Original Article

Feasibility of Simultaneous Integrated Boost Intensity Modulated Radiotherapy treatment plans in patients with localized carcinoma prostate

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ABSTRACT

Aim: To dosimeterically analyze Simultaneous Integrated Boost Intensity Modulated Radiotherapy (SIB-IMRT) treatment plan in prostate cancer patients, in terms of target coverage and dose to organs at risk. To determine radiobiological effect of this technique on target and normal tissues using Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). **Materials and Methods:** Twenty patients with localized prostate cancer 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, small bowel, penile bulb and bilateral femoral heads. For all patients, SIB IMRT plan was created. The prescription dose to the PTV P + SV is 74 Gy delivered in 27 fractions over 5.5 weeks and the dose to PTV LN is 54 Gy delivered in 27 fractions over 5.5 weeks. The treatment plan was analyzed in terms of their dose–volume histograms, target volume covered by 95% of the prescription dose (V 95%), and maximum and mean structure doses (Dmax and Dmean). Also an analysis was done on TCP and NTCP obtained with the plan. NTCP was calculated by Lyman Kutcher Burman (LKB) model. **Results:** All the critical structures received doses within the dose constraints specified for the SIB IMRT plan. The volume of rectum and bladder receiving 65 Gy or more ($V > 65$ Gy) was 18.23% and 24.05%. The mean doses to both bladder and rectum were 59 ± 3 Gy and 57 ± 4 Gy respectively. NTCP of 0.01 ± 0.02% for bladder, 4.31 ± 2.61% for rectum and 8.25 ± 7.98% for small bowel was achieved with SIB-IMRT plans. **Conclusions:** SIB-IMRT is dosimetrically and radiobiologically feasible treatment technique for prostate cancer IMRT.

Key words: Dosimetric analysis, prostate cancer, Simultaneous Integrated Boost Intensity Modulated Radiotherapy IMRT

INTRODUCTION

3 Dimensional Conformal radiation therapies (3DCRT) has long been used for treatment of prostate cancer patients. In this strategy, different dose levels are delivered to different target volumes in several phases, though the dose per fraction used (typically 1.8 - 2.0 Gy) is same 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 5 to 7 weeks to complete. The fractionation schemes used in 3DCRT can also be used in Intensity Modulated radiation therapy (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. 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 when it is designed

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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 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/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. The radiobiological effect of this strategy on the tumor and normal tissues can be found out by determining Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP).

Therefore, this planning study has been undertaken to analyze dosimetric aspects of treatment with SIB-IMRT plans, in terms of dose–volume histograms (DVHs) using dose statistics; and radiobiological aspect in terms of TCP and NTCP, and to determine the feasibility of its use at our institute, where patients have been treated till now with sequential IMRT plans.

MATERIALS AND METHODS

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

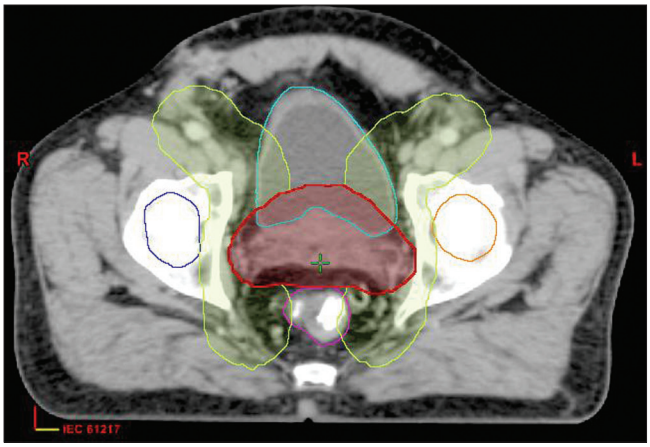

Figure 1: Delineation of target volumes and normal tissues

A planning 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 hours prior to CT scan. Oral contrast was given by dissolving 40 ml urograffin in 2 litres 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 L1-L2 junction to 3 cm below 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 vesicals) and normal tissues (bladder, rectum, small bowel, penile bulb and bilateral femoral heads) was done for each patient on individual axial CT slices on Eclipse TPS, according to ICRU report #50.[5] Whole Prostate was contoured as GTV. Two separate CTVs were defined. CTV (P + SV) defines CTV for prostate and seminal vesicles; and CTV (LN) accounts for microscopic disease in pelvic LNs. Contouring of pelvic LNs was done according to Taylors guidelines.[6] To account for organ motion and set up uncertainty, PTV (P + SV) SIB was defined by uniformly expanding CTV (P + SV) by 1 cm in anterior, both sides laterally and in cranio-caudal direction; but only 0.6 cm posteriorly to allow rectal sparing. Similarly PTV (LN) SIB was created by expanding CTV LN uniformly by 1 cm [Figure 1]. Rectum was contoured and delineated from anal margin to rectosigmoid junction. The outermost extent of small bowel loops within the peritoneal cavity was outlined. Bladder, femoral heads and penile bulb were contoured as per their extent in CT images.

