Advances in Radiation Oncology (2021) 6, 100691

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Effect of Postoperative Radiation Therapy Timing on Survival in Pediatric and Young Adult Ependymoma

Sunny Shah, MS,[a,1] Kevin Gates, MS,[a,1] Chase Mallory, BHS,[a,1] Muni Rubens, PhD, MPH,[a] Ossama M. Maher, MD,[b] Toba N. Niazi, MD,[c] Ziad Khatib, MD,[b] Rupesh Kotecha, MD,[a] Minesh P. Mehta, MD,[a] and Matthew D. Hall, MD, MBA[a,*]

[a]*Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida;* [b]*Department of Pediatric Oncology,* [c]*Department of Pediatric Neurosurgery, Nicklaus Children's Hospital, Miami, Florida*

Received October 28, 2020; revised February 5, 2021; accepted March 8, 2021

Abstract

Purpose: Postoperative radiation therapy (RT) is commonly used for World Health Organization grade II-III intracranial ependymoma. Clinicians generally aim to begin RT ≤5 weeks after surgery, but postoperative recovery and need for second look surgery can delay the initiation of adjuvant therapy. On ACNS 0831, patients were required to enroll ≤8 weeks after initial surgery and begin adjuvant therapy within 3 weeks after enrollment. The purpose of this study was to determine the optimal timing of RT after surgery.

Methods and Materials: The National Cancer Database was queried for patients (aged 1-39 years) with localized World Health Organization grade II-III intracranial ependymoma treated with surgery and postoperative RT. Overall survival (OS) curves were plotted based on RT timing (≤5 weeks, 5-8 weeks, and >8 weeks after surgery) and were compared by log-rank test. Factors associated with OS were identified by multivariate analysis. After 2009, complete data were available on whether patients underwent gross total resection or subtotal resection. Planned subset analysis was performed to examine the effect of RT timing on OS in patients with known extent of resection.

Results: In the final analytical data set of 1043 patients, no difference in 3-year OS was observed in patients who initiated RT ≤5 weeks, 5 to 8 weeks, and >8 weeks after surgery (89.8% vs 89.1% vs 88.4%; $P = .796$). On multivariate analysis, grade III tumors (hazard ratio, 2.752; 95% confidence interval, 1.969-3.846, $P < .001$) and subtotal resection (hazard ratio, 2.253; 95% confidence interval, 1.405-3.611, $P < .001$) were significantly associated with reduced OS. Timing of RT, total RT dose, age, and other factors were not significant. These findings were affirmed in the subset of patients treated between 2010 and 2016, when extent of resection was routinely recorded.

Conclusions: Delayed postoperative RT was not associated with inferior survival in patients with intracranial ependymoma. Delayed RT initiation may be acceptable in patients who require longer postoperative recovery or referral to an appropriate RT center, but should be minimized whenever practical.

Sources of support: This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: R.K. reports grants from Novocure, Inc, and grants from Medtronic, Inc, which are outside the submitted work. M.P.M. reports personal fees from Mevion, nonfinancial support from Viewray, personal fees from Karyopharm, personal fees from Tocagen, personal fees from Astra-Zeneca, personal fees from Blue Earth Diagnostics, personal fees from Celgene, and personal fees from Abbvie outside of the submitted work. M.P.M. served on the board of directors for Xcision and Oncoceutics. M.D.H. reports an honorarium from Accuray, Inc, for services outside the submitted work.

*Corresponding author: Matthew D. Hall, MD, MBA; E-mail: matthewha@baptisthealth.net

[1] Contributed to this work equally

https://doi.org/10.1016/j.adro.2021.100691

Introduction

Ependymoma is the second-most common malignant intracranial tumor in pediatric patients, with approximately 1372 new cases diagnosed per year in the United States.[1] Pediatric ependymoma are almost exclusively located within the brain, with two-thirds residing in the posterior fossa. Maximal safe resection is the primary curative treatment in all patients. Adjuvant radiation therapy (RT) is generally recommended in patients with World Health Organization (WHO) grade II-III ependymoma after maximal safe resection.[2] The role of chemotherapy is not well characterized[3]; however, in very young patients, adjuvant chemotherapy may be used to delay RT due to concerns about late adverse effects.[4-6]

The optimal timing between surgical resection and adjuvant RT has been examined in medulloblastoma[7,8] but not in ependymoma. Many physicians strive to begin within 5 weeks of surgery, similar to many malignant brain tumors. Selected patients, however, may experience unavoidable delays to enable adequate postoperative recovery or to facilitate referral to a high volume pediatric center. All patients in Children's Oncology Group ACNS 0121 and ACNS 0831 (NCT01096368) were required to enroll within 8 weeks of initial surgery and initiation of adjuvant therapy within 3 weeks from enrollment. Currently, there are limited data demonstrating the effect of delayed RT on overall survival (OS).

