

## Therapeutic Impact of Cytoreductive Surgery and Irradiation of Posterior Fossa Ependymoma in the Molecular Era: A Retrospective Multicohort Analysis

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### A B S T R A C T

#### Purpose

Posterior fossa ependymoma comprises two distinct molecular variants termed EPN\_PFA and EPN\_PFB that have a distinct biology and natural history. The therapeutic value of cytoreductive surgery and radiation therapy for posterior fossa ependymoma after accounting for molecular subgroup is not known.

#### Methods

Four independent nonoverlapping retrospective cohorts of posterior fossa ependymomas (n = 820) were profiled using genome-wide methylation arrays. Risk stratification models were designed based on known clinical and newly described molecular biomarkers identified by multivariable Cox proportional hazards analyses.

#### Results

Molecular subgroup is a powerful independent predictor of outcome even when accounting for age or treatment regimen. Incompletely resected EPN\_PFA ependymomas have a dismal prognosis, with a 5-year progression-free survival ranging from 26.1% to 56.8% across all four cohorts. Although first-line (adjuvant) radiation is clearly beneficial for completely resected EPN\_PFA, a substantial proportion of patients with EPN\_PFB can be cured with surgery alone, and patients with relapsed EPN\_PFB can often be treated successfully with delayed external-beam irradiation.

#### Conclusion

The most impactful biomarker for posterior fossa ependymoma is molecular subgroup affiliation, independent of other demographic or treatment variables. However, both EPN\_PFA and EPN\_PFB still benefit from increased extent of resection, with the survival rates being particularly poor for subtotally resected EPN\_PFA, even with adjuvant radiation therapy. Patients with EPN\_PFB who undergo gross total resection are at lower risk for relapse and should be considered for inclusion in a randomized clinical trial of observation alone with radiation reserved for those who experience recurrence.

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## INTRODUCTION

Ependymoma is the third most common posterior fossa tumor of childhood and a major cause of morbidity and mortality in pediatric oncology, occurring across the entire age spectrum.<sup>1-16</sup> Current therapy for posterior fossa ependymoma in children is aggressive surgical resection followed by involved-field radiation, resulting in 7-year event free-survival of 65%.<sup>12,15</sup> Despite the high mortality rate, trials of cytotoxic chemotherapy have failed to reveal a clear survival benefit for chemotherapy over surgery and radiation alone, although definitive pediatric randomized trials of maintenance chemotherapy are still recruiting through cooperative groups ([ClinicalTrials.gov](https://clinicaltrials.gov) identifiers: NCT01096368 and NCT02265770).<sup>15,17</sup> In adults, posterior fossa ependymoma is frequently treated with surgery alone.<sup>18</sup>

Numerous publications have suggested that the most powerful prognostic factor for posterior fossa ependymoma is the extent of surgical resection or, more appropriately, the amount of residual tumor after surgery. This has entailed an aggressive surgical approach, with some oncologists and surgeons tolerating serious neurologic deficits, including the need for tracheostomies and gastrostomy tubes, as an inevitable cost in the attempt to achieve tumor-free survival, including potentially morbid second-look surgery.

Because the majority of ependymomas within the neuroaxis are histologically similar, historically they had been thought to compose one disease, but they were subsequently recognized to be biologically distinct in the supratentorial, posterior fossa, and spinal compartments of the CNS.<sup>19</sup> More recently, integrated genomic approaches have clearly shown the existence of the following three distinct molecular variants of posterior fossa ependymoma: EPN\_PFA, EPN\_PFB, and subependymoma. EPN\_PFA occurs primarily in infants and young children, whereas EPN\_PFB occurs primarily in older children and adults.<sup>20-23</sup> Subependymomas are grade 1 tumors with an excellent prognosis restricted to older adults. Patients with EPN\_PFB have an excellent outcome, with survival rates in excess of 90%, whereas patients with EPN\_PFA have a poor outcome. Curiously, neither EPN\_PFA nor EPN\_PFB has any recurrent somatic single nucleotide variants, and both demonstrate a low rate of mutation across the genome.<sup>21</sup> The complete lack of recurrent somatic single nucleotide variants implies that targeted therapy using small molecules directed against recurrent mutations is unlikely to be a successful strategy for patients with posterior fossa ependymoma. EPN\_PFA is characterized by relatively increased DNA methylation compared with EPN\_PFB, and preclinical studies suggest that epigenetic modulating agents might be beneficial for patients with EPN\_PFA.<sup>21</sup>

All prior studies of the therapeutic value of cytoreductive surgery and external-beam radiation done in the pre-molecular era have not accounted for subgroup affiliation and might therefore be confounded by clinical differences in response to therapy between EPN\_PFA and EPN\_PFB. In addition to extent of resection and provision of radiotherapy, age at presentation was a strong posterior fossa ependymoma risk factor in the pre-molecular era literature. It is unclear whether younger age is an independent risk factor or is merely a reflection of the enrichment of patients with EPN\_PFA in younger cohorts. Thus, it is unclear whether older patients with EPN\_PFA will do well, whereas younger patients with

EPN\_PFB will do poorly. Previous studies from our group and others have suggested that the two posterior fossa ependymoma subgroups may have disparate responses to therapy.<sup>20,21</sup> To determine the true value of extent of resection, radiation therapy, and age at presentation as biomarkers in the molecular era, we present the largest retrospective cohort of posterior fossa ependymomas ever assembled and determine the validity and strength of known biomarkers after accounting for molecular subgroup.

## METHODS

Three hundred five posterior fossa ependymomas were obtained from the Hospital for Sick Children and from collaborating centers from around the world through the Global Ependymoma Network of Excellence (GENE) consortium from 1990 to 2014. Samples were all collected in accordance with the approval of the Hospital for Sick Children Research Ethics Board and local institutional research ethics boards. To account for unobserved variables, three independent nonoverlapping validation cohorts were assembled from the prospective St Jude Children's Research Hospital (n = 112, RT1 cohort), the Collaborative Ependymoma Research Network (n = 121, CERN cohort), and the German Cancer Research Center/Burdenko Neurosurgical Institute (n = 261, Burdenko cohort). Full details of the cohorts, sample processing, collection of clinical annotations, and statistical analysis are found in the Appendix (online only).

## RESULTS

### **Demographics of Posterior Fossa Ependymoma Cohorts**

Posterior fossa ependymomas from all four cohorts had molecular subgroup determined using unsupervised hierarchical clustering of genome-wide methylation arrays, as recently described.<sup>23</sup> In total, we analyzed 820 posterior fossa ependymomas, which were subsequently found to include 678 EPN\_PFAs and 142 EPN\_PFBs, with EPN\_PFBs more highly enriched in the CERN and Burdenko cohorts, as reflected by the median age (Table 1). Demographics and treatment details of each of the four cohorts are listed in Table 1. Grade was not included as a variable because a previous reanalysis of several prospective cohort studies showed the existing WHO histologic classification to be unreliable as a result of profound intraobserver variability, confounding its utility in clinical risk stratification.<sup>24</sup> The median age of patients with EPN\_PFA was almost identical across all four cohorts, with a combined median age of 3 years (Appendix Fig A1, online only; overall age range, 0 to 77 years; GENE: median, 3.6 years; range, 0 to 72 years; St Jude RT1: median, 2.38 years; range, 0.62 to 22.76 years; CERN: median, 4 years; range, 0 to 67 years; Burdenko: median, 4 years; range, 0 to 65 years). Children younger than age 5 years almost exclusively had EPN\_PFA (three EPN\_PFB tumors in patients < 5 years old); however, 45% of pediatric patients age 10 to 17 years had EPN\_PFB tumors. Adults largely had EPN\_PFB, although 11% of adults had EPN\_PFA tumors. Overall, 236 deaths and 420 progression events were observed, and median follow-up time of the entire cohort was 6.7 years (95% CI, 6.0 to 7.2 years).

### **Subgroup Affiliation Is the Most Powerful Prognostic Marker for Posterior Fossa Ependymoma**

To determine the prognostic value of ependymoma subgroups, we performed a Cox proportional hazards regression model across

**Table 1.** Demographic and Treatment Characteristics of All Four Cohorts

Characteristic	No. of Patients (%)			
	GENE (n = 326)	St Jude's RT1 (n = 112)	CERN (n = 121)	Burdenko (n = 261)
Median age, years (interquartile range)	3.6 (1.87-7.45)	2.38 (1.57-4.99)	4 (2-25.5)	4 (2-8.5)
Male sex	175 (53.6)	61 (54.5)	63 (52.1)	152 (58.2)
GTR	221 (68.9)	92 (82.1)	68 (56.7)	138 (53.3)
Adjuvant first-line radiation	250 (78.6)	112 (100)	72 (59)	196 (75.1)
Adjuvant chemotherapy	138 (44.5)	0	42 (34.7)	164 (62.8)
Disease progression	148 (45.7)	40 (35.7)	72 (59.5)	146 (55.9)
Dead	104 (31.9)	41 (33.9)	28 (25)	63 (24.2)
Subgroup				
EPN_PFA	275 (84.4)	104 (92.9)	86 (71.1)	213 (81.6)
EPN_PFB	51 (15.6)	8 (7.1)	35 (28.9)	48 (18.4)

NOTE. Data were missing for the following: GTR: GENE, n = 4; CERN, n = 1; Burdenko, n = 2; adjuvant first-line radiation: GENE, n = 8; adjuvant chemotherapy: GENE, n = 16; disease progression: GENE, n = 2; and sex: Burdenko, n = 16. Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection (< 5 mm residual disease).

all four cohorts incorporating age, extent of surgical resection, adjuvant external-beam irradiation, subgroup, and cohort stratification (Table 2, Appendix Tables A1-A3, online only). No significant predictor-cohort interaction was identified for any of these variables with the exception of adjuvant radiation, which had a stronger effect in the GENE cohort; thus, we proceeded to pool all four cohorts in a multivariable analysis (Appendix Table A4, online only). After accounting for treatment variables, subgroup affiliation remained a highly significant predictor of progression-free survival (PFS; hazard ratio [HR], 2.14; 95% CI, 1.31 to 3.49;  $P = .002$ , Table 2; Appendix Tables A1 and A3 report each cohort individually) and overall survival (OS; HR, 4.30; 95% CI, 1.88 to 9.87;  $P < .001$ ; Table 2; Appendix Tables A1 and A3 report each cohort individually). Administrative censoring at 10 years did not significantly alter the multivariable analysis (Appendix Tables A2 and A3). The HR for subgroup affiliation (HR, 4.30) was the highest of the examined biomarkers. Extent of resection, adjuvant external-beam irradiation, and male sex were also significant independent predictors of PFS and OS, whereas age at diagnosis and delivery of chemotherapy were not. We then evaluated the survival of patients with EPN\_PFA versus EPN\_PFB in each cohort individually. Across the four cohorts, EPN\_PFA had significantly worse PFS and OS compared with

EPN\_PFB (Table 2; Appendix Fig A2, online only; Appendix Tables A1 and A2).

