblastoma but we are unable to confirm status at the primary site.

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other known prognostic factors: yes chemotherapy (2/13) versus no chemotherapy (4/15), classic histology (6/21) versus desmoplastic/unknown histology (0/7), treatment before year 2000 (4/17) versus treatment after year 2000 (2/11), and once-a-day fractionation (5/15) versus twice-a-day fractionation (1/13).

Second Tumors Following Treatment
The only second tumor to develop in the 28 patients in this series was a follicular thyroid cancer that was diagnosed 22 years after radiotherapy for medulloblastoma. This patient was alive without evidence of medulloblastoma or thyroid cancer 26 years after initial treatment.

DISCUSSION
The Value of Treatment
A question in adult oncology is the value of cancer cure relative to competing causes of death from noncancer problems. Our results demonstrate that control of medulloblastoma was of major importance in our adult patients. As shown in Figure 1, overall, cause-specific, and progression-free survival rates are almost identical. This indicates that tumor recurrence determines survival in this patient population, at least over the decade following diagnosis. These findings likely reflect the fact that most adults with medulloblastoma present in the "young adult" age range. The median age in our series was 25 years.

<table>
<thead>
<tr>
<th>Location of Recurrence</th>
<th>Median Time to Recurrence (Range)</th>
<th>No. of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All recurrences</td>
<td></td>
<td>11 pts (39% of pts) 2.4 y (0.4-7.3 y)</td>
</tr>
<tr>
<td>Posterior fossa (+ spinal seeding)</td>
<td>6 pts (55% of pts) 2 y (0.4-7.3 y)</td>
<td></td>
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<tr>
<td>Spinal canal or intracranial without recurrence in the posterior fossa</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Isolated extraneural recurrence (all bone metastases)</td>
<td>4 pts (36% of recurrences) 2.4 y (range, 0.5-3 y)</td>
<td></td>
</tr>
<tr>
<td>Unknown location</td>
<td>1 pt</td>
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While most patients in our series appear to be cured, there is considerable margin for improvement in treatment of adult medulloblastoma. About 40% (11/28 patients) of the patients in our series developed a disease recurrence even though the majority of patients were in the standard-risk category at diagnosis.

Pattern of Recurrence
Data are scarce on the pattern of recurrence in adult medulloblastoma following radiotherapy in M0 to M3 patients. A recent paper by Kocakaya et al12 summarizes the world literature on adult medulloblastoma.3–11 As demonstrated in the meta-analysis, most publications focus on survival and include patients with all stage categories. Adult medulloblastoma is known to relapse, with recurrence rates reported at around 40%.12,13 Most relapses are seen in the posterior fossa, although extraneural recurrences do occur.12,14 The median time to relapse varies between 18 and 50 months.12–15 Thus, relapse is common, and long-term follow-up is important.

Our results confirm that the main obstacle to achieving a high cure rate for patients with medulloblastoma is an inability to control the tumor at the primary site. In our series, 55% of recurrences included a recurrence at the primary site, although extraneural recurrences do occur.12,14 The median time to relapse varies between 18 and 50 months.12–15 Thus, relapse is common, and long-term follow-up is important.

Potential Implications of Our Findings
Small patient numbers and the absence of a prospective study design make it impossible to draw definitive conclusions about any issue related to adult medulloblastoma. A major limitation of our study, and all publications on adult medulloblastoma, is the lack of information on molecular subtype. It is now clear in the pediatric population that molecular subtype is a powerful predictor of clinical outcome.17–19

We need more information to determine how to incorporate molecular subtyping into recommendations for treatment of adults with medulloblastoma but it is likely that molecular phenotype will drive clinical management in the near future. Given the many limitations of our series and the other published studies, at this point in time, our results prompt us to consider 4 modifications to our treatment approach with patients who present with medulloblastoma in the adult age group:

Increase the Intensity of Looking for Occult Bone Metastasis During Initial Staging
We plan to include positron emission tomography (PET) or skeletal scintigraphy (bone scan) as part of initial staging in all of our adult patients with medulloblastoma.

We are struggling with the decision to add bone marrow biopsy as a routine staging study. It is possible that the bone
metastases that we observed in our series were a manifestation of bone marrow disease that we did not recognize at diagnosis. Bone marrow biopsy is a standard part of the staging in children with medulloblastoma, but there are no accurate data on the rate of a positive result in older children or adults with no suggestion of bone metastasis by clinical exam, routine laboratory and imaging studies. Current guidelines on treatment of adult medulloblastoma from the National Comprehensive Cancer Network do not require bone marrow biopsy. The specific wording is that bone marrow biopsy should be done “if clinically indicated.”

Increase Radiotherapy Dose to the Primary Site

As the primary location of recurrence is at the primary site, and recurrence usually leads to death from medulloblastoma, in our Gainesville practice, we plan to increase the final dose to the primary site in adult patients to 59.4 Gy at 1.8 Gy per treatment. We do not know of data evaluating dose response for tumor control above 54 Gy in children or adults with medulloblastoma, so this plan is not evidence-based. As is now standard in many centers treating pediatric patients, our primary site boost after completing craniospinal radiotherapy is limited to the resection cavity plus visible tumor plus a 0.5-cm to 1.0-cm margin.

Add Chemotherapy Following Radiotherapy in Medically Fit Patients

Chemotherapy following radiotherapy is now standard in most pediatric patients with medulloblastoma. Current National Comprehensive Cancer Network guidelines specific for adult medulloblastoma recommend platinum-based chemotherapy after radiotherapy in all high-risk cases. In standard-risk cases, the guidelines present chemotherapy as an option but do not require it. Since 36% (4/11 patients) of recurrences in our series were bone metastases without recurrence in the neural axis in patients with standard-risk disease, our plan is to recommend postradiotherapy chemotherapy to all adults unless contraindicated because of comorbidity. This recommendation is supported by a recent study from the National Cancer Database.

Follow-up to Include Positron Emission Tomography or Bone Scan Twice a Year for 3 Years

In response to the finding that isolated extraneural recurrence was not rare in our adult series, our plan is to perform PET or bone scan every 6 months for at least 3 years following the completion of treatment unless symptoms warrant more frequent imaging. The latest bone metastasis in our series presented 3 years after treatment so it is unclear how long systemic imaging will be useful. This plan for imaging follow-up is not supported by data in our study and we do not know of other studies evaluating this topic.

REFERENCES