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A Dosimetric Comparison of Proton and Intensity Modulated Radiation Therapy in Pediatric Rhabdomyosarcoma Patients Enrolled on a Prospective Phase II Proton Study

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Abstract

Background—Pediatric rhabdomyosarcoma (RMS) is highly curable, however, cure may come with significant radiation related toxicity in developing tissues. Proton therapy (PT) can spare excess dose to normal structures, potentially reducing the incidence of adverse effects.

Methods—Between 2005 and 2012, 54 patients were enrolled on a prospective multi-institutional phase II trial using PT in pediatric RMS. As part of the protocol, intensity modulated radiation therapy (IMRT) plans were generated for comparison with clinical PT plans.

Results—Target coverage was comparable between PT and IMRT plans with a mean CTV V_{95} of 100% for both modalities (p=0.82). However, mean integral dose was 1.8 times higher for IMRT (range 1.0-4.9). By site, mean integral dose for IMRT was 1.8 times higher for H&N (p<0.01) and GU (p=0.02), 2.0 times higher for trunk/extremity (p<0.01), and 3.5 times higher for orbit (p<0.01) compared to PT. Significant sparing was seen with PT in 26 of 30 critical structures assessed for orbital, head and neck, pelvic, and trunk/extremity patients.

Conclusions—Proton radiation lowers integral dose and improves normal tissue sparing when compared to IMRT for pediatric RMS. Correlation with clinical outcomes is necessary once mature long-term toxicity data are available.

Keywords

Pediatrics; Rhabdomyosarcoma; Protons

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INTRODUCTION

Pediatric RMS accounts for 3.8% of solid malignancies in children under the age of 19 years and is the most common soft tissue sarcoma in childhood[1,2]. Advances in systemic and local therapy have led to increased survival rates, with more than 70% of children becoming long term survivors[3,4]. Radiation therapy (RT) is an integral component of treatment in many of these patients but can be associated with both short and long-term morbidity, depending upon the volume treated and the dose delivered[5-10]. RMS may occur at almost any site in the body, and acute toxicity and late complications from radiation therapy depend on the location being treated.

Proton radiotherapy can decrease normal tissue doses by a factor of 2-3 and therefore holds promise in reducing the toxicity of treatment[11,12]. Previous dosimetric studies comparing proton therapy and IMRT in RMS and other cancers have demonstrated greater sparing of the ipsilateral and contralateral critical structures in both head and neck and genitourinary sites[13-18]. This sparing occurs through the specific physical properties of protons that both eliminate exit dose to normal tissues and reduce entrance dose at depth.

Since 2005, Massachusetts General Hospital (MGH) and MD Anderson Cancer Center (MDACC) have enrolled pediatric patients on a joint phase II trial, incorporating proton RT into standard RMS treatment regimens. As part of the trial, each child receives both a proton RT plan used for treatment as well as an IMRT plan for dosimetric comparison. In this study, we report the dosimetric results for those pediatric RMS patients treated on study.

MATERIALS AND METHODS

From February 2005 to October 2012, 54 pediatric RMS patients were treated with passively scattered proton RT on study. Patient characteristics are presented in the supplemental section (Table 1, supplement).

For radiation planning, patients were placed in a customized site-specific immobilization device in the treatment position and computed tomographic simulation provided images at 1.25-2.5mm for head and neck and orbital patients and at 2.5-mm for tumors below the neck. The gross tumor volume (GTV) included the primary tumor and any pathologically involved or enlarged regional lymph nodes, and was contoured by a pediatric radiation oncologist. The clinical treatment volume (CTV) was generated manually to cover areas of suspected microscopic involvement. For protons, the planning target volume (PTV) was achieved by using a 3mm “smear” for compensator calculations and an additional margin to the aperture edge, range, and modulation (2-5mm depending on anatomic site) to account for uncertainty in the path length and patient set up. A uniform 3mm PTV was added to IMRT plans. When possible, an MRI scan was anatomically registered to the planning treatment CT scan to facilitate target delineation. Normal tissue structures were contoured and/or checked by the treating pediatric radiation oncologist and centrally reviewed for consistency. All patient plans were reviewed and approved by the treating physician prior to treatment. Target and normal tissue volumes were held constant for both proton and IMRT planning. The dose delivered by protons is expressed as Gy_{RBE} which uses a relative

biologic effectiveness (RBE) of 1.1 for protons to convert physical to biologic dose, based upon estimates of relative biologic effectiveness of protons relative to Cobalt-60[19]. For ease of presentation, proton doses in this paper are expressed as Gy.

