

Original Article

Influence of catheters on predicted tumour control probability and severity of acute genitourinary toxicity during high-dose-rate brachytherapy prostate boost

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Abstract

Purpose: High-dose-rate brachytherapy (HDR) boost is an effective method for dose escalation when treating prostate cancer. Optimal number and location of catheters play key role in radiation dose delivery. We studied the impact of catheters and associated trauma on the dose uncertainties and urethral toxicity.

Methods and Materials: Between July 2008 to August 2009, 50 patients with prostate cancer were treated with 46 Gy of external irradiation of whole pelvis (2 Gy per fraction) and two HDR brachytherapy fractions (each 14 Gy) at the end of 10 fractions of external beam. All brachytherapy implants were planned using real-time, ultrasound-based planning system. Variables were prostate and urethral volumes, number of catheters and their mean distance from base of bladder and dose volume histogram parameters. All data were collected during first implant only. The toxicities were graded according to Radiation Therapy Oncology Group Toxicity Criteria. Statistical analysis was done on SPSS version 17.0.

Results: The mean number of catheters implanted was 12.38 (8–19), and number of attempts per needle to achieve desired position was 1.6 (range = 0–5). Mean distance between the catheters tips to contrast filled bladder was 3.2 mm (1–8 mm) after the adjustment. Distances >5 mm showed lower doses to prostate and lower predicted tumour control probability (TCP) ($p < 0.01$). No correlation was found between numbers of catheters implanted, attempts per catheter and severity of acute genitourinary (GU) toxicity. Significant correlation was found between severity of acute GU toxicity and urethral V130, V150 ($p < 0.001$).

Conclusion: Dose decline and subsequently lower TCP were seen for the greater distances between the needles and bladder. Acute GU toxicity increased with higher urethral, but severity of acute GU toxicity does not increase with increase in prostate/urethral volumes, number of catheters needles and attempts.

Keywords

High-dose-rate brachytherapy; prostate; needles; tumour control probability; acute genitourinary toxicity

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INTRODUCTION

Recent studies have shown increased prostate cancer cure rates with dose escalation of radiation dose.^{1,2} However, in order to maximize dose to the prostate, it is necessary to minimize dose to rectum and bladder. Three dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) has shown better results in terms of delivering higher radiation doses to the prostate and acceptable acute and late genitourinary (GU) and gastrointestinal (GI) toxicity.^{3,4} However, some of the issues, for example uncertainties regarding target localization, organ motion and setup errors, may offset the advantages of 3D-CRT and IMRT.⁵

High-dose-rate brachytherapy (HDR) is an alternative method to deliver higher dose to the target as with needles in place only insignificant movements occur during treatment. Furthermore, a steep dose gradient between target and adjacent organs at risk spares the surrounding organs from being exposed to an excessive radiation dose despite the delivery of a higher dose to the prostate.⁶

However, similar to setup errors in external beam radiotherapy (EBRT), various factors may cause the dose uncertainties in HDR brachytherapy, including needle induced trauma and subsequent change in target volume,⁷ edema resolution between fractions,⁸ visualization of urethra⁹ and computed tomography (CT) slice thickness.¹⁰ The desired position or depth of needles is the key point for successful dose delivery and is highly dependent on operator's experience. Higher number of attempts per catheter may result in increased trauma along the needle track and may cause increased GU toxicity. After the implantation, individual needles do not move relative to one another or to perineal templates used, but there is a tendency for them to displace inferiorly relative to the prostate as a single unit,¹¹ this can lead to under dosage of prostate. Various methods have been proposed to compensate this movement.¹²

Our study aimed to evaluate the impact of catheters position, their number and repeated catheter manipulations on the optimal dose to

the prostate and urethra, tumour control probability (TCP) and on the severity of acute GU toxicity; subsequently these results were used to find the solutions for adequate position, number of the catheters and various dosimetric parameters.

MATERIALS AND METHODS

Patients and treatment techniques

Fifty consecutive patients, after written consent for the treatment, received 192-iridium (Ir^{192}) HDR brachytherapy boost to prostate along with 3D-CRT between July 2008 to August 2009. Study protocol was approved by institutional ethical committee before patients' accrual. The characteristics of the patients are shown in Table 1. Briefly, conformal radiotherapy was administered with high-energy photons of 15MV X-rays at total dose of 46 Gy. Total dose was given in five times weekly with fraction doses of 2 Gy. All patients were treated by conformal radiotherapy using multi-leaf collimators. HDR brachytherapy was given in two sessions at 20 and 40 Gy of EBRT. In a dedicated room, keeping patient in lithotomy position under spinal anaesthesia, urologists inserted needles transperineally into the prostate guided by transrectal ultrasonography cranial images after identifying contrast filled urethra.

