Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2014 October 1; 90(2): 354–361. doi:10.1016/j.ijrobp.2014.05.051.

Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity

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Abstract

Background—We compared proton beam therapy (PBT) with intensity-modulated radiation therapy (IMRT) for pediatric craniopharyngioma in terms of disease control, cyst dynamics, and toxicity.

Methods—We reviewed records from 52 children treated with PBT (n=21) or IMRT (n=31) at two institutions in 1996−2012. Endpoints were overall survival (OS), disease control, cyst dynamics, and toxicity.

Results—At 59.6 months' median follow-up (PBT 33 mo vs. IMRT 106 mo, $P < 0.001$), the 3 year outcomes were 96% for OS, 95% for nodular failure-free survival (NFFS) and 76% for cystic failure-free survival (CFFS). Neither OS nor disease control differed between treatment groups (OS $P=0.742$; NFFS $P=0.546$; CFFS $P=0.994$). During therapy, 40% of patients had cyst growth (20% requiring intervention); immediately after therapy, 17 patients (33%) had cyst growth (transient in 14), more commonly in the IMRT group (42% vs. 19% PBT, $P=0.082$); and 27%

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Presented in part at the American Radium Society 95th Annual Meeting, Scottsdale AZ, April 27-May 1, 2013.

Disclaimers: The authors declare no conflicts of interest.

experienced late cyst growth (32% IMRT, 19% PBT, *P*=0.353), with intervention required in 40%. Toxicity did not differ between groups. On multivariate analysis, cyst growth was related to visual and hypothalamic toxicity (*P*=0.009 and 0.04). Patients given radiation as salvage therapy (for recurrence) rather than adjuvant therapy had higher rates of visual and endocrine (*P*=0.017 and 0.024) dysfunction.

Conclusions—Survival and disease-control outcomes were equivalent for PBT and IMRT. Cyst growth is common, unpredictable, and should be followed during and after therapy, as it contributes to late toxicity. Delaying RT until recurrence may result in worse visual and endocrine function.

Keywords

craniopharyngioma; proton therapy; radiation therapy; cyst growth

Introduction

Craniopharyngiomas arise in the suprasellar region. Despite their non-infiltrative growth pattern, their dense adherence to and compression of nearby critical structures make treatment difficult.[1,2] Numerous reports during the past few decades suggest that subtotal resection followed by radiation therapy (RT) produces outcomes superior to those of aggressive surgery alone.[3-16] Contemporary strategies hence favor maximal safe resection, to limit potential surgical morbidity, followed by adjuvant RT. However, concerns regarding radiation-induced toxicities, including vascular changes, cognitive deficiencies, and secondary malignancies, persist.

Many published findings on outcome and toxicity after RT involve the use of relatively old RT techniques. Technologic improvements in imaging and in radiation planning and delivery have improved the conformality of radiation doses to target volumes and reduced the doses to nearby normal tissues. The current standard of care at many treatment centers is photon-based intensity-modulated radiation therapy (IMRT); however, the superior dose profiles provided by proton beam therapy (PBT) have prompted the increased use of PBT where available.

A challenging component of craniopharyngioma management is the potential for cystic growth during or after RT. As radiation becomes more conformal and the use of particle therapy (e.g., PBT) becomes more prevalent, monitoring and accounting for cyst changes during treatment are essential to avoid underdosing target structures or overdosing critical structures.[17-23] Furthermore, cystic components of craniopharyngiomas can also change after RT is completed. However, both the incidence and implications of such changes are unclear and complicate the evaluation of treatment response.[24,25] Significant expansion of cysts after treatment may compress critical structures, necessitating additional invasive procedures. Transient asymptomatic enlargement, however, may reflect only a response to treatment, as has been noted for other high- and low-grade tumors. In such cases, additional procedures may be unnecessary and could impart additional treatment-related morbidity.[6,7]

To clarify these issues, we evaluated a large group of pediatric patients with craniopharyngioma treated at two institutions with modern RT techniques to compare outcomes, cyst dynamics and late toxicity after IMRT versus PBT.