At MGH, the XiO planning system™ (CMS, Inc., St. Louis, MO) was used for both proton and IMRT planning. At MDACC, an Eclipse treatment planning system™ (Varian Medical Systems, Palo Alto, CA) was utilized for proton therapy planning and Pinnacle treatment planning system™ (Philips Medical Systems, Fitchburg, WI) for IMRT comparison plans. Target volume and normal tissue constraints were derived from the Children's Oncology Group protocols for RMS (www.childrensoncologygroup.org). Dose–volume histograms were generated and compared for organs at risk (OAR). The percent of normal tissue spared by using protons was calculated using the following equation:

$$\frac{100 \times (\text{mean x-ray dose} - \text{mean proton dose})}{\text{mean x-ray dose}}$$

The integral dose (D_{int}), defined as the total energy deposited in patients, was calculated by summing the energy deposited in each individual voxel ($Edep_i$) of the patient CT image. Edep_i was computed using the voxel volume (V_i), CT Hounsfield unit data (HU) to calculate the voxel density (ρ_i), and the voxel dose (D_i) using the following equation:

$$D_{int} = \sum_i Edep_i = \sum_i (V_i * \rho_i (HU)) * D_i$$

Event free survival (EFS), overall survival (OS), and local control (LC) rates were estimated by the Kaplan-Meier method. Continuous dosimetry values were compared using paired t-tests, while Fisher's exact test was used for categorical comparisons. Two-sided tests were employed and $p<0.05$ was used to determine statistical significance. Data analysis was performed using SAS version 9.2.

RESULTS

Median follow up for all 54 patients was 3.9 years. The 3/5 year event free survival and overall survival was 69%/65% and 80%/77% respectively. Local control at 3 and 5 years was 78%/78%. Toxicity was favorable with only 3 patients developing late grade 3 toxicity. These consisted of a unilateral cataract (orbital primary), chronic otitis (PM mastoid primary), and retinopathy with decreased visual acuity (orbital primary). No toxicities higher than grade 3 were observed. To date there have been no reported secondary malignancies. A complete description of toxicity for this trial is given in a separate publication discussing clinical outcomes[20].

A median of 7 beams were used in IMRT plans (range 4-9), and for proton plans the median was 3 beams (range 1-7) (Table 1, supplement). Coverage of target volumes was equivalent between PT and IMRT plans. Due to the difference in PTV generation with PT, CTV was used to compare coverage. The mean CTV V_{95} (percent volume receiving at least 95% of the prescription dose) was 100% for both modalities (range 97-100% for PT and 98-100%

for IMRT) (p=0.82). The mean CTV V_{100} was 98% for PT (range 95-100%) and 99% for IMRT (range 97-100%) (p=0.64). The mean maximum dose (D_{Max}) was 107% (range 101-112%) for PT and 106% (range 103-110%) for IMRT (p = 0.17). Comparative dosimetry for PT and IMRT plans are shown in Figure 1.

In all 54 cases, the integral dose was calculated for IMRT and PT plans. The integral dose represents the total energy deposited in a patient and is given in joules rather than gray because of the latter's dependence on patient weight (Gy = J/Kg). Integral dose was 18 J for PT and 32 J for IMRT (p=<0.01) with a mean integral dose 1.8 times higher for IMRT (range 1.0-4.9). By site, mean integral dose for IMRT was 1.8 times higher for genitourinary (p=0.02) and head and neck sites (p<0.01), 2.0 times higher for trunk and extremity sites (p<0.01), and 3.5 times higher for orbital sites (p=<0.01) when compared to PT. Individual results are shown in Figure 2.

Statistically significant sparing was seen with PT in all disease sites with 3 or more patients and in 26 of 30 OARs assessed. Results are presented as mean dose and in volume percent at clinically significant intervals.

There were 27 patients with non-orbital head and neck (H&N) tumors and of these 24 were parameningeal sites. Tumors were classified as “central” in 9 cases and “lateral” in 18 cases. For central sites, dose to paired organs such as the parotid glands was recorded individually for each gland and then pooled for analysis without assigning laterality. In the lateral cases, paired organs were designated as “ipsilateral” or “contralateral” and results are reported as such. Median RT dose was 50.4 Gy (range 36-52.2 Gy). Complete dosimetric results for head and neck patients are presented in table 1.