**EPN\_PFA Carries a Poor Prognosis Independent of Age at Diagnosis**

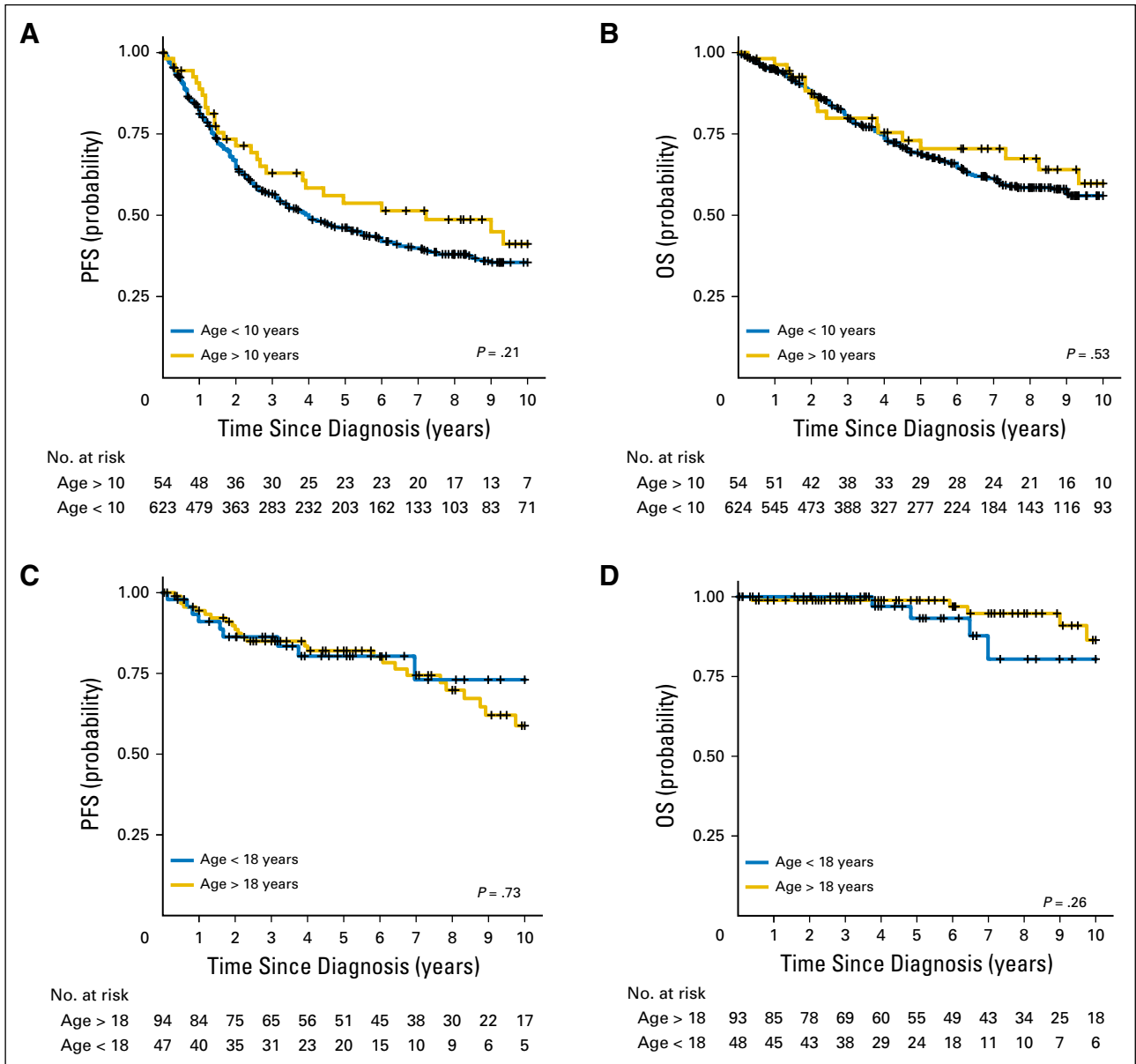
In the premolecular era, age was an important prognostic factor for patients with posterior fossa ependymoma. We assessed the relative hazard for EPN\_PFA and EPN\_PFB depending on age and found that the relative risk of an EPN\_PFA tumor is relatively constant across all age groups with a slight decrease for adults and is consistently higher than for EPN\_PFB across the entire age spectrum (Appendix Fig A3, online only). We restricted our survival analysis to patients older than age 10 years, and EPN\_PFA remained a significant predictor of poor outcome for both 10-year PFS ( $P = .001$ ) and 10-year OS ( $P < .001$ ; Appendix Fig A4 and Appendix Table A5, online only). Finally, to determine whether older children with EPN\_PFA have a poor outcome, we stratified age as less than or greater than 10 years and found no significant difference in either PFS or OS, confirming that the poor prognosis attributed to EPN\_PFA is not solely a result of the young age of the cohort (Fig 1). A similar analysis was done for EPN\_PFB, where survival was stratified as greater than or less than 18 years with no significant difference in survival, further reaffirming that EPN\_PFB is a favorable-risk group independent of age at diagnosis (Fig 1). As such, we conclude that the poor prognosis of EPN\_PFA and the excellent prognosis of EPN\_PFB are independent of age at diagnosis, confirming the results of the multivariable Cox regression analysis.

**Surgical Cytoreduction of EPN\_PFA Is Prognostic Independent of Subgroup**

Extent of resection is identified in multiple publications as the single most important predictor of outcome for patients with posterior fossa ependymoma. However, poor-prognosis EPN\_PFA tumors are a difficult surgical challenge as a result of their lateral location and occurrence in small infants who have a small blood volume, whereas good-prognosis EPN\_PFB tumors are comparatively straightforward to resect as a result of their midline location and occurrence in an older age group. We hypothesized that the

**Table 2.** Multivariable Cox Proportional Hazards Regression Model of Progression-Free and Overall Survival

Variable	Hazard Ratio	95% CI	P
Progression-free survival (n = 777)			
Age	0.99	0.98 to 1.00	.13
Male	1.25	1.02 to 1.54	.03
Incomplete resection	1.84	1.49 to 2.28	< .001
Adjuvant first-line radiation	0.63	0.49 to 0.79	< .001
Chemotherapy	1.04	0.81 to 1.34	.76
EPN_PFA subgroup	2.14	1.31 to 3.49	.002
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.12
Male	1.41	1.97 to 1.85	.01
Incomplete resection	2.13	1.60 to 2.82	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.72	< .001
Chemotherapy	0.90	0.65 to 1.26	.54
EPN_PFA subgroup	4.30	1.88 to 9.87	< .001



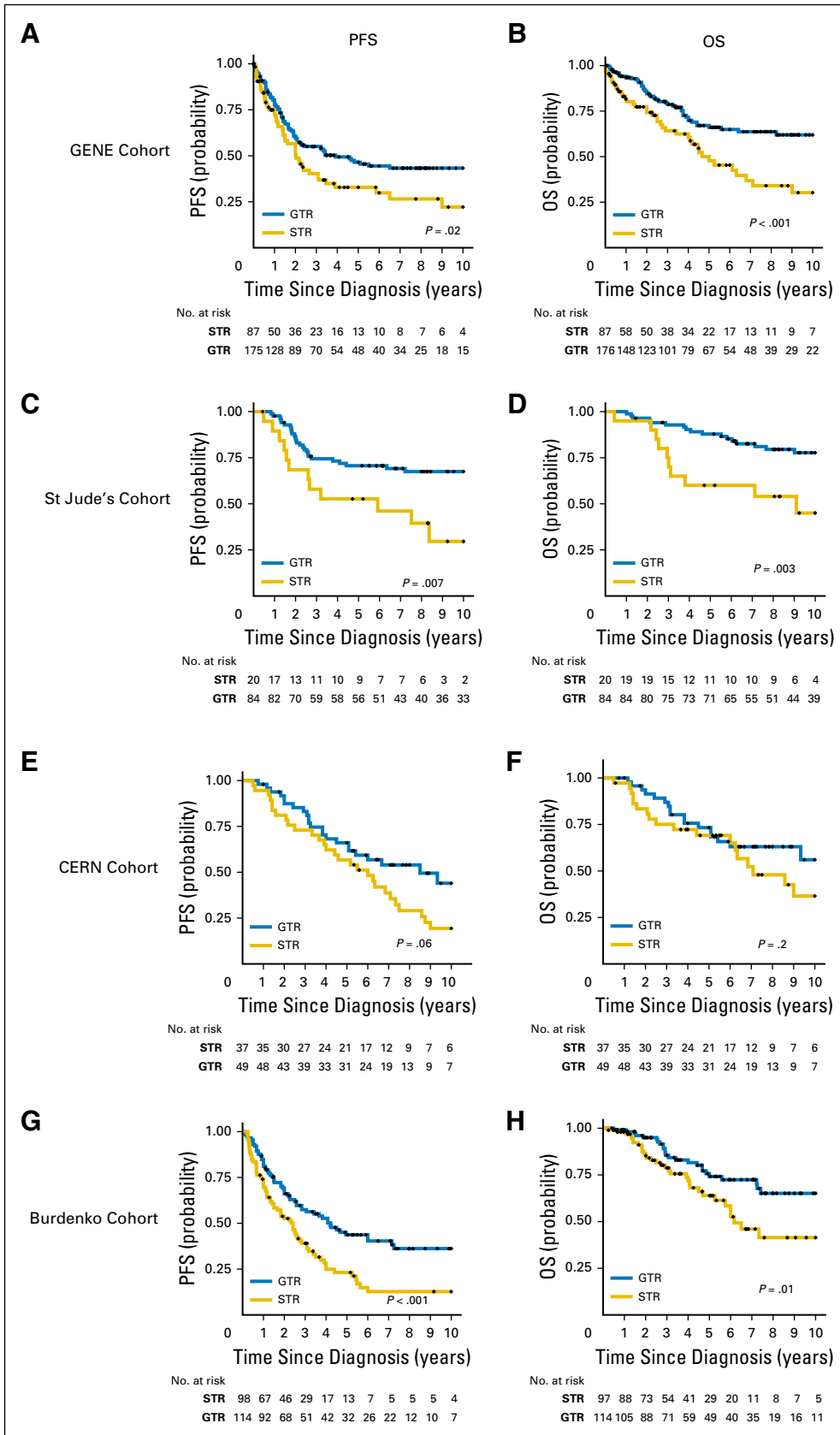
**Fig 1.** Survival of EPN\_PFA and EPN\_PFB stratified by age. (A) Progression-free survival (PFS) and (B) overall survival (OS) of EPN\_PFA stratified by age greater than or less than 10 years. (C) PFS and (D) OS of EPN\_PFB stratified by age greater than or less than 18 years. *P* values determined using log-rank test.

previously observed therapeutic value for surgical cytoreduction was confounded by the poor natural history of EPN\_PFA tumors, which are difficult to resect, compared with the benign natural history of EPN\_PFB tumors, which are less difficult to resect.

