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The effect of radiation therapy techniques (IMRT vs. 3DCRT) on outcome in patients with intermediate risk rhabdomyosarcoma enrolled in COG D9803—A report from Children's Oncology Group

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Abstract

Purpose—To compare dosimetric parameters of intensity modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3DCRT) in patients with intermediate risk rhabdomyosarcoma (RMS), and to analyze their effect on local-regional control (LRC) and failure-free survival (FFS).

Methods and Materials—The study population consisted of 375 patients enrolled on Children's Oncology Group protocol D9803, receiving IMRT or 3DCRT. Dosimetric data was collected from 179 patients with an available composite plan. Chi-square or Fisher's exact tests were used to compare patient characteristics and radiotherapy (RT) parameters between the two groups. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared using log-rank tests. Cox analysis was used to examine the effect of RT technique on FFS after adjusting for primary site and risk group.

Results—The median follow-up time was 5.7 and 4.2 years for patients receiving 3DCRT and IMRT respectively. No differences in 5 year failure of LRC (18% vs. 15%) and FFS (72% vs. 76%) were noted between the two groups. Multivariate analysis revealed no association between RT technique and FFS. Patients with primary tumors in parameningeal (PM) sites were more likely to receive IMRT than 3DCRT. IMRT became more common during the later years of the

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study. Patients receiving IMRT were more likely to receive $>50\text{Gy}$, photon energy of $\leq 6\text{MV}$, and $>5\text{ RT fields}$ than those who received 3DCRT. There was improved coverage of the IMRT planning target volume (PTV) by the prescription dose compared to the 3DCRT with similar target dose heterogeneity.

Conclusions—IMRT improved target dose coverage when compared to 3DCRT, though an improvement in LRC or FFS could not be demonstrated in this population. Future studies comparing integral dose to non-target tissue and late RT toxicity between the two groups is warranted.

Keywords

Rhabdomyosarcoma; Intermediate risk; IMRT/3DCRT

Introduction

The intermediate-risk group of patients with rhabdomyosarcoma (RMS) on the Soft Tissue Sarcoma Protocol D9803 of the Children's Oncology Group have a 4-year failure-free survival (FFS) of 68–73% when treated with Vincristine/Actinomycin-D/Cyclophosphamide (VAC) or VAC/ Vincristine/Topotecan/Cyclophosphamide (VTC) chemotherapy, radiotherapy, and surgery (1). The 5-year local failure rates for patients with localized parameningeal (PM) RMS in IRS-II through IRS-IV range from 17% – 37% (2). Therefore, it is critical to improve local regional control (LRC) in patients with newly diagnosed RMS, especially PM-RMS. Three-dimensional conformal radiation therapy techniques (3DCRT) are considered standard of care for pediatric radiation therapy planning and most clinical outcome data with long follow-up have been generated using 2DRT and 3DCRT. On the other hand, intensity-modulated radiation therapy (IMRT) offers the potential to provide improved target coverage and lower radiation dose to surrounding critical organs, when compared to 3DCRT. Several studies with smaller sample sizes have suggested an advantage in local control of RMS using IMRT when compared to a historic control group either with 2DRT or 3DCRT technique (3–7). However, there is no comparative study of IMRT vs. 3DCRT in these patients. Therefore, we investigated the LRC and Failure-free survival (FFS) following the use of IMRT versus 3DCRT in patients with RMS on protocol D9803. Our central hypothesis is that IMRT improves not only target coverage and surrounding critical organ sparing, but also LRC. The aims of our study were: 1) to determine factors which favor the use of IMRT instead of 3DCRT; and 2) to compare the effect of IMRT to that of 3DCRT on LRC and FFS.