The aim of our study was to analyze the association between the time interval from surgical resection to adjuvant RT on OS in patients with ependymoma using the National Cancer Database (NCDB). We hypothesized that delayed adjuvant RT may be associated with decreased OS.

Methods and Materials

Study design and population

We analyzed deidentified patient data obtained from the NCDB, a large hospital-based registry that captures approximately 70% of all cancer incidence in the United States from more than 1500 hospitals accredited by the Commission on Cancer. The NCDB is a joint project of the Commission on Cancer and the American College of Surgeons. The data used in the study were derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed or the conclusions drawn from these data by the investigators. After evaluation and approval of the research design by the clinical trials office, institutional review board approval was not required for this study.

Patients with ependymoma between the ages of 1 and 39 years were identified in the NCDB data set using primary site and histology codes.[1] The analytical cohort was generated to include patients who received diagnoses of ependymoma between 2004 and 2016, which yielded 2433 subjects. Patients were excluded if they had WHO grade I or IV tumors, history of prior malignancy, metastatic disease, received radiation doses <50 or ≥61.5 Gy, or had incomplete data for vital status or date of last contact. Patients were also excluded if they received only 1 treatment modality with either surgery or RT or received RT before surgery. The final analytical cohort included 1043 patients. The selection criteria for the final data set are illustrated in Figure 1.

Complete information on extent of surgical resection was not included in the NCDB until 2010. A planned subgroup analysis was performed for all patients who had complete information on extent of surgical resection, classified as either gross total resection (GTR) or subtotal resection (STR)/biopsy. This yielded 565 patients for this subgroup analysis, representing all patients diagnosed and treated from 2010 to 2016.

The primary exposure of our study was time between initial surgery and the start of adjuvant RT, divided into 3 strata (<5 weeks, 5-8 weeks, >8 weeks). The primary outcome was OS. Additional covariates included age (1-20, 21-39), race, sex, WHO grade (II, III), tumor location (supratentorial, infratentorial), extent of surgical resection (GTR, STR), Charlson Deyo comorbidity score (0, 1, 2, or 3), insurance status (private, Medicaid/government, uninsured), distance from hospital (≤50 miles, >50 miles), year of diagnosis (2004-2006, 2007-2009, 2010-2012, 2013-2015), household income (stratified by quartile), and RT dose (≤54 Gy, >54 Gy).

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc, Chicago, IL). Differences between categorical variables were compared using the χ^2 test. Survival curves were plotted using the Kaplan-Meier product limit method and were compared using the log-rank test. Multivariate proportional hazards analysis (MVA) with backward stepwise regression was used to identify factors associated with OS. Two-sided P values $< .05$ were considered statistically significant. The proportional hazards assumption was tested for a nonzero slope in the generalized linear model using scaled Schoenfeld residuals. Multiple imputation methods were used to address limitations due to missing data.

Results

Patient demographics and tumor characteristics are presented in Table 1. Median age was 9 years (interquartile range, 3-22). Younger patients (age <21 years) and

