Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 979–986, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.11.065

CLINICAL INVESTIGATION **Brain**

PROTON RADIOTHERAPY FOR CHILDHOOD EPENDYMOMA: INITIAL CLINICAL OUTCOMES AND DOSE COMPARISONS

Shannon M. MacDonald, M.D.,* Sairos Safai, Ph.D.,* Alexei Trofimov, Ph.D.,* John Wolfgang, Ph.D.,* Barbara Fullerton, Ph.D.,† Beow Y. Yeap, Sc.D.,‡ Thomas Bortfeld, Ph.D.,* Nancy J. Tarbell, M.D.,* and Torunn Yock, M.D.*

Departments of *Radiation Oncology, and ‡Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and †Department of Otology and Laryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Purpose: To report preliminary clinical outcomes for pediatric patients treated with proton beam radiation for intracranial ependymoma and compare the dose distributions of intensity-modulated radiation therapy with photons (IMRT), three-dimensional conformal proton radiation, and intensity-modulated proton radiation therapy (IMPT) for representative patients.

Methods and Materials: All children with intracranial ependymoma confined to the supratentorial or infratentorial brain treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this study. Seventeen patients were treated with protons. Proton, IMRT, and IMPT plans were generated with similar clinical constraints for representative infratentorial and supratentorial ependymoma cases. Tumor and normal tissue dose–volume histograms were calculated and compared.

Results: At a median follow-up of 26 months from the start date of radiation therapy, local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Subtotal resection was significantly associated with decreased local control ($p = 0.016$). Similar tumor volume coverage was achieved with IMPT, proton therapy, and IMRT. Substantial normal tissue sparing was seen with proton therapy compared with IMRT. Use of IMPT will allow for additional sparing of some critical structures.

Conclusions: Preliminary disease control with proton therapy compares favorably with the literature. Dosimetric comparisons show the advantage of proton radiation compared with IMRT in the treatment of ependymoma. Further sparing of normal structures appears possible with IMPT. Superior dose distributions were accomplished with fewer beam angles with the use of protons and IMPT. © 2008 Elsevier Inc.

Ependymoma, Pediatric brain tumors, Proton beam radiation.

INTRODUCTION

Ependymomas are relatively rare malignancies accounting for 8–10% of intracranial pediatric tumors, with most cases occurring in children younger than 4 years (1, 2). One third of intracranial childhood ependymomas occur in the cerebral hemispheres. The remaining two thirds occur in the posterior fossa, arising along the lining of the fourth ventricle (3, 4). Standard treatment for patients with both supratentorial and infratentorial ependymoma consists of maximal surgical resection followed by radiation therapy (1, 5, 6). Critical structures, including the brainstem, cranial nerves, cochlea, and brain, lie in close proximity to treatment volumes, which, in addition to very young age at diagnosis, makes a highly conformal treatment most desirable.

Excellent control rates have been achieved with radiation therapy to the initially involved area of disease, which is now the accepted standard of care (7–11). Despite this reduction in treatment volume compared to historical radiation volumes, healthy uninvolved tissues receive radiation. In addition, because ependymomas occur in the very young, these patients can expect to experience worse adverse late effects from radiation therapy to the brain compared to older children or adults. Because morbidities are related to the normal tissues irradiated in the process of treating the tumor, it is of critical importance to improve dose conformity to the tumor bed. Complications of central nervous system (CNS) radiation in the pediatric population are well documented and include developmental and neurocognitive deficits, neuroendocrine

Reprint requests to: Shannon M. MacDonald, M.D., Department of Radiation Oncology, Massachusetts General Hospital, Cox 340, 100 Blossom Street, Boston, MA 02114. Tel: (617) 726-5184; Fax: (617) 726-3603; E-mail: smacdonald@partners.org

Presented at the 49th Annual Meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO), Los Angeles, CA, October 28–November 1, 2007.

Conflict of interest: none.

Received Aug 20, 2007, and in revised form Nov 13, 2007. Accepted for publication Nov 23, 2007.

dysfunction, growth abnormalities, sensorineural hearing loss, vascular events, and second malignancies (12–15). These late effects of treatment are a substantial source of morbidity and mortality, can impair quality of life, and affect the ability to function normally in society.

The unique characteristics of proton therapy offer major advantages in optimizing prescription dose to tumor volumes while sparing normal tissues. The chief advantage of proton radiotherapy is the sparing of normal tissue through the elimination of exit dose and reduction in entrance dose.

Currently, the majority of proton therapy is delivered through passive beam-scattering methods by using range compensators and apertures, which are custom designed to deliver a homogeneous dose distribution conforming to the distal edge of the target for each field (16). Intensity-modulated proton therapy (IMPT) refers to plans that deliver the dose to the target by the superimposition of individually *inhomogeneous* fields (17–19). The IMPT allows for increased dose-shaping capabilities with improved conformity not only at the distal region of the target, but also to the proximal target edge from a given field. At the present time, IMPT cannot be delivered efficiently with passive scattering beams alone and requires implementation of active scanning methods, which have the additional advantage of reduced neutron contamination, which may drive down the risk of second malignancy compared with passively scattered techniques (20, 21).

In this study, we report early clinical outcomes, including LRF, DFS, overall survival, and toxicities for patients with childhood ependymoma treated with three-dimensional (3D) conformal proton therapy. This represents the first report of clinical outcomes using proton radiation for pediatric CNS ependymoma. Similar to other comparative planning studies, we show the dosimetric advantage of proton radiotherapy over intensity-modulated radiation therapy (IMRT) for the treatment of childhood ependymoma by comparing dose–volume histograms for tumor volumes and normal tissues (22–24). In addition, we show that further tissue sparing may be achieved for selected patients when the techniques of intensity modulation are applied to proton therapy.

