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Original article

Quality of life outcomes in proton and photon treated pediatric brain tumor survivors

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ABSTRACT

Background: Radiotherapy can impair Health Related Quality of Life (HRQoL) in survivors of childhood brain tumors, but proton radiotherapy (PRT) may mitigate this effect. This study compares HRQoL in PRT and photon (XRT) pediatric brain tumor survivors.
Methods: HRQoL data were prospectively collected on PRT-treated patients aged 2–18 treated at Massachusetts General Hospital (MGH). Cross-sectional PedsQL data from XRT treated Lucile Packard Children's Hospital (LPCH) patients provided the comparison data.
Results: Parent proxy HRQoL scores were reported at 3 years for the PRT cohort (PRT-C) and 2.9 years (median) for the XRT cohort (XRT-C). The total core HRQoL score for the PRT-C, XRT-C, and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively ($p = 0.002$; $p = 0.024$; $p < 0.001$). The PRT-C scored 10.3 and 10.5 points higher than the XRT-C in the physical (PhSD) and psychosocial (PsSD) summary domains of the total core score (TCS, $p = 0.015$; $p = 0.001$). The PRT-C showed no difference in PhSD compared with the normative population, but scored 6.1 points less in the PsSD ($p = 0.003$). Compared to healthy controls, the XRT-C scored lower in all domains ($p < 0.001$).
Conclusions: The HRQoL of pediatric brain tumor survivors treated with PRT compare favorably to those treated with XRT and similar to healthy controls in the PhSD.
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Although radiotherapy is an essential part of treatment for many pediatric brain tumor patients, it is also known to contribute to late side effects in survivors [1]. These late health effects are due, in part, to the radiation of uninvolved tissues in the beam path that can negatively affect normal development and function. Some of these late effects include neurocognitive or behavioral effects, endocrine abnormalities, vascular effects [2–4], and second tumors. The severity of radiation-related late morbidities is associated with younger age at treatment, higher doses of radiation and larger volumes of normal tissue receiving significant radiation dose [5–7]. These late effects are associated with lower direct and indirect measures of Health-Related Quality of Life (HRQoL) [3,8–12]. Proton radiotherapy can deliver less radiation dose to normal tissues than photon radiotherapy, because of the underlying physics intrinsic to its dose deposition and when compared with external beam photon techniques [13,7,14–16]. Because of the dose sparing to normal tissues, it has been widely hypothesized that the lower radiation dose to normal tissue may reduce the incidence and/or severity of late effects [17].

Growing evidence has begun to document the health outcome benefit of proton radiotherapy in the pediatric cancer population [15,18,19]. However, it is important to determine whether these health benefits translate into improved HRQoL. Thus, this study compares HRQoL outcomes in proton and photon treated cohorts [20].

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Methods

HRQoL data on proton cohort

Primary prospective HRQoL data were collected on pediatric brain tumor patients and survivors treated with proton therapy at MGH after approval by the MGH Institutional Review Board (IRB). All study subjects were recruited while receiving proton therapy at MGH and provided informed consent. Children between the ages of 2–18 and their parents were initially surveyed during treatment and then annually thereafter. All patients were assessed through parent-proxy report versions (PPR, for children age 2 and up) of the PedsQL Core Module [21–24]. Detailed methodology for this cohort was previously published [20]. In this study, the median year of radiation treatment was 2007 with the interquartile range (IQR) of 2006–2007.

HRQoL data photon (XRT) cohort

At the time of embarking on this analysis, three published studies used the same PedsQL tool to assess HRQoL outcomes in pediatric brain tumor patients [9,25,26]. However, only one study had sufficient numbers, a comparable time period to our study, and adequate clinical detail to merit comparison [25]. This resultant study is a collaborative effort between Harvard-affiliated Massachusetts General Hospital (MGH) investigators and Stanford-affiliated Lucile Packard Children's Hospital (LPCH) investigators in Palo Alto, California.

LPCH is a large, tertiary referral center and a highly regarded center of excellence in pediatric and radiation oncology. The LPCH data are derived from an IRB approved cross-sectional study administered to consenting patients and/or families in their routine follow up clinic from November 2001 to September 2002. The median radiation treatment year was 2000 (IQR: 1998–2001).