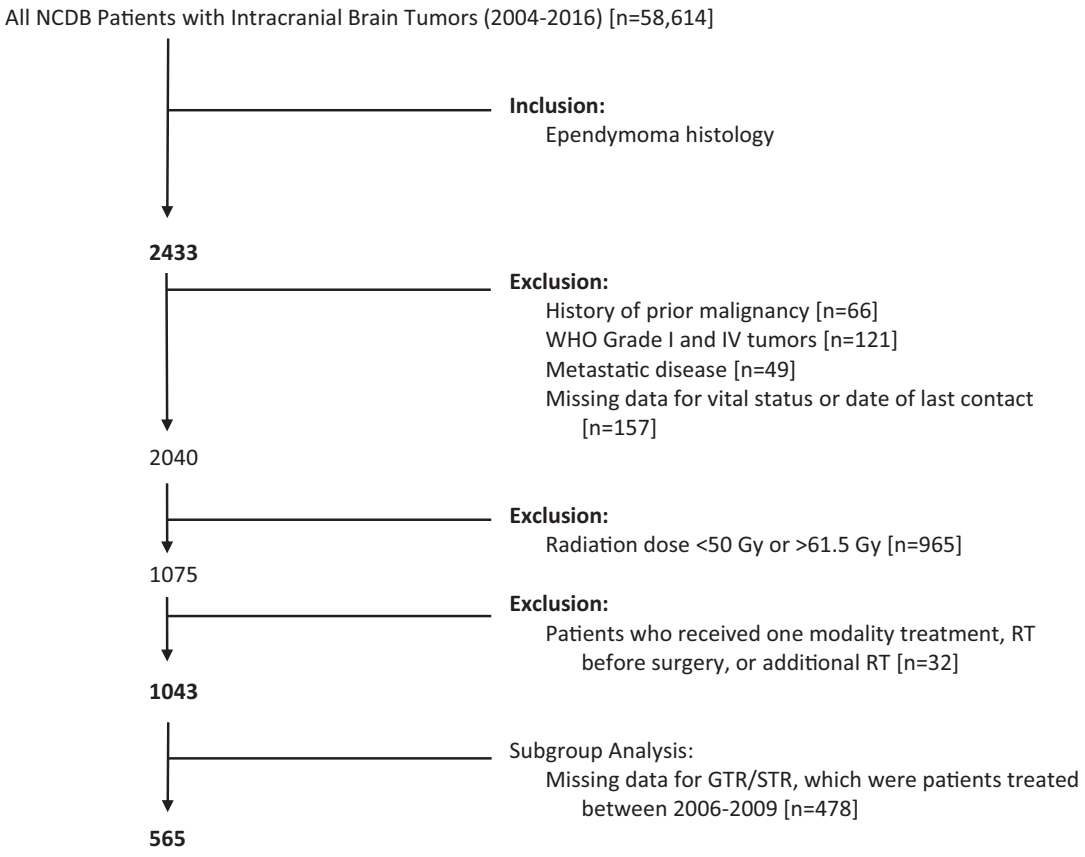


Figure 1 Inclusion and exclusion criteria used to select the primary analytical data set and the planned subgroup analysis.

those with grade III tumors were more likely to begin postoperative RT earlier after initial surgery than older patients and those with grade II tumors. All other comparisons showed no significant and/or no clear discernable difference between the groups. Median follow-up was 4.77 years for surviving patients. At the close-out date, 17.3% of patients had died.

In this cohort, no significant OS difference was observed between patients who received adjuvant RT <5 weeks, 5 to 8 weeks, or >8 weeks after surgical resection, with 3-year OS rates of 89.8%, 89.1%, and 88.4% (P = .796), respectively. The Kaplan-Meier plots are illustrated in Figure 2. Similarly, no significant difference in OS was observed in the subgroup of patients treated between 2010 and 2016 with known extent of surgical resection (P = .802). The Kaplan-Meier curves for this subgroup are shown in Figure 3.

On MVA, we observed no significant association between the timing of postoperative RT and OS (Table 2). In the complete data set, WHO grade III tumors were significantly associated with increased hazard of death (hazard ratio [HR], 2.752; 95% confidence interval [CI], 1.969-3.846, P < .001) compared with WHO grade II tumors. STR was also associated with an increased risk of death (HR, 2.253; 95% CI, 1.405-3.611, P <.001). Age, sex, race, distance from hospital, household income, insurance, tumor location, RT dose, and Charlson Deyo score demonstrated no association with OS.

In the subgroup of patients with known extent of resection, MVA illustrated similar findings relative to the primary analytical cohort. WHO grade III tumors (HR, 4.296; 95% CI, 2.334-7.906, P < .001) and STR (HR, 2.267; 95% CI, 1.381-3.721, P = .001) remained significant on MVA. Postoperative RT timing and other additional variables were not associated with OS.

Discussion

We evaluated the effect of the time interval between surgery and postoperative RT on survival in patients with intracranial ependymoma using a large hospital-based registry. Our study demonstrated no significant difference in OS between patients who received early versus delayed RT in the NCDB.

