Original Article

Dosimetric comparison of standard three-dimensional conformal radiotherapy followed by intensity-modulated radiotherapy boost schedule (sequential IMRT plan) with simultaneous integrated boost–IMRT (SIB IMRT) treatment plan in patients with localized carcinoma prostate

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ABSTRACT

Aims: Dosimeteric and radiobiological comparison of two radiation schedules in localized carcinoma prostate: Standard Three-Dimensional Conformal Radiotherapy (3DCRT) followed by Intensity Modulated Radiotherapy (IMRT) boost (sequential-IMRT) with Simultaneous Integrated Boost IMRT (SIB-IMRT).

Material and Methods: Thirty patients were enrolled. In all, the target consisted of PTV P + SV (Prostate and seminal vesicles) and PTV LN (lymph nodes) where PTV refers to planning target volume and the critical structures included: bladder, rectum and small bowel. All patients were treated with sequential-IMRT plan, but for dosimetric comparison, SIB-IMRT plan was also created. The prescription dose to PTV P + SV was 74 Gy in both strategies but with different dose per fraction, however, the dose to PTV LN was 50 Gy delivered in 25 fractions over 5 weeks for sequential-IMRT and 54 Gy delivered in 27 fractions over 5.5 weeks for SIB-IMRT. The treatment plans were compared in terms of dose–volume histograms. Also, Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) obtained with the two plans were compared.

Results: The volume of rectum receiving 70 Gy or more (V > 70 Gy) was reduced to 18.23% with SIB-IMRT from 22.81% with sequential-IMRT. SIB-IMRT reduced the mean doses to both bladder and rectum by 13% and 17%, respectively, as compared to sequential-IMRT. NTCP of 0.86 ± 0.75% and 0.01 ± 0.02% for the bladder, 5.87 ± 2.58% and 4.31 ± 2.61% for the rectum and 8.83 ± 7.08% and 8.25 ± 7.98% for the bowel was seen with sequential-IMRT and SIB-IMRT plans respectively.

Conclusions: For equal PTV coverage, SIB-IMRT markedly reduced doses to critical structures, therefore should be considered as the strategy for dose escalation. SIB-IMRT achieves lesser NTCP than sequential-IMRT.

Key words: Carcinoma prostate, intensity-modulated radiotherapy, normal tissue complication probability, simultaneous integrated boost, sequential intensity-modulated radiotherapy, tumor control probability

INTRODUCTION

In conventional three-dimensional conformal therapy (3DCRT), different dose levels for each treatment site are delivered in several phases and the same doses per fraction are used (typically 1.8 –2.0 Gy) for all target volumes.[1] The field sizes are reduced in stages to limit the dose to microscopic and subclinical disease, to protect critical structures. This kind of fractionation approach requires the creation of different treatment plans for each phase of treatment and might take five to seven weeks to complete. The fractionation schemes used in 3DCRT can also be used in intensity-modulated radiotherapy (IMRT). For example, the initial and the boost phase of treatments may be delivered in two stages, similar to 3DCRT, or the initial target volume may be treated with 3DCRT followed by sequential-IMRT boost to the gross tumor volume (as was done in this study). However, it may be difficult to optimize the remaining boost portion of the treatment plan once a large portion of the dose has already been delivered using the initial fields. Several investigators suggested that IMRT has an ability to create much superior dose distributions

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when it is designed and delivered using the simultaneous integrated boost (SIB-IMRT) fractionation scheme,[2-4] in which the doses for initial and boost fields are delivered in same number of fractions. Mohan *et al*[3] compared two-phase IMRT (sequential-IMRT) and SIB-IMRT fractionation schemes for the treatment of a head-and-neck phantom case. The study showed that the dose distributions with SIB-IMRT were more conformal, and the schedule was more convenient for patients, with reduction in the length of the RT course and in the overall treatment cost.