To determine the relationship between subgroup and extent of resection after accounting for molecular subgroup, we compared PFS and OS in each subgroup individually stratified by extent of resection. When comparing subtotal resection (STR) versus gross total resection (GTR) in EPN\_PFA, STR was highly predictive of a dismal PFS and OS (Fig 2 and Appendix Table A6, online only). In a multivariable Cox proportional hazards model that included adjuvant chemotherapy and radiation, survival remained dismal for STR EPN\_PFA (Appendix Tables A7 and A8, online only). Although we observed some variability in the effect of extent of

resection across the four cohorts, we did not observe a statistically significant difference in or heterogeneity of the effect of extent of resection in EPN\_PFA across cohorts (interaction  $P = .80$  for PFS,  $P = .53$  for OS). Male sex was a significant independent predictor of poor outcome across all four cohorts in GTR in a multivariable analysis restricted to EPN\_PFA, although STR is a high-risk group in both male and female patients (Appendix Fig A5, online only, and Appendix Table A7). Within EPN\_PFA, female patients with a GTR had a 5-year PFS of 0.652 (95% CI, 0.581 to 0.732), whereas male patients with a GTR had a 5-year PFS of 0.455 (95% CI, 0.393 to 0.527).

The value of first-line (adjuvant post-surgical) radiotherapy could only be compared with no radiation in the GENE, CERN, and Burdenko cohorts, because all patients in the prospective

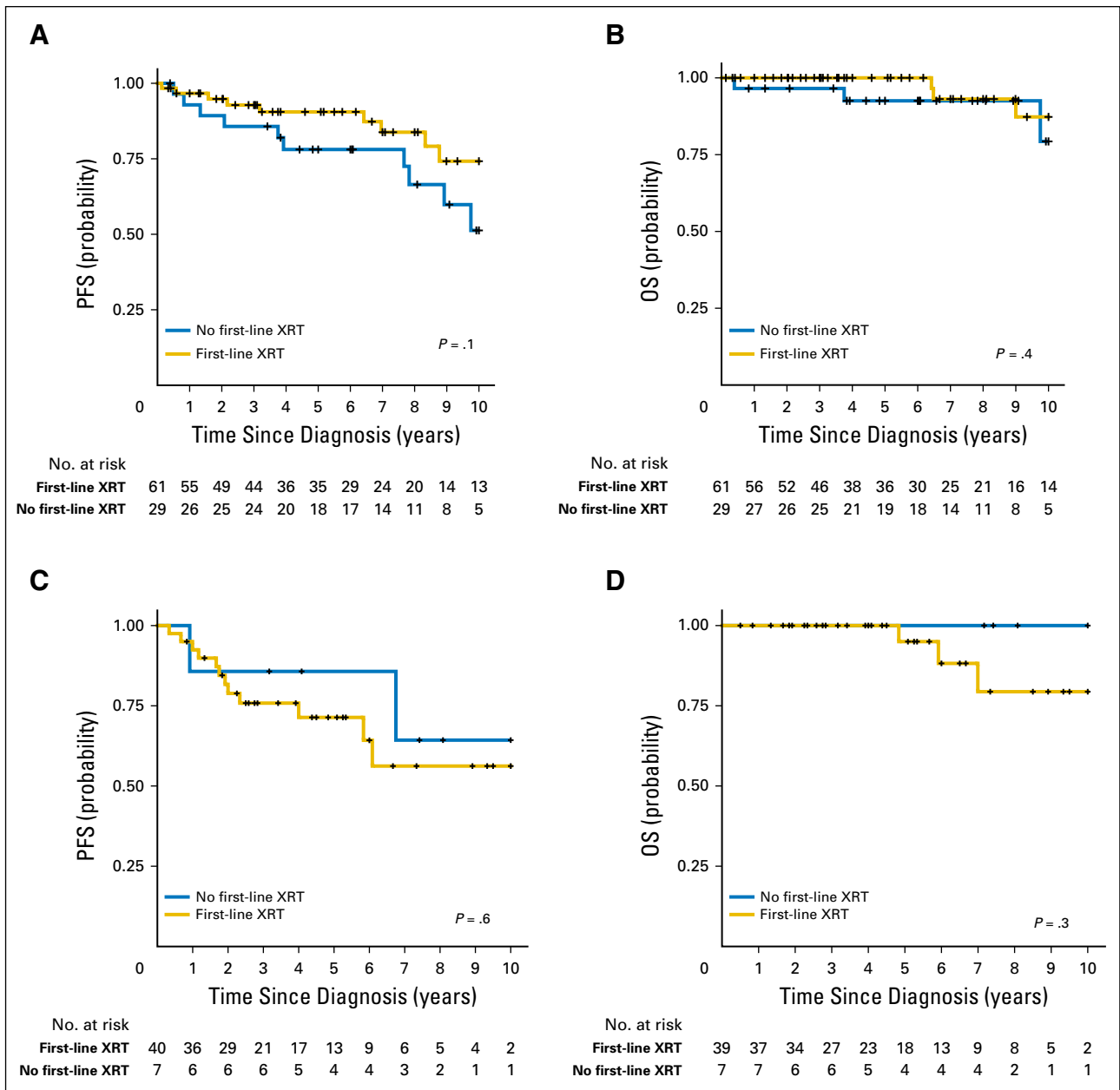


**Fig 2.** (A, C, E, and G) Progression-free survival (PFS) and (B, D, F, and H) overall survival (OS) of EPN\_PFA stratified by extent of resection across all four cohorts. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection; STR, subtotal resection (> 5 mm residual disease). *P* values determined using log-rank test.

St Jude RT1 cohort received adjuvant postoperative radiation. Strikingly, survival for STR EPN\_PFA was not different between those who received first-line external-beam radiation and those who did not in the CERN and Burdenko cohorts (Appendix Fig A6, online only). In the GENE cohort, there was a statistically significant difference by a univariable analysis in patients who did not receive radiation; however, survival remains poor even in patients with subtotal resections who received external-beam irradiation. These data suggest that the benefit of post-surgical first-line adjuvant external-beam irradiation for patients with EPN\_PFA is limited in the face of a subtotal resection and that these patients should be prioritized for clinical trials of novel therapy.

**Patients With GTR EPN\_PFB Have an Excellent Prognosis**

As a result of limited patient numbers, we combined patients with EPN\_PFB from the GENE, St Jude RT1, and CERN cohorts and demonstrated that STR results in a high risk of relapse (10-year PFS for GTR, 0.740; 95% CI, 0.550 to 0.859; 10-year PFS for STR, 0.50; 95% CI, 0.271 to 0.692). These findings were confirmed in a cohort of patients with EPN\_PFB treated at the Burdenko Institute (Fig 3). As a result of the similar behavior of the two cohorts and the relatively small number of patients with EPN\_PFB in each cohort, we combined all patients in our subsequent multivariable analysis. In a multivariable analysis restricted to EPN\_PFB, a similar

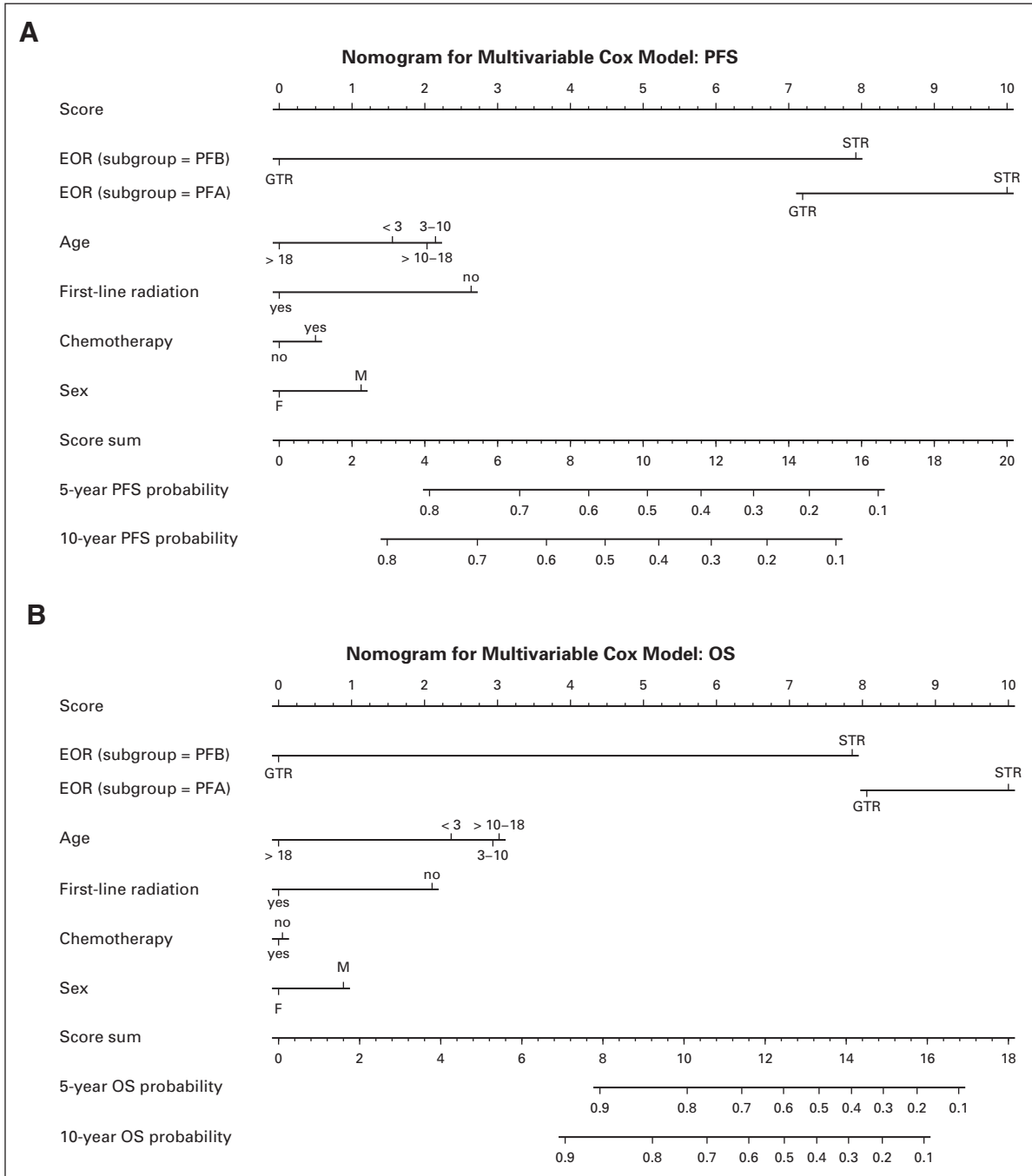


**Fig 3.** Value of adjuvant post-operative first-line external-beam irradiation (XRT) in EPN\_PFB. (A) Progression-free survival (PFS) and (B) overall survival (OS) of EPN\_PFB across the Global Ependymoma Network of Excellence, St Jude’s, and Collaborative Ependymoma Research Network cohorts. (C) PFS and (D) OS of EPN\_PFB across the Burdenko cohort. P values determined using log-rank test.