To our knowledge, no large database studies to date have evaluated the effect of postoperative RT timing on outcomes in ependymoma. Patteson and colleagues[9] recently reported no detriment in OS or local control if RT started within 9 weeks in a single institution study of

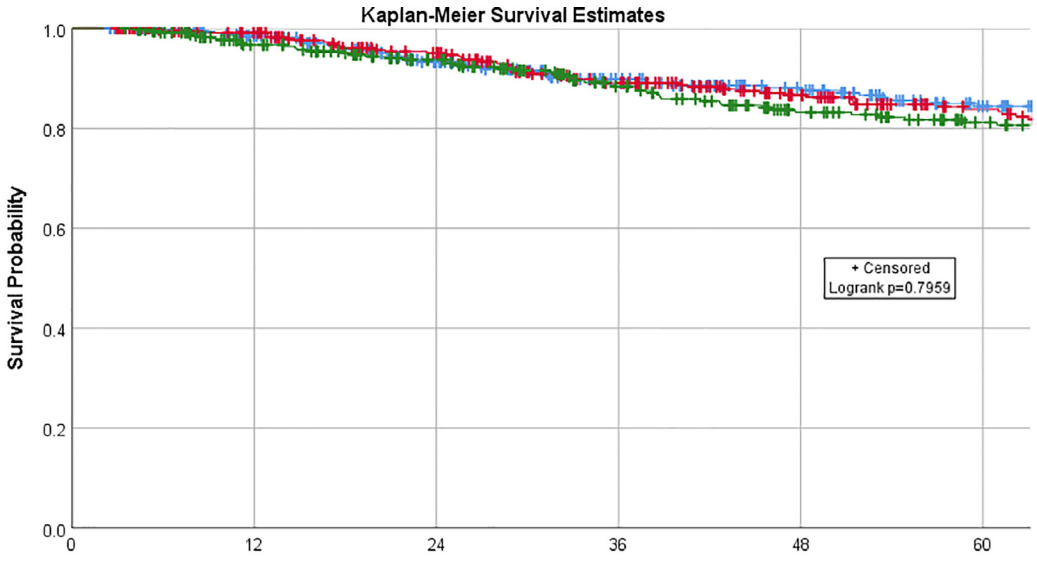
Table 1 Patient demographics and tumor characteristics

Patient characteristics	Total		Time to RT <5 weeks		Time to RT 5-8 weeks		Time to RT >8 weeks		*P* value
	No.	%	No.	%	No.	%	No.	%	
Total age (years)	1043	100	334	100	363	100	346	100	
									< .001
1-20	752	72.1	266	79.6	274	75.5	212	61.3	
21-39	291	27.9	68	20.4	89	24.5	134	38.7	
Race									.673
White	828	79.4	263	78.7	296	81.5	269	77.8	
Nonwhite	153	14.7	53	15.9	46	12.7	54	15.6	
Unknown	62	5.9	18	5.4	21	5.8	23	6.7	
Sex									.076
Male	576	55.2	191	57.2	211	58.1	174	50.3	
Female	467	44.8	143	42.8	152	41.9	172	49.7	
Charlson Deyo score									.570
0	953	91.4	307	91.9	333	91.7	313	90.5	
1	64	6.1	19	5.7	22	6.1	23	6.7	
2	15	1.4	3	0.9	7	1.9	5	1.5	
3	11	1.1	5	1.5	1	0.3	5	1.5	
Insurance									.107
Private	630	60.4	197	59.0	236	65.0	197	56.9	
Medicaid/gov.	341	32.7	112	33.5	108	29.8	121	35.0	
Uninsured	54	5.2	22	6.6	14	3.9	18	5.2	
Unknown	18	1.7	3	0.9	5	1.4	10	2.9	
Residential distance to hospital (miles)									.815
≤50 miles	790	75.7	252	75.5	279	76.9	259	74.9	
>50 miles	253	24.3	82	24.6	84	23.1	87	25.1	
Median income									.107
1st quartile (Lowest)	248	23.8	72	21.6	94	25.9	82	23.7	
2nd quartile	198	19.0	68	20.4	58	16.0	72	20.8	
3rd quartile	270	25.9	78	23.4	99	27.3	93	26.9	
4th quartile (Highest)	324	31.1	113	33.8	112	30.9	99	28.6	
Unknown	3	0.3	3	0.9	0	0.0	0	0.0	
Year of diagnosis									.612
2004-2006	242	23.2	78	23.4	92	25.3	73	20.8	
2007-2009	236	22.6	79	23.7	84	23.1	73	21.1	
2010-2012	273	26.2	90	27.0	90	24.8	93	26.9	
2013-2015	292	28.0	87	26.1	97	26.7	108	31.2	
WHO grade									.004*
Grade II	576	55.2	166	49.7	195	53.7	215	62.1	
Grade III	467	44.8	168	50.3	168	46.3	131	37.9	
Tumor location									.320
Infratentorial	355	34.0	112	33.5	118	32.5	125	36.1	
Supratentorial	392	37.6	126	37.7	150	41.3	116	33.5	
Unknown	296	28.4	96	28.7	95	26.2	105	30.4	
Surgical resection									.005*
GTR	378	36.2	130	38.9	130	35.8	118	34.1	
STR	188	18.0	47	14.1	57	15.7	84	24.3	
Unknown	477	45.7	157	47.0	176	48.5	144	41.6	
RT dose (Gy)									< .001*
≤54	367	35.2	102	30.5	113	31.1	152	43.9	
>54	676	64.8	232	69.5	250	68.9	194	56.1	