Compared to sequential-IMRT, SIB-IMRT may be easier to use, because the same plan is used for the entire course of treatment. However, SIB-IMRT schemes typically result in higher fractional boost doses (>2.2 Gy per fraction). This suggests that normal tissues embedded within the target regions may receive higher doses per fraction compared to the doses given by sequential-IMRT delivery techniques. Therefore, sequential-IMRT may be more appropriate than SIB-IMRT when the dose given to the normal tissues is the major concern. To analyze these two different aspects of treatment with SIB-IMRT plans, in this planning study, the target coverage and normal tissue-sparing for both sequential-IMRT and SIB-IMRT plans for localized prostate cancer were compared in terms of dose–volume histograms (DVHs) using dose statistics. Simultaneously, the radiobiological effect of the two strategies on the tumor and normal tissues was analyzed by comparing tumor control probability (TCP) and normal tissue complication probability (NTCP).

MATERIALS AND METHODS

Thirty histologically proven cases of localized carcinoma prostate enrolled in this study were scheduled to undergo treatment with 3DCRT followed by IMRT boost schedule as per the department treatment protocol. However, planning was also done for SIB-IMRT and dosimetric analysis was done.

A planning computed tomography (CT) scan was done for each patient. Patients were prepared by giving oral and rectal contrast for proper tumor delineation. They were kept fasting for 4 h prior to CT scan. Oral contrast was given by dissolving 40 ml urograffin in 2 liters of water and given in 35-40 min before CT scan. Rectal contrast was given by dissolving 20 ml urograffin in 30 ml normal saline. For intravenous contrast 100 ml of Iohexol dye was used. No immobilization device was used.

After marking fiducials, patients were scanned from the L1-L2 junction to 3 cm below the ischial tuberosity with 2.5 mm slice thickness. These images were transferred to Eclipse treatment planning system (TPS), Varian associates, Palo Alto, CA, USA.

Contouring of both the target (prostate and seminal vesicles and normal tissues (bladder, rectum and small bowel) was done for each patient on individual axial CT slices on Eclipse TPS, according to International Commission on Radiation Units and Measurements (ICRU) report 50 and the same contours were used for the two treatment techniques.[5] Whole prostate was contoured as GTV. Two separate CTVs were defined. One for prostate and seminal vesicles {CTV (P + SV)}, the other accounting for microscopic disease in pelvic LNs {CTV (LN)}. Contouring of pelvic LNs was done according to Taylor's guidelines.[6] To account for organ motion and set-up uncertainty, PTV (P + SV) was defined by uniformly expanding CTV (P + SV) by 1 cm in the anterior, both sides laterally and in the cranio-caudal direction, but only 0.6 cm posteriorly to allow rectal sparing [Figure 1a]. Similarly PTV (LN) was created by expanding CTV LN uniformly by 1 cm [Figure 1b]. Rectum was contoured and delineated from the anal margin to the rectosigmoid junction. The outermost extent of the small bowel loops within the peritoneal cavity was outlined.

