Iranian Journal of Medical Physics

ijmp.mums.ac.ir

Planning Target Volume Margin Assessment Using Daily Cone Beam Computed Tomography Image Verification in Prostate Cancer Patients

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ARTICLE INFO

Article type:
Original Paper

Article history:
Received: June 11, 2023
Accepted: Dec 02, 2023

Keywords:
Prostate
Intensity Modulated Radiotherapy
Cone-Beam Computed Tomography

ABSTRACT

Introduction: Conformal radiation techniques are widely used in prostate cancer treatment as it improves the therapeutic ratio. However, inter- and intra-fraction variations remain challenging, which reflects on the planning target volume (PTV) margin. This study aimed to determine the benefit of daily Cone Beam Computed Tomography (CBCT) in reducing the PTV margin.

Material and Methods: 51 patients over 3 years were included in the study. PTV was obtained by applying 8mm in left-right (LR) and anterior (A), 5mm in posterior (P) and 8mm in superior-inferior (SI) directions of clinical target volumes (CTV). Pelvic bones of CBCT were matched with the planning CT scan and manually adjusted with soft tissue, assessing the total inter-fraction error. Values were registered in left-right (X), superior-inferior (Y), and anterior-posterior (Z) directions.

Results: The median age was 71 years and 84.3% were in the high-risk group. The mean inter-fraction error (Mp) was obtained in all three principal axes (x, y, z). The majority had shifts ≤ 0.3cm. None recorded a shift >1cm. The Random errors were 0.44cm in LR (X), 0.36cm in SI (Y) and 0.40cm in AP (Z) directions. The systematic errors were 0.05cm in LR (X), 0.04cm in SI (Y) and 0.04cm in AP (Z) directions. The PTV margin was calculated using van Herk's formula and obtained as 0.68cm.

Conclusion: Routine use of CBCT significantly reduces the random and systematic errors and ensures safer dose escalation with reduced PTV margin.

► *Please cite this article as:*
Ullattil PK, Susheela LJ, Nair HM, Remesan Nair A, Nair SS, Sreelekshmi G, Bhaskaran P, Kunheri B. Planning Target Volume Margin Assessment Using Daily Cone Beam Computed Tomography Image Verification in Prostate Cancer Patients. Iran J Med Phys 2025; 22: 50-55. 10.22038/ijmp.2023.65971.2135.

Introduction

Radiotherapy (RT) for localized prostate cancer aims at increased therapeutic ratio with a higher lethal dose to the tumour and better sparing of normal tissues. It can be achieved using conformal techniques such as 3-Dimensional Conformal Radiotherapy (3D CRT), Intensity Modulated Radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), which translates into improved survival rates, local control and decreased toxicities compared to conventional techniques.[1,2]. However, inter-fraction and intra-fraction variations, specifically due to bladder and rectum filling, are a major concern. Consequently, under-treatment of the target or over-dosage of critical structures may arise. Differences in the actual and expected doses received by the prostate, rectum, and bladder are observed in prostate IMRT, due to daily setup variations and organ motion [3-5]. The extent of these differences is significantly affected by the planning target volume (PTV) margins. Daily image guided radiotherapy (IGRT) can improve the treatment accuracy while reducing uncertainty [6]. Several studies have suggested that PTV margins can be reduced with the use of IGRT. Most of these have focused on translational shifts using Electronic Portal Imaging Devices (EPID) and PTV calculations based on the van Herk formula [7,8]. More recently, there has been an increase in the use of cone beam CT (CBCT) for accurate organ localization and assessment of organ position variations [9-11]. This study aimed to determine the PTV margin required in IGRT using CBCT in prostate cancer patients.

Materials and Methods

This was a retrospective study conducted in the Department of Radiation Oncology at a tertiary cancer care centre. All localized prostate cancer patients who received IGRT (VMAT) using CBCT were included in this analysis. A total of 51 patients who received treatment over 3 years were included. All patients were treated with strict bladder and rectal protocols before CT

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simulation and each day prior to the treatment. All patients were advised to take laxatives the previous night to achieve an empty rectum. Patients were asked to void and drink 4 to 6 glasses of water 30 minutes before CT simulation to maintain the same bladder filling throughout treatment. CT simulation was done with Siemens Somatom Emotion CT simulator, in the supine position with hands placed overhead. Appropriate immobilization devices such as headrest, wing board, knee and footrest, etc., were used. A slice thickness of 2.5mm was obtained for better delineation of target volumes and critical structures.

The treating physicians delineated the clinical target volumes (CTV) and PTV according to the Radiation Therapy Oncology Group (RTOG) protocols 0415 and 0521[12,13]. The PTVs were obtained by using three-dimensional automatic expansions of CTV, applying 8mm in left-right (LR) and anterior (A), 5mm in posterior (P) and 8mm in superior-inferior (SI) directions. A dose of 70Gy in 28 fractions in 2.5Gy per fraction was prescribed to the PTV (Figure 1). VMAT planning was done with the Monaco treatment planning system (Version 5.11.03).

