## Title

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# A systematic review of treatment outcomes in pediatric patients with intracranial ependymomas

## A review

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*Object*. Ependymoma is the third most common primary brain tumor in children. Tumors are classified according to the WHO pathological grading system. Prior studies have shown high levels of variability in patient outcomes within and across pathological grades. The authors reviewed the results from the published literature on intracranial ependymomas in children to describe clinical outcomes as they relate to treatment modality, associated mortality, and associated progression-free survival (PFS).

*Methods*. A search of English language peer-reviewed articles describing patients 18 years of age or younger with intracranial ependymomas yielded data on 182 patients. These patients had undergone treatment for ependymoma with 1 of 5 modalities: 1) gross-total resection (GTR), 2) GTR as well as external beam radiation therapy (EBRT), 3) subtotal resection (STR), 4) STR as well as EBRT, or 5) radiosurgery. Mortality and outcome data were analyzed for time to tumor progression in patients treated with 1 of these 5 treatment modalities.

*Results*. Of these 182 patients, 69% had supratentorial ependymomas and 31% presented with infratentorial lesions. Regardless of tumor location or pathological grade, STR was associated with the highest rates of mortality. In contrast, GTR was associated with the lowest rates of mortality, the best overall survival, and the longest PFS. Children with WHO Grade II ependymomas had lower mortality rates when treated more aggressively with GTR. However, patients with WHO Grade III tumors had slightly better survival outcomes after a less aggressive surgical debulking (STR+EBRT) when compared with GTR.

*Conclusions*. Mortality, PFS, and overall survival vary in pediatric patients with intracranial ependymomas. Pathological classification, tumor location, and method of treatment play a role in outcomes. In this study, GTR was associated with the best overall and PFS rates. Patients with WHO Grade II tumors had better overall survival after GTR+EBRT and better PFS after GTR alone. Patients with WHO Grade III tumors had better overall survival after STR+EBRT. Patients with infratentorial tumors had improved overall survival compared with those with supratentorial tumors. Progression-free survival was best in those patients with infratentorial tumors following STR+EBRT. Consideration of all of these factors is important when counseling families on treatment options.
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**Key Words** • **brain tumor** • **ependymoma** • **surgery** • **outcomes** • **oncology**

Ependymoma is the third most common primary brain tumor in children, accounting for 6%–10% of all intracranial tumors.[26,55] Infratentorial ependymomas make up 15% of posterior fossa tumors in the pediatric population.[62] They are slightly more common in males than females and peak in incidence between birth and 4 years of age.[55] Pathologically, ependymomas are classified according to the WHO grading system. The WHO classification system separates ependymomas into 3 groups based on histopathological criteria: Grade I (myxopapillary); Grade II, which is further subdivided into 4 subtypes (cellular, papillary, clear-cell, and tanycytic); and Grade III (anaplastic). Grade I tumors are benign and are thought of as a separate clinical and pathological entity (subependymoma). Therefore, only WHO Grade II and III ependymomas are considered in this study. Despite this well-defined classification system, prior studies have shown high levels of variability in patient outcome within and across pathological grades.[23,69,87]

Unlike other primary brain tumors, intracranial ependymomas provide a challenging prognostic scenario. There have been discrepancies involving the roles that age, extent

*Abbreviations used in this paper:* EBRT = external beam radiation therapy; GTR = gross-total resection; PFS = progression-free survival; STR = subtotal resection.

