Predictors of functional recovery in adults with posterior fossa ependymomas

Clinical article

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Object. After complete resection and radiation therapy, the 10-year overall survival rates for adult patients with posterior fossa ependymomas approach 85%. This favorable outcome profile emphasizes the critical importance of functional preservation to this patient population. Here, the authors identify predictors of functional outcome following microsurgical resection of adult posterior fossa ependymomas.

Methods. The authors identified adult patients with newly diagnosed WHO Grade II posterior fossa ependymomas who underwent microsurgical resection at the Barrow Neurological Institute from 1990 to 2011. Clinical and radiographic variables were collected, including volumetric extent of resection, foramen of Luschka extension, cystic changes, peritumoral T2 signal changes, Karnofsky Performance Scale (KPS) score, National Institutes of Health Stroke Scale (NIHSS) score, progression-free survival (PFS), and overall survival (OS).

Results. Forty-five patients were identified, with a median clinical follow-up of 103 months. The median PFS and OS were 6.8 and 8.6 years, respectively. Extent of resection and adjuvant radiotherapy were predictive of improved PFS (p = 0.005) and were nonsignificantly associated with improved OS. Univariate analysis revealed that tumor size (p < 0.001), cystic changes (p < 0.01), postoperative T2 signal (p < 0.01), and CSF diversion (p = 0.048) predicted functional and neurological recovery rates, based on KPS and NIHSS scores, respectively. Multivariate regression analysis identified tumor size (p < 0.001), cystic changes (p = 0.01), and CSF diversion (p = 0.02) as independent predictors of slower functional recovery, while only tumor size (p = 0.007) was an independent predictor of neurological recovery. Specifically, by 6 weeks postoperatively, baseline KPS score was recovered by only 43.8% of patients with tumors larger than 30 cm3 (vs 72.4% patients with tumors < 30 cm3), 35.3% of patients with cystic tumors (vs 78.6% of patients with noncystic tumors), and 46.7% of patients requiring CSF diversion (vs 70% of patients not requiring CSF diversion).

Conclusions. Greater extent of resection and adjuvant radiotherapy significantly improve PFS in adult patients with posterior fossa ependymomas. Tumor size, cystic changes, and the need for CSF diversion were independent predictors of the rate of functional recovery in this patient population. Taken together, these functional outcome predictors may guide preoperative estimations of recovery following microsurgical resection.

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Key Words • cystic • ependymoma • extent of resection • infratentorial • oncology

Ependymomas comprise 2%–5% of all intracranial tumors in adults, with most of these lesions occurring in the infratentorial compartment. Previous studies have reported 10-year overall survival (OS) rates ranging from 50% to 83%,14–16 highlighting the relatively favorable prognosis for this patient population. Several parameters have been associated with improved survival, including patient age,1,7,8,9,13 tumor location (supra- vs infratentorial),1,7,9,14,15 histological grade,1,6,7,9,16 extent of resection (EOR),1,7–9,13–16 adjuvant radiotherapy5,14,16 and preoperative functional status.5,14 Surprisingly, few data exist to describe the functional recovery and quality of life for these patients after treatment. To date, the only specific inquiry into the postoperative recovery of adult patients was based on patient surveys from 118 adult patients with ependymomas examining symptom severity, disability, and work status following treatment.2 In these patients, 48% reported not yet returning to work and 31% were receiving disability benefits. However, heterogeneity in tumor locations and treatment paradigms precluded reliable conclu-
sions regarding the functional and neurological outcomes of these patients. Specifically, starkly different patterns of disability and independence were observed among postoperative patients with ependymomas involving the brain compared with those with ependymomas involving the spinal cord. Taken together, these data support the utility of characterizing the neurological and functional outcome profiles for a homogeneous population of adult patients with ependymoma after microsurgical resection. In this retrospective study, we examined only adult patients with posterior fossa ependymomas who had undergone aggressive resection and asked whether their functional and neurological recovery rates could be predicted using preoperative and perioperative parameters.

Methods

Patient Population

We identified 72 adult patients with newly diagnosed intracranial ependymomas treated surgically at Barrow Neurological Institute between 1990 and 2011. Central neuropathology review, based on WHO guidelines,1,1 confirmed a diagnosis of WHO Grade II ependymoma for all patients. To limit sample heterogeneity, we excluded patients with Grade III (anaplastic) histopathology (n = 6), supratentorial tumors (n = 5), or less than 1 year of clinical follow-up data (n = 16). The Institutional Review Board of St. Joseph’s Hospital and Medical Center approved this retrospective study.