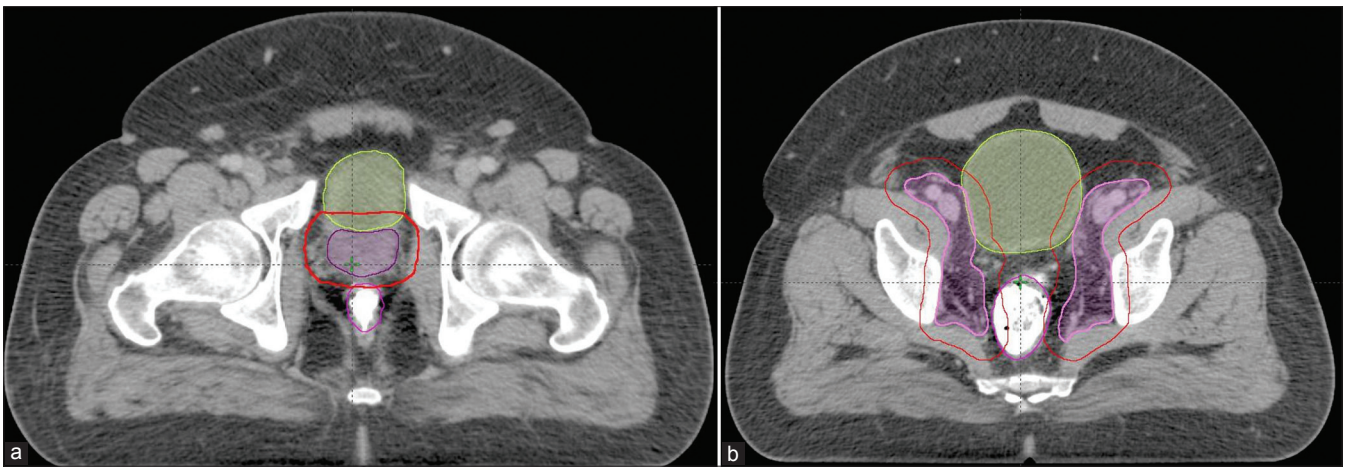

Figure 1: Contouring of target volumes and organs at risk (a) CTV P + SV (pink), PTV P + SV (red), Bladder (yellow), Rectum (light pink) Contouring of target volumes and organs at risk (b) CTV LN (pink), PTV LN (red)

Treatment planning was then done for two different techniques using ECLIPSE TPS as follows:

3DCRT + IMRT BOOST PLAN (SEQUENTIAL-IMRT PLAN)

In this two-phase strategy, the initial phase was planned with 3DCRT technique on TOTAL PTV [made by adding PTV (P + SV) and PTV (LN)] by four 6 MV or 15 MV fields (anterior, posterior, right lateral and left lateral) shaped with multileaf collimators [Figure 2]; to which the dose of 50 Gy was prescribed, which was delivered in 25 fractions over 5 weeks.

Further 24 Gy boost dose in 12 fractions in 2.5 weeks was planned to be delivered with IMRT, prescribed to PTV (P + SV) only, by seven equally spaced 6 MV coplanar fields [Figure 3].

SIB-IMRT PLAN

For this plan, PTV (P + SV) SIB and PTV (LN) SIB were delineated separately on same CT images for the purpose of dosimetric comparison. The above two target volumes are the same as were used in sequential IMRT plans, only they are named differently so that SIB plans can be made with them. Field placements have been shown in Figure 4a and 4b for PTV P+SV and PTV LN, respectively. The dose prescription was, however, different for this plan.

The doses prescribed to PTV (P + SV) SIB and PTV (LN) SIB were 74 Gy delivered in 27 fractions in 5.5 weeks @ 2.74 Gy per fraction and 54 Gy delivered in 27 fractions in 5.5 weeks @ 2 Gy per fraction respectively.

