Childhood Intracranial Ependymoma

Twenty-year Experience From a Single Institution

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BACKGROUND. Because few large studies of pediatric ependymoma treatment are available, the authors believed that a retrospective review of treatment outcomes from a single institution would yield potentially valuable information regarding potential prognostic factors. In this article, they report their 20-year institutional experience with this disease.

METHODS. Medical records were reviews of patients with intracranial ependymoma who received their initial treatment at the Children's Hospital of Philadelphia (CHOP)/Hospital of the University of Pennsylvania (HUP) between January 1980 and December 2000. Of the 61 patients who were identified, 49 patients underwent primary therapy at CHOP/HUP and formed the basis for the study. Actuarial overall survival (OS) and progression-free survival (PFS) were determined by the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and Cox proportional-hazards models.

RESULTS. With median follow-up of 110.2 months, the 5-year OS and PFS rates were 66.2% and 40.7%, respectively. Older age and higher radiation dose significantly predicted for improved OS. Anaplastic histology predicted for decreased PFS. Cervical spinal cord extension resulted in decreased OS primarily caused by failures outside the primary site. Patients who had a favorable prognosis (aged $\geq$3 years, no dissemination or cord extension, complete resection, and radiation dose $\geq$54 grays [Gy]) had 5-year OS and PFS rates of 83.1% and 60.6%, respectively.

CONCLUSIONS. In this study of patients with pediatric intracranial ependymoma, OS and PFS rates were concordant with the rates published in other modern series. The finding of a dose response up to 54 Gy supported the current trend toward dose escalation. Tumor extension to the cervical spine was identified as a predictor for failure outside of the primary site. Although the survival rates were encouraging, there is still significant room for improvement in the management of this disease. ***Cancer* 2007;110:432–41.** © *2007 American Cancer Society.*

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Intracranial ependymomas are a common brain tumor in children and comprise approximately 2% to 9% of all central nervous system (CNS) tumors in this age category.[1,2] Although these tumors typically arise infratentorially, often filling the fourth ventricle, they can arise not only in any ventricle but also in the brain parenchyma.[3,4] Intracranial ependymomas are classified histologically as low-grade or high-grade/anaplastic.[5,6] Whereas some investigators have reported no clear-cut differences in outcome between these groups, recent studies suggest that, in fact, patients with anaplastic ependymomas have a worse outcome.[7–10] One reason why differences in outcomes between low- and high-grade ependymomas have been difficult to

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detect may be that, despite its histologically *benign* appearance, low-grade ependymomas can display very aggressive local behavior.

Current therapeutic standards for intracranial ependymoma include surgery to achieve maximal feasible tumor resection followed by radiation therapy (RT).[11] The extent of resection is one of the strongest prognostic factors for predicting survival in patients with these tumors. Previous studies reported a statistically significant improvement in survival after macroscopic (gross) total resection (GTR) versus subtotal resection.[3,4,12] Accordingly, the current Children's Oncology Group (COG) study (ACNS0121) for intracranial ependymoma emphasizes the importance of GTR and advocates the use of neoadjuvant chemotherapy to help improve the resectability of tumors that previously were deemed unresectable. However, even if a GTR is achieved, these tumors typically will recur unless adjuvant RT is given.[4,13] RT dose response in ependymomas has been demonstrated for doses from 45 gray (Gy) to 50 Gy.[7,13] Despite these doses, local failure remains a major problem. Therefore, currently, most patients receive an RT dose in the middle 50-Gy to 60-Gy range.

Although there are many studies of patients with intracranial ependymoma, relatively few have reported a large, single-institutional pediatric population with long follow-up.[4,7,10,12–17] Studies from institutions that treat a high volume of such patients provide important outcome benchmarks and may allow identification of additional prognostic factors that have not been appreciated previously. This article reports the outcome and identifies factors that affect prognosis in all patients who were diagnosed and treated primarily at the Children's Hospital of Philadelphia (CHOP) and Hospital of the University of Pennsylvania (HUP) from 1980 to 2000.

MATERIALS AND METHODS

Sixty-one pediatric patients with intracranial ependymoma who underwent surgery between January 1980 and December 2000 were identified from the tumor registry at CHOP. After eliminating patients who were not treated and followed subsequently at CHOP or HUP, 49 patients remained and formed the basis of the current study. A subset of these patients (those who were diagnosed before 1989; N = 19) was included as part of a previous study from our institution but, for the current report, had longer follow-up.[7] With only 1 exception, all patients who were included in the study were aged $\leq$18 years at diagnosis; the exception was a patient aged 20 years at diagnosis who was included because initial surgery was performed at CHOP. All data were obtained from patient charts at CHOP and/or HUP. Charts were reviewed for details of patient and tumor characteristics, treatments received, and outcome. Approval for this study was obtained from the appropriate Institutional Review Board prior to undertaking the study.

