

## Characterization of recurrence patterns and outcomes of medulloblastoma in adults: The University of Texas MD Anderson Cancer Center experience

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### Abstract

**Background.** Medulloblastoma in adults is rare and treatment decisions are largely driven from pediatric literature. We sought to characterize recurrent medulloblastoma in adults.

**Methods.** From a single-institution dataset of 200 adult patients diagnosed with medulloblastoma during 1978–2017, those with recurrence were analyzed for clinical features, treatment, and outcome.

**Results.** Of the 200 patients, 82 (41%) with median age of 29 years (18–59) had recurrence after a median follow-up time of 8.4 years (95% CI = 7.1, 10.3). Of these, 30 (37%) were standard-risk, 31 (38%) were high-risk, and 21 (26%) had unknown-risk diseases at the time of initial diagnosis. Forty-eight (58%) presented with recurrence outside the posterior fossa, of whom 35 (43%) had distant recurrence only. Median Progression-free survival (PFS) and OS from initial surgery were 33.5 and 62.4 months, respectively. Neither PFS nor OS from initial diagnosis differed between the standard-risk and high-risk groups in those who experience recurrence ( $P = .505$  and  $.463$ , respectively).

Median OS from first recurrence was 20.3 months, also with no difference between the standard-risk and high-risk groups ( $P = .518$ ). Recurrences were treated with combinations of re-resection (20 patients; 25%), systemic chemotherapy (61 patients; 76%), radiation (29 patients; 36%), stem cell transplant (6 patients; 8%), and intrathecal chemotherapy (4 patients; 5%). Patients who received radiation at recurrence had better OS (32.9 months) than those who did not (19.2 months) ( $P = .034$ ).

**Conclusions.** Recurrent medulloblastoma in adults has a poor prognosis irrespective of initial risk stratification. Recurrence commonly arises outside the posterior fossa years after initial diagnosis.

### Key Points

- Medulloblastoma in adults frequently recurs outside the primary site and has poor prognosis.
- Clinical risk stratification at initial diagnosis does not affect survival after first recurrence.
- Radiation at recurrence is associated with improved survival compared to other modalities.

### Importance of the Study

Data on medulloblastoma in adults are scarce, particularly with regard to long-term natural history and recurrence, and there is substantial variation in treatment modalities and reported survival. This is the largest retrospective single-institution series of recurrent adult medulloblastoma reported to date. We characterized clinical patterns, treatment modalities, responses to treatment, and survival outcomes. These results inform understanding of the natural history of adult medulloblastoma, the impact of treatments, and appropriate endpoints for future clinical trials. Fifty-eight

percent of recurrences occurred outside the posterior fossa as leptomeningeal disease or distant metastasis including outside the central nervous system (CNS), suggesting the importance of CNS and systemic restaging at recurrence. Overall survival (OS) from the time of recurrence did not differ between patients with standard risk and those with high-risk disease according to the initial clinical risk stratification. Importantly, radiation at the time of recurrence was associated with improved OS.

Medulloblastoma is a highly cellular malignant embryonal tumor that most frequently arises in the posterior fossa of children, in whom it represents 8.4% of all primary central nervous system (CNS) neoplasms.<sup>1</sup> Medulloblastoma arising after the age of 15 years is rare, with approximately 150 new cases in the United States annually.<sup>1</sup> Most of these cases occur in adolescents and young adults; fewer than 8% of all medulloblastoma cases occur in patients aged 40 years and older.<sup>1,2</sup> Owing to the low incidence of adult medulloblastoma and limited data from prospective trials, treatment paradigms for adult medulloblastoma continue to be informed by pediatric data and expert opinion. To date, there are no definitive therapy recommendations for treatment in adults<sup>3</sup> and outcomes for adults have improved slightly over the past 2 decades,<sup>4</sup> in contrast to pediatric patients in whom long-term survival has been increasing.<sup>5</sup> A growing body of evidence suggests that adult medulloblastoma can behave differently from medulloblastoma in the pediatric population, including worse outcomes within molecular subgroups,<sup>6–8</sup> and that further clinical characterization of adult medulloblastoma is required to optimize treatment strategies and improve outcomes.