Equivalent doses (EQD2) received by tumor and normal

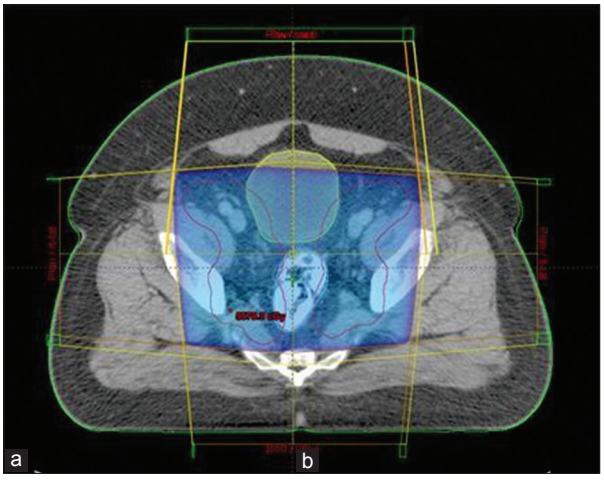

Figure 2: Field arrangements for initial 3DCRT plan

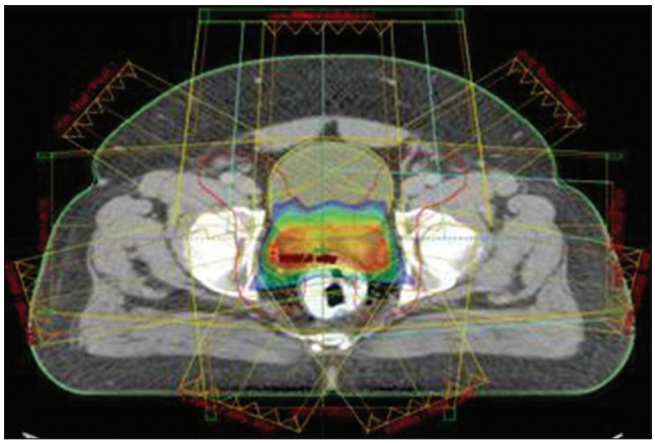

Figure 3: Field arrangements for final IMRT boost plan

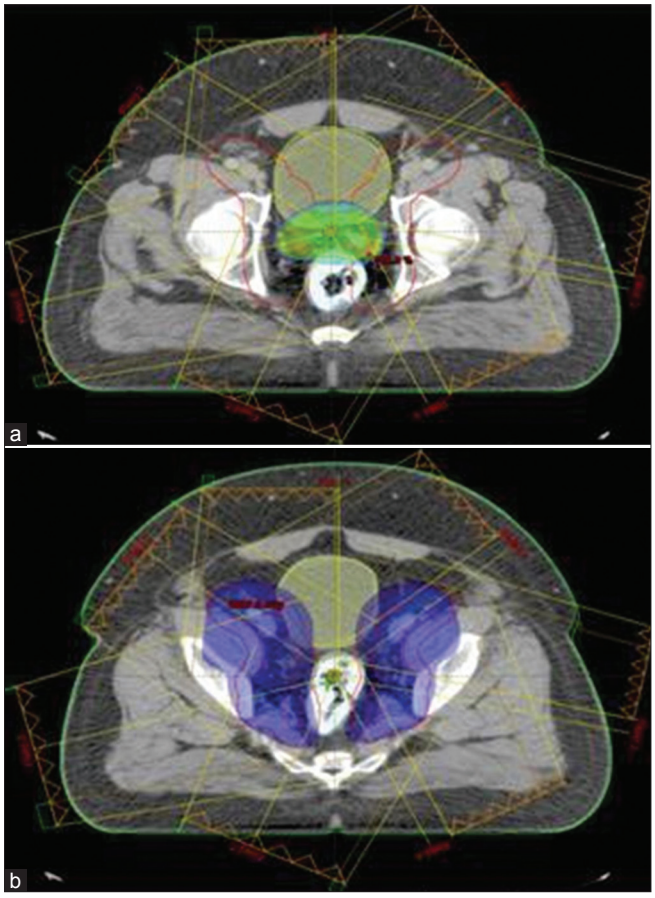

Figure 4: Field arrangements for SIB-IMRT plan (a) CT slice showing (PTV P + SV) SIB. (b) CT slice showing (PTV LN) SIB

Table 1: Equivalent doses received by tumor and normal tissues by both sequential and SIB-IMRT plans

	BED 1.5	BED 3
Sequential-IMRT	172.66 Gy	123.33 Gy
SIB-IMRT	209.17 Gy	141.58 Gy
	EQD2 1.5	EQD2 3
SIB-IMRT	89.64 Gy	85.29 Gy

BED1.5: Biological equivalent dose with α/β taken as 1.5 BED 3: Biological equivalent dose with α/β taken as 3 EQD2 1.5: Equivalent dose at 2 Gy per fraction with α/β taken as 1.5 EQD2 3: Equivalent dose at 2 Gy per fraction with α/β taken as 3

tissues by both sequential and SIB-IMRT plans are summarized [Table 1].