Table 1. Patient characteristics

Variables	
Number of patients	50
Average age (range)	66(45–84)
Stage	
T2	32 (64%)
T3	16 (32%)
T4	2 (4%)
Gleason score	
≤6	2 (4%)
7	2 (4%)
8–10	46 (86%)
PSA before androgen ablation (ng/ml)	33.54 (6–192)
PSA at time of EBRT (ng/ml)	7(1–14)
Number of needles implanted	12 (8–19)
EBRT (total dose)	46 Gy ÷ 23
Fractionation of brachytherapy	14 Gy × 2
Median follow-up (months)	12(3–16)

PSA = prostate-specific antigen; EBRT = external beam radiotherapy.

After all the procedure was completed, real-time images were obtained and all organs (prostate, urethra, bladder and rectum) were contoured with help of radiologist, and treatment planning was done on Flexiplan version 2.2. Dwell positions were activated at 2.5 mm along each needle. Dwell times were optimized using reverse planning optimization algorithm. The prescribed dose was 14 Gy at periphery of prostate and the mean prostate dose was 10 Gy; urethral dose constraints were kept low so that mean urethral dose does not exceed beyond 10 Gy. All data were collected during first session of brachytherapy.

All patients underwent androgen blockade prior to radiotherapy, which was continued with and after radiotherapy.

Number and attempts per catheter

During the procedure, the total catheters implanted were counted and also number of attempts per catheter to achieve desired position was recorded. Correlation analysis was done between number of catheters and different prostate volumes.

Mean catheters distance

The base of urinary bladder was taken as surrogate for the base of prostate (extreme caudal part of prostate). Thereafter, actual distances between the tips of all catheters and the base of bladder were measured separately on anteroposterior (AP) plain radiographs of pelvis with 12 inch C-arm unit (OEC 9800Plus; GE Medical Systems) (Figure 1) and on digitally reconstructed AP images from ultrasonography images of implanted catheters. The catheters were pushed in their optimal positions if distances were unacceptable. Catheter positions were again checked.

Dose volume histogram (DVH) evaluation

The DVH derived from Flexiplan version 2.2 treatment planning system. The prostate volumes, urethra volumes, percentages of entire prostate and urethral volume receiving 10, 30, 50, 80, 100, 120 and 150% of prescribed dose (V10, V30, V50, V80, V100, V120 and V150) were recorded. Analysis was done between position of catheters and D90 (dose received by 90% of prostate volume).

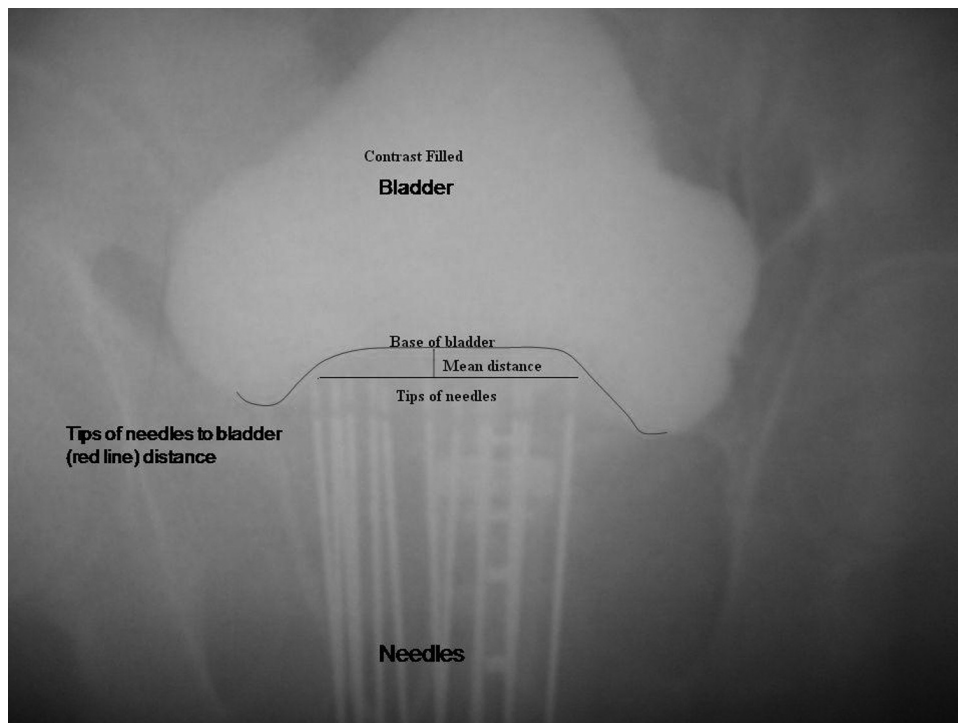


Figure 1. Mean tips of catheters to bladder distance.

