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ON THE BENEFITS AND RISKS OF PROTON THERAPY IN PEDIATRIC CRANIOPHARYNGIOMA

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Abstract

Purpose—Craniopharyngioma is a pediatric brain tumor whose volume is prone to change during radiation therapy. We compared photon- and proton-based irradiation methods to determine the effect of tumor volume change on target coverage and normal tissue irradiation in these patients.

Methods and Materials—For this retrospective study, we acquired imaging and treatment-planning data from 14 children with craniopharyngioma (mean age, 5.1 years) irradiated with photons (54 Gy) and monitored by weekly magnetic resonance imaging (MRI) examinations during radiation therapy. Photon intensity-modulated radiation therapy (IMRT), double-scatter proton (DSP) therapy, and intensity-modulated proton therapy (IMPT) plans were created for each patient based on his or her pre-irradiation MRI. Target volumes were contoured on each weekly MRI scan for adaptive modeling. The measured differences in conformity index (CI) and normal tissue doses, including functional sub-volumes of the brain, were compared across the planning methods, as was target coverage based on changes in target volumes during treatment.

Results—CI and normal tissue dose values of IMPT plans were significantly better than those of the IMRT and DSP plans ($p < 0.01$). Although IMRT plans had a higher CI and lower optic nerve doses ($p < 0.01$) than did DSP plans, DSP plans had lower cochlear, optic chiasm, brain, and scanned body doses ($p < 0.01$). The mean planning target volume (PTV) at baseline was 54.8 cm^3, and the mean increase in PTV was 11.3% over the course of treatment. The dose to 95% of the PTV was correlated with a change in the PTV; the R^2 values for all models, 0.73 (IMRT), 0.38 (DSP), and 0.62 (IMPT), were significant ($p < 0.01$).

Conclusions—Compared with photon IMRT, proton therapy has the potential to significantly reduce whole-brain and -body irradiation in pediatric patients with craniopharyngioma. IMPT is the most conformal method and spares the most normal tissue; however, it is highly sensitive to target volume changes, whereas the DSP method is not.

Keywords

Craniopharyngioma; Proton; IMPT; Adaptive planning

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INTRODUCTION

Craniopharyngioma is a locally aggressive intracranial tumor. There are approximately 120 cases diagnosed each year in the United States in patients aged younger than 19 years. The peak age of incidence ranges from 8 to 10 years (1). Younger patients appear to be the most vulnerable to the effects of irradiation, which is commonly used in conjunction with limited surgery and for those with tumor progression after attempted gross total resection. Current efforts in radiation oncology are focused on reducing the dose delivered to normal tissues in support of the hypothesis that reducing dose to normal brain tissues correlates favorably with long-term functional outcomes.

The use of highly focused methods of irradiation to treat craniopharyngioma can be challenging, because these tumors include solid and cystic components (2). The latter is prone to change in volume during treatment, which may compromise target volume coverage. Changes in the cyst volume may also adversely alter the position of normal tissues. Because of the possibility of target volume expansion, magnetic resonance imaging (MRI) during radiation therapy (RT) with the potential for adaptive therapy is crucial to avoid target compromise (3, 4).

From 1998 to 2003, we implemented a protocol that required MRI examinations at Weeks 3 and 5 of treatment for all patients with craniopharyngioma. Patients were treated with conformal RT for 6 weeks with a clinical target volume (CTV) margin of 10 mm and planning target volume (PTV) margin of 5 mm. Preliminary results of this study were reported (5) and showed that 3 of 28 patients required a change in their treatment plan as a result of cyst expansion. When we subsequently reduced the CTV and PTV margins to 5 mm and 3 mm, respectively, we modified our protocol to require weekly MRI using a dedicated radiation oncology magnetic resonance (MR) system. More frequent imaging was considered necessary because of the smaller target volume margins and our concern that changes observed previously when the margins were substantially larger would be clinically significant. Adaptive treatment planning was considered when the contour of the gross tumor volume (GTV) on a given weekly MRI examination intersected with or exceeded the CTV contour that was being used for treatment. Most patients were treated by use of forward-planned three-dimensional conformal RT and fewer by use of intensity-modulated radiation therapy (IMRT) to decrease the amount of planning time and required quality-assurance measures when an adaptive plan was indicated.

In addition to minimizing target volume margins, we have sought to determine the role of newer treatment methods, including proton therapy, for the treatment of craniopharyngioma. Because of the sharp decrease in dose distal (and in some cases lateral) to the targeted volume, proton therapy may be more susceptible to target volume changes than photon therapy, when one is considering the treatment of a dynamic tumor such as craniopharyngioma.

