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A Dosimetric Analysis of Radiation Therapy Oncology Group (RTOG) 0321: the Importance of Urethral Dose

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Abstract

Purpose—RTOG 0321 is the first multi-institutional cooperative group HDR prostate brachytherapy trial with complete digital brachytherapy dosimetry data. This is a descriptive report of the data and an analysis of toxicity.

Methods and Materials—Patients are treated with EBRT 45 Gy and one HDR implant with 19 Gy in 2 fractions. Implants are done with TRUS guidance, and CT-compatible non-metallic catheters. HDR planning is done on ≤ 3 mm-thick CT slices. The “mean DVH” of the PTV, implanted volume (IP), and organs at risk are calculated. This includes the mean and standard deviation of the volume at ten-percentage-point intervals from 10%–200% of the prescribed dose. The conformal index (COIN), homogeneity index (HI), catheters/implant, and patients/institution are calculated. Multivariate analysis and Hazard Ratios calculation of all the variables against reported Grade ≥ 2 (G2+) GU adverse events (CTCAEv3) are performed.

Results—Dosimetry data is based on 122 eligible patients from 14 institutions. The mean of PTV, IP, catheters/implant, and patients/institution are: 54 cc, 63 cc, 19 and 9. The mean of $\%V100_{PTV}$, $V80_{Bladder}$, $V80_{Rectum}$, and $V120_{Urethra}$ were: 94%, 0.40cc, 0.15cc, and 0.25cc. There are too few G2+ GI AE for correlative analysis, thus the analysis has been performed on the more common G2+ GU AE. There are positive correlations noted between both acute and late G2+ GU AE and urethral dose at multiple levels. Positive correlations with late AE are seen with PTV and IP at high-dose levels. A negative correlation is seen between HI and acute AE. A higher patient accrual rate is associated with a lower rate of G2+ acute and late AE.

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CONFLICT OF INTEREST
None for all authors

Conclusions—Higher urethral dose, larger high dose volumes and lower dose homogeneity are associated with greater toxicities. A mean DVH comparison at all dose levels should be used for quality control and future research comparison.

Keywords

Prostate cancer; High Dose Rate; Brachytherapy; RTOG; Multi-institutional clinical trial

INTRODUCTION

RTOG 0321 is the first and only cooperative group, prospective HDR prostate brachytherapy trial. The trial has been completed in May 2006. After adequate follow-up for evaluation of its primary end point, the trial result has been published in 2010. The study shows that the HDR brachytherapy technique resulted in a low rate of treatment-related toxicity, with an acute grade 3+ adverse event rate of 2% and late grade 3+ adverse event rate of 2%.[1] Apart from establishing the safety of HDR boost in a multi-institutional cooperative trial setting, RTOG 0321 is also the only such trial with a set of complete digital HDR brachytherapy dosimetry data. This digital data set provides a unique opportunity to study the HDR brachytherapy dosimetry.

The primary goal of this analysis is to set forth a detailed description of the HDR brachytherapy dosimetry from RTOG 0321. Since the dosimetry data is captured in digital three-dimensional format, we present the data as DVH of the target and organs at risk (OAR). We accomplish this by constructing the “mean DVH” for each volume of interest. On each histogram we plot the group’s mean volume from 10% to 200% of the prescribed dose at ten percentage-point intervals. The actual mean and the standard deviation at each dose level are presented in a table format. With this data, the readers will be able to reconstruct each DVH in their planning system for comparison. It can be used to compare with specific dose limits currently used in the clinic, or perhaps even more optimally, as a gauge globally to the full-range of doses on a DVH curve. With each comparison, the physician will know immediately if the dose is within the standard deviation of the mean, on any part of the DVH. With modern HDR planning systems, the dwell times can then be re-optimized, if deemed necessary, prior to the treatment delivery. Another potential application of this data may be for comparison with another novel radiotherapy modality to see if there is a significant difference in dosimetry prior to embarking on clinical investigations.

RTOG 0321 is not initially designed to test any possible relationship between dose and toxicity. Due to the intrinsic dose heterogeneity within the brachytherapy target volume, however, we are able to examine for possible relationships between dose with the outcome. Specifically, we hypothesize that there is a correlation between OAR dose with toxicity. Furthermore, results from permanent seed implant boost in RTOG 0019 suggest a relationship between favorable implant dosimetry and institution experience (using institutional accrual as a metric of experience).[2] We, therefore, hypothesize that there may be an association between implant dosimetry, clinical outcome and institutional accrual. Finally, a prior study suggest that implant techniques such as the number of catheters used in

the implant affect dosimetry outcome. [3] We therefore will investigate whether there is an association between dosimetry quality, clinical outcome and number of catheters used per implant.