METHODS AND MATERIALS

Patients

All patients with supratentorial and infratentorial CNS ependymoma treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this retrospective study. Seventeen patients were identified. A dedicated planning contrast-enhanced computed tomography (CT) scan was obtained. Patients were immobilized with a custom Aquaplast facemask (WFR Aquaplast, Wyckoff, NJ). A separate high-definition magnetic resonance image (3-mm slices, no skip) was performed, and the T1 postgadolinium and/or flair sequence was anatomically registered to the CT scan by using CMS Focal Fusion software to facilitate volume definition. The tumor bed and residual tumor were contoured as the gross tumor volume. Several patients were coenrolled on the Children's Oncology Group ACNS 0121 ependymoma trial, and a 1-cm margin was added to the gross tumor volume for clinical tumor volume (CTV) as required for the protocol. For some earlier patients not on protocol, the CTV was defined as the tumor bed at risk and any area judged at risk of microscopic extension, which generally comprised a margin around that tumor bed of 1–1.5 cm. An additional margin of 8–10 mm was added around the CTV to account for both penumbra and planning target volume together, which accounts for a setup margin of approximately 3 mm. Brass apertures and Lucite compensators were custom made for each field. Daily positioning was achieved based on bony landmarks with diagnostic-quality orthogonal X-rays compared with digitally reconstructed radiographs. A computer program assists therapists in making patient couch shifts in 6 *df* to more accurately align patients (16).

The proton dose was prescribed in cobalt gray equivalent (CGE) using the relative biologic effectiveness value of 1.1 (25). Critical normal tissues were contoured for each patient. These included brainstem, optic chiasm, optic nerves, lenses, cochlea, pituitary gland, hypothalamus, temporal lobes, and whole brain. Generally accepted tolerance doses were used. If tumor was adjacent to or involving the brainstem, a small volume was permitted to exceed 54 CGE. Field arrangements were chosen to minimize dose to critical structures while maximizing target coverage. Most patients were treated with a three- or four-field technique. For infratentorial tumors, patients generally were treated with posterior-anterior, RPO, and LPO fields with a superior field only if it improved coverage and/or avoidance of such critical structures as brainstem. For supratentorial tumors, a variety of field arrangements were used depending on the location of the tumor. Only 3 patients had a cone down or boost for the purpose of decreasing the volume of brainstem receiving a dose greater than 54 CGE.

Dosimetric comparisons

For two representative cases, we compared IMRT, 3D conformal proton beam, and IMPT radiation treatment plans for a posterior fossa ependymoma occupying the fourth ventricle and extending along the right foramen of Luschka and a supratentorial ependymoma. Both patients were treated with conformal proton radiation with a rotational gantry system.

Standard proton planning was performed with XiO planning software (CMS Inc., St. Louis, MO). The Francis H. Burr Proton Therapy Center provides a rotational gantry system and maximum proton beam energy of 231 MeV. A four-field technique was used in both cases using superior, posterior-anterior, right lateral oblique, and left lateral oblique beam directions. The CTV prescription was 55.8 CGE.

To create the IMPT plan, CT data and contours were transferred to the inverse treatment planning system, KonRad Pro, developed at the German Cancer Research Center, Germany (18, 26). The scientific version of KonRad used in the present work allows optimization of dose distributions not only for photon, but also for proton radiation and carbon beam therapy. Plan optimization is performed for several irradiation fields simultaneously by using the inverse planning technique based on the Newton gradient method (27). In this study, the IMPT plan was optimized for discrete pencil beam spots by using three coplanar beam orientations with beam angles of 140, 180, and 220 for the infratentorial case. These fields were adopted from the 3D proton plan. The superior field was omitted because it did not add to the quality of the IMPT plan. Three fields were also used for the supratentorial IMPT plan. The IMRT plans were generated for both patients, again using the Konrad planning system.

Statistical analysis

Rates of local control, progression-free survival, and overall survival were estimated by using the Kaplan-Meier method.

Follow-up was measured from the initiation of proton radiotherapy until local recurrence, distant failure, or death; patients who had not reached the event of interest were censored at their last follow-up. Log-rank test was used to compare local control rates by the extent of surgical resection; the exact two-sided p value was computed by using StatXact 6 (Cytel, Cambridge, MA).

Ethical considerations

Institutional review board approval was obtained before record and plan review. Complete anonymity of names and medical record numbers was maintained.

RESULTS

Seventeen patients (six males, 11 females) were treated with proton radiotherapy between November 2000 and March 2006. Median prescribed dose was 55.8 CGE (range, 52.2–59.4 CGE). Age at diagnosis ranged from 13 months to 12.8 years, with a median age of 3.6 years. Thirteen patients had a gross total resection before radiation therapy, and 4 were considered to have a subtotal resection. Thirteen patients had infratentorial tumors and 4 had supratentorial tumors. Seven patients had Grade III ependymoma, and 10 patients had Grade II ependymoma. Seven patients were enrolled on the Children's Oncology Group protocol ACNS 0121. Four patients received chemotherapy. Chemotherapy was delivered after resection and before radiation therapy for 3 of the 4 patients because of gross residual disease. The other received chemotherapy after subtotal resection and was considered to have a complete response after chemotherapy; no adjuvant radiation was given at this time. This patient experienced recurrence 2 years later. At the time of recurrence, she underwent a GTR and received radiation. At a median follow-up of 26 months from the start date of radiation therapy (range, 43 days to 78 months), local control, progression-free survival, and overall survival rates were 86% ± 9% (SE), 80% ± 10%, and 89% ± 10%, respectively. Two patients experienced local recurrence and 1 patient failed distally in the thoracic spine; all other patients remain disease free. Both patients who failed locally had infratentorial tumors and subtotal surgical resections; 1 patient had a Grade III ependymoma, the other had a Grade II tumor. Subtotal surgical resection was associated significantly with worse local control ($p = 0.016$). In 1 patient, local recurrence ultimately led to death after subtotal resection and more chemotherapy. In the other patient, recurrence was diagnosed radiographically and the patient is living with the recurrent/persistent disease after radiosurgery and is on chemotherapy. The patient, who failed distally in the thoracic spine, had a Grade III tumor. This patient underwent gross total resection followed by adjuvant local field radiation therapy and currently is without evidence of disease. Endocrine, auditory, and neurocognitive data were collected for most patients. Although no late toxicity was reported to date, it is too early to conclusively report late toxicity for this group of patients.