Patients with medulloblastoma are typically stratified into standard-risk and high-risk groups according to traditional pediatric paradigms, such as the Packer staging system, based on clinical criteria including patient age, extent of resection, histology, and degree of tumor dissemination. Standard-risk patients are those older than 3 years with  $<1.5 \text{ cm}^2$  of residual disease and no metastasis; all others are considered high-risk.<sup>9</sup> This stratification has been useful for determining treatment intensity as well as estimating prognosis. Histologic phenotype also impacts survival with large cell/anaplastic (LC/A) portending a poor prognosis while desmoplastic/nodular and especially medulloblastoma with extensive nodularity (MBEN) correspond with a better prognosis.<sup>10</sup> Additionally, research over the past decade has revealed at least 4 molecular subgroups of medulloblastoma with distinct clinical and molecular characteristics and DNA methylation statuses variably impacting survival. In adults, these subgroups are Sonic Hedgehog (accounting for approximately 60% of cases), group 4 (20%–25%), Wingless/Int1 (15%), and group 3 (extremely rare in adults).<sup>11</sup>

Across these subgroups, the standard of care for both standard-risk and high-risk patients generally includes

maximal safe resection followed by craniospinal irradiation with a boost to the posterior fossa or tumor bed and sites of focal CNS metastasis when present,<sup>12</sup> with the radiation dose depending on risk status.<sup>12,13</sup> The benefit of first-line chemotherapy for standard-risk adult patients has been controversial, although recent studies, including one prospective trial, have demonstrated the feasibility and survival benefit of adjuvant chemotherapy.<sup>12,14–16</sup> It has been previously demonstrated that adjuvant chemotherapy led to superior outcomes and neoadjuvant chemotherapy is associated with inferior outcomes in adult medulloblastoma.<sup>17,18</sup>

Long-term survival is possible in adults; however, outcome after recurrence tends to be poor across all ages, with failure in the posterior fossa being the most common.<sup>19</sup> Relapse occurs in approximately 30% of pediatric cases and is associated with very high mortality despite a variety of attempted treatments, including re-resection, re-irradiation, high-dose chemotherapy with autologous stem cell transplant (SCT), and experimental therapy in clinical trials.<sup>20–22</sup> Late relapse is more common in adults than in the pediatric population,<sup>23</sup> particularly in standard-risk patients.

To date, only small series have been published regarding characteristics and outcomes of recurrent adult medulloblastoma.<sup>23,24</sup> In this single-institution retrospective study, we described the clinical characteristics, treatment strategies, and survival outcomes of 82 adults with recurrent medulloblastoma, a subgroup of 200 adults with medulloblastoma whose data were previously published by our group.<sup>18</sup>

## Methods

### Patient Selection

A total of 200 adults with medulloblastoma initially diagnosed at 18 years of age or older were seen in adult neuro-oncology, neurosurgery, and radiation oncology clinics at The University of Texas MD Anderson Cancer Center (Houston, TX) from January 1978 through April 2017. We selected for further analysis the subset of patients who experienced at least one recurrence during the follow-up period.

### Data Collection

The protocol for data collection were approved by the MD Anderson Cancer Center Institutional Review Board. A comprehensive data collection instrument were built in the REDCap database, in which we recorded patient demographics; vital status; date of death or last follow-up; clinical characteristics, including risk stratification at initial diagnosis; and recurrence data, which included symptoms, location of recurrence, treatment, and survival following recurrence.

The extent of resection was categorized as gross total resection (no residual disease), near-total resection ( $\leq 1.5$  cm<sup>2</sup> of residual disease), subtotal resection ( $>1.5$  cm<sup>2</sup> of residual disease), biopsy, or unknown. Extent of resection was obtained from radiology reports

or clinical notes, and when the extent of resection was not clear from these, postoperative magnetic resonance imaging studies were reviewed, when available. Medulloblastoma was confirmed pathologically at MD Anderson in almost all patients. Leptomeningeal disease was determined radiographically and/or with cerebrospinal fluid analysis.

### Statistical Analysis

Descriptive statistics (frequency distribution, mean [ $\pm$  standard distribution], and median [range]) were used to summarize patient characteristics. Progression-free survival (PFS) was defined as the time from initial surgery to the time of disease progression or death, whichever occurred first. Overall survival (OS) was defined as (1) the time from initial surgery to the time of death, or (2) the time from first recurrence to the time of death. First recurrence was defined as first histological confirmation of recurrence (or imaging demonstration of recurrence if histological confirmation was not obtained). For events that had not occurred by the time of data analysis, times were censored at the time of last contact at which the patient was known to be progression-free (for PFS) or the last time the patient was known to be alive (for OS). The distributions of the time-to-event outcomes were estimated using the Kaplan–Meier method.<sup>25</sup> Log-rank test<sup>26</sup> was performed to test the difference in survival between groups.

