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Original Article

Dose variation during hypofractionated image-guided radiotherapy for prostate cancer: Planned versus delivered

Vedang Murthy, Pragya Shukla, Pranjal Adurkar, Zubin Master, Umesh Mahantshetty, Shyam K. Shrivastava

Department of Radiation Oncology and Medical Physics, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Mumbai, Maharashtra, India

For correspondence:
Dr. Vedang Murthy, Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai – 410 210, Maharashtra, India.
E-mail: vedangmurthy@gmail.com

ABSTRACT

Aims: To determine variation in the actual doses delivered to the organs at risk and the target in patients treated for localized carcinoma of the prostate using image-guided radiotherapy.

Materials and Methods: Ten patients treated with helical TomoTherapy underwent daily target localization with megavoltage CT, on which the prostate, rectum and bladder were recontoured. The planned adaptive module was used for dose recalculation. The study endpoints were to analyse the variations in certain dose-volume parameters of the rectum and bladder (BD_{2cc}, RD_{2cc}, $BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, $RV_{70\%}$), the maximum anteroposterior (AP) and lateral rectal diameters, the volume of the CTV receiving 100% of the prescription dose (CTV $V_{100\%}$) and the dose to 100% of the CTV (CTV $D_{100\%}$).

Results: The difference between the planned and delivered target doses (CTV V100% and CTV D100%) was small and clinically insignificant indicating adequate target coverage during treatment. There was a large variation in the AP and lateral rectal diameters, with no particular trend or correlation to dose parameters being noted during the course of treatment. The mean AP diameter during treatment was significantly less than the planned diameter ($P < 0.05$). The percentage of fractions where the delivered BV100%, BV70%, RV100%, and RV70% was more than the planned values were 42.8%, 17.1%, 45.4%, and 44.4%, respectively. The delivered BD2cc and RD2cc were similar to their planned values.

Conclusions: This study demonstrates the usefulness of daily soft tissue image guidance in negating the effects of physiological variation of the rectum and bladder on the dose delivered to the prostate.

KEY WORDS: Dose reconstruction, hypofractionation, image-guided radiotherapy, prostate cancer

INTRODUCTION

Steep dose gradients in intensity-modulated radiation therapy (IMRT) provide better conformity to complex target volumes. Its increasing use brings forth the need to improve accuracy of the treatment by accounting for both inter- and intra-fraction motion. The planning CT scan represents only a frozen snapshot of the anatomy, which may differ substantially from the actual treatment position on a daily basis due to organ deformation and internal motion. This has led to the use of imaging techniques for the preparation and delivery of a radiotherapy treatment collectively referred to as image-guided radiotherapy (IGRT). Though a number of imaging modalities are being used for daily image guidance in prostate cancer radiotherapy, computed tomography (CT) is considered the most powerful as it provides volumetric data.[1-3]

The shape of the prostate during a course of radiotherapy is influenced by the degree of rectal and bladder filling or emptying. The resultant variations in delivered doses within the pelvis, specifically to the rectum and the bladder have been addressed previously.[4] While low rectal volumes during planning have been associated with increased acute and late toxicity,[5] increased volumes have been found to be related with biochemical and local failure.[6]

Based on its perceived low α/β ratio, hypofractionation in prostate cancer is expected to be associated with improved clinical outcome.[7-9] However, normal tissues like rectum, which are prone to late complications, are sensitive to a larger dose per fraction. With the increasing use of dose escalation in prostate carcinoma delivered with hypofractionation, the dose delivered to the normal tissue and the resultant increase in toxicity needs to be considered while planning treatment.[10]

This study aimed to determine the variation in the actual dose delivered to the organs at risk (OAR) and the relationship between target

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coverage and anatomical changes during a course of radical hypofractionated radiotherapy to the prostate and pelvic nodal region, in patients with high-risk carcinoma prostate.

MATERIALS AND METHODS

Ten consecutive patients with adenocarcinoma prostate, treated on TomoTherapy Hi-ART II, between 2008 and 2010, were included in this study. They were all treated with the same hypofractionated protocol, receiving 60Gy to the prostate and 45Gy to the pelvic nodes as a simultaneous integrated boost (SIB), in 20 fractions. Informed consent was obtained according to institutional ethics committee requirements. The planning process followed for all patients was uniform and is described below:

All patients were simulated on a Siemens Somatom 4S CT scanner with IV contrast, using a slice thickness of 3 mm. They were immobilized in the supine position using a knee rest and scanned from the third lumbar vertebrae to the middle of the femurs. No bowel preparation was done prior to the planning CT scan. A bladder filling protocol was followed, in which 30 minutes prior to the planning CT, all patients were asked to void completely and drink 500 ml of plain water. Three lead fiducials were placed (one anterior at symphysis pubis and two laterally) on the skin surface at the points of laser intersection and these points were permanently tattooed for daily treatment setup.