MATERIALS AND METHODS

Patients

Eligible patients were identified from institutional databases at _____ and _____ (both in _____) after permission was obtained from the respective institutional review boards. Inclusion criteria were (1) histologic confirmation of craniopharyngioma, (2) patient age ≤18 years at time of RT, and (3) treatment with IMRT or PBT from 1996 through 2012. Once PBT was available, it was used to treat all pediatric craniopharyngioma patients between 2007 and 2012.

Patient characteristics extracted from the records included age at time of RT, demographics, tumor size at diagnosis, and presenting symptoms (visual deficits, hydrocephalus, endocrine deficiencies). Surgical intervention variables captured included: date of first surgery, extent of resection, number of surgeries, and surgical complications.

Radiation treatment was considered definitive (if only biopsy or cyst drainage had been done previously), postoperative/adjuvant (after either a subtotal resection [STR] or a gross total resection [GTR]), or salvage (for disease that recurred after previous interventions). Radiation dose, fractionation, and modality (IMRT vs. PBT) were noted. The number of interval scans obtained during RT (to monitor cyst size and ensure adequate target coverage) was recorded as well.

Disease progression was further categorized as growth of the solid, nodular disease component versus cystic changes, the latter recorded as (1) occurring during RT, (2) early cyst enlargement (≤3 months after RT), and (3) late cyst growth (>3 months after RT). The date of first progression of nodular versus cystic growth was based on serial magnetic resonance imaging.

Findings on late toxicity were extracted from multidisciplinary clinical evaluations, laboratory values, and imaging. Changes in symptoms were recorded as being before treatment vs. after surgery vs. late (after RT). Endocrinopathies were defined as deficiencies requiring supplementary medication and confirmed by laboratory screening. Panhypopituitarism was diagnosed by the primary clinician as a deficiency of >3 anterior pituitary hormones. Any deviation in baseline vision (field cuts or acuity) on physical and ophthalmologic examination was recorded as a visual change. Because formal neurocognitive testing was not obtained on all patients, data concerning cognitive toxicity could not be retrospectively extracted. Vascular toxicities including moyamoya, stroke, and vessel malformations were identified on cranial imaging. Hypothalamic obesity was based on the primary clinician's diagnosis of morbid or hypothalamic obesity during follow-up.

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics, and categorical data were analyzed by using Fisher's exact test. Survival times were calculated from the RT end date to the first occurrence of the considered event. The Kaplan-Meier method was used to calculate OS and cystic and nodular progression-free survival times. Log-rank tests were used to assess the equality of the survival function across groups. A two-sided 5% significance level was used for analysis.

The Cox proportional hazard model was used for univariate and multivariate analysis to assess the effect of patient, tumor, and other factors on the endpoints. Multivariate assessment was done by backwards elimination, with all factors found to have a *P* value of 0.25 or less on univariate analysis included in the assessment. Estimated hazards are reported. The Wald test was used to assess the influence of covariates on the model. Stata/MP v13.0 was used for data analysis.

RESULTS

Patient Characteristics and Tumor Management

Fifty-two patients (21 treated with PBT and 31 with IMRT) met the criteria for this analysis; patient, disease, and treatment characteristics are summarized in Table 1.

Upfront surgical interventions varied. The first surgical procedure was definitive in 26 patients (STR n=20,GTR n=6). Just over one third of patients (n=20) required more than one surgical procedure before RT (Table 1).

RT was delivered to doses of 50.4-54 Gy at 1.8 Gy per fraction. Thirty one children were treated with IMRT, and 21 were treated with PBT (Table 1). Most of the PBT was delivered with passive scatter techniques (n=18).

As expected, follow-up was shorter for the PBT group ($P<0.001$), because PBT was not available until 2006. Otherwise, the groups were well balanced (Table 1).