Tumour control probability calculation (TCP):

The method for calculating TCP was based on linear quadratic (LQ) and TCP models by Wang et al.¹³ Summarized equation is as follows:

$$TCP = e^{-KS}$$

Where e is exponential and K is cell number of tumour clonogens. The value of this parameter depends on the risk level of patient groups. For low, intermediate and high-risk prostate cancer, K values are 1.6×10^6 , 3.0×10^6 and 1.1×10^7 cells. S is surviving fraction of cells irradiated to total dose. S was calculated by following equation according to LQ model.

$$S(D) = \exp(-\alpha D - \beta D^2)$$

Where D is the dose at which cells survive, and the dimensions of the parameters were $\alpha = \text{Gy}^{-1}$ and $\beta = \text{Gy}^{-2}$ and the α/β ratio was considered 1.5 for prostate cancer. The interpretation of above equation is that cell killing results from the interaction of two elementary damaged species—probably DNA double strand breaks to produce dicentric chromosomal aberration which cause lethality.

The resultant TCP were plotted against catheters distances from the bladder (in our patients all calculation were done considering all patients with high risk).

Acute GU toxicity grading

Acute GU toxicities were graded on the toxicity criteria of Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer (RTOG/EORTC CTC). Correlation and univariate analyses were done. Furthermore, the effect of number of attempts per catheters and their number on severity of acute GU toxicity was also evaluated.

Statistical analysis

All descriptive data, statistical tests correlation and chi-square test were analysed by using Statistical Package for the Social Sciences (SPSS) version 17.0.

RESULTS

Total number of catheters implanted and number of attempts per needle

The mean number of catheters implanted was 12.38 (range = 8–19), and number of attempts per catheter to optimize the position was 1.6 (range = 0–5). The mean prostate volume was 27.54 cc (10.8–69.0). No correlation was found between the prostate volume (p value 0.5) and number of catheters implanted (p value 0.3) (Figure 2).

Mean catheter distance and TCP analysis

Mean distance between the tips of catheters to base of bladder was 3.2 mm (1–8 mm) after adjustment. Before adjustment, mean distance was 6 mm. At 5 mm distance, D90 dose was 8.4 Gy prescribed dose, and for distances more than 5 mm, D90 dose dropped abruptly to 6 Gy at 8 mm ($p < 0.01$). Greater distances even showed lower D90 (Figure 3). This decrease in dose to the prostate resulted in lower relative TCP: 0.95, 0.95 and 0.66 for 3 mm, 5 mm and 6 mm distances of catheters to bladder ($p < 0.01$) (Figure 4).

DVH data

The urethra is organ at risk (OAR) within the target, that is, prostate. Its position makes urethra to receive doses similar to prescribed doses. Mean urethral volume was 0.34 cc (0.1–0.8 cc). Mean urethral D90 was 7.5 Gy (5–11). No correlation was seen between very close positions of catheters to urethral doses, as dwell position and time were kept low or nil during treatment.

Acute GU toxicity and severity analysis

The main acute toxicities were dysuria, increased frequency and nocturia. The distribution of acute GU toxicity was as follows: Grade 0 = 58% (29 patients), Grade 1 = 20% (10 patients), Grade 2 = 14% (7 patients) and Grades 3 and 4 = 6% (1 patient). Severity of acute GU toxicity did not increase with number of catheters implanted, needling attempts. Similarly, no correlation was seen between the severity and the prostate volumes. The severity of acute GU toxicity was found to increase