of resection, and use of adjuvant radiation play. Other patient series have not found definitive correlations between clinical outcome and common predictive factors such as age, location, or pathology.[80] To date, it has been difficult to reliably prognosticate patient outcome based on clinical features, histology, or treatment modality. Therefore, researchers have worked toward trying to understand which features may or may not influence patient outcomes. Some authors have associated younger age at diagnosis of intracranial ependymoma with a poorer prognosis.[14,35,42,80] This may be because diagnosis is often delayed in younger children, thereby identifying more pathologically advanced disease, which is associated with a poor outcome.[14,57] There is also debate as to whether pathology plays a contributing role in ependymoma outcome. In a report of 40 pediatric patients, the Children's Cancer Group found no difference in PFS across WHO grades.[68] In contrast, however, other groups have found improved PFS as well as overall survival in patients diagnosed with WHO Grade II tumors compared with those with WHO Grade III tumors.[35,53,76] Current treatment strategies include resection, radiation therapy alone or as an adjuvant to surgery, and chemotherapy alone or as an adjuvant to resection.[38,48,65] The current standard of care for pediatric patients with cranial ependymoma is resection, if possible, followed by radiation therapy alone.[65] Though many centers do use chemotherapy today as an adjuvant to resection for these patients, it is not included as part of the current accepted standard of care. Furthermore, patients undergoing chemotherapy alone have higher rates of morbidity, mortality, and tumor progression when compared with those undergoing radiation therapy alone, suggesting that as a solitary treatment and possibly as an adjuvant to resection, radiation therapy is superior to chemotherapy.[9] In addition, this retrospective review spans cases reported in the literature over 40 years when chemotherapy was not used. Therefore, we have not included patients treated with chemotherapy alone or as an adjuvant treatment to resection in this study.

We have reviewed the published literature to find pediatric patients diagnosed with intracranial ependymoma who have undergone GTR, STR, GTR as well as adjuvant EBRT, STR as well as EBRT, and radiosurgery alone. We excluded patients who had been treated with chemotherapy. We then investigated how death and time to tumor recurrence in these patients differ with respect to the chosen treatment option or when taking tumor location or pathological grade into account. Using results from the published literature, we aimed to describe current knowledge regarding clinical outcomes as they relate to tumor pathology, tumor location, treatment modality, associated mortality, and PFS. Our findings are consistent with mixed results in the literature. We conclude that mortality rate, PFS, and overall survival vary in pediatric patients with intracranial ependymomas based on pathological classification, tumor location, and method of treatment.

## Methods

### *Data Collection*

A PubMed search using the key words "ependymoma" and "pediatric" returned 197 peer-reviewed articles investigating patients with spinal and cranial ependymomas. Ninety-one of these publications included only patients less than or equal to 18 years old. We then excluded publications describing spinal ependymomas alone. This left 65 publications that described 295 patients with intracranial ependymomas published between 1969 and 2010. We were only interested in patients with intracranial ependymomas who were treated with 1 of 5 treatment modalities: GTR, GTR+EBRT, STR, STR+EBRT, and radiosurgery. In addition, we excluded studies that reported grouped or aggregated data. Only those references that contained disaggregated data describing patients who had 1) undergone treatment by 1 of the 5 treatment modalities listed above, and 2) described patient demographic, diagnostic, and pathological data, data describing patients' symptoms, data describing tumor location, and posttreatment outcome data were included in this analysis. Disaggregated data are defined as data for individual patients that are extracted and presented in the text in such a way that relevant data can be linked to an individual patient presented in the study. One hundred eighty-two patients met these criteria and were included in this analysis.[1–8,10,11,13,15,17–21,24,25,27–34,36–38,40,41,44–47,49–51,54,56,58–61,63,67,70–72,74,75,77,78,81–86,88]

### *Data Analysis*

Statistical analyses were performed using SPSS statistical software. Survival and mortality data were evaluated using the Kaplan-Meier test with log-rank analysis. The Kaplan-Meier test was used to analyze mortality data because each patient was followed for varying lengths of time, some of whom died during that time period and others who did not. Because we do not have definitive death data on all patients, survival curves representing death and time to death were chosen. Morbidity after treatment for intracranial ependymomas was reported for only 9 of the entire 182-patient sample and therefore could not be analyzed.

## Results

### *Study Population*

Disaggregated data results were reviewed from 182 patients age 18 years old or younger with a diagnosis of intracranial ependymoma. These patients were treated with GTR, GTR+EBRT, STR, STR+EBRT, or radiosurgery alone (Table 1). Of these 182 patients, 57% were male, 41% were female, and the sex was unknown in 2%. The average age at initial presentation was 7.9 years, with a range of 2.4 months to 18 years. Patients were followed up between 11 days and 25 years. There were some patients who died in the immediate postoperative period and therefore represent shorter follow-up intervals. Of the 76 patients in the STR+EBRT and the GTR+EBRT groups, 36 patients (47.4%) were treated with craniospinal irradiation, and the remaining 40 patients received radiation to the brain alone. However, the criteria used to determine if a patient received craniospinal radiation or cranial irradiation alone were not described in sufficient detail and could not be extracted from the literature.