All surgery was performed by neurosurgeons at CHOP. Extent of surgical resection was determined by reviewing a combination of the operative notes and/or postoperative imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) reports. All tissue specimens were diagnosed by a neuropathologist at CHOP. All diagnoses of leptomeningeal tumor spread were made on the basis of MRI and/or lumbar puncture for cytology. RT was delivered using linear accelerator-based, megavoltage radiation through a variety of techniques, including craniospinal treatment with standard methods and either opposed lateral portals or other multifield methods for focal treatment. Craniospinal irradiation (CSI) was given as part of initial RT for evidence of dissemination at presentation (5 patients), the presence of anaplastic histology (3 patients), and locally advanced tumor in 1 patient aged 17 years. General anesthesia was used in younger patients for simulation and/or treatment when appropriate. A variety of chemotherapeutic regimens was used, which included the following agents: vincristine, methyllomustine, cisplatin, carboplatin, cyclophosphamide, ifosphamide, etoposide, methotrexate, and/or temozolomide. Patients were followed both clinically and with serial imaging (MRI studies in the great majority of patients).

All statistical analyses were performed using STATA software (version 3.0; Computer Resource Center, Santa Monica, Calif). Overall survival (OS) and progression-free survival (PFS) curves were generated using the Kaplan-Meier method. In most patients, OS and PFS were calculated from the time of initial diagnosis. However, for the evaluation of radiation parameters (eg, RT dose), OS and PFS were calculated from the start of RT. The time to failure was defined based either on the date of the appearance of recurrent tumor (primary or distant sites) or the date when it was documented that residual disease was increasing in size. Again, for the evaluation of RT parameters, if a patient failed after initial deferral of RT, then the date of failure after RT was used to calculate PFS. The log-rank test was used to determine whether survival curves differed significantly in subgroup analyses. Univariate and multivariate analyses for potential prognostic factors were performed using a Cox proportional-hazards model. When building the multivariate models, factors with

TABLE 1
Patient and Tumor Characteristics

Characteristics	No. of patients
Patient no. and follow-up	
No. of patients in study	49
Median follow-up for all patients (range), mo	61.0 (9.5–237.1)
No. of patients alive at last follow-up	30
Median follow-up for surviving patients, mo (range)	110.2 (9.5–237.1)
Age, y	
Median	5.5
Range	1.1–20.3
Sex	
Male	28
Female	21
Tumor location	
Infratentorial	31
Supratentorial	18
Histology	
Low grade	33
High grade or anaplastic	11
Unknown	5
Extension to cervical cord	
Yes	13
No	36
Dissemination at presentation	
Yes	6
No	34
Unknown	9

P values >.200 were excluded. A 2-tailed Fisher exact test was used to correlate contiguous tumor extension into the cervical spinal cord region at time of initial diagnosis with subsequent failures outside of the primary site. A 2-tailed Fisher exact test also was used to correlate contiguous tumor extension into the cervical spinal cord region at time of initial diagnosis with subsequent failures outside of the primary site.

RESULTS

Patient/Tumor Characteristics and Treatment Parameters

Patient and tumor characteristics are summarized (Table 1). Our series had a slight male preponderance (ratio, 1.33), consistent with what others have reported.[7,12] The median age at presentation was 5.6 years. Fifteen percent of patients had evidence of CNS dissemination at diagnosis. Tumors in 25% of patients were anaplastic. Slightly less than 66% of patients had their primary tumor site in the posterior fossa, and the remaining tumors were supratentorial in location. The most common presenting symptom was vomiting, which was reported by 69% of patients. Other common presenting symptoms included headache (53%), ataxia (27%), head tilt (8%), and seizure (6%).

TABLE 2
Treatment Parameters

Parameter	No. of patients
Surgery	
GTR	30
STR/biopsy	16/2
Unknown	1
RT	
No. of patients receiving RT	47
Initial postoperative RT	34*
Salvage RT	13
Volume irradiated	
Entire craniospinal axis	9
Focal only	38
Median craniospinal dose (range), Gy	36 (18.0–36)
Median total dose (range), Gy	55.8 (42.0–72)
No. of patients receiving the following dose range	
<50 Gy	2
≥50 Gy to <54 Gy	6
≥54 Gy	39
Median fractions used (range)	31 (21–72)
RT fractionation scheme used	
Conventional fractionation (once daily)	41
Hyperfractionation (twice daily)	6
Median duration of RT (range), d	43 (30–78)
Median time from initial surgery to RT (range), d	33 (6–706)
Chemotherapy	
No. of patients receiving chemotherapy with initial treatment	32†
Treated prior to RT	13*
Treated after RT	23

GTR indicates macroscopic (gross) total resection; STR, subtotal resection; RT, radiation therapy; Gy, grays.
*Includes 2 patients who received pre-RT chemotherapy but who began RT within the standard 4 to 6 weeks after resection.
†Four patients received chemotherapy both prior to and after RT.