For patients without clinical or radiological involvement of seminal vesicles (SV), the CTV consisted of the whole prostate gland including any extracapsular spread and the base of the SV, defined as the proximal 0.5 cm of the SV. The distal, uninvolved SV was included in the pelvic nodal volume. For patients with SV involvement and T3b disease, the entire prostate and whole of the SV were included in the CTV. A margin of 7 mm was grown in all directions including posteriorly, to obtain the PTV. The CTV for prophylactic lymph node irradiation was contoured according to the RTOG guidelines.[11] The CTV covered the major vessels (the external and internal iliac vessel) from the level of L5–S1 to the beginning of the obturator foramen. The caudal part of the volume included the distal part of the SV when it was uninvolved clinicoradiologically. An isotropic margin of 7 mm was grown around the nodal CTV to generate the nodal PTV.

The rectum was contoured as a solid structure starting from recto-sigmoid flexure up to the bottom of ischial tuberosity. The entire bladder was drawn as a solid structure from the dome to the base including the wall. Bowel was represented by a single solid structure encompassing the peritoneal cavity and any loops of bowel in the pelvis. The upper extent was kept constant at 5 cm superior to the uppermost extent of the pelvic nodal PTV to have comparability of the dose volume data. Both femoral heads were drawn within the acetabulum without including the neck of the femur.

All image and volume datasets were transferred to the TomoTherapy treatment planning station (version 2.3.5, TomoTherapy Inc., USA) for inverse planning. All plans were generated with a 2.5 cm field width, a pitch of 0.3 and a maximum modulation factor of 3.0. These parameters have already been explained previously.[12] The planning objectives were that at least 95% of the PTV received the prescription dose and that the maximum PTV dose did not exceed 105% of the prescription dose. The dose constraints for the OARs during planning were based on the previously published data from the hypofractionated arm of the CHHIP trial.[13]

Before each treatment, all patients were asked to repeat the bladder filling protocol to ensure constant bladder filling. No specific rectal preparation was done. Megavoltage CT (MVCT) images were acquired for each fraction using the on-board scanner of the TomoTherapy unit and were co-registered to the simulation CT using automatic fusion of bony anatomy. The registration was further adjusted manually to account for inter-fractional motion and ensure that the prostate was within the PTV.

The Planned Adaptive module (Version 3.1.5.3) of the TomoTherapy system was used to retrospectively analyze every fraction for the ten patients. The prostate, bladder, and rectum were re-contoured on each MVCT scan to account for daily deformation, and the modified structure set was saved. One radiation oncologist (PS) and one medical physicist (PA) performed the re-contouring to maintain consistency. The rectum was re-contoured only within the scanned MVCT volume. This scanned volume varied from day to day and sometimes did not include the entire length of the rectum up to the recto-sigmoid flexure. Similarly, only the volume of bladder covered by the MVCT scan was re-contoured. The delivered dose was recalculated for the merged MVCT image and new structure. This resulted in a separate DVH for each fraction of every patient, which yielded the data points for this study. The resulting prostate (CTV) and OAR dose distributions, as delivered, were compared to those of the original treatment plans. Additionally, the maximum anteroposterior (AP) and lateral rectal diameters were recorded and the difference from their planned values was calculated.

As there was a daily variation in the length of the rectum and bladder scanned in the MVCT, absolute dose-volume parameters were used instead of percentage-based parameters. The specific DVH parameters studied were the dose to 2cc of the rectum and bladder (BD_{2cc}, RD_{2cc}), the absolute volume of the rectum and bladder (in cc) receiving 100% and 70% of the prescription dose ($BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, $RV_{70\%}$), the maximum AP and lateral rectal diameters, the volume of the CTV receiving 100% of the prescription dose (CTV $V_{100\%}$) and the dose to 100% of the CTV volume (CTV $D_{100\%}$). The coverage index (CI) was calculated per fraction using the formula for each patient.