**TABLE 1: Demographic data for 182 pediatric patients with intracranial ependymomas***

| Variable | Number (%) |
|---|---|
| sex | |
| male | 104 (57) |
| female | 74 (41) |
| unknown | 4 (2) |
| age at presentation | |
| average (yrs) | 7.9 |
| range | 2.4 mos to 18 yrs |
| length of follow-up | |
| average (mos) | 63.8 |
| range | 11 days† to 25.2 yrs |
| treatment | |
| GTR | 56 (30.8) |
| GTR+EBRT | 43 (23.6) |
| STR | 13 (7.1) |
| STR+EBRT | 33 (18.1) |
| radiosurgery | 37 (20.3) |
| tumor location | |
| supratentorial | 125 (68.7) |
| infratentorial | 57 (31.3) |
| tumor pathology | |
| WHO Grade II | 115 (63.2) |
| WHO Grade III | 64 (35.2) |
| unknown | 3 (1.6) |

* All data given as number of patients (%) unless otherwise indicated.
† Includes patients who died in the immediate postoperative period.

Patients treated with chemotherapy alone were not included in the 5 treatment groups because chemotherapy has been associated with worse outcomes compared with radiation therapy[9] and thus may influence mortality, morbidity, or PFS and because the current standard of care treatment for intracranial ependymoma does not include chemotherapy.[65] The largest group of patients underwent GTR alone (30.8%). Approximately 69% of the 182 patients had supratentorial ependymomas while the other 31% were infratentorial ependymomas. We also studied patient characteristics and outcomes based on tumor pathological grade because the WHO grade may influence tumor behavior and patient outcome (Tables 1 and 2). Of note, age at presentation and length of follow-up were equally distributed between WHO grades. However, for patients with either WHO Grade II or Grade III diagnoses, there were more supratentorial than infratentorial tumors reported.

*Mortality Rate*

Overall, STR regardless of intracranial ependymoma location or pathological grade was associated with the highest rates of mortality (Fig. 1A). After undergoing GTR, patients with intracranial ependymomas had the lowest rates of mortality and best overall survival (16.1 years). This was followed closely by GTR+EBRT and STR+EBRT. To understand how pathological grade effects survival after treatment, we stratified patients according to tumor grade. If a tumor was classified as WHO Grade II, GTR+EBRT portended the best survival rates (21 years; Fig. 1B). Overall, patients with WHO Grade II tumors who were treated with less aggressive modalities did worse than those who underwent GTR. In contrast, if a tumor was WHO Grade III, patients with those tumors who underwent STR+EBRT had the best survival outcomes (30 years) when compared with other treatment modalities (Fig. 1C).

When evaluated according to tumor location, patients with infratentorial ependymomas had a lower overall incidence of mortality when compared with supratentorial tumors (Fig. 1D and E). This trend remained true when comparing each treatment modality between supratentorial and infratentorial locations as well. The exceptions to this trend were treatment with radiosurgery alone or GTR to a lesser extent. Radiosurgery had better mortality outcomes when used for supratentorial tumors compared with their infratentorial counterparts, with patients living 12.7 years on average compared with 4 years after treatment, respectively.

*Progression-Free Survival*

After treatment, patients who had undergone GTR had the longest PFS (12.7 years) compared with all other treatment modalities (Fig. 2A). We investigated whether tumor location affected PFS. For infratentorial tumors, PFS was best if a patient underwent less aggressive resection (STR, STR+EBRT, or radiosurgery; Fig. 2C). In contrast, for supratentorial tumors, the more aggressive GTR and GTR+EBRT resulted in the longest time to recurrence/progression (Fig. 2B).

Time to progression for supratentorial WHO Grade II tumors was best after GTR (Fig. 2D), whereas PFS for infratentorial WHO Grade II tumors was extended the longest after STR or STR+EBRT (Fig. 2E). Supratentorial Grade III ependymomas demonstrated the longest PFS after GTR when compared with other treatment strategies (Fig. 2F), whereas patients with infratentorial Grade III tumors fared best after STR+EBRT (Fig. 2G).