## Results

### Clinical Characteristics

Eighty-two of the two hundred patients (41%) were identified as having experienced at least one recurrence; the median follow-up time for the 200 patients was 8.4 years (95% CI = 7.1, 10.3). The median follow-up time for the 82 patients with recurrence was 17.2 years (95% CI = 11.6, not reached). Clinical characteristics are summarized in [Table 1](#). Thirty patients (37%) had been classified as standard-risk and 31 (38%) as high-risk diseases; risk status was unknown in 21 patients (26%). The most frequent symptoms reported at the time of recurrence were headache (61 patients; 74%), nausea (31 patients; 38%), vomiting (29 patients; 35%), ataxia (24 patients; 29%), and dizziness (18 patients; 22%) ([Supplementary Table 1](#)). Among histologic subtypes, there were 30 patients (37%) with classic medulloblastoma, 28 patients (34%) with desmoplastic, 3 patients (4%) with LC/A, and 21 (26%) with unknown histology. At initial diagnosis, one LC/A case was classified as high-risk based on extra-CNS metastasis and LMD, one was standard-risk, and one was unknown risk. Thirty-four patients (42%) had recurrence within the posterior fossa only, while 48 patients (58%) presented with distant recurrence ([Figure 1](#)), including 20 patients (42%) with leptomeningeal disease, 17 (35%) with extra-CNS disease (bone, bone marrow, lung, pleura, lymph nodes, and subcutaneous soft tissue), 9 (19%) with recurrence intradurally in the spine, and 7 (15%) with supratentorial recurrence. Five patients (6%) presented with leptomeningeal disease and a distant dominant metastatic

**Table 1.** Clinical Characteristics of Patients With Recurrent Medulloblastoma

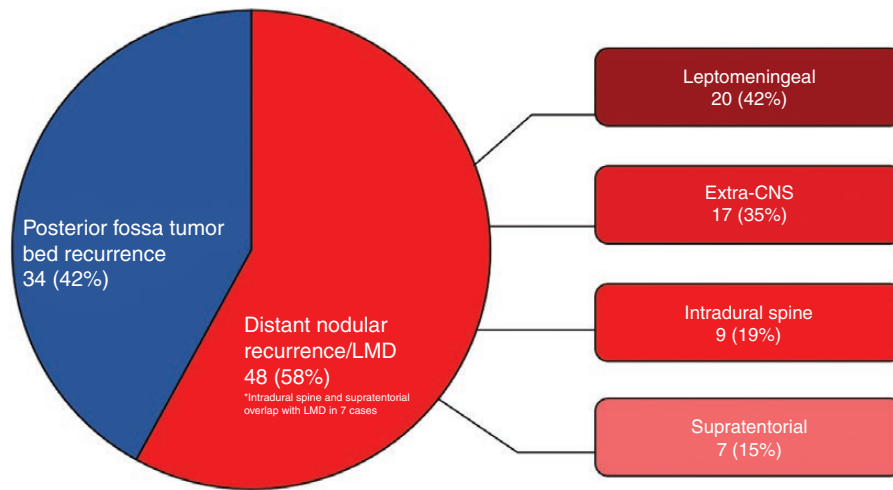
Patients With Recurrence (n = 82)		
Characteristic	n	%
<i>Sex</i>		
Male	52	63.4
Female	30	36.6
<i>Age, years</i>		
≤29	43	52.4
>29	39	47.6
<i>Metastasis*</i>		
M+	11	13.4
M0	37	45.1
Unknown	34	41.5
<i>Risk group*</i>		
Standard	30	36.6
High	31	37.8
Unknown	21	25.6
<i>Histology</i>		
Classic	30	36.6
Desmoplastic	28	34.1
Large cell/anaplastic	3	3.7
Unknown	21	25.6
<i>Initial localization</i>		
Vermis	22	26.8
Fourth ventricle	8	9.8
Left cerebellum	26	31.7
Right cerebellum	24	29.3
Other	9	11.0
Unknown	7	8.5
<i>First-line treatment</i>		
<i>Initial surgery</i>		
Gross total resection	41	50.0
Near-total resection	3	3.7
Subtotal resection	30	36.6
Biopsy	1	1.2
Unknown	7	8.5
Radiation therapy	78	95.1
<i>Chemotherapy</i>		
Neoadjuvant	16	19.5
Concurrent	9	11.0
Adjuvant	27	32.9
Intrathecal	12	14.6

\*At initial diagnosis.

nodule. Thirteen patients (16%) had simultaneous local and distant recurrence, while 35 patients (43%) had distant recurrence only.

Seventy-seven (93.9%) patients had received craniospinal irradiation at initial diagnosis (2 received whole brain

radiation, 1 received only posterior fossa radiation, and 2 were unknown). All patients had data available on treatment received at the time of first recurrence (Table 2). Twenty patients (25%) underwent re-resection, and 61 (76%) were treated with salvage chemotherapy. A variety of



**Figure 1.** Locations of recurrence. LMD – leptomeningeal disease; Extra-CNS – extradural disease including bone, bone marrow, lung, pleura, lymph nodes, and subcutaneous soft tissue; Intradural spine – nodular intradural disease involving spinal cord; Supratentorial – nodular intradural disease involving brain.