Imaging During RT

Given the unpredictability of craniopharyngioma cyst dynamics, periodic imaging during RT ensures that the tumor is covered adequately by the prescribed dose throughout the entire treatment course. Only 44% of the patients among the entire cohort (PBT n=19, IMRT n=5) had imaging during RT; most of these patients had been treated before the importance of interval imaging was published.[23] Of those patients who did undergo surveillance imaging during RT, 2 PBT treated patients underwent MRI while the other 22 patients underwent CT imaging; 10 (19%) experienced documented cyst growth with 5 requiring changes in the treatment plan. Two patients required cyst decompression (one with anatomic changes after decompression that required RT re-planning), and the other three required adaptive re-planning (one required two re-plans). Six children had documented cyst contraction during RT, which did not require re-planning. Four patients had improvement in visual symptoms during RT, some related to cyst contraction.

No correlation was found between imaging during RT and late cyst growth (P=0.764) or nodular progression (P=0.493). Cyst growth during RT was unrelated to late cyst growth on univariate analysis (P=0.099).

Outcomes

With a median follow-up of 59.6 months for the entire cohort (PBT 33 mo vs. IMRT 106 mo; P<0.001), the 3-year OS rate was 96%, and the median survival time was not reached. Nodular recurrences of a solid tumor component were considered distinct from cyst growth and analyzed separately. The 3-year cystic failure-free survival (CFFS) and nodular failure-free survival (NFFS) rates for the entire group were 75.5% and 95.0%.

No difference in OS was found between patients treated with PBT or IMRT (3-year OS 94.1% PBT vs. 96.8% IMRT, P=0.742) (Figure 1). The 3-year CFFS and NFFS rates were also similar between groups (CFFS 67.0% PBT and 76.8% IMRT, P=0.994), but more of the IMRT group had late cystic growth (10-year CFFS rate 67.8%). One patient in each treatment group had nodular failure (3-year NFFS rates 91.7% PBT vs. 96.4% IMRT, P=0.546); the patient treated with PBT had progression at 26 months and the patient with IMRT at 24 months. No differences by RT intent (salvage vs. definitive or adjuvant) were observed in 3-year OS, CFFS, or NFFS rates (P=0.294 OS, P=0.412 CFFS, and P=0.951 NFFS). To assess the potential impact of shorter follow-up for patients treated with PBT, data points were censored at 3 years and data re-analyzed. This analysis confirmed there was no statistical difference between PBT and IMRT for any outcome measure.

Four of the 52 patients had died at the time of analysis, one from cyst progression after STR and adjuvant RT and the other three from treatment-related morbidity (uncontrolled diabetes insipidus and postoperative neurologic injury).

Cyst Dynamics After RT

Seventeen patients (33%) had imaging evidence of early cyst growth (within 3 months of completing RT) with a greater percentage occurring in the IMRT group (42% vs. 19% PBT) (Table 1). This apparent difference was not significant (P=0.082). Fourteen of the 17 patients with early cyst growth had only transient enlargement that resolved on follow-up imaging.

Fourteen patients (27%) had late cyst growth (>3 months after RT) with no difference between groups (32% IMRT vs. 19% PBT, P=0.353), and 6 patients required additional intervention (3 cyst drainage, 2 catheter placement, and 1 surgical fenestration) (Table 1).

The reasons why some patients had early or late cyst growth and others did not are unclear. . We hypothesized that patients with low frequency or without surveillance imaging may be at increased risk for post-treatment cyst growth due to marginal misses from dynamic cyst enlargement while on treatment. However, less frequent surveillance imaging was not correlated with early cyst growth (P=0.376). Similarly, late cyst growth was not impacted by the use of surveillance imaging (P=0.764).

Univariate analysis of factors that influenced (or may have been influenced by) persistent cyst growth (Table 2) included hypothalamic obesity (HR 5.14, *P*=0.004) and visual function (HR 5.68, *P*=0.004). On multivariable analysis, however, only hypothalamic obesity (HR 3.46, *P*=0.04) and visual function (HR 6.01, *P*=0.009) retained significance (Table 2).

Toxicity

The potential for long-term survival among patients with this type of tumor underscores the importance of minimizing treatment-related toxicity. In our study, over 50% of patients had some peri-operative morbidity, with nearly 40% effected by either diabetes insipidus (n=10) or panhypopituitarism (n=10). The extent of surgery (GTR vs. STR vs. other) before RT did not correlate with postoperative endocrine (*P*=0.096) or visual (n=11) (*P*=0.64) complications. Patients who had more surgical procedures before RT may have had more visual complications after surgery, but this apparent difference was not statistically significant (*P*=0.072).