For dosimetric comparison, two representative cases (supratentorial and infratentorial) were selected. The IMRT and IMPT plans were generated and compared with standard proton plans. All plans were normalized so that 55.8 Gy/CGE covered 95% of the CTV. Comparable tumor volume coverage was achieved with IMPT, standard (3D-conformal) proton therapy, and IMRT. Substantial normal tissue sparing was seen with the proton therapy compared with IMRT. Use of IMPT allowed for additional sparing of critical structures (Tables 1 and 2; Figs. 1 and 2). For the supratentorial plan, improvement in organ sparing with IMPT was most pronounced in the dose to the hypothalamus. Both infratentorial and supratentorial plans showed improved sparing of whole brain and temporal lobes with protons compared with IMRT. The IMPT provided further sparing of these structures. This was achieved with a decreased number of treatment fields; four with standard proton therapy and only three with IMPT.

Tables 1 and 2 list doses received by 5%, 50%, and 90% of each structure, as well as the mean dose for each structure. Figures 1 and 2 show dose–volume histograms for tumor volumes and normal structures for the infratentorial and supratentorial plans, respectively. Proton radiation therapy decreased dose to all normal structures evaluated. Less benefit was derived for normal structures directly adjacent

Table 1. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with an infratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	6	45	<0.1	<0.1	9	48	<0.1	<0.1	13	54	2	0.4
Temporal lobe	2	13	<0.1	<0.1	4	21	<0.1	<0.1	16	48	11	1
Brainstem	24	57	16	< 0.1	33	56	37	4	39	57	47	7
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	12	16	12	7
Optic chiasm	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	6	17	4	3
Left cochlea	<0.1	0.1	<0.1	<0.1	2	5	2	1	37	38	37	36
Right cochlea	29	34	29	24	35	43	36	26	43	45	43	41
Hypothalamus	<0.1	<0.1	<0.1	<0.1	0.2	1	0.1	<0.1	11	25	10	3
CTV	57	58	57	56	57	58	57	56	57	58	57	56
GTV	57	58	57	56	57	58	57	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

Table 2. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with a supratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	5	27	0	<0.1	7	37	0.2	<0.1	12	45	3	0.5
Temporal lobe	8	19	8	<0.1	11	30	14	<0.1	23	47	23	3
Brainstem	21	57	4	<0.1	22	56	7	<0.1	23	58	8	2
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	2	3	2	2
Optic chiasm	<0.1	<0.1	<0.1	<0.1	0.1	0.3	<0.1	<0.1	3	4	3	2
Left cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	3	4	3	2
Right cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	2	2	2	1
Hypothalamus	15	47	13	0.3	22	49	20	4	22	50	22	6
CTV	56	57	56	56	56	57	56	56	57	58	57	56
GTV	57	57	57	56	56	56	56	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

to or encompassed by the CTV. The IMPT provided further normal tissue sparing for most structures.

Figure 3 shows axial views of the IMRT, proton, and IMPT plans for treatment of an infratentorial ependymoma. Dose distributions are shown at the level of the cochlea and temporal lobes. For the infratentorial plan, the left cochlea received a mean dose of 37 Gy with IMRT, 2 CGE with protons, and less than 0.1 CGE with IMPT. Mean dose received by the

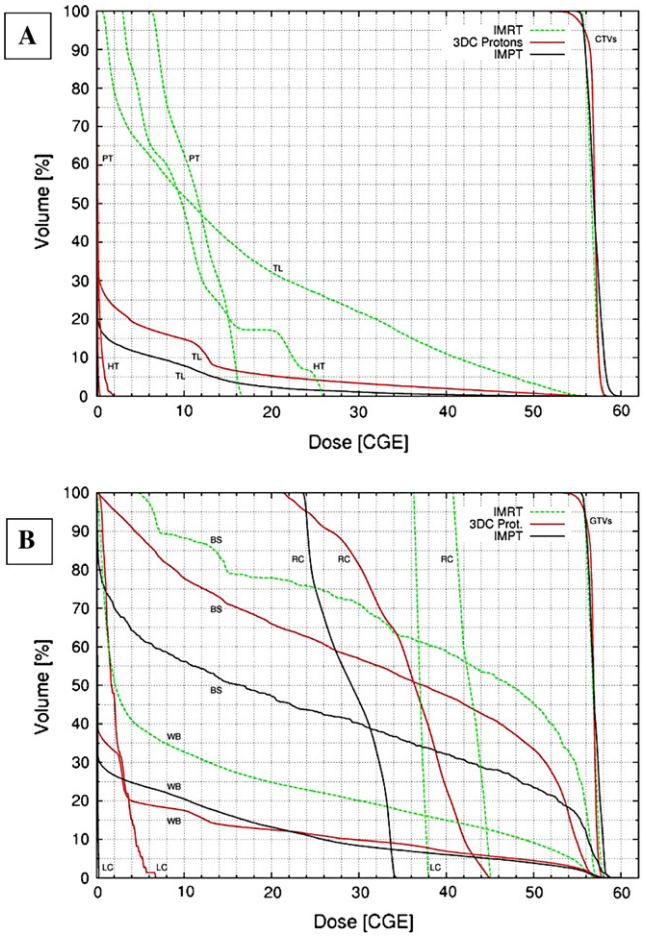

Fig. 1. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC proton), and intensity-modulated proton therapy (IMPT) plans for infratentorial ependymoma: (A) clinical tumor volume (CTV), temporal lobes (TL), pituitary (PT), hypothalamus (HT), (B) gross tumor volume (GTV), right cochlea (RC), left cochlea (LC), brainstem (BS), and whole brain (WB).

