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ONCOLOGY: RESEARCH ARTICLE

Prolongation of radiotherapy duration is associated with inferior overall survival in patients with pediatric medulloblastoma and central nervous system primitive neuroectodermal tumors

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Abstract

Background: The importance of radiotherapy (RT) duration in medulloblastoma in the modern era of chemotherapy has not been well elucidated. The aim of this study was to determine the impact of RT treatment duration on overall survival (OS) in pediatric medulloblastoma and cenral nervous system neuroectodermal tumors (PNETs).

Methods: The National Cancer Database (NCDB) was queried to identify patients with newly diagnosed medulloblastoma and CNS PNETs diagnosed between 2004 and 2014. Patients were excluded if they had extraneural metastasis, did not receive standard craniospinal irradiation dose, had a nonstandard total dose outside of 54 or 55.8 Gy, did not receive adjuvant chemotherapy, or if the RT duration was outside of the expected range of 37 to 80 days. The Kaplan-Meier estimator was used to estimate the association between RT duration (≤45 days or >45 days) and OS. Multivariate Cox regression was used to assess other confounders of OS.

Results: Six-hundred twenty-five patients met inclusion criteria, of which 181 were assigned to the "RT long" (>45 days) cohort (29.0%) and 444 (71.0%) to the "RT short" group (≤45 days). The five-year OS for the "RT short" compared with "RT long" cohort was 82.2% versus 70.9%, respectively (log-rank, $P < 0.0037$). For average risk patients, the five-year OS was 84.6% versus 86.4% for "RT short" and "RT long," respectively (log-rank, $P = 0.40$). However, for high-risk patients, five-year OS was 77.7% versus 51.0% (log-rank, $P < 0.0001$) in the "RT short" and "RT long" cohorts.

Conclusion: For patients with high-risk medulloblastoma and CNS PNETs, RT duration >45 days was associated with inferior OS.

KEYWORDS
medulloblastoma, PNET, RT duration

1 | INTRODUCTION

Medulloblastoma represents the most common CNS embryonal tumor in childhood and accounts for 10% of all childhood brain tumors and 50% of all posterior fossa tumors.[1,2] Pineoblastomas and other CNS

Abbreviations: NCDB, National Cancer Database; OS, overall survival; PNET, primitive neuroectodermal tumor; RT, radiation therapy

embryonal tumors typically occur in the supratentorial region and were previously known as supratentorial primitive neuroectodermal tumors but are now being characterized as a variety of entities in the newest WHO CNS tumor classification.[3] Radiotherapy (RT), in conjunction with chemotherapy, plays a critical role in the postoperative management in medulloblastoma and PNETs. Standard-risk medulloblastoma patients are given lower doses (approximately 23.4 Gy) craniospinal irradiation (CSI) followed by a tumor bed boost combined with adjuvant chemotherapy.[4] Medulloblastoma patients with high-risk disease and patients treated prior to 2016 with supratentorial PNETs are typically treated similarly with higher CSI doses of 36 Gy and a boost to the tumor bed with additional adjuvant chemotherapy. In addition to the critical role of RT in medulloblastoma and PNETs, delays in completion of RT have been shown to have a detrimental impact on overall survival (OS).[5-7] However, it is not known if all radiation oncology providers are aware of these recommendations and follow this practice. Therefore, we used data from the National Cancer Database (NCDB) to determine the impact of RT treatment duration on OS in pediatric patients treated for medulloblastoma or other supratentorial embryonal tumors, characterized as PNETs in the National Cancer Database (NCDB) prior to 2014.

2 | METHODS

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the sources of the deidentified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. Data within the NCDB include basic demographics, cancer staging, comorbidities, therapies delivered during the first course of treatment, and OS. The NCDB does not capture disease recurrence or salvage therapies.