Forty patients (77%) were found to have a least one additional endocrinopathy after RT, 24 (46%) of which were new onset panhypopituitarism. Of the other sixteen patients, hypothyroidism (n=7, 13%) and hypogonadism (n=4, 8%) were most common. Thirteen patients were diagnosed with hypothalamic obesity (PBT n=4, IMRT n=9; *P*=0.523). Two events were directly correlated with surgical toxicity. The remaining 11 may have resulted from surgery but were not diagnosed until after RT or alternatively were due to the combined effects of surgery and RT.

Cranial imaging in 5 patients suggested vascular injury (PBT n=2, IMRT n=3; *P*=1.0): 3 had symptomatic strokes, 1 had a radiologic vascular malformation, and 1 had radiologic moyamoya .

No differences in late RT toxicity were identified in children treated with PBT versus IMRT (Table 3). In the 22 patients receiving RT as salvage therapy, there was significantly more morbidity related to visual (*P*=0.017) and endocrine (*P*=0.024) dysfunction and a higher rate of panhypopituitarism (*P*=0.023) compared with patients who received RT as definitive or adjuvant therapy.

DISCUSSION

This study represents a multi-institutional evaluation of one of the largest groups of pediatric patients with craniopharyngioma treated with PBT to date, and is the only comparison of such patients with patients treated with modern, conformal photon-based IMRT.

As PBT becomes increasingly available worldwide, clinical studies of its efficacy are important to validate previous dosimetric evidence of its advantages over photon-based therapy.[20-22] Published 10-year survival rates range from 83% to 91% and are consistent with our finding of 86%.[12,17] Notably, however, no difference in OS was observed between treatment groups (*P*=0.742). Equivalency had been suggested by previous retrospective studies, but until this study a comparison cohort was not available.[18,19,26]

Considerable variability and ambiguity in disease progression definitions complicate comparisons between studies. Of studies defining control as growth of the solid component of the tumor, control rates range from 92% to 100% when fractionated RT is given after STR.[13] Alternatively, Merchant *et al.* defined progression as growth of the solid portion *or* persistent cystic growth more than 3 years after treatment; they reported similar control rates (88%-96%).[17]

We considered solid and cystic growth separately, as each may be associated with unique outcomes. Our NFFS rates at 3 years (95%) were consistent with previous reports.[13,17] Cyst growth is more challenging to control (3-year CFFS rate 76%), but its biologic significance is undefined. Importantly, there were no differences between PBT and IMRT in 3-year nodular (P=0.546) or cystic (P=0.994) outcomes.

Patterns of cystic change in craniopharyngiomas remain underreported. Cyst growth has a significant impact on treatment planning. Frequent surveillance imaging during treatment allows for tighter RT dose distribution since cyst enlargement can be monitored. Our rate of intervention prompted by cyst growth during RT was 20% among those imaged, slightly less than previously reported (35%) but still noteworthy.[23] The influence of surveillance imaging on long-term outcomes, however, is not fully understood. We found no difference in CFFS between patients with and without interval imaging (p=0.764).

Cyst growth seems to be of two types–early yet transient growth and slowly progressive, late growth. One-third of our patients experienced cyst growth immediately after RT, and all but 3 cases subsequently resolved. Two other groups reported similar observations, with rates of transient, early cyst growth as high as 52%.[24,25] Interestingly, although the cysts reached their maximum dimension in less than 2 months after RT, they took 10 months to contract.[24] Transient cyst expansion after RT is not unique to craniopharyngiomas, and has also been reported for pilocytic astrocytoma.[27]

The high rate of early cyst growth after photon-based RT (52%) reported by Shi *et al* is similar to IMRT (photon) -treated group (42%). The similarity in early cyst growth between these two photon-treated groups and the difference in regard to the proton group (19%) is notable (P=0.082). Early cyst growth suggests that cysts do not respond to RT in the same way as does the solid component; the lag time for cysts to contract after RT is analogous to the time needed for late tissue remodeling and vascular fibrosis.