Treatment planning was then done for SIB IMRT technique using ECLIPSE TPS. The beam arrangements used for this technique are summarized in Table 1.

Field placements have been shown in Figure 2 for PTV (P + SV) SIB and PTV (LN) SIB, respectively. The prescription dose to the PTV(P + SV) SIB is 74 Gy delivered in 27 fractions over 5.5 weeks and the dose to PTV (LN) SIB is 54 Gy delivered in 27 fractions over 5.5 weeks.

Equivalent doses (EQD2) received by tumor and normal tissues by SIB-IMRT plans are summarized [Table 2].

Table 1: Beam arrangements for the simultaneous integrated boost intensity modulated radiotherapy plan

	SIB-IMRT
Treatment Field arrangement	7 field IMRT from beginning 205°, 257°, 309°, 0°, 51°,102°, 153° gantry angles

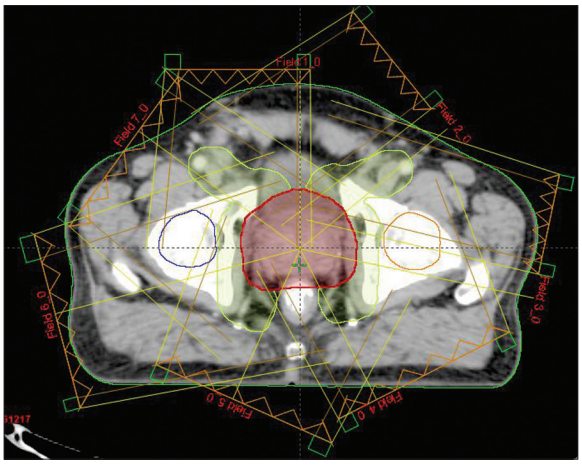

Figure 2: Field arrangement for Simultaneous Integrated Boost Intensity Modulated Radiotherapy plan

Table 2: Equivalent doses received by tumor and normal tissues by simultaneous integrated boost intensity modulated radiotherapy plans

Tumor BED 1.5	Normal tissues BED
209.17 Gy	141.58 Gy
EQD2 1.5	**EQD2 3**
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

The planning goals were to cover 100% of the target volume with 95% 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 more than 65 Gy ($V > 65$ Gy) to <25% and <40%, respectively.[7] A mean small bowel dose of <35 Gy; and 50% volume of penile bulb receiving dose < 50 Gy was considered acceptable. The volume of bilateral femoral heads receiving 50 Gy was limited to less than 5% i.e. V50 < 5%. The dose constraints were defined according to recent Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations.[8] Plans were evaluated both quantitatively analyzing dose volume histograms and qualitatively by visually inspecting isodose curves. Analysis was done in terms of target volume coverage and doses received by normal organs:

Target volumes

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: Maximum dose (D max); mean dose (D mean); volume of rectum and bladder receiving 65 Gy (>V65), volume of femoral heads receiving 50 Gy (V 50).[9]

For radiobiological analysis

To predict the biological impact of this treatment technique on prostate tumor and normal organs, the radiobiological models were used, which relies 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 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]

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

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

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

Where t is defined as

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

and

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

In 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.

RESULTS

PTV coverage (mean)

The volume of PTV P + SV and PTV LN receiving 95% of prescribed dose (V95) is 100% and 99% respectively. Also, the mean doses to these target volumes, as given in Table 3, clearly indicate that the desired target coverage is achieved adequately by SIB IMRT plans.

Doses to organs at risk

The mean dose to the rectum was 57 ± 4 Gy. SIB IMRT achieved the desired rectal dose constraint goal. The rectal V > 65 Gy was 18.2%, as can be seen in Table 4.

The mean dose to the bladder was 59 ± 3 Gy for SIB-IMRT. The bladder *V* > 65 Gy was 24.05% using SIB-IMRT.

The mean dose to the small bowel was 34 ± 1 Gy, and the volume of penile bulb receiving 50 Gy was 46%. Also the average volume of femoral head receiving 50 Gy was 4% only.

The dose volume histograms for rectum, bladder, small bowel, penile bulb and bilateral femoral heads obtained with SIB IMRT plan clearly indicate that SIB IMRT plans adequately achieved the constraints [Figure 3].

Tumor control probability and normal tissue complication probability

Table 5 shows that TCP is 94.84 ± 0.99% for prostate and 99.43 ± 0.27% for lymph nodes with SIB-IMRT plans. The values demonstrate that the higher dose per fraction used for prostate tumor can help achieve high tumor control probability.

