



Dosimetric coverage of the prostate, normal tissue sparing, and acute toxicity with high-dose-rate brachytherapy for large prostate volumes

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ABSTRACT

Purpose: To evaluate dosimetric coverage of the prostate, normal tissue sparing, and acute toxicity with HDR brachytherapy for large prostate volumes.

Materials and Methods: One hundred and two prostate cancer patients with prostate volumes >50 mL (range: 5-29 mL) were treated with high-dose-rate (HDR) brachytherapy ± intensity modulated radiation therapy (IMRT) to 4,500 cGy in 25 daily fractions between 2009 and 2013. HDR brachytherapy monotherapy doses consisted of two 1,350-1,400 cGy fractions separated by 2-3 weeks, and HDR brachytherapy boost doses consisted of two 950-1,150 cGy fractions separated by 4 weeks. Twelve of 32 (38%) unfavorable intermediate risk, high risk, and very high risk patients received androgen deprivation therapy. Acute toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Results: Median follow-up was 14 months. Dosimetric goals were achieved in over 90% of cases. Three of 102 (3%) patients developed Grade 2 acute proctitis. No variables were significantly associated with Grade 2 acute proctitis. Seventeen of 102 (17%) patients developed Grade 2 acute urinary retention. American Urological Association (AUA) symptom score was the only variable significantly associated with Grade 2 acute urinary retention ($p=0.04$). There was no ≥ Grade 3 acute toxicity.

Conclusions: Dosimetric coverage of the prostate and normal tissue sparing were adequate in patients with prostate volumes >50 mL. Higher pre-treatment AUA symptom scores increased the relative risk of Grade 2 acute urinary retention. However, the overall incidence of acute toxicity was acceptable in patients with large prostate volumes.

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INTRODUCTION

Use of high-dose-rate brachytherapy (HDR) for prostate cancer has increased over the last decade (1). HDR brachytherapy has produced excellent outcomes as either monotherapy (2) or as a boost in combination with external beam radiation therapy (EBRT) (3, 4).

The Groupe Européen de Curietherapie (GEC) European Society for Radiotherapy and Oncology (ESTRO)-European Association of Urology (EAU) consider prostate volumes larger than 60 mL to be less suitable for HDR brachytherapy due to increased pubic arch interference and concerns regarding greater toxicity (5). Similarly, the American Brachytherapy Society has su-

ggested that prostate volumes greater than 50 mL constitute a relative contraindication to HDR brachytherapy (6).

The purpose of this study is to evaluate dosimetric coverage of the prostate, normal tissue sparing, and acute toxicity with HDR brachytherapy in patients with prostate volumes >50 mL.

MATERIALS AND METHODS

Patient Characteristics

Patient records were reviewed after institutional review board approval was obtained. Patients were included in this study if they had clinically localized prostate cancer, prostate volumes greater than 50 mL, and underwent HDR

brachytherapy without or with intensity modulated radiation therapy (IMRT) at a single institution between 2009 and 2013. Prostate volume was calculated using pre-treatment computed tomography (CT) scans. The mean $\pm$ standard deviation prostate volume was 68 ± 16 mL (range, 51-129 mL). National Comprehensive Cancer Network (NCCN) definitions of very low, low, intermediate, high, and very high recurrence risk groups were used (7). Patient characteristics are presented in Table-1. All patients received alpha blockers for a minimum of one month after HDR brachytherapy.

HDR Brachytherapy Monotherapy

Prostate cancer patients with very low risk disease and an expected survival of ≥ 20 years, low

Table 1 - Patient characteristics.