Methods and Materials

The study population consisted of patients enrolled on the COG protocol D9803, whose primary aim was to compare VAC chemotherapy to VAC alternating with VTC (1). Eligible protocol patients were: younger than 50 years, stage 1, 2, or 3, clinical group I, II, III alveolar RMS or undifferentiated sarcoma; or stages 2 and 3, clinical group III embryonal or botryoid RMS; or patients ≤ 10 years old with stage 4, clinical group IV embryonal or botryoid RMS and had tissue submitted for central review of tumor material. Excluded were patients with stage 4, clinical group IV embryonal RMS who were > 10 years of age and those with CNS metastatic disease. Radiotherapy was specified for any patient with Group II, III or IV disease, with the radiotherapy technique (2D, 3DCRT, IMRT, etc.) at the discretion of the treating radiation oncologist. Most patients started radiation therapy at week 12, except those patients with Clinical Group III tumors of a parameningeal site who had documented evidence of intracranial extension. These patients started radiation therapy within the first two weeks of the initiation of the first cycle of chemotherapy. Radiation

therapy treatment records were submitted to the Quality Assurance Review Center (QARC) to assess compliance with the protocol guidelines. Patients were selected for inclusion in the current analysis if they received 3DCRT or IMRT and had one treatment plan or, if multiple plans, a composite of these plans available for review. Patients who received treatment with 2D radiotherapy, brachytherapy, or a mixed technique of both 3DCRT and IMRT were excluded. Demographics collected were age, gender, race, primary site, T stage and size, N stage, histology, Clinical Group, radiation dose, energy, number of fields, elapsed days, and duration of RT. Treatment plans were reviewed and information extracted regarding gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV); maximum ($D_{\max}$), mean (D_{mean}) and minimum ($D_{\min}$) dose; dose received by 5% of the volume (D_5), 95% of the volume (D_{95}) and % volume receiving 95% of the prescribed dose (V_{95}). For patients with available dose volume histogram (DVH) data, volumetric data for the surrounding critical normal organs receiving 5 (V_5), 10 (V_{10}), and 20 (V_{20}) Gy was also collected. Dose to non-specific tissue (defined as the body surface contour in the treatment area –PTV – all critical organs) was also collected when available. Target coverage heterogeneity indices were calculated as D_5 - D_{95} , $(D_5$ - $D_{95})/D_{\text{mean}}$, and D_5/D_{95} . Study endpoints were FFS, LRC, secondary cancer, and acute toxicity.

Chi-square or Fisher's exact tests were used to compare the difference in proportions for baseline patient characteristics and RT delivery parameters between IMRT and 3DCRT groups. The Mann-Whitney test was used to compare the treatment target volume, dose coverage and homogeneity between the two groups. Time to event distributions were estimated using the Kaplan–Meier method and were compared using the log-rank test. Time to failure of LRC was estimated using cumulative incidence curves. FFS was defined as the interval from enrollment to the first occurrence of disease progression, relapse or death from any cause. Cox proportional hazards regression analysis was used to examine the effect of IMRT and 3DCRT on FFS to adjust for prognostic risk factors. The assumption of proportionality was verified for all models. A p-value of less than or equal to 0.05 was considered significant.

Results

Patient Characteristics and Radiation Therapy Delivery Variables

A total of 616 patients were enrolled in COG protocol D9803. Three hundred seventy five patients were identified as having received either 3DCRT or IMRT, and 179 of these had sufficient dosimetric data for analysis. Table 1 shows the distribution of patient characteristics according to treatment groups (3DCRT vs. IMRT). Patients receiving 3DCRT were similar to those receiving IMRT with respect to baseline characteristics, with the exception of primary site. Patients in the IMRT group were more likely to have RMS at a parameningeal (PM) site or PM with intracranial extension (63% vs. 38%); none of the patients receiving IMRT had an extremity primary site or non-bladder/prostate genitourinary (B/P GU) site and only one (1%) patient had a retroperitoneal primary site [compared to 38 (13%) receiving 3DCRT, $p<0.0001$]. Table 2 shows the distribution of radiation therapy delivery variables between the two treatment groups. Relative to 3DCRT patients, a larger proportion of IMRT patients received a dose of $>50\text{Gy}$ (74% vs. 58%, $p=0.04$), photon energy of $\leq 6\text{MV}$ (98% vs. 62%, $p<0.0001$), and >5 RT fields (69% vs. 14%, $p<0.0001$).