The PedsQL was administered to 134 brain tumor survivors who were 1–21 years of age at the time of treatment, 63 of whom had received *photon* radiation, completed the parent proxy-reported PedsQL, and were 2–18 years old at the time of treatment. Study recruits were assessed with the standard PPR version. Socioeconomic status (SES) indicators were not collected or analyzed in this cohort.

PedsQL survey instrument

The PedsQL is a commonly used and previously validated assessment of HRQoL for general populations of children as well as children with chronic health conditions. The PedsQL survey results in a score with a range from 0 to 100, with 100 representing the best quality of life. PedsQL total scores are computed and are divided into two major sub domains, physical summary score and the psychosocial summary score. The psychosocial summary score is further sub divided into 3 parts, emotional functioning, social functioning and school functioning, which are also reported here [21].

Statistical analysis

Patient demographics and basic clinical data are reported in Table 1. Fisher's exact test was used to compare the distribution of patient characteristics between the MGH and LPCH cohorts. Overall PedsQL scores and subscale scores for the two cohorts and normative population are shown in Table 2. PedsQL scores were further reported by diagnosis category (Table 3): medulloblastoma/PNET (M/PNET), ependymoma/high-grade glioma/(E/HGG), low-grade glioma (LGG), and germ cell tumors (GCT). Figures for other low-grade neoplasm (LGN) are shown but, due to small sample size, should be interpreted with caution. Mean scores for the core module, including its subscales, are reported. Core scores from Tables 2 and 3 are graphically represented in Fig. 1a and b.

Two-sample t-tests were used to determine if the scores from the two cohorts were significantly different, while a one-sample test was used to compare the scores from each cohort to those from a normative pediatric population [27]. As the marginal error rates are of primary interest, rather than an experiment-wise rate, the data analysis in Tables 2 and 3 has not been adjusted for multiple comparisons. All analyses were conducted using SAS software (Version 9·2; Copyright (c) 2002–2003 by SAS Institute Inc., Cary, NC, USA). All p-values are based on a two-sided hypothesis with significance testing at a 0.05 level.

Results

Fifty-seven pediatric brain tumor patients treated with PRT at the MGH were enrolled in the study between the years 2004 and 2009 and completed the year 3 PedsQL assessment by October 2012. Sixty-three pediatric brain tumor patients treated with the XRT at LPCH were assessed between 2001 and 2002, in a cross-sectional style with a median follow-up of 2.9 years. Table 1 includes demographic and clinical characteristics of both cohorts. There is no significant difference between the cohorts in age, gender, surgery type, diagnostic group or tumor location; however, the LPCH cohort was more racially diverse and had a higher proportion of patients treated with a lower total dose of radiation. However, neither race nor radiation dose correlated with HRQoL outcomes.

The mean PedsQL total core score for the MGH proton cohort and for the LPCH photon cohort was 75.9 and 65.4 respectively ($p = 0.002$). The proton cohort scored statistically better in the physical summary score (10.2 points; $p = 0.015$) and the psychosocial summary domain (10.5 points, $p = 0.001$). Within the subdomains of the psychosocial summary score, the proton cohort scored better with regard to emotional and social functioning, but did not differ significantly from the photon group in school functioning, which was the sub-domain in which both cohorts scored the lowest (see Table 2).

The PedsQL scores from a normative healthy child population are also shown in Table 2. The proton cohort PedQL score is 5.0 points lower than that of the normative healthy population ($p = 0.024$) and the photon cohort is 13.3 points lower ($p < 0.001$). In the proton cohort, the QoL difference from the normative population is largely driven by lower scores in the social and school functioning domains of the psychosocial summary score. There was no difference in the physical summary score domain between the proton and normative population cohorts. In contrast, in the photon cohort, the total core, physical summary and psychosocial summary scores, as well as the sub domains for the psychosocial summary score, were significantly lower than those for the normative population.

Table 3 shows the comparison of the HRQoL scores by tumor type in the MGH proton and LPCH photon cohorts. There were statistically significant differences in the total core score of the children treated for M/PNET, E/HGG, and LGG, favoring the proton cohorts. In the M/PNET cohort, the proton cohort scores 9.8 points better than the photon cohort for total core score ($p = 0.05$). This difference is due to a larger difference in the physical summary score (13.0 points difference, $p = 0.044$), compared with the psychosocial summary difference which was not significant, (7.8 points, $p = 0.113$). In the E/HGG and LGG subgroups, the opposite was true. The largest contributor to the statistically significant difference in total core scores (17.9 points, $p = 0.023$; 22.9 points, $p = 0.017$ respectively) was the difference in the psychosocial summary scores (20.8, $p = 0.006$; 24.5, $p = 0.004$ respectively). There

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Table 1
Patient characteristics for the MGH proton and LPCH photon pediatric brain tumor cohorts.