All patients were treated in Linear Accelerator - Elekta Synergy with 6 MV photons, equipped with 40 pairs of multileaf collimators (MLC) [1 cm each at isocenter] for beam modulation. The Electronic Portal Imaging Device, iViewGT (Version 3.4) and the CBCT system, Intuity X-ray Volume Imaging (XVI Version 4.5, Elekta) were employed for real-time image verification. Daily CBCT imaging was performed utilising the pelvis Medium 15 (M-15) preset. Following image acquisition, automatic image registration was executed between the reference and real-time CBCT images utilising the grey-value Translational and Rotational algorithm. Further automated correction was applied on the Elekta Precise treatment couch before radiation delivery.

To determine the setup error, pelvic bones of CBCT (B match) were matched with the planning CT scan. It was then manually adjusted to overlap the prostate on the planning CT and CBCT scans through a grey-value-based soft-tissue matching (T match), assessing the total inter-fraction error (setup + organ motion). Values of inter-fraction setup and total positioning displacements were registered for the three principal axes, in left-right (X), superior-inferior (Y), and anterior-posterior (Z) directions. Motion of the prostate relative to the bony anatomy was defined as the difference between T match and B match. Positive values for X, Y and Z shifts indicate left, superior and anterior displacements of the isocentre.

CBCT was taken on all days for the study population during the course of RT. The variation along X (lateral shift), Y (in and out shift), and Z (up and down shift) were noted.

Statistical details

Individual Errors were calculated as follows:

For each patient, x_1, x_2, x_3 .....x_{28} are the variations along X direction, y_1, y_2, y_3....y_{28} are the variations along Y direction and z_1, z_2. z_3..... z_{28} are the variations along Z direction. The average value (mean change) along each direction was calculated. For calculating standard deviation (SD) 'non-biased' or n-1 method was used.

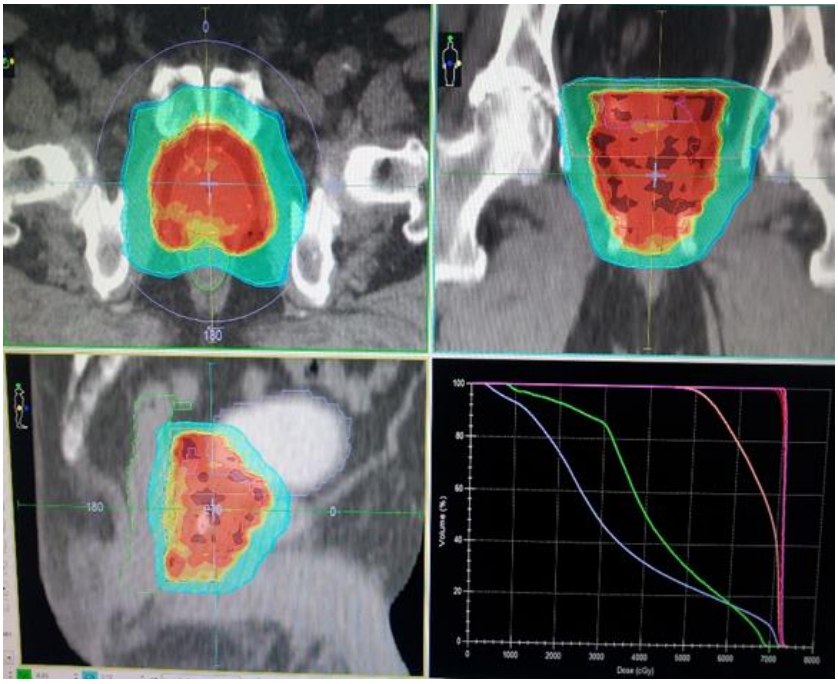

Figure 1. Dose distributions in a prostate cancer patient planned by volumetric-modulated arc therapy (VMAT). Colour wash areas (Red): Receiving 100% dose (70 Gy), (Orange): Receiving ≥ 95% dose, (Cyan): Receiving ≥ 50Gy dose. Red line: Planning target volume; Light Blue line: Urinary bladder; Light Green Line: Rectum

Systematic Errors

It is the average difference between the planned and executed treatment due to errors in the data handling system or inappropriate use of instruments. SD of these average values along each direction respectively gives the systematic error. [14]

Random Errors

It is the uncertainty between planned and executed treatment due to inter and intra-fraction variations. The root mean squares of the SD values along each direction give random errors [14,15].

Population Errors were calculated as follows[7,14-18]:

Consider a group of P (51) patients, a number of F_p (28) measured fraction for each patient P and a measurement X_{pf} for each measured fraction.