For CNS structures, significant sparing for PT was seen in all OARs examined with the greatest sparing in the hypothalamus, temporal lobes, brainstem, and cerebellum. Moderate dose reductions were also noted in the optic nerves, optic chiasm, and pituitary. In non-CNS structures, the most significant sparing occurred in the lens, maxilla, mandible, and lacrimal gland. Doses to the retina, skin, parotid gland, and thyroid showed no or minimal differences.

There were 12 patients with orbital rhabdomyosarcoma, 9 with a left-sided primary and 3 with a right-sided primary. Median RT dose was 45 Gy (range 45-50.4 Gy). Both ipsilateral and contralateral temporal lobes and lacrimal glands showed significant sparing with PT plans, as did the hypothalamus, pituitary, and maxilla. Contralateral lens dose and retina was also spared with PT. Minimal differences were seen in the ipsilateral optic nerve dose and skin doses were similar. Complete dosimetric results are shown in table 2.

Only one patient on study had a primary in the chest region, a left shoulder primary that received 50.4 Gy. All OARs showed improvement with PT, though statistical significance could not be calculated for a single case. (Table 2, supplement).

Two patients presented with abdominal tumors, one biliary primary and one left paraspinal primary, both treated to 50.4 Gy. Due to small numbers (n=2), statistical significance between the two groups could not be shown. Despite the limited numbers, notable

reductions in ipsilateral and contralateral kidney dose were seen in both cases (Table 3, supplement).

There were 12 patients with primaries in the pelvic region, 7 prostate or bladder primaries, 3 extremity tumors in the groin or thigh, and 2 perianal primaries. Median dose was 50.4 Gy (range 36-50.4 Gy). Doses to the testes were reported together due to minimal dose variation between each testicle, while the doses to the left and right ovaries and growth plates are presented individually. Important reductions in gonadal doses (ovaries and testes) were seen with the use of PT. The growth plates and pelvic bones were also spared significant dose with PT plans. Femoral head dose was improved with PT, though doses with both modalities were generally low. Dose reductions with PT were also seen in the vagina, uterus, and penile bulb with variable in significance (Table 4, supplement).

Mean dose and mean percent volumes for OARs are useful for describing general trends in a large data set such as ours, but tend to wash out significant individual case differences. Figure 3 presents the individual dosimetric results for select critical structures. To demonstrate comparative risks for late effects in tissues with well-established dose tolerances, the number of patients with OARs exceeding clinically significant levels for PT vs IMRT are provided in Table 3.

DISCUSSION

This study represents the first comparison of proton vs photon dosimetry for patients enrolled on a prospective clinical trial, and with 54 patients it also stands as the largest published dosimetric series for RMS. Rather than selecting patients for comparison based on tumor location, as has been done in prior studies, we present the results for every RMS patient on study over the course of 7 years. In doing so, our data more closely resembles the demographics for pediatric RMS patients treated at a high volume center. Although IMRT plans were not used for treatment, multiple iterations were generated in the majority of cases to achieve optimal coverage while respecting the tissue tolerance of critical structures. In some cases, target volume coverage was altered to improve sparing of these critical structures, as would be done if the plans were used for actual treatment. Prior dosimetric studies for select patients with parameningeal, orbital, and genitourinary RMS showed similar benefits with proton RT compared to IMRT, and this study adds confirmation to these results on a larger scale[15,16,18].

Arguments against the widespread adoption of proton therapy, as highlighted by De Ruysscher et al. and others, have stemmed from the contention that the main benefit of protons, the reduction in the medium and low dose regions, is of little clinical significance to patients[21,22]. Our data, summarized in table 4, show that these reductions lead to important sparing by PT in multiple structures with well-defined tolerances. Growth hormone deficiency from RT to the hypothalamus has been shown at an incidence of 50% at 16 Gy and 99% at 35 Gy[23]. In our study hypothalamic dose with PT was lower for 90% of all orbital and H&N patients and doses above 16 Gy were seen in 6 PT patients (15%) and 12 IMRT patients (30%) and above 35 Gy in 1 PT patient (3%) and 5 (15%) IMRT patients. Growth hormone deficiency in children has been linked to multiple co-morbidities including

poor growth, altered energy metabolism and body composition, cognitive impairment, cardiovascular disease, and diminished quality of life [23-27]. Furthermore, growth hormone monitoring and replacement for pediatric patients comes at an annual cost of over $13,000[28].