pattern emerges, where an incomplete resection is an independent predictor of both PFS and OS (Appendix Tables A9 and A10, online only). However, OS for patients with GTR EPN\_PFB is extremely favorable, with a 10-year OS of 0.961 (95% CI, 0.753 to 0.994), compared with patients with STR EPN\_PFB, who had a 10-year OS of 0.667 (95% CI, 0.308 to 0.870; Appendix Fig A7, online only). Interestingly, the PFS for patients with EPN\_PFB who did not receive external-beam irradiation was 0.451 (95% CI, 0.216 to 0.661); however, the OS was 0.823 (95% CI, 0.519 to 0.943). These

data suggest that a subset of patients with EPN\_PFB can be cured by surgery alone after GTR (Fig 3). Of the three nonirradiated patients with EPN\_PFB who died, two had an STR and one had a GTR. A substantial portion of patients with EPN\_PFB who experience recurrence after initially withholding radiation can potentially be successfully treated by repeat surgery and delayed delivery of radiation (Fig 3). Indeed, the effect of a GTR versus an STR in EPN\_PFB was significant for both the three combined cohorts and for the Burdenko cohort ( $P = .02$  in univariable Cox regression



**Fig 4.** Nomogram of (A) progression-free survival (PFS) and (B) overall survival (OS) of posterior fossa ependymoma based on the multivariable Cox proportional hazards model. Each effect is translated into a risk score. The individual risk scores need to be totaled by the reader. The score sum can be translated into predicted 5- and 10-year PFS and OS probabilities. EOR, extent of resection; F, female; GTR, gross total resection; M, male; STR, subtotal resection.

analysis). Because the long-term effects of radiation for posterior fossa ependymoma in young adults who are cured can be quite severe,<sup>25-28</sup> these data provide the necessary clinical equipoise for initiation of a clinical trial of initial radiation avoidance in patients with GTR EPN\_PFB ependymoma.

## DISCUSSION

We have defined the demographic and prognostic properties of the two subgroups of posterior fossa ependymoma across the largest cohort of posterior fossa ependymoma assembled to date. Although three of the cohorts consist of retrospective data, the St Jude RT1 cohort was prospectively followed and homogeneously treated. The cohort is of such a large size that it will not likely be repeated in our lifetime, nor is a prospective clinical trial randomly assigning extent of resection in posterior fossa ependymoma patients likely.

We have shown that although EPN\_PFA occurs primarily in infants and EPN\_PFB is diagnosed primarily in adults, in children age 10 to 17 years, there is equal representation of both subgroups. Moreover, in adults, approximately 11% of patients have EPN\_PFA. Across the entire age spectrum, we show that subgroup is the most powerful predictor of outcome, suggesting that in patients older than age 5 years, there is significant information to be gained in routine subgrouping of patients with posterior fossa ependymoma. Extent of resection, although no longer the most powerful predictor of outcome, remains prognostic in both subgroups. In particular, patients with STR EPN\_PFA constitute a high-risk group with a poor outcome. Finally, we have shown that a subset of patients with EPN\_PFB can be treated with surgery alone without external-beam irradiation, suggesting a trial of observation alone may be warranted in this subset of patients. Overall, in a prediction model of subgroup, treatment, and extent of resection as depicted in a nomogram, we find that EPN\_PFA is the strongest predictor of poor outcome (Fig 4). Male sex was also an independent predictor of poor outcome in our analysis across all four cohorts, which is consistent with previous reports.<sup>12</sup> Interestingly the survival advantage in females is most pronounced in the setting of GTR EPN\_PFA. A more comprehensive integrated genomic study will likely be required to clarify this association; however, it is noteworthy that females with a GTR have 10-year survival rates approximately 15% higher than males.

Our finding that patients with STR EPN\_PFA have a dismal outcome has significant implications to the design of future clinical trials. Although a simple proximate solution would be to suggest GTR in all patients, this is frequently not possible as a result of brainstem invasion. Additionally, this subset of EPN\_PFA seems to confer the least benefit from adjuvant external-beam irradiation and could potentially benefit from novel therapies. Previous studies of chemotherapy have shown only limited activity against posterior fossa ependymoma, with high-dose chemotherapy with autologous stem-cell support resulting in 3-year event-free survival of less than 30%, consistent with the survival we observed.<sup>29,30</sup> The role of adjuvant chemotherapy will require completion and reporting of long-term outcomes in the open studies of both the European Society of Pediatric Oncology (SIOPe) and the Children's Oncology Group (ACNS0831), where patients are randomly assigned to maintenance chemotherapy. Our findings across four independent

cohorts of posterior fossa ependymoma suggest that STR EPN\_PFA should be prioritized for first-line investigational agents, such as DNA demethylase inhibitors and EZH2 inhibitors, to provide an opportunity to assess activity of these agents prior to radiation.<sup>21</sup> Indeed, even patients with GTR EPN\_PFA have OS rates of close to 50%, suggesting aggressive surgeries are not curative, and novel approaches would benefit this group as well.

We also find that STR confers a significantly poorer prognosis in EPN\_PFB. Considering that the 10-year OS for EPN\_PFB is greater than 85% with a complete resection, we feel that a GTR should be attempted where possible. The EPN\_PFB data are limited by small numbers of STR patients and, as such, warrant some caution in interpretation. Major limitations of our study are a lack of central review of postoperative imaging in the three retrospective cohorts, retrospective design of the study without uniform follow-up imaging to identify progression, and treatment heterogeneity. Indeed, nonenhancing residual tumor can be missed even with modern postoperative magnetic resonance imaging. A large prospective radiographic study using modern three-dimensional magnetic resonance imaging volumetrics with a receiver operating curve will be needed to determine precisely how much residual tumor is truly predictive of a poor prognosis.

Finally, our finding that EPN\_PFB can potentially be cured without external-beam irradiation has profound implications. Across the EPN\_PFB cohort, we demonstrate many patients who have not experienced recurrence despite the lack of radiation therapy. Therefore, our data suggest that radiation in EPN\_PFB can be initially withheld and that patients who experience recurrence can potentially be treated with salvage resection and radiation. The ability to successfully treat patients with EPN\_PFB with repeat surgery and radiation therapy is demonstrated by the large difference between PFS and OS in this patient population. Considering that the majority of adult posterior fossa ependymoma patients are not treated on open protocols, prospective evaluation will be crucial to determine the optimal treatment approach. We feel that our data support consideration of a prospective clinical trial of observation alone for GTR EPN\_PFB, which could potentially spare patients the toxic effects of radiation.<sup>31</sup> The age group in which this could confer the highest benefit would be the older pediatric and adolescent population, in whom radiation has significant effects on learning and memory, and this approach could significantly improve long-term quality of life in this subset of patients.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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## **Appendix**

### **Methods**

#### **Patient Cohort**

All frozen samples were snap frozen and stored at  $-80^{\circ}\text{C}$ . Both frozen and formalin-fixed paraffin-embedded (FFPE) samples were collected from diagnosis and, in four instances, from relapse. Criteria for inclusion were an institutional histologic diagnosis of grade 2 or greater ependymoma and location within the posterior fossa. FFPE tissue was collected as scrolls or unstained slides. The Global Ependymoma Network of Excellence cohort was deemed the discovery cohort. Samples from three additional cohorts were collected and processed in an identical manner, including central pathologic review by a single pathologist in each of the three cohorts. Patients from the three additional cohorts have been partially reported in other cohort studies.<sup>12,23,24</sup> Subtotal resection was defined as greater than 5 mm of postoperative residual disease in at least two planes on postoperative magnetic resonance imaging or postoperative contrast-enhanced computed tomography scan as per the guidelines of the Children's Oncology Group based on institutional radiologic reports. A gross total resection was defined as less than 5 mm of postoperative residual disease on postoperative magnetic resonance imaging or postoperative contrast-enhanced computed tomography based on institutional radiologic reports. Assessment of clinical variables pertaining to treatment and survival were performed at local institutions blinded to the molecular subgrouping. Grading was not included as a variable as a result of previous reports showing the extreme interobserver variability of this measure.<sup>24</sup>

#### **DNA Extraction**

Fresh-frozen posterior fossa ependymomas were stored at  $-80^{\circ}\text{C}$  before processing for extraction of DNA. For frozen samples, DNA extraction was performed using a proteinase K digestion and phenol:chloroform:isoamyl alcohol extraction and ethanol precipitation.<sup>25</sup> FFPE samples were processed using the Qiagen DNeasy FFPE extraction kit (Qiagen, Hilden, Germany), as per the manufacturer's instructions.<sup>26</sup> Samples were quantified using Picogreen (Life Technologies, Waltham, MA).