METHODS AND MATERIALS

Patient Population

All patients are staged based on the AJCC staging 6th edition. The patients eligible for this study must have the following combinations of factors: (1) Clinical stage T1c-T2c, Gleason score 2–6 and PSA >10, but ≤ 20; (2) clinical stage T3a-T3b, Gleason score 2–6 and PSA ≤ 20; or (3) clinical stage T1c-T3b, Gleason score 7–10 and PSA ≤ 20. All patients must be clinically N0, M0. Patients are ineligible for this study if they had prior TURP, radical surgery for prostate cancer, hip prosthesis, prior pelvic or prostate radiation, or chemotherapy for prostate cancer. The maximum institutional accrual limit is 20 patients.

External Radiation Therapy

The clinical target volume (CTV) for the external beam portion of the treatment is defined as the prostate and seminal vesicles or whole pelvis, depending on the lymphatic risk. If 2/3 PSA + [(GS-6) × 10] is > 15%, then whole pelvis radiation is required. Daily doses of 1.8 Gy given five times per week for a total dose of 45 Gy are delivered using three-dimensional conformal techniques.

HDR Brachytherapy

The overall treatment course is limited to less than eight weeks. All HDR afterloading catheters are required to be CT-compatible and placed with transrectal ultrasound (TRUS) guidance. No fewer than 14 catheters must be in the CTV to ensure adequate coverage without excessive hot spots. Three-dimensional, CT based brachytherapy treatment planning was required. Dwell time in dwell positions located outside of the target volume are turned down or off in order to minimize irradiating normal tissue. The definition of volumes is in accordance with ICRU Report 58: Dose and Volume Specification for reporting interstitial therapy.[4] The CTV is defined based the treatment-planning CT scan. The brachytherapy CTV includes the prostate and any extra-capsular extension. The Planning Target Volume (PTV) equals the CTV. OAR contoured includes the bladder, rectum, and urethra. When contouring the bladder and rectum, the outer-most border of the mucosa is contoured. For the urethra, the outer surface of the Foley catheter within the prostate is contoured. The prescription dose of 19 Gy is delivered in two fractions. The goal is to deliver the prescribed dose to at least 90% of the PTV. The volume of bladder and rectum receiving 75% of the prescribed dose has to be limited to less than 1 cc (V75 rectum and V75 bladder < 1 cc) and the volume of urethra receiving 125% of the prescribed dose has to be limited to less than 1 cc (V125 urethra < 1 cc). The first HDR treatment is delivered on the day of the catheter placement. The second treatment using the same plan is delivered within 24 hours after the first treatment with no less than 6 hours between fractions.

Statistical Methods

For the descriptive analysis, the dosimetry data are extracted via an Excel spreadsheet from Image-Guided Therapy Quality Assurance Center (ITC), Washington University, located in St. Louis, Missouri. The mean DVH of the PTV, implanted volume, and OAR are plotted. Implanted volume is defined as the volume received the 100% of the prescribed dose, including volume outside of the PTV. Each DVH include the mean volume from 10% to 200% of the prescribed dose constructed at ten–percentage-point intervals. The standard deviations of the mean volume at each interval are also calculated. Both the average conformal index (COIN) [5] and homogeneity index (HI) [6] are also calculated using an Excel spreadsheet

All treatment-related, acute and late adverse event (AE) data are obtained from the RTOG Statistical Center, Philadelphia, Pennsylvania. This is the same data set used for reporting RTOG 0321's primary analysis. All adverse events are graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, per the protocol. Acute AE period is defined based on RTOG standard, as 9 months from the start of protocol treatment and late AE period starts from the end of 9 month from the start of protocol treatment. Multivariate analysis and calculation of Hazard Ratios (HR) and confidence intervals (CI) of all the variables against Grade 2 or higher (G2+) GU and GI adverse events are performed. The dose-volume data is fitted on a logistic regression model to predict G2+ GU AE. The results are summarized using Hazard Ratios (HR).

Data on institutional accrual, and number of catheters per implant are also collected from the Statistical Center. The participating institutions are divided based upon institutional accrual into four groups: (1) Very Low Accrual (1 to 5 patients); (2) Low Accrual (6 to 10 patients); (3) Medium Accrual (11 to 15 patients); and (4) High Accrual (16 to 20 patients). A Chi-square test has been performed between groups with and without reported G2+ GU and GI AE. Similarly, Chi-square test statistics are used to test the relationship between the number of catheters used per implant versus AE.

RESULTS

Dosimetry data is based on 121 eligible patients (129 enrolled) with a set of complete data from 14 institutions. The mean (range) of PTV and implanted volume are 54 cc, (19–130 cc) and 63 cc (26–147 cc). The mean (range) of $\%V100_{PTV}$, $V80_{Bladder}$, $V80_{Rectum}$, $V120_{Urethra}$, are 94% (87–99), 0.40 cc (0–3.2), 0.15 cc (0–1.1), and 0.25 cc (0–1.1), respectively. Because there was a large range of PTV, we have divided the DVH data into four quartiles of PTV, with the cut-points at 19 cc, 39 cc, 52 cc, 64 cc, and 130 cc. The data for mean DVH is set forth in Table 1 and plotted in Figure 1.

