LETTER TO THE EDITOR

Underutilization of proton therapy in the treatment of pediatric central nervous system tumors: an analysis of the National Cancer Database

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Radiotherapy (RT) is a mainstay in the treatment of pediatric brain and spinal cord tumors. Indications for RT include the histological type, the extent of the tumor at diagnosis and/or post-operatively, the availability and utilization of chemotherapy regimens, and the age of the child. The sequelae of RT on the developing CNS have been well-described, and it is typically avoided in children under the age of 3. RT is most commonly delivered by fractionated external beam radiotherapy, which includes the modalities of 2D radiotherapy (2DRT), 3D conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) and proton therapy. Each of these techniques can be considered an improvement on the prior in terms of how precisely the radiotherapy is delivered to the target volume. More conformal radiotherapy techniques result in lower doses to the sensitive surrounding normal tissues, and lower late effects of RT.

In the Childhood Cancer Survivor Study, over 80% of 5-year survivors had at least one chronic morbidity, and had higher rates of endocrine disorders, hearing deficits and neurological issues compared with siblings [1]. Moreover, cranial RT was associated with higher risks of cognitive impairment and secondary malignancy. Children who received cranial RT doses over 50 Gy had a 7% risk of in-field second malignancy. Cognitive impairment was proportion to the doses used for specific tumor types, and dose of RT to the frontal and temporal lobes was associated with lower rates of employment and marriage.

Proton therapy can reduce the dose to normal tissues because these heavy particles have unique physical properties resulting in a very different dose profile in tissue. Protons can penetrate the body to a specific depth, based on their initial energy, and then deposit dose in a sharp, discrete peak with no additional dose in the exit path. These unique beams can dramatically change how radiation dose falls off into normal tissues. There are already a few reports that have demonstrated the superiority of protons relative to photons in vulnerable pediatric populations [2–5]. In general, the radiation oncology community, as well as stakeholders among payors and policy makers, agree that pediatric solid tumors, and specifically pediatric CNS tumors, are ideal indications for the use of protons [4,5]. While proton therapy centers are still uncommon, the accessibility of proton therapy has been expanding geographically.

In this report, we used the National Cancer Database (NCDB) to study the patterns of utilization of different radiotherapy techniques for the treatment of pediatric CNS malignancies. Our hypothesis was that utilization of proton therapy has increased significantly over the past 10 years. As secondary endpoints, we examined the relationship between clinical and sociodemographic parameters, with use of advanced RT modality, and overall survival. We also examined the trends of IMRT utilization from 1998 to 2011.

Methods

Data source/patients

The National Cancer Database (NCDB), a national hospital-based oncology database, was used to conduct a retrospective, cohort study of pediatric patients diagnosed from 2004 through 2013 in the U.S. Variables captured include basic demographics, socioeconomic characteristics, cancer staging, treatment course and vital status. This study period reflected a time during which inclusion of radiotherapy was an accepted standard treatment for various CNS malignancies.

From 2004 to 2013, there are 18,686 pediatric patients with brain tumors within the NCDB. Only patients within the age range of 0–18 years, histologic diagnosis of primary CNS malignancies, and receipt of known radiation therapy modality were included. Patients were excluded if they were >18 years of age ($n = 1530$), were not coded to be in receipt of 2D/3D-CRT or IMRT ($n = 15{,}013$), or did not have a diagnosis of primary CNS malignancy ($n = 80$). For purposes of minimizing confounding effects from all known covariates, we also excluded patients with any missing data points in all clinicopathologic parameters of interest ($n = 1609$). With the above inclusion criteria, the study analysis was limited to 454 patients.