In this report we used the MRI data acquired from the serial evaluations of 14 pediatric patients with craniopharyngioma who received RT to study the dosimetric differences across photon IMRT, double-scatter proton (DSP) therapy, and intensity-modulated proton therapy (IMPT); differences in conformity index (CI) relative to the target volumes, the radiation dose to normal structures, and the sensitivity of the different planning methods to target changes based on weekly MRI during RT were noted.

METHODS AND MATERIALS

Patients

Criteria for inclusion in this study included age younger than 18 years, diagnosis of craniopharyngioma, RT at our institution between 2004 and 2007, and a minimum of 4 surveillance MRI evaluations during RT.

Imaging and treatment planning

A treatment-planning MRI scan was obtained approximately 1 week before initiation of RT. The GTV for the baseline plan was contoured on the T2-weighted MRI scan in all cases and supplemented by information from a co-registered post-contrast T1-weighted MRI scan and a treatment-planning computed tomography (CT) scan. The CTV and PTV margins used for treatment planning were 5 mm and 3 mm, respectively. The prescribed dosage was 54 Gy delivered at 1.8 Gy per fraction, 5 days per week, for a total of 6 weeks.

Plan comparisons

A 5-field IMRT plan, a 3-field DSP plan, and a 4-field IMPT plan, all of which were non-coplanar, were created for each patient by use of the Eclipse 8.1 treatment-planning system (Varian Medical Systems, Palo Alto, CA). The proton plans were created with a proximal and distal margin of 2 mm beyond the PTV. In our interpretation of ICRU (International Commission on Radiation Units & Measurements) Report 78 (6), despite the lack of sensitivity of protons to source–surface distance changes, a PTV is required for proton planning to account for changes in tumor size, shape, and composition (internal margin) and uncertainty in MR-CT image registration and patient positioning and alignment (setup margin). Because our standard 3-mm PTV was more than large enough to account for these potential changes and uncertainties, we added an additional 2 mm beyond the PTV to account for the uncertainty of the distal edge, instead of the conventional 3 mm beyond the CTV, which would have been chosen based on the standard 3.5% calculation for tumors with distal margins of approximately 8 cm in tissue. The lateral margins were set to 8 mm beyond the PTV, which was used to create the aperture for DSP and spot placement for IMPT.

Each of the 3 fields of the DSP plans fully covered the target. These fields included a right–anterior–superior beam, a left–anterior–superior beam, and a vertex (superior) beam. The 4-field IMPT plans used the same beam arrangement as the DSP with the addition of a posterior–superior beam. The beam spot size for the IMPT plans was 1 cm full width at half maximum. Because of the limitations of the treatment planning system (TPS) regarding IMPT, the distal margin was explicitly included in the form of a margin around the PTV, labeled TPS_PTV. The TPS_PTV was used during optimization. The proton beams were chosen to minimize the effects of their distal edges on crucial brain structures. The fifth beam included in the IMRT plans was an anterior–superior beam. All plans were normalized so that the dose to 95% of the PTV (D_{95}) for each patient was 54 Gy.

As the basis for plan comparison, the dose to 5% of the tissue volume (D_5) was recorded for serial-type structures (*i.e.*, optic chiasm, optic nerves, and brainstem), and the mean dose was calculated for parallel-type structures (*i.e.*, scanned body, brain, cochleae, temporal lobes, and hippocampus). The percentage of the scanned body that received 5% (V_5) and 20% (V_{20}) of the prescribed dose was also recorded.

The CI was calculated based on the method described by van't Riet *et al.* (7). This equation calculates the CI using the target volume covered by the reference isodose (TV_{RI}), target volume (TV), and volume of reference isodose (V_{RI}):

$$CI=(TV_{RI} * TV_{RI})/(TV * V_{RI})$$

For calculation purposes, the reference isodose was 95% and the TV was the PTV. The values for this index range from 0 to 1, with 1 indicating a perfect match between the TV and the V_{RI}.

Simulated adaptive plans

The plans created by use of targets contoured on the simulation MRI scan were considered the baseline plans. A T2-weighted MRI scan was acquired approximately once a week during the 6-week treatment course. For each study, the T2 sequence was registered to the treatment-planning CT scan. A new GTV was then contoured, and the appropriate margins were added to create a new CTV and PTV, which were labeled as adaptive targets. The dose delivered by the base plan to the base contours and that delivered to the adaptive contours were calculated for each patient. The correlation between the volumetric change of the target and loss of target coverage was investigated for the baseline plans on the adaptive targets. In addition, the current clinically used adaptive criterion for three-dimensional conformal photon plans was investigated. The criterion consists of creating an adaptive plan when the new GTV contour exceeds any portion of the CTV contour being used for treatment.