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$$CI = \frac{CTV\ V_{100}(cc)}{V_{target}(cc)}$$

These acquired parameters, for the re-contoured structure sets, were compared to the original treatment plan parameters. Moreover, the differences in the rectal diameters were correlated with the coverage parameters (using Pearson correlation coefficient) to determine if geographical miss and rectal deformation were related. The planned and delivered parameters were tested for statistical significance using the paired t-test.

RESULTS

Out of the 200 fractions, a total of 187 fractions were analyzed as images could not be retrieved for few and in others the whole prostate was not scanned. The delivered mean CTV $V_{100\%}$ was 98.2% (SE=0.46) and the planned mean CTV $V_{100\%}$ was 99.6% (SE=0.04). The mean delivered CTV $D_{100\%}$ was 2.97Gy (SE= 0.01) whereas the planned CTV $D_{100\%}$ was 3.03Gy (SE= 0.003). Both these differences were found to be statistically significant ($P<0.05$). The mean CI achieved during treatment delivery was 98.36% while the mean planned CI was 99.79% ($P<0.05$). One patient (patient 10) in the study had a CI that was substantially less than its planned value for 88% of the fractions (mean CI of 84.6% versus 100%) as seen in Figure 1. The reason for this difference has been elaborated in the discussion.

The AP and lateral rectal diameters during treatment varied from the diameters in the planning scan [Figure 2]. No particular pattern with time was observed in the variation in both AP and lateral rectal diameters during the course of radiation. The mean AP diameter during treatment was significantly less than the planned diameter [Table 1].

No correlation was seen for the CI with the AP and the lateral rectal diameters (Pearson coefficient: -0.162 and 0.074, respectively). Figure 3 shows the variation of the parameters $BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, and $RV_{70\%}$, from their planned values, as a box and whisker plot. The difference of the delivered $BV_{100\%}$ and $RV_{100\%}$, from the planned values, was not statistically significant (p-value = 0.081) and is shown in Table 2. The delivered BD_{2cc} and RD_{2cc} (indicating a hot spot) was similar to their planned values and are shown in Figure 4.

The percentage of fractions where the delivered $BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, and $RV_{70\%}$ was more than the planned values were 42.8%, 17.1%, 45.4%, and 44.4%, respectively. In 17.6% of the fractions, the rectum received a high dose i.e., 2 cc of the rectum received over 105% of the prescribed dose [Figure 5]. For two out of the ten patients, this occurred in over 50% of the fractions. Similarly, in 33.2% of the fractions, 2 cc of the bladder received over 105% of the prescribed dose and for three out of the ten patients, this occurred in over 50% of the fractions.

Table 1: Anteroposterior and lateral rectal diameter during treatment versus plan

Diameter Mean SD	Planned (cm) Mean	SD	Treatment (cm)		*P*-value
AP (*N*=187)	4.31	1.04	3.84	0.67	0.000
Lat (*N*=187)	3.96	0.72	3.85	0.86	0.129