Recognizing transient cyst growth is critical for sparing patients unnecessary intervention. We recommend that if there is asymptomatic, early cyst growth immediately after RT, interventions should be avoided and the patients closely monitored. The more challenging scenario is when cysts persist and continue to grow. Although most late cyst growth eventually stabilized in our group (57%), these children experienced morbidity (visual outcomes and hypothalamic obesity) from the cyst progression, which emphasizes the need for close observation and intervention for continued cyst expansion.

Perioperative morbidity rates range from 8% to 14%, with rates of diabetes insipidus after conservative surgery of 33% and postoperative panhypopituitarism in the high teens.[5-8,12,14,16,28] Radiation also impacts endocrine function. In our study, new

endocrinopathies after RT (77%) were consistent with other published rates (85%-95%).[15] However, we observed higher rates of panhypopituitarism than recently reported (30%),[28] suggesting this toxicity may be underreported in the literature. Our study also shows the rate of panhypopituitarism continues to increase with time, as suggested by the greater frequency observed in our IMRT group due to longer follow-up. Importantly though, while endocrine dysfunction is often attributed to RT, the location of the tumor, unpredictable nature of cyst growth, and surgical manipulation must also be considered as contributing factors.[8,29]

Hypothalamic obesity is a morbid treatment-related toxicity. We observed a relatively low rate of obesity attributable to hypothalamic dysfunction (25%) compared to a recent report suggesting only 25% of craniopharyngioma patients maintained a normal body mass.[30] However, without prospectively collected data, understanding the interplay between hypothalamic obesity, other endocrine deficiencies, socioeconomic influences, and populational trends will remain difficult.

Neurocognitive and behavioral outcomes are also challenging to quantify retrospectively. Two previous reports suggested that patients treated for craniopharyngioma did not have significant long-term changes in IQ, daily living skills, or self-reported quality of life indicators.[26,31] . Future studies including the use of formal neurocognitive testing are warranted and ongoing.

Notably, delaying RT until disease progression resulted in worse toxicity profiles, rather than less treatment-related toxicity as intended. Progressive cyst growth severely affected both vision and rates of hypothalamic obesity, and reserving RT until disease progression negatively affected endocrine function as well resulting in higher rates of panhypopituitarism. Therefore, based on these observations and previous reports, we recommend RT not be withheld in the adjuvant setting.

Specific indicators of PBT clinical benefit have not yet been identified. In this analysis, we observed no difference in late toxicity between patients treated with PBT compared with IMRT. However, given the proximity of craniopharyngiomas to many critical structures that cannot be avoided, the value of PBT for this disease is in minimizing the integral dose associated with IMRT to brain and vasculature;[22] more sensitive measures of benefit need to be developed through prospective data collection and formal neurocognitive testing.

This study did have limitations. We attempted to overcome the limitations of small sample sizes associated with a rare pediatric disease by performing a comparative, multi-institutional analysis. Despite our having more patients than most studies, the number of events was still limited, and this study was subject to the biases inherent in any retrospective analysis. Moreover, the inclusion of more than one institution increased the sample size, but also introduced non-standardized follow-up and complicated late effect evaluations.

Several important differences exist between the two cohorts that warrant mention: the treatment decade, length of follow-up, and use of surveillance imaging during RT. Surveillance imaging was not regularly incorporated into clinical practice until 2006, which coincided with the initiation of PBT treatments. While these imbalances do not appear to have influenced outcomes, they warrant consideration when interpreting the results.

For future studies, standardizing definitions of recurrence and collecting prospective quality of life and neurocognitive metrics would certainly improve meaningful follow-up for children with craniopharyngioma.

CONCLUSIONS

Current treatments for craniopharyngiomas offer excellent survival and control rates but can nevertheless have significant morbidity. Uniform classifications of disease progression among studies is important to facilitate comparisons between nodular and cyst control rates. We found that PBT and IMRT produced equivalent outcomes related to survival and solid and cystic disease control. Cyst growth is common during and after RT and should be accounted for in treatment planning and follow-up; late cyst growth significantly influences morbidity. Delaying RT until disease progression may worsen visual and endocrine function. Prospective quality-of-life and neurocognitive studies are needed to better define late toxicity and identify clinically meaningful quality indicators.