#### **Genome-Wide DNA Methylation Profiling**

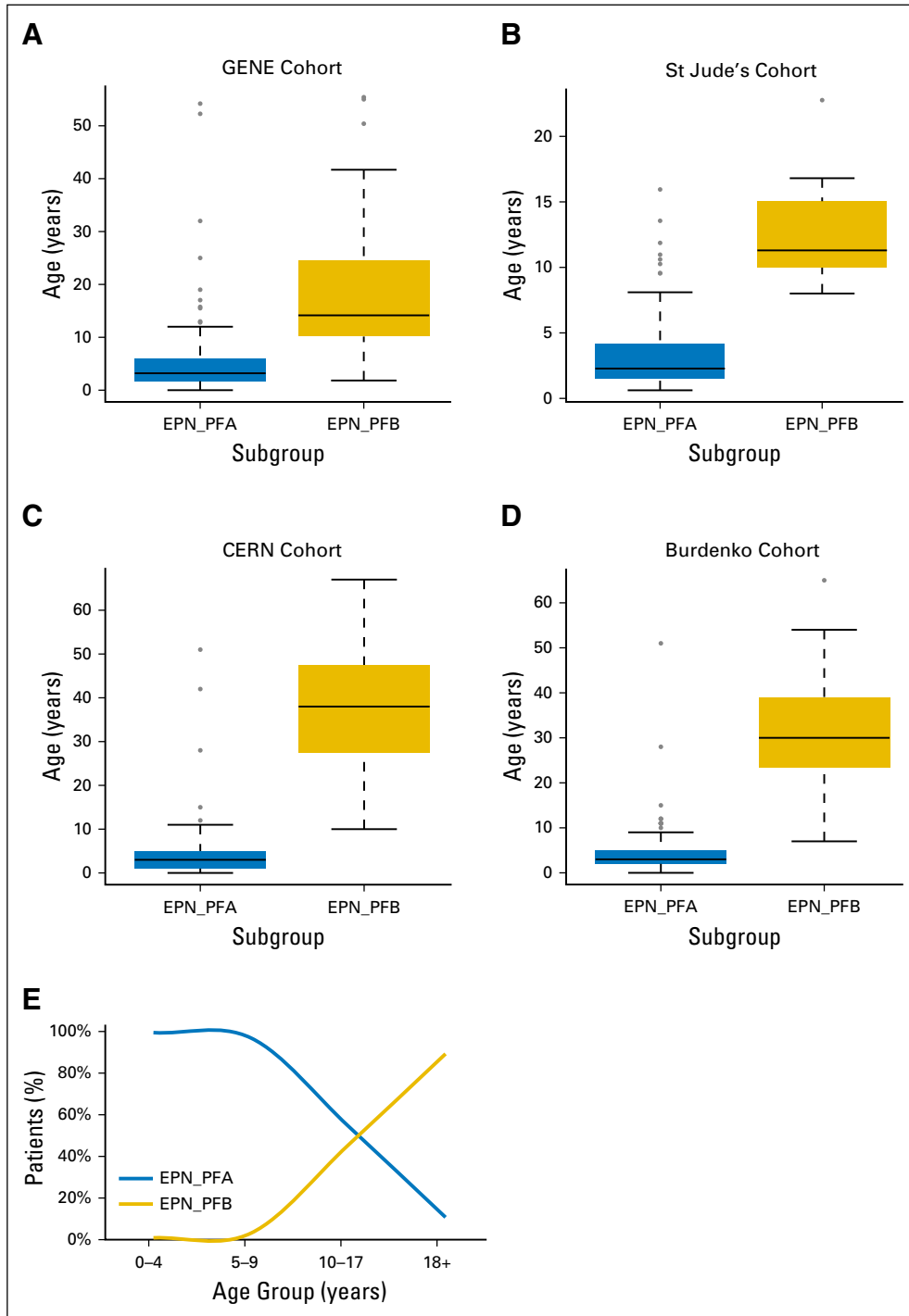
All samples were analyzed on the Illumina Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA) at the Princess Margaret Genomics Centre (Toronto, Ontario, Canada), the St Jude Children's Research Hospital (Memphis, TN), or the German Cancer Research Center (Heidelberg, Germany) according to the manufacturer's instructions and as previously described. All analysis was conducted in the R Statistical Environment (v3.1.3; [www.r-project.org](http://www.r-project.org)). Raw data files (.idat) were processed as previously described, and ependymoma subgroup affiliation was assigned as per a recently released classifier using unsupervised hierarchical clustering.<sup>23</sup> Thirty-five grade 1 ependymomas (myxopapillary and subependymomas) were excluded from the analysis based on this classifier. Eleven samples diagnosed as ependymomas by local institutions did not cluster with posterior fossa ependymoma and were removed from the analysis.

#### **Statistical Analysis**

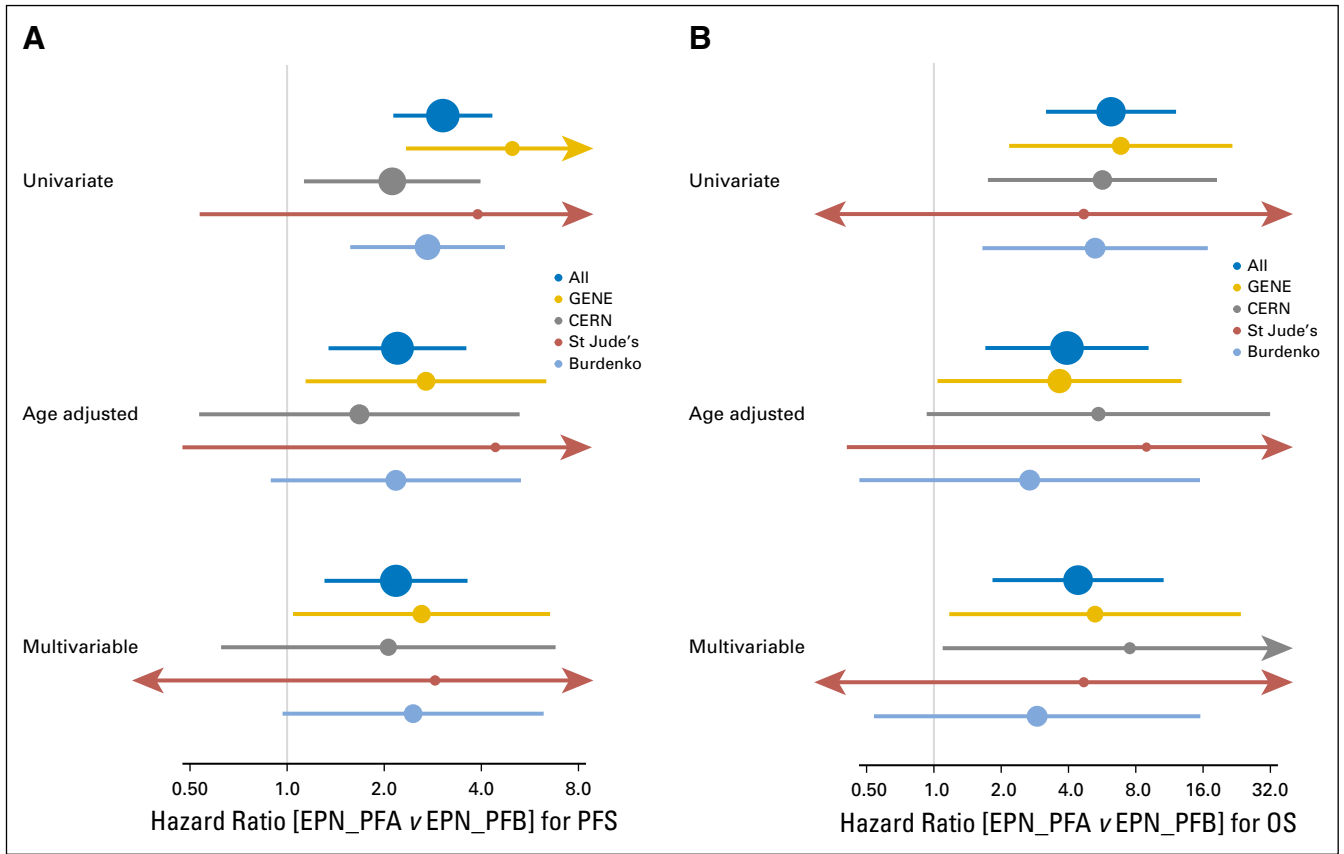
Progression-free survival and overall survival were right censored at 10 years and analyzed using the Kaplan-Meier method, and *P* values were determined using the log-rank test. Administrative censoring at 10 years was performed to ensure a reasonable completeness of follow-up across all four cohorts as a result of declining patient numbers at longer follow-up times. Administrative censoring resulted in only 1.6% of additionally censored patients at the end of the follow-up period for overall survival. As such, both continuous and censored data are presented. Survival data are presented as survival estimates including 95% CIs. A progression event was defined as the earliest time point between two assessment times with clear radiologic progression as reported by the local institution, and progression-free survival was defined as the interval between the initial diagnosis (typically surgery) and the progression event. Overall survival was calculated as the time from surgery to the time of death from any cause as reported by the referring institution. Associations between covariates and risk groups were tested using the Fisher's exact test. Univariable and multivariable Cox proportional hazards regression was used to estimate hazard ratios including 95% CIs. In pooled analysis, cohort was included as a stratification variable in the Cox model. In some EPN\_PFB subgroup analysis, Firth correction was applied as a result of monotone likelihoods.<sup>27</sup> Age-dependent relative hazards for PFA/PFB subgroups were estimated from a Cox model with



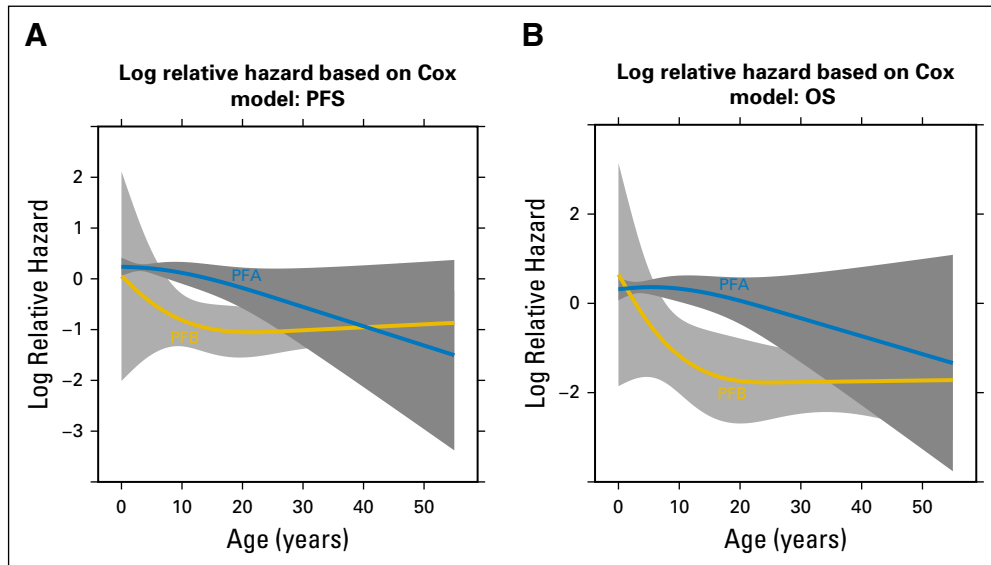
age and subgroup interaction and a restricted cubic spline function with three knots for age to allow for a nonlinear relationship. All *P* values reported are two-sided. All statistical analyses were performed in the R statistical environment (v3.1.2), using R packages of survival (v2.37-7), rms (4.3-1), Coxphf (v1.1), and ggplot2 (v1.0.0).



**Fig A1.** (A-D) Boxplots of the age distribution of EPN\_PFA and EPN\_PFB, where boxes represent median and interquartile range and whiskers represent 95% CIs. (E) Proportion of patients with EPN\_PFA and EPN\_PFB in each age group. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence.



**Fig A2.** Forest plots of EPN\_PFA versus EPN\_PFB across all cohorts and each cohort individually as a univariate analysis, age-adjusted univariate analysis, and multivariable analysis for (A) progression-free survival (PFS) and (B) overall survival (OS). CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence.