Patient Characteristics	Category	Number (%)
Age (years)	Median	69
Gleason Score	≤ 6	38 (37)
	7	48 (47)
	≥ 8	16 (16)
Recurrence Risk Group	Very Low to Low	34 (33)
	Intermediate	47 (46)
	High to Very High	21 (21)
Pre-treatment Prostate-Specific Antigen (ng/mL)	<10	82 (80)
	10-20	12 (12)
	>20	8 (8)
Prostate Volume (mL)	Median	62
Body Mass Index	Median	28.7
Androgen Deprivation Therapy	No	86
	Yes	16
Pre-treatment American Urological Association Symptom Score	Median	6
	1-7 (Mild Symptoms)	38 (37%)
	8-19 (Moderate Symptoms)	63 (63%)
	20-35 (Severe Symptoms)	0 (0%)

risk disease and an expected survival of ≥ 10 years, or “favorable” intermediate risk disease were treated with HDR brachytherapy monotherapy to the prostate. “Favorable” intermediate risk patients were defined as those with a Gleason score $3+4=7$, American Joint Committee on Cancer clinical $\leq T2b$ disease (8), and $\leq 50\%$ positive core biopsies (2).

Patients underwent HDR brachytherapy monotherapy according to American Brachytherapy Society consensus guidelines (6). Patients were placed under general anesthesia, put in the low dorsal lithotomy position, and prepared and draped in sterile fashion. A #16 Foley catheter was inserted into the bladder and 5 mL of diatrizoate contrast was injected into the catheter balloon. A biplane trans-rectal ultrasound (TRUS) probe was inserted into the rectum and mounted on an adjustable stepper stabilizer. A prostate template was attached to the front of the TRUS stabilizer unit.

Fourteen to eighteen ProGuide™ (Nucletron, Veenendaal, Netherlands) HDR brachytherapy treatment catheters were inserted into the prostate transperineally under TRUS guidance. Each treatment catheter was carefully advanced so as to not penetrate the inferior bladder wall or come within 1.0 cm of the prostatic urethra. Once the treatment catheters were in position, the prostate template was sutured onto the perineum and locked. Upon completion of treatment catheter placement, the prostate template was removed.

The clinical target volume (CTV) consisted of the prostate as defined by CT scan. The planning target volume (PTV) was the same as the CTV. The PTV was treated with two 1,350–1,400 cGy fractions. One fraction was delivered with each iridium-192 (Ir-192) implant, and the two implants were separated by 2–3 weeks. Prostate doses were recorded as the minimum dose that covered more than 90% of the prostate volume expressed as a percentage of the prescription dose (prostate D90). Prostate volumes were recorded as the fractional volume of the prostate that received 100% of the prescribed dose (prostate V100), 150% of the prescribed dose (prostate V150), and 200% of the prescribed dose (prostate V200). The urethral volume was recorded as the fractional volume of the urethra that received 150% of the prescribed dose (urethra V150). The urethral dose was the dose de-

livered to 10% of the urethral volume expressed as a percentage of the prescribed dose (urethra D10). The rectal volume was recorded as the fractional volume of the rectum that received 75% of the prescribed dose (rectum V75). Rectal doses were recorded as the maximum dose received by 2 mL of the rectum expressed as a percentage of the prescribed dose (rectal D2 mL). The bladder volume was recorded as the fractional volume of the bladder that received 75% of the prescribed dose (bladder V75). Bladder doses were expressed as the maximum dose received by 2 mL of the bladder expressed as a percentage of the prescribed dose (bladder D2 mL). Dosimetric goals are presented in Table-2. No androgen deprivation therapy (ADT) was given to HDR brachytherapy monotherapy patients, e.g., to down-size the prostate.

HDR Brachytherapy + IMRT $\pm$ ADT

“Unfavorable” intermediate risk patients had a Gleason score $4+3=7$, clinical T2c disease, or $>50\%$ positive core biopsies (9, 10). Unfavorable intermediate risk and high risk patients were treated with an HDR brachytherapy boost consisting of two 950–1,150 cGy fractions and IMRT to the prostate and proximal 1.0 cm of the seminal vesicles to 4,500 cGy in 25 fractions over 5 weeks without or with ADT (4). The two HDR brachytherapy fractions were delivered 1 1/2 weeks before the start of IMRT and 2 1/2 weeks after the start of the IMRT. The CTV for each HDR brachytherapy fraction consisted of the prostate as defined by CT scan. In cases with extraprostatic extension on MRI or biopsy, the CTV was expanded to include disease outside of the prostate with a 0.3 cm margin. In cases with seminal vesicle invasion on MRI, the CTV was expanded to the seminal vesicle involvement. The PTV was the same as the CTV. Four fiducial gold markers were transrectally inserted into the left and right mid lateral prostate and the prostatic base and apex at the time of the first HDR brachytherapy implant. The markers made it possible to determine the location of the prostate using electronic portal imaging immediately prior to each IMRT treatment and thereby deliver image-guided radiation therapy (11). No IMRT was delivered the day of the second HDR brachytherapy fraction.