Treatment parameters for patients on this study are summarized (Table 2). Although maximal primary tumor resection was the objective in all patients, a GTR was accomplished in only 63% of patients. Adjuvant therapy with RT was the treatment of choice for the great majority of patients. In this setting, RT generally was started from 4 weeks to 6 weeks after surgical resection. However, 13 patients received chemotherapy postoperatively as initial adjuvant therapy. Of these 13 patients, 2 patients proceeded to planned RT after the typical 4- to 6-week delay postresection, and 11 patients received chemotherapy with the objective of delaying or deferring RT until the child was older. Ten of these 11 patients ultimately went on to receive RT at a median time between diagnosis and the start of RT of 13.8 months (range, 4.2–23.5 months). Of the 10 patients who eventually received RT, 6 patients were treated for progressive/persistent disease, and 4 patients received planned RT at a predetermined interval after the initial diagnosis according the individual treat-

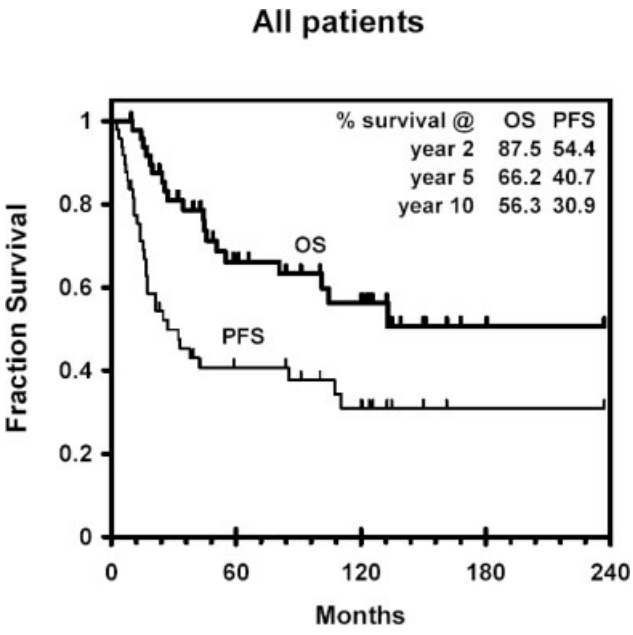

FIGURE 1. Overall survival (OS) and progression-free survival (PFS) from the time of diagnosis are illustrated for all evaluable patients (N = 49) with intracranial ependymoma who were included in the current study. Times when patients were censored are denoted by tick marks. The percentages of patients who survived and who survived without disease at 2 years, 5 years, and 10 years are shown in the upper right corner.

ment protocol. Four patients were not treated immediately with any adjuvant therapy postresection. Of these patients, 3 (1 of whom underwent reresection) ultimately went on to receive RT at 4.2 months, 5.1 months, and 44.9 months after their initial diagnosis, when their tumors recurred. These 3 patients all had infratentorial disease and remained alive and free of disease post-RT with a total follow-up that ranged from 8.4 years to 15 years. The other patient who did not receive adjuvant RT had supratentorial disease and low-grade histology; this patient was lost to follow-up without evidence of recurrence at 23 months.

Outcomes of Therapy in All Patients

The median follow-up for all patients (n = 49) and for the patients who remained alive at last follow-up (n = 30) were 61.0 months and 110.2 months (range: 9.5–237.1 months), respectively. OS and PFS curves for all patients are shown in Figure 1. The median PFS was 27.2 months, whereas the median OS was not reached. The OS rates at 2 years, 5 years, and 10 years were 87.5% (95% confidence interval [95% CI], 74.3–94.2%), 66.2% (95% CI, 50.1–78.2%), and 56.3% (95% CI, 39.1–70.3%), respectively. The PFS rates at 2 years, 5 years and 10 years were 54.4% (95% CI, 39.4–67.2%), 40.7% (95% CI, 26.6–54.3%), and 30.9% (95% CI, 17.3–45.5%), respectively. At the time of last follow-up, 31 patients had failed initial therapy. The pattern of these failures is summarized in Table 3. The majority of failures were at the site of initial disease only (68%), and 16% of failures involved only tumor outside of the initial disease site.

TABLE 3
Sites of Failure After Initial Therapy

Site of failure	No. of patients
Local only	21
Distant only	5
Local and distant	5

Analysis for Potential Prognostic Factors

Subgroup analysis of these patients using the log-rank test revealed that age ≥3 years and radiation dose ≥54 Gy significantly predicted for both improved OS and improved PFS (Fig. 2A-D). When patients who had delayed RT, because they received either initial chemotherapy (N = 10) or no other adjuvant therapy (N = 3), were compared with patients who received immediate postoperative RT, and the length of OS did not differ significantly (Fig. 3). However, the curves suggest a somewhat worse outcome for patients with RT delay, although the small patient numbers likely contributed to the lack of statistical significance. One additional factor that predicted a longer OS was absence of disease extension to the cervical spinal cord (Fig. 4A). It is noteworthy that, in an evaluation of treatment failure patterns, we observed a higher number of patients with failures outside of the primary site (exoprimary) when tumor extended through the foramen magnum. When the analysis was limited to patients who had a posterior fossa primary tumor and no initial dissemination, >70% of patients with exoprimary failure had cord extension, whereas only approximately 10% of patients with disease confined to the posterior fossa had exoprimary failure ($P = .013$; Fisher exact test) (Fig. 4B). Because this study included many patients who had 1 or more unfavorable feature(s), we separately examined our patients with good features (aged ≥3 years, no dissemination or cord extension, GTR, dose ≥54 Gy) and observed that OS and PFS at 5-years were improved at 83.1% (95% CI, 47.2–95.5%) and 60.6% (95% CI, 29.4–81.4%), respectively (Fig. 5); this compares favorably with what has been reported by others.[9,18,19]