For measurement of a setup error in the AP direction, the average patient error can be:,

$$Mp = \Sigma_{f=1-Fp} (X_{pf}/F_p) \quad (1)$$

The total number of measured fractions N and their overall mean M, can be calculated as:

$$N = \Sigma_{p=1-51} (F_p) \text{ i.e., } (N= 51\times28=1428) \quad (2)$$

$$M = 1/N \times \Sigma_{p=1-51}.(\Sigma_{f=1-28} (X_{pf})) \quad (3)$$

For total patient P, the standard deviation of the random error is given by[14-18]:

$$\sigma = [1/ (N-P) \Sigma_{p=1-51}.(\Sigma_{f=1-28} (X_{pf} - Mp))^2]^{1/2} \quad (4)$$

The standard deviation $\sum$ of the systematic error is given by [14-18]:

$$\Sigma = [P/N(P-1) \Sigma_{p=1-51} (F_p) (Mp-M)^2]^{1/2} \quad (5)$$

For a single patient P, the standard deviation of the random error is given by [17]:

$$\sigma_P = \left[\frac{1}{F_P-1}\sum_{f=1}^{F_P}(X_{pf} - M_p)^2\right]^{1/2} \quad (6)$$

The overall mean (M) should be close to zero. If not, it means there is a systematic error similar for all the patients. The SD of the mean patient error ($\sum$) tells us how large the systematic error is for an individual patient and the SD of the random errors (σ) quantifies the day-to-day variations.

PTV margin:

For 90% of the patients to receive a minimum 95% CTV dose or more, a margin is added first to cover 90% of the preparation (systematic) errors. To this, another margin is added to cover the penumbra and execution (random) errors such that the CTV + first margin lie within the 95% isodose.[7,14,16-18]

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) [7]

$$\text{PTV margin} = 2.5 \sum + 0.7 \sigma \quad (7)$$

$\sum$= quadratic sum of SD of all preparation (systematic) errors

σ = quadratic sum of SD of all execution (random) errors

Results

A total of 51 patients treated with IGRT for carcinoma of the prostate were analyzed for this study. The median age was 71 (ranging from 51 to 82). Based on the D'Amico risk stratification, 8 (15.6%) were intermediate-risk and 43 (84.3%) were high-risk. All patients had a histological diagnosis of acinar adenocarcinoma.

To obtain the population-based random and systematic error, we initially calculated the inter-fraction error (setup + organ motion) daily (28 fractions) for all the patients (51 patients) in all three principal axes (x,y,z). Then the mean inter-fraction error (Mp) was obtained for each patient in our cohort. Interestingly, a shift >1cm was not recorded along left-right (LR), superior-inferior (SI) or anterior-posterior (AP) directions. We observed a shift between 0.7 to ≤1cm only in one patient (1.9%) along the SI direction. A shift between 0.3 to ≤0.7cm was recorded in eight (15.6%) along LR, seven (13.7%) along SI and nine (17.6%) along AP directions. The majority of patients had shifts ≤ 0.3cm along all three directions, i.e. 43 (84.3%) along LR, 43 (84.3%) along SI and 42 (82.3%) along AP directions. The inter-fraction error in all three principal axes is shown in Table 1. We calculated and obtained our overall population mean (M) as 0.008cm in left-right (X), 0.180cm in superior-inferior (Y) and -0.148cm in anterior-posterior (Z) directions, respectively, using equations (1)(2)(3).

Table 1. Inter-fraction error in all three principal axes

	X	Y	Z
<0.3cm	43 (84.3%)	43 (84.3%)	42 (82.3%)
0.3 to <0.7cm	8 (15.6%)	7 (13.7%)	9 (17.6%)
0.7cm to ≤1cm	-	1 (1.9%)	-
>1 cm	-	-	-

Table 2. Calculation of population random and systematic errors for 51 patients

	X	Y	Z
$\Sigma_{51}\Sigma_{28}(X_{pf} - Mp)^2$	271.08	177.19	219.1
$\Sigma_{51}(Mp - M)^2$	3.21	2.35	2.76
Random error (σ)	0.44	0.36	0.4
Systematic error (Σ)	0.05	0.04	0.04

Table 3. Quadratic sum of random (σ) and systematic (Σ) error and Planning Target Volume (PTV) margin calculation

Coordinates	Σ	σ
X	0.05	0.44
Y	0.04	0.36
Z	0.04	0.4
Quadratic sum	0.08	0.7
PTV margin 2.5Σ+0.7σ	0.68	

Thus, population random errors in our cohort were 0.44 cm in LR (X), 0.36 cm in SI (Y) and 0.40 cm in AP (Z) directions. Similarly, population systematic errors were 0.05 cm in LR (X), 0.04 cm in SI (Y) and 0.04 cm in AP (Z) directions. The population random and systematic errors are shown in Table 2. The PTV margin was calculated using van Herk's formula and obtained as 0.68cm. Table 3 shows the quadratic sum of random and systematic error and PTV margin calculation.