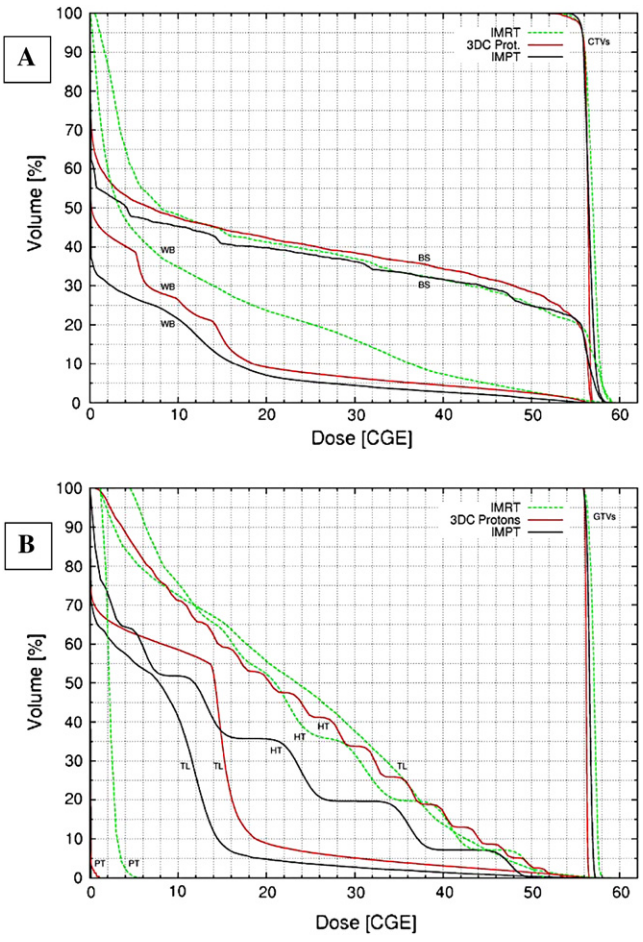

Fig. 2. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC Prot.), and intensity-modulated proton therapy (IMPT) plans for supratentorial ependymoma: (A) clinical tumor volume (CTV), brainstem (BS), whole brain (WB), (B) gross tumor volume (GTV), temporal lobes (TL), pituitary (PT), and hypothalamus (HT).