	MGH protons ($N = 57$)	LPCH photons ($N = 63$)	p-Value
Demographics			
Median age at RT (Range)	7.0 (2.0–14.0)	7.7 (2.3–18.0)	0.585
Gender			0.608
Male	50.9%	55.6%	
Child's race			<0.001
White (non-hispanic)	84.2%	50.8%	
Other	15.8%	49.2%	
Clinical data			
Diagnosis			0.095
Medulloblastoma/PNET	33.3%	46.0%	
Ependymoma/high grade glioma	26.3%	19.1%	
Low-grade glioma	10.5%	19.1%	
Other low-grade neoplasm	17.5%	4.8%	
Germ cell tumor/germinoma	12.3%	11.1%	
Tumor location			0.051
Posterior fossa[†]	47.4%	65.1%	
Surgery type			0.806
No surgery/biopsy only	17.5%	15.9%	
Definitive surgery	82.5%	84.1%	
Hydrocephalus treatment			0.058
Yes (VP shunt or 3rd ventriculostomy)	5.3%	16.1%	
No	94.7%	83.9%	
Chemotherapy			0.053
Yes	52.6%	69.8%	
Radiation dose			0.023
<50 Gy	10.5%	23.8%	
50–54 Gy	71.9%	71.4%	
>54 Gy	17.5%	4.8%	
Median radiation treatment year	2007 (IQR, 2006–2007)	2000 (IQR, 1998–2001)	<0.001

Abbreviations key: MGH, Massachusetts General Hospital; LPCH, Lucile Packard Children's Hospital.
p-Values reflect the difference between the MGH and LPCH cohorts.
[†] Posterior fossa includes posterior fossa, 4th ventricle, brainstem, cerebellum, tectum. Other tumor locations included 3rd ventricle, pineal, pituitary, suprasellar, supratentorial brain and thalamus.

Table 2
Mean parent-reported PedsQL Core scores in the MGH proton and LPCH photon cohort.

Mean (SD) QOL scores	MGH protons ($N = 57$)	LPCH photons ($N = 63$)	p-Value	Data from normative child population[*]	p-Value for difference between MGH and normative child data	p-Value for difference between LPCH and normative child data
Total core score	75.9 (16.3)	65.4 (18.4) $N = 62$	0.002	80.9 (16.7)	0.024	<0.001
Physical summary score	78.4 (23.4)	68.1 (22.0) $N = 62$	0.015	81.4 (23.2)	0.337	<0.001
Psychosocial summary score	74.5 (14.9)	64.0 (18.7) $N = 62$	0.001	80.6 (16.52)	0.003	<0.001
Emotional functioning score	76.0 (16.1)	65.8 (22.0)	0.004	77.9 (20.7)	0.377	<0.001
Social functioning score	79.7 (19.4)	63.6 (23.7) $N = 62$	<0.001	85.4 (19.2)	0.031	<0.001
School functioning score	67.8 (20.6)	62.5 (22.3) $N = 53$	0.197	77.8 (22.0)	<0.001	<0.001

Note: N's for the specific category are given because not all patients filled out every sub category of the survey.
[*] *Source:* Varni JW, Seid M, Kurtin PS. PedsQLTM: reliability and validity of the pediatric quality of life inventory TM Version 4.0 generic core scales in healthy and patient populations. Med Care 2001; 39: 800–12.

were no statistically significant differences in either the LGN or GCT group.

Discussion

This is the first post-treatment comparison of HRQoL outcomes between pediatric proton and photon treated cohorts. This is also the first published comparison of HRQoL outcomes of a large prospectively followed cohort of pediatric patients treated with PRT with normative data from healthy children. The data reported here demonstrate the improved long-term HRQoL outcomes of children treated with PRT.