The NCDB was queried to identify patients with newly diagnosed medulloblastoma or CNS primitive neuroectodermal tumor (PNET) treated between 2004 and 2014. Inclusion and exclusion criteria were designed to include those patients treated in the standard fashion with trimodality therapy (surgery, RT, and chemotherapy), as well as to exclude patients who may have data errors in the fields which we are assessing. Included patient diagnoses included medulloblastoma (and any variant, nodular/desmoplastic, large cell/anaplastic, classic, or PNET). Histology codes included were 9470 (medulloblastoma, NOS), 9471 (desmoplastic medulloblastoma), 9472 (medullomyoblastoma), 9473 (PNET), and 9474 (large cell medulloblastoma). Other inclusion criteria were (1) age ≤21 years, (2) surgical resection of the primary tumor, and (3) treatment with chemotherapy. Patients were excluded for the following reasons: (1) metastases outside of the CNS; (2) nonstandard craniospinal irradiation dosing (CSI) outside the range of 18, 23.4, or 36 Gy; (3) RT overall treatment times that were outside of the expected range of 37 to 80 days; (4) patients who had a nonstandard total radiation dose that was not either 54 or 55.8 Gy. RT treatment times were calculated by counting the number of days elapsed, including nontreatment weekend days, from the start of RT until the last treatment day of RT. By convention, the first day was considered day zero. Notably, patients cannot receive 50.4 Gy of RT in standard daily fractionation (1.8 Gy/treatment) faster than 37 days and a treatment with no breaks to 54 Gy can be delivered in 39 elapsed days. Radiation can be delayed if a child has an event during radiation requiring a break but extensions greater than 80 days or less than 37 days were thought to be most likely data entry errors or accelerated hyperfractionation and, therefore, these patients were excluded. High-risk disease delineation is not specifically collected in the NCDB database but inferred by the CSI dose for the purposes of this analysis. When risk status was not given, we inferred risk status as "high risk" when patients were given 36 Gy of CSI. The primary objective of this study was to determine if prolongation of RT was associated with inferior OS. RT was considered prolonged if the duration of RT was >45 days. The rationale of this cutoff point is based on previous published data which showed that RT prolongation >45 days was associated with inferior local control and relapse-free survival.[6] A separate cutoff point of >50 days was also analyzed as this has been shown to also be associated with inferior OS.[5] Patients who completed RT in ≤45 days or >45 days were assigned to the "RT short" and "RT long" cohorts, respectively, for the statistical analysis. A similar analysis was performed for patients who completed RT in ≤50 days or >50 days, respectively.

2.1 | Statistical analysis

OS was measured from the start of RT to the date of death or last known date of follow-up. OS for the entire cohort and by RT duration ("RT short" and "RT long") was estimated using the Kaplan-Meier method and we evaluated the effect of prognostic factors on OS using both univariate and multivariate Cox proportional hazards regression. To ensure that the interval between surgery and RT was not a confounder, we included this variable in the univariate and multivariate analysis. Patient characteristics significantly associated with RT duration or OS were included in the multivariate model. We used the Fisher exact test to explore the relationship between various patient characteristics. To improve model stability, we combined and/or excluded groups whose number of deaths was too small (e.g., <5 deaths). To determine if the effect of prolonged RT on OS was consistent among risk subgroups, we fit an interaction term between RT duration and risk stratification into a univariate Cox model. To represent this interaction in the multivariate model, we created a new grouping variable with three categories: average risk, high-risk with RT short, and high-risk with RT long. All *P* values refer to two-sided tests and are deemed statistically significant if ≤0.05. Statistical analyses were performed using the R statistical package v3.5.