**Table 2.** Summary of Survival by Risk Status and Treatment Modality From the Time of Recurrence\*

Risk Group	N	Events	Median Survival (Months)	1-Year Survival Rate	5-Year Survival Rate	10-Year Survival Rate
<i>PFS from time of initial surgery</i>						
All	81	81	33.5 (28.1–37.1)	0.81 (0.71–0.88)	0.17 (0.1–0.26)	0.02 (0–0.08)
Standard risk	30	30	29.9 (19.6–38.8)	0.77 (0.57–0.88)	0.17 (0.06–0.32)	0.00
High risk	30	30	32.4 (19.0–44.6)	0.80 (0.61–0.9)	0.13 (0.04–0.28)	0.03 (0–0.15)
Unknown risk	21	21	35.4 (23.6–57.7)	0.90 (0.67–0.98)	0.24 (0.09–0.43)	0.05 (0–0.2)
<i>OS from time of initial surgery</i>						
All	82	70	62.4 (52.3–77.8)	0.98 (0.91–0.99)	0.53 (0.41–0.63)	0.15 (0.07–0.24)
Standard risk	30	24	54.7 (41.0–82.4)	0.97 (0.79–1)	0.44 (0.25–0.62)	0.05 (0–0.21)
High risk	31	30	61.3 (44.6–84.1)	0.97 (0.79–1)	0.50 (0.31–0.66)	0.17 (0.06–0.32)
Unknown risk	21	16	83.4 (48.8–116.9)	1.00	0.66 (0.42–0.82)	0.22 (0.06–0.45)
<i>OS from time of recurrence</i>						
All	82	69	23.8 (19.0–28.4)	0.74 (0.63–0.82)	0.13 (0.06–0.22)	0.02 (0–0.08)
Standard risk	30	24	20.3 (10.6–26.0)	0.64 (0.43–0.78)	0.12 (0.02–0.3)	0.00
High risk	30	29	25.7 (14.6–30.6)	0.79 (0.6–0.9)	0.10 (0.03–0.24)	0.00
Unknown risk	21	16	28.4 (12.6–37.0)	0.81 (0.57–0.92)	0.19 (0.05–0.41)	0.10 (0.01–0.33)
<i>OS from time of recurrence, by treatment modality</i>						
Re-resection	20	18	26.0 (12.6–30.6)	0.84 (0.59–0.95)	0.20 (0.06–0.4)	0.00
Chemotherapy	61	52	24.4 (19.2–28.6)	0.77 (0.64–0.85)	0.13 (0.06–0.25)	0.03 (0–0.12)
Radiation	29	25	32.9 (23.8–42.2)	0.86 (0.67–0.95)	0.20 (0.07–0.38)	0.00
SCT	6	6	25.2 (19.2–37.0)	1.00	0.00	0.00
IT therapy	4	3	11.6 (3.0–NR)	0.50 (0.06–0.84)	0.00	0.00

\*Due to limited data on second recurrence, PFS from time of first recurrence was not analyzable.

**Abbreviations:** IT, intrathecal; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplant.

cytotoxic therapies were utilized, including cyclophosphamide plus etoposide-based regimens; nitrogen mustard, vincristine, procarbazine, and prednisone; cisplatin plus lomustine-based regimens; temozolomide; and ifosfamide,

carboplatin, and etoposide. Twenty-nine patients (36%) underwent various re-irradiation treatments, which included Gamma Knife radiosurgery, local photon irradiation, and craniospinal irradiation. Six patients (8%) underwent a

first or second SCT, and 4 (5%) received intrathecal chemotherapy. Thirty-eight patients (48%) underwent treatment with more than one modality at recurrence.