One significant departure from previous practice on the current COG ACNS0121 protocol is to observe patients with low-grade ependymomas of the supra-

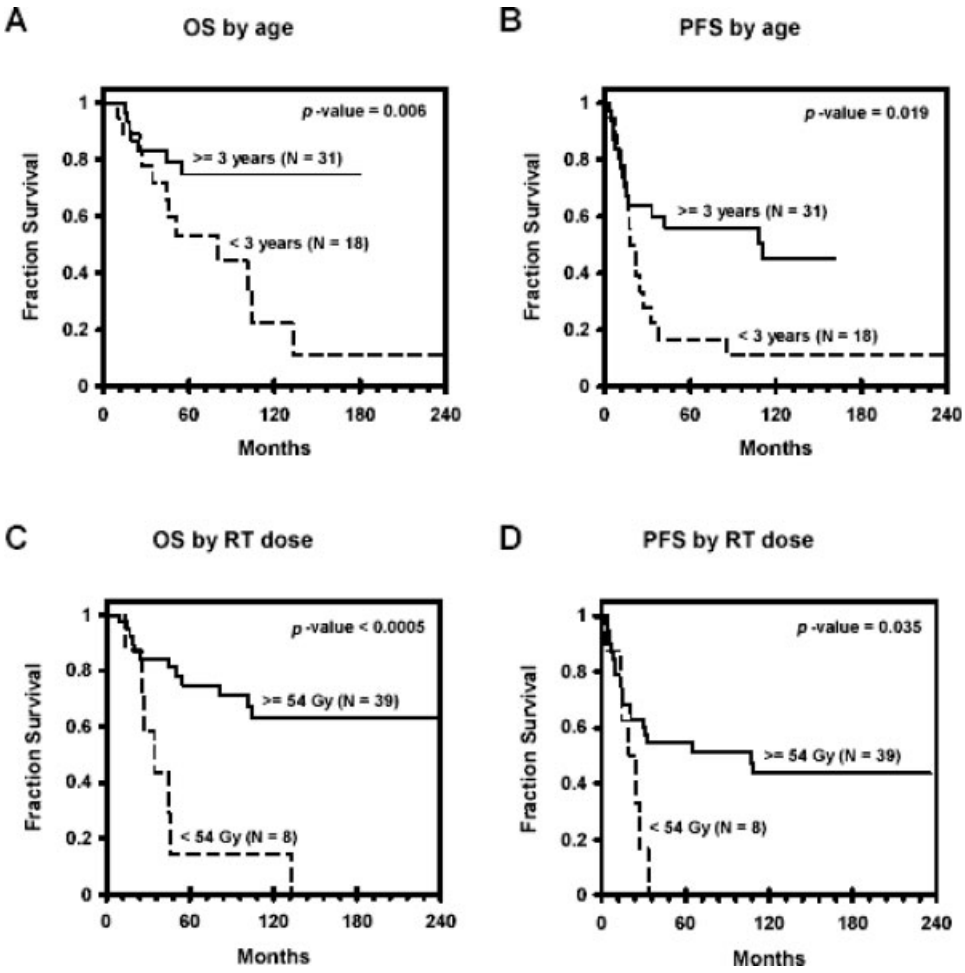

FIGURE 2. Overall survival (OS) (A and C) and progression-free survival (PFS) (B and D) are illustrated from the time of diagnosis according to patient age at diagnosis (≥3 years vs <3 years) (A and B) and from the start of radiation therapy (RT) according to the total radiation dose used (≥54 grays [Gy] vs <54 Gy) (C and D). All patients (N = 49) were considered in the analysis for age (A and B), whereas only patients who received RT (N = 47) were considered in the analysis for RT dose (C and D). Curves were compared by using the log-rank test, and the resulting *P* values are denoted in the upper right corner of each graph.

tentorial brain who have undergone macroscopic resection, reserving RT for salvage of treatment failures. To determine the outcomes of patients on our study that fell in this category, we chose to examine patients with supratentorial tumors, GTR, and no evidence of CNS dissemination and determined outcomes by tumor grade. All 7 patients with these characteristics and low-grade histology (6 of whom received RT and none of whom received immediate postoperative chemotherapy) were alive at last follow-up with a median follow-up >11 years. By contrast, all 4 patients with these characteristics and anaplastic histology (all of whom received RT and 1 of whom also received immediate postoperative chemotherapy) failed therapy, and 3 of them died within 5 years of diagnosis ($P = .016$). In addition, further questions remain regarding the outcome of patients with supratentorial versus infratentorial primaries. Therefore, we chose to compare the OS of patients with nondisseminated, macroscopically resected, and low-grade histology tumors according to primary disease site, and the OS rates at 5 years and 10 years were 81.8% and 54.5%, respectively, for patients with infratentorial primary tumors (N = 11) compared with 100% at both time points for patients with supratentorial primary tumors (N = 7). For our defined subset of patients, this factor approached statistical significance ($P = .088$).