Abbreviations: GTR = gross total resection; RT = radiation therapy; STR = subtotal resection; WHO = World Health Organization.
* Significant values with $P < 0.05$.

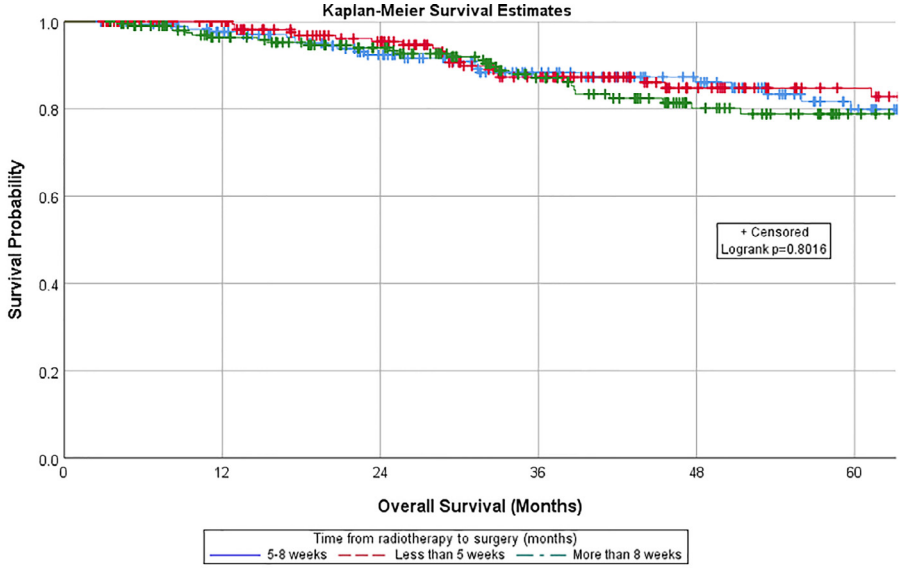
145 patients with intracranial ependymoma. The authors reported a trend toward inferior local control in WHO grade II patients after GTR/ (near total resection) with RT initiation later than 9 weeks after surgery but did not observe this in grade III patients.[9] No such discrepancy based on WHO grade was observed in this analysis.

The effect of RT timing on OS was previously evaluated in medulloblastoma using the NCDB. Chin and



Less than 5 weeks	334	301	259	215	182	144
5-8 Weeks	363	329	287	242	199	168
More than 8 Weeks	346	306	266	216	175	147

Figure 2 Overall survival curves as a function of postoperative radiation therapy timing in the primary analytical data set (n = 1043 patients). No significant difference in overall survival was observed as a function of radiation therapy timing.



Less than 5 weeks	177	160	130	91	74	43
5-8 Weeks	187	164	133	97	60	43
More than 8 Weeks	201	174	144	99	66	43

Figure 3 Overall survival curves as a function of postoperative radiation therapy timing in patients treated between 2010 and 2016 (n = 565), when extent of surgical resection was known in all patients.

colleagues[8] reported no clear effect on survival from delaying RT up to 90 days after surgery. Of note, the authors found that initiation of RT within 3 weeks of surgery was associated with inferior survival, although they noted that this finding may have been explained by an imbalance in adverse factors, such as presence of metastatic disease, in that group.[8] Owing to concern regarding neurocognitive deficits after craniospinal irradiation,