NTCP as calculated by LKB models show that NTCP for rectum is 4.31 ± 2.61% and 0.01 ± 0.02% for bladder. NTCP for small bowel is 8.25 ± 7.98%, which indicates higher complication probability for bowel, than for rectum and bladder. The larger variation in the complication probability for bowel compared to other structures, may relate to the different extent of bowel delineation in different patients, due to higher mobility of bowel compared to other normal structures.

Table 3: Doses to target volumes with simultaneous integrated boost intensity modulated radiotherapy plans

V 100% (Volume receiving 100% of prescribed dose)	
PTV P + SV	98.07 ± 0.34%
PTV LN	98.32 ± 0.45%
V 95% (Volume receiving 95% of prescribed dose)	
PTV P + SV	100 ± 0.0%
PTV LN	99.27 ± 0.67%
Mean dose	
PTV P + SV	76 ± 1 Gy
PTV LN	58 ± 8 Gy

Table 4: Doses to critical organs with simultaneous integrated boost intensity modulated radiotherapy plans

Bladder	
Dmax (Gy)	78 ± 8
Dmean (Gy)	59 ± 3
V_65 Gy (%)	24.05
Rectum	
Dmax (Gy)	78 ± 9
Dmean (Gy)	57 ± 4
V_65 Gy (%)	18.23
Small Bowel	
Dmax (Gy)	71 ± 7
Dmean (Gy)	34 ± 1

Table 5: Tumor control probability and normal tissue complication probability with simultaneous integrated boost intensity modulated radiotherapy plans

TCP Prostate (%)	94.84 ± 0.99
TCP Lymph nodes (%)	99.43 ± 0.27
NTCP Bladder (%)	0.01 ± 0.02
NTCP Rectum (%)	4.31 ± 2.61
NTCP Small Bowel (%)	8.25 ± 7.98

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.

With 3DCRT techniques using standard dose fractionation regimens (1.8 - 2 Gy/#), delivery of higher doses has been possible, but the probability of late grade 2 rectal and urinary toxicity increases. There is evidence for a significant increase in late rectal complications when more than 25% of the rectum received 70 Gy or greater.[14]

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 8 weeks, causing inconvenience and extra costs to patients. However, evidence of a smaller a/b ratio for 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 rationale 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 with SIB-IMRT technique (utilizing the hypofractionated and biologically escalated dose), and analyzed its feasibility in terms of dosimetric and radiobiological aspect.

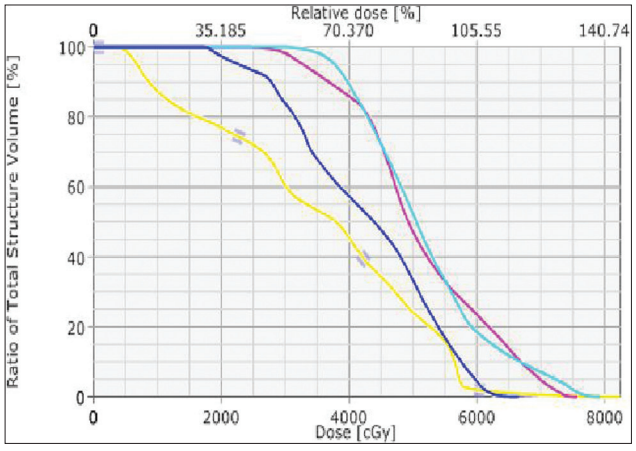

Figure 3: Dose volume histogram showing curves for rectum (magenta), bladder (light blue), small bowel (yellow), femur (dark blue)

In this study, on analysing the dosimetric indices, it was found that SIB-IMRT plans adequately achieved the desired dose constraints to normal tissues, without compromising the target volume coverage.

Despite the appeal of SIB-IMRT techniques 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 brings 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 the dose in SIB plans 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 hypofractiontion, 74 Gy was delivered with SIB plans, 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 a/b 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 a/b ratio is 1.5, and about 78.56 Gy at 2 Gy/fraction if the a/b ratio is 10, which is good for higher tumor control. But for late-reacting tissues with a/b 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 BED in SIB plans we expected to get higher tumor control probability (TCP) with SIB. 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 takes into account the dose fractionation effects,[11] but for analyzing SIB IMRT plan on DVH, this model has been used in our study. Contrary to the expected complication probability results, NTCP was found to be significantly low with the hypo fractionation schedule used. On comparing these results with the studies in 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 low NTCP values achieved with SIBIMRT clearly shows that SIBIMRT, inspite of using high dose per fractions, lead to less normal tissue complications because of highly conformal plans generated with this radiation technique. However, the outcomes presented in this study are dosimetric only. The clinical outcome in terms of acute and late toxicities, and control rates will be more useful to determine the feasibility of this treatment technique.

CONCLUSION

Our study showed that SIB-IMRT would produce the least normal tissue complications with adequate tumor control. 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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