Univariate analysis using the Cox proportional-hazards model was also performed to evaluate potential prognostic factors in this patient cohort, and the results are summarized in Table 4. It has been demonstrated previously that a greater degree of resection improves local control and survival.

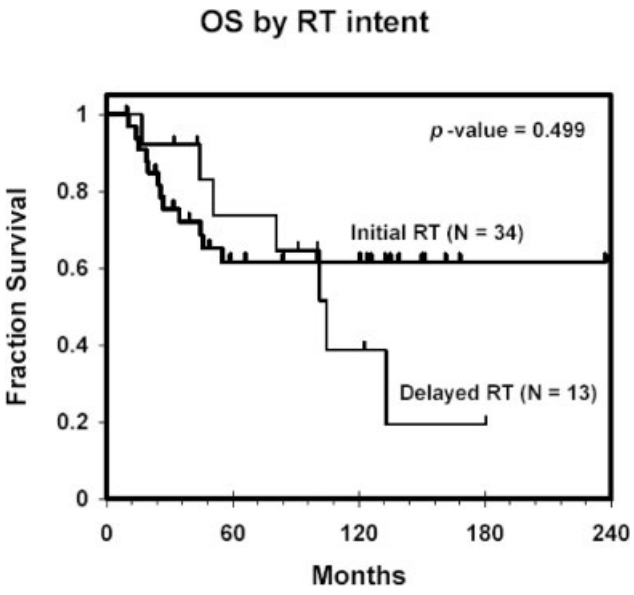

FIGURE 3. Overall survival (OS) from the time of diagnosis is illustrated according to whether patients received initial or delayed radiation therapy (RT) is shown. The number of patients in each category is indicated. Curves were compared by using the log-rank test, and the resulting *P* value is denoted in the upper right. Times when patients were censored are denoted by tick marks.

Similarly, the current results indicate that patients who undergo GTR appear to have improved outcomes compared with patients who undergo less than complete resection, although the difference did not reach statistical significance at the .05 level for PFS (Table 4). In addition, consistent with the subgroup analysis described above, RT dose ≥54 Gy, age ≥3 years, and absence of spinal cord extension were predictive of improved OS, and higher radiation dose and age ≥3 years were predictive of improved PFS at statistically significant levels. Even when only patients who received a minimum of 50 Gy were considered (6 patients received 50–54 Gy, and 39 patients received ≥54 Gy), the higher dose predicted improved OS at a statistically significant level ($P = .013$).

Multivariate analyses are summarized in Tables 5 and 6. Two separate analyses are presented, because examination of the RT dose required calculation of OS and PFS from the initiation of RT rather than from initial diagnosis. In our initial multivariate analysis of all evaluable patients (N = 44), only greater resection continued to predict improved OS at a statistically significant level, although age ≥3 years demonstrated a strong trend toward predicting improved OS (Table 5). When PFS was considered as the endpoint, tumor grade, age, and cord extension were the factors included in the multivariate model.