Local Regional Control and Survival

The median follow-up for patients treated with 3DCRT and IMRT is 5.7 years (range 0–9.4 years) and 4.2 years (range 0–9.0 years), respectively. Figure 1 displays the cumulative incidence curves for time to failure of LRC. The cumulative incidence of time to failure of LRC at 5 years for patients treated with 3DCRT is 18% (95% CI: 11%, 25%) and for IMRT

15% (95% CI: 0, 29%). The estimated 5-year FFS is 72% (95% CI: 66%, 77%) and 76% (95% CI: 71%, 81%) for 3DCRT and IMRT patients. There is no statistical difference in failure of LRC ($p=0.48$, log-rank test, Figure 1) and FFS ($p=0.29$, log-rank test, Figure 2) between these two patient populations.

Given the significant difference in the distribution of primary sites between the two treatment groups (64% of IMRT patients had PM primaries versus 37% of 3DCRT patients) a multivariate Cox regression analysis was performed to adjust for site and to stratify by risk group (definition in Table 1). The analysis showed no significant difference in risk of FFS according to RT techniques (Hazard Ratio (HR) comparing IMRT to 3DCRT 0.74, 95% Confidence Interval (CI): 0.44–1.26). A Cox regression analysis was also performed for the subset of patients with the primary site of PM or PM with intracranial extension only. This analysis also showed no significant difference in risk of FFS between treatment group (HR 0.91, 95% CI: 0.49–1.66) when adjusted for risk group.

Acute Toxicity

The potential association of RT technique and acute toxicities was analyzed after stratifying patients according to start date of their RT (within 2 weeks of study entry for PM sites with intracranial extension, and at week 12 for all others). The major toxicity distributions were similar between IMRT and 3DCRT groups for PM patients who started RT within the first two weeks of study entry. However, for patients with head and neck primary sites who started RT at week 12, IMRT patients were more likely to have lymphopenia ($p=0.03$) and less likely to have platelet transfusion ($p=0.05$) or radiation dermatitis ($p=0.05$) when compared to 3DCRT patients. There was no difference in the development of secondary cancers within the follow up time of the study (Table 1).

Treatment target coverage, normal critical organs sparing

The PTV receiving 95% of the prescribed dose (PTV_{V95}) and the mean and maximum doses to PTV and GTV were significantly greater for IMRT patients than 3DCRT patients ($p<0.05$) (Table 3). There was no significant difference in dose heterogeneity indices, which were calculated in three different ways [D_5/D_{95} , D_5-D_{95} , and $(D_5-D_{95})/D_{\text{mean}}$] (Ratio and difference of doses delivered to 5% and 95% volume). The mean volume of PTV in the IMRT group was similar to that in 3DCRT group. There was no difference in the frequency of major and minor deviations on volume and dose between the IMRT and 3DCRT groups (Table 5). We observed no significant difference between the IMRT and 3D-CRT groups in terms of V_5 , V_{10} , and V_{20} for brain, spinal cord, optic chiasm and pituitary in all head and neck primary sites (Table 4). We did observe both significantly lower V_{20} and mean dose to the brainstem in the IMRT group. V_5 , V_{10} , and V_{20} (Volume of the following organs received 5, 10 and 20 Gy) for the contralateral cochlea, parotid and lens were also similar in the two groups for lateralized head and neck primary sites ($p>0.05$, data not shown). In addition, the results of this study show that the mean $\pm$ standard deviation for V_5 , V_{10} , V_{20} , $D_{\text{min}}/D_{\text{prescription}}$, $D_{\text{mean}}/D_{\text{prescription}}$ and $D_{\text{max}}/D_{\text{prescription}}$ of the non-specific tissue for the IMRT group were $45.6\% \pm 22\%$, $35.1\% \pm 17.6\%$, $30\% \pm 37\%$, $0.1\% \pm 0.3\%$, $24.6\% \pm 14.1\%$ and $111.4\% \pm 8.3\%$ respectively.