3 | RESULTS

We identified 4918 patients diagnosed with medulloblastoma from 2004 to 2014, which formed the initial data set. After applying the exclusion criteria previously described, 4,293 patients (the vast

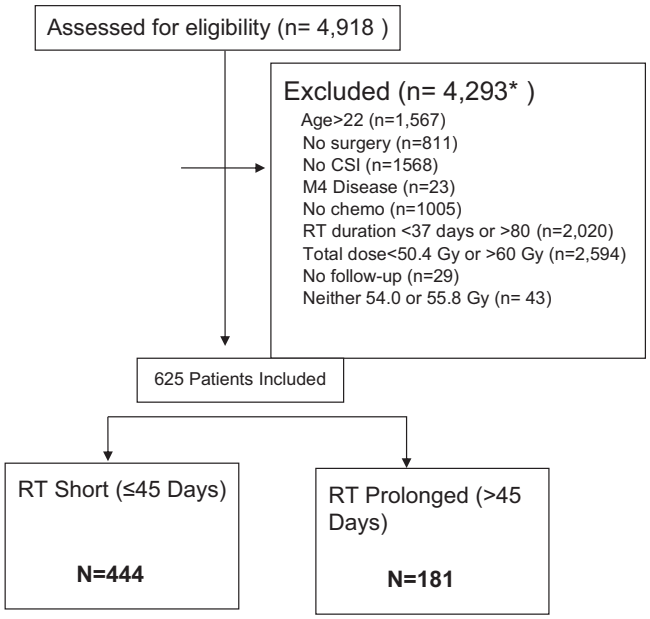

FIGURE 1 Flow diagram of patient selection

majority were under 21 years old) were removed from the analysis. Our final data set comprised 625 pediatric patients, of which 181 were assigned to the "RT long" (> 45 days) cohort (28.9%) and 444 (71.0%) to the "RT short" group (≤ 45 days). A flow diagram of the selection criteria is shown in Figure 1. The baseline pretreatment demographic, socioeconomic, and tumor characteristics are presented in Table 1.

The median OS among survivors ($n = 473$) was 6.8 years (0.23-13.0) and the median OS for the entire cohort was 7.1 years (0.23-13.0). The five-year OS for the entire cohort was 79.0% (Figure 2). The median time and range for RT completion was 44 days (38-80 days). The five-year OS for "RT short" compared with the "RT long" cohort was 82.2% versus 70.9%, respectively (Figure 2, HR: 1.62; $P = 0.0037$). For high-risk patients, the five-year OS for the "RT short" versus "RT long" was 77.7% versus 51.0% (Figure 3A; HR: 2.35; $P < 0.0001$), respectively. For patients with average risk medulloblastoma, there was no difference in survival with RT duration, with a five-year OS for the "RT short" compared with the "RT long" of 84.6% and 86.4%, respectively (Figure 3B; HR: 0.78; $P = 0.40$). The five-year OS was 67.6% versus 33.4% for "RT short" versus "RT long" for patients with PNETs (Figure 3C; HR: 2.71; $P = 0.002$). Similar to the effect of RT prolongation on OS among high-risk patients, among those diagnosed with a PNET, RT prolongation was associated with two times the rate of death compared with RT short (HR = 2.35 and HR = 2.7, respectively). A comparison of patient characteristics between the medulloblastoma and PNET cohort is shown in Supporting Information Table S1.

On univariate analysis, RT duration >45 days, PNET histology, higher total dose, and risk stratification were associated with inferior OS (Table 2; $P = 0.0037$, <0.0001, <0.0001, <0.0001, respectively). Interestingly, although non-white/other/unknown race was associated with prolonged RT duration compared with white race (Table 1), it did not significantly affect OS in the univariate analysis ($P = 0.43$).

For Cox modeling, variables fit in the multivariate model included RT duration, risk stratification (average vs high risk), histology (PNET vs non-PNET), M stage, total dose (55.8 vs 54.0), and race (white vs non-white/other/unknown). Both high-risk disease and RT prolongation was significantly associated with OS when controlling for the other characteristics (HR = 3.65; $P < 0.0001$). PNET histology was associated with one of the worst rates of OS (HR = 2.36; $P < 0.0001$). On univariate analysis, we found a significant interaction between RT duration and risk stratification on OS ($P < 0.0001$) and therefore combined risk stratification and duration into a single variable (Table 3). On multivariate analysis, we found that while patients who had high-risk disease had inferior OS regardless of short or prolonged RT duration (HR = 1.25; $P = 0.34$ and HR = 3.65; $P<0.0001$, respectively), those high-risk patients with prolonged RT (>45 days) had over three times risk of death compared with high-risk patients treated within 45 days.