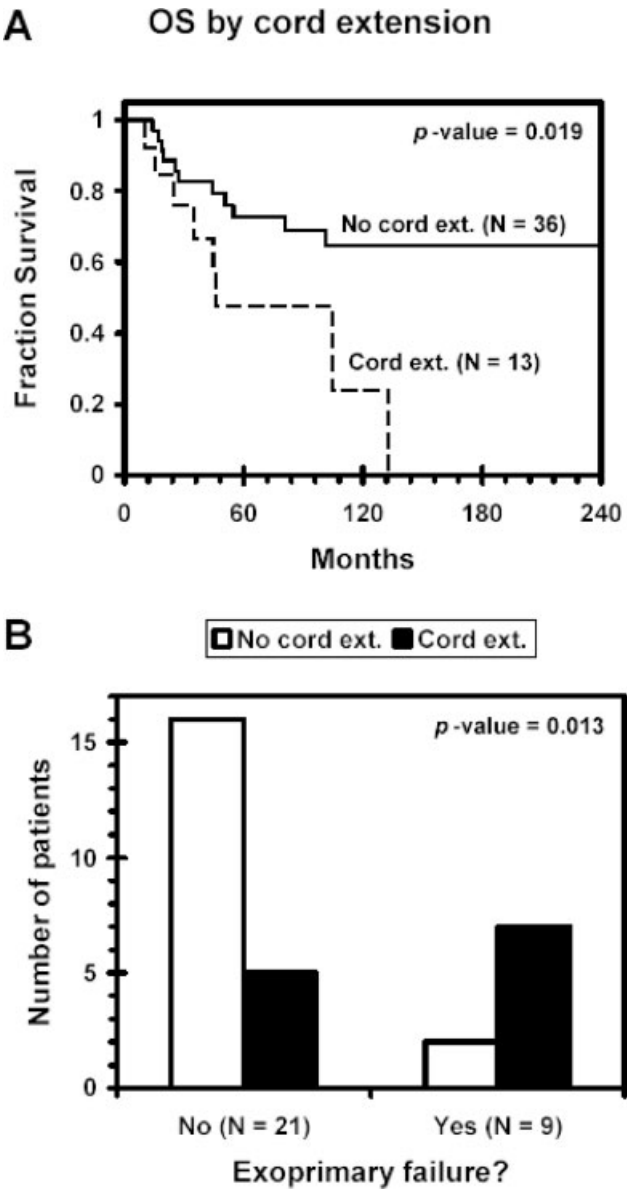

FIGURE 4. (A) Overall survival (OS) from the time of diagnosis is illustrated according to the presence or absence of tumor extension (ext.) to the cervical cord. The number of patients in each category is indicated on the graph. Curves were compared using the log-rank test, and the resulting *P* value is denoted in the upper right corner. (B) This bar graph shows the number of patients with or without an exoprimary failure according to whether they had tumor extension to the cervical cord (dark bars) or not (white bars). Only patients who had an infratentorial primary tumor and no evidence of dissemination at initial diagnosis were included in the analysis. The number of patients in each category is indicated. The categories were compared by using a 2-tailed Fisher exact test, and the resulting *P* value is denoted in the upper right corner.

Of these, only low-grade histology and age ≥3 years were predictive of improved PFS at a statistically significant level (Table 5). When RT dose was included in the multivariate analysis, only analyzable patients who received RT were evaluated (N = 42). In this analysis, age ≥3 years, GTR, and low-grade histology predicted for improved OS, whereas low-grade histology, lack of cervical cord extension, and RT dose ≥54 Gy predicted for improved PFS (Table 6). Surprisingly, CNS dissemination status did not predict patient outcomes in either univariate analysis or multivariate analysis in this study.

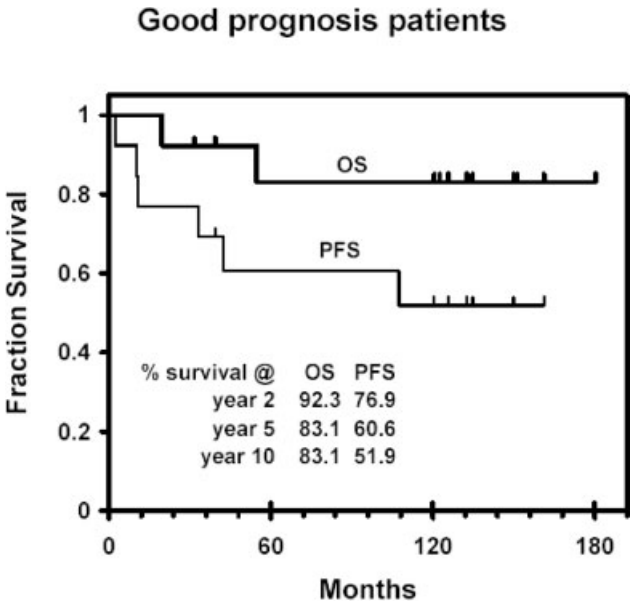

FIGURE 5. Overall survival (OS) and progression-free survival (PFS) are illustrated from the time of diagnosis for patients who had favorable prognostic features (aged ≥3 years, no dissemination or cord extension, macroscopic total resection, and radiation dose ≥54 grays; N = 13). The times when patients were censored are denoted by tick marks. The percentages of patients who survived and who surviving without disease at 2 years, 5 years, and 10 years are indicated.

DISCUSSION

We report the results of treatment of 49 pediatric patients with intracranial ependymoma at CHOP and HUP over 20 years. One strength of this study is the long duration of follow-up, with a median of nearly 10 years for patients who remained alive at last follow-up. The PFS and OS rates at 5 years were 40.7% and 66.2%, respectively, for all patients but were significantly better for the patients (n = 13) who had favorable features (60.6% and 83.1%, respectively). These results compare favorably with the 74.7 ± 5.7% 3-year PFS reported by Merchant et al. on a Phase II trial that explored the use of 3-dimensional conformal radiation therapy at St. Jude Children's Research Hospital.[19] However, direct comparisons between these 2 series remain difficult. It must be noted that, although we excluded patients aged <3 years in our group of patients with good prognostic features, the St. Jude trial included significant numbers of patients in that age group. The St. Jude data will require further maturation to allow accurate assessment of treatment outcomes on that study.