**Fig A3.** Plot of age at diagnosis as a function of the log<sub>10</sub> of the hazard ratios of EPN\_PFA versus EPN\_PFB for (A) progression-free survival (PFS) and (B) overall survival (OS).

Treatment of Posterior Fossa Ependymoma Subgroups

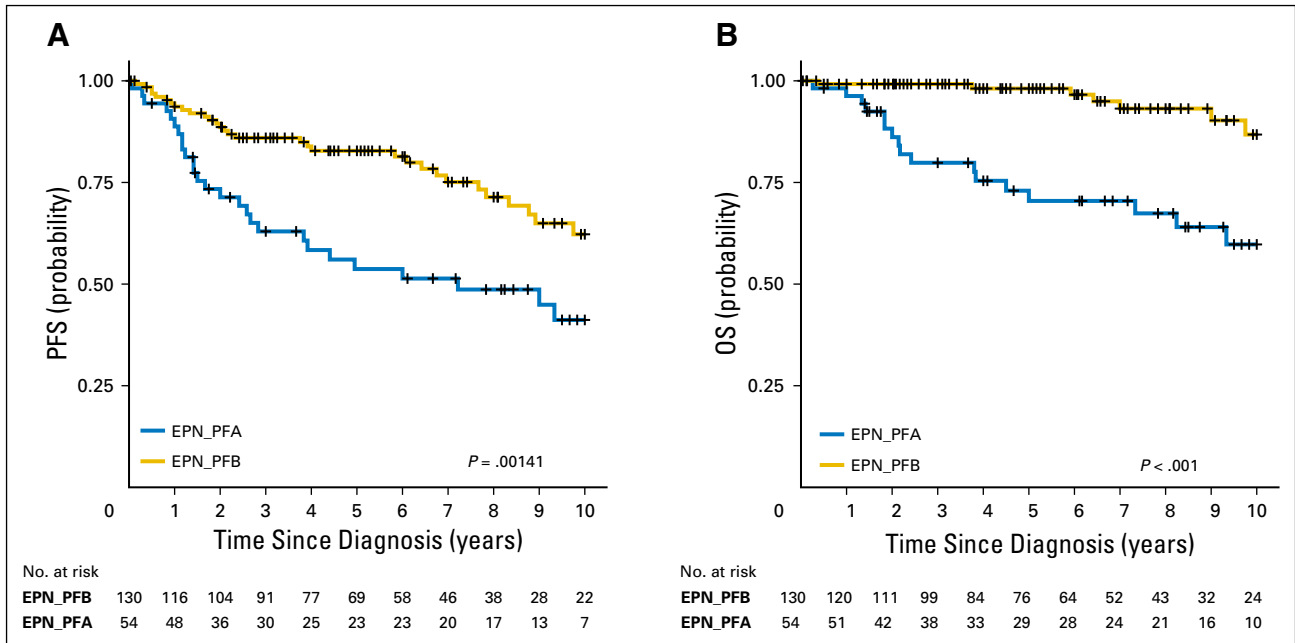


Fig A4. Survival by subgroup in patients with an age at diagnosis of greater than 10 years for (A) progression-free survival (PFS) and (B) overall survival (OS).

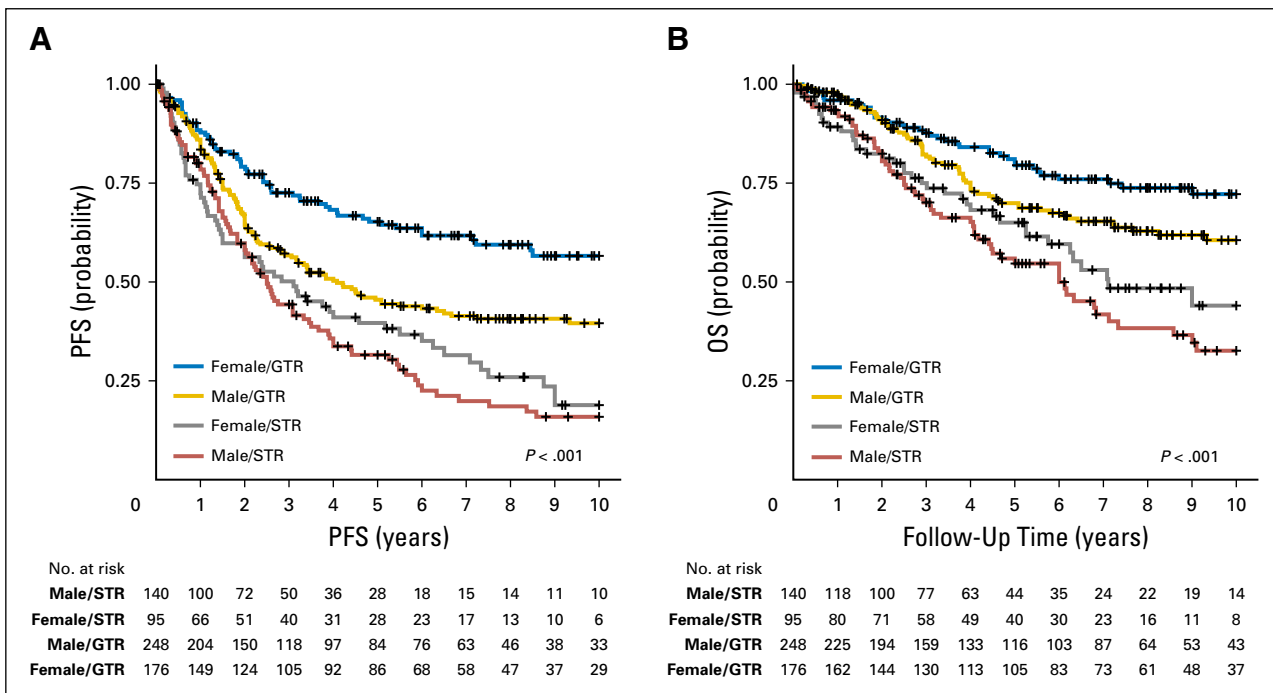
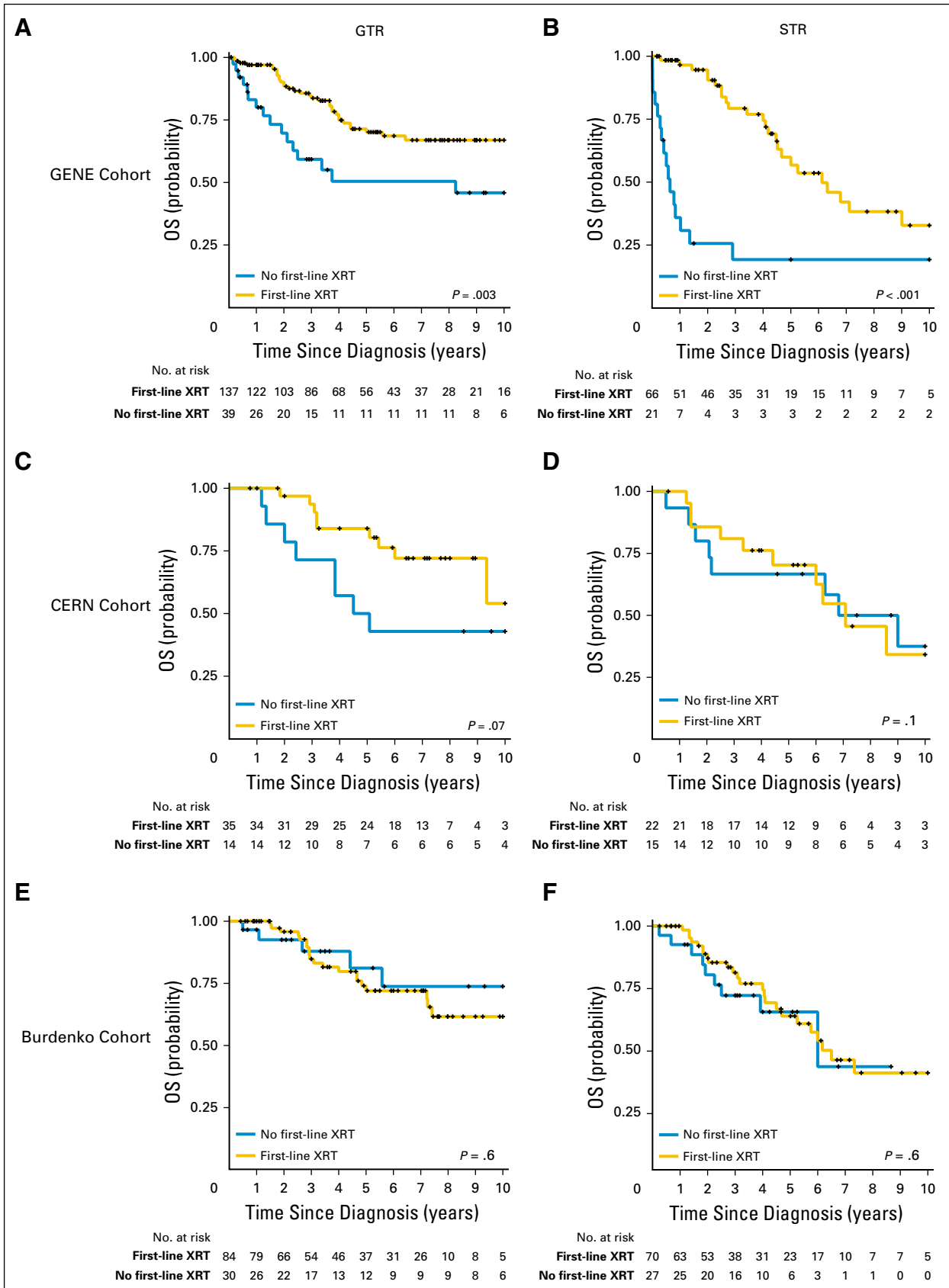
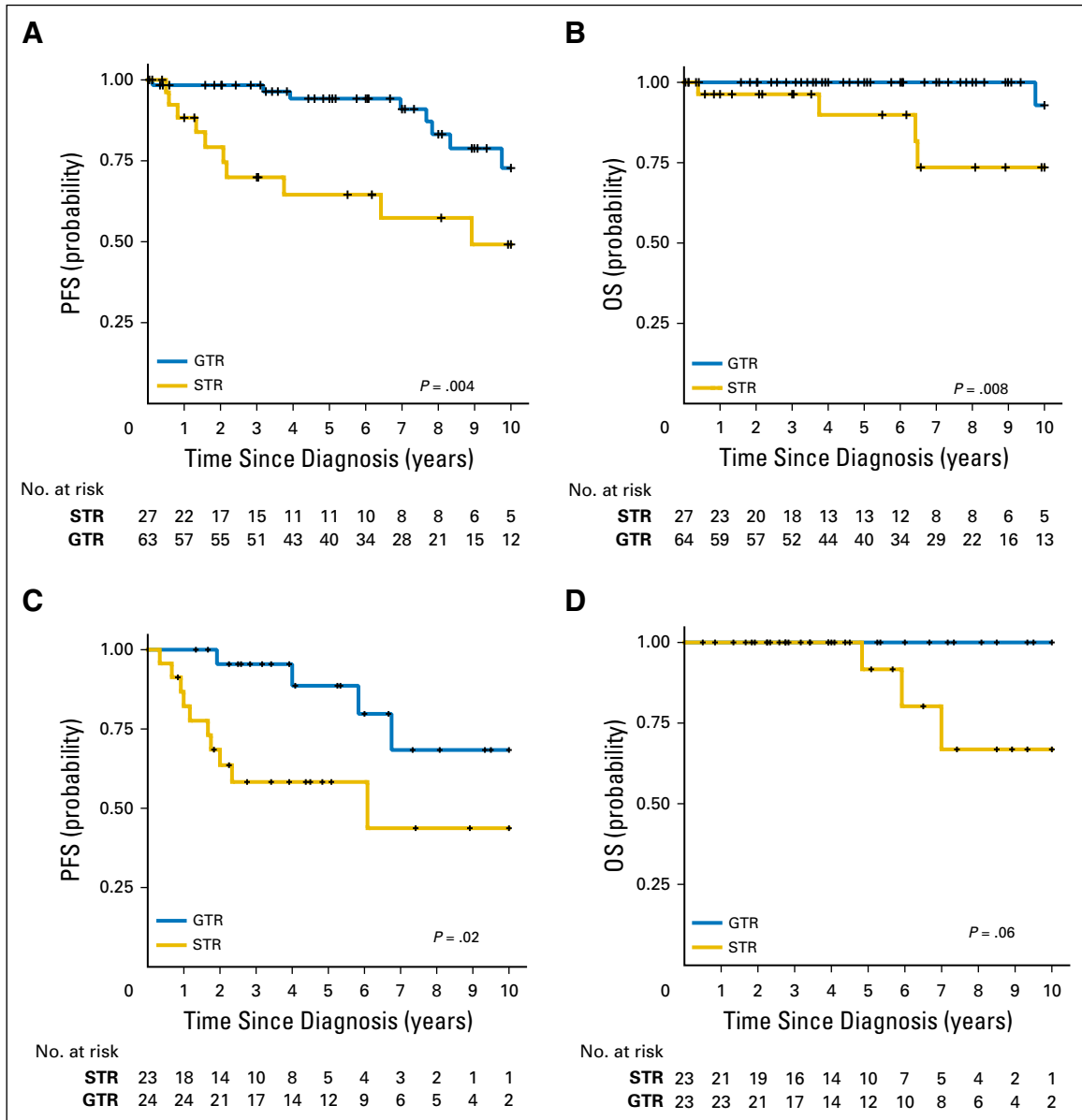