Acknowledgments

Research Support: This work was supported in part by Cancer Center Support (Core) Grant CA016672 to The University of Texas MD Anderson Cancer Center.

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SUMMARY

Pediatric craniopharyngiomas are effectively treated with radiation, but no studies exist comparing outcomes between intensity modulated and proton beam radiation therapy. We reviewed the outcomes for patients treated with both radiation modalities to compare disease control, cyst dynamics, and toxicity. Disease control was equivalent between modalities. Cyst changes were common during and after treatment, and close follow-up is needed in order to prevent unnecessary interventions.

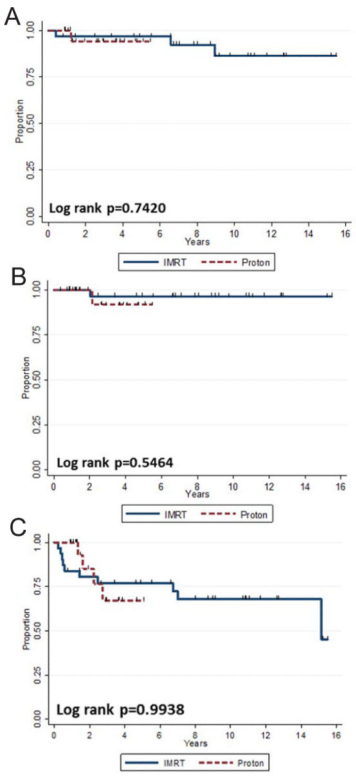

Fig. 1.

Survival curves according to treatment. (A) Overall survival; (B) nodular failure-free survival; (C) cystic failure-free survival. Treatment modality (proton beam therapy [PBT] vs. intensity-modulated (photon) radiation therapy [IMRT]) did not affect any of these survival outcomes.

Table 1

Patient, Disease, and Treatment Characteristics by Treatment Group (n=52)

	Treatment Groups			
Variable	**All Patients Value or No. (%)**	**PBT Value or No. (%)**	**IMRT Value or No. (%)**	***P* Value**
Follow-up time, months				
Median	59.6	33.1	106.1	<0.001
Range	4.7-185.3	10.5-65.6	8.9-185.3	
Age, years				
Median	8.9	9.1	8.8	1.00
Tumor size, cm				
Median	3.8	4.5	3.6	0.19
Sex				
Male	23 (44)	9 (43)	14 (45)	1.00
Female	29 (56)	12 (57)	17 (55)	
Ethnicity				
Asian	1 (2)	1 (5)	0 (0)	0.540
African American	13 (25)	4 (19)	9 (29)	
Hispanic	19 (37)	9 (43)	10 (32)	
Caucasian	19 (37)	7 (33)	12 (39)	
Presenting symptoms				
Headaches	31 (60)	16 (76)	15 (48)	0.038
Visual defects	36 (69)	11 (52)	25 (81)	0.083
Endocrinopathies	16 (31)	4 (19)	12 (39)	0.22
Extent of first surgery				
Other[1]	26 (50)	7 (33)	19 (61)	0.032
Subtotal resection	20 (38)	9 (43)	11 (35)	
Gross total resection	6 (12)	5 (24)	1 (3)	
Number of surgeries				
1	32 (62)	15 (71)	17 (55)	0.749
2	13 (25)	4 (19)	9 (29)	
3	6 (12)	2 (10)	4 (13)	
4	1 (2)	0 (0)	1 (3)	
Radiation dose			1	
Median	50.4 Gy	50.4 Gy(RBE)	50.4 Gy	
Radiation Intent				
Postoperative	23 (44)	8 (38)	15 (48)	0.586
Definitive	7 (13)	4 (19)	3 (10)	
Salvage	22 (42)	9 (43)	13 (42)	
Re-imaging during RT				
None	28 (54)	2 (10)	26 (84)	
1x	4 (8)	4 (19)	0 (0)	