Clinical, radiographic, and outcome data were collected from inpatient and outpatient records, telephone interviews, and the national Social Security Death Index. Characteristics identified for each case included tumor size, cystic tumor changes, peritumoral T2-weighted MR signal change, tumor extension into the foramen of Luschka, volumetric EOR, and the need for permanent CSF diversion.

For all patients, neurological examination was performed by an attending neurosurgeon at each preoperative and postoperative visit. To dynamically assess neurological recovery, the National Institutes of Health Stroke Scale (NIHSS)5,17 was adapted as an outcome parameter. The NIHSS assesses 15 neurological functions, grading the severity of impairment for each function individually, ranging from 0 (best) to 42 (worst) points. The Karnofsky Performance Status (KPS)10 was used to assess functional recovery at baseline, as well as at 1 week, 6 weeks, and 1 year postoperatively.

Tumor Volume and EOR Calculation

The EOR for each case was determined by comparing MR images obtained before surgery to those obtained within 48 hours after surgery. A blinded, retrospective 3D volumetric analysis of pre- and postoperative MR images was performed by a neuroradiologist. Manual segmentation was performed with region-of-interest measurements of tumor volumes (in cubic centimeters) based on contrast-enhancing tissue seen on T1-weighted MR imaging. The EOR was calculated as follows: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume. Volume measurements were obtained without consideration of patient outcome.

Radiation Treatment Algorithm

Prior to 2004, our institutional practice with regard to postoperative radiotherapy for posterior fossa ependymomas was mixed. However, following an intramural study that radiotherapy after gross-total resection (GTR) provided better control than GTR alone,14 all patients at our institution received radiotherapy after surgery for posterior fossa ependymomas. The cohort in this study from 1990 to 2011 thus includes patients in both eras of adjuvant therapy management at our institution.

Statistical Analysis

Age, EOR, KPS scores, NIHSS scores, and tumor volumes were analyzed as continuous variables. Medians and means, as well as ranges, were calculated for continuous variables to summarize these characteristics. In some instances, means were calculated with their SDs. Counts and percentages were defined for categorical variables. Comparison of patient and treatment characteristics among groups was done using the Wilcoxon rank-sum test for continuous or ordinal variables.

To evaluate the prognostic value of the variables under consideration, a Cox proportional hazards model was used to identify all categories associated with improved survival or functional outcome. Variables that were significant at the α = 0.2 level in the univariate analysis were then entered into a multivariate model for consideration. The forward stepwise selection technique was then used to select the final variables to retain. Only variables that were statistically significant at the p = 0.01 level were included in the final model. Kaplan-Meier curves were then constructed to summarize the relative impact of each category on OS and progression-free survival (PFS). Statistically significant differences were assessed using the log-rank test. All statistical analyses were completed using Statistica 64 (StatSoft, Inc.).

Results

Patient and Tumor Characteristics

We identified 45 adult patients with WHO Grade II posterior fossa ependymomas who were microsurgically treated at the Barrow Neurological Institute from 1990 to 2011 (Table 1). The mean patient age at diagnosis was 44.2 years (range 18–78 years), and 24 patients (53%) were male. The mean clinical follow-up duration was 102.6 months (range 12.6–263.5 months), with no patient unaccounted for. The most common presenting symptoms were headache (n = 23, 51.1%), nausea/vomiting (n = 16, 35.6%), visual problems (n = 8, 17.8%), and gait or balance difficulty (n = 8, 17.8%). The median KPS score at presentation was 90 (range 40–100), and the median NIHSS score at presentation was 1 (range 0–4). Based on preoperative MR imaging, 21 patients (47%) demonstrated evidence of obstructive hydrocephalus.

Treatment Outcomes

The median preoperative tumor volume was 18.5 cm3.
Functional recovery predictors for posterior fossa ependymomas

Table 1: Patient, tumor, and treatment characteristics (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment characteristics</td>
<td></td>
</tr>
<tr>
<td>EOR</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>97%</td>
</tr>
<tr>
<td>range</td>
<td>70–100%</td>
</tr>
<tr>
<td>GTR</td>
<td>32 (71)</td>
</tr>
<tr>
<td>residual tumor in cm³</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0.9</td>
</tr>
<tr>
<td>range</td>
<td>0–13</td>
</tr>
<tr>
<td>increased postop T2 signal</td>
<td>25 (56)</td>
</tr>
<tr>
<td>permanent CSF diversion</td>
<td>15 (33)</td>
</tr>
<tr>
<td>complications</td>
<td>8 (18)</td>
</tr>
<tr>
<td>adjuvant radiation</td>
<td>31 (69)</td>
</tr>
</tbody>
</table>

* Categorical values are expressed as the count (%).