The mean (range) of COIN and HI are 0.75 (0.49–0.87) and 0.63 (0.39–0.85). The mean (range) of number of catheters per implant and patients per institution are 19 (13–29), and 9 (2–19), respectively.

Acute Adverse Events

The acute adverse events analysis is based on follow up information available as of 11/18/08, time of the primary analysis. There has been a total of 36 acute GU G2+ adverse events and 3 acute GI G2+ adverse events. Because there are too few G2+ GI AE, the analysis has been performed on G2+ GU AE only. The types of GU adverse events are: pollakiuria 58%, urinary retention 25%, cystitis / spasms 5.2%, urinary incontinence 2.8% and other 8.3%. There are positive correlations between acute G2+ GU AE and urethral dose at multiple dose levels, most significantly at $V120_{Urethra}$ [HR 8.66, CI (2.2–33), p = 0.002]. The calculated Hazard Ratios at each dose-volume is plotted in Figure 2.

There is a negative association between acute adverse events and Homogeneity Index (HI) [HR 0.006, CI (<0.001–0.30), p = 0.01]. There is no significant association found between the conformal index and the number of catheters used per implant. A summary of the results is shown in Table 2. The patients from institutions with higher institutional accrual have a lower frequency of acute G2+ GU adverse event (p = 0.006).

Late Adverse Events

The late adverse events analysis is based on follow up information available as of 11/18/08. The median follow up time of these 121 cases is 2.47 years. There has been a total of 28 late GU G2+ AE and 5 late GI G2+ AE. Because there are too few G2+ GI AE, the analysis has been performed on G2+ GU AE only. The types of GU adverse events are: pollakiuria 64%, cystitis 18%, urinary incontinence 7%, urethral stricture 3.5%, urinary retention 3.5% and other 3.5%. There are positive correlations between late G2+ GU AE and urethral dose at multiple dose levels above $V110_{Urethra}$, most significantly at $V130_{Urethra}$ [HR 15.1, CI (4.1–55.2), p <0.0001]. There are also positive correlations between late G2+ GU adverse events with PTV and Implanted Volume from $V140_{PTV}$ to $V200_{PTV}$ and $V150_{Implant}$ to $V200_{Implant}$, respectively. The calculated Hazard Ratio at each dose-volume is plotted in Figure 3.

There is no significant association between late AE and Homogeneity Index (HI), conformal index (COIN), and number of catheters used per implant. A summary of the results is shown in Table 2. The patients from institutions with higher institutional accrual have a lower frequency of late G2+ GU AE (p = 0.016).

DISCUSSION

Modern brachytherapy has evolved from two-dimensional to three-dimensional treatment planning. In a three-dimensional planning system, a significant amount of resources is spent to capture the vast amount of imaging information. A systematic approach is needed for the analysis and clinical application of this data. Furthermore, the clinical relevance of this data should be documented whenever possible.

RTOG 0321 has demonstrated that HDR prostate brachytherapy boost can be delivered safely along with external beam radiotherapy. The study documented a low frequency of toxicity. To disseminate this technology and to replicate the clinical result, we have provided a detailed description of the HDR dosimetry from the study using the mean DVH. This data

should allow planners to rapidly compare current DVH with patients from RTOG 0321. The ability to rapidly compare across the whole DVH, rather than just at a few dose points, should improve the quality and consistency of HDR brachytherapy planning. Furthermore, since a variety of different dose constraints have be reported in the literature[7], individual can compare the quality of dosimetry in this study to their own experience.

It is important, however, to point out some limitations of this approach. First of all, it assumes the data follows a normal distribution and can thus be described using means and standard deviations. This is unlikely to be the case in some parts of the DVH, such as doses falling near the dose constraint. Second, the data does not take into account the clinical condition of each patient. For example, a lower dose may be better in some patients with pre-existing medical conditions, such as diabetes or poor baseline urinary function. Third, for the data to be meaningful, the structures must be contoured according to the protocol. In RTOG 0321, the urethra contours are per protocol in 110 cases, 4 cases with major corrections required are un-evaluable, and 7 cases are missing contours.