Table 2 - Dosimetric results achieved with HDR brachytherapy.

Dosimetric Endpoint	Goal	Achieved Mean	Achieved Standard Deviation	Achieved Range
Prostate				
D90 (%)	>90 and <130	105	3	87-111
V100 (%)	>90	94	2	87-98
V150 (%)	<50	27	3	20-36
V200 (%)	<25	11	2	7-22
Urethra				
V150 (%)	0	0.0	0.0	0.0-0.0
D10 (%)	<115	108	2	105-120
Rectum				
V75 (mL)	<1.0	0.2	0.3	0.0-1.5
D2 mL (%)	<75	54	10	33-75
Bladder				
V75 (mL)	<1.0	0.7	0.5	0.0-3.0
D2 mL (%)	<80	65	6	45-79

Patients were simulated for IMRT with an empty rectum using a pelvic CT scan with 0.3 cm slices. Forty mL normal saline mixed with 10 mL non-ionic contrast was injected into the bladder and urethra at the time of simulation in order to perform a cystogram and urethrogram, respectively. The CTV for IMRT consisted of the prostate and inferomedial 1.0 cm of the seminal vesicles as defined by CT and magnetic resonance imaging (MRI) scans. In cases with extraprostatic extension on MRI or biopsy, the CTV for IMRT was expanded to include disease outside of the prostate based on CT-MRI fusion. In cases with seminal vesicle invasion on MRI, the CTV for IMRT was expanded to include the entire involved seminal vesicle. The PTV consisted of the CTV with 0.5 cm expansion posteriorly, inferiorly, and superiorly and 0.7 cm expansion anteriorly and laterally. The minimum allowable dose delivered to the PTV was 93% of the prescribed dose, and the maximum allowable dose delivered to the PTV was 115% of the prescribed dose. At least 98% of the PTV received $\geq 95\%$ of the prescribed dose (12). Rectal and bladder dose-volume histograms (DVHs) were created. The

dosimetric goals for IMRT were that no more than 15% of the rectal volume should receive >4,100 cGy and no more than 15% of the bladder volume should receive >4,000 cGy.

Biologically Effective Doses (BED_{1.5})

Assuming an α/β ratio of 1.5 for prostate cancer (13), the biologically effective doses (BED_{1.5}) with HDR brachytherapy monotherapy to a total dose of 2,700-2,800 cGy in 2 fractions versus an HDR brachytherapy boost to 1,900-2,300 cGy in 2 fractions in combination with IMRT to 4,500 cGy in 25 fractions are 27,000-28,933 cGy, and 23,833-29,833 cGy, respectively.

ADT

ADT always consisted of a gonadotropin-releasing hormone agonist. In most cases, ADT also included an anti-androgen. The median duration of a gonadotropin-releasing hormone agonist was 4 months in a neoadjuvant and concomitant setting for intermediate-risk disease and 28 months in a neoadjuvant, concomitant, and adjuvant setting for high risk or very high risk

disease. The median duration of an anti-androgen was one month starting two weeks prior to the gonadotropin-releasing hormone agonist. Twelve of 32 (38%) unfavorable intermediate risk, high risk, and very high risk patients received ADT. ADT use in these cases was at the discretion of the patients and began two months prior to the start of radiotherapy. None of the patients who received ADT had a history of congestive heart failure or myocardial infarction.

Acute Toxicity

The severity of adverse effects was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (14).