The planning goals were to cover 95% of the target volume with 100% of the prescription dose and to keep the critical structure doses at or below known tolerance limits. The goals for the rectum and bladder were to limit the volumes receiving 70 Gy ($V > 70$ Gy) or more to <25% and <40%, respectively.[7-8] Optimization was done and isodose distributions for each plan were normalized such that 95% of the PTV volume was covered by 100% of the prescription dose ($V100\%$)

Plans were evaluated both quantitatively by analyzing dose volume histograms and qualitatively by visually inspecting isodose curves.

For dosimetric comparison, a plan sum was made for sequential-IMRT plan which gave the total dose received by the prostate and seminal vesicles (P + SV), lymph nodes (LN), critical structures (bladder, rectum, small intestine) by the whole sequential-IMRT plan i.e. the initial 3DCRT phase of treatment and the IMRT boost phase of treatment. To make a plan sum we assumed that one of the plans has homogenous dose distribution for all the organs evaluated, which is true for 3DCRT plan.

This sequential-IMRT plan was then compared with SIB-IMRT plan in terms of target volume coverage and doses received by normal organs i.e.

Target Volumes: (PTV P + SV) and (PTV LN): Maximum dose (D max), mean dose (D mean), volumes covered by 100% of prescribed dose (V100%), volumes covered by 95% of prescribed dose (V95%)

Normal structures: rectum, bladder and intestine: Maximum dose (D max); mean dose (D mean); dose received by 1/3rd, 2/3rd, 100% of normal structures, volume of rectum and bladder receiving 70 Gy (V70) by evaluating dose–volume histograms (DVHs) for the two respective plans.[9]

RADIOBIOLOGICAL COMPARISON

To predict the biological impact of the two treatment techniques on prostate tumor and normal organs, the radiobiological models were used, which rely on an implicit estimation of the tumor control probability (TCP) and normal tissue complication probability (NTCP) arising from a given dose distribution using equivalent uniform dose (EUD) based on DVH reduction method defined by the Lyman-Kutcher-Burman (LKB) model.[10]

EUDs were calculated from differential DVHs with tissue specific parameters: $n = 0.12$ for the rectum and $n = 0.5$ for bladder.[11]

The TCP was calculated using the Poisson statistics given below (Equation 1) with D_{50} and γ_{50} representing the two parameters describing the dose and normalized slope at the point of 50% probability of control.[12]

$$TCP = \left(\frac{1}{2}\right)^{\exp[2\gamma_{50}(1-D/D_{50})/\ln 2}} \quad ...(1)$$

The NTCP was calculated using the LKB[10] model as follows:

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t}\exp\left(-\frac{t^2}{2}\right)dt \quad ...(2)$$

where t is defined as

$$t = \frac{D - TD_{50}(v)}{m.TD_{50}(v)} \quad ...(3)$$

and

$$TD_{50}(v) = TD_{50}(1)\cdot v^{-n} \quad ...(4)$$

In the above equations, the parameters D, n, m and TD50 determine the EUD delivered to the structure of interest, volume dependence of NTCP, the slope of NTCP vs. dose and the tolerance dose to the whole organ leading to a 50% complication probability, respectively.

Statistical analysis was performed using the statistical package for social sciences (SPSS) software v 16.0. Sequential IMRT and SIB-IMRT bladder, rectum and intestine doses were compared using Wilcoxon signed rank test. All tests were two- tailed and P value < 0.05 was considered significant.