Table 2: The mean differences of the $BV_{100\%}$ and $RV_{100\%}$ from the plan

Difference from Plan	Mean	SD
$BV_{100\%}$	-0.092	0.27
$RV_{100\%}$	-0.81	0.32

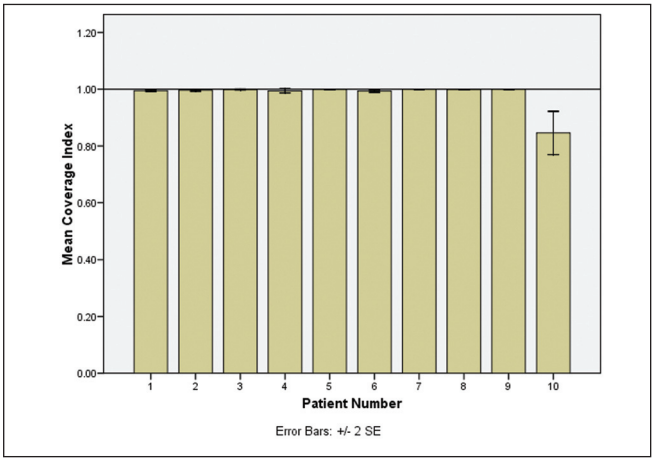

Figure 1: CI: Treatment versus plan

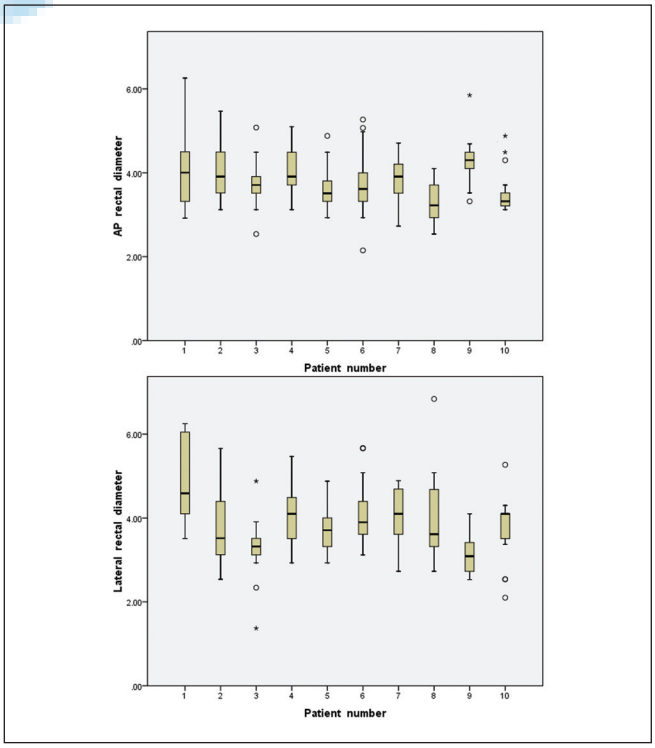

Figure 2: Rectal diameters in the anteroposterior and lateral directions

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DISCUSSION

The present study was an attempt to systematically document the effectiveness of IGRT in delivering the planned doses to the target while demonstrating the variations in the actual doses delivered to the OARs. Dose recomputation on the daily MVCT imaging dataset obtained in the treatment position enabled us to determine the actual position of the prostate, rectum and bladder as well as the dose delivered per fraction, although intra-fraction variability was still unaccounted for.

With the use of hypofractionated regimens, inter-fraction motion assumes greater importance as each fraction accounts for a larger percentage of the total dose and therefore each instance of geographical miss results in a potentially greater chance of treatment failure. Ideally, it would be desirable to be able to deliver 100% of the prescribed dose to 100% volume of the prostate gland (CTV $V_{100\%}$ = 100%). While this was achieved in most patients for a majority (85%) of the fractions, the mean delivered CTV $V_{100\%}$ dose was lower than the mean planned CTV $V_{100\%}$ by 1.4%. Although this was statistically significant, it may not be clinically relevant. The same was true for the delivered CTV $D_{100\%}$ of 2.97Gy. The target coverage parameters (including CI) were slightly 'spoilt' by the findings in one patient [patient number 10, Figure 1]. This was because this patient's planned 100% isodose showed a very tight fit around the CTV i.e., 99.8% of CTV volume received 100% of the dose and any minor shift in the prostate position moved it outside the planned CTV volume. For this patient it was found that 100% of the

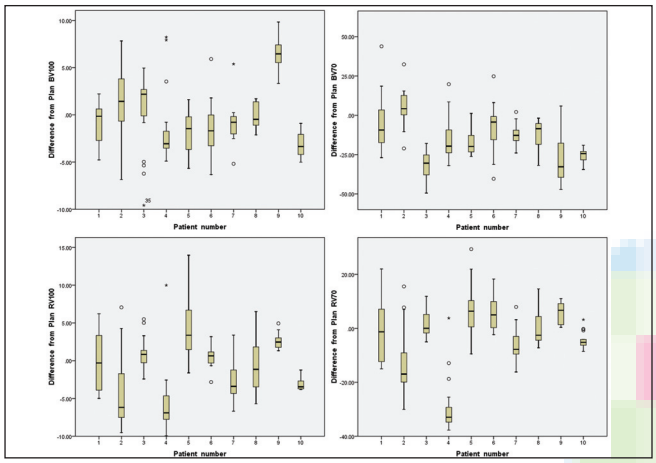

Figure 3: Difference between delivered and planned $BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, and $RV_{70\%}$¬