## Discussion

There are many factors that influence the most appropriate treatment option for patients with intracranial ependymomas.[12] Tumor location, size, surrounding anatomical structures, tumor appearance, genotype, comorbidities, clinical symptoms, and patient age may all contribute to determining which treatment modality to offer a particular patient.[23,79] This study suggests that pathological grade and tumor location may have some influence on outcome (both mortality and time of PFS) after treatment.

Degrees of resection (STR or GTR) were reviewed in a study of 92 pediatric patients with ependymomas from the Italian Pediatric Neuro-oncology Group. Gross-total resection resulted in improved overall survival compared with STR (69.8% vs 32.5%, respectively), as well as improved PFS (57% vs 11%, respectively).[66] These data support improved outcomes after GTR compared with STR

**TABLE 2: Demographic data stratified by WHO pathology grade***

| Variable | Grade II (n = 115) | Grade III (n = 64) | Unknown Grade (n = 3) |
|---|---|---|---|
| sex | | | |
| male | 67 (58.3) | 36 (56.3) | 1 |
| female | 47 (40.9) | 25 (39.1) | 2 |
| unknown | 1 (0.9) | 3 (4.7) | 0 |
| age at presentation (yrs) | | | |
| average | 8.1 | 7.8 | |
| range | 0.25–18 | 0.2–18 | |
| length of follow-up | | | |
| average (mos) | 62.8 | 66.2 | |
| range | 11 days† to 25.2 yrs | 11 days† to 23 yrs | |
| tumor location | | | |
| supratentorial | 70 (60.9) | 53 (82.8) | 2 |
| infratentorial | 45 (39.1) | 11 (17.2) | 1 |

* All data given as number of patients (%) unless otherwise indicated.
† Includes patients who died in the immediate postoperative period.

as reported years earlier by Horn et al.[35] Radiation therapy is often used as an adjunct to resection in patients with ependymomas who are older than 3 years. However, the benefit of EBRT has also been debated in the literature. A Phase III study has shown that following STR, children have better PFS outcomes following high-dose hyperfractionated radiation when compared with lower-dose conventionally fractionated radiation. In a different study investigating intensity-modulated radiation therapy after STR, it was shown that radiation does not change local tumor control.[43,73] We noted that in our study, patients had the highest survival rates after GTR or GTR+EBRT (Fig. 1A). These results considered only resection modality and did not factor in any contribution from tumor location or pathological grade; not surprisingly, a complete resection yields more favorable outcome for patients. Once we accounted for how pathological grade affected survival in each treatment modality, children with WHO Grade II ependymomas were found to have superior survival outcomes after GTR than after other treatment methods (Fig. 1B). In contrast, the higher grade anaplastic WHO Grade III ependymomas were associated with improved survival rates after STR+EBRT, which did have a slight advantage over GTR (Fig. 1C). Perhaps STR is superior to GTR with respect to survival in these patients with more aggressive, WHO Grade III tumor pathologies because a more conservative surgical approach that avoids aggressive maneuvers for tumor resection may decrease resection-related morbidities and/or mortality for those tumors with unfavorable anatomical locations. Overall, when both pathological grade and treatment modality are accounted for, patients with intracranial WHO Grade III ependymomas who are treated with more aggressive (GTR) or less aggressive (radiosurgery) modalities do worse than those who undergo STR with adjuvant EBRT. It appears that, in the setting of all ependymomas, complete resection or near-total resection supplemented with radiation therapy becomes paramount to eradicate disease and ensure the best opportunity for survival.

We next investigated tumor behavior based on location (either supratentorial or infratentorial). Of all intracranial ependymomas reported in the literature, approximately 42% were supratentorial and 58% were infratentorial in location. However, disaggregated data were available for only 125 supratentorial tumors and 57 infratentorial tumors (68.7% and 31.3% of intracranial tumors, respectively), and therefore only this subset of tumors met inclusion criteria and are analyzed here. Based on location alone, patients with infratentorial ependymomas had better mortality outcomes than those patients with supratentorial tumors (Fig. 1D and E). Infratentorial mass lesions in the posterior fossa often cause symptoms sooner than their supratentorial counterparts.[22] Perhaps patients with posterior fossa tumors will subsequently present to care earlier in their disease course and treatment can be initiated sooner. This may potentially support better outcomes with reduced mortality. In contrast, supratentorial lesions, occupying a larger compartment, cause clinical symptoms and therefore are identified later, resulting in delayed initiation of treatment.