Fig A5. Sex as a function of extent of resection in EPN\_PFA for (A) progression-free survival (PFS) and (B) overall survival (OS).  $P$  values were determined using the log-rank test. GTR, gross total resection; STR, subtotal resection.



**Fig A6.** Overall survival (OS) of EPN\_PFA for the four cohorts divided by (A, C, and E) gross total resection (GTR) and (B, D, and F) subtotal resection (STR). P values were determined using the log-rank test. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; XRT, radiotherapy.

Treatment of Posterior Fossa Ependymoma Subgroups



**Fig A7.** Progression-free survival (PFS) and overall survival (OS) EPN\_PFB stratified by extent of resection for (A and B) the combined Global Ependymoma Network of Excellence (GENE), St Jude's, and Collaborative Ependymoma Research Network (CERN) cohorts and (C and D) the Burdenko Cohort. GTR, gross total resection; STR, subtotal resection.

**Table A1.** Multivariable Cox Proportional Hazards Model of Survival Across All Posterior Fossa Ependymomas

Variable	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
GENE cohort (PFS, n = 304; OS, n = 305)				
Subgroup EPN_PFA	2.66 (1.14 to 6.23)	.02	6.11 (1.38 to 27.01)	.02
Age	0.97 (0.95 to 0.99)	.008	0.96 (0.93 to 0.99)	.02
Incomplete resection	1.87 (1.31 to 2.67)	< .001	2.37 (1.55 to 3.64)	< .001
Adjuvant first-line radiation	0.30 (0.21 to 0.44)	< .001	0.29 (0.18 to 0.45)	< .001
Adjuvant first-line chemotherapy	1.07 (0.74 to 1.55)	.72	0.75 (0.47 to 1.20)	.23
Male	1.19 (0.86 to 1.66)	.30	1.26 (0.83 to 1.89)	.28
CERN cohort (PFS, n = 120; OS, n = 120)				
Subgroup EPN_PFA	2.08 (0.65 to 6.66)	.22	6.95 (1.13 to 42.71)	.04
Age	1.00 (0.97 to 1.03)	.89	1.01 (0.97 to 1.05)	.73
Incomplete resection	1.59 (0.91 to 2.79)	.10	1.79 (0.87 to 3.70)	.12
Adjuvant first-line radiation	0.70 (0.43 to 1.14)	.15	0.62 (0.33 to 1.17)	.14
Adjuvant first-line chemotherapy	0.95 (0.51 to 1.79)	.88	0.79 (0.37 to 1.72)	.56
Male	1.17 (0.73 to 1.90)	.51	2.12 (1.07 to 4.21)	.03
St Jude RT1 cohort (PFS, n = 112; OS, n = 112)				
Subgroup EPN_PFA	1.40 (0.25 to 7.96)	.70	4.94 (0.43 to 698.63)	.23
Age	0.99 (0.89 to 1.10)	.87	1.05 (0.91 to 1.17)	.51
Incomplete resection	2.75 (1.42 to 5.33)	.003	3.27 (1.47 to 6.90)	.005
Male	2.16 (1.15 to 4.06)	.009	2.72 (1.23 to 6.74)	.01
Burdenko cohort (PFS, n = 241; OS, n = 241)				
Subgroup EPN_PFA	2.49 (0.98 to 6.35)	.06	2.72 (0.51 to 14.67)	.24
Age	0.99 (0.96 to 1.02)	.61	0.98 (0.93 to 1.04)	.49
Incomplete resection	2.03 (1.43 to 2.89)	< .001	2.00 (1.19 to 3.37)	.009
Adjuvant first-line radiation	1.11 (0.74 to 1.66)	.61	1.08 (0.60 to 1.95)	.80
Adjuvant first-line chemotherapy	0.99 (0.65 to 1.49)	.94	1.38 (0.71 to 2.66)	.34
Male	1.10 (0.76 to 1.58)	.62	0.85 (0.50 to 1.45)	.55

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

**Table A2.** Multivariable Cox Proportional Hazards Regression Model of 10-Year Progression-Free and Overall Survival

Variable	Hazard Ratio	95% CI	P
Progression-free survival (n = 777)			
Age	0.99	0.97 to 1.00	.09
Male	1.25	1.01 to 1.54	.04
Incomplete resection	1.88	1.51 to 2.33	< .001
Adjuvant first-line radiation	0.63	0.50 to 0.81	< .001
Adjuvant first-line chemotherapy	1.02	0.79 to 1.32	.87
EPN_PFA subgroup	2.18	1.31 to 3.62	.003
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.13
Male	1.40	1.06 to 1.84	.02
Incomplete resection	2.14	1.61 to 2.84	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.71	< .001
Adjuvant first-line chemotherapy	0.91	0.66 to 1.27	.6
EPN_PFA Subgroup	4.27	1.86 to 9.81	< .001



**Treatment of Posterior Fossa Ependymoma Subgroups**

**Table A3.** Multivariable Cox Proportional Hazards Model of 10-Year Survival Across All Posterior Fossa Ependymoma

Variable	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
<b>GENE cohort (PFS, n = 304; OS, n = 305)</b>				
Subgroup EPN_PFA	2.61 (1.04 to 6.53)	.04	5.26 (1.17 to 23.60)	.03
Age	0.96 (0.93 to 0.99)	.005	0.96 (0.92 to 1.00)	.03
Incomplete resection	1.90 (1.33 to 2.72)	< .001	2.49 (1.61 to 3.87)	< .001
Adjuvant first-line radiation	0.29 (0.20 to 0.43)	< .001	0.27 (0.17 to 0.43)	< .001
Adjuvant first-line chemotherapy	1.01 (0.69 to 1.47)	.96	0.75 (0.47 to 1.22)	.25
Male	1.16 (0.83 to 1.61)	.40	1.20 (0.79 to 1.82)	.40
<b>CERN cohort (PFS, n = 120; OS, n = 120)</b>				
Subgroup EPN_PFA	2.08 (0.65 to 6.66)	.22	7.52 (1.09 to 51.67)	.04
Age	1.00 (0.97 to 1.03)	.89	1.00 (0.96 to 1.05)	.73
Incomplete resection	1.59 (0.91 to 2.79)	.10	1.82 (0.86 to 3.85)	.12
Adjuvant first-line radiation	0.70 (0.43 to 1.14)	.15	0.67 (0.53 to 1.28)	.22
Adjuvant first-line chemotherapy	0.95 (0.51 to 1.79)	.88	0.77 (0.35 to 1.68)	.51
Male	1.17 (0.73 to 1.90)	.51	2.02 (1.01 to 4.04)	.05
<b>St Jude RT1 cohort (PFS, n = 112; OS, n = 112)</b>				
Subgroup EPN_PFA	2.87 (0.31 to 26.73)	.35	4.68 (0.40 to 662.59)	.25
Age	1.00 (0.90 to 1.11)	1.00	1.05 (0.91 to 1.18)	.47
Incomplete resection	2.77 (1.42 to 5.38)	.003	3.49 (1.56 to 7.45)	.003
Male	2.42 (1.25 to 4.67)	.009	3.16 (1.38 to 8.30)	.006
<b>Burdenko cohort (PFS, n = 241; OS, n = 241)</b>				
Subgroup EPN_PFA	2.46 (0.97 to 6.24)	.06	2.90 (0.54 to 15.55)	.21
Age	0.99 (0.96 to 1.02)	.63	0.98 (0.93 to 1.04)	.52
Incomplete resection	2.00 (1.40 to 2.84)	< .001	2.01 (1.18 to 3.42)	.01
Adjuvant first-line radiation	1.09 (0.73 to 1.64)	.66	1.10 (0.60 to 2.03)	.75
Adjuvant first-line chemotherapy	1.01 (0.66 to 1.54)	.96	1.31 (0.67 to 2.54)	.43
Male	1.10 (0.76 to 1.58)	.62	0.84 (0.49 to 1.42)	.51

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

**Table A4.** Predictor-Cohort Interaction Likelihood Ratio Test for Both Progression-Free Survival and Overall Survival

Predictor	P	
	PFS	OS
EPN subgroup	.35	.84
Age	.09	.68
Extent of resection	.79	.49
Sex	.37	.14
Adjuvant first-line chemotherapy	.70	.82
Adjuvant first-line radiation	< .001	.009

NOTE. Values represent the P values for a likelihood ratio test for predictor-cohort interaction.  
Abbreviations: OS, overall survival; PFS, progression-free survival.