A similar analysis was performed for RT duration >50 days. On univariate and multivariate analyses, RT duration greater 50 days was found to be associated with inferior OS for patients with high-risk disease (Supporting Information Tables S2 and S3).

We also investigated the impact of surgery to RT interval as a potential confounder. While surgery to RT interval >40 days was associated with inferior OS on univariate analysis (HR: 2.46, $P = 0.044$), this association was not seen in the multivariate model (Table 3, HR: 1.02, $P = 0.94$).

4 | DISCUSSION

The role of RT in medulloblastoma and other CNS PNET tumors has evolved over the last several decades but remains central to curing these tumors. Our analysis of multi-institutional data demonstrates the importance of keeping overall RT treatment time compressed in the setting of modern multimodality therapy for medulloblastoma and other CNS PNETs. In our study, we show that prolongation of radiation duration beyond 45 days is associated with a decrement in OS and that this finding is most pronounced in patients with high-risk medulloblastoma at diagnosis.

To our knowledge, this is the largest study to date to show the impact of RT duration on OS. This impact of RT duration on OS is consistent with previous evidence demonstrating the negative impact of RT prolongation on OS. Del Charco et al. have demonstrated that RT duration greater than 45 days was associated with both inferior local control and freedom from relapse at five years.[6] Another study by Paulino and colleagues demonstrated five-year freedom from progression of 67% versus 42% for RT duration <50 days and ≥50 days, respectively.[5] Back et al. performed a retrospective study of 189 pediatric medulloblastoma patients treated with adjuvant RT and noted that on multivariate analysis, RT duration was associated with relapse-free survival.[8] It should be noted that only a small proportion of patients received adjuvant chemotherapy in the Del Charco (21%) and Paulino (35%) studies, which may explain the relatively larger benefit of keeping RT duration short in that series. In the randomized PNET-3 study, which compared pre-RT chemotherapy versus RT

TABLE 1 Patient characteristics

		RT duration		
	All $N = 625$	RT prolonged (>45 days) $N = 181$	RT short (≤ 45 days) $N = 444$	*P*
Age in years	9 (1.0-21.0)	8 (1.0-21.0)	9 (1.0-21.0)	
≤3	52 (8.3%)	13 (7.2%)	39 (8.8%)	0.632
>3	573 (91.7%)	168 (92.8%)	405 (91.2%)	
Sex				0.47
Female	230 (36.8%)	71 (39.2%)	159 (35.8%)	
Male	395 (63.2%)	110 (60.8%)	285 (64.2%)	
Race				**<0.0001**[a]
Black	80 (12.8%)	33 (18.2%)	47 (10.6%)	
Other or unknown	52 (8.3%)	26 (14.4%)	26 (5.9%)	
White	493 (78.9%)	122 (67.4%)	371 (83.6%)	
Comorbidity score				0.38
0	583 (93.3%)	166 (91.7%)	417 (93.9%)	
1-4	42 (6.7%)	15 (8.3%)	27 (6.1%)	
Histology				0.12
Classic, NOS, or desmoplastic	542 (86.7%)	153 (84.5%)	389 (87.6%)	
Large cell or anaplastic	22 (3.5%)	4 (2.2%)	18 (4.1%)	
PNET	61 (9.8%)	24 (13.3%)	37 (8.3%)	
Risk stratification				**0.010**
Average risk	395 (63.2%)	100 (55.2%)	295 (66.4%)	
High risk	230 (36.8%)	81 (44.8%)	149 (33.6%)	
M stage[b]				0.29
M0	543 (86.9%)	156 (86.2%)	387 (87.2%)	
M1-M3	59 (9.4%)	21 (11.6%)	38 (8.6%)	
Total dose (Gy)				**<0.0001**
54.0	371 (59.4%)	85 (47.0%)	286 (64.4%)	
55.8	254 (40.6%)	96 (53.4%)	158 (35.6%)	