Discussion

IGRT in prostate localization using different techniques defines a steep dose gradient between the target and the OAR, which reflects a higher dose rate to the target with minimal dose distribution to the surrounding critical structures [19-21]. Consequently, this translates into a higher cure rate and better local control [22]. Kilovoltage (kV) CBCT is used to assess an accurate prostate position and correct the inter-fraction variations before treatment [23]. It helps to reduce the PTV margin that was accounted for prostate motion, eventually reducing the dose to the OAR [24-26].

The use of IGRT after daily kV CBCT provided valuable information regarding organ motion, especially in relation to bony anatomy, inter and intra-fraction variability among patients. It also highlights the importance of adaptive radiation therapy in the present era.

In this retrospective study, we observed that the random errors of setup and organ motion along all three principle axes (LR, SI, AP) were a few mm (≤4 mm), whereas the systematic errors were much lower (0.5mm). This confirms the accurate and precise positioning of patients daily before treatment. Several studies have reported maximum organ movement along the AP (Z) direction [27-29], probably due to the daily variability in rectal and bladder filling. Our study noted only -0.148 cm mean population shift along the AP (Z) direction. The lesser displacement may be because of the strict rectum and bladder volume protocols during CT simulation and daily treatment [28-29]. In the case of loaded bowel, we encouraged the patients to take laxatives and at times, enema too was prescribed.

Palombarini et al. [30] analyzed the inter-fraction setup error and organ motion using kV CBCT in 18 patients in 2012. They reported 95% of prostate motion along X and Y directions noted with an 8 mm margin and 70% of displacement along Z directions. This conveys that significant variations could occur despite daily alignment using skin tattoos. Thus, conventional methods without image guidance could increase toxicity to critical organs and miss targets. Hanley et al. [31] evaluated patient positioning uncertainty using port films in 50 patients. In this study, a total of 1239 port films and 300 simulator films were analyzed. The systematic setup errors were -0.1±1.9 mm, 0.4±1.4 mm and -0.3±1.3 mm in the LR, SI and AP directions, whereas the random setup errors in the LR, SI and AP directions were 2.0 mm, 1.7 mm and 1.9 mm, respectively. Nederveen et al. [32] analyzed 23 patients using portal images and reported the mean systematic prostate displacement to be 0.0±1.0 mm, 0.0±2.3 mm and 1.0±4.1 mm in the LR, AP and SI directions. The mean systematic setup error was 0.0±2.1 mm, -1.0±4.4 mm and 0.1±2.1 mm for LR, AP and SI directions. In our study, we obtained lesser systematic error compared to random error. Random errors were 0.44 cm in LR (X), 0.36 cm in SI (Y) and 0.40 cm in AP (Z) directions. Similarly, systematic errors were 0.05 cm in LR (X), 0.04 cm in SI (Y) and 0.04 cm in AP (Z) directions. We found that both random and systematic errors were predominant in LR (X) direction.

Apart from identifying the source of error, the advantage of determining random and systematic error is its use in deriving a safety margin or PTV margin [7,33,34]. Other methods used for calculating the PTV margin were the SD calculation method [35] and incorporating the tumour geometry near the beam edge [36].

We calculated the PTV margin using the van Herk formula [7], based on which ≥95% of the prescribed dose should cover the PTV at least in 90% of the patients. We calculated and obtained a PTV margin of 0.68cm in our study. Here, both setup error and organ displacement were considered. Thus, a PTV margin of 0.68 cm ensures better target coverage and prevents target missing. This is comparable to the observations of Paluska et al. [37], who compared the fiducial and bony landmark-based setup for the prostate. He suggested that the PTV margin be reduced to 0.7cm with the fiducial setup and cautioned not to reduce the margin to less than 1cm otherwise.

As none of the patients in the study recorded a shift of 10mm, we suggest that reducing the margin to less than 10mm can be safely practised, provided strict bladder and rectum protocols are ensured. However, our study is retrospective and has certain limitations. Intra-fraction variability was not considered. Also, we could not analyze inter-fraction setup error and organ

displacement correlation separately. The clinical outcome data of these patients were also not explored.

Conclusion

IMRT of prostate cancer patients using image guidance with kV CBCT is a precise and feasible technique. IGRT is highly helpful in verifying the targets and OAR before delivering RT. Routine use of CBCT images significantly reduces the random and systematic errors and ensures safer dose escalation with reduced PTV margin. However, reducing the PTV margins to less than 7mm may only be safe with proper image guidance.

Acknowledgment

We thank the faculty and staff of the department of Radiation Oncology for the cooperation extended to this study.

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