**Table A5.** The 5- and 10-Year Survival of Patients With EPN\_PFA and EPN\_PFB Older Than Age 10 Years

Survival	EPN_PFA	EPN_PFB
No. of patients	54	128
Median PFS (95% CI)		
5-year PFS	0.537 (0.413 to 0.698)	0.828 (0.761 to 0.900)
10-year PFS	0.412 (0.283 to 0.600)	0.622 (0.513 to 0.756)
Median OS (95% CI)		
5-year OS	0.705 (0.585 to 0.849)	0.981 (0.955 to 1.000)
10-year OS	0.598 (0.458 to 0.780)	0.868 (0.771 to 0.977)

Abbreviations: OS, overall survival; PFS, progression-free survival.

**Table A6.** The 5- and 10-Year Survival of Patients With EPN\_PFA Stratified by GTR and STR Across Four Cohorts

Survival	Median (95% CI)			
	GENE	St Jude's	CERN	Burdenko
<b>GTR</b>				
5-year PFS	0.467 (0.386 to 0.544)	0.707 (0.596 to 0.793)	0.667 (0.515 to 0.781)	0.453 (0.354 to 0.547)
5-year OS	0.688 (0.605 to 0.756)	0.879 (0.786 to 0.933)	0.739 (0.587 to 0.843)	0.781 (0.682 to 0.853)
10-year PFS	0.425 (0.339 to 0.508)	0.676 (0.561 to 0.767)	0.459 (0.299 to 0.606)	0.369 (0.261 to 0.476)
10-year OS	0.628 (0.533 to 0.710)	0.774 (0.660 to 0.854)	0.567 (0.389 to 0.711)	0.661 (0.526 to 0.766)
<b>STR</b>				
5-year PFS	0.370 (0.261 to 0.479)	0.526 (0.287 to 0.719)	0.568 (0.394 to 0.708)	0.261 (0.175 to 0.356)
5-year OS	0.535 (0.413 to 0.643)	0.590 (0.345 to 0.770)	0.681 (0.499 to 0.809)	0.658 (0.540 to 0.753)
10-year PFS	0.259 (0.141 to 0.394)	0.301 (0.102 to 0.531)	0.218 (0.100 to 0.365)	0.143 (0.067 to 0.247)
10-year OS	0.327 (0.194 to 0.467)	0.451 (0.214 to 0.663)	0.401 (0.221 to 0.575)	0.433 (0.280 to 0.577)

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection; OS, overall survival; PFS, progression-free survival; STR, subtotal resection.

**Table A7.** Multivariable Cox Proportional Hazards Model of Survival in EPN\_PFA

Variable	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
<b>All cohorts (PFS, n = 645; OS, n = 646)</b>				
Age	0.98 (0.96 to 1.00)	.08	0.99 (0.96 to 1.01)	.26
Incomplete resection	1.71 (1.37 to 2.14)	< .001	2.05 (1.52 to 2.76)	< .001
Adjuvant radiation	0.64 (0.50 to 0.82)	< .001	0.52 (0.38 to 0.72)	< .001
Adjuvant chemotherapy	1.04 (0.81 to 1.35)	.74	0.89 (0.63 to 1.26)	.51
Male	1.31 (1.05 to 1.62)	.02	1.39 (1.04 to 1.85)	.02
<b>GENE cohort (PFS, n = 258; OS, n = 259)</b>				
Age	0.96 (0.93 to 0.99)	.007	0.96 (0.91 to 1.00)	.03
Incomplete resection	1.68 (1.17 to 2.42)	.005	2.26 (1.46 to 3.49)	< .001
Adjuvant radiation	0.31 (0.21 to 0.45)	< .001	0.28 (0.18 to 0.45)	< .001
Adjuvant chemotherapy	1.08 (0.74 to 1.58)	.68	0.78 (0.49 to 1.25)	.30
Male	1.10 (0.79 to 1.55)	.57	1.17 (0.77 to 1.78)	.46
<b>CERN cohort (PFS, n = 86; OS, n = 86)</b>				
Age	1.00 (0.96 to 1.04)	.92	1.01 (0.97 to 1.06)	.53
Incomplete resection	1.63 (0.85 to 3.12)	.14	1.80 (0.83 to 3.88)	.13
Adjuvant radiation	0.73 (0.43 to 1.25)	.25	0.61 (0.31 to 1.18)	.14
Adjuvant chemotherapy	0.89 (0.46 to 1.72)	.73	0.77 (0.35 to 1.67)	.50
Male	1.40 (0.81 to 2.43)	.23	2.51 (1.18 to 5.33)	.02
<b>St Jude's RT1 cohort (PFS, n = 104; OS, n = 104)</b>				
Age	1.00 (0.90 to 1.12)	.94	1.04 (0.91 to 1.19)	.61
Incomplete resection	2.71 (0.40 to 5.26)	.003	3.26 (1.49 to 7.12)	.003
Male	2.42 (1.25 to 4.69)	.009	2.86 (1.21 to 6.77)	.02
<b>Burdenko cohort (PFS, n = 197; OS, n = 197)</b>				
Age	0.99 (0.96 to 1.03)	.77	1.01 (0.96 to 1.06)	.70
Incomplete resection	1.88 (1.30 to 2.71)	< .001	1.84 (1.08 to 3.12)	.02
Adjuvant radiation	1.12 (0.74 to 1.70)	.60	1.02 (0.56 to 1.85)	.94
Adjuvant chemotherapy	0.98 (0.64 to 1.49)	.92	1.42 (0.73 to 2.78)	.30
Male	1.19 (0.81 to 1.77)	.38	0.89 (0.51 to 1.53)	.66

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Treatment of Posterior Fossa Ependymoma Subgroups

**Table A8.** Multivariable Cox Proportional Hazards Model of 10-Year Survival in EPN\_PFA

Variable	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
All cohorts (PFS, n = 645; OS, n = 646)				
Age	0.98 (0.96 to 1.00)	.07	0.99 (0.96 to 1.01)	.26
Incomplete resection	1.74 (1.39 to 2.18)	< .001	2.05 (1.52 to 2.76)	< .001
Adjuvant radiation	0.65 (0.50 to 0.83)	< .001	0.52 (0.38 to 0.72)	< .001
Adjuvant chemotherapy	1.03 (0.80 to 1.34)	.80	0.89 (0.63 to 1.26)	.51
Male	1.31 (1.05 to 1.63)	.02	1.39 (1.04 to 1.85)	.02
GENE cohort (PFS, n = 258; OS, n = 259)				
Age	0.95 (0.92 to 0.99)	.008	0.96 (0.91 to 1)	.03
Incomplete resection	1.74 (1.21 to 2.52)	.003	2.26 (1.46 to 3.49)	< .001
Adjuvant radiation	0.31 (0.21 to 0.45)	< .001	0.28 (0.18 to 0.45)	< .001
Adjuvant chemotherapy	1.03 (0.70 to 1.51)	.88	0.78 (0.49 to 1.25)	.30
Male	1.09 (0.78 to 1.53)	.62	1.17 (0.77 to 1.78)	.46
CERN cohort (PFS, n = 86; OS, n = 86)				
Age	1.00 (0.96 to 1.40)	.92	1.01 (0.97 to 1.06)	.53
Incomplete resection	1.91 (0.98 to 3.75)	.06	1.80 (0.83 to 3.88)	.13
Adjuvant radiation	0.84 (0.47 to 1.48)	.54	0.61 (0.31 to 1.18)	.14
Adjuvant chemotherapy	0.82 (0.42 to 1.61)	.57	0.77 (0.35 to 1.67)	.50
Male	1.46 (0.82 to 2.59)	.20	2.51 (1.18 to 5.33)	.02
St Jude's RT1 Cohort (PFS, n = 104; OS, n = 104)				
Age	1.01 (0.90 to 1.12)	.9	1.04 (0.91 to 1.19)	.61
Incomplete resection	2.77 (1.43 to 5.38)	.003	3.26 (1.49 to 7.12)	.003
Male	2.59 (1.31 to 5.10)	.006	2.86 (1.21 to 6.77)	.02
Burdenko cohort (PFS, n = 197; OS, n = 197)				
Age	0.99 (0.96 to 1.03)	.80	1.01 (0.96 to 1.06)	.70
Incomplete resection	1.84 (1.28 to 2.66)	.001	1.84 (1.08 to 3.12)	.02
Adjuvant radiation	1.10 (0.72 to 1.67)	.66	1.02 (0.56 to 1.85)	.94
Adjuvant chemotherapy	1.00 (0.65 to 1.54)	.99	1.42 (0.73 to 2.78)	.30
Male	1.19 (0.81 to 1.77)	.38	0.89 (0.51 to 1.53)	.66

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

**Table A9.** Multivariable Cox Proportional Hazards Model of Survival in EPN\_PFB in All Cohorts

Variable	Progression-Free Survival (n = 132)		Overall Survival (n = 132)	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.99 (0.97 to 1.02)	.70	0.98 (0.92 to 1.04)	.45
Incomplete resection	3.93 (1.78 to 8.68)	< .001	11.32 (1.24 to 100.41)	.03
Adjuvant radiation	0.49 (0.21 to 1.14)	.10	0.53 (0.09 to 3.06)	.48
Adjuvant chemotherapy	1.64 (0.45 to 5.92)	.45	5.37 (0.45 to 64.12)	.18
Male	0.76 (0.37 to 1.59)	.47	0.76 (0.15 to 3.79)	.74

Abbreviation: HR, hazard ratio.

**Table A10.** Multivariable Cox Proportional Hazards Model of 10-Year Survival in EPN\_PFB in All Cohorts

Variable	Progression Free Survival (n = 132)		Overall Survival (n = 132)	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.99 (0.96 to 1.02)	.52	0.97 (0.91 to 1.04)	.38
Incomplete resection	4.30 (1.89 to 9.77)	< .001	11.06 (1.24 to 98.32)	.03
Adjuvant radiation	0.49 (0.21 to 1.16)	.10	0.51 (0.09 to 2.99)	.45
Adjuvant chemotherapy	1.51 (0.42 to 5.41)	.45	4.93 (0.42 to 58.18)	.20
Male	0.69 (0.32 to 1.47)	.33	0.77 (0.15 to 3.84)	.75

Abbreviation: HR, hazard ratio.