

## Research Letter

# Patterns of Care and Utilization Disparities in Proton Radiation Therapy for Pediatric Central Nervous System Malignancies



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## Abstract

**Purpose:** Proton radiation therapy (PR) is well established in the treatment of pediatric malignancies in the central nervous system (CNS) with dosimetric advantages that reduce late radiation therapy (RT) effects. In this analysis, we sought to evaluate the utilization of PR in children with primary CNS malignancies and characterize the clinical and sociodemographic factors predictive of receipt of PR.

**Methods and Materials:** The National Cancer Database was queried to identify all pediatric patients with primary CNS malignancies treated with curative intent RT from 2004 to 2017. Clinical characteristics and demographics were analyzed using standard *t* and  $\chi^2$  testing. Predictors of PR receipt were identified with univariable and multivariable logistic regression.

**Results:** We identified 9126 patients  $\leq 18$  years of age treated with RT between 2004 and 2017, of which 1045 (11.5%) received PR. PR usage continued to increase significantly, from  $<1\%$  in 2004 to 28% in 2017. The proportion of white and Asian patients receiving PR for nonhigh-grade glioma and nonmeningioma CNS malignancies during the study period rose from  $<1\%$  for both to 35% and 44%, respectively, and in black patients the proportion rose from  $<1\%$  to 26%. Multivariable predictors of receipt of PR include year of diagnosis, age  $<6$  years, income level, distance from PR facility, and histology; multivariable predictors of receipt of photon RT include black race, rural residence, and Medicaid insurance. These factors remained significant when isolating the most recent 5 years of data.

**Conclusions:** Proton radiation therapy usage for CNS malignancies increased significantly during the study period. Despite the potential clinical advantages of PR for pediatric primary CNS malignancies, there are notable socioeconomic, geographic, and racial disparities in the receipt of PR that persisted despite the increased availability and accessibility. Further study is warranted to identify how to address the disparities and better support these patients.

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## Introduction

Proton radiation therapy (PR) is well established in the treatment of pediatric primary central nervous system (CNS) malignancies, with known dosimetric advantages compared with traditional photon radiation and increasing retrospective evidence showing reduced risk of late

effects including cognitive decline and secondary malignancy.<sup>1-18</sup>

Prior publications have reported on national PR practice patterns, which were notable for racial and sociodemographic disparities in the application of proton therapy.<sup>19</sup> In the years since the most recent national level database analysis was published, the number of available proton therapy centers increased by about 200%.<sup>20,21</sup> In this analysis, we sought to evaluate the effect of increased availability and access to PR on patterns of care reported in a national level database.

## Methods and Materials

The National Cancer Database is a national level registry of deidentified patient clinical and sociodemographic data representing about 70% of cancer diagnoses and collected from about 1500 medical centers in the United States. We queried the database to identify all pediatric patients  $\leq 18$  years of age who received a primary diagnosis of CNS malignancy between 2004 and 2017. Patients were included for analysis if they received nonpalliative intent radiation therapy and were nonmetastatic at presentation. Additional clinical and sociodemographic data included tumor histology, radiation technique, year of diagnosis, age at diagnosis, race, ethnicity, insurance type, Charlson comorbidity index, distance from treatment facility, community type, and family income. Geographic region and type of treatment center (academic vs community) were unavailable as they are not coded for patients  $\leq 18$  years of age. Tumor histology was divided into low-grade glioma (LGG), high-grade glioma, ependymoma (EP), medulloblastoma (MB), primitive neuroectodermal tumor (PNET), craniopharyngioma (CPG), germ cell

tumors (GCT), meningioma, atypical teratoid or rhabdoid tumor (ATRT), and other.

Standard  $t$  and  $\chi^2$  testing were used to characterize clinical and sociodemographic differences between proton and photon groups. Univariable and multivariable logistic regression models were used to identify predictors of receipt of PR. A significance threshold was set at  $P < .05$  for all analyses. Statistical analysis was performed in STATA/IC-14.