Memory functions are largely localized to the temporal regions of the brain and Armstrong et al. found an increased risk for memory difficulties and task efficiency with increasing dose above ≥30 Gy to the temporal lobes[29,30]. Survivors who received temporal region irradiation also experienced significantly more difficulty in social functioning, including lower overall wage earning and marriage rates in these studies. In our cohort, PT spared significant temporal lobe dose for H&N and orbital patients with a mean temporal lobe V_{20} 2.0 times higher and V_{30} 1.7 higher for IMRT plans. The most significant sparing was seen in lateralized H&N tumors where the ipsilateral V_{20} and V_{30} were reduced by 44% and 31% respectively.

Dry eye syndrome (DES) following RT has been linked to doses delivered to lacrimal glands. Tolerance doses for the entire gland with conventional fractionation are estimated to be in the range of 30 to 40 Gy and Mendenhall et al. found that DES occurred at a rate of 6% with 35–40 Gy to the lacrimal gland and a rate of 50% at 45 Gy or higher[31-33]. In our study, lacrimal doses above 35 Gy occurred in 3 PT patients (4%) and 9 IMRT patients (12%) and above 45 Gy in 3 PT patients (4%) and 5 IMRT patients (6%).

Orbital and H&N patients were spared significant lens dose with PT as well. Lens dose of >6 Gy was seen in 16 (21%) of PT patients and 35 (45%) of IMRT patients and a lens dose of >12 Gy was seen in 10 (13%) of PT patients and 13 (17%) of IMRT patients. The majority of those > 12 Gy had orbital tumors. Data in adult patients shows a 33% risk of progressive cataracts after 2.5 to 6.5 Gy, and 66% after 6.5 to 11.5 Gy[32]. Increased sensitivity in younger patients is suspected and Hall et al. found a risk of opacities at lens doses of <0.5 Gy and calculated a 35–50% increase in the risk of opacity development per unit of Gray during childhood[34]. Cataracts in younger children can lead to astigmatism and visual complications if left untreated, but the decision to undertake surgical repair is not trivial. Pediatric patients are subject to a higher rate of complications than their adult counterparts and a risk of blindness and enucleation exists due to infection, hemorrhage, and retinal detachment following repair[35,36].

Fertility preservation is an area of great interest in pediatric RMS and recent COG trials have attempted to decrease cyclophosphamide doses to this end. Radiation also plays a role and fractionated RT doses of 2 Gy to the testes and 6 Gy to the ovaries are thought to represent a 50% risk of sterility, while doses above 12 Gy the testes and 8 Gy to the ovaries likely represents a 100% risk[37-39]. In our pelvic cohort, testicular doses above 2 Gy were seen in 4 cases with PT (25%) and 10 IMRT cases (63%). No patients had a testicular dose over 12 Gy with PT while 6 patients (38%) exceeded this dose with IMRT. Ovarian doses above 6 Gy/12 Gy were seen in 25%/13% of PT patients and 63%/38% of IMRT patients.

Finally, recent clinical data from a mixed pediatric and adult population of over 1000 patients has suggested a reduction in second tumor rates in a proton treated population[40]. No

difference was noted in “in field malignancies” and therefore it is likely the reduction of integral dose to normal tissues outside the target volume that leads to this improvement. In our cohort, integral dose was reduced by 1.8 times for all sites using PT and one could expect a similar reduction in second cancers for pediatric RMS.

Significant OAR sparing by PT was seen in all tumor sites and in 26 of 30 structures examined (excluding the sites with <3 patients each). While significant sparing was observed for both central and lateral primaries, the lateral tumors provided for the greatest dose savings to structures compared with more central tumors. Similarly, serial organs (chiasm, brainstem, spinal cord) showed less benefit with PT and the maximum dose was often lower with IMRT, highlighting IMRT's ability for conformality in the high dose regions. In contrast, parallel organs (temporal lobes, mandible/maxilla, pelvic bones) as well as organs sensitive to low doses of RT (hypothalamus, gonads) consistently showed benefit. Few patients had abdominal and chest tumors but kidney, lung, and heart doses were lower with PT. Proton studies in patients with Hodgkins disease and soft tissue sarcoma have shown similar benefit in these regions[41-43]. It should be noted that all patients in this study were treated with passively scattered proton RT. As scanned beam capabilities improve and become more widely available, the use of IMPT should augment these observed benefits to a greater extent.