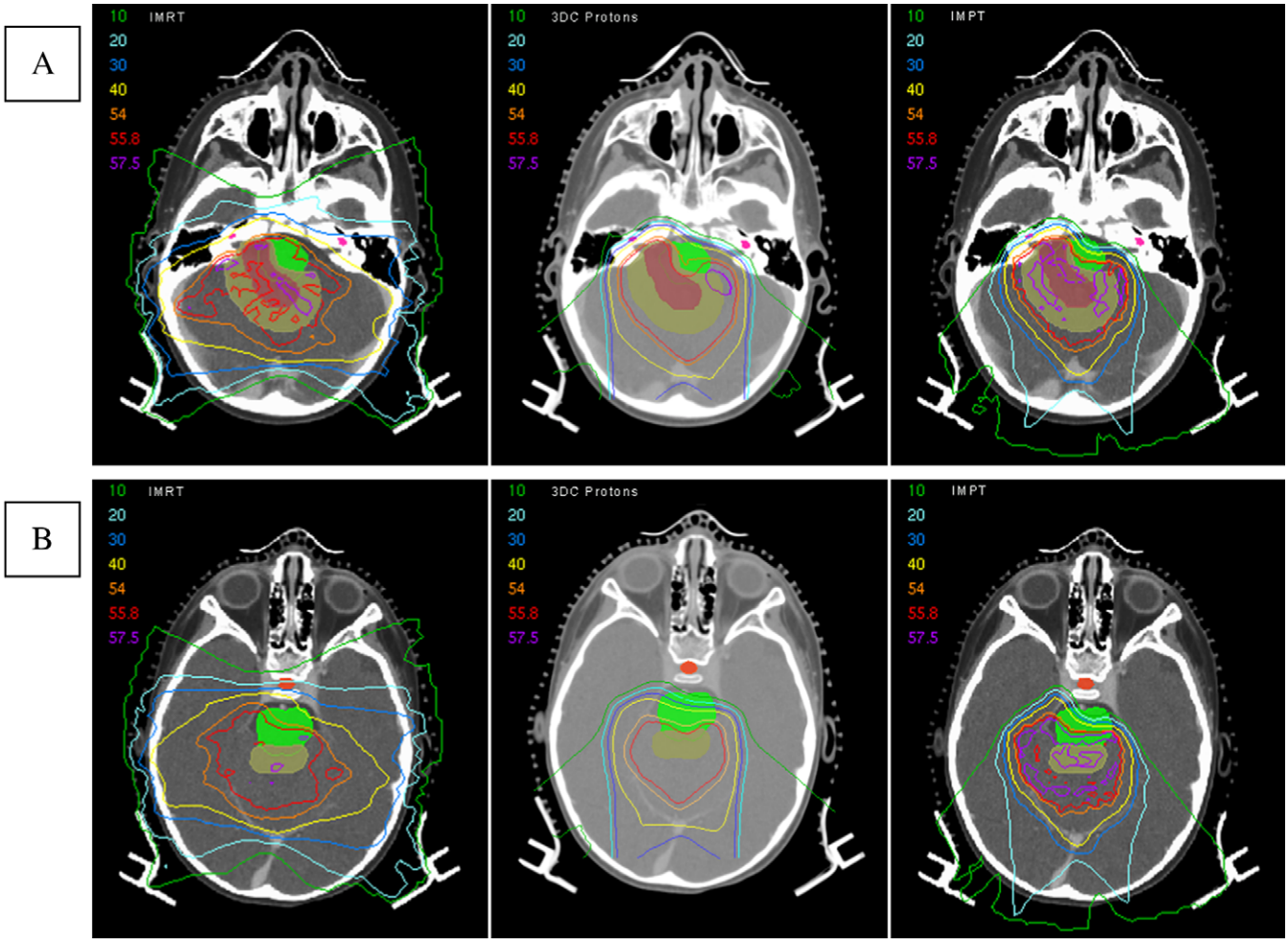

Fig. 3. Intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans shown in the axial plane at the level of the (A) cochlea and (B) temporal lobes and pituitary gland. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons show improved sparing of the cochlea, cerebellum, pituitary gland, and temporal lobes. The IMPT plan shows superior proximal target conformity and further sparing of structures.

temporal lobes was 16 Gy with IMRT. This was reduced to 4 CGE with protons and 2 CGE with IMPT. A similar benefit was seen with the dose received by the whole brain. Five percent and 50% of the pituitary received 16 and 12 Gy with IMRT, respectively. The dose to 5% and 50% of this structure with both proton and IMPT plans was less than 1 CGE in each case. The hypothalamus received a mean dose of 10.7 Gy with IMRT. For protons, mean dose was 0.2 CGE, and no measurable dose was delivered with IMPT. Similarly, dose to the brainstem was reduced with proton treatment. Dose–volume histograms (Figs. 1 and 2) visibly show the benefit of protons for the brain and other CNS structures. Figure 4 shows sagittal and coronal views and illustrates the rapid dose falloff of proton radiation.

Similar to the infratentorial plan, greater sparing of CNS structures was shown for proton and IMPT planning for the supratentorial case. The hypothalamus was in close proximity to the CTV for this particular case. The IMPT planning provided substantially greater sparing for this particular structure (Fig. 5).

DISCUSSION

This study shows excellent early outcomes using proton radiation for the treatment of patients with localized ependymoma. Consistent with several prior studies, we found a significant correlation between subtotal resection and subsequent local failure (6, 28). No significant late toxicity after radiation was reported to date in patients followed up since 2000. Dose distributions for proton therapy compare favorably with IMRT plans. The IMPT appears to allow for further sparing of some critical structures.

Fortunately, disease control for childhood ependymoma has improved significantly during the past several years, and the 3- to 5-year survival rate range now is 60–80% (7, 29–31). However, late side effects of radiation therapy are still worrisome for this group of patients because of the proximity of these tumors to critical tissues and the exceptionally young age at diagnosis.

Currently, the most widely available technique to minimize toxicity to normal tissue without compromising dose