## Results

We identified 9126 patients between the age of 0 and 18 years with primary CNS malignancies, of which 1045 (11.3%) received PR and 8081 (87.7%) received photons. The mean ages of patients receiving PR and non-PR were 8.1 and 9.2 years, respectively ( $P < .01$ ). Patients receiving PR were more likely to be  $\leq 5$  years of age ( $P < .01$ ), be treated after 2009 ( $P < .01$ ), be white ( $P < .01$ ), be privately insured ( $P < .01$ ), belong to a higher income bracket ( $P < .01$ ), live  $>50$  miles from the treatment center ( $P = .02$ ), reside in a metropolitan area ( $P < .01$ ), and have EP, MB, PNET, GCT, or ATRT tumor histology ( $P < .01$ ). Baseline characteristics between treatment groups are shown in Table 1.

The results of univariable and multivariable analysis of the entire patient cohort for the receipt of PR is shown in Table 2. Factors predictive of receipt of PR include age  $\leq 5$  years of age ( $P < .01$ ), year of diagnosis 2009 and later ( $P < .01$ ), income  $> \$35,000$ ,  $>50$ -mile distance from the treatment facility, and EP, MB, PNET, GCT, ATRT, and other histology (all  $P < .01$ ). CPG was not predictive of PR. Patients were less likely to receive PR if they were of the black race ( $P < .01$ ), had Medicaid insurance ( $P < .01$ ), and had an urban ( $P = .05$ ) or rural ( $P < .01$ )

**Table 1** Baseline patient characteristics

Characteristic	Photons, n (%)		Protons, n (%)		P value
Age, y					<.01
0-5	2279	28	373	29	
6-10	2519	31	339	31	
11-18	3283	41	333	32	
Year of diagnosis					<.01
2004-2008	3022	37	84	8	
2009-2012	2411	30	231	22	
2013-2017	2648	33	730	70	
Race					<.01
White	6189	77	794	76	
Black	1079	13	68	7	

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**Table 1** (Continued)

Characteristic	Photons, n (%)		Protons, n (%)		P value
Asian	329	4	50	5	
Native American/Eskimo	55	1	10	1	
Native HI/Pacific Islander	20	<1	4	<1	
Other/unknown	409	5	119	11	
Ethnicity					.81
Non-Hispanic/unreported	6820	85	878	86	
Hispanic white	1136	14	141	14	
Hispanic black	32	<1	3	<1	
Insurance status					<.01
Privately insured	4734	63	702	72	
Medicaid	2768	37	276	28	
Charlson comorbidity index					.18
0	7407	92	977	93	
1	359	4	39	4	
2	245	3	22	2	
3 +	70	1	7	1	
Income (\$)					<.01
<30,000	1049	15	76	8	
30,000-34,999	1256	17	116	12	
35,000-45,999	2025	28	284	31	
46,000 +	2892	40	450	49	
Distance from treatment, miles					0.02
<50	5349	72	643	67	
51-200	1733	23	255	27	
>200	391	5	59	6	
Community type					<.01
Metro	6413	83	892	90	
Urban	853	11	72	7	
Rural	485	6	27	3	
Histology					<.01
Low-grade glioma	1862	24	114	11	
High-grade glioma	1803	23	99	10	
Ependymoma	1034	13	239	23	
Medulloblastoma	1967	25	379	37	
PNET	286	4	40	4	
Craniopharyngioma	59	1	9	1	
Germ cell tumors	350	4	59	6	
Meningioma	119	2	11	1	
ATRT	203	3	51	5	
Other	153	2	28	3	

Abbreviations: ATRT = atypical teratoid/rhabdoid tumor; HI = Hawaiian Islander; PNET = primitive neuroectodermal tumor.