RESULTS

PTV Coverage (Mean)

The average volume of PTV P + SV and PTV LN receiving 100% of prescribed dose is slightly lesser for SIB-IMRT plans, but the difference is not statistically significant. Also, the average volume of PTV P + SV and PTV LN receiving 95% of prescribed dose is 100% and 99%, respectively, and is similar for both the techniques, thus indicating equal PTV coverage achievable with both plans. The mean dose to PTV P + SV was lesser for SIB-IMRT plans. However, the mean dose to PTV LN was very similar for both the techniques [Table 2].

Doses to organs at risk

The mean dose to the rectum was reduced from 64 ± 2 Gy using sequential-IMRT to 57 ± 4 Gy using SIB-IMRT. Significantly lower minimum, mean and maximum doses were delivered to the rectum by SIB-IMRT plans as compared to sequential-IMRT plans ($P < 0.05$). Both planning techniques achieved the desired rectal dose constraint goal. The rectal $V > 70$ Gy was 22.8% using sequential-IMRT and 18.2% using SIB-IMRT and was statistically significant ($P < 0.05$) [Table 3].

The mean dose to the bladder was reduced from 68 ± 3 Gy for sequential-IMRT to 59 ± 3 Gy for SIB-IMRT. The bladder $V > 70$ Gy was 34.8% using sequential-IMRT and 24.05% using SIB-IMRT and was statistically significant ($P < 0.05$).

The mean dose to the small bowel with the use of sequential-IMRT and SIB-IMRT varied as follows: 38 ± 1 Gy using sequential and 34 ± 1 Gy using SIB-IMRT, however, this could not reach a statistically significant value.

The dose-volume histograms for the rectum, bladder and small bowel obtained with the two plans clearly indicate the superiority of the SIB-IMRT plans in achieving lower doses to these organs compared to sequential-IMRT plans [Figure 5].

Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) [Table 4].

TCP for both prostate and LN is significantly high with SIB-IMRT plans compared to sequential-IMRT plans reaching as high as 95% for prostate and 99% for lymph nodes.

NTCP as calculated by LKB models shows that NTCP for rectum is 4.3% with SIB plans as compared to 6% with sequential plans and the difference is statistically significant. For bladder the NTCP is only 0.01% for SIB plans, compared to 0.86% for sequential plans. However, for the intestine, a similar complication probability has been found.

DISCUSSION

The development of conformal techniques has enabled more sparing of normal tissue from high doses as compared to the conventional techniques. In the last decade, the outcomes of prostate dose escalation trials[13,14] are encouraging, indicating that higher doses delivered using conformal techniques lead to higher rates of tumor control, with acceptable levels of complications.

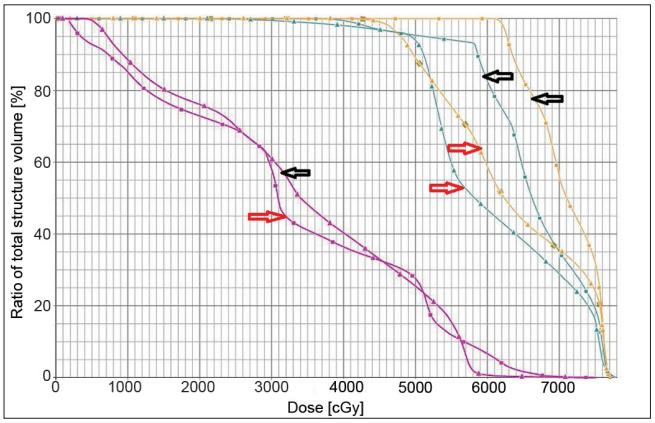

Figure 5: Comparison of Dose Volume Histograms (DVH) obtained for small bowel (magenta), rectum (light blue), and bladder (light pink) with sequential-IMRT plans (black arrows) and SIB-IMRT plans (red arrows)

With 3DCRT techniques using standard dose fractionation regimens (1.8–2 Gy per fraction), delivery of higher doses has been possible, but the probability of late Grade 2 rectal and urinary toxicity increases. There is evidence of a significant increase in late rectal complications when more than 25% of the rectum received a dose of 70 Gy or greater.[12]