[a]Comparison made between those of non-white/other/unknown ($n = 132$) or white race.
[b]Missing $n = 23$ (3.7%).

alone, prolongation of RT >50 days was associated with inferior event-free survival (EFS) and OS on multivariate analysis, regardless of whether the patient received both chemotherapy and RT or RT alone after surgery.[7] In our study, we selected all patients who received chemotherapy, in an attempt to reduce any selection bias because that is the current standard of care in the pediatric population. RT duration still had a significant impact on OS, even in the presence of adjuvant chemotherapy. Several other recent large database studies have illuminated the important role of RT timing in medulloblastoma. Dressler et al. published a pattern of care study in the NCDB and demonstrated that RT had the greatest impact on OS for pediatric medulloblastoma.[9]

An intriguing finding in our study is that the benefit of keeping RT duration short was limited to the subset of patients with high-risk medulloblastoma and supratentorial PNETs. Although medulloblastoma is known to be a relatively radiosensitive tumor, the surviving fraction is thought to be 28% at 2 Gy.[10] Therefore, it could be hypothesized that repopulation of surviving clonogens, more likely to happen in those with high-risk patients due to more aggressive tumor biology and faster proliferation rate, could explain the importance of keeping the total RT duration as short as possible. This hypothesis is supported in the head and neck literature, where prolonged radiation treatment time has been associated with inferior OS in patients with squamous cell carcinoma.[11-13] This hypothesis is further supported by the survival decrement seen in the subgroup of patients with supratentorial PNET. Previously, a subgroup analysis of the PNET-3 study failed to show a statistically significant survival decrement to prolonged RT duration in supratentorial PNET patients.[14] However, there were only 62 patients with supratentorial PNET in the study and treatment was heterogeneous with some patients receiving both chemotherapy and RT and others receiving RT alone.

There are several limitations that must be acknowledged in this study. First, this is a retrospective study and therefore selection