## Survival Outcomes

### Survival from time of initial surgery.—

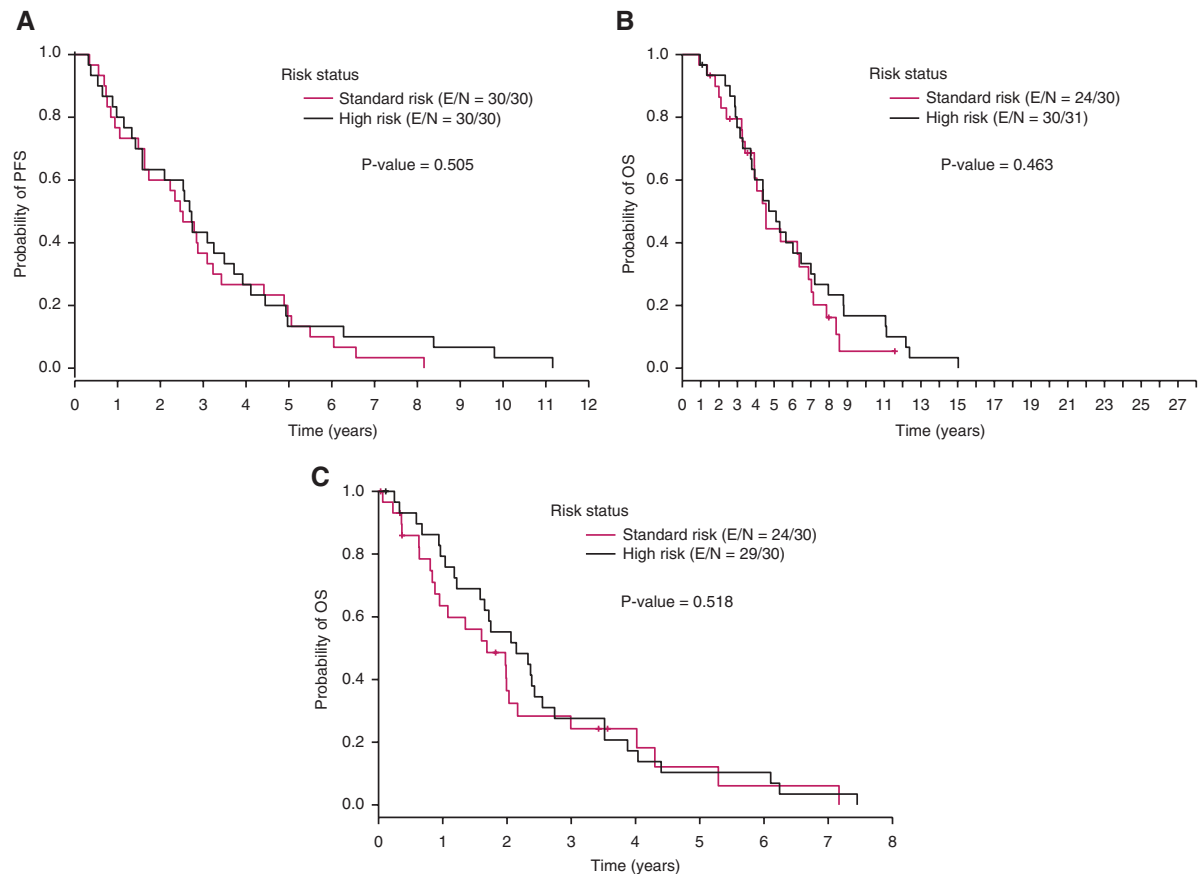
One high-risk patient with missing date of first recurrence was excluded from the PFS analysis. Among the 81 patients with known date of first recurrence, median PFS from the time of initial surgery was 33.5 months. Median PFS was 29.9 months for standard-risk patients, 32.4 months for high-risk patients, and 35.4 months for those with unknown risk (Table 2). There was no difference in median PFS between the standard-risk and high-risk groups ( $P = .505$ ) (Figure 2A). Among the cases with LC/A histology, the patients classified as high-risk, standard-risk, and unknown risk based on clinical criteria experienced tumor recurrence at 4.0 months, 8.7 months, and 56.9 months respectively.

Median OS from the time of initial surgery was 62.4 months. Median OS was 54.7 months for standard-risk patients, 61.3 months for high-risk patients, and 83.4 months

for those with unknown risk (Table 2). A single patient surviving 27 years contributed to the trend in the unknown-risk group. There was no difference in median OS between the standard-risk and high-risk groups ( $P = .463$ ) (Figure 2B).

### Survival from time of recurrence.—

Sixty-nine of the eighty-two patients (84%) died during follow-up. Data on second recurrence was not available on sufficient patients to report PFS from the time of first recurrence. Median OS after recurrence was 20.3 months (95% CI, 10.6–26.0 months) for standard-risk patients, 25.7 months (95% CI, 14.6–30.6 months) for high-risk patients, and 28.4 months (95% CI, 12.6–37.0 months) for those with unknown risk (Table 2). There was no difference in OS from time of recurrence between the standard-risk and high-risk groups ( $P = 0.518$ ) (Figure 2C). The 1-year OS rates for all, standard-risk, and high-risk patients were 74% (95% CI = 63%, 82%), 64% (95% CI = 43%, 78%), and 79% (95% CI = 60%, 90%), respectively; the 5-year OS rates for all, standard-risk, and high-risk patients were 13% (95% CI = 6%, 22%), 12% (95% CI = 2%, 30%), and 10% (95% CI = 3%, 24%), respectively; and the 10-year OS rates for all, standard-risk, and high-risk patients were 2% (95% CI = 0%, 8%), 0%, and 0%, respectively.