In a large scale, multi-institutional prospective phase II study, proton radiotherapy for pediatric RMS demonstrates improved normal tissue sparing compared to IMRT. Further correlation with clinical outcomes is needed once our data matures to determine whether the dosimetric benefits observed translate into reduced rates of late toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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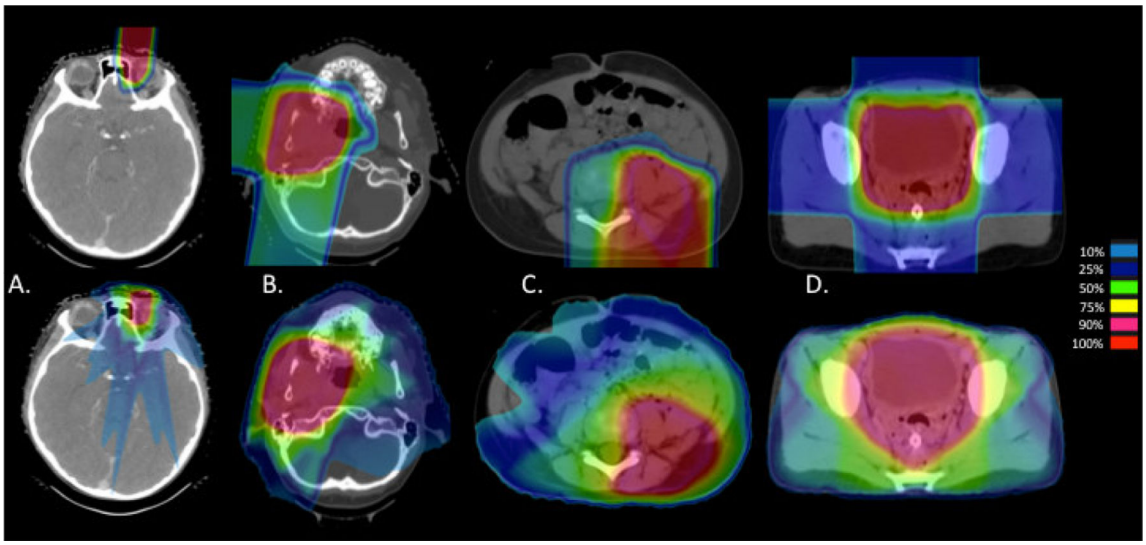

Figure 1.

Comparative proton (above) and IMRT (below) dosimetry for primaries of the (A) orbit, (B) parameninges, (C) trunk, and (D) pelvis