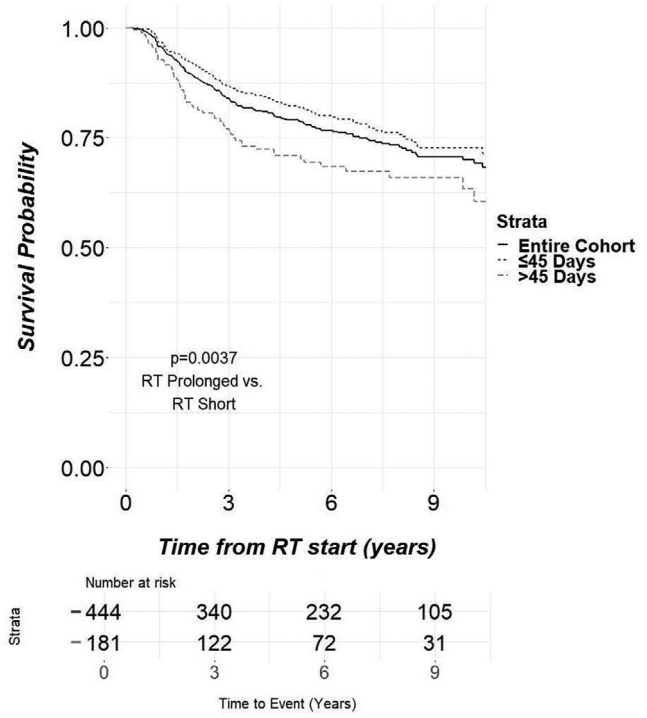

FIGURE 2 Overall survival for entire cohort and by RT duration

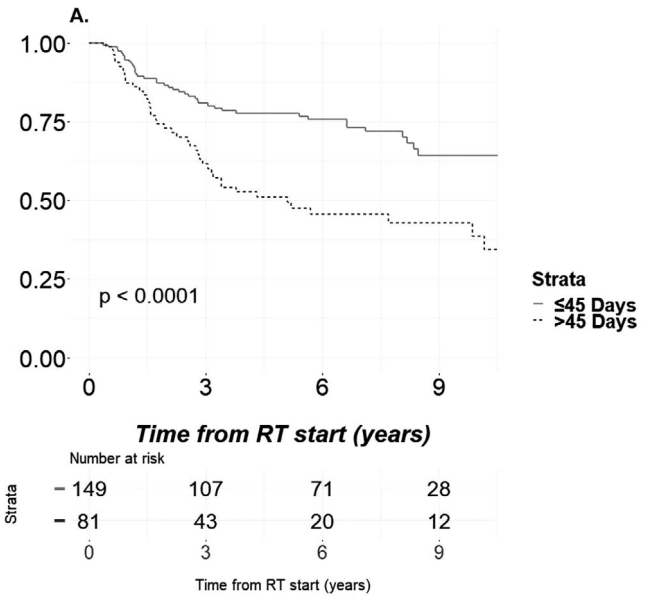

FIGURE 3 Overall survival by RT duration among subgroups: (A) high-risk patients, (B) average risk, and (C) PNETs

TABLE 2 Cox univariate analysis of clinical factors on overall survival

Patient characteristics	Deaths	HR	*P*
RT duration			
Continuous	152	1.04	0.064
Short (≤45 days)	96	1.0	
Prolonged (>45 days)	56	1.62	**0.0037**
Short (≤50 days)	138	1.0	
Prolonged (>50 days)	14	1.59	0.10
Age (years)			
Continuous	152	1.0	0.91
≤3	15	1.0	
>3	137	0.82	0.48
Sex			
Female	52	1.0	
Male	100	1.17	0.36
Race			
White	123	1.0	
Non-white/other/unknown	29	0.85	0.43
Comorbidity score			
0	142	1.0	
1 to 4	10	0.92	0.80
Histology			
Non-PNET	114	1.0	
PNET	38	2.65	<**0.0001**
Risk stratification			
Average risk	69	1.0	
High risk	83	2.42	<**0.0001**
M stage[a]			
M0	126	1.0	
M1-M3	20	1.56	0.062
Total dose (Gy)			
54.0	81	1.0	
55.8	71	1.39	**0.044**
Surgery to RT interval (days)[b]			
≤40 days	113	1.0	
>40 days	38	1.46	**0.044**

[a]Excludes 23 missing stage.
[b]Excludes 4 missing data.

bias could be a factor. For example, patients with a higher total dose would have a longer RT duration, and the dose and duration could be indicative of patients who had an incomplete resection or had more aggressive tumors. We attempted to control for this by excluding patients who had a total RT dose >55.8 Gy and placing total dose in our univariate and multivariate models. Next, specific details regarding the intensity of chemotherapy were unavailable, which could impact the outcomes between the two cohorts. Furthermore, extent of resection is another important risk factor that has been shown to impact OS in medulloblastoma.[15,16] Because a significant number of patients did not have extent of resection available, we were unable to assess this in the analysis. While multiple imputation is one method to address missing data, the validity of this approach is questionable when significant data are missing and works better when data are missing randomly across several predictors. Next, data regarding salvage

TABLE 3 Cox multivariate analysis regrouped with risk and RT duration

Variable	Deaths	HR (95% CI)	*P*
Surgery to RT interval (days)			
≤40	107		
>40	38	1.02 (0.68-1.51)	0.94
Histology			
Non-PNET	108		
PNET	37	2.36 (1.55-3.61)	**<0.0001**
Race			
White	116		
Non-white/other/unknown	29	0.87 (0.58-1.31)	0.50
Risk stratification and RT duration			
Average risk	67		
High risk + RT short	37	1.25 (0.78-2.0)	0.35
High risk + RT prolonged	41	3.63 (2.29-5.77)	**<0.0001**
M Stage			
M0	125		
M1-M3	20	1.18 (0.71-2.00)	0.52
Total dose (Gy)			
54.0	78		
55.8	67	0.86 (0.60-1.23)	0.40