**Table 2 Predictors of receipt of proton radiation therapy**

Predictor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age, y						
0-5	1.6	1.4-1.9	<.01	1.3	1.1-1.6	.01
6-10	1.3	1.1-1.6	<.01	1.1	0.9-1.4	.31
11-18	-	-	-	-	-	-
Year of diagnosis						
2004-2008	-	-	-	-	-	-
2009-2012	3.5	2.7-4.5	<.01	4.2	3.2-5.7	<.01
2013-2017	10	7.9-13	<.01	11	8.5-15	<.01
Race						
White	-	-	-	-	-	-
Black	0.48	0.38-0.63	<.01	0.62	0.45-0.85	<.01
Asian	1.2	0.87-1.6	.28	1.1	0.77-1.6	.56
Native American/Eskimo	1.4	0.72-2.8	.31	1.4	0.54-3.4	.52
Native HI/Pacific Islander	1.6	0.53-4.6	.42	1.8	0.55-6.1	.33
Other/unknown	2.3	1.8-2.8	<.01	2.3	1.7-3.1	<.01
Ethnicity						
Non-Hispanic/unreported	-	-	-	-	-	-
Hispanic white	0.96	0.80-1.2	.70	1.0	0.80-1.3	.83
Hispanic black	0.73	0.22-2.4	.60	0.63	0.08-5.0	.66
Insurance status						
Privately insured	-	-	-	-	-	-
Medicaid	0.67	0.58-0.78	<.01	0.62	0.51-0.75	<.01
Charlson comorbidity index						
0	-	-	-	-	-	-
1	0.82	0.59-1.2	.26	0.70	0.45-1.1	.10
2	0.68	0.44-1.1	.09	0.90	0.52-1.5	.68
3 +	0.76	0.35-1.7	.49	1.0	0.38-2.6	.98
Income (\$)						
<30,000	-	-	-	-	-	-
30,000-34,999	1.3	0.94-1.7	.11	1.1	0.75-1.5	.74
35,000-45,999	1.9	1.5-2.5	<.01	1.5	1.1-2.0	.02
46,000 +	2.2	1.7-2.8	<.01	1.6	1.2-2.3	.01
Distance from treatment, miles						
<50	-	-	-	-	-	-
51-200	1.2	1.1-1.4	<.01	1.4	1.2-1.8	<.01
>200	1.3	0.94-1.7	.12	1.6	1.1-2.5	.02
Community type						
Metro	-	-	-	-	-	-
Urban	0.61	0.47-0.78	<.01	0.72	0.53-0.99	.05
Rural	0.4	0.27-0.59	<.01	0.47	0.29-0.75	<.01

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**Table 2** (Continued)

Predictor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Histology						
Low-grade glioma	-	-	-	-	-	-
High-grade glioma	0.9	0.68-1.2	.44	0.82	0.59-1.2	.25
Ependymoma	3.8	3.0-4.8	<.01	3.9	2.9-5.2	<.01
Medulloblastoma	3.2	2.5-3.9	<.01	3.6	2.8-4.7	<.01
PNET	2.3	1.6-3.3	<.01	3.3	2.1-5.2	<.01
Craniopharyngioma	2.5	1.2-5.2	.01	1.9	0.72-5.3	.19
Germ cell tumors	2.8	2.0-3.9	<.01	3.4	2.2-5.0	<.01
Meningioma	1.5	0.79-2.9	.21	2.0	0.95-4.0	.07
ATRT	4.1	2.9-5.9	<.01	3.7	2.3-5.7	<.01
Other	3.0	1.9-4.7	<.01	3.6	2.1-6.2	<.01

Abbreviations: ATRT = atypical teratoid/rhabdoid tumor; CI = confidence interval; HI = Hawaiian Islander; PNET = primitive neuroectodermal tumor.

residence. The same factors remained significantly predictive if we restricted analysis to the most recent 5 years of data.

We performed a subset multivariable analysis for receipt of PR isolating histologies for which data support PR, including LGG, EP, MB, PNET, CPG, GCT, and ATRT (n = 6652), as shown in Table 3. The factors predictive of receipt or nonreceipt of PR were identical to those of the entire cohort, with the exception of urban residence no longer being significant.