In this study, we find increased acute and late toxicity is related to a higher urethral dose. Increased late toxicity is related to a higher high dose volumes (hot spots) in PTV and implanted volume. Increased acute toxicity was also associated with a lower Homogeneity Index. These findings are interesting for multiple reasons. First, it suggests that the dose-limiting structure for prostate HDR brachytherapy is in the target volume (urethra). This is in contrast to external beam radiotherapy, where the rectum is the dose-limiting structure. There are both supporting evidences[8–13] and contradicting evidence[14] for this finding in the published literature. The identification of the dose limiting structure is important to further limit treatment related toxicity and for the development of improved treatment techniques. HDR brachytherapy combined with external beam radiotherapy exploits this difference in dose limiting structure and may be possible to further improve outcomes without higher toxicity for locally advance prostate cancer. Clinical evidence already suggests the advantage of this approach as it has been demonstrated recently by a prospective randomized study between an HDR boost versus external beam radiotherapy by Hoskin et al.[15]

Second, the findings document the importance of dose planning inside the brachytherapy target volume. These findings support the routine use of three-dimensional treatment planning and the use of advanced treatment planning techniques to control the dose in the target volume. We hope the data will help standardize and improve the quality and consistency of treatments and clinical outcomes. The data also suggest there may be opportunities to further improve treatment. Two feasible approaches capitalizing on this technology: (1) intra-prostatic dose escalation using existing hot spots[16–18]; and (2) decrease urethral dose with low-dose tunnel[19] have already been demonstrated in studies. Techniques like these and others may further improve outcome.

Similar to RTOG 0019 for permanent seed boost, RTOG 0321 has again demonstrated the importance of institution experience, this time linked to better clinical outcome.[2] The exact reason for this association cannot be adequately addressed in this study since our analysis is

limited to dosimetry. However, we hope the lessons learned in this study about dosimetry will make HDR brachytherapy better and less operator experience dependent.

It is important to point out the unique nature of this trial and some trial design features that worked well and others that did not work as well. This is the first prospective multi-institutional prostate HDR boost study. Another prospective single institutional study has not found an association between OAR dose and toxicity.[14] This may be because the techniques used were more homogenous, and led to smaller dose variations and fewer adverse events to show any correlation. Fourteen institutions have participated in this study due to a preset limit on institutional accrual. An accrual limit may have delayed the time to reaching the final accrual goal but allowed for a mixture of treatment approaches. This design has ultimately proved important. Conversely, the lack of heterogeneity may be the reason why this study has failed to show the catheter number effect. The protocol sets the lower limit of 14 catheters per implant. Above this limit, the clinical effect due to catheter number could not be detected. Finally, the primary end point of the study is based on grade 3+ toxicities, but systematic collection of low-grade toxicities even without the quality of life measures ultimately has proven useful. Most importantly, it is the systematic collection of digital three-dimensional CT based dosimetry data that has made this *post hoc* analysis a success. The importance in understanding HDR brachytherapy dosimetry can be made even in this modest sized clinical study. All of this is made possible because of the digital database infrastructure. Credit for this work goes to the NCI, and RTOG (especially Dr. James Purdy).

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REFERENCES

1. Hsu IC, Bae K, Shinohara K, et al. Phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate: preliminary results of RTOG 0321. International journal of radiation oncology, biology, physics. 2010 Nov 1; 78(3):751–758.
2. Lee WR, Bae K, Lawton CA, et al. A descriptive analysis of postimplant dosimetric parameters from Radiation Therapy Oncology Group P0019. Brachytherapy. 2006 Oct-Dec;5(4):239–243. [PubMed: 17118317]
3. Charra-Brunaud C, Hsu IC, Weinberg V, Pouliot J. Analysis of interaction between number of implant catheters and dose-volume histograms in prostate high- dose-rate brachytherapy using a computer model. International journal of radiation oncology, biology, physics. 2003 Jun 1; 56(2): 586–591.
4. (ICRU Report 58) Dose and volume specification for reporting interstitial therapy. Paper presented at: International Commission on Radiation Units and Measurements; Bethesda, MD. 1997.
5. Baltas D, Kolotas C, Geramani K, et al. A conformal index (COIN) to evaluate implant quality and dose specification in brachytherapy. International journal of radiation oncology, biology, physics. 1998; 40(2):515–524.
6. Wu A, Ulin K, Sternick ES. A dose homogeneity index for evaluating 192 Ir interstitial breast implant. Medical Physics. 1988; 15:104–107. [PubMed: 3352544]