Most of the previous dose escalation trials used conventional daily doses of about 2 Gy per fraction. For total doses higher than 80 Gy, the treatment times will be prolonged to more than eight weeks, causing inconvenience and extra costs to patients. However, evidence of a smaller α/β ratio for

Table 2: Comparison of doses to target volumes between sequential and SIB-IMRT plans

	Sequential IMRT	SIB-IMRT	*P* value
V 100% (Volume receiving 100% of prescribed dose)			
PTV P + SV	98.55 ± 0.21 %	98.07 ± 0.34 %	0.7
PTV LN	98.74 ± 0.78 %	98.32 ± 0.45 %	0.08
V 95% (Volume receiving 95% of prescribed dose)			
PTV P + SV	100 ± 0.0 %	100 ± 0.0 %	0.3
PTV LN	99.74 ± 0.43 %	99.27 ± 0.67 %	0.8
MEAN DOSE			
PTV P + SV	78 ± 1 Gy	76 ± 1 Gy	0.003
PTV LN	59 ± 1 Gy	58 ± 8 Gy	0.015

Table 3: Comparison of doses to critical organs between sequential and SIB-IMRT plans

	Sequential-IMRT	SIB-IMRT	*P* value
Bladder			
Dmax (Gy)	79 ± 1	78 ± 8	0.02
Dmean (Gy)	68 ± 3	59 ± 3	0.005
V_70 Gy (%)	34.84	24.05	0.007
Rectum			
Dmax (Gy)	79 ± 1	78 ± 9	0.04
Dmean (Gy)	64 ± 1	57 ± 4	0.02
V_70 Gy (%)	22.81	18.23	0.008
Small Bowel			
Dmax (Gy)	70 ± 7	71 ± 7	0.3
Dmean (Gy)	38 ± 1	34 ± 1	0.06

Table 4: Comparison of tumor control probability and normal tissue complication probability between sequential and SIB-IMRT plans

	Sequential-IMRT	SIB-IMRT	*P* value
TCP Prostate (%)	91.11 ± 0.60	94.84 ± 0.99	0.001
TCP Lymph nodes (%)	97.41 ± 1.8	99.43 ± 0.27	0.001
NTCP Bladder (%)	0.86 ± 0.75	0.01 ± 0.02	0.001
NTCP Rectum (%)	5.87 ± 2.58	4.31 ± 2.61	0.03
NTCP Small Bowel (%)	8.83 ± 7.08	8.25 ± 7.98	0.46

prostate tumors suggests that it would be beneficial to hypofractionate the dose to increase the therapeutic ratio and decrease the overall treatment time.[15]

Keeping the above two rationales in mind, i.e. a hypofractionated as well as an escalated dose regimen can improve the therapeutic outcome in terms of increased local tumor control rate of prostate cancer, we designed a study where SIB-IMRT technique (utilizing the hypofractionated and biologically escalated dose), was compared with the sequential 3DCRT followed by IMRT boost technique (utilizing a conventional fractionation of 2 Gy per fraction). The later regimen is routinely used in our department and many other institutes for treating prostate cancer.

In this study, on analyzing the dosimetric indices, it was found that SIB-IMRT plans were significantly superior to sequential-IMRT plans in terms of normal tissue sparing. Regarding PTV coverage, both the plans attained similar PTV coverage. But for doses to organs at risk, the SIB plans achieved significantly lower doses to the rectum and bladder as compared to sequential-IMRT plans.

Despite the appeal of the SIB-IMRT technique being superior to sequential-IMRT plans, two important aspects of the fractionation scheme and actual radiation delivery technique need to be discussed.

First, there remains a question of radiobiological consequences of using higher dose per fraction per day in SIB plans (2.74 Gy/fraction in this study) over the normal tissues (rectum, bladder and small bowel) adjacent to the target regions (prostate). The use of higher fractional boost doses in SIB plans places the normal tissues at greater risk as compared to sequential-IMRT plans. This phenomenon brings up the very important and rather poorly studied concept of biologic equivalent dose.