RESULTS

Patient characteristics

This retrospective study included 14 patients (median age, 5.1 years; range, 3.2–15.8 years). The treatment-planning CT scan was obtained from the vertex of the head to the apex of the lungs. The mean scanned volume was 5,164 ± 1,403 cm^3. Nine patients had surveillance treatment-planning MRI examinations weekly during RT. Three patients had 5 MRI studies during treatment, and two had only 4. Nine patients had tumor growth during treatment. Figure 1 shows the MR images of a patient who had target growth during therapy. Two patients required at least 1 cyst aspiration during RT to reduce the size of the tumor; both patients underwent an aspiration during the first week of treatment, and one had 2 additional aspirations at Weeks 3 and 5 of therapy.

Photon therapy versus proton therapy

The normal tissue dose and target volume conformity data used to compare IMRT, DSP, and IMPT plans are presented in Table 1. The CI and normal tissue doses were significantly better ($p < 0.01$) for the IMPT plans than for the IMRT and DSP plans, except for the brainstem. There was no difference in brainstem D_5 when we compared methods. IMRT had a higher CI and lower optic nerve dose ($p < 0.01$) than DSP; however, DSP had lower cochlear, chiasm, brain, and body doses ($p < 0.01$). Considering all patients, we found that the D_5 for the brainstem ranged from 54.9 to 55.3 Gy and the mean maximum dose ranged from 56.0 to 57.1 Gy. Figure 2 depicts the average dose–volume histograms for the whole brain and left cochlea by planning method. Although IMRT was more conformal than DSP, the V_5 of the body was 44.2% for IMRT compared with 15.7% for DSP. The decrease in integral dose when using proton therapy is implied in Fig. 3, which displays the dose distribution for IMRT and IMPT. The V_5 of IMPT was 17.0%.

Adaptive planning is essential in pediatric craniopharyngioma

The mean PTV at baseline was 54.8 cm^3 (range, 28.8–112.2 cm^3). As mentioned previously, 9 of 14 patients had tumor growth during RT (Fig. 4). The mean change in the PTV was an 11.3% increase (range, 20.9% decrease to 44.7% increase). Target growth was most often

seen during the first 3 weeks of treatment (Fig. 4). Target coverage was lost when the baseline plan was used on the adaptive targets for each planning method (Fig. 5). The coefficients of determination (R^2) were 0.73, 0.38, and 0.62 for IMRT, DSP, and IMPT, respectively; all were statistically significant ($p < 0.01$). The linear regression equations, with the y-intercept set to 0, were $y = -0.033x$, $y = -0.083x$, and $y = -0.552x$ for IMRT, DSP, and IMPT, respectively. In these equations y represents the percent change in D_{95}, and x represents the percent change in PTV. Target coverage in IMPT was 60% more sensitive to changes in volume than that in IMRT, and DSP was relatively insensitive to target changes.

The clinical criterion of creating an adaptive plan whenever the new GTV contour exceeds any portion of the CTV contour under treatment has been simple to implement in the clinic and appears to be well suited for three-dimensional conformal RT. The 9 patients with target growth received a total of 50 MRI examinations during RT. The GTV contour exceeded the baseline CTV contour in 26 of the 50 evaluations. For IMRT, the mean D_{95} loss when the GTV contour exceeded the CTV contour was 10.7% ± 3.4%. The mean D_{95} loss when there was no intersection of the contours was 4.8% ± 3.5%. For DSP, these losses were 2.8% ± 2.1% and 0.7% ± 0.9%, respectively. For IMPT, they were 18.7% ± 7.5% and 5.9% ± 4.3%, respectively. Given that a 2% loss of coverage may be acceptable, this criterion can be used for DSP but not for IMRT or IMPT.

DISCUSSION

This study clearly shows that target growth during RT is a significant problem for children with craniopharyngioma. When unaccounted for, target growth may adversely affect tumor control rates and normal tissue. Target growth was observed in the majority (64.3%) of cases in our series and often early in the treatment course. Considering that 2 patients underwent cyst aspiration during treatment, the data presented in this report represent a conservative estimate of target growth. It is not clear which patients are not at risk for target growth, nor have we defined the best method for imaging during RT.