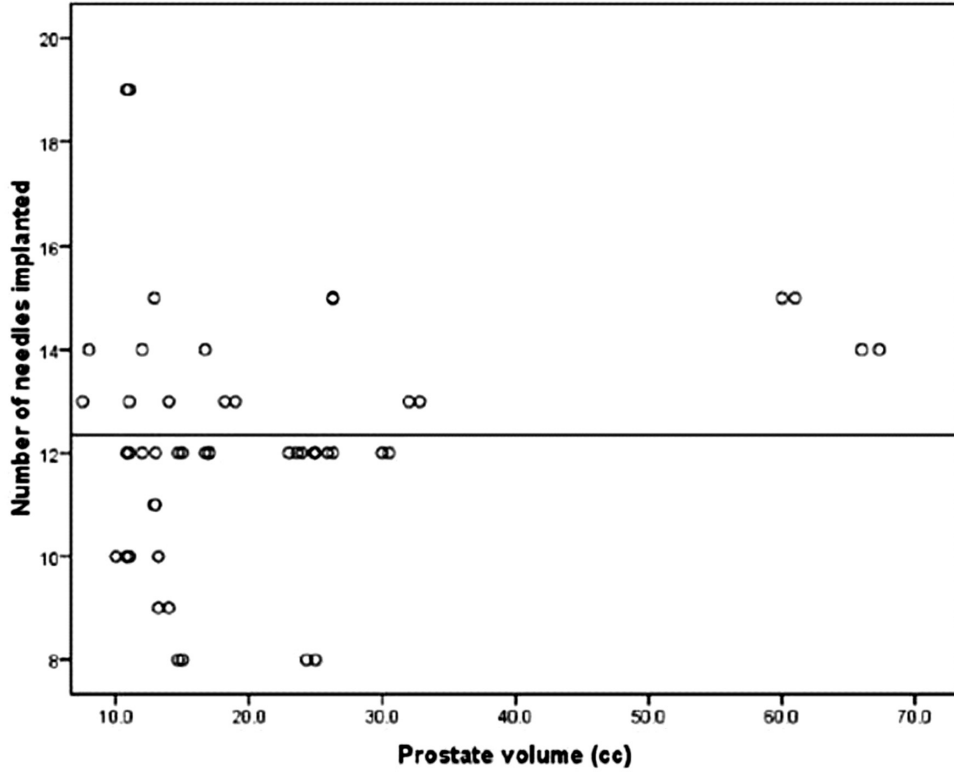


Figure 2. Correlation between the prostate volume and number of catheters implanted.

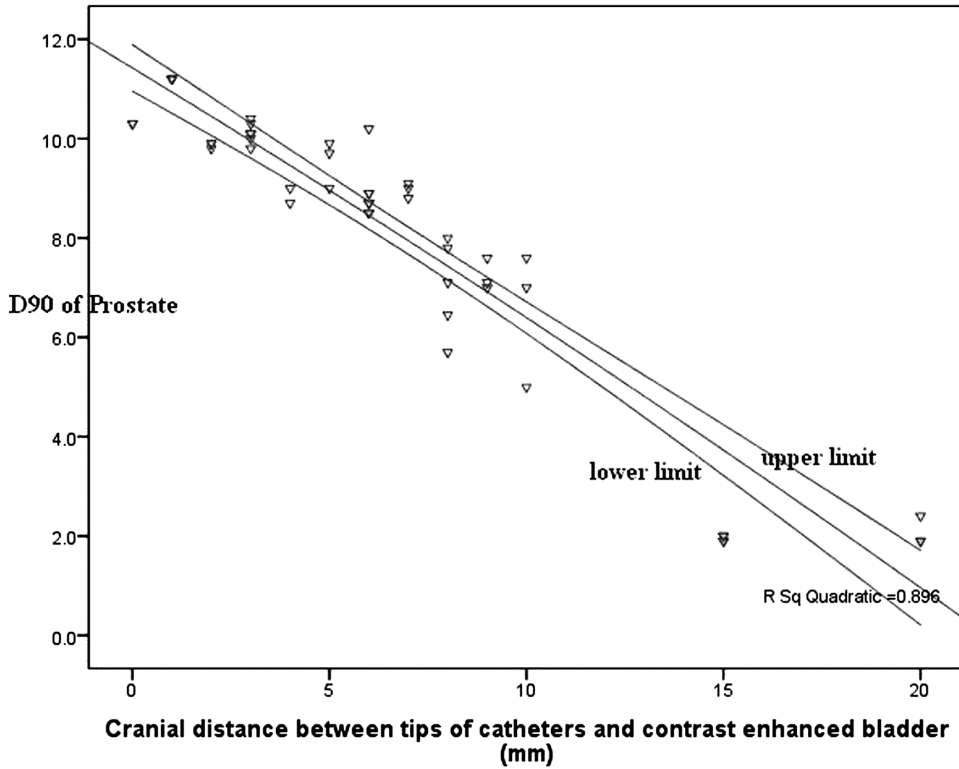


Figure 3. D90 (dose received by 90% of prostate volume) of prostate decrement with increase in distance between tips of catheters and base of bladder.