7. Yamada Y, Rogers L, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy. 2012 Jan-Feb;11(1):20–32. [PubMed: 22265435]
8. Ghadjar P, Keller T, Rentsch CA, et al. Toxicity and early treatment outcomes in low- and intermediate-risk prostate cancer managed by high-dose-rate brachytherapy as a monotherapy. Brachytherapy. 2009 Jan-Mar;8(1):45–51. [PubMed: 19038584]
9. Ghadjar P, Matzinger O, Isaak B, et al. Association of urethral toxicity with dose exposure in combined high-dose-rate brachytherapy and intensity-modulated radiation therapy in intermediate- and high-risk prostate cancer. Radiother Oncol. 2009 May; 91(2):237–242. [PubMed: 19167121]
10. Ishiyama H, Kitano M, Satoh T, et al. Genitourinary toxicity after high-dose-rate (HDR) brachytherapy combined with Hypofractionated External beam radiotherapy for localized prostate cancer: an analysis to determine the correlation between dose-volume histogram parameters in HDR brachytherapy and severity of toxicity. International journal of radiation oncology, biology, physics. 2009 Sep 1; 75(1):23–28.
11. Sullivan L, Williams SG, Tai KH, Foroudi F, Cleeve L, Duchesne GM. Urethral stricture following high dose rate brachytherapy for prostate cancer. Radiother Oncol. 2009 May; 91(2):232–236. [PubMed: 19097660]
12. Ghadjar P, Rentsch CA, Isaak B, Behrensmeier F, Thalmann GN, Aebersold DM. Urethral toxicity vs. cancer control--lessons to be learned from high-dose rate brachytherapy combined with intensity-modulated radiation therapy in intermediate- and high-risk prostate cancer. Brachytherapy. 2011 Jul-Aug;10(4):286–294. [PubMed: 21030318]
13. Hindson BR, Millar JL, Matheson B. Urethral strictures following high-dose-rate brachytherapy for prostate cancer: Analysis of risk factors. Brachytherapy. 2013 Jan; 12(1):50–55. [PubMed: 22561217]
14. Morton GC, Loblaw DA, Sankreacha R, et al. Single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate-risk prostate cancer: analysis of short- and medium-term toxicity and quality of life. International journal of radiation oncology, biology, physics. 2010 Jul 1; 77(3):811–817.
15. Hoskin PJ, Bownes P, Bryant L, Ostler P. HDR Monotherapy Brachytherapy for Localised Prostate Cancer. Clin Oncol (R Coll Radiol). 2007 Apr.19(3 Suppl):S7.
16. Menard C, Susil RC, Choyke P, et al. MRI-guided HDR prostate brachytherapy in standard 1.5T scanner. International journal of radiation oncology, biology, physics. 2004 Aug; 59(5):1414–1423.
17. Pouliot J, Kim Y, Lessard E, Hsu IC, Vigneron DB, Kurhanewicz J. Inverse planning for HDR prostate brachytherapy used to boost dominant intraprostatic lesions defined by magnetic resonance spectroscopy imaging. International journal of radiation oncology, biology, physics. 2004 Jul 15; 59(4):1196–1207.
18. Kim Y, Hsu IC, Lessard E, Kurhanewicz J, Noworolski SM, Pouliot J. Class solution in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI. Radiother Oncol. 2008 Jul; 88(1):148–155. [PubMed: 18083260]
19. Cunha JA, Pouliot J, Weinberg V, Wang-Chesebro A, Roach M 3rd, Hsu IC. Urethra low-dose tunnels: Validation of and class solution for generating urethra-sparing dose plans using inverse planning simulated annealing for prostate high-dose-rate brachytherapy. Brachytherapy. 2011 Sep 20.