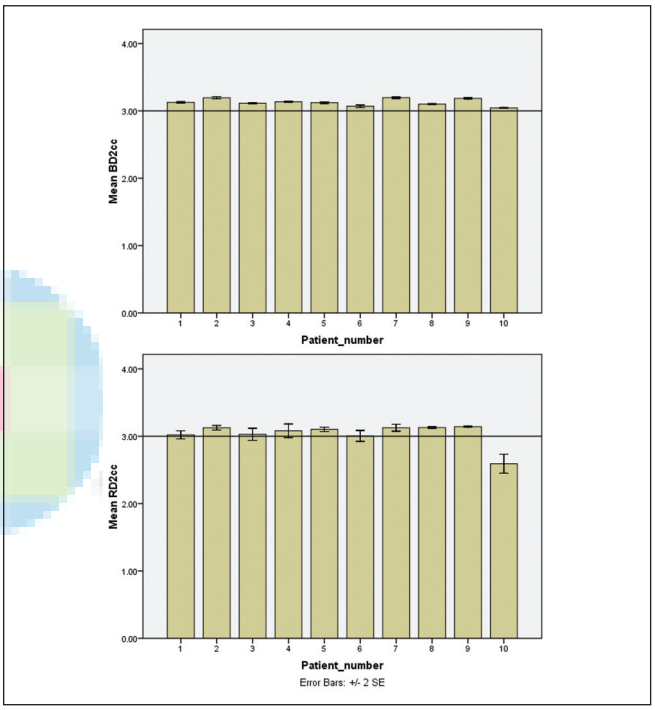

Figure 4: Delivered and planned BD_{2cc} and RD_{2cc}

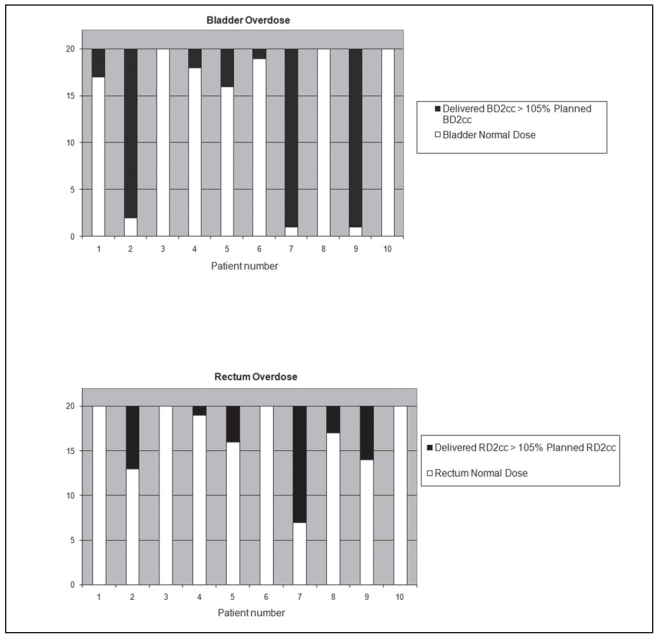

Figure 5: OAR overdosage compared to treatment plan

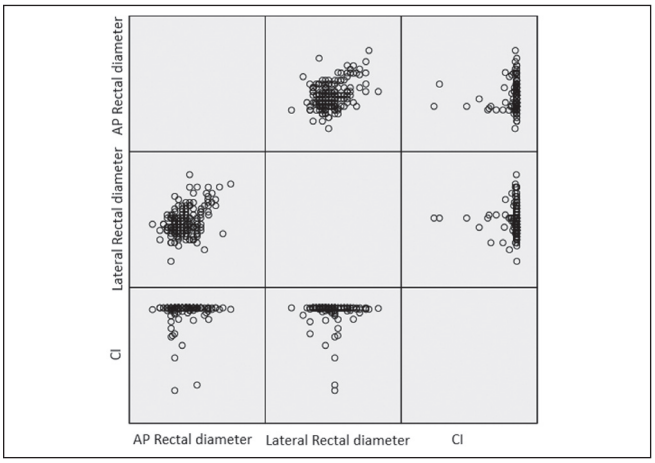

Figure 6: Rectal diameter versus CI

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prostate was adequately covered by the 99% isodose (instead of 100%) for all fractions. The adequacy of prostate coverage using daily MVCT imaging and $D_{95\%}$ as the coverage parameter has previously been reported.[14] We have shown this with even stricter criteria using $V_{100\%}$ and $D_{100\%}$ for CTV prostate. Based on these data, it can be inferred that using daily soft tissue image guidance can ensure adequate target coverage despite rectal and bladder positional variations.