Isolating patients with EP only (n = 1273), multivariable logistic regression demonstrated that Asian race was

predictive of receipt of PR (hazard ratio [HR], 2.79; P = .01), and predictors of nonreceipt included black race (HR, 0.44; P = .04) and Medicaid insurance (HR, 0.50; P <.01). For patients with MB (n = 2346), black race was no longer a significant predictor of PR use, although higher income levels (HR, 1.88; P = .04) and Medicaid insurance (HR, 0.60; P <.01) remained significant.

During the study period, the proportion of pediatric patients receiving PR increased from <1% in 2004 to 28% in 2017. Among the group of patients with LGG, EP, MB, PNET, GCT, and ATRT, that proportion increased from 1% to 44% during the same period, with 45% of EP and

**Table 3** Predictors of receipt of proton therapy limited to LGG, EP, MB, PNET, CPG, GCT, and ATRT

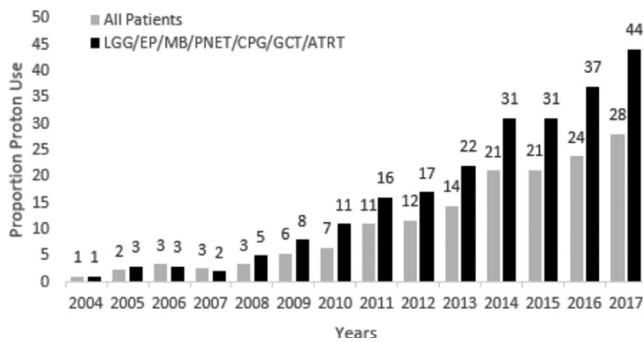
Predictor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age, y						
0-5	1.3	1.1-1.6	<.01	1.3	1.1-1.7	<.01
6-10	1.2	1.01-1.4	.04	1.2	0.9-1.5	.21
11-18	-	-	-	-	-	-
Year of diagnosis						
2004-2008	-	-	-	-	-	-
2009-2012	4.3	3.2-5.8	<.01	5.0	3.6-6.8	<.01
2013-2017	13	10-17	<.01	13	9.7-17.8	<.01
Race						
White	-	-	-	-	-	-

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Table 3 (Continued)

Predictor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Black	0.48	0.36-.63	<.01	0.63	0.45-0.90	.01
Asian	1.3	0.95-1.8	.10	1.2	0.84-1.8	.29
Native American/Eskimo	1.6	0.80-3.2	.19	1.5	0.58-3.9	.41
Native HI/Pacific Islander	1.6	0.46-5.8	.45	1.6	0.40-6.6	.50
Other/unknown	2.2	1.7-2.8	<.01	2.1	1.9-4.0	<.01
Ethnicity						
Non-Hispanic/unreported	-	-	-	-	-	-
Hispanic white	0.87	0.71-1.1	.20	0.94	0.71-1.2	.66
Hispanic black	0.56	0.13-2.4	.43	0.70	0.08-5.8	.74
Insurance status						
Privately insured	-	-	-	-	-	-
Medicaid	0.66	0.56-0.78	<.01	0.62	0.50-0.76	<.01
Charlson comorbidity index						
0	-	-	-	-	-	-
1	0.84	0.58-1.2	.34	0.72	0.45-1.2	.18
2	0.85	0.51-1.4	.53	0.90	0.46-1.7	.74
3 +	1.2	0.49-2.8	.73	1.5	0.54-4.3	.42
Income (\$)						
<30,000	-	-	-	-	-	-
30,000-34,999	1.3	0.94-1.9	.10	1.2	0.80-1.8	.40
35,000-45,999	2.1	1.6-2.8	<.01	1.7	1.2-2.4	.01
46,000 +	2.4	1.8-3.2	<.01	1.9	1.3-2.7	<.01
Distance from treatment, miles						
<50	-	-	-	-	-	-
51-200	1.26	1.06-1.49	.01	1.6	1.3-2.0	<.01
>200	1.35	0.98-1.87	.07	1.7	1.1-2.7	.02
Community type						
Metro	-	-	-	-	-	-
Urban	0.65	0.50-0.85	<.01	0.76	0.54-1.1	.11
Rural	0.40	0.26-0.61	<.01	0.46	0.27-0.78	<.01
Histology						
Low-grade glioma	-	-	-	-	-	-
Ependymoma	3.8	3.0-4.8	<.01	3.9	2.9-5.2	<.01
Medulloblastoma	3.2	2.5-3.9	<.01	3.6	2.8-4.7	<.01
PNET	2.3	1.6-3.3	<.01	3.3	2.1-5.3	<.01
Craniopharyngioma	2.5	1.2-5.2	.01	1.9	0.70-5.2	.21
Germ cell tumors	2.8	2.0-3.9	<.01	3.4	2.2-5.1	<.01
ATRT	4.1	2.9-5.9	<.01	3.7	2.4-5.8	<.01