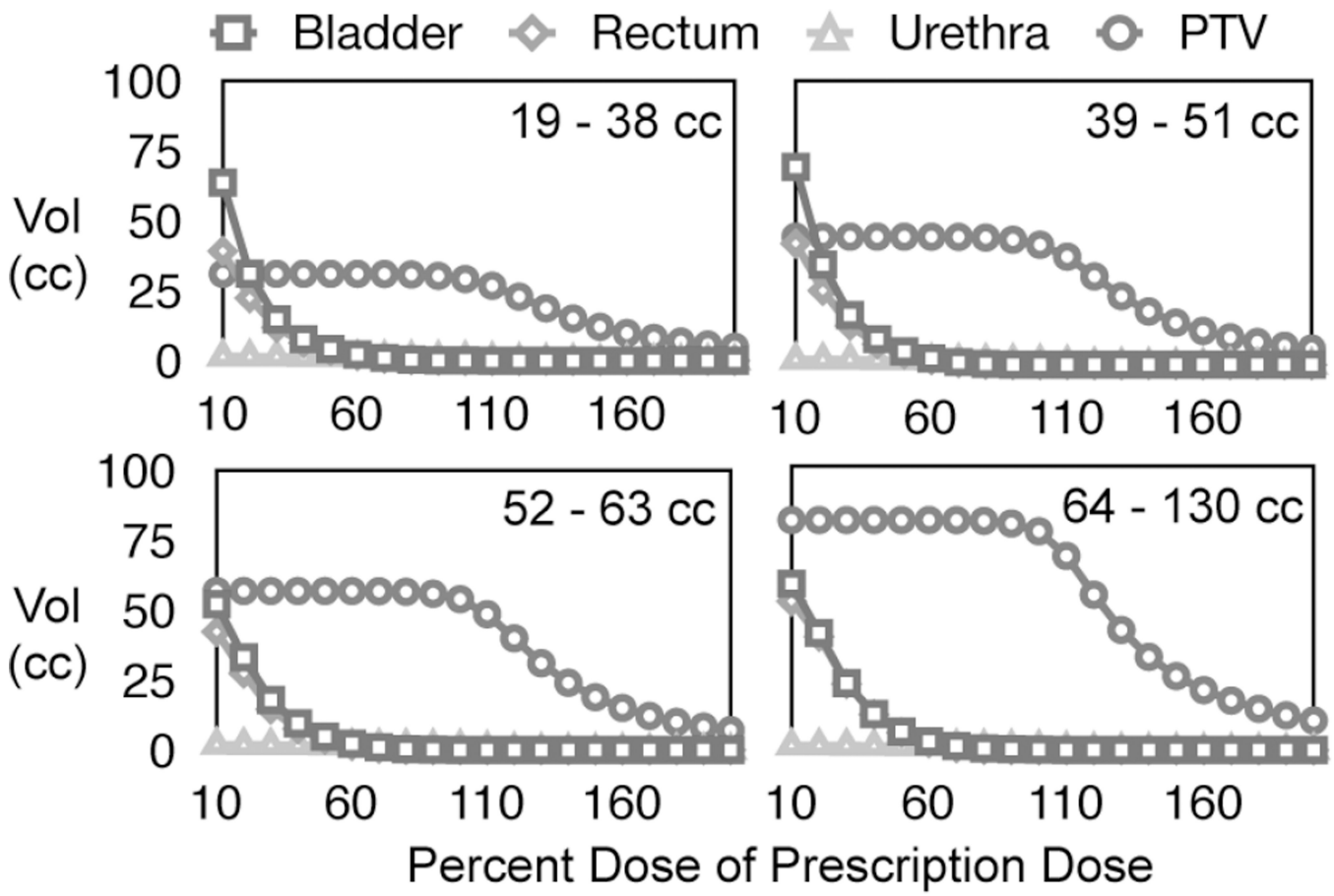

Figure 1.
Mean DVH of PTV and OAR by PTV quartiles

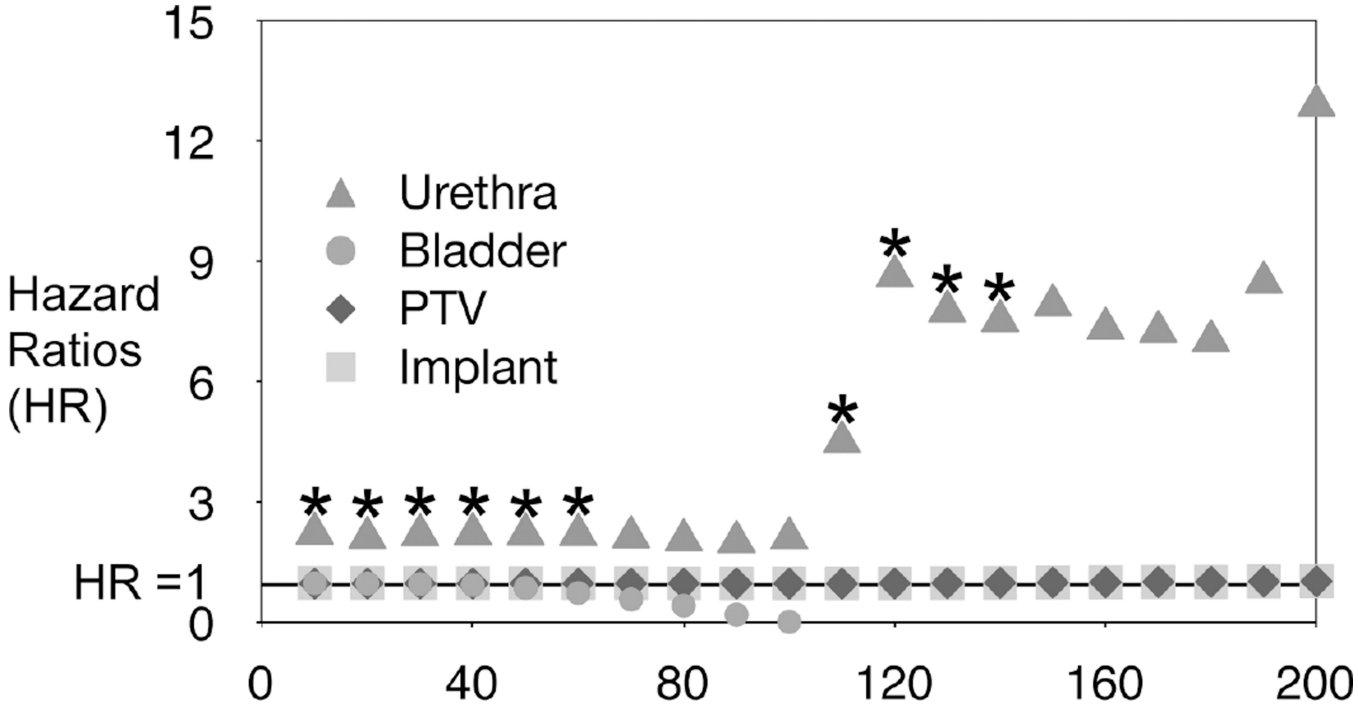

Figure 2.