Statistics

Statistical analysis was performed using Minitab® Statistical Software version 16 (Minitab®, Inc, State College, PA). A two sided $p \leq 0.05$ was considered significant. Means, standard deviations, and minimum and maximum values of the dosimetric parameters were calculated. Multivariate logistic regression analysis was used to assess the association between prostate volume, body mass index (BMI), pre-treatment American Urological Association (AUA) symptom score, total HDR dose, dosimetric parameters (D90, V100) and the occurrence of $\geq$ Grade 2 acute urinary retention and acute proctitis.

RESULTS

Median follow-up was 14 months. Dosimetric results achieved with HDR brachytherapy are presented in Table-2. In terms of prostate coverage and sparing of the urethra, rectum, and bladder, dosimetric goals were achieved in over 90% of cases.

Three of 102 (3%) patients developed Grade 2 acute proctitis. Seventeen of 102 (17%) patients developed Grade 2 acute urinary retention requiring placement of a Foley catheter for less than 6 weeks. Only AUA symptom score was significantly associated, on multivariate analysis, with Grade 2 acute urinary retention (odds ratio 1.14, 95% confidence interval 1.01-1.28, $p=0.04$). No variables

were significantly associated with Grade 2 acute proctitis. There was no $\geq$ Grade 3 acute toxicity.

DISCUSSION

Monroe et al. (15) performed a study of 54 patients who received either HDR brachytherapy monotherapy or HDR brachytherapy as a boost to EBRT. Large prostate volumes did not affect dosimetric coverage of the prostate, with prostate D90, V100 and V150 meeting the dosimetric goals. In addition, genitourinary and gastrointestinal toxicity in patients with prostates > 50 mL was consistent with previously-reported toxicity for small prostates (6, 16). Le et al. (17) performed a study of 164 prostate cancer patients who underwent HDR brachytherapy monotherapy and found no significant difference in prostate D90 or V100 with prostate volumes > 50 mL. In patients with larger glands, a significantly higher biochemical control of disease was observed, with no difference in late toxicity. They concluded that gland size should not be considered in the selection of patients for HDR brachytherapy. White et al. (18) reported that HDR brachytherapy allows the physician to consistently achieve complete prostate target coverage and maintain normal tissue dose constraints for organs at risk over target volumes ranging from 12-109 mL. Similarly, in this study, prostate coverage and sparing of the urethra, rectum, and bladder were dosimetrically achieved in over 90% of cases with prostate volumes ranging between 51 mL and 129 mL (Table-2).

In this report, ADT was only given to 12/32 (38%) unfavorable intermediate risk, high risk, and very high risk patients. Neoadjuvant ADT may be used to down-size an enlarged prostate due to benign prostatic hyperplasia (BPH) regardless of the recurrence risk group (6, 19). However, ADT has been implicated in brachytherapy-related morbidity such as urinary retention (20). Also, there may be a significant detriment in quality of life due to ADT (21).

In the present report, the incidence rate of Grade 2 acute urinary retention was 17%. This is consistent with the literature (22). There was an independent association on multivariate analysis between pre-treatment AUA symptom score and

acute urinary retention. An increased pre-treatment AUA symptom score may be due to BPH (21). Some groups have reported that high AUA symptom scores are associated with an increased risk of urinary retention (24, 25). Similar findings were observed in this study. AUA symptom scores improve after brachytherapy significantly faster in patients receiving alpha blockers (26).

A brachytherapy boost offers a potential radiobiological benefit over conventionally-fractionated IMRT by delivering hypofractionated treatment, which may increase the sensitivity of prostate cancer to radiation therapy by favorably affecting the α/β ratio (27-29). This may explain why some have observed improved biochemical disease-free survival with IMRT and a brachytherapy boost compared with IMRT alone, though there is a greater risk of late genitourinary toxicity (30). There was no $\geq$ Grade 3 acute toxicity due to an HDR brachytherapy boost and IMRT without or with ADT in the present study.

Limitations of this study are primarily related to its retrospective nature, limited number of patients, and short follow-up. Nevertheless, this is one of the few reports on HDR brachytherapy in men with large prostates.

CONCLUSIONS

Prostate volumes greater than 50 mL do not constitute a relative contraindication to HDR brachytherapy.

CONFLICT OF INTEREST

None declared.

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