Discussion

The rationale for selecting IMRT rather than standard 3DCRT radiotherapy technique is to improve the therapeutic ratio by delivering a more conformal dose to the target while effectively limiting dose to surrounding critical organs. There are few studies comparing IMRT to 3DCRT for pediatric cancers. To our knowledge, this is the first comparative study to evaluate the effect of IMRT versus 3DCRT on clinical outcome in patients with

rhabdomyosarcoma. Although our analyses demonstrate that LRC and FFS were similar for both techniques, there was superior target coverage with IMRT when compared to 3DCRT. Surprisingly, we failed to show a dosimetric difference between 3DCRT and IMRT in critical organ-sparing capabilities in the head and neck.

Target coverage, LRC and FFS

Veldeman et al. reviewed clinical studies that compared IMRT with non-IMRT and reported on overall survival (OS), disease-free survival (DFS), quality of life, treatment-induced toxicity and surrogate endpoints (8). The potential of IMRT to improve survival and LRC was shown in some case series, but has not been investigated in randomized clinical trials (RCT). In retrospective studies, Chao et al. reported the advantage of IMRT over non-IMRT for head and neck cancer in adults for OS and DFS but no advantage for LRC (9). Liao et al. reported that IMRT was at least as good as 3DCRT for LRC and superior for OS for non-small-cell lung cancer (10). In pediatric patients, single center studies with small numbers of patients have reported an advantage in LRC of RMS using IMRT techniques (3–7) compared to a historical non-IMRT control group.

By contrast, the results of our study show no correlation between clinical outcome (LRC/FFS) and radiation technique. It is possible that IMRT will result in superior LRC and FFS when additional follow-up is available, but as local failure typically occurs within 5 years of diagnosis, we believe these data are reliable. In our dosimetric analysis, we observed that the V_{95} of the PTV is significantly higher using IMRT than with 3DCRT (97 ± 5 vs. 94 ± 10 , $p=0.03$) suggesting better target coverage. This dosimetric advantage of target coverage apparently did not translate into a better LRC for this study population. However, we did not find worse LRC with IMRT as compared with 3DCRT, although marginal miss is a potential concern for worse LRC when using IMRT. It is possible that the PTV consisting of a generous 2 cm margin around the GTV in this protocol may have prevented us from observing an inferior LRC due to a marginal miss. The fact that the frequency of deviations of the PTV in this study is similar in the two groups implies no difference in physician compliance with the recommended margins between the IMRT and 3DCRT groups. If the margin size is reduced in future protocols, an inferior LRC using IMRT because of marginal miss could become significant. Furthermore, we would not conclude that the superior target coverage associated with IMRT is unnecessary or unimportant. It is quite possible that the dose coverage by 3DCRT, though inferior to that of IMRT, was sufficient for tumor control at the doses specified in this study. Future studies using lower radiotherapy doses might well show lower LRC with inferior coverage as the “true minimum” radiotherapy dose is approached. Theoretically, the difference in coverage between IMRT and 3DCRT may be explained if the target coverage is sacrificed to meet dose constraints for nearby critical normal organs with 3DCRT, and this is less likely to be necessary with IMRT. However, our data show no difference in the frequency of major and minor deviations on volume and dose between the IMRT and 3DCRT groups (Table 5).

Sparing of surrounding normal critical organs

Of 26 case series testing toxicity endpoints for variable cancer sites, for IMRT group, 18 showed a reduced toxicity, 6 showed no difference and 2 showed worse toxic effects (8). A RCT in adults with nasopharyngeal cancer by Pow et al. provided evidence of IMRT sparing salivary-gland function which also translated into significant improvement in xerostomia-related variables of quality of life compared with non-IMRT treatment (11). In our study, among patients with head and neck RMS who began radiation ≥ 10 weeks from entry onto study, no patient treated with IMRT developed radiation dermatitis compared to 9 treated with 3DCRT. This may have been the result of an overall lower and more homogeneous skin dose delivered with IMRT.