We also investigated PFS or time to tumor recurrence in the study population. Irrespective of pathological grade or location, patients had the best PFS at 12.7 ± 1.5 years following GTR (Fig. 2A). Not surprisingly, a more complete resection was more likely to yield a longer time to tumor recurrence. Patients with infratentorial tumors had longer PFS times if less aggressive STR or STR+EBRT approaches were undertaken (Fig. 2B, C, E, and G). Perhaps outcomes after less aggressive surgeries are better in the infratentorial space because, compared with the supratentorial compartment, the posterior fossa contains delicate neural structures such as cranial nerves and the brainstem that have low thresholds for injury, swelling, and inflammation. In contrast, the anterior and middle cranial fossae allow the surgeon to attempt a complete resection because there is more anatomical space to accommodate cerebral swelling following open surgery.

These data are important tools that can assist the

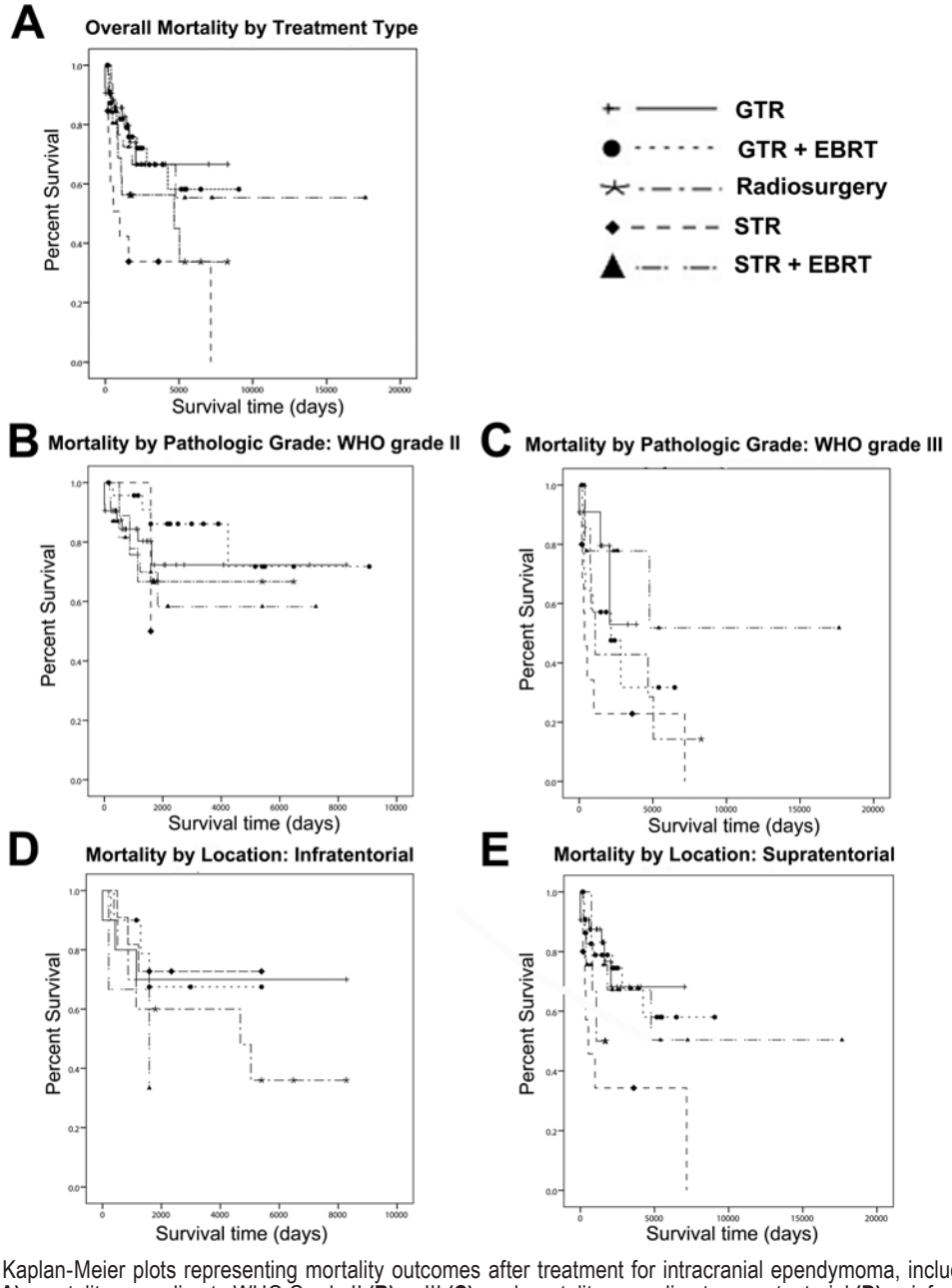


**Fig. 1.** Kaplan-Meier plots representing mortality outcomes after treatment for intracranial ependymoma, including overall mortality **(A)**, mortality according to WHO Grade II **(B)** or III **(C)**, and mortality according to supratentorial **(D)** or infratentorial **(E)** location.

physician in counseling patients and their families on treatment options and outcome trends.[10,64] For example, it is important that the patient who presents with an infratentorial ependymoma be counseled that surgery with a goal of GTR yields the best survival results, though it may increase the likelihood of associated morbidity. However, a patient presenting with a supratentorial ependymoma may be counseled that STR followed by EBRT may be the appropriate surgical strategy for that patient. Likewise, it can be argued that the intraoperative pathological diagnosis identifying WHO grade as well as specific genetic markers of ependymomas should be used to guide the surgeon on how aggressive he or she should be when weighing possible morbidity associated with the extent of resection.[16] Gain of chromosome 1 on the long arm at position 25 (1q25), loss of *RAC2*, and amplification of *TPR* have all been associated with shorter survival rates.[39,52] More objective analyses of pediatric intracranial ependymomas are needed to advise to practitioners, patients, and families on likelihood of PFS, overall survival, and associated morbidity of resections when choosing the most appropriate patient-specific treatment strategy.

The primary limitation of this work is that it is a retrospective study. We are limited by data collected from various patient populations via numerous studies. There was no uniform required length of follow-up, nor were there any uniform reporting standards to compare across studies. In addition, we had disaggregated data on only