therapies are not provided in the NCDB, which can also influence outcomes in the study cohorts. Another limitation is the relatively small number of CNS PNET patients (n = 83) that were analyzed in our study. It is now known that CNSPNETs are a heterogeneous group of tumors, which are now classified according to their molecular subtype, including C19MC-amplified embryonal tumor with multilayered rosettes (ETMR), AT/RT with SMARCB1 (INI1) alterations, and non-C19MC-altered medulloepithelioma, among others. The significant molecular heterogeneity of these tumors with the small number of patients in our study makes it difficult to generalize the impact of RT duration to any specific subgroup. Furthermore, given the retrospective nature of this database, outcomes related to specific subgrouping of medulloblastoma (WNT, SHH, group 3, and group 4) were not available for analysis. Finally, data entry errors exist in this database, and we made every effort to include only patients with data that appeared plausible to the current treatment paradigms. As shown in our selection criteria, 2,020 patients were excluded for RT time <37 days or >80 days. The large number of patients in this range raises concerns regarding the accuracy of the data in those patients. One potential hypothesis that could explain these outliers is if the interval from surgery to the start of RT or the interval of surgery to the end of RT was mistakenly recorded in those patients. If not accounted for, this subset of patients could potentially confound the results. Therefore, strict inclusion criteria were enforced and patients were excluded who had clear errors and whose radiation treatment dose did not conform to current modern standard-of-care guidelines. Strategies to eliminate database entry errors, including incorporation of artificial intelligence methods to improve data fidelity, should be explored in future studies. Notably, time of disease progression is not collected, and thus this analysis could only be performed on OS and not disease-free or EFS.

It is important to note that approximately 30% of patients required greater than 45 days to complete RT. Radiation oncologists in partnership with their pediatric oncology colleagues should be cognizant of RT delays and make every effort to avoid them, particularly in patients with high-risk features such as high-risk disease or unfavorable histology. In this data set, patients who had high-risk disease were more likely to have prolonged RT duration. This may be in part due to the higher dose of CSI, which may portend more frequent treatment breaks due to toxicity such as myelotoxicity, or it may be in part due to more toxic concurrent chemotherapy such as daily carboplatin. The treating radiation oncologist can consider alternate strategies to avoid RT delay, such as planning the boost portion of treatment upfront and delivering this if the child cannot tolerate CSI (due to myelotoxicity or length of treatment or other reason). This simply requires awareness of the importance of minimizing delays and preparing all phases of treatment upfront so that the treatment fields could be interchanged seamlessly. Careful coordination of care with a multidisciplinary team of pediatric oncologists, nurses, radiation oncologists, and surgeons is necessary in order to prevent RT interruptions and support patients through treatment. Close partnership with the pediatric oncology team is needed in order to manage hematologic toxicity with growth colony-stimulating factor or blood product transfusion support. This is especially important in patients with high-risk medulloblastoma receiving concurrent daily carboplatin, as per COG protocol ACNS 0332. Of note, the use of concurrent carboplatin should be discouraged in high-risk patients as there are data demonstrating no benefit in PNETs[17] and may add additional toxicity that could potentially introduce RT breaks. Finally, aggressive medical management of nausea, dehydration, and infectious complications is important to prevent potentially avoidable treatment delays.

In summary, this is the largest study to date to demonstrate the adverse impact of prolonged RT delivery (>45 days) on survival for patients with pediatric medulloblastoma and other PNETs. The data demonstrate that approximately 30% of patients are being treated with prolonged RT delivery, which is directly contributing to worse disease control and survival. RT breaks should be minimized to provide the best opportunity for long-term cure in this patient population. Careful multidisciplinary evaluation and discussion with pediatric oncology and surgery are critical in crafting strategies to minimize treatment delays.

DATA AVAILABILITY STATEMENT

The data are available through the National Cancer Database and can be requested from the CoC directly.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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