Our experience imaging children during treatment for craniopharyngioma began by obtaining MRI scans during Weeks 3 and 5 of RT as part of a prospective study to monitor normal tissues for radiation effects in a prospective study conducted between 1998 and 2003 (5). In that experience, tumor cyst expansion was observed in some cases, thereby prompting an assessment of our methods and increased vigilance in on-treatment evaluations. More than half of the patients showed cyst expansion during treatment, and a nearly equal number required cyst aspiration; however, only a few required a change in treatment planning attributed to the relatively large CTV (10 mm) and PTV (3–5 mm) margins used in that protocol. Because of the effect of collateral irradiation of normal tissues, we and other authors have sought to further reduce the dose to normal tissues by reducing CTV margins (8) to approximately 5 mm and PTV margins uniformly to 3 mm. The smaller CTV margin has been justified not only based on the issue of normal tissue irradiation but also based on the experience that a 10-mm margin results in high rates of tumor control and knowledge that craniopharyngioma is a minimally invasive tumor with low rates of brain invasion and limited ectopia (9). The smaller PTV is achievable because of newer methods of localization and verification including the use of cone-beam CT (10).

Considering the findings of this study, we conclude that surveillance imaging during treatment of craniopharyngioma is imperative. There are dose and conformity advantages to using protons over photons and a potential benefit of using the nonuniform proton-scanning method IMPT. Using proton therapy in general and IMPT in particular, we may be able to greatly reduce the dose to normal tissues, thereby potentially reducing the adverse systemic

effects of irradiation by lowering the integral dose. Concern exists regarding the potential hazard of neutron dose from proton therapy. However, it has been shown that the neutron dose for IMPT is quite low (11) and that, because of the decreased integral dose, the risk of secondary malignancies is lower for proton therapy than photon therapy (12).

Weekly or more frequent high-resolution imaging during proton therapy should be a requirement for patients with craniopharyngioma. Combining imaging for localization and treatment verification with surveillance of tumor would be ideal; however, high-resolution CT imaging is not the best means of imaging craniopharyngioma. Since 2005, our studies have relied on a dedicated departmental MR system that is used at least once weekly in the treatment course of children with craniopharyngioma. Because daily MRI is not logistically feasible, even with a dedicated system, our algorithm for adaptive treatment provided for treatment plan changes or cyst aspiration (when feasible) when the GTV contour approached or exceeded the CTV contour in any plane. In most cases the goal was to respond with a new treatment plan as soon as possible, preferably within 2 days. For cases in which the change was dramatic, an effort was made to immediately modify the treatment plan for the following day. Although CT findings are diagnostically specific for craniopharyngioma, MRI is fundamentally superior to CT imaging for determining tumor extent (13), treatment planning, and on-treatment monitoring. It provides better resolution of cystic and solid tumor interfaces with normal tissue, as well as contrast of thin-walled cystic structures adjacent to CSF spaces, and is not susceptible to beam hardening and the limitations associated with imaging near the base of the skull and when the tumor extends into the posterior fossa. CT might be acceptable in the absence of MRI but would require more effort and would contribute more radiation dose to normal tissues. Ideally, on-treatment imaging should be performed daily; however, the best current method, cone-beam CT, may be capable of imaging the tumor complex but not in the same manner as conventional CT or with the same capabilities as MRI.

On the basis of the linear regression equation and the strength of the correlation, a 5% change in the PTV may be cause to investigate the necessity of an adaptive plan when using IMPT. A 10% change in PTV should evoke the same response for IMRT, and a 25% change in PTV should evoke that for DSP. Our current clinical criterion for adaptive planning that includes creation of a new treatment plan when the GTV contour exceeds the treatment CTV contour is valid for DSP but not for IMRT or IMPT. Given the normal tissue sparing, decreased integral dose, and relative insensitivity to target changes, DSP may be the best proton method to deploy for fractionated treatment of craniopharyngioma in the absence of high-frequency (more than once per week) and high-resolution imaging during treatment.

Despite the fact that we found IMRT to have a larger CI than DSP in this study, we also found a 3-fold difference in the integral dose (V_5) values between IMRT and DSP, suggesting a systemic benefit to proton therapy over photon therapy. The systemic effects of focal central nervous system irradiation are often not considered in the broad view of radiation-related effects. We have shown that focal irradiation in children with brain tumors results in cytokine responses that are measurable in serum during and after RT (14).