Study variables

Our variable of main interest was modality of radiation therapy (RT) utilized. This parameter was grouped into 2D/3D-

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CRT, IMRT and Proton therapy. Demographic and clinical data included gender, race/ethnicity (white, black or other), age (<3 vs. ≥3), indicators of median household income, insurance status (categorized as private, Medicare, Medicaid or uninsured), Charlson-Deyo Co-morbidity Score (CDCS) (categorized 0, 1 and 2+), distance from facility (classified as <12.5 miles, 12.5–50 miles, ≥50 miles) and vital status. Treatment facility type (categorized as Community Cancer Program, Comprehensive Community Cancer Program and Academic/Research Program [including NCI-designated Comprehensive Cancer Centers]) and geographic region (categorized into 9 predefined regions) were not available for analysis per the NCDB data use guidelines.

Using chi-square tests, we assessed the association of RT modality with age, gender, race, socioeconomic status (household income), insurance status, distance from facility, presence of and CDCS. A multivariable logistic regression model was used to identify independent determinants of the use of proton therapy.

Results

Descriptive statistics

The analysis examined 454 pediatric patients with primary CNS malignancies who met inclusion criteria. Median age was 12 years (range: 0–18); 55.5% were male and 44.5% were female. Table 1 summarizes patient clinicopathologic characteristics by RT modality. The RT modalities used were the following: PT ($n = 37$, 8.2%) and non-PT ($n = 417$, 91.8%). All patients received RT; the median dose was 50.4 Gy (similar for both IMRT and PT group).

As seen in Table 1, majorities of patients were white (79.5%), young age (<3 years) (93.4%), low CDCS (92.3%), higher annual income level (>$46,000, 41.6%), moderate distance to treatment facility (12.5–49.9 miles, 39.7%) and favorable insurance status (66.1%). The histologies treated were the following: ependymoma (21.7%), meningioma (17.1%), medulloblastoma (8.0%), glioblastoma (8.0%), neuronal/mixed tumors (9.4%), astrocytomas (21.2%), oligodendroglioma (0.5%), malignant glioma NOS (8.3%) and nerve sheath tumors (5.9%).

As depicted in the multivariate odds ratio adjustments in Table 2, patients were more likely to receive PT if they were of male gender (OR = 1.89, 95% CI: 1.19–2.94; $p < .01$), younger age (OR = 6.2, 95% CI: 2.32–16.55; $p < .01$), from zip codes with higher median household incomes (OR = 1.24, 95% CI: 0.58–2.65; $p = .58$), those with private insurance (OR = 6.57, 95% CI: 0.89–48.24; $p = .06$), and those traveling ≥50 miles from the treatment facility (OR = 2.38, 95% CI: 1.31–4.32; $p < .01$).

Utilization of advanced RT modalities

During this study time period from 2004 to 2013, there was a significant decrease in use of 2D/3D-CRT from 91.2% to 47.8%, with a subsequent increase in IMRT utilization from 5.9% to 39.1% and increase in PT utilization from 2.9% to 13.0% (Figures 1 and 2).

Discussion

Our analysis of the NCDB has demonstrated increasing utilization of the highly conformal techniques of IMRT and

Table 1. Clinicopathologic parameters by use of proton therapy (versus non-proton therapy).

		RT modality		
Parameter	All patients, *N* (%)	Non-proton therapy *N*/%	Proton therapy *N*/%	*p* Value
Overall	454	417	37	n/a
Gender				.87
Male	252	231	21	
Female	202	186	16	
Race				.79
White	361	330	31	
Black	60	56	4	
Other	33	31	2	
Age (years)				<.01[a]
<3	424	394	30	
3+	30	23	7	
Charlson-Deyo Co-morbidity Score				.86
0	419	384	35	
1	17	16	1	
2+	18	17	1	
Insurance status				.04[a]
Uninsured or Medicaid	148	141	7	
Private insurance/Other	289	259	30	
Median household income (pt's zip code)				.04[a]
<$30,000	56	52	4	
$30,000–35,999	67	67	0	
$36,000–45,999	134	120	14	
≥$46,000	183	164	19	
Distance from facility				.01[a]
<12.5 miles	132	125	7	
12.5–49.9 miles	180	157	23	
≥50 miles	142	135	7	

[a]Statistically significant.