Abbreviations: ATRT = atypical teratoid/rhabdoid tumor; CI = confidence interval; EP = ependymoma; CPG = craniopharyngioma; GCT = germ cell tumors; HI = Hawaiian Islander; LGG = low-grade glioma; MB = medulloblastoma; PNET = primitive neuroectodermal tumor.



**Figure 1** Proportion of pediatric patients receiving proton therapy by year. Gray bars show entire patient cohort and black bars show cohort limited to patients with LGG, EP, MB, PNET, CPG, GCT, and ATRT. *Abbreviations:* ATRT = atypical teratoid/rhabdoid tumor; EP = ependymoma; CPG = cranio-pharyngioma; GCT = germ cell tumors; LGG = low-grade glioma; MB = medulloblastoma; PNET = primitive neuroectodermal tumor.

47% of patients with MB receiving PR in 2017 (Fig. 1). The proportion of white and Asian patients receiving PR for LGG, EP, MB, PNET, GCT, and ATRT during the study period rose from <1% for both to 35% and 44%, respectively, and in black patients the proportion rose from <1% to 26%. Mean proportion of white, Asian, and black patients receiving PR across the study period was 14%, 15%, and 7%, respectively.

## Discussion

In this report, we have detailed the national level practice patterns of PR in the treatment of pediatric primary CNS malignancies. Higher income levels, private insurance, greater distance from the treatment facility, nonrural residence, and nonblack race were independent predictors of receipt of PR on multivariable analysis.

Expectedly, PR usage has expanded significantly in recent years, with around a quarter of all reported pediatric patients with CNS receiving PR in 2016 and 2017, including nearly half of all patients with EP and MB. This finding is in concert with the increased number and improved geographic distribution of PR centers across the United States and may have been influenced by reports on reduced rates of late cognitive decline, slowing of processing speed, and secondary malignancies that were published during the study period.<sup>13-15,20</sup>

Unfortunately, there continues to be a statistically significant deficit in PR usage for patients who are black, live in rural areas, and have Medicaid insurance. Although the cost-effectiveness for the health care system of PR for pediatric CNS malignancies has been studied, it may still be that insurance coverage and travel and housing costs for the patient may be a deterrent, as the majority of proton patients in this cohort traveled >50 miles for

treatment.<sup>22-24</sup> When isolating the most recent 5 years of data, the same predictors were significant, suggesting that there has not been an improvement in the racial and socioeconomic disparities in PR use. This is especially concerning when a recent SEER analysis demonstrated that black children with CNS malignancies have worse survival compared with matched white, non-Hispanic children.<sup>25</sup> More study is needed to determine why these disparities in utilization have persisted and how we can better support patients who are black, from lower socioeconomic groups, or geographically isolated to ensure they have equal access to best care practices.

Although the proportion of pediatric patients receiving PR for CNS malignancies has greatly increased over time owing to the increased number and wider distribution of PR centers, there continue to be disparities in access, with patients who are nonblack, privately insured, or from higher-income households being more likely to receive PR. Given the increasing data showing important late toxicity benefits to PR compared with photon radiation therapy, our field needs to address how to improve PR accessibility for all families.

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