Table 2 Multivariate analysis for overall survival

Variable	Entire data set (n = 1043) HR (95% CI)	*P* value	Subgroup (n = 565) HR (95% CI)	*P* value
Time to adjuvant RT (weeks)				
<5	Reference		Reference	
5-8	0.902 (0.623-1.305)	.583	0.819 (0.445-1.507)	.521
>8	1.075 (0.739-1.563)	.706	0.973 (0.545-1.736)	.926
WHO tumor grade				
Grade II	Reference		Reference	
Grade III	2.752 (1.969-3.846)	< .001*	4.296 (2.334-7.906)	< .001*
Tumor location				
Infratentorial	Reference		Reference	
Supratentorial	0.748 (0.509-1.098)	.138	0.767 (0.415-1.420)	.399
Unknown	0.937 (0.639-1.376)	.741	0.873 (0.450-1.694)	.688
Surgical resection				
GTR	Reference		Reference	
STR	2.253 (1.405-3.611)	< .001*	2.267 (1.381-3.721)	.001*
Unknown	1.429 (0.958-2.131)	.0810		
RT dose (Gy)				
≤54	Reference		Reference	
>54	1.040 (0.738-1.465)	.822	1.069 (0.610-1.875)	.815
Age				
1-20	Reference		Reference	
21-39	0.880 (0.601-1.288)	.510	1.109 (0.632-1.946)	.718
Race				
White	Reference		Reference	
Nonwhite	0.423 (0.246-0.727)	.002	0.465 (0.213-1.016)	.055
Unknown	0.762 (0.371-1.565)	.458	0.592 (0.139-2.516)	.477
Sex				
Male	Reference		Reference	
Female	0.813 (0.596-1.108)	.190	0.879 (0.536-1.443)	.611
Charlson Deyo score				
0	Reference		Reference	
1	1.157 (0.665-2.013)	.606	1.090 (0.424-2.801)	.859
2	0.915 (0.223-3.759)	.902	0.772 (0.101-5.886)	.803
3	1.242 (0.296-5.220)	.767	1.387 (0.177-10.892)	.756
Insurance status				
Private	Reference		Reference	
Medicaid/Medicare/govt.	1.064 (0.757-1.497)	.720	1.308 (0.761-2.248)	.331
Uninsured	1.402 (0.715-2.747)	.325	1.759 (0.684-4.523)	.241
Unknown	2.408 (1.025-5.655)	.044	7.371 (1.935-28.075)	.003
Residential distance to hospital (miles)				
≤50	Reference		Reference	
>50	0.759 (0.517-1.114)	.159	0.550 (0.282-1.073)	.080
Median income				
1st quartile (lowest)	Reference		Reference	
2nd quartile	1.200 (0.763-1.885)	.430	1.324 (0.664-2.640)	.425
3rd quartile	0.842 (0.550-1.289)	.430	0.788 (0.371-1.677)	.537
4th quartile (highest)	0.703 (0.452-1.094)	.118	0.880 (0.447-1.734)	.713
Unknown	3.332 (0.435-25.496)	.246		
Year of Diagnosis				
2004-2006	Reference			
2007-2009	1.123 (0.752-1.677)	.570		
2010-2012	0.004 (0.000-0.039)	< .001*	Reference	
2013-2015	0.002 (0.000-0.025)	< .001*	0.586 (0.331-1.040)	.068

Abbreviations: CI = confidence interval; GTR = gross total resection; HR = hazard ratio; RT = radiation therapy; STR = subtotal resection; WHO = World Health Organization.

* Significant values with $P < 0.05$.

younger patients with medulloblastoma less commonly receive RT than older patients. Kann and colleagues[7] reported that deferral of RT in patients with medulloblastoma between 3 to 8 years of age was associated with significantly worse OS in the NCDB, affirming the importance of RT on survival in this population.

Adjuvant RT is generally recommended after maximal safe resection of grade II-III intracranial ependymoma. The role of RT has also been questioned in selected populations, including children with grade II supratentorial tumors after GTR and adults.[10,11] Mature results from ACNS 0831 will provide further information on the former group. The role of adjuvant RT is arguably more controversial in adults. Prabhu and colleagues[11] reported no OS benefit with adjuvant RT in adults (≥22 years old) who received RT. In that cohort, 80% of patients had grade II tumors and two-thirds were supratentorial compared with 55.2% grade II and 37.6% supratentorial in this study. We hypothesize that differences in the incidence of different molecular subtypes of ependymoma between pediatric and adult patients may explain this observed variation in tumor characteristics and potentially lead to the observed differences in survival between manuscripts. In 2016, Ramaswamy and colleagues[12] reported clinically significant OS differences for patients with posterior fossa A and B (PFA and PFB) infratentorial tumors, and a clear benefit from adjuvant RT in PFA tumors. The authors concluded that selected patients with PFB tumors may safely be observed after GTR, but validation in a prospective trial is needed to definitively address this hypothesis.