CONCLUSION

Proton therapy, whether DSP or IMPT, dramatically reduces the dose of irradiation delivered to the whole brain and body, as compared with that associated with IMRT. The DSP method is relatively insensitive to changes in target volume. IMPT is the most conformal treatment and spares the most normal tissue, but it is highly sensitive to target changes. Therefore patients should be closely monitored if this method is used.

Acknowledgments

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References

1. Kalapurakal JA. Radiation therapy in the management of pediatric craniopharyngiomas—A review. Childs Nerv Syst. 2005; 21:808–816. [PubMed: 16075214]
2. Helperin, EC.; Constine, LS.; Tarbell, NJ., et al. Pediatric radiation oncology. 4. Philadelphia: Lippincott Williams & Wilkins; 2005.
3. Winkfield KM, Linsenmeier C, Yock TI, et al. Surveillance of craniopharyngioma cyst growth in children treated with proton radiotherapy. Int J Radiat Oncol Biol Phys. 2009; 73:716–721. [PubMed: 18676089]
4. Kornguth D, Mahajan A, Frija E, et al. Shape variability of craniopharyngioma as measured on CT-on-rails during radiotherapy treatment. Int J Radiat Oncol Biol Phys. 2006; 66:S259–S260.
5. Merchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. J Neurosurg. 2006; 104:94–102. [PubMed: 16506496]
6. International Commission on Radiation Units & Measurements. ICRU Report 78: Prescribing, recording, and reporting proton beam therapy. Bethesda, MD: ICRU; 2007.
7. van't Riet A, Mak ACA, Moerland MA, et al. A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: Application to the prostate. Int J Radiat Oncol Biol Phys. 1997; 37:731–736. [PubMed: 9112473]
8. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: Biology, therapy, and late effects. Semin Radiat Oncol. 2010; 20:58–66. [PubMed: 19959032]
9. Weiner HL, Wisoff JH, Rosenberg ME, et al. Craniopharyngiomas: A clinicopathological analysis of factors predictive of recurrence and functional outcome. Neurosurgery. 1994; 35:1001–1010. discussion 1010–1001. [PubMed: 7885544]
10. Beltran C, Krasin MJ, Merchant TE. Inter- and intrafractional positional uncertainties in pediatric radiotherapy patients with brain and head and neck tumors. Int J Radiat Oncol Biol Phys. 2010 In Press. 10.1016/j.ijrobp.2009.12.057
11. Schneider U, Agosteo S, Pedroni E, et al. Secondary neutron dose during proton therapy using spot scanning. Int J Radiat Oncol Biol Phys. 2002; 53:244–251. [PubMed: 12007965]
12. Miralbell R, Lomax A, Cella L, et al. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. Int J Radiat Oncol Biol Phys. 2002; 54:824–829. [PubMed: 12377335]
13. Freeman MP, Kessler RM, Allen JH, et al. Craniopharyngioma: CT and MR imaging in nine cases. J Comput Assist Tomogr. 1987; 11:810–814. [PubMed: 3655043]
14. Merchant TE, Li C, Xiong X, et al. Cytokine and growth factor responses after radiotherapy for localized ependymoma. Int J Radiat Oncol Biol Phys. 2009; 74:159–167. [PubMed: 19019565]

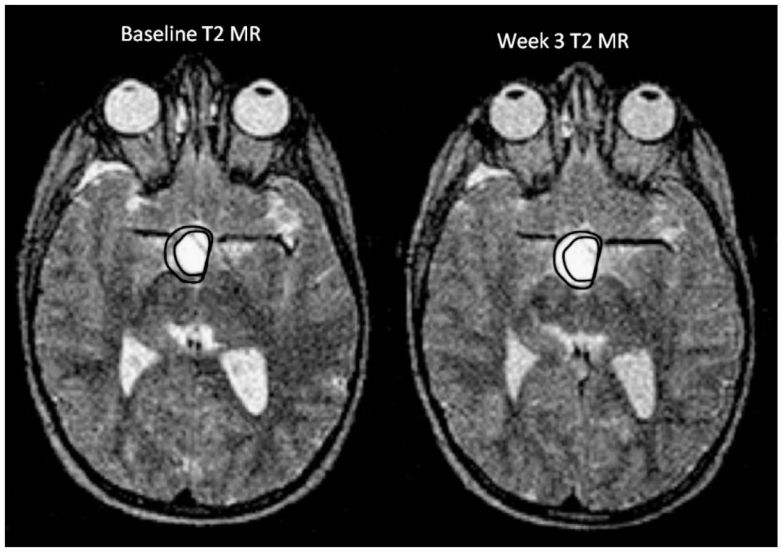

Fig. 1.
Baseline (left) and on-treatment (right) T2-weighted magnetic resonance images of a single patient. The inner contours represent the baseline gross tumor volume, and the outer contours represent the volume at Week 3 of treatment. The maximum in-plane separation between the two contours shown is 6 mm.