Hazard Ratios of Acute Adverse Event versus Dose-Volume. HR greater than 1 implies increased hazard for higher volume and HR less than 1 implies decreased hazard with higher volume. Asterisk (*) indicates statistically significant associations.

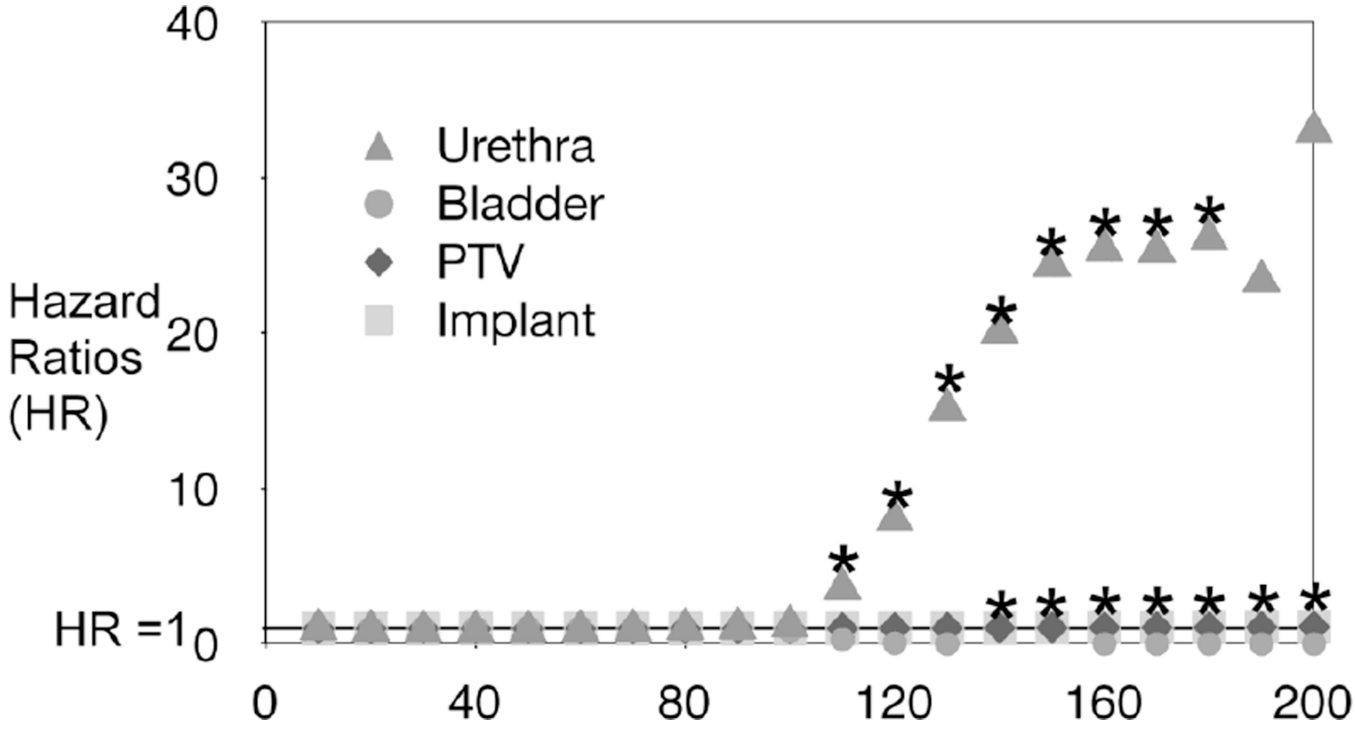

Figure 3.

Hazard Ratios of Late Adverse Event versus Dose-Volume. HR greater than 1 implies increased hazard for higher volume and HR less than 1 implies decreased hazard with higher volume. Asterisk (*) indicates statistically significant associations.