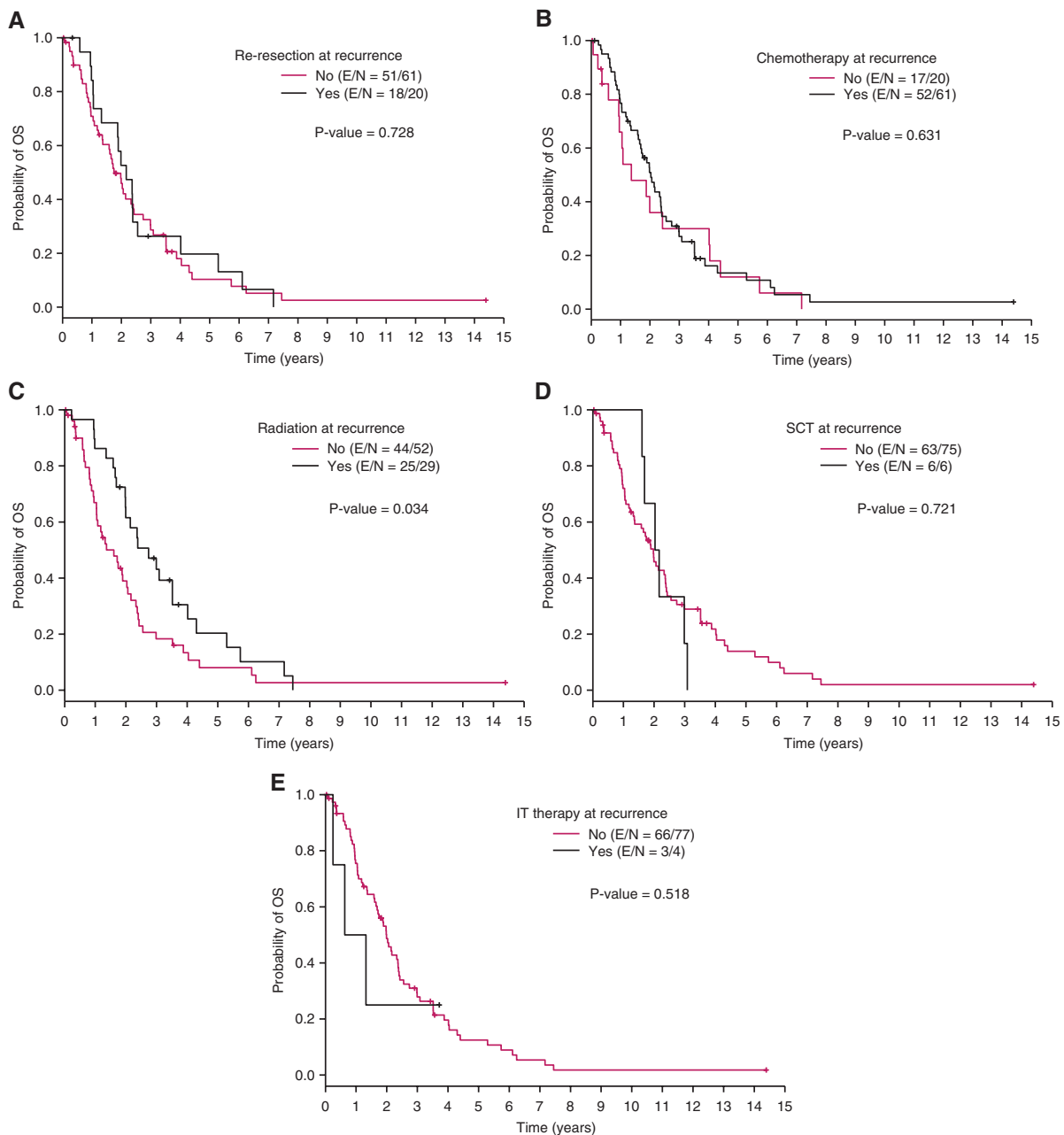
**Figure 2.** A. Progression-free survival (PFS) from date of initial surgery. B. Overall survival (OS) from date of initial surgery. C. Overall survival (OS) from time of first recurrence. E/N – number of patients with event/ number of total patients.

**Survival from time of recurrence by treatment modality.—**

Median OS by modality of treatment at first recurrence was 26.0 months for re-resection, 24.4 months for chemotherapy, 32.9 months for radiation, 25.2 months for SCT, and 11.6 months for intrathecal chemotherapy (Table 2). Patients who received radiation at recurrence had significantly better OS than those who did not (32.9 months vs. 19.2 months;  $P = .034$ ) (Figure 3). There was no difference in OS between patients who did and did not undergo re-resection, chemotherapy, SCT, or intrathecal chemotherapy at recurrence.