(range 1.5–88.8 cm³), and all patients underwent image-guided microsurgical resection of their tumor. The median postoperative tumor volume was 0.0 cm³ (range 0.0–13.4 cm³), equating to a 100.0% median EOR (range 69.7%–100.0%). Despite their large size, no tumors demonstrated significant peritumoral edema (based on increased T2-weighted MR signal) in the adjacent cerebellum or brainstem on preoperative MR imaging. Extension into the foramen of Luschka, however, was found in 16 cases (36%), and cystic changes were observed in 17 tumors (38%).

On postoperative imaging, 25 patients (56%) had an increased T2-weighted MR signal in the tissue surrounding the resection cavity. Surgical complications were encountered in 8 patients (18%), including 4 patients with wound infections, 3 with CSF leaks, and 1 patient with a posterior inferior cerebellar artery territory stroke. Permanent CSF diversion through a ventriculoperitoneal shunt was required for 15 patients (33%).

Thirty-one patients (69%) underwent adjuvant radiotherapy, including 19 after GTR and 12 after subtotal resection (STR). Thirteen patients (29%) underwent GTR without subsequent radiotherapy. Of the patients receiving radiotherapy, 10 (32%) underwent stereotactic radiosurgery, and 21 (68%) underwent intensity-modulated radiation therapy. There were no significant differences in OS (p = 0.63) or PFS (p = 0.49) on the basis of radiation modality.

The impact of EOR and adjuvant radiotherapy on OS and PFS were visualized using Kaplan-Meier analysis (Fig. 1). Patients were grouped into 4 categories based on the EOR (GTR vs STR) and whether they received adjuvant radiation therapy (Table 2). Only one patient had STR only; this patient was excluded from this analysis. Using the log-rank test, a significant difference was found between the mean PFS intervals for patients with GTR and radiation therapy (9.0 ± 4.6 years [± SD]) compared with patients with GTR alone (6.8 ± 3.0 years) (p = 0.005) and for patients with GTR and radiation therapy (9.0 ± 4.6 years) compared with patients with STR and radiation therapy (5.4 ± 3.2 years) (p = 0.003). There was no
significant difference in mean PFS between patients who underwent GTR alone (6.8 ± 3.0 years) compared with those who underwent STR and radiation therapy (5.4 ± 3.2 years) (p = 0.49). Similarly, the mean OS intervals were not significantly different between patients with GTR and radiation therapy (9.6 ± 4.6 years) compared with STR and radiation therapy (6.4 ± 4.3 years) (p = 0.23).

**Functional and Neurological Outcomes**

Functional and neurological outcomes, assessed by the KPS and NIHSS, respectively, demonstrated distinct patterns of recovery. Specifically, 75.6% of all patients recovered their baseline functional status by 1 year postoperatively, whereas 31.1% showed a similar recovery in their neurological status over the same period (Fig. 2). In univariate analyses, preoperative tumor volumes larger than 30 cm$^3$ were associated with worsened functional and neurological status at 1 week, 6 weeks, and 1 year postoperatively (p < 0.001) (Fig. 2A). Cystic changes on preoperative MR images (Fig. 2B) and hyperintense T2-weighted MR signal surrounding the resection cavity (Fig. 2C) were also associated with worsened functional and neurological status at 1 week and 6 weeks (p < 0.01), and at 1 year postoperatively (p < 0.05). Notably, of 21 patients with a postoperative T2-weighted MR signal and an initial decline in functional status, 17 (80%) had a T2-weighted hyperintense signal extending into the floor of the fourth ventricle. On univariate analysis, patients requiring CSF diversion were also identified as having worse functional and neurological status at 6 weeks postoperatively (p < 0.05) (Fig. 2D). Interestingly, residual tumor was another significant predictor of worsened functional outcome at 1 year postoperatively (p = 0.046), but was not associated with depressed neurological status (p = 0.054). Other screened clinical variables, including age, sex, foramen of Luschka tumor extension, volumetric EOR, complications, and adjuvant radiotherapy, were not significantly associated with functional or neurological outcomes.

A subsequent multivariate linear regression analysis was performed using the covariates identified above to determine independent predictors of functional and neurological recovery. This statistical model identified preoperative tumor volume (p < 0.001, $b = -0.56$), cystic tumor changes (p = 0.01, $b = -0.33$), and CSF shunting (p = 0.018, $b = -0.33$) as independent predictors of functional recovery. Multivariate regression analysis also identified preoperative tumor volume as independently predictive of neurological recovery (p = 0.007, $b = 0.47$).