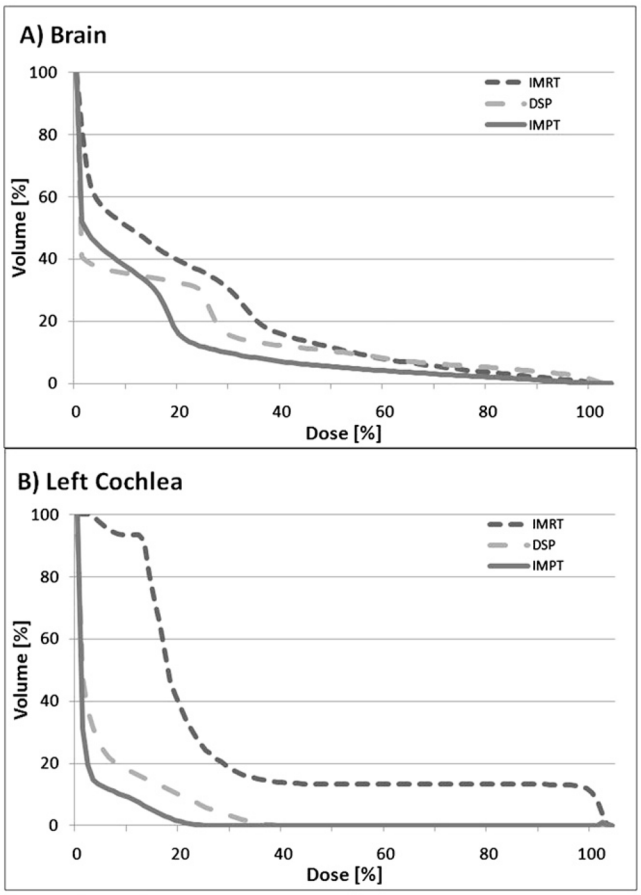

Fig. 2.
Mean dose–volume histograms for whole brain (A) or left cochlea (B) for 3 planning methods: intensity-modulated radiation therapy (IMRT) (dotted line), double-scatter photon (DSP) therapy (dashed line), and intensity-modulated photon therapy (IMPT) (solid line).

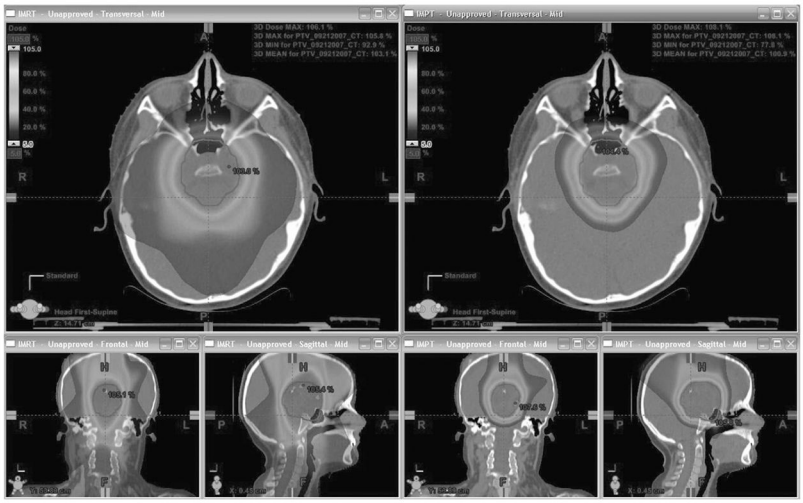

Fig. 3.

Side-by-side dose wash comparison of intensity-modulated radiation therapy (IMRT) plan (left) and intensity-modulated photon therapy (IMPT) plan (right) for a typical patient. The dose range shown is 5% to 105%. The dramatic decrease in the low-dose area, particularly the lack of exit dose for the IMPT plan, should be noted.