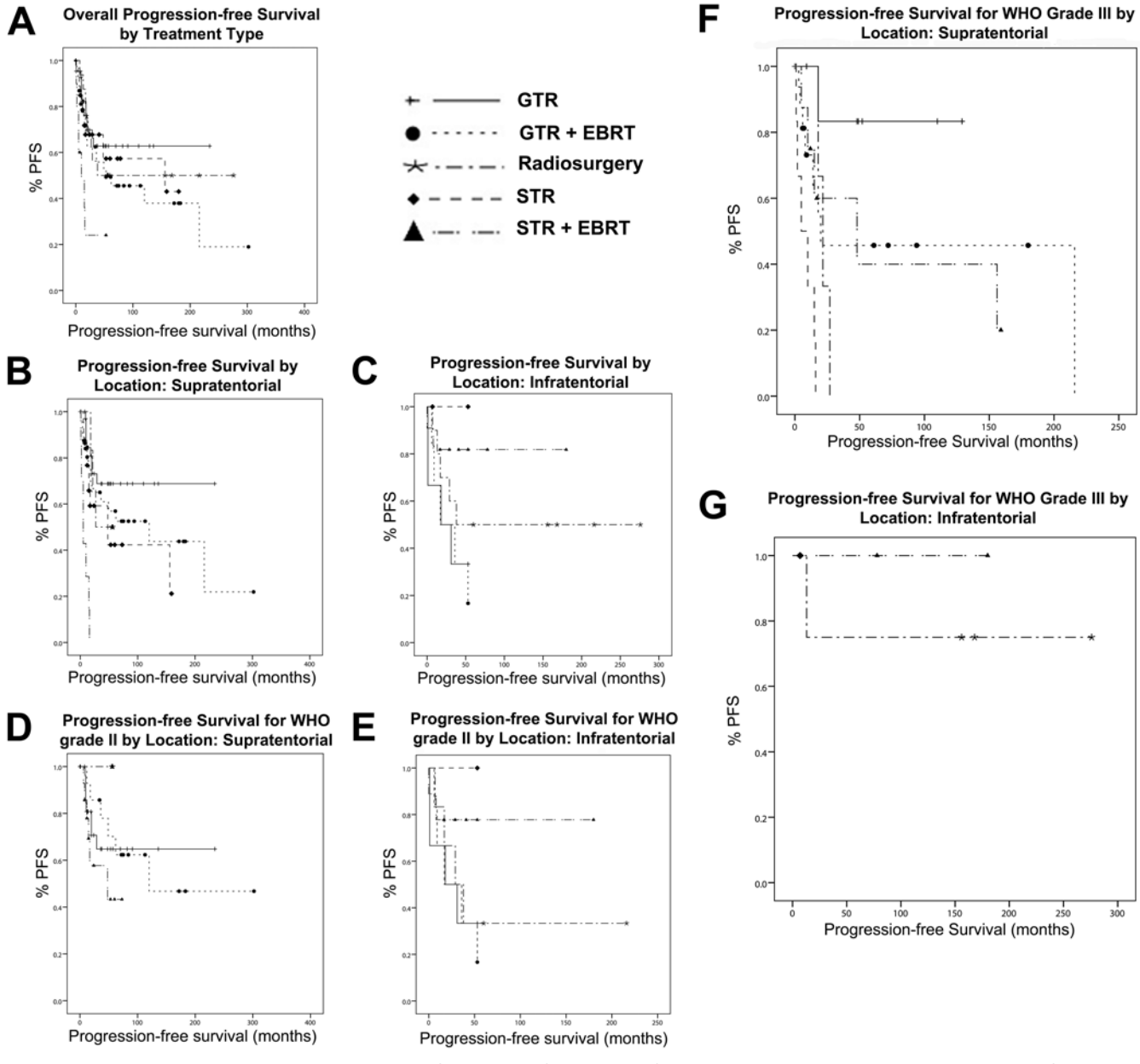


**Fig. 2.** Kaplan-Meier plots representing PFS outcomes after treatment for intracranial ependymomas, including overall PFS **(A)**, PFS according to supratentorial **(B)** or infratentorial **(C)** tumor location, PFS for low-grade (WHO Grade II) tumors based on supratentorial **(D)** or infratentorial **(E)** location, and PFS for high-grade (WHO Grade III) tumors based on supratentorial **(F)** or infratentorial **(G)** location.

182 patients, which when divided among the 5 distinct treatment modalities, results in a small patient cohort representing each treatment modality. In addition, although we attempted to look at morbidity data across this heterogeneous population, due to the extremely low rates of morbidity reporting, it was difficult to tease out more than just anecdotal information for patients undergoing treatment of intracranial ependymomas. This highlights the importance of adhering to uniform reporting standards in the future to most accurately understand patient outcomes following intracranial ependymoma resection, radiation therapy, or a combination of the two. Although the 5 treatment modalities discussed were chosen because of current accepted standard-of-care protocols, many institutions are treating patients with chemotherapy. The group of patients that have received chemotherapy alone, in addition to resection or in addition to radiation therapy, is a population that is not addressed here and may provide additional information about how pediatric patients with ependymomas respond to therapy.

## Conclusions

Clinical outcomes, including PFS and mortality, vary in pediatric patients with intracranial ependymomas. When counseling families on treatment options for these

patients, it is important to consider probable pathological grade, tumor location, and projected feasible extent of resection. All these factors contribute to the outcome profile for individual patients. Neurosurgeons should continue to consider each patient presentation uniquely, weighing the above-mentioned factors in treatment selection strategy.

### 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: Auguste, Cage, Gupta. Acquisition of data: Cage, Aranda. Analysis and interpretation of data: Cage. Drafting the article: Auguste, Cage. 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: Auguste. Statistical analysis: Cage. Administrative/technical/material support: Auguste, Aranda, Gupta, Sun, Parsa. Study supervision: Auguste.

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