We observed no dosimetric difference between 3DCRT and IMRT in sparing brain, optic chiasm, pituitary, contra-lateral cochlea, parotid and lens for those with head and neck RMS. A possible explanation is that strict adherence to the protocol-recommended upper dose limits for nearby critical normal organs may have prohibited us from observing the differences between 3DCRT and IMRT in critical organ-sparing capabilities. Hein et al. reported dosimetric results in an IMRT and 3DCRT comparison study in 5 intraorbital tumor sites. The results showed strict adherence to protocol criteria prohibited lens sparing within compliance criteria for the majority of intraorbital tumor locations. Lens doses were reduced significantly using IMRT as opposed to 3DCRT, after protocol definitions were changed by substituting the minimum dose constraint (95%) of the PTV with required minimum volume coverage (95%) with the prescribed dose (12).

Disparity in use of IMRT as a function of primary tumor sites

One reason for the disparity in frequency of IMRT vs. 3DCRT as a function of site may be a lack of superior dose distribution with IMRT for sites such as extremity and pelvis. Therefore, insurance authorization for IMRT may be difficult to obtain over the more standard 3DCRT without evidence of a superior dosimetric distribution with IMRT. To date, the pediatric literature supporting IMRT has been confined to the head and neck, orbit, and parameningeal sites. Thus clinicians may not have requested authorization to use IMRT for other sites, such as extremity, bladder/prostate, and retroperitoneal sites. The fact that the delivery of immediate RT was achieved in the complex PM and PM with intracranial extension patients who needed IMRT confirms that complexity of RT (such as IMRT) can be administered without delay.

The risk of non-specific tissue radiation

There is concern of carcinogenesis following radiation therapy in young patients (13–16). The interest in IMRT for the treatment of pediatric patients has also raised concern about possible increased volume of peripheral non-specific tissue receiving low dose radiation (12, 17). However, results from several studies have shown that IMRT allows for improved target conformity and critical tissue sparing without increasing integral dose and volume of normal tissue exposed to low doses (18–20). Unfortunately, dose to the non-specific tissue was only available in the IMRT group; thus comparison between the two groups could not be performed.

The limitations of the study

The limitations in our study include: 1) it is a retrospective analysis of a phase III trial; 2) dosimetry data was collected only from those with an available composite plan, and 3) IMRT was used more often in the later years of the study introducing a possible selection bias. Additionally, the failure to identify a dosimetric difference in critical organ-sparing may be due to the wide heterogeneity of head and neck primary sites and tumor sizes in our cohort.

Conclusion

Both 3DRT and IMRT are valuable techniques for the treatment of RMS. Our data show that IMRT improves dosimetric target coverage though this did not translate into a statistically significant improvement in LRC or FFS when compared to 3DCRT. However, clinical advantages of improved coverage with IMRT may not become apparent until treatment regimens using the (as yet unknown) minimal effective dose for RMS are explored. Therefore, lack of demonstrated clinical benefit in this specific setting should not be used as justification for accepting inferior target coverage with 3DCRT if better coverage can be achieved with IMRT. Potential disadvantages in using IMRT are the need for more

technical support than required with 3DCRT both in routine clinical practice and clinical trials, and a theoretical increase in the risk of secondary cancers if a higher integral dose is delivered. The evaluation of this latter concern will require longer follow up of larger numbers of pediatric patients.

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Figure 1. Cumulative incidence of failure of local regional control in patients treated with 3DCRT (solid line), compared with that in patients treated with IMRT (dotted line) indicating no significant difference between the groups.

Figure 2. Failure-free Survival in patients treated with 3DCRT (solid line), compared with that in patients treated with IMRT (dotted line) indicating no significant difference between the groups.