For many malignant pediatric and adult brain tumors, postoperative RT regularly begins within 5 weeks of initial surgery to reduce the risk that any microscopic or gross residual disease may repopulate after surgery.[13] Delaying RT initiation, however, may provide several competing benefits. For example, it may also enable time for patients to undergo second look surgery to achieve GTR or permit patients to complete inpatient physical therapy when necessary. Finally, it may provide adequate time to develop a high quality treatment plan or be referred to a high volume pediatric RT center.

In this analysis, both STR and WHO grade III tumors were significantly associated with inferior OS, consistent with prior studies.[14-16] Male gender was previously reported as an adverse risk factor, but was not significant in this analysis.[15] Metastatic disease is another known adverse prognostic factor, but such patients were excluded from this analytical set. Of note, no dose response was observed for patients receiving <54 Gy in either the primary cohort or the subgroup analysis with known extent of surgical resection. This finding is concordant with 2 recent reports[9,17] but not with a recent NCDB analysis. Ager and colleagues[18] reported a dose response for OS in children aged 2 to 18 treated with >54 Gy with no benefit from dose escalation observed in adults and children <2 years old. After adjusting for significant prognostic factors in the MVA, delayed RT timing was not associated with an elevated HR for death in this analysis.

Several limitations in our study must be acknowledged. First, selection and information biases are oftentimes inseparable from retrospective analyses and must be considered when applying our results to clinical practice. Extent of resection was reported in only 54.3% of the primary analytical cohort, which cannot be easily overcome. Missing information can affect results in registry-based series, and data coding errors certainly exist within large databases. A planned subset analysis demonstrated no clear difference in the survival estimates observed in only the patients with known GTR/STR status. The completeness of the remaining available data and this step helped to counter the possibility that the observed effect was due to selection bias. Of note, the role of adjuvant chemotherapy is still uncertain in pediatric ependymoma,[3] but it may be elucidated by cooperative group trials.

In the NCDB, outcome measures were limited to OS; data regarding local and distant failure and cancer-specific survival cannot be extracted. Although this is a known limitation of NCDB analyses, the predominant cause of mortality in children diagnosed with malignant brain tumors is either related to the tumor or its treatment. This is particularly true during early follow-up, with competing risks of death rising in later years[19] as the incidence of significant comorbidities related to curative therapy increases.[20,21] Although the NCDB provides adequate power to address hypotheses regarding RT timing, duration of follow-up remains one limitation. Ependymoma can recur >5 years after diagnosis and treatment, and long-term follow-up is important for this[5] and other pediatric brain tumors. We acknowledge that follow-up was only 4.77 years in this study, and that delayed RT may lead to an increased risk of local failure and a resulting effect on survival with longer follow-up than in this data set. In addition, due to its granularity, large databases like the NCDB do not provide a clear explanation for why particular treatments were selected, such as why patients received delayed RT. For example, selected patients who received delayed RT may have done so after a second look surgery; this could potentially explain the observed lack of difference in OS in this analysis as a function of RT timing. We further recognize that observational studies cannot replace randomized data as the standard for outcomes research, although registry data can address important clinical questions not adequately evaluated in randomized trials.

Molecular subtype information for ependymoma is not included in the NCDB. This classification system is contemporary[22] and evolving[23,24] and has only recently been

incorporated into routine testing. Of note, ACNS 0121 demonstrated no clear difference in event-free survival between PFA and B infratentorial tumors or based on RELA fusion status but did identify significantly inferior event-free survival with 1q gain.[4,15] In the future, molecular data should be regularly recorded in cooperative group trials and large registries for ependymoma and other brain tumors to better understand the effect of molecular subtype on outcomes.