Variable	All Patients Value or No. (%)	Treatment Groups PBT Value or No. (%)	IMRT Value or No. (%)	*P* Value
2x	10 (19)	7 (33)	3 (10)	
3x	3 (6)	3 (14)	0 (0)	
Weekly	7 (13)	5 (24)	2 (6)	
Cyst change during RT				
Growth	10 (19)	6 (29)	4 (13)	
Contraction	6 (12)	6 (29)	0 (0)	
No change	8 (15)	8 (37)	0 (0)	
Unknown	28 (54)	1 (5)	27 (87)	
Treatment change during RT due to cyst growth				
Yes	5 (10)	2 (10)	3 (10)	
No	20 (38)	17 (81)	3 (10)	
N/A	27 (52)	2 (10)	25 (81)	
Cyst growth ≤3 months after RT				
Yes	17 (33)	4 (19)	13 (42)	0.082
No	34 (65)	17 (81)	17 (55)	
Unknown	1 (2)	0 (0)	1 (3)	
Cyst growth >3 months after RT				
Yes	14 (27)	4 (19)	10 (32)	0.353
No	38 (73)	17 (81)	21 (68)	
Cyst growth after RT requiring intervention				
Yes	6 (12)	3 (14)	3 (10)	
No	46 (88)	18 (86)	28 (90)	

Abbreviations: PBT, proton beam therapy; IMRT, intensity-modulated radiation therapy; RT, radiation therapy

[2] Not different between treatment groups

[1] Cyst drainage, fenestration, shunting

Table 2

Univariate and Multivariate Analysis of Predictors and Morbidity of Cyst Growth

Variable	Hazard Ratio	95% CI	*P* Value
Univariate Analysis			
Sex	1.03	0.36–2.97	0.957
Ethnicity			
Hispanic	1.07	0.24–4.81	0.929
Caucasian	2.24	0.65–7.68	0.202
Age at RT	0.96	0.83–1.10	0.553
RT treatment year	1.11	0.98-1.27	0.103
RT modality (PBT vs. IMRT)	1.00	0.29–3.46	0.994
Re-imaging during RT	2.88	0.83–9.98	0.095
Cyst growth during RT	3.98	0.77–20.57	0.099
RT intent (adjuvant/definitive vs. salvage)	0.62	0.21–1.88	0.402
RT dose	1.00	1.00–1.01	0.169
Early cyst growth (≤3 months after RT)	0.59	0.16–2.15	0.425
Late panhypopituitarism	1.60	0.43–5.90	0.483
Vascular toxicity	1.53	0.34–6.94	0.578
Hypothalamic obesity	5.14	1.68–15.75	0.004
Visual toxicity	5.68	1.74–18.61	0.004
Multivariate Analysis			
RT treatment year	1.15	1.00–1.31	0.043
Visual toxicity	6.01	1.55–23.30	0.009
Hypothalamic obesity	3.46	1.06–11.30	0.040

Abbreviations: CI, confidence interval; RT, radiation therapy; PBT, proton beam therapy; IMRT, intensity-modulated (photon) radiation therapy

Table 3

Disease- and Treatment-related Morbidity Identified After Radiation

	Treatment Groups			
Variable	**All Patients Value or No. (%)**	**PBT Value or No. (%)**	**IMRT Value or No. (%)**	***P* Value**
***Late Morbidity*[1]**				
Vascular	5 (10)	2 (10)	3 (10)	1.00
Vision	5 (10)	1 (5)	4 (13)	0.637
Hypothalamic obesity	13 (25)	4 (19)	9 (29)	0.523
Endocrinopathy	40 (77)	16 (76)	24 (77)	1.00
Panhypopituitarism	24 (46)	7 (33)	17 (55)	0.162
Other[2]	16 (31)	9 (43)	7 (23)	0.139

Abbreviations: PBT, proton beam therapy; IMRT, intensity-modulated (photon) radiation therapy.

[1] Toxicities newly acquired from start of radiation

[2] Growth hormone deficits, hypothyroidism, adrenal insufficiency, sexual hormone deficiencies