Table 1

Patient Characteristics by RT Technique

Variable		IMRT (n=87)		3DCRT (n=288)		p-value
		n	%	n	%	
Age:	<10 years	59	68	217	75	
	>=10 years	28	32	71	25	0.17
		mean=8, SD=7		mean=7, SD=6		
Sex:	Male	50	58	188	65	
	Female	37	42	100	35	0.20
Race	White	63	72	205	71	
	Hispanic	8	9	34	12	
	Black	12	14	35	12	
	Other	4	5	14	5	0.91
	Extremity	0		34	12	
Site	GU B/P	16	18	41	14	
	GU non-B/P	0		15	5	
	H/N, Orbit	6	7	25	9	
	PM	46	53	90	31	
	PM, Intracranial Extension	9	10	19	7	
	Retroperitoneal	1	1	38	13	
	Other	9	10	26	9	<0.0001
	T1	37	44	121	43	
	T2	48	56	163	57	0.90
	≤5	34	40	114	40	
Tumor size (composite)	>5	51	60	170	60	1.00
N stage (composite)	N-0	69	81	231	81	
	N-1	16	19	54	19	1.00
Histology (composite)	EMB/BOT/SPIN	49	57	141	49	
	ALV/UDS/RHAB NOS	37	43	144	51	0.27
Group (composite)	I	2	2	12	4	

Variable		IMRT (n=87)		3DCRT (n=288)		p-value
		n	%	n	%	
	II	4	5	38	13	
	III	74	87	216	76	
	IV	5	6	20	7	0.11
	ALV/UDS, Stage I or Group I	8	9	45	16	
Risk group stratum (based on composite data)	ALV/UDS, other patients	17	20	74	26	
	EMB, Stage 2/3, Group III	34	39	95	33	
	EMB, Group IV, age<10	3	3	14	5	
	PM ± intracranial extension	25	29	60	21	0.22
Secondary Cancer	No	85	98	277	96	
	Yes	2	2	11	4	0.74

P-value represents difference in proportions.

GU B/P: Genitourinary Bladder/Prostate

GU non-B/P: Genitourinary non-Bladder/Prostate

H/N: Head/Neck; PM: Parameningeal

EMB: embryonal; BOT: botryoid; SPIN: spindal

ALV: alveola; UDS: undifferentiated

RHAB NOS: Rhabdomyosarcoma not otherwise specified.

Table 2**RT Delivery by Technique**

Variable	IMRT (n=87)		3DCRT (n=288)		p-value
	n	%	n	%	
Dose					
<40 Gy	9	10	53	18	
40–50 Gy	15	17	69	24	
>50 Gy	63	72	166	58	0.04
Energy					
≤6MV	85	98	175	61	
>6MV	1	1	22	8	
Mix	1	1	79	28	
proton	0		8	3	<0.0001
# of RT fields					
≤4	6	7	242	85	
5–7	57	68	36	13	
>7	21	25	5	2	<0.0001
Elapsed days/fractions					
≤1.4 (no break)	49	56	168	59	
1.4–1.75 (1 week break)	32	37	98	34	
≥1.75 (>1 week break)	6	7	20	7	0.91
Time of RT					
<12weeks	25	29	67	24	
12–15weeks	41	47	143	50	
>15weeks	21	24	75	26	0.64

P-value represents difference in proportions.

Table 3

Treatment Target volume, Dose Coverage and Homogeneity

	3DCRT		IMRT		P-value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
(D ₅ -D ₉₅)/D _{mean}					
PTV (%)	97	11 $\pm$ 11	41	11 $\pm$ 6	0.25
CTV (%)	25	10 $\pm$ 14	9	12 $\pm$ 6	0.03
GTV (%)	100	6 $\pm$ 5	28	8 $\pm$ 6	0.003
V ₉₅					
PTV (%)	118	94 $\pm$ 10	50	97 $\pm$ 5	0.03
CTV (%)	32	98 $\pm$ 5	11	98 $\pm$ 3	0.64
GTV (%)	130	98 $\pm$ 5	33	99 $\pm$ 2	0.12
D _{mean} /D _{prescription}					
PTV (%)	103	100 $\pm$ 6	43	102 $\pm$ 6	<0.0001
CTV (%)	27	102 $\pm$ 3	10	99 $\pm$ 17	0.13
GTV (%)	114	101 $\pm$ 6	29	104 $\pm$ 4	<0.0001
D _{max} /D _{prescription}					
PTV (%)	122	107 $\pm$ 7	50	115 $\pm$ 9	< 0.0001
CTV (%)	33	108 $\pm$ 6	10	114 $\pm$ 5	0.0004
GTV (%)	142	106 $\pm$ 7	34	114 $\pm$ 10	< 0.0001
Volume					
PTV (cc)	118	277 $\pm$ 273	51	206 $\pm$ 168	0.21
CTV (cc)	29	119 $\pm$ 100	10	118 $\pm$ 122	0.62
GTV (cc)	129	74 $\pm$ 67	36	61 $\pm$ 53	0.38

P-value calculated from the Mann-Whitney test

D₅ and D₉₅: Dose received by 5% and 95% volumes.