In summary, our NCDB analysis demonstrated no clear survival effect with delayed RT in pediatric and young adult patients with localized intracranial ependymoma. Selected patients, including those with metastatic disease, may benefit from early RT administration. Given the clear importance of GTR on survival, we advise complete surgical resection whenever feasible, even if second look surgery is required, leading to a delay in adjuvant RT. This approach is consistent with ACNS 0121 and ACNS0831.[15] Routine delays in postoperative RT should be *avoided,* but these data suggest that it may be considered in selected patients who may benefit from second look surgery, require additional time for adequate healing, or to facilitate referral to a high volume RT center.

References

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol*. 2018;20(suppl_4):iv1–iv86.
2. Hübner JM, Kool M, Pfister SM, Kajtler KW. Epidemiology, molecular classification and WHO grading of ependymoma. *J Neurosurg Sci*. 2018;61:46–55.
3. Timmerman B, Kortmann RD, Kuhl J, et al. Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: Results of the German prospective trials HIT 88/89 and HIT 91. *Int J Radiat Oncol Biol Phys*. 2000;46:287–295.
4. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. A prospective study of conformal radiation therapy for pediatric ependymoma. *Lancet Oncol*. 2009;10:258–266.
5. Marinoff AE, Ma C, Guo D, et al. Rethinking childhood ependymoma: A retrospective, multi-center analysis reveals poor long-term overall survival. *J NeuroOncol*. 2019;135:201–211.
6. Ruangkanchanasetr R, Swangsilpa T, Puataweepong P, et al. Outcome of postoperative radiation therapy for pediatric intracranial ependymoma: A single-institution review. *Childs Nerv Syst*. 2019; 35:1313–1321.
7. Kann BH, Park HS, Lester-Coll NH, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. *JAMA Oncol*. 2016;2:1574–1581.
8. Chin AL, Moding EJ, Donaldson SS, et al. Survival impact of postoperative radiotherapy timing in pediatric and adolescent medulloblastoma. *Neuro Oncol*. 2018;20:1133–1141.
9. Patteson BE, Baliga S, Bajaj B, et al. Clinical outcomes in a large pediatric cohort of patients with ependymoma treated with proton radiotherapy. *Neuro-oncol.*. 2021;23:156–166.
10. Brown DA, Goyal A, Takami H, et al. Radiotherapy in addition to surgical resection may not improve overall survival in WHO grade II spinal ependymomas. *Clin Neurol Neurosurg*. 2020;189: 105632.
11. Prabhu RS, Corso CD, Ward MC, et al. The effect of adjuvant radiotherapy on overall survival in adults with intracranial ependymoma. *Neurooncol Pract*. 2020;7:391–399.
12. Ramaswamy V, Hielscher T, Mack SC, et al. Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: A retrospective multicohort analysis. *J Clin Oncol*. 2016;34:2468–2477.
13. Blumenthal DT, Won M, Mehta MP, et al. Short delay in initiation of radiotherapy may not affect outcome of patients with glioblastoma: A secondary analysis from the radiation therapy oncology group database. *J Clin Oncol*. 2009;27:733–739.
14. Merchant TE, Bendel AE, Sabin ND, et al. Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. *J Clin Oncol*. 2019;37:974–983.
15. Massimino M, Miceli R, Giangaspero F, et al. Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. *Neuro Oncol*. 2016;18:1451–1460.
16. Indelicato DJ, Bradley JA, Rotondo RL, et al. Outcomes following proton therapy for pediatric ependymoma. *Acta Oncol*. 2018;57: 644–648.
17. Indelicato DJ, Ioakeim-Ioannidou M, Bradley JA, et al. Proton therapy for pediatric ependymoma: Mature results from a bicentric study. Int J Radiat Oncol Biol Phys. 2021. S0360-3016(21)00087-0. Advance online publication.
18. Ager BJ, Christensen MT, Burt LM, Poppe MM. The value of high-dose radiotherapy in intracranial ependymoma. *Pediatr Blood Cancer*. 2019;66:e27697.
19. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100:1368–1379.
20. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2009; 101:946–958.
21. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med*. 2016; 374:833–842.
22. Pajtler KW, Witt H, Sill M, et al. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. *Cancer Cell*. 2015;27:728–743.
23. Pajtler KW, Wen J, Sill M, et al. Molecular heterogeneity and CXorf67 alterations in posterior fossa group A (PFA) ependymomas. *Acta Neuropathol*. 2018;136:211–226.
24. Cavalli FMG, Hübner JM, Sharma T, et al. Heterogeneity within the PF-EPN-B ependymoma subgroup. *Acta Neuropathol*. 2018; 136:227–237.