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Comparison of Testicular Dose Delivered by Intensity-Modulated Radiation Therapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT) in Prostate Cancer Patients

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Abstract

Introduction—A small decrease in testosterone has been documented after prostate irradiation, possibly due to incidental dose to the testes. Testicular dose from prostate external beam radiation plans with either IMRT or VMAT were calculated to investigate any difference.

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Methods—Testicles were contoured for 16 patients being treated for localized prostate cancer. Two plans were created for each patient, one with IMRT and one with VMAT. No specific attempt was made to reduce testicular dose. Minimum, maximum and mean dose to the testicles was recorded for each plan.

Results—Of the 16 patients, 4 received a total dose of 7800cGy to the prostate alone, 7 received 8000cGy to the prostate alone, and 5 received 8000cGy to the prostate and pelvic lymph nodes. The mean (range) of the mean testicular dose with an IMRT plan was 54.7cGy (21.1-91.9) and 59.0cGy (25.1-93.4) with a VMAT plan. In 12 cases, mean VMAT dose was higher than mean IMRT dose, with a mean difference of 4.3cGy ($p=0.019$).

Summary—There was a small, but statistically significant increase in mean testicular dose delivered by VMAT compared with IMRT. Despite this, it is unlikely that there is a clinically meaningful difference in testicular dose from either modality.

Keywords

Testicle dose; Prostate cancer; Volumetric Modulated Arc Therapy; Intensity Modulated Radiation Therapy

Introduction

An awareness of testosterone in men's health and prostate cancer has been rapidly increasing in the United States, evidenced by the dramatic rise in testosterone replacement therapy prescriptions[1]. The impact of testosterone on overall health and cancer control is appreciated but the true effect is unknown. A small decrease in serum testosterone has been documented after prostate irradiation [2, 3], but the data are limited. This phenomenon has been confirmed in the setting of treatment of the prostate with intensity-modulated radiation therapy (IMRT)[4].

One hypothesis to explain this decrease in testosterone after radiation attributes the decline to incidental dose delivered to the testes during external beam radiation. The incidental radiation dose delivered to the testicles during a course of IMRT for the treatment of prostate cancer has been shown to range between 84-630 cGy when considering field size, beam energy, and contribution from image guidance[5].

IMRT is an external beam radiation technique that is commonly used to treat prostate cancer with high doses of radiation by providing highly conformal radiation delivered from a limited number of beam angles. Volumetric-modulated arc therapy (VMAT) is a version of IMRT, where instead of delivering radiation from several discrete beam angles, radiation is delivered continuously as the treatment gantry rotates in an arc around the patient. This technique has the advantage of shorter treatment times while producing treatment plans with highly conformal high dose regions. The tradeoff for this modality is greater spread of low dose radiation to normal tissues.

Given the proximity of the testicles to prostate radiation fields and the known incidental doses delivered to the testicles via IMRT, we hypothesized that VMAT would deliver more scatter dose to the testicles than an IMRT plan. We calculated the testicular dose from

prostate external beam radiation plans with either IMRT or VMAT to investigate any difference between the two modern modalities in patients treated with dose escalation.

Methods

Patient Selection

We selected 16 patients being treated for localized prostate cancer that had consented to inclusion in the institutional review board-approved, prospectively collected Fox Chase Cancer Center prostate cancer database. We selected 5 low-risk patients to allow for comparison between 7800 cGy and 8000 cGy prescriptions. We also selected 5 high-risk patients that had lymph node volumes treated to a dose of 5600 cGy included as part of their target, to compare larger versus smaller treatment fields. The other 6 patients were intermediate risk and were treated to the prostate and proximal seminal vesicles with a prescription dose of 8000 cGy. Treatment planning

For each of these patients, computed tomography (CT) simulation and a magnetic resonance imaging (MRI) simulation were performed in the radiation oncology department as part of our institutional radiation treatment planning protocol. Patients were simulated in the supine position while immobilized in an alpha cradle (Smithers Medical Products, Akron, OH). The CT scans for each of the patients selected included the entire scrotum in the scan. The CT and MRI scans were fused together using the VelocityAI contouring software (Version 2.8, Velocity Medical Solutions, Atlanta, GA) to allow for contouring of normal tissues and target volumes. The clinical target volume was defined as prostate and proximal seminal vesicles (caudal 1cm) for patients with low risk cancer and included the distal seminal vesicles for intermediate risk patients and lymph node volumes for high risk patients. The clinical target volume was expanded 8mm in all directions except posteriorly, where it was expanded 5mm to create the planning target volume. Normal tissue structures including the bladder, rectum, urethra, penile bulb and penile corpora were contoured for each patient as part of this radiation treatment planning protocol. Additionally, the scrotum of each patient was contoured as a solid structure to allow for the calculation of radiation dose to the testicles, although there was no specific attempt to reduce testicular dose or dose constraint applied. The linear distance from the mid-prostate to the mid-testicular contour was measured for each patient.