**Discussion**

Although the clinical value of resecting posterior fossa ependymomas in adults is well documented, expectations of functional and neurological recovery are poorly understood. To address this question, we reviewed a homogeneous adult patient population with posterior fossa ependymomas who underwent standard microsurgical resection and adjuvant radiotherapy. Clinical and radiographic predictors of functional recovery included tumor size, cystic changes, CSF shunting, and prior KPS score, while only tumor size and prior NIHSS score were independent predictors of neurological recovery. Our findings also validated the utility of multimodal therapy, because adjuvant radiation therapy after GTR significant-

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TABLE 2: Survival outcome by treatment group*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Patients</th>
<th>Mean PFS (yrs)</th>
<th>Mean OS (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STR</td>
<td>1</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>STR+radiation</td>
<td>12</td>
<td>5.4</td>
<td>6.4</td>
</tr>
<tr>
<td>GTR</td>
<td>13</td>
<td>6.8</td>
<td>7.3</td>
</tr>
<tr>
<td>GTR+radiation</td>
<td>19</td>
<td>9.0</td>
<td>9.6</td>
</tr>
</tbody>
</table>

* p values for comparisons showing a significant difference are PFS for STR+radiation versus GTR+radiation (p = 0.003) and GTR versus GTR+radiation (p = 0.005).
ly improved PFS compared with GTR alone (9.0 vs 6.8 years, \( p = 0.005 \)) and compared with adjuvant radiation therapy and STR (9.0 vs 5.4 years, \( p = 0.003 \)). We also observed a nonsignificant trend toward improved OS with GTR plus adjuvant radiation therapy compared with GTR alone (9.6 vs 7.3 years, \( p = 0.18 \)).

There are, however, important limitations to our retrospective study design that should be considered. The low overall number of patients in the study, resulting in even smaller subgroups, can result in exaggerated differences between groups owing to outliers. Selection and reporting bias are also important considerations because only patients with adequate 1-year follow-up could be included. Finally, because the study spans 21 years, changes in technology and surgical practice may have influenced patient outcomes differently at the beginning and end of

**Fig. 2.** Functional (KPS) and neurological (NIHSS) recovery based on various patient- and tumor-specific factors. Larger tumor volume (>30 cm³) (A) and cystic tumor changes (B) on preoperative MRI were significantly associated with slower functional and neurological recovery rate at 1 week, 6 weeks, and 1 year postoperatively. T2 signal change in the parenchyma around the resection cavity on postoperative MR images was significantly associated with slower functional and neurological recovery in univariate analysis at 1 week, 6 weeks, and 1 year postoperatively (C). While there was no significant difference in recovery for patients based on the presence or absence of hydrocephalus, those patients requiring shunt procedures for CSF diversion had significantly lower KPS scores at 6 weeks postoperatively and NIHSS scores at 6 weeks and 1 year postoperatively (D). The plus sign indicates the presence of the feature and the minus sign indicates the absence of the clinical feature. *\( p < 0.05 \) in univariate analysis; **\( p < 0.05 \) in multivariate regression analysis.
the study period (for example, the change in our radiation treatment algorithm).

In a recent online survey of adult patients with ependymomas of the brain and spinal cord, over half (56%) of all patients did not return to work, and 37% were receiving disability benefits at a median follow-up of 4 years. While these findings did not identify predictors of recovery, they emphasized the considerable risk from ependymoma surgery to patient quality of life. In comparison, we found that 16% of patients had not returned to work by 1 year postoperatively, highlighting the heterogeneity of functional outcomes and likely comparatively favorable neurological outcomes for posterior fossa ependymomas.

Our results show that although ependymomas portend a favorable prognosis compared with other adult brain tumors of the posterior fossa, their treatment is not without risk. As demonstrated in this and other studies, a significant number of patients have long-term functional and neurological deficits from disease treatment, even when their tumors do not recur. Future studies are needed to correlate patient outcomes with comprehensive quality of life surveys to identify treatment-related features, as well as specific neurological deficits, which most severely impact recovery.

**Conclusions**

Posterior fossa ependymomas in adult patients have a relatively favorable prognosis, which can be maximized through a combination of microsurgical resection and adjuvant radiotherapy. However, despite 10-year overall survival rates as high as 83%, many patients do not completely recover their functional and neurological baseline following treatment. Patients at particular risk for incomplete recovery include those with larger tumor size, cystic tumors, and a need for CSF diversion. In future studies, these preoperative predictors of patient outcome should be correlated with detailed quality of life metrics to develop management strategies that anticipate and minimize poor recovery profiles.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sanai, Mirzadeh. Acquisition of data: Mirzadeh, Bina, Kusne. Analysis and interpretation of data: Sanai, Mirzadeh. Drafting the article: Sanai, Mirzadeh. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sanai. Statistical analysis: Mirzadeh. Administrative/technical/material support: Sanai, Coons, Spetzler.

**References**