The daily positional and dosimetric variations of the rectum and bladder did not reveal any particular pattern in the maximum rectal diameters over the four week course of treatment. Two recent studies have attempted to determine the doses to the prostate and OARs using weekly or less frequent KVCT scans.[15,16] However, assessing the actual doses delivered to the target and OARs by interpolating data from fewer (i.e. weekly) scans is fraught with uncertainties, given the random nature of the physiological organ motion as demonstrated in this study. In a previous study, Kupelian *et al*., using daily MVCT images, arrived at similar conclusions regarding the randomness of rectal shape and position during a course of radiotherapy.[14]

Due to the variability and unpredictability in the movement and filling of the rectum and the bladder, the planned dose has been found to be a poor predictor of the actual doses delivered to these organs.[15,16] This was found to be true in our study where the $BV_{100\%}$, $BV_{70\%}$, $RV_{100\%}$, and $RV_{70\%}$ were found to be significantly different from the planned values. The variability in doses delivered to the OAR was greater than the variability in the target. This is consistent with the findings of Kupelian *et al*., who reported that there was significant daily variation in the rectal dose unlike doses for the prostate.[14] This is because during image guidance, emphasis is placed on matching the target volume and the position of the OARs is not corrected for.

Absolute rectal volume, rather than the percent of rectal volume, receiving the prescribed dose, has been found to be an independent predictor of late rectal bleeding. Although severe rectal toxicity is more dependent on the highest dose to the rectum, minimum to moderate rectal toxicity is mostly related to rectal volumetric parameters. Using absolute volume also avoids the dependence on the extent of rectal volume contours which tend to be variable especially in the scenario of adaptive planning using KVCT or MVCT data. When the rectal volume in the high dose region is over 15 cc, there is an increased probability of having rectal bleeding (22% vs. 5%). This interpretation was based on the planning data and the recommendation that not more than 15 cc of the planned rectal volume should receive the prescribed dose.[17] In our study, the above planning constraint was met in all the patients and only six of the 187 (3.2%) treatment fractions analysed had a rectal volume of >15cc (and all less than 17cc) receiving the prescribed dose. This is an encouraging finding and may be attributed to the daily soft tissue image guidance used.

In a retrospective analysis, de Crevoisier *et al*.,[6] reported that rectal distension on planning CT increases the risk of local and biochemical failure and decreases the risk of rectal toxicity. However, no form of image guidance was used to identify inter-fraction internal prostate position in this study. Kupelian *et al*.,[18] in a non-randomized study showed that rectal distension, as determined by rectal volume, did not affect the rate of biochemical failure in patients treated with daily IGRT using transabdominal ultrasound localization when compared with historical controls. The data from this study substantiates the latter finding by demonstrating the adequacy of target coverage by using IGRT. The daily targeting of the prostate gland using IGRT corrects any positional error of the prostate introduced by rectal distension at the time of the planning CT and negates the effects of organ deformation during treatment. This was further supported by the poor correlation between the rectal diameter and the conformity index [Figure 6] in this study.

There was large variation in the rectal diameter throughout the treatment of four weeks consistent with the report of Chen *et al*.,[15] with the mean AP diameter during treatment being significantly less than the planned diameter. Although daily soft tissue matching largely negated the effects of rectal variation on the prostate dose, we have not evaluated the effects of intra-fraction motion as reported in studies using cine MRI,[19] implanted markers,[20] multiple CT scans,[21,22] or ultrasounds.[23,24] Even though the inter-fraction prostate displacement is taken into account by IGRT, any attempt at reduction of PTV margins with IGRT should take into consideration the intra-fraction displacement that may still occur.

The actual radiation dose and the volume of the bladder irradiated may be affected by the variability in the daily filling of the bladder.[25-27] If the bladder volume is decreased, more of the bladder wall is included in the radiation field and vice versa. Pinkawa *et al*. reported that by asking the patients to have a full bladder at the time of the initial treatment planning and during the treatment, the mean bladder volume can be kept at the same level.[28] In keeping with this a uniform bladder filling protocol was followed for all patients. Kupelian *et al*. had observed that there is less variation in the bladder volumes receiving the relatively high daily doses compared with the variation observed in rectal doses from the plan.[14] In our study we found that the mean differences of the volume, receiving high dose, from the plan was not significant for both the rectum and the bladder. This observation can be attributed to the practice of keeping the mean volume of bladder at the time of planning and during all the treatment fractions same by following a uniform bladder filling protocol. However, no such preparation was done for the rectum.

CONCLUSION

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This study highlights the large variation in the position, shape and consequently the actual doses delivered to rectum and bladder during a course of hypofractionated image-guided radiotherapy. Encouragingly, the effect of physiological variation on dose to the prostate was negated due to the daily soft tissue image guidance with the prostate receiving the intended planned dose.

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