Two plans were created for each patient using the Eclipse external beam treatment planning software (Version 10.0, Varian Medical Systems, Palo Alto, CA), which utilizes an anisotropic analytical algorithm (AAA); one plan with IMRT and the other with VMAT (RapidArc, Varian). Creating two plans for each patient allowed for the minimization of the effect of anatomic variation on the analysis. The dose prescription used was 7800 cGy for low risk patients or 8000 Gy for intermediate or high risk patients, prescribed in 200 cGy daily fractions to cover 95% of the planning target volume for the prostate and proximal seminal vesicles and 5600 cGy in 140 cGy daily fractions to the distal seminal vesicles or lymph nodes if they were targeted. The photon energy used for all patients was 10 MV. IMRT plans were created with a configuration of 8 coplanar beams. VMAT plans were created with two coplanar arcs, a 360 degree arc and a 270 degree arc. Image-guidance was

used for all patients and consisted of conebeam CT scans, radiofrequency (RF) beacons, or gold fiducials with an electronic portal imaging device (EPID).

Phantom Measurement

Two solid water phantoms, each milled to hold a PTW 0.6cc Farmer chamber, were used to measure dose at 13cm from the isocenter (the mean mid-testicular to mid-prostate distance) from a representative 2-arc VMAT plan (200 cGy/fx $\times$ 40 fxs). The Eclipse treatment planning system was used to calculate a mean dose to the isocenter and the point representing the testicular dose. The VMAT treatment plan was then delivered in QA mode of a Varian iX linear accelerator to the phantom. The percent difference between measured and calculated dose was calculated for the central region of the target dose distribution and in the out-of-field testicular region. This procedure was repeated for a typical 8-field, step-and-shoot IMRT plan.

Statistics

Minimum, maximum and mean dose to the testicles were obtained from the treatment planning system and recorded for each plan. The maximum dose was defined as the dose to a single voxel. The difference in mean dose to the testicles was calculated by subtracting the mean IMRT dose from the mean VMAT dose for each patient. Paired Wilcoxon rank sum test was used to assess the significance of a difference in dose between the two treatment modalities. A p-value less than 0.05 was considered to be statistically significant. Pearson's correlation was used to assess dose similarity, with values > 0.7 considered to be consistent with a strong positive correlation.

Results

The patient characteristics of the 16 patients in this cohort are presented in Table 1. Of the 16 patients, 4 were treated to a total dose of 7800 cGy to the prostate alone, 7 were treated to 8000 cGy to the prostate alone, and 5 were treated to 8000 cGy to the prostate and pelvic lymph nodes. The mean mid-prostate to mid-testes distance was 13.0 cm (standard deviation 1.5 cm; range, 11.0-15.9 cm). The mean, maximum and minimum testicular dose for IMRT and VMAT plans are presented in Table 2.

In 12 cases, the mean testicular dose treated with VMAT was higher than the mean testicular dose treated with IMRT, with a mean difference of 4.3 cGy ($p=0.019$). The mean testicular dose with VMAT was 7.9% higher than the mean testicular dose with IMRT. Difference in mean testicular dose remained significant when considering only the 11 patients who were treated to the prostate alone, with a mean difference of 6.4 cGy ($p=0.005$). Correlation between testicular mean dose with VMAT and testicular mean dose with IMRT was high at 0.93 (95% CI 0.80-0.98). As expected, given the small difference between the two prescription doses, no difference was evident in testicular dose based upon prescription dose of 8000 cGy vs. 7800 cGy ($p>0.05$).

Regarding the phantom measurement of a single VMAT plan and IMRT plan, the calculated mean dose for a single fraction by the treatment planning system to the isocenter was 244.0 cGy and the mean dose 13cm away was 0.7cGy. Charge recorded and converted to dose

measured by the ionization chambers at the isocenter was 248.0 cGy and charge measured and converted to dose 13 cm away (point representing location of the testicles) was 1.4 cGy. For the IMRT plan, the calculated mean dose of the target was 253.9 cGy compared to a measured dose of 258.4 cGy, and the calculated dose 13cm away was 1.0 cGy compared to a measured dose of 2.21cGy. The percent difference between measured and calculated dose in the central region of the target dose distribution is approximately 1.6% for the VMAT plan compared with 1.8% for the IMRT plan. The percent difference between measured and calculated dose in the out-of-field testicular region is approximately 102.9% and 120.7% VMAT and IMRT delivery, respectively.

Discussion

The goal of this study was to compare the difference in testicular radiation dose for prostate cancer patients treated with IMRT or VMAT. The use of IMRT for the treatment of localized prostate cancer allows for dose escalation, which has been shown to improve clinical outcomes, while also providing better sparing of normal organs at risk[6]. First used in 2007, VMAT has enjoyed significant utilization due to its ability to deliver highly conformal radiation plans in a fraction of the time of a fixed beam IMRT plan[7]. VMAT has been shown to be able to deliver plans with improved rectal wall and femoral head sparing compared to IMRT[8]. For high dose volumes, VMAT plans are felt to be equivalent or possibly superior compared to IMRT plans. For dose to more distant normal tissues, the integral dose, defined as the volume of tissue receiving dose, is considered. Due to the beam orientation from VMAT plans, there is greater spread of low dose radiation to the surrounding normal tissues. The integral dose has been reported as 7-9% higher with VMAT than with IMRT when comparing plans for high-risk prostate cancer [9]. This increased low dose spread to surrounding normal tissue with VMAT is consistent with the findings of our study, which demonstrates a 7.3% higher mean dose to the testes for VMAT plans compared to IMRT plans.