The proton cohort total core score (75.9) is 5 points less than the healthy population (80.9; $p = 0.024$) [27]. However, when it is put into the context of children with other pediatric chronic diseases such as diabetes (76.6), obesity (75.0) and asthma (68.8), or all cancers (including leukemias) (68.5), the PRT cohort is either the same or compares favorably [24]. In contrast, the photon cohort's total

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Table 3
Mean parent-reported PedsQL core scores by diagnosis in the MGH proton and LPCH photon cohorts.

	Medulloblastoma/PNET		Ependymoma/high-grade glioma		Low-grade glioma		Other low-grade neoplasm		Germ cell tumor	
	MGH $n = 19$	LPCH $n = 29$	MGH $n = 15$	LPCH $n = 12$	MGH $n = 6$	LPCH $n = 12$	MGH $n = 10$	LPCH $n = 3$	MGH $n = 7$	LPCH $n = 7$
Total core score (SD)	76.3 (14.0)	66.5 (17.7) $N = 28$	77.1 (19.5)	59.2 (18.6)	86.7 (11.8)	63.8 (19.1)	71.2 (15.0)	56.2 (19.9)	69.4 (18.8)	78.4 (17.3)
		0.050		**0.023**		**0.017**		0.182		0.372
Physical summary score (SD)	81.1 (18.6)	68.1 (22.5) $N = 28$	79.6 (29.4)	66.7 (20.1)	85.4 (18.5)	65.4 (26.5)	74.0 (19.6)	58.3 (21.3)	68.8 (31.4)	79.5 (16.4)
		0.044		0.206		0.119		0.257		0.439
Psychosocial summary score (SD)	73.8 (14.3)	66.0 (17.5) $N = 28$	75.8 (15.2)	55.0 (20.6)	87.3 (8.7)	62.8 (16.8)	69.7 (15.5)	55.0 (19.2)	69.8 (15.9)	77.9 (18.1)
		0.113		**0.006**		**0.004**		0.198		0.391
Emotional functioning (SD)	76.1 (15.3)	69.1 (20.2)	77.0 (16.7)	50.0 (22.0)	87.9 (14.5)	67.6 (18.1)	68.5 (18.4)	50.0 (32.8)	74.3 (12.4)	82.9 (15.2)
		0.211		**0.001**		**0.030**		0.223		0.271
Social functioning (SD)	79.0 (13.8)	62.3 (23.1) $N = 28$	82.7 (18.8)	57.9 (25.5)	92.5 (14.1)	62.4 (24.4)	77.5 (22.5)	65.0 (13.2)	67.1 (28.3)	80.0 (24.0)
		0.003		**0.008**		**0.014**		0.388		0.377
School functioning (SD)	66.3 (25.5)	67.8 (19.2) $N = 23$	67.7 (19.2)	56.7 (27.6) $N = 11$	80.8 (17.2)	55.9 (18.2) $N = 10$	63.0 (15.7)	50.0 (36.1)	67.9 (17.3)	70.0 (21.0) $N = 6$
		0.828		0.245		**0.017**		0.365		0.844
Median age at follow-up	10.0	10.0	10.0	10.4	14.0	10.2	10.0	13.5	14.0	16.0
Follow-up (years)	3.0	2.4 (median)	3.0	1.7 (median)	3.0	4.8 (median)	3.0	0.4 (median)	3.0	2.5 (median)

Note: p-Values show the difference between the MGH and LPCH scores for each set of cells and have been bolded when significant (at $p \leqslant 0.05$).