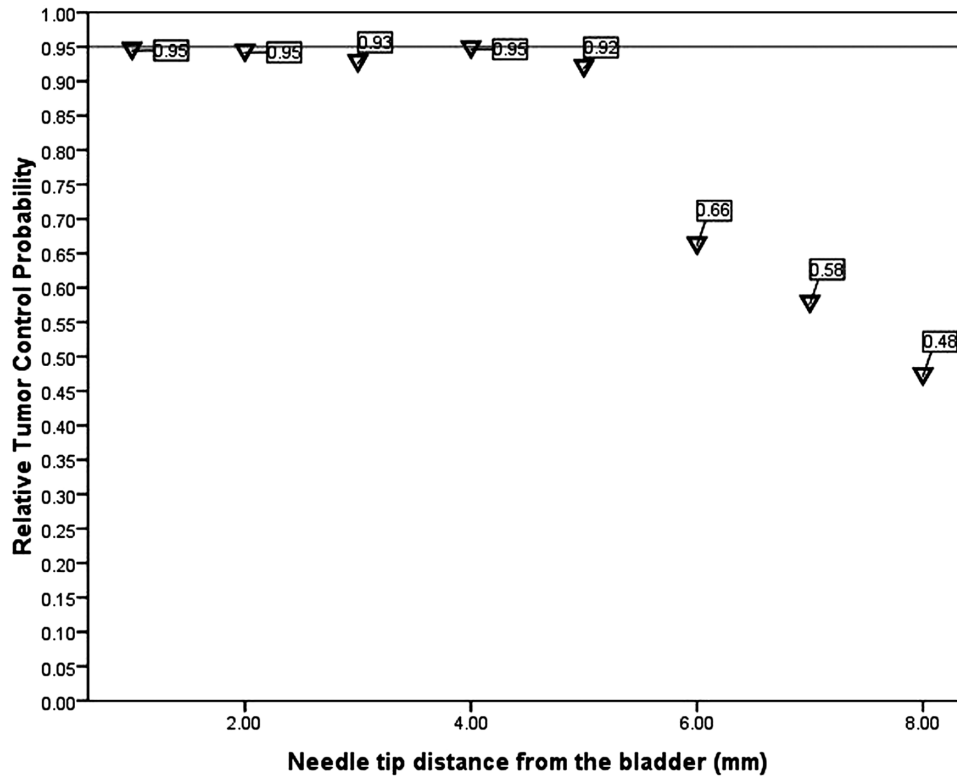


Figure 4. Predicted tumour control probability decreases with increase in gap between catheters and bladder.

with urethral V10, V30, V50, V80 and V100 but did not show significance (p value = 0.9) until V120 and V130 were achieved (p value 0.001) (Figure 5).

DISCUSSION

Our study found no apparent correlation between number of catheters implanted and prostate volumes and acceptable dose distribution, but theoretically fewer needles may cause dose inhomogeneities. Study by Brunaud et al. showed a well-acceptable dose distribution for bigger prostates with fewer needles as compared to smaller prostates. Furthermore, this study found increased V150 with fewer needles. This may seem paradoxical at first, but it is related to the inverse square distance.¹⁴

Mean distances between the tips of catheters to base of bladder strongly correlated with D90 and tumour-control probability. Distances more than 5 mm resulted in significant reduction of D90 and relative lower tumour-control probabilities.

Though our method of measuring the distances of tips of catheters from contrast filled bladder may carry some errors, due to ultrasonography-based online contouring and verification, negligible change in catheters orientation can occur as compared to CT-based reconstructed imaging and contouring. We did not use fiducial markers due to cost issues. As fiducial markers are inserted before catheter insertion, their position may change due to prostate stretching during needle implantation.¹⁵ We did not measure the distances in lateral radiographs where catheter positions may change secondary to prostate edema, which is considered insignificant factor.