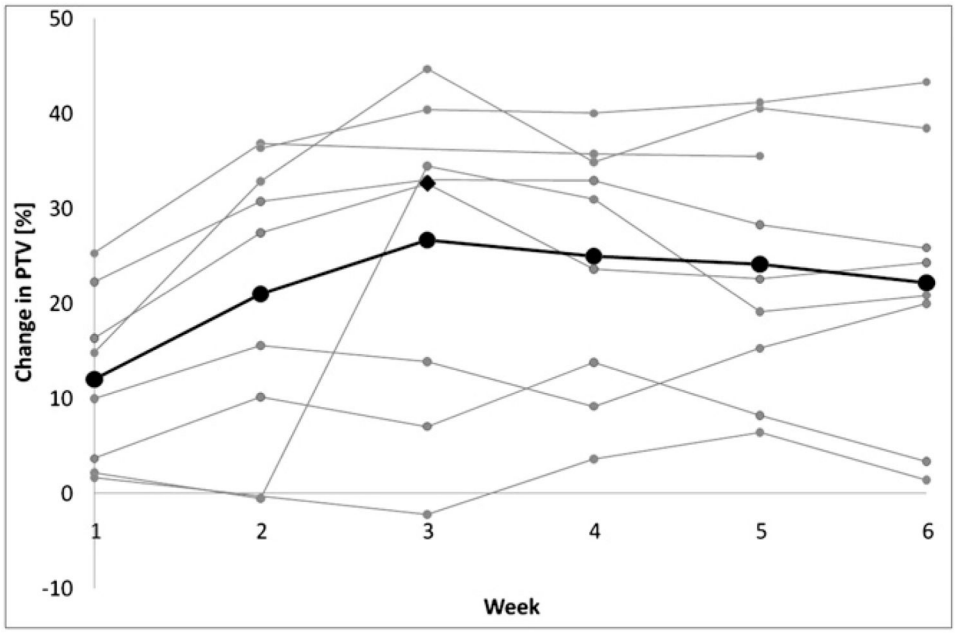

Fig. 4.
Mean changes (black line) and individual changes (gray lines) in planning treatment volume (PTV) for the 9 patients who showed target growth during the 6 weeks of radiation therapy.

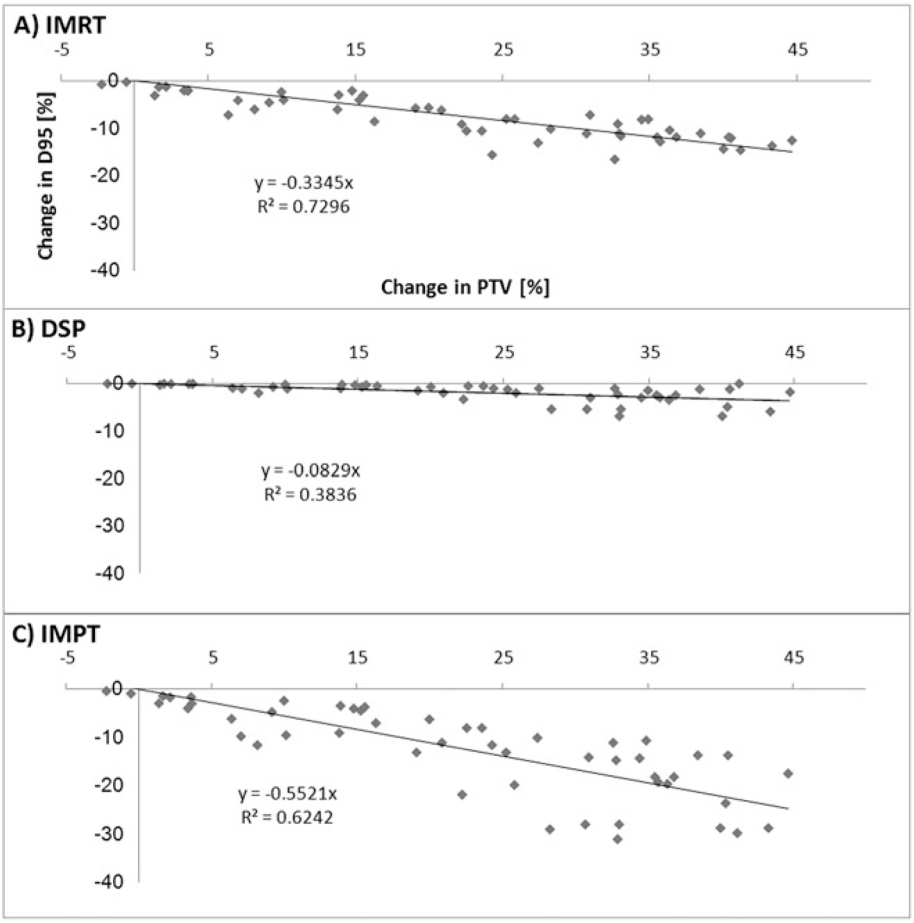

Fig. 5.