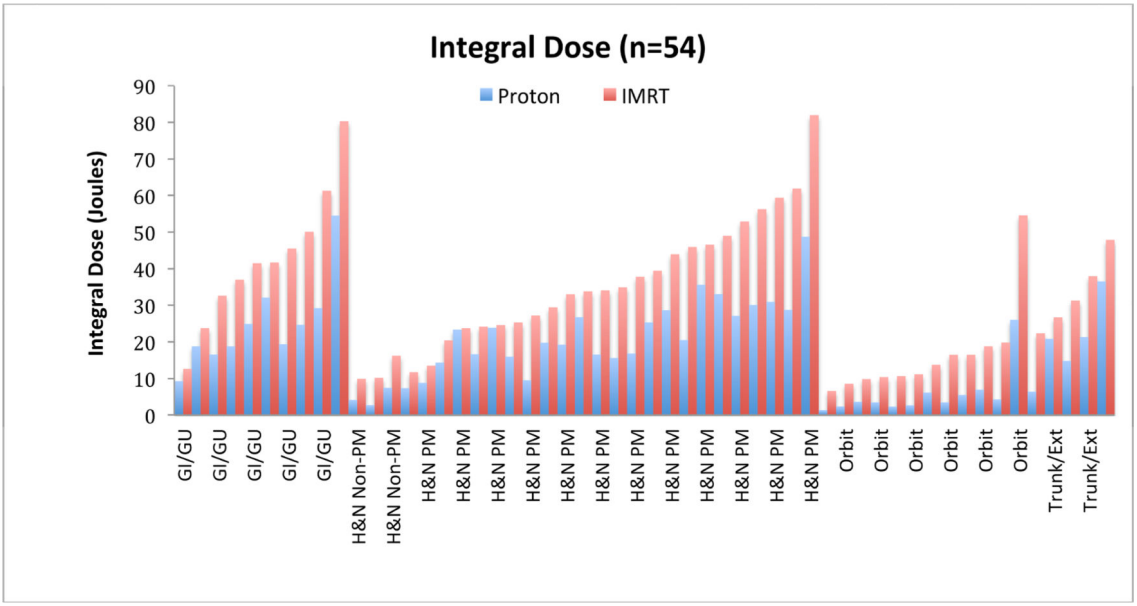

Figure 2.

Integral dose values in joules for proton and IMRT plans for each of the 54 patients on study

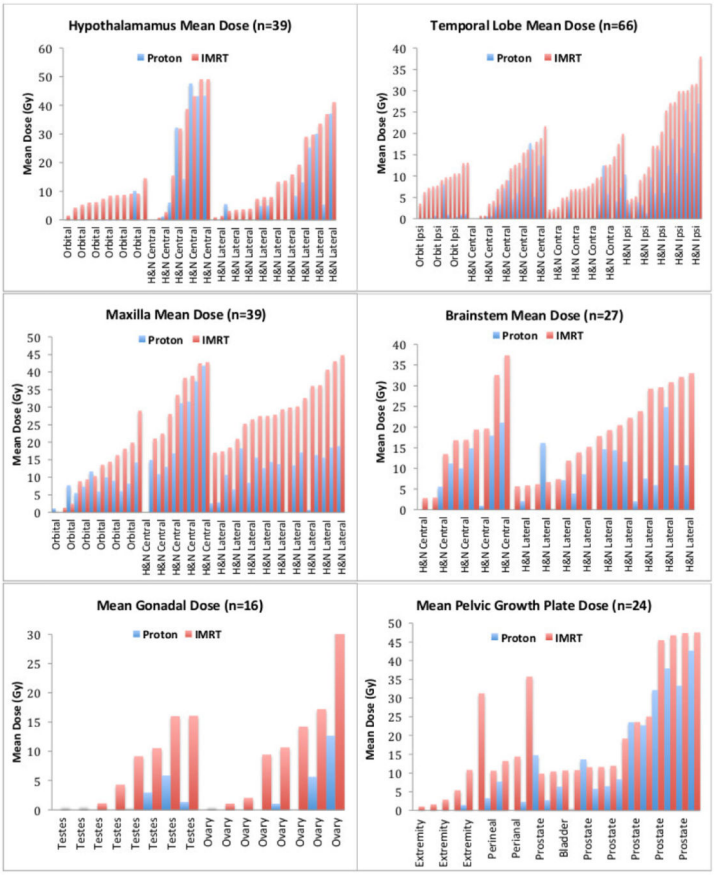

Figure 3.

Individual patient dose for select OARs (organs at risk). (A) Hypothalamic mean dose for all orbital and head and neck (H&N) patients. (B) Temporal lobe mean doses for orbital (ipsilateral lobe only) and H&N patients (ipsilateral and contralateral lobes). (C) Maxillary mean dose for all orbital and H&N patients. (D) Brainstem mean dose for H&N patients only. (E) Mean gonad doses for the 12 pelvic patients (paired testicles displayed as a single OAR, paired ovaries as separate OARs). (D) Growth plate mean doses for the 12 pelvic patients