**Discussion**

This is the largest retrospective single-institution series of adult patients with recurrent medulloblastoma reported to date. Given that prospective clinical data for this population are scarce, retrospective analysis of well-annotated data with long-term follow-up continues to be important to inform our understanding of late outcomes, recurrence, and the impact of various treatments and to generate data to support future clinical trial endpoints.



**Figure 3.** Overall survival from time of first recurrence in patients who did and did not receive the following treatments at recurrence: (A) re-resection, (B) chemotherapy, (C) radiation, (D) stem cell transplant, and (E) intrathecal therapy. Patients who received radiation had significantly better OS than patients who did not receive radiation at recurrence ( $P = .034$ ). E/N – number of patients with event/ number of total patients.

In our previously published cohort of 200 patients initially diagnosed with medulloblastoma as adults ( $\geq 18$  years of age), we observed a 5-year PFS rate of 55% and a median PFS of more than 6 years.<sup>18</sup> PFS for the entire cohort was driven by patients who did not have a recurrence and who had less aggressive tumors and/or more appropriate therapy. In contrast, among the 82 patients in the present analysis, who experienced tumor recurrence during follow-up, median PFS from initial surgery was less than 3 years, with a 5-year PFS rate of 17%, and there was no significant difference in PFS between patients stratified as high-risk and those stratified as standard-risk on the basis of their clinical features at presentation. We also found that for the patients with recurrence, median OS was 5.2 years from initial surgery, compared to 8.8 years for the entire 200-patient cohort.

Our findings regarding the timing of first recurrence in adults with medulloblastoma are generally in line with what has previously been reported. A multi-institutional series of 156 adults with medulloblastoma treated between 1975 and 1991 showed a 5-year event-free survival (EFS) rate of 61% and a median PFS of 30 months over a median follow-up of 5.9 years.<sup>27</sup> The other large series of adults to date, which captured longer-term outcomes (with a median follow-up of 9 years) and better represents modern surgical and radiation techniques, included 29 patients, of whom 5 had recurrence at a median of 20.4 months after completing initial therapy.<sup>28</sup> Small, prospective adult medulloblastoma trials including 10 and 11 patients showed 5-year PFS rates of 55% and 72%,<sup>13,17</sup> and most recently, the NOA-07 study, which included 30 patients treated with up-front craniospinal irradiation with vincristine followed by eight cycles of cisplatin, lomustine, and vincristine, demonstrated a 3-year EFS rate of 66.6% after a median follow up of 58 months and with 83% of patients still without progression.<sup>16</sup>

As shown by our series and others, prognosis from the time of recurrence is universally poor in both children and adults with medulloblastoma. A study of 40 pediatric patients found that from the time of relapse, median EFS was 1 year, median OS was 19.2 months, and the 5-year OS rate was 8.2%.<sup>29</sup> Previously published data on adult patients indicated a median OS of 21 months after first recurrence in a series of 17 patients.<sup>23</sup> In our series, we found that median OS from time of first recurrence across all patients was 23.8 months; OS was similar between risk groups, at 20.3 months for standard-risk patients and 25.7 months for high-risk patients ( $P = .518$ ). Although the difference between groups was not statistically significant, the fact that the median survival was numerically longer in the high-risk group than in the standard-risk group calls into question the utility of risk stratification at initial diagnosis based solely on clinical factors (extent of tumor resection, dissemination) in predicting prognosis upon recurrence. However, this finding may have been driven by some combination of (1) the relatively low number of patients with known risk status and the large number with unknown risk status, (2) patients who were classified as high-risk owing to less than gross total resection but who did not have metastatic disease at presentation, (3) differences in treatment received at initial diagnosis, as most standard-risk patients did not receive chemotherapy at initial diagnosis, whereas

high-risk patients typically did, and (4) molecular factors not captured by this analysis that may contribute to variations in cancer behavior.

Indeed molecular subtyping, along with histological phenotype, is critical to the characterization of medulloblastoma biology including in the relapsed setting,<sup>30</sup> representing a significant limitation of our study. It is likely that most patients included in the dataset had SHH tumors, similar to the overall population of adults with medulloblastoma, given the predominant location (cerebellar hemispheres) and histological subtypes most commonly found in our series (desmoplastic and classical). Despite these limitations posed by heterogeneity within our molecularly agnostic cohort, this aggregation of single-institution experience likely aligns with real-world practice in which molecular data are not consistently available, especially for patients who were diagnosed prior to the more recent incorporation of molecular analysis for Neuro-Oncology patients.