For calculating the TCP, we used biological parameters of Wang et al.; however, these vary widely. Our calculated TCP would not necessarily translate in lower disease-free survival, but minimizing the catheter distances from bladder by adjustment before treatment delivery can change the outcome. Recent study by Tiong et al., using similar parameters as we used in our study, found median relative TCP

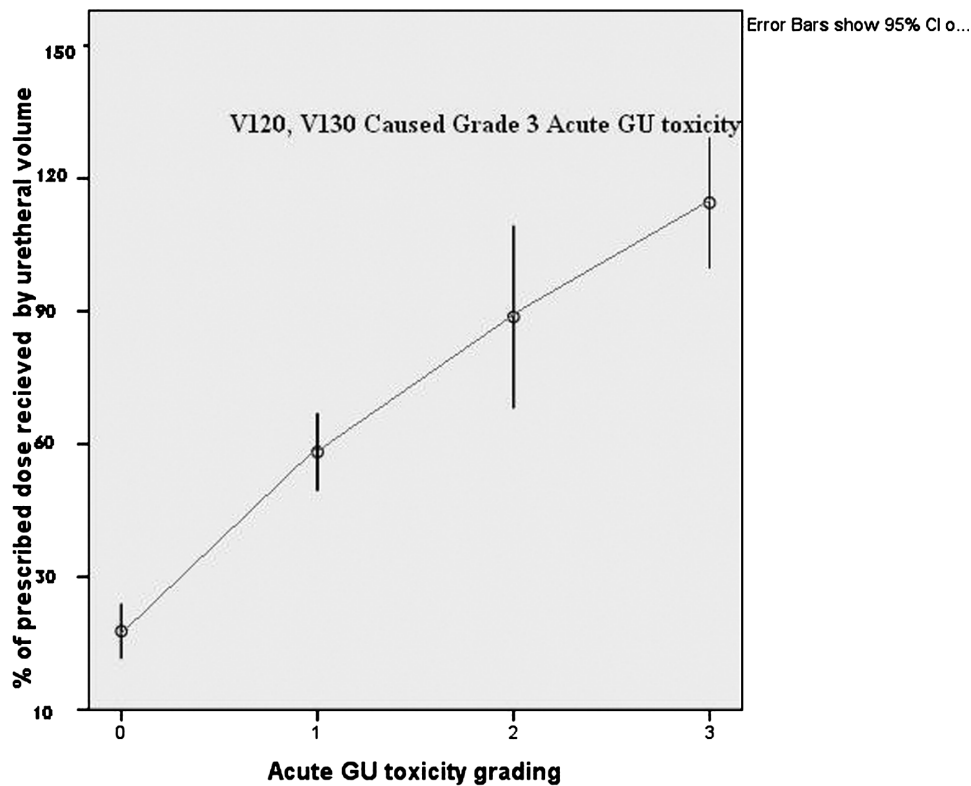


Figure 5. Correlation between urethral doses with acute genitourinary toxicity.

was 0.998, 0.964, 0.797 and 0.265 for caudal catheter displacements of 3, 6, 9 and 12 mm, respectively ($p < 0.01$ when all medians were compared).¹⁶

Regarding the factors influencing the severity of acute GU toxicity, the DVH data showed strong correlation between acute GU grading and urethral V120 and V130. The position of urethra itself makes it difficult to avoid delivering a higher dose. We made possible efforts to keep lower or zero dwell positions and dwell times for catheter which were adjacent to the urethra. Akimoto et al. also found that large volume of urethra receiving either prescribed dose or lesser may be related to severity of acute GU toxicity.¹⁷

We did not find any correlation between severity of acute GU toxicity and number of catheters implanted and number of attempts done per catheter to achieve desired position. One reason could be that we used inverse planning system to optimize the dose. Studies

reported higher incidence of acute GU toxicity with fewer catheters used in geometric optimization algorithms. However, further study is required to determine the optimal number of catheters and attempts per catheter. Similarly, prostate volumes did not show any influence on severity of acute GU toxicity.

CONCLUSIONS

Following factors must be considered while planning a patient for HDR boost.

1. Mean catheter to base of bladder (or fiducial markers if used) distances shall be kept less than 5 mm. Increased distances reduce the dose distribution and relative TCP.
2. V120 to V130 of urethra shall be minimized to reduce the acute GU toxicity.
3. Upto five attempts per catheter insertion, we did not see any correlation with acute GU toxicity. Further study is required to see any impact of repeated attempts on GU toxicity.

4. Dwell positions and dwell times shall be minimized for catheters which are very close to urethra.

Conflicting interests

No potential conflict of interest, no grant received.

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