TABLE 4
Univariate Analysis of Potential Prognostic Factors

	OS		PFS		
Factor*	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	**Better prognosis**
Dose: <54 Gy vs ≥54 Gy (N = 47)†	.003	4.77 (1.76–12.88)	.044	2.58 (1.03–6.50)	≥54 Gy
Age: <3 y vs ≥3 y	.012	3.55 (1.34–9.35)	.024	2.37 (1.13–4.98)	≥3 y
Presence of cord extension	.028	2.92 (1.13–7.55)	.155	1.77 (0.80–3.91)	No cord extension
Extent of resection (N = 48)	.029	2.63 (1.11–6.23)	.058	1.84 (0.98–3.46)	GTR
Tumor grade (N = 44)	.082	2.37 (0.89–6.30)	.033	2.37 (1.08–5.21)	Low grade
Presence of dissemination (N = 40)	>.200	NS	>.200	NS	—
Diagnosis era: 1980s vs 1990s	>.200	NS	>.200	NS	—
Supratentorial vs infratentorial	>.200	NS	>.200	NS	—
Pre-RT chemotherapy to delay RT	>.200	NS	.179	1.73 (0.77–3.89)	No pre-RT chemotherapy
Post-RT chemotherapy (N = 47)†	>.200	NS	>.200	NS	—
Race	>.200	NS	>.200	NS	—
Sex	>.200	NS	>.200	NS	—

OS indicates overall survival; PFS, progression-free survival; HR, hazards ratio; 95% CI, 95% confidence interval; Gy, grays; GTR, macroscopic (gross) total resection; NS, not significant; RT, radiation therapy.
*The number of patients is 49 except when indicated otherwise.
†The endpoints used were OS and PFS from the time RT was initiated.

TABLE 5
Multivariate Analysis of Potential Prognostic Factors in All Evaluable Patients

	OS		PFS		
Factors (N = 44)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	**Better prognosis**
Extent of resection	.038	2.67 (1.06–6.73)	—	—	GTR
Age: <3 y vs ≥3 y	.056	2.82 (0.97–8.21)	.042	2.33 (1.03–5.24)	≥3 y
Presence of cord extension	.177	2.05 (0.71–5.88)	.125	1.97 (0.82–4.71)	No cord extension
Tumor grade	.192	1.93 (0.71–5.27)	.013	2.92 (1.28–6.68)	Low grade

OS indicates overall survival; PFS, progression-free survival; HR, hazards ratio; 95% CI, 95% confidence interval; GTR, macroscopic (gross) total resection.

TABLE 6
Multivariate Analysis of Potential Prognostic Factors in All Evaluable Patients Who Underwent Radiation Therapy

	OS*		PFS*		
Factor, N = 42	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	**Better prognosis**
Age: <3 y vs ≥3 y	.003	4.99 (1.76–14.14)	—	—	≥3 y
Extent of resection	.012	3.34 (1.32–8.44)	—	—	GTR
Tumor grade	.059	2.64 (0.96–7.23)	.008	3.41 (1.41–8.26)	Low grade
Presence of cord extension	—	—	.015	3.22 (1.27–8.12)	No cord extension
Dose: <54 Gy vs ≥54 Gy	—	—	.022	3.24 (1.19–8.81)	≥54 Gy

OS indicates overall survival; PFS, progression-free survival; HR, hazards ratio; 95% CI, 95% confidence interval; GTR, macroscopic (gross) total resection; Gy, grays.
*The endpoints used were OS and PFS from the time radiation therapy was initiated.

It has been suggested by some retrospective studies that patients with supratentorial tumors fare worse than patients with tumor originating in the posterior fossa.[10,17,20] Our data do not indicate a significant difference in outcome between these 2 groups, which is in agreement with most published studies.[3,7–9,13,16,18,19] However, when only patients with nondisseminated, macroscopically resected, low-grade histology tumors are considered, poorer outcomes for patients with infratentorial tumors approach statistical significance. In fact, our study suggests that patients with a low-grade ependymoma at a supratentorial site actually have very good outcomes after GTR and calls into question the need for postoperative RT in these patients. It is noteworthy that, of the 4 patients in our study who were observed after surgery, 3 patients had low-grade histology and underwent GTR. Of these, the patient with a supratentorial primary remained disease-free during follow-up, whereas the 2 patients with infratentorial tumors progressed and required RT. Although the numbers are small, our data are consistent with the conclusions of some previous small surgical series[21,22] and the current approach of ACNS0121, which observes patients who have nondisseminated supratentorial ependymomas with low-grade histology after GTR.

Overall, our results are in agreement with previous reports, which indicated that age, degree of resection, dose of radiation, and tumor grade can influence outcome in this disease.[4,7,10,12,16] These factors all correlated with PFS and/or OS to varying extents. Surprisingly, 1 factor that was not identified as prognostic in our study was the presence of CNS dissemination at diagnosis. We believe that low patient numbers likely contributed to the lack of significance found for this factor. It is possible that patients whose staging MRI scans demonstrated areas of abnormal enhancement, in fact, did not have metastatic disease, as has been noted in prior publications.[23,24] With respect to RT dose response, although the standard of care for treatment of localized ependymoma is in the middle 50-Gy range with standard fractionation, the evidence of an RT dose response has been observed previously for doses up to 45 Gy to 50 Gy.[7,13] Our series demonstrated a dose response up to 54 Gy; this is in line with what many consider to be the recommended RT dose. Because this study did not include many patients who received doses greater than the middle 50-Gy range,

we were unable to address whether further improvement in response is observed with higher doses of radiation. However, because local failures continue to be a significant problem with these tumors, Merchant et al. used a dose of 59.4 Gy in a single-institution study with good results, albeit with short follow-up.[19] The current multi-institutional ACNS0121 protocol also is exploring the use of this higher dose for the treatment of intracranial ependymomas.