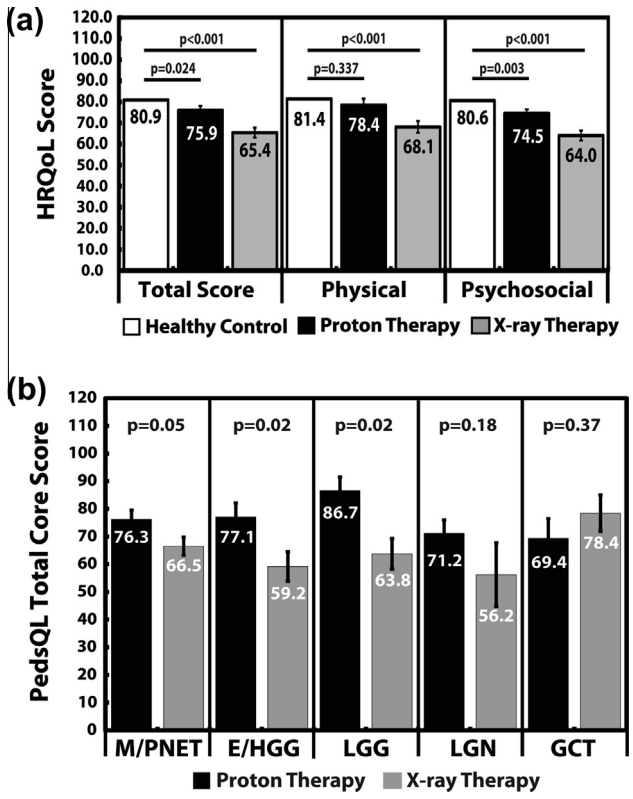

Fig. 1. (a) PedsQL scores in the proton, photon and normative cohorts. (b) Total PedsQL core scores by diagnostic group and radiation type in MGH proton and LPCH photon cohorts. The bars represent the SEM (standard error of the mean).

core score is 65.4 and 15.5 points lower than the healthy controls ($p < 0.001$). This is consistent with different previously published cohort of all brain tumor patients (irrespective of radiotherapy use) 64.5 [9].

The post treatment HRQoL scores of the proton and photon treated cohorts were also compared directly. The proton cohort scored 10.5 points higher for the total core score and similarly in the physical summary and psychosocial summary scores (10.3 and 10.5 respectively). School functioning was the only sub-domain that was not different between the two cohorts and was the lowest score of both cohorts. Scores were 10–15.3 points less than what the normative population reports. These findings highlight an opportunity to improve the school experience for the childhood brain tumor survivor through better services and accommodations for any deficits related to the tumor and treatment. In many circumstances accommodations can be improved. Furthermore, the standard deviations (SDs) are relatively large (20.6–22.3) in this category suggesting variability in what the children experience in their schools. Interestingly, the SD is also relatively large in the data from the normative population which suggests heterogeneity in the school experience as well. It is reassuring for comparability that the SDs across the cohorts and in the various domains (see Table 2) are quite similar.

HRQoL scores differed between the proton and photon cohorts by diagnosis. Children with a diagnosis of M/PNET, E/HGG, or LGG, and treated with protons scored higher in overall core measures and in many of the sub-domains than children in the photon cohort. However, the pattern of differences within the domains of the total cores score varied by diagnosis. These differences may be explained if we presume that radiotherapy to the body has a greater relative effect on the physical health QoL outcomes (physical summary score) and radiotherapy to the brain has a greater relative effect on the psychosocial summary score.

In the M/PNET group, the difference was greater in the physical summary domain than the psychosocial summary domain. These patients are treated with craniospinal irradiation (CSI) which targets the whole brain and spine in order to sterilize the CSF where tumor cells circulate. With the proton modality, there is no exit dose to the body beyond the vertebral bodies, which better spares the bowels, heart and lungs as well as gonadal organs in females. Each of these organs receives between 50% and 80% of the prescription dose with photon techniques, compared to 0–5% with proton therapy. It is likely that tissue sparing with PRT translates into better

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HRQoL in the physical domain. There was less of a difference in the psychosocial domain in the M/PNET patients, which is likely because both the proton and photon cohorts include many whole brain radiotherapy patients, where the dose sparing benefit to the normal brain with protons is diluted.

Using this same logic, it makes sense that it was the significant difference in psychosocial summary score that contributed most heavily to the significant difference in total core scores for the E/HGG and the LGG groups. In both these groups, typically only the involved tumor bed is irradiated, not the whole brain. Therefore, the difference in integral dose to the brain between the photon and proton cohorts will be greatest and is reflected in the psychosocial domain scores.

In contrast to the M/PNET, E/HGG and LGG groups, there was no statistically significant difference between cohorts for children with LGN or GCTs. Both of these comparisons are likely underpowered. In addition, the GCT cohort had higher median ages of 14 and 16 years respectively when compared to the other disease types. Adverse health effects from radiation in the pediatric population are more pronounced the younger a child is at the time of radiotherapy. Therefore, differences may not be detectable at this older age [28].