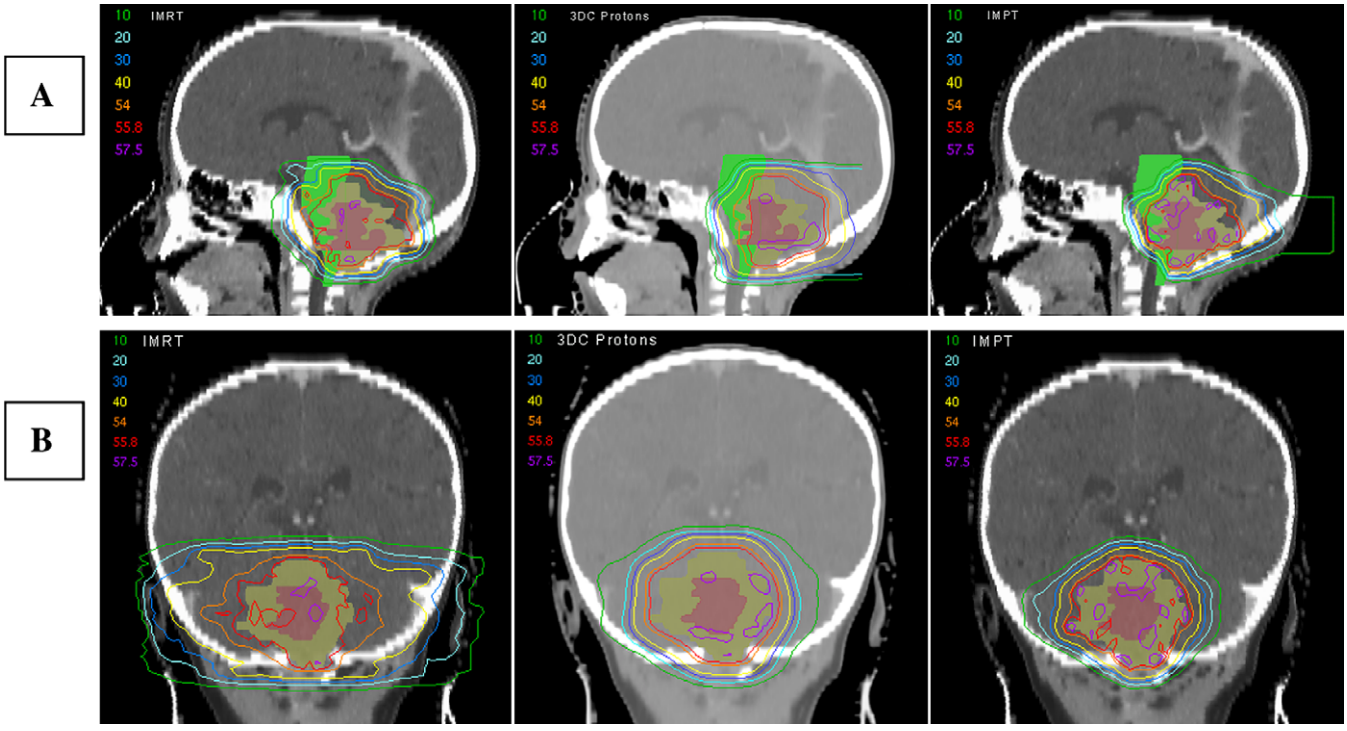

Fig. 4. (A) Sagittal views show increased conformity and complete sparing of the structures anterior to the target volume with protons and intensity-modulated proton therapy (IMPT). The IMPT plan shows further better dose shaping to the proximal target volume. (B) Coronal views show increased sparing of normal tissue lateral and superior to the tumor volume. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow.

to the target volume is IMRT. Proton radiation therapy is another modality available at select centers. The distinct physical properties of protons allow for complete sparing of normal tissues beyond the end range of the proton beam, and proton irradiation was shown to provide superior dose distributions for many pediatric and adult malignancies (23, 32, 33). It is accepted as a radiation treatment by many of the pediatric cooperative group trials, and its availability, while still limited, is expanding.

The techniques used for IMRT can also be applied to protons (IMPT), providing even more conformal dose distributions, further minimizing the dose delivered to normal structures and with the added advantage of decreasing neutron scatter. At present, IMPT is available for clinical

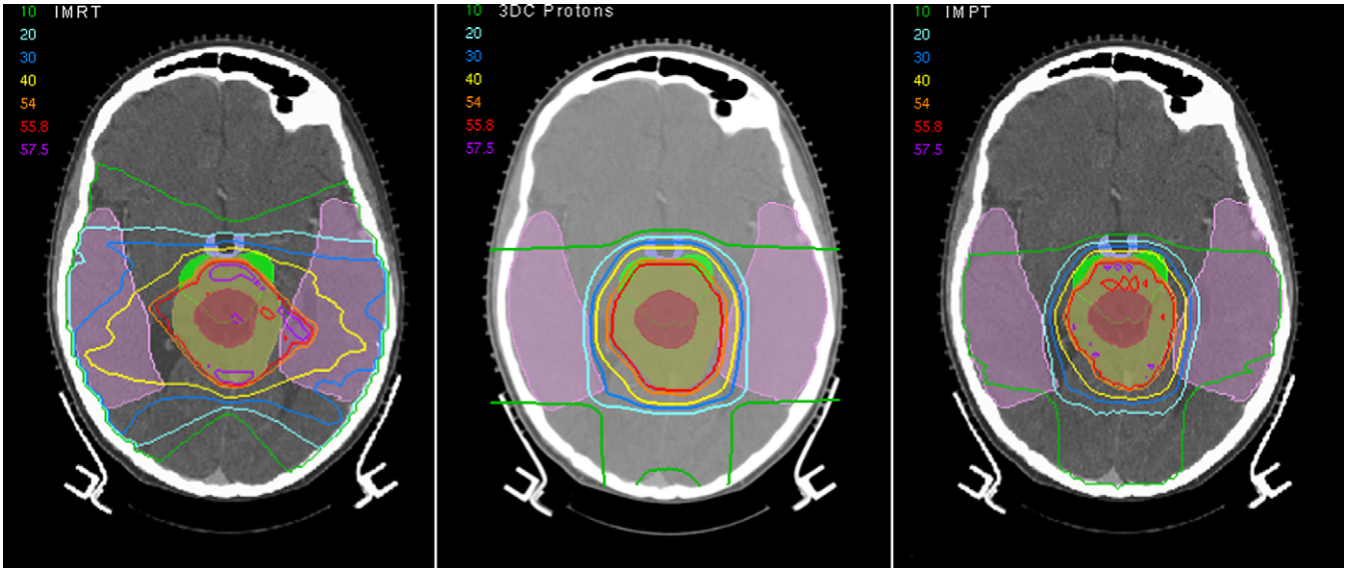

Fig. 5. Axial views at the level of the temporal lobes and hypothalamus of intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans for a patient with supratentorial ependymoma. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons and IMPT show increased sparing of the temporal lobes. The IMPT plan provides greater sparing of the hypothalamus.

treatment at only one institution in Europe, but its broad application is desirable because it further improves upon that which can be achieved with proton radiotherapy.

Cognitive impairment, a well-documented late toxicity of whole-brain radiation in the pediatric population, was correlated with dose and younger age of the child undergoing irradiation (34, 35). Fewer data are available about the cognitive toxicities associated with 3D conformal irradiation. Merchant *et al.* (36) recently published the effects of conformal radiation therapy on IQ in 88 children with localized ependymoma treated with conformal radiation therapy to a dose of 54–59.4 Gy. This study found that increased irradiation of specific areas of the brain (*i.e.,* supratentorial brain and left temporal lobe) correlated with lower IQ scores. In our study, proton therapy reduced the dose to 5%, 50%, and 90% of the whole brain and temporal lobes compared with IMRT. The IMPT reduced these doses even further. Additional studies are needed to better determine the effects of radiation on particular areas of the brain, but decreasing the amount of normal brain irradiated, particularly in the high-dose regions, appears to minimize neurocognitive effects of radiation.