Comparisons of relative decrease in planning treatment volume (PTV) with that of dose to 95% of PTV (D_{95}) are shown for the 9 patients who had target growth during the 6 weeks of radiation therapy. Intensity-modulated radiation therapy (IMRT) (A) and intensity-modulated photon therapy (IMPT) (C) were sensitive to changes in PTV, whereas double-scatter photon (DSP) therapy (B) was not. The values (diamonds) represent every adaptive target for the 9 patients. The R^2 values shown were all statistically significant ($p < 0.001$).

Table 1

Comparisons of photon-based and proton-based planning methods

Measure	Planning method	Mean ± SD	*p* Value vs. IMRT	*p* Value vs. DSP
Conformity index	IMRT	0.71 ± 0.04		
	DSP	0.50 ± 0.04	<0.001	
	IMPT	0.84 ± 0.04	<0.001	<0.001
Right cochlea D_{50} (Gy)	IMRT	15.31 ± 8.62		
	DSP	8.08 ± 12.57	0.005	
	IMPT	4.20 ± 8.14	<0.001	0.016
Left cochlea D_{50} (Gy)	IMRT	11.28 ± 3.60		
	DSP	2.71 ± 4.35	<0.001	
	IMPT	1.16 ± 2.41	<0.001	0.021
Right temporal lobe D_{50} (Gy)	IMRT	8.51 ± 3.79		
	DSP	8.17 ± 4.37	0.391	
	IMPT	5.92 ± 3.03	<0.001	<0.001
Left temporal lobe D_{50} (Gy)	IMRT	7.25 ± 2.70		
	DSP	7.45 ± 3.69	0.721	
	IMPT	5.17 ± 2.62	<0.001	<0.001
Right hippocampus D_{50} (Gy)	IMRT	19.29 ± 10.96		
	DSP	19.17 ± 13.46	0.903	
	IMPT	13.87 ± 11.04	<0.001	<0.001
Left hippocampus D_{50} (Gy)	IMRT	17.97 ± 8.42		
	DSP	18.44 ± 12.18	0.733	
	IMPT	11.99 ± 8.80	<0.001	<0.001
Optic chiasm D_5 (Gy)	IMRT	55.92 ± 0.32		
	DSP	54.82 ± 0.36	<0.001	
	IMPT	55.34 ± 0.38	0.001	0.001
Right optic nerve D_5 (Gy)	IMRT	45.17 ± 8.80		
	DSP	49.77 ± 6.03	0.001	
	IMPT	42.55 ± 11.50	0.030	0.002
Left optic nerve D_5 (Gy)	IMRT	43.34 ± 11.17		
	DSP	46.58 ± 10.69	0.026	
	IMPT	39.98 ± 13.80	0.010	0.001
Brainstem D_{50} (Gy)	IMRT	55.35 ± 0.72		
	DSP	54.89 ± 0.34	0.037	
	IMPT	55.16 ± 0.70	0.198	0.214
Whole brain D_{50} (Gy)	IMRT	12.22 ± 2.56		
	DSP	9.48 ± 2.26	<0.001	
	IMPT	7.58 ± 1.90	<0.001	<0.001
Maximum dose (Gy)	IMRT	56.99 ± 0.34		
	DSP	56.03 ± 0.43	<0.001	
	IMPT	57.11 ± 0.91	0.607	0.002

Measure	Planning method	Mean ± SD	*p* Value vs. IMRT	*p* Value vs. DSP
Body D_{50} (Gy)	IMRT	6.32 ± 1.65		
	DSP	3.61 ± 1.07	<0.001	
	IMPT	2.83 ± 0.83	<0.001	<0.001
Body V_5 (%)	IMRT	44.2 ± 0.09		
	DSP	15.7 ± 0.04	<0.001	
	IMPT	17.0 ± 0.04	<0.001	<0.001
Body V_{20} (%)	IMRT	17.5 ± 0.05		
	DSP	13.3 ± 0.03	<0.001	
	IMPT	6.2 ± 0.02	<0.001	<0.001
Body (cm^3)		5,164 ± 1,403		

Abbreviations: IMRT = intensity-modulated radiation therapy; DSP = double-scatter proton; IMPT = intensity-modulated proton therapy; D_{50} = dose to 50% of structure; D_5 = dose to 5% of structure; V_5 = volume of tissue receiving 5% of prescribed dose; V_{20} = volume of tissue receiving 20% of prescribed dose.