Table 1

OAR doses for all head and neck patients including parameningeal primaries

Head and Neck		Central H&N Primary (n=9)				Lateral H&N Primary (n=18)			
Structure	**Dose**	**Proton**	**IMRT**	**% Spared**	**P Value**	**Proton**	**IMRT**	**% Spared**	**P Value**
Chiasm	Mean (Gy)	26	28	7	0.35	15	24	38	< 0.01
	V45 (%)	35	37	5	0.11	5	14	64	0.34
Pituitary	Mean (Gy)	32	35	9	0.02	25	33	24	< 0.01
	V30 (%)	64	67	4	0.17	49	63	22	0.03
Hypothalamus	Mean (Gy)	9	15	40	< 0.01	7	15	53	< 0.01
	V16 (%)	27	46	41	0.02	19	35	46	0.03
Brainstem	Mean (Gy)	9	18	50	< 0.01	8	18	56	< 0.01
	V30 (%)	8	21	62	0.07	9	22	59	0.02
Cerebellum	Mean (Gy)	3	12	75	< 0.01	5	15	67	< 0.01
	V20 (%)	1	18	94	0.05	7	26	73	< 0.01
Maxilla	Mean (Gy)	22	30	27	< 0.01	15	30	50	< 0.01
	V20 (%)	48	71	32	< 0.01	32	70	54	< 0.01
	V30 (%)	38	55	31	< 0.01	26	44	41	< 0.01
Mandible	Mean (Gy)	11	19	42	< 0.01	12	24	50	< 0.01
	V20 (%)	25	47	47	< 0.01	24	50	52	< 0.01
	V30 (%)	17	28	39	0.08	20	33	39	< 0.01
Thyroid	Mean (Gy)	2	4	50	0.12	2	3	33	0.09
	V10 (%)	6	11	45	0.22	5	8	38	0.17
Optic Nerves	Mean (Gy)	30	30	0	0.60	--	--	--	--
	V50 (%)	27	34	21	0.36	--	--	--	--
Optic Nerve$_{Ipsi}$	Mean (Gy)	--	--	--	--	25	31	19	0.01
	V50 (%)	--	--	--	--	11	6	−45	0.45
Optic Nerve$_{Contra}$	Mean (Gy)	--	--	--	--	9	21	57	< 0.01
Temporal Lobes	Mean (Gy)	6	10	40	< 0.01	--	--	--	--
	V20 (%)	10	18	44	0.01	--	--	--	--
	V30 (%)	8	9	11	0.01	--	--	--	--
Temp Lobe$_{Ipsi}$	Mean (Gy)	--	--	--	--	12	21	43	< 0.01
	V20 (%)	--	--	--	--	23	44	48	< 0.01
	V30 (%)	--	--	--	--	18	31	42	< 0.01
Temp Lobe$_{Contra}$	Mean (Gy)	--	--	--	--	2	9	78	< 0.01
	V20 (%)	--	--	--	--	4	10	60	0.05
	V30 (%)	--	--	--	--	1	3	67	0.04
Lens	Mean (Gy)	3	5	40	0.02	--	--	--	--
	V5 (%)	20	48	58	0.01	--	--	--	--
Lens$_{Ipsi}$	Mean (Gy)	--	--	--	--	2	9	78	0.01
	V5 (%)	--	--	--	--	16	63	75	< 0.01
Lens$_{Contra}$	Mean (Gy)	--	--	--	--	0.2	6	97	< 0.01
	V5 (%)	--	--	--	--	0	46	100	< 0.01

Head and Neck		Central H&N Primary (n=9)				Lateral H&N Primary (n=18)			
Structure	**Dose**	**Proton**	**IMRT**	**% Spared**	**P Value**	**Proton**	**IMRT**	**% Spared**	**P Value**
Retina	Mean (Gy)	16	18	11	0.47	--	--	--	--
	V45 (%)	8	6	−25	0.88	--	--	--	--
Retina$_{Ipsi}$	Mean (Gy)	--	--	--	--	13	19	32	0.01
	V45 (%)	--	--	--	--	8	5	−38	0.12
Retina$_{Contra}$	Mean (Gy)	--	--	--	--	3	11	73	< 0.01
Cochlea	Mean (Gy)	19	19	0	0.57	--	--	--	--
	V36 (%)	17	4	−76	0.18	--	--	--	--
Cochlea$_{Ipsi}$	Mean (Gy)	--	--	--	--	36	39	8	0.24
	V36 (%)	--	--	--	--	62	63	2	0.83
Cochlea$_{Contra}$	Mean (Gy)	--	--	--	--	5	17	71	< 0.01
	V20 (%)	--	--	--	--	12	32	63	0.06
Lacrimal Gland	Mean (Gy)	6	11	45	< 0.01	--	--	--	--
	V20 (%)	9	25	64	0.02	--	--	--	--
Lacrimal$_{Ipsi}$	V30 (%)	4	4	0	0.25	--	--	--	--
	Mean (Gy)	--	--	--	--	9	15	40	< 0.01
	V20 (%)	--	--	--	--	18	29	38	0.02
	V30 (%)	--	--	--	--	11	19	42	0.08
Lacrimal$_{Contra}$	Mean (Gy)	--	--	--	--	1	8	88	< 0.01
Parotid Gland	Mean (Gy)	18	26	31	0.08	--	--	--	--
	V36 (%)	22	21	−5	0.33	--	--	--	--
Parotid$_{Ipsi}$	Mean (Gy)	--	--	--	--	37	39	5	0.06
	V36 (%)	--	--	--	--	66	64	−3	0.66
Parotid$_{Contra}$	Mean (Gy)	--	--	--	--	2	11	82	< 0.01
Skin	DMax (Gy)	32	32	0	0.75	44	44	0	0.63