In most of the studies done so far with SIB in prostate, there is presumed equivalence of the SIB schedule to standard fractionation schedules. This is done by using a dose in SIB plans which is biologically equivalent to the dose delivered at 2 Gy/fraction, so as not to exceed the normal tissue complication rates.

In the present study, in order to achieve an escalated dose along with hypofractionation, equivalent dose was not calculated, rather similar 74 Gy was delivered with SIB plans (as was used in sequential-IMRT plans), but at high dose per fraction (2.74 Gy/fraction) so as to achieve a biologically higher dose with SIB plans. Therefore, using the linear quadratic model according to the presumed α/β ratio for prostate cancer, the total equivalent dose of 74 Gy delivered at 2.74 Gy/fraction with SIB would be about 89.64 Gy at 2 Gy/fraction if the α/β ratio is 1.5, and about 78.56 Gy at 2 Gy/fraction if the α/β ratio is 10, which is good for higher tumor control. But for late-reacting tissues with α/β ratio closer to 3, the 74 Gy at 2.74 Gy/fraction schedule would be expected to produce worse toxicity rates than the 74 Gy at 2 Gy schedule as the equivalent dose at 2 Gy/fraction is 85.29 Gy.

Therefore using higher biological equivalent dose (BED) in SIB plans we expected to get higher tumor control probability (TCP) with SIB as compared to sequential-IMRT plans. But whether this higher BED can also lead to increased normal tissue complication probability (NTCP) or not, has been analyzed in this study. The important assumption of the LKB model[10] used to calculate NTCP, is that it does not explicitly take into account the dose fractionation effects,[11] but for comparing two plans on DVH, this model has been used in our study. Contrary to the expected complication probability results, NTCP was found to be significantly lower with the hypofractionation schedule used. On comparing these results with the studies in the literature,[16] we concluded that the lower rates of complication probabilities could be achieved in our study because of the use of highly conformal and critical structure-sparing SIB plans for the dose-escalated hypofractionation schedule as compared to using 3DCRT or IMRT plans. The second issue with the delivery of hypofractionated schedules is the delivery technique. The reason that previous hypofractionation schedules were associated with excessive toxicity and the more modern schedules seem to be better tolerated is likely related to increased sophistication in treatment delivery with improved design of the delivery plans and improved targeting.

A more important aspect of modern delivery is the clinical use of image guidance. The series of patients in the present study were all treated with EPIDs (electronic portal imaging device) as the daily image guidance system. The intrafraction motion (real-time motion of the prostate during treatment delivery) is only lately being characterized.[17] Until the target (i.e., the prostate) position is known accurately every day during the course of treatment and during the actual radiation delivery, the benefits of hypofractionation with either external beam radiation or brachytherapy will be questioned.

The outcomes presented in this study are essentially comparable to the outcomes reported in the literature.[3,4,18,19] The striking difference in this study, however, from other studies is, not using the same BED for the SIB fractionation schedule as was used for the sequential-IMRT schedule, so as to achieve higher tumor control rates as mentioned previously. The lower NTCP values achieved with SIB-IMRT clearly show that SIB-IMRT, in spite of using high dose per fraction, lead to less normal tissue complications because of highly conformal plans generated with this radiation technique.

CONCLUSION

Our study showed that SIB-IMRT would produce the least normal tissue complications with almost the same amount of tumor control compared to sequential two-phase treatment plan. Moreover, SIB-IMRT can produce a better physical dose distribution by finding better mathematical solutions by inverse planning techniques. The TCP and NTCP can play a vital role in planning and evaluation when delivering very high doses in individual patients. SIB-IMRT can also increase the machine throughput as the treatments are delivered in a shorter period compared to a two-phase treatment.

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