Table 2. Correlates for receipt of proton therapy.

	OR	Lower 95% CI	Upper 95% CI	*p* Value
Gender				
Male	1.00 (Ref.)			
Female	0.53	0.34	0.84	<.01[a]
Race				
White	1.00 (Ref.)			
Black	0.65	0.28	1.49	.31
Other	0.93	0.43	2.00	.85
Age (years)				
3+	1.00 (Ref.)			
<3	6.20	2.32	16.55	<.01[a]
Charlson-Deyo Co-morbidity Score				
0	1.00 (Ref.)			
1	0.86	0.33	2.20	.75
2+	0.47	0.11	2.02	.31
Insurance status				
Private insurance	6.57	0.89	48.24	.06[a]
Medicaid	5.64	0.73	43.79	.10
Medicare	3.82	0.33	43.97	.28
Median household income (pt's zip code)				
<$30,000	1.00 (Ref.)			
$30,000–$35,999	0.17	0.05	0.64	<.01[a]
$36,000–$45,999	0.97	0.45	2.12	.95
$46,000+	1.24	0.58	2.65	.58
Distance from facility				
<12.5 miles	1.00 (Ref.)			
12.5–49.9 miles	1.61	0.93	2.78	.09
≥50 miles	2.38	1.31	4.32	<.01[a]

OR: odds ratio.
[a]Statistically significant.

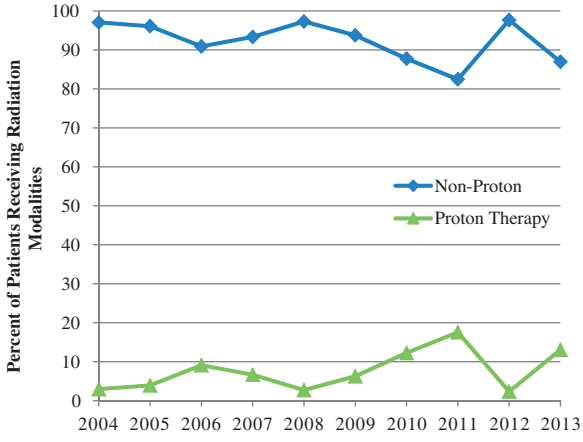

Figure 1. Percentage of pediatric CNS patients undergoing proton therapy and non-proton therapy, between 2004 and 2013, by year of diagnosis.

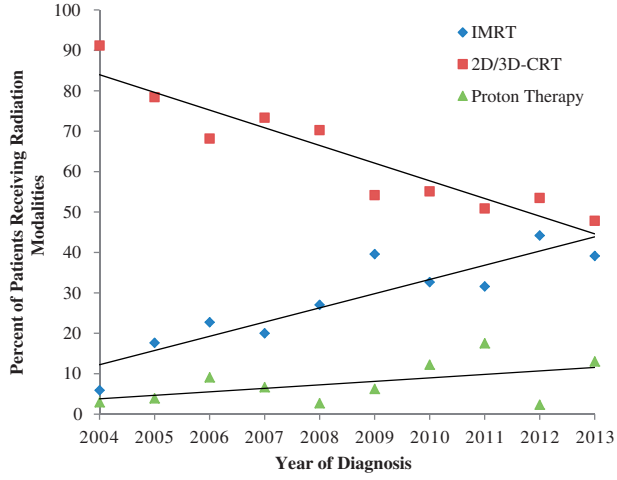

Figure 2. National trends in the use of 3D-CRT, IMRT, and proton therapy from 2004 to 2013, by year of diagnosis. During this study time period from 2004 to 2013, there was a significant decrease in use of 2D/3D-CRT from 91.2% to 47.8%, with a subsequent increase in IMRT utilization from 5.9% to 39.1% and increase in PT utilization from 2.9% to 13.0%.