Neuroendocrine abnormalities are another familiar complication of radiation therapy. Although it is possible for IMRT to provide some sparing of the pituitary and hypothalamus, even small doses can be significant. Reduced growth hormone secretion is the most common endocrinopathy induced by radiation and may be caused by hypothalamic or pituitary dysfunction (37). Growth hormone deficit generally occurs at a minimum hypothalamic dose of 18 Gy, but was reported at doses as low as 10 Gy for a single-fraction treatment and 12 Gy delivered in standard fractionation (38). Dosimetric evaluation of 3D conformal plans shows that although the largest effect of hypothalamic radiation is in the high-dose area, even very low doses of radiation can result in a decrease in growth hormone (39). Improved sparing of the hypothalamus was shown for both comparisons. For the patient with supratentorial ependymoma, differences in dose to the hypothalamus were marked and represented perhaps the greatest advantage for the use of IMPT. Although doses to the hypothalamus were lower for the infratentorial case, improvement was accomplished with protons and IMPT, and differences were in the range that could result in a clinical difference (maximum of 26 Gy for IMRT vs. 2 CGE for protons and 0.0 for IMPT). The typically young age and significant growth potential for children with ependymoma makes any sparing of the hypothalamic-pituitary axis desirable.

It is clear that radiation dose delivered to the cochlea causes sensorineural hearing loss. However, the dose at which this hearing loss occurs is not well documented (14). Merchant *et al.* (40) examined the effect of radiation dose on sensorineural hearing loss and concluded that the average dose to the cochlea should be kept at less than 32 Gy during a 6-week course of radiation, and preferably less than 18–20 Gy. It is possible that with longer follow-up, this dose will be even lower. In this study, we show that a marked decrease in dose to the cochlea can be achieved when proton radiation is used for the treatment of patients with infratentorial ependymoma. Mean dose to the left cochlea was 37 Gy with IMRT. Mean doses delivered to the left cochlea with protons and IMPT were 2 CGE and less than 0.1 CGE, respectively. Although an individual case will determine the amount of sparing that can be achieved of the cochlea, taken in aggregate, proton radiotherapy, with either 3D conformal fixed proton fields or with IMPT, improves upon the sparing of these important structures.

When delivering radiation therapy to the adult population, minimizing the dose to organs that are already below the normal tissue tolerance may not provide a large clinical benefit. However, for the developing pediatric patient who may live several decades after treatment with radiation therapy, the probability of late complications or radiation-induced malignancies is much greater. Miralbell *et al.* (20) assessed the potential influence of improved dose distribution with proton beam radiation and IMPT compared with 3D conformal photon radiation and IMRT on the induction of second malignancies. Treatment plans were compared for 1 patient with rhabdomyosarcoma of the paranasal sinus and 1 patient with medulloblastoma. The risk of second malignancy was estimated with a model based on guidelines from the International Commission on Radiologic Protection. The IMPT was superior to other modalities with regard to reduction in second malignancy risk. The expected risk of radiation-induced malignancy for IMPT was almost 2.4 times less than that for the conformal photon plan and about half the risk expected for IMRT. Protons (with or without intensity modulation) decreased the estimated risk compared with photon planning (with or without intensity modulation). In this study, we show that proton radiotherapy can provide superior normal tissue sparing with a decreased integral dose compared with IMRT. In these plans, IMPT provided a further decrease in the amount of normal tissue receiving radiation through beam optimization and by allowing for omission of the superior field.

Proton therapy provides similar target coverage and greater normal tissue sparing with significantly fewer beam angles. Six beams were used for the IMRT plans, four beams for the conformal proton plans, and three for IMPT plans. Decreasing the number of beam angles used simplifies the delivery of treatment, reduces the time needed for patient setup, and decreases the number of opportunities to introduce error.

The main focus of all technological advances in radiation therapy is to deliver sufficient dose to the target volume while decreasing the amount of normal tissue receiving radiation and the dose to normal tissue exposed. The ability to accomplish this task is dependent on the inherent properties of the type of radiation used and method of delivery. We report early clinical outcomes for patients with childhood ependymoma treated with proton radiation. This study clearly shows the advantages of protons over IMRT for representative patients with supratentorial and infratentorial ependymoma. Increased capabilities of delivering protons with a computer-optimized spot-scanning technique, IMPT, were also shown for these cases. The young age at diagnosis and proximity of critical structures in patients with ependymoma makes the application of proton radiation therapy a very attractive method of delivering treatment.