V₉₅: % volume received 95% prescribed dose.

D_{mean}, D_{max} and D_{prescription}: Mean, maximum and prescription doses.

GTV: Gross tumor volume.

CTV: Clinical target volume.

PTV: Planning target volume.

Table 4

Dosimetric parameters for normal midline organs in all head and neck sites with prescription dose of ≥ 5000 cGy

Site	3DCRT		IMRT		P-value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
Brain					
V ₅ (%)	7	55 $\pm$ 25	16	53 $\pm$ 31	0.79
V ₁₀ (%)	7	46 $\pm$ 29	16	38 $\pm$ 26	0.38
V ₂₀ (%)	7	35 $\pm$ 34	16	14 $\pm$ 16	0.07
D _{Mean} (cGy)	7	1309 $\pm$ 898	15	1082 $\pm$ 669	0.53
Brainstem					
V ₅ (%)	22	88 $\pm$ 26	20	95 $\pm$ 12	0.66
V ₁₀ (%)	22	82 $\pm$ 35	20	88 $\pm$ 20	0.19
V ₂₀ (%)	22	72 $\pm$ 40	20	50 $\pm$ 36	0.04
D _{Mean} (cGy)	19	3678 $\pm$ 1093	22	2708 $\pm$ 1169	0.006
Spinal Cord					
V ₅ (%)	45	62 $\pm$ 29	22	72 $\pm$ 20	0.33
V ₁₀ (%)	45	55 $\pm$ 29	22	66 $\pm$ 21	0.26
V ₂₀ (%)	45	41 $\pm$ 32	22	50 $\pm$ 33	0.30
D _{Mean} (cGy)	41	1809 $\pm$ 1108	23	2026 $\pm$ 1470	0.84
Optic Chiasm					
V ₅ (%)	53	86 $\pm$ 33	29	96 $\pm$ 19	0.21
V ₁₀ (%)	53	82 $\pm$ 36	29	94 $\pm$ 20	0.20
V ₂₀ (%)	53	70 $\pm$ 43	29	73 $\pm$ 39	0.92
D _{Mean} (cGy)	46	3525 $\pm$ 1678	27	3530 $\pm$ 1239	0.53
Pituitary					
V ₅ (%)	24	98 $\pm$ 9	20	90 $\pm$ 31	0.79
V ₁₀ (%)	24	91 $\pm$ 22	20	90 $\pm$ 31	0.30
V ₂₀ (%)	24	79 $\pm$ 37	20	75 $\pm$ 41	0.96

Site	3DCRT		IMRT		P-value
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
D _{Mean} (cGy)	19	3589 $\pm$ 1546	19	5707 $\pm$ 9487	1.00

P-value calculated from the Mann-Whitney test

V5, V10 and V20: %Volume received 5, 10 and 20 Gy.

D_{Mean}: Mean dose.

Table 5

Major and minor deviation in volume and dose

		IMRT (n=87)		3DCRT (n=288)		P-value
		n	%	n	%	
Major deviation in volume	No	84	97	275	95	1.00
	Yes	3	3	13	5	
Major/minor deviation in volume	No	77	88	252	87	1.00
	Yes	10	12	36	13	
Major deviation in dose	No	84	97	282	98	0.44
	Yes	3	3	6	2	
Major/minor deviation in dose	No	81	93	269	93	1.00
	Yes	6	7	19	7	
Major deviation in volume and dose	No	82	94	269	93	1.00
	Yes	5	6	19	7	
Major/minor deviation In volume and dose	No	72	83	238	83	1.00
	Yes	15	17	50	17	

P-value is for difference in proportions