proton RT in patients with CNS tumors receiving radiotherapy. However, there continues to be dramatic under-utilization of proton radiotherapy in this population. Pediatric CNS malignancies are a well-accepted indication for proton therapy. The American Society of Radiation Oncology (ASTRO) includes all pediatric solid malignancies in its model policy for payor coverage [5]. Among payers, federal and private agencies alike offer coverage for pediatric CNS malignancies. Until recently, some payers specifically included pediatric CNS malignancies on their coverage policies even while excluding other pediatric malignancies. Thus as a society, all stakeholders appear to have reached early consensus on the value of proton therapy when irradiating intracranial targets in children. This consensus can be ascribed to (1) the well-described, unintended risks of low-dose RT on the developing brain (2) studies that have demonstrated the dosimetric superiority of proton beam RT compared with photon techniques and (3) early clinical data supporting improved clinical outcomes with proton therapy relative to photon-treated children.

For example, Zhang et al compared the risks of second malignancy and cardiac mortality in a cohort of pediatric medulloblastoma patients ($n = 17$) [6]. Standard proton (passively scattered) or photon (field-in-field) craniospinal irradiation (CSI) plans were created in a commercially available treatment planning system. This study demonstrated that the ratios of lifetime attributable risk (RLARs)

(proton/photon) demonstrated significantly lower risks with proton compared with photons. (RLAR of 0.10–0.22) for second malignancy and ran 0.20–0.53 for second cancer mortality, respectively. Similarly, reductions were seen in the cardiac mortality risks with protons. Merchant et al compared photon and proton plans in 40 patients with optic pathway glioma, craniopharyngioma, infratentorial ependymoma or medulloblastoma (10 patients each) [7]. These data suggested that protons resulted in lower doses to organs at risk such as the cochlea and hypothalamus when not adjacent to the primary tumor volume. Likewise, larger OARs (e.g., supratentorial brain or temporal lobes) received less incidental RT in the low and intermediate dose ranges. These differences in physical dose were then applied to longitudinal models of cognitive effects after RT. Proton RT was associated with higher IQ scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma.

Clinical data on the benefit of protons are accumulating. Among the best data is the report from Chung and Yock in which the authors matched 588 patients treated with protons at the Harvard cyclotron from 1973 to 2001 to 588 patients treated with photon therapy from the Surveillance, Epidemiology and End Results Program [2]. Controls were matched for age, gender, year of treatment, cancer histology and treatment site. The primary outcome was the incidence of second malignancy. With a median follow-up time was 6.7 years for proton patients and 6.0 years for photon patients, the rate of second malignancies was 5.2% among the proton cohort (29 patients) vs. 7.5% in photon cohort (42 patients). On multivariate analysis adjusting for confounders, treatment with proton therapy was associated with a decreased risk of second malignancy [adjusted hazard ratio, 0.52 (95% confidence interval, 0.32–0.85), $p = .009$] when compared with photon therapy.

Given the findings from our data, it is tempting to speculate on the reasons behind the significant underutilization of proton therapy for pediatric CNS tumors. In our estimation, the most plausible explanation is also the simplest: access to care. There are currently too few proton therapy centers, making travel to a center impossible for most families. Due to the prohibitive cost of proton therapy, the current delivery model consists of large, multi-room centers that consolidate care in metropolitan tertiary care centers that can build these centers. This model of delivery may be failing many patients, children and adults, who are likely to benefit from charged particle therapy. Now that less expensive systems are available in the market, the installation of smaller units in less densely populated areas of the United States may help improve access to this modality.

Ethics approval

This research involved analysis of de-identified patient data from the NCDB and was deemed to have Institution Review Board exemption.

Availability of data and materials

The data used in the study are derived from a de-identified NCDB file after applying for access through an open application process. The ACS/CoC are not responsible for the analytic methodology employed. Authors had full access to all of the data in the study and take responsibility for the accuracy of the data analysis.

Disclosure statement

There are no disclosures or conflicts of interest to report.

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