REFERENCES

1. Merchant TE. Current management of childhood ependymoma. *Oncology (Williston Park)* 2002;16:629–642, 644; discussion, 645–626, 648.
2. Ries L. Cancer statistics review. National Cancer Institute; 2000.
3. Hukin J, Epstein F, Lefton D, *et al*. Treatment of intracranial ependymoma by surgery alone. *Pediatr Neurosurg* 1998;29: 40–45.
4. Smyth MD, Horn BN, Russo C, *et al*. Intracranial ependymomas of childhood: Current management strategies. *Pediatr Neurosurg* 2000;33:138–150.
5. Merchant TE, Fouladi M. Ependymoma: New therapeutic approaches including radiation and chemotherapy. *J Neurooncol* 2005;75:287–299.
6. van Veelen-Vincent ML, Pierre-Kahn A, Kalifa C, *et al*. Ependymoma in childhood: Prognostic factors, extent of surgery, and adjuvant therapy. *J Neurosurg* 2002;97:827–835.
7. Merchant TE, Mulhern RK, Krasin MJ, *et al*. Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. *J Clin Oncol* 2004;22: 3156–3162.
8. Rousseau P, Habrand JL, Sarrazin D, *et al*. Treatment of intracranial ependymomas of children: Review of a 15-year experience. *Int J Radiat Oncol Biol Phys* 1994;28:381–386.
9. Salazar OM, Castro-Vita H, VanHoutte P, *et al*. Improved survival in cases of intracranial ependymoma after radiation therapy. Late report and recommendations. *J Neurosurg* 1983; 59:652–659.
10. Goldwein JW, Corn BW, Finlay JL, *et al*. Is craniospinal irradiation required to cure children with malignant (anaplastic) intracranial ependymomas? *Cancer* 1991;67:2766–2771.
11. Goldwein JW, Leahy JM, Packer RJ, *et al*. Intracranial ependymomas in children. *Int J Radiat Oncol Biol Phys* 1990;19: 1497–1502.
12. Paulino AC. The local field in infratentorial ependymoma: Does the entire posterior fossa need to be treated? *Int J Radiat Oncol Biol Phys* 2001;49:757–761.
13. Donahue B. Short- and long-term complications of radiation therapy for pediatric brain tumors. *Pediatr Neurosurg* 1992; 18:207–217.
14. Fong RS, Beste DJ, Murray KJ. Pediatric sensorineural hearing loss after temporal bone radiation. *Am J Otol* 1995;16:793–796.
15. Constine LS, Woolf PD, Cann D, *et al*. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med* 1993; 328:87–94.
16. Bussiere MR, Adams JA. Treatment planning for conformal proton radiation therapy. *Technol Cancer Res Treat* 2003;2: 389–399.
17. Oelfke U, Bortfeld T. Intensity modulated radiotherapy with charged particle beams: Studies of inverse treatment planning for rotation therapy. *Med Phys* 2000;27:1246–1257.
18. Oelfke U, Bortfeld T. Inverse planning for photon and proton beams. *Med Dosim* 2001;26:113–124.
19. Lomax AJ, Boehringer T, Coray A, *et al*. Intensity modulated proton therapy: A clinical example. *Med Phys* 2001;28: 317–324.
20. 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.
21. Pedroni E, Bacher R, Blattmann H, *et al*. The 200-MeV proton therapy project at the Paul Scherrer Institute: Conceptual design and practical realization. *Med Phys* 1995;22:37–53.
22. McAllister B, Archambeau JO, Nguyen MC, *et al*. Proton therapy for pediatric cranial tumors: Preliminary report on treatment and disease-related morbidities. *Int J Radiat Oncol Biol Phys* 1997;39:455–460.
23. St Clair WH, Adams JA, Bues M, *et al*. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004;58:727–734.
24. Lin R, Hug EB, Schaefer RA, *et al*. Conformal proton radiation therapy of the posterior fossa: A study comparing protons with three-dimensional planned photons in limiting dose to auditory structures. *Int J Radiat Oncol Biol Phys* 2000;48:1219–1226.
25. Paganetti H, Niemierko A, Ancukiewicz M, *et al*. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002;53:407–421.
26. Nill S, Bortfeld T, Oelfke U. Inverse planning of intensity modulated proton therapy. *Z Med Phys* 2004;14:35–40.
27. Trofimov A, Bortfeld T. Optimization of beam parameters and treatment planning for intensity modulated proton therapy. *Technol Cancer Res Treat* 2003;2:437–444.
28. Nazar GB, Hoffman HJ, Becker LE, *et al*. Infratentorial ependymomas in childhood: Prognostic factors and treatment. *J Neurosurg* 1990;72:408–417.
29. Timmermann B, Kortmann RD, Kuhl J, *et al*. Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: Results of the German prospective trials HIT 88/89 and HIT 91. *Int J Radiat Oncol Biol Phys* 2000;46: 287–295.
30. Perilongo G, Massimino M, Sotti G, *et al*. Analyses of prognostic factors in a retrospective review of 92 children with ependymoma: Italian Pediatric Neuro-oncology Group. *Med Pediatr Oncol* 1997;29:79–85.
31. Pollack IF, Gerszten PC, Martinez AJ, *et al*. Intracranial ependymomas of childhood: Long-term outcome and prognostic factors. *Neurosurgery* 1995;37:655–666; discussion, 666–667.
32. Yock T, Schneider R, Friedmann A, *et al*. Proton radiotherapy for orbital rhabdomyosarcoma: Clinical outcome and a dosimetric comparison with photons. *Int J Radiat Oncol Biol Phys* 2005;63:1161–1168.
33. Lee CT, Bilton SD, Famiglietti RM, *et al*. Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: How do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys* 2005;63: 362–372.
34. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. *J Clin Oncol* 1991;9:1348–1356.
35. Radcliffe J, Bunin GR, Sutton LN, *et al*. Cognitive deficits in long-term survivors of childhood medulloblastoma and other noncortical tumors: Age-dependent effects of whole brain radiation. *Int J Dev Neurosci* 1994;12:327–334.
36. Merchant TE, Kiehna EN, Li C, *et al*. Radiation dosimetry predicts IQ after conformal radiation therapy in pediatric patients with localized ependymoma. *Int J Radiat Oncol Biol Phys* 2005;63:1546–1554.
37. Lustig RH, Schriock EA, Kaplan SL, *et al*. Effect of growth hormone-releasing factor on growth hormone release in children with radiation-induced growth hormone deficiency. *Pediatrics* 1985;76:274–279.
38. Rappaport R, Brauner R. Growth and endocrine disorders secondary to cranial irradiation. *Pediatr Res* 1989;25:561–567.
39. Merchant TE, Goloubeva O, Pritchard DL, *et al*. Radiation dose-volume effects on growth hormone secretion. *Int J Radiat Oncol Biol Phys* 2002;52:1264–1270.
40. Merchant TE, Gould CJ, Xiong X, *et al*. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. *Int J Radiat Oncol Biol Phys* 2004;58:1194–1207.