Testosterone in males is primarily produced by Leydig cells in the testes. Studies reporting the effect of less than 1 Gy show that those doses do not appear to affect Leydig cell function[10]. One study with long term follow-up of young men treated with radiation for Hodgkin's lymphoma, found that doses <70cGy can result in transient elevation of serum follicle stimulating hormone (FSH) and oligospermia, but have no evident effect on luteinizing hormone (LH) or testosterone[11]. Radiation dose to the testes has been reported for external beam radiation delivered through a four-field technique to the pelvis for prostate and rectal cancers and has been shown to be in the range of 200-400 cGy[3, 12]. These two studies, along with one from Pickles *et al.* [2] which did not measure testicular dose, demonstrated a decrease in serum testosterone after radiation.

In this cohort of 16 patients, the mean dose to the testicles was low regardless of the modality used, ranging from 21.1-93.4 cGy, with a maximum value <400 cGy. Comparison of the difference in mean dose to the testicles between the two delivery modalities demonstrates higher dose with VMAT than IMRT. The magnitude of the difference is quite small (all <21 cGy) and not likely to cause a clinically evident difference.

Incidental testicular irradiation due to IMRT for the treatment of prostate cancer was recently reported by King *et al*[5]. For their study, they considered additional contribution of dose due to field size, beam energy, and use of daily image guidance. Mean testicular dose ranged from 68 cGy for a prostate only field with 6MV photons to 220 cGy for a pelvic nodal field treated with 15MV photons. These values included a correction factor that was obtained from thermoluminescent dosimeter (TLD) measurements and applied to the calculated results from the treatment planning software. Daily portal MV image guidance contributed a mean dose of 350 cGy if the testes were in the imaging portal and 16 cGy if out of field. The data from our current study, although slightly lower than reported by King *et al.*, do support the result from this previous study as our data are simply from the treatment planning system and do not include correction for TLD measurements or contribution from portal imaging.

The findings from this study are limited by the small sample size. However, the intra- and inter-patient testicular doses are largely consistent within this dataset and when compared to the previous study by King, *et al.* Additionally, the testicular dose from both modalities were very low due to the target of interest, the testes, being outside of the treatment field and not in the same axial plane with the treatment beams. Therefore, dose was not being modulated to avoid the target structure and the primary contribution of dose was due to scatter. The treatment planning system is not optimized to model dose at such low levels, as evidenced by our phantom measurements. Given the uncertainties with calculating scatter dose this far out-of-field, MLC leaf transmission, head leakage modeling, etc., this was expected. However, since this study is performing a relative comparison of testicular dose between VMAT and IMRT using the same treatment planning system/optimization algorithm, we expect the comparison to be valid even if the absolute dose is different from the phantom measurement. Further study would include in vivo dosimetry to confirm the dose to the testicles as calculated by the treatment planning system, as well as pre- and post-RT serum testosterone levels to provide clinical correlation.

Conclusion

There is a small but statistically significant increase in incidental mean testicular dose when external beam radiotherapy for prostate cancer is delivered by VMAT compared with IMRT. The findings from this study are consistent with prior data suggesting a higher integral dose for VMAT. Despite this, it is unlikely that the choice of treatment modality would result in a clinically meaningful difference in radiation dose to the testes.

This study supports existing data for dose delivered to the testes with IMRT during the treatment of prostate cancer. Further study regarding the sensitivity of Leydig cells to radiation, associated suppression of testosterone, and effect on a patient's sexual function would be useful.

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Table 1

Patient Characteristics

Number of Patients (%)	
Prescription Dose (cGy)	
7800	4 (25)
8000	12 (75)
Treated Volume	
Prostate/Seminal Vesicles	11 (69)
Prostate + Lymph Nodes	5 (31)
Image Guidance	
RF Beacons	8 (50)
Conebeam CT	4 (25)
Gold Fiducials/EPID	4 (25)
Prostate-Testes Separation (cm)	
Mean(Standard Deviation)	13.0 (1.5cm)
Range	11.0-15.9

Table 2

Testicular Dose for IMRT and VMAT plans

	IMRT Mean Dose [cGy] (Range)	VMAT Mean Dose [cGy] (Range)	p-value
Mean Testicular Dose	54.7 (21.1-91.9)	59.0cGy (25.1-93.4)	p=0.019
Maximum Testicular Dose	161.7 (55.6-367.5)	170.8 (57.5-395.8)	p=0.023
Minimum Testicular Dose	17.1 (0-34.7)	19.5 (0.1-38.6)	p=0.535