Abbreviations: ipsi, ipsilateral; contra, contralateral, temp; temporal.

Table 2

OAR doses for all orbital primary patients

Orbit		Orbital Primary (n=12)			
Structure	**Dose**	**Proton**	**IMRT**	**% Spared**	**P Value**
$Lens_{Ipsi}$	Mean (Gy)	26	32	19	0.19
	V5 (%)	89	99	10	0.10
$Lens_{Contra}$	Mean (Gy)	0	3	100	< 0.01
	V5 (%)	0	23	100	0.05
$Retina_{Ipsi}$	Mean (Gy)	33	40	18	< 0.01
	V45 (%)	34	48		0.09
$Retina_{Contra}$	Mean (Gy)	0.1	8	99	< 0.01
	V20 (%)	0	11	100	0.04
Optic $Nerve_{Ipsi}$	Mean (Gy)	31	37	16	0.03
	V45 (%)	33	40	18	0.27
Lacrimal $Gland_{Ipsi}$	Mean (Gy)	19	35	46	< 0.01
	V30 (%)	31	65	52	< 0.01
Lacrimal $Gland_{Contra}$	Mean (Gy)	0	5	100	< 0.01
Hypothalamus	Mean (Gy)	1	8	88	< 0.01
	V16 (%)	3	13	77	0.02
Pituitary	Mean (Gy)	4	15	73	< 0.01
	V20 (%)	5	19	74	0.10
Temp $Lobe_{Ipsi}$	Mean (Gy)	1	9	89	< 0.01
	V20 (%)	2	10	80	< 0.01
Temp $Lobe_{Contra}$	Mean (Gy)	0	4	100	< 0.01
	V10 (%)	0	7	100	0.03
Maxilla	Mean (Gy)	7	12	42	0.02
	V20 (%)	15	25	40	0.05
Skin	DMax (Gy)	43	42	−2	0.68

Abbreviations: ipsi, ipsilateral; contra, contralateral, temp; temporal.

Table 3

OAR dose levels for critical structures

Organ At Risk	Patients Above Dose Level		
	Mean Dose	Protons (%)	IMRT (%)
Lens (n=78)	> 2 Gy	25 (32)	64 (81)
	> 6 Gy	16 (21)	36 (46)
	> 12 Gy	10 (13)	13 (17)
Hypothalamus (n=39)	> 5 Gy	13 (33)	27 (69)
	> 16 Gy	6 (15)	12 (30)
	> 35 Gy	1 (3)	5 (15)
Pituitary (n=39)	> 20 Gy	16 (41)	21 (54)
	> 30 Gy	15 (38)	18 (46)
	> 40 Gy	10 (26)	15 (38)
Testes (n=16)	Any Dose	12 (75)	16 (100)
	> 2 Gy	4 (25)	10 (63)
	> 12 Gy	0 (0)	6 (38)
Ovaries (n=8)	Any Dose	3 (38)	8 (100)
	> 6 Gy	2 (25)	5 (63)
	> 12 Gy	1 (13)	3 (38)
Lacrimal Gland (n=78)	> 20 Gy	11 (14)	21 (27)
	> 35 Gy	3 (4)	9 (12)
	> 45 Gy	3 (4)	5 (6)
Growth Plates (n=24)	> 10 Gy	8 (33)	19 (79)
	> 20 Gy	6 (25)	8 (33)
	> 30 Gy	4 (17)	6 (25)