Our data support the hypothesis that PRT produces better HRQoL outcomes compared to XRT. HRQoL measures are correlated with health outcomes, which should also be better with proton therapy due to greater sparing of dose to normal tissues. Preliminary neurocognitive data of a proton cohort at 2 years of follow-up have shown that neurocognitive effects common in a mixed brain tumor population can be partially mitigated by the normal tissue sparing properties of protons [19]. Three year follow-up data from a medulloblastoma cohort treated on a prospective trial also showed some reduction of late effects compared with published photon cohorts [29]. In a previous publication, we showed that HRQoL scores correlated with full scale IQ and scores on behavioral measures [20]. An important next step in analyzing outcomes of the pediatric brain tumor proton cohort would be to correlate health outcomes, such as hearing, endocrine function and other conditions, to HRQoL data to see if these measurable health outcomes are at least partly responsible for the higher HRQoL scores.

While the comparisons of HRQoL with the normative population and photon cohorts support the hypothesis that proton radiotherapy may help improve HRQoL, these comparisons must be interpreted in light of a number of limitations. First, the data collection methods at LPCH and MGH differ. The LPCH cohort study is a one-time cross sectional analysis with a median follow up of 2.9 years and the MGH data are based on a prospective longitudinal study using year three assessments to best match their follow up. Second, we are comparing data from two institutions with possibly different treatment approaches and who serve different patient populations. These potential differences could have an impact on HRQoL outcome. Third, the proton cohort likely includes a larger proportion of patients from a higher socio-economic status (SES), which may be associated with better HRQoL, although the data on the effects of SES on HRQoL are conflicting [3,9,10,30]. We do not have a method to account for this in the present study as neither site collected SES indicators. Fourth, radiation dose and volumes can affect health outcomes [31], with a significantly larger proportion of the LPCH cohort receiving a lower radiation dose. However, this would be expected to skew the results in favor of the LPCH cohort, further strengthening the finding of improved HRQoL outcomes with PRT. On the other hand, volume of brain irradiated was not collected in either cohort, which has also been shown to affect health outcome. If either the proton or photon cohort had systematically larger volumes targeted, the results would be negatively skewed in that cohort. However, such a systematic skew would be unlikely. The analysis by disease type mitigates this potential confounding factor on our data set by separating out those patients most likely to have been treated with CSI (large volume) radiotherapy. However, for the patients receiving involved field or partial brain irradiation [31] the proton cohort will have had less volume of normal brain irradiated since integral dose is cut by a factor of 2 or more on average [32]. In fact, as previously addressed, we believe the higher psychosocial scores in patients treated with protons (E/HGG and LGG diagnostic groups) are due to the relative sparing of normal brain. Fifth, treatment options and techniques have changed over time, which could influence the results. The MGH cohort includes patients that were treated on average (median) 7 years later than the LPCH cohort. The more recently treated proton cohort at MGH may have benefited from improved techniques over time in all the treatment arenas, including surgery, chemotherapy and radiation therapy, which would skew the results to favor the proton cohort.

While this study is truly unique and the first of its kind, greater follow up is needed as late effects of treatment manifest over time [33]. The MGH prospective study will continue for at least 10 years after treatment and we are working to find an appropriate prospectively accrued photon comparison group. Additionally, this study uses parent reports for all cohorts including the normative data, which are both a strength and a weakness. There could be a parental bias in families who choose PRT. While patient reported outcomes remain the gold standard, both Varni et al. and our previous work have nevertheless shown that the parent proxy reports and child self reports are highly correlated [20]. The advantage here is that some patients, (e.g. the preliterate or neurologically impaired) can still participate in these HRQoL outcome studies. Parent reporting is a good proxy for HRQoL outcomes in children [20,25,27], and are notably better than provider or clinician reported outcomes, which is the only other alternative.

In summary, our findings show that HRQoL in a proton treated pediatric brain tumor cohort appear somewhat better than the HRQoL outcomes in a cohort of children treated with photons a few years earlier. Perhaps even more telling is HRQoL outcomes in the proton cohort are only slightly worse than that of the healthy child population and either comparable or better than children with other chronic diseases [24]. Importantly, the direct comparison with the source data from the LPCH photon cohort supports (but does not prove) that proton radiotherapy may be making a positive difference in pediatric brain tumor survivors. However, given the limitations of the study discussed above, a direct and contemporary comparison of proton and photon cohorts with the same data collection methodology and accounting for SES status is a necessary next step to more fully evaluate the benefits of proton radiotherapy in pediatric brain tumor survivors.

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