Table 1

Cumulative DVH Data for Bladder, PTV, Rectum, and Urethra

PTV N		Percent Prescribed Dose																			
		10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200
19–38 cc N=30	Bladder Mean	63.6	31.1	14.8	7.7	4.2	2.2	1.0	0.4	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Bladder STDEV	30.7	13.3	6.5	3.6	2.0	1.1	0.7	0.4	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	PTV Mean	31.0	31.0	31.0	31.0	31.0	31.0	31.0	30.8	30.3	29.2	26.8	22.9	18.7	15.1	12.1	9.9	8.2	6.8	5.8	5.0
	PTV STDEV	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.8	5.5	4.9	4.3	3.6	3.1	2.7	2.4	2.1	1.8	1.6
	Rectum Mean	39.2	22.4	11.8	6.4	3.5	1.8	0.8	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Rectum STDEV	15.2	7.5	3.9	2.4	1.5	0.9	0.5	0.3	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra Mean	1.5	1.5	1.4	1.4	1.3	1.3	1.2	1.1	1.1	1.0	0.7	0.3	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0
	Urethra STDEV	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1
39–51 cc N=31	Bladder Mean	69.7	35.2	17.5	9.0	4.7	2.3	0.9	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Bladder STDEV	44.7	16.1	7.3	3.8	2.1	1.2	0.5	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	PTV Mean	45.1	45.1	45.1	45.1	45.1	45.1	45.0	44.8	44.1	42.3	38.1	31.1	24.1	18.8	14.8	11.9	9.7	8.0	6.7	5.7
	PTV STDEV	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.8	3.7	3.7	3.6	3.6	4.0	4.2	4.0	3.6	3.2	2.8	2.4	2.1
	Rectum Mean	42.8	26.1	13.8	7.2	3.7	1.7	0.6	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Rectum STDEV	17.3	8.4	4.6	2.9	1.8	1.1	0.6	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra Mean	1.8	1.8	1.7	1.7	1.6	1.5	1.5	1.4	1.3	1.2	0.8	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra STDEV	0.8	0.8	0.7	0.6	0.6	0.5	0.5	0.4	0.4	0.4	0.4	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
52–63 cc N=31	Bladder Mean	52.1	33.2	17.9	9.5	4.8	2.3	1.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Bladder STDEV	27.5	18.6	9.4	4.4	2.0	1.0	0.6	0.3	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	PTV Mean	56.8	56.8	56.8	56.8	56.8	56.8	56.7	56.5	55.8	53.9	48.5	39.9	31.0	24.0	18.9	15.0	12.2	10.0	8.4	7.1
	PTV STDEV	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.5	3.5	3.5	3.6	4.3	4.7	4.6	4.1	3.5	3.0	2.5	2.2	1.9
	Rectum Mean	42.3	27.4	14.5	7.5	3.7	1.6	0.5	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Rectum STDEV	21.1	11.4	5.9	3.3	1.8	1.0	0.5	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra Mean	1.9	1.8	1.8	1.7	1.6	1.6	1.5	1.5	1.4	1.3	0.8	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra STDEV	0.7	0.6	0.6	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.5	0.3	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0
64–130 cc N=30	Bladder Mean	58.6	41.2	23.6	12.7	6.5	3.1	1.4	0.6	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Bladder STDEV	30.0	17.6	9.8	5.7	3.3	2.0	1.2	0.8	0.5	0.2	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

PTV N		Percent Prescribed Dose																		
		10	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**
	PTV Mean	81.0	81.0	81.0	81.0	81.0	81.0	81.0	80.7	79.8	77.1	68.4	54.7	42.3	32.8	26.0	21.1	17.4	14.5	12.2	10.4
	PTV STDEV	19.3	19.3	19.3	19.3	19.3	19.3	19.3	19.3	19.2	18.5	15.4	12.1	10.4	9.7	9.0	8.1	7.3	6.4	5.5	4.8
	Rectum Mean	52.4	39.9	23.3	12.5	6.1	2.5	0.7	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Rectum STDEV	24.6	15.9	8.7	4.9	2.7	1.5	0.7	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Urethra Mean	1.6	1.6	1.5	1.4	1.4	1.3	1.3	1.3	1.2	1.1	0.6	0.3	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0
	Urethra STDEV	0.7	0.6	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1

Table 2

Hazard Ratios for COIN, HI, Catheters/implant. Patient Accrual.

	Hazard Ratio (CI) for Acute AE	Hazard Ratio (CI) for Late AE
COIN**	0.421 (0.002, 72.701), p = 0.74	125.1 (04, >1000), p = 0.10
HI**	0.006 (<0.001, 0.299), p = 0.01*	0.02 (0.0003, 1.98), p = 0.10
Number of Catheters/implant**	1.045 (0.932, 1.173), p = 0.45	1.030 (0.921, 1.15), p = 0.59
Patient Accrual/Institution†	p = 0.006*	p = 0.016*

Asterisk (*) indicates statistically significant associations.

** Based on fitting Fine-Gray regression model of hazard of G2+ GU adverse event.

† Based on the chi-square test.