In addition to confirming prior reports that the factors described above have prognostic significance, we observed that direct extension of tumor to the cervical spinal cord was associated with worse outcomes. In particular, patients who had such extension had a significantly elevated risk of failure distant to the primary site. We are uncertain about the reason for this association. One possibility is that tumors that are able to expand sufficiently to track down the cord may have an elevated risk of occult dissemination in the CNS at presentation. This includes the possibility that tumor fragments more frequently may be carried caudally because of alterations in CSF flow when tumor involves this restriction point at the foramen magnum. Alternatively, surgical resection of tumor that extends to the cord may increase the likelihood of dissemination. Finally, it is possible that tumor that extended to the spinal cord was not treated adequately because of inadequate imaging and fields, leading to a marginal miss. This last scenario seems unlikely, because, under those circumstances, we also would expect an increased risk of local failure.

Treatment guidelines currently do not support the use of CSI for localized intracranial ependymoma.[14] Overall, our data generally support this policy, because only approximately 15% of failures were located completely away from the primary site. However, because we did observe a high incidence of exoprimary failures in patients with extension of disease to the cervical spinal cord, the question regarding the use of full CNS irradiation in selected patients may need to be revisited. Cord extension as a negative prognostic factor in intracranial ependymomas needs to be confirmed in other studies. However, if it is borne out as a significant prognostic factor, then there are potential implications in the workup and management of such patients. At a minimum, it emphasizes the need for vigilant evaluation for CNS dissemination using spinal MRI and multiple lumbar punctures for CSF cytology to increase sensitivity for finding CSF spread. CSI most likely still should not be offered routinely unless there is documented CNS dissemination, even in patients with cord extension.

Because RT to the brain can have major neuropsychological sequelae, especially in patients aged <3 years, chemotherapy has been attempted as a means of delaying or avoiding RT to permit more time for brain maturation. In our series, 11 patients received chemotherapy with the objective of delaying RT, whereas an additional 4 patients did not receive any immediate therapy postoperatively. Although these patients did not have worse outcomes at a statistically significant level, the graphs suggest a possibility of poorer outcomes; thus, this approach of delaying RT needs to be taken with caution. These results are in line with past experience. Although ependymomas do respond to a variety of chemotherapies, to our knowledge to date, no regimens have proven effective at prolonging survival in patients with this disease.[3,4,9,18,20,25] Duffner et al. reported the use of chemotherapy to delay RT in infants (aged <3 years) who had a variety of brain tumors; in that report, PFS was only 42 $\pm$ 9.3% at 2 years in patients with ependymoma.[26] Similarly, Grill et al. reported the results of a French Society of Pediatric Oncology protocol that explored delaying or avoiding RT through the use of postoperative chemotherapy in young children (aged $\pm$ 5 years) who had intracranial ependymoma.[27] In that study, the 4-year PFS rte was only 22% $\pm$ 11%. These results are substantially worse than would be expected for patients who receive immediate RT. With these poor outcomes in infants and young children using the chemotherapy-first approach, ACNS0121 calls for treating infants as young as age 1 year with postoperative RT without much delay. Even if modern focal RT techniques are used in these infants, many practitioners still worry that radiation dose to the brain in such young patients will result in intelligence quotient (IQ) declines. However, investigators at St. Jude have reported that treatment of patients in this age group with conformal RT did not lead to significant, measurable declines in neurocognitive function, giving further support for the use of such an approach,[19] and those investigators subsequently developed mathematical models for predicting IQ based on patient age and brain dose-volume histograms that confirm the small effects of conformal therapy to the posterior fossa on IQ in most patients.[28]

In conclusion, for all patients in our study, the 5-year PFS rate was only approximately 40% despite the receipt of multimodality therapy. Even with favorable features, a patient could expect a 5-year PFS rate of approximately 60% in our series. Examination of patients treated in the 1980s versus the 1990s did not reveal significant differences in outcomes (Table 4), suggesting that advances in imaging and treatment technologies over that period have not

had a significant impact on our ability to control these tumors. Therefore, major improvement in outcomes will likely come from altering treatment approaches (eg, addition of molecularly targeted therapy) rather than refining treatment technique. Overall, in addition to confirming previous findings by others, our study demonstrated an RT dose response up to 54 Gy and indicated that tumor extension to the cervical spine results in worse outcomes because of an increased risk of exoprimary failures. Our dose-response data and the finding that most failures are local gives us hope that further dose escalation to 59.4 Gy on the current COG study will improve control rates. The current COG protocol also seeks to improve outcomes by improving resection extent prior to RT (through use of chemotherapy and second-look surgery) and by treating children aged <3 years with up-front RT. It remains to be determined whether this approach will yield better treatment results. Whatever the approach, these brain tumors must be treated aggressively, because even low-grade or *benign* histology lesions can be difficult to control.

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