Treatment at the time of recurrence in our cohort was heterogeneous, and we found that any radiation therapy at recurrence improved OS compared to other modalities. It was previously shown, in a series of 38 pediatric patients with recurrent disease, that re-irradiation improved the OS rate from initial diagnosis to 55% at 5 years and 33% at 10 years versus 46% and 0% at 5 and 10 years, respectively, for patients who did not undergo re-irradiation ( $P = .036$ ), although an increased rate of radiation necrosis was seen.<sup>31</sup> A prospective pediatric study showed a non-statistically significant difference in EFS favoring re-irradiation following high-dose chemotherapy with autologous stem cell rescue.<sup>32</sup> Other case series have demonstrated favorable long-term outcomes after re-irradiation, including 8-year PFS in an adult following re-irradiation without re-resection.<sup>33,34</sup> Our data also suggest a survival benefit of re-irradiation at the time of recurrence; however, we note that this result may have been confounded by patient selection (for example, superior functional status or differences in location of recurrent tumor) or other unknown factors (for example, molecular subgroup), given the non-randomized origin of these data, and our analysis does not account for differing combinations and sequences of re-irradiation with other treatments.

The 6 patients in our cohort who received SCT at recurrence had a 100% 1-year OS rate with a median OS of 25.2 months after recurrence; 5 experienced documented re-recurrence. These patients were carefully selected for SCT and likely represent those with optimal functional status and lack of significant comorbid conditions. Further prospective studies will be useful in determining the utility of SCT and its optimal combination with other modalities. Surgery at recurrence did not appear to impact OS, although it remains an important option in well-selected cases, with anecdotal evidence supporting its use.<sup>35</sup> Importantly, our data suggest that the treatment plan should be decided in the context of systematic restaging, given the high probability of out-of-field or leptomeningeal metastasis.

Median OS from time of recurrence was numerically longer in those who received chemotherapy at recurrence (24.4 months) than in those who did not (16.4 months), but the difference did not reach statistical significance. This may reflect selection bias if those who did not receive



chemotherapy were not candidates owing to declining functional status. Analysis of outcomes following treatment with chemotherapy at recurrence was limited by heterogeneous selection of regimens, highlighting the need for further prospective studies to establish standard practices for treating recurrence with chemotherapy. Platinum- or cyclophosphamide-based therapies are commonly favored<sup>7</sup> although less toxic regimens such as single-agent temozolomide and combinations of bevacizumab, irinotecan, and temozolomide have shown benefit for both children and adults in case reports.<sup>36-39</sup> Intrathecal chemotherapy did not appear to be beneficial in our population, although selection of patients with advanced disease likely partially accounted for the poor OS in this group.

We found that 58% of recurrences arose outside of the posterior fossa, either as distant metastases or as leptomeningeal metastases, and that a significant proportion (43%) of patients presented with recurrence exclusively outside the primary site of disease. This indicates the need for magnetic resonance imaging of the spine during surveillance instead of performing magnetic resonance imaging of the brain only. Furthermore, our finding that 35% of patients developed extra-CNS metastases suggests a low threshold for systemic imaging via computed tomography or positron emission tomography scans if there are suspicious clinical findings. In line with previous reports of late recurrence in adults, we observed recurrences beyond 8 years from initial treatment, emphasizing the need for long-term follow-up even in patients with stable disease.

Further studies with larger combined datasets that account for molecular features and variation in treatment strategies are needed to better understand which factors are most contributory to prolonging PFS and OS in adults with medulloblastoma. With growing access to targeted therapies and chemotherapeutic clinical trials (SJMB12, NCT01878617; SJDAWN, NCT03434262; PersoMed-I, NCT04402073; and Alliance AMBUSH Trial<sup>40</sup>), and surgical trials (PBTC-053, NCT03904862) specifically including adults, subsequent studies must factor in optimal combinations of treatment modalities that include new targeted and immunotherapeutic approaches at recurrence.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* online.

## Keywords

adult medulloblastoma | recurrent medulloblastoma | risk stratification | treatment at recurrence

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## Conflicts of Interest

The authors have no conflicts of interest to declare.

## Authorship

Conceptualization of data collection: MPP and VKP. Provision of patient listings: AM and DS. Building the Research Electronic Data Capture (REDCap) database: KDA and MMBG. Collection of data on individual patients: MPP, NM, MM, and MMBG. Performance of the statistical analyses: HL, KRH, and YY. Contribution to the data analysis and significant portions of the manuscript writing: TAG, MPP, NM, HL. Participation in patient care: GF, MGM, JTH, GNR, JSW, DNY, ACP, SMG, AM, SK, DIS, WZ, SPW, RAH, JDG, NM, AM, VKP, and MPP. All authors were involved in writing, editing, and approval of the final manuscript.

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