Original Article

Dosimetric correlation of acute and late toxicities in high-risk prostate cancer patients treated with three-dimensional conformal radiotherapy followed by intensity modulated radiotherapy boost

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ABSTRACT

Introduction: In prostate cancer, higher radiation doses are often related to higher local control rates. However, the clinical effect of these higher doses on normal tissue toxicities is generally overlooked. We dosimetrically analyze sequential intensity modulated radiotherapy (IMRT) plans in high-risk prostate cancer patients and correlate them with acute and late normal tissue toxicities.

Materials and Methods: Twenty-five high-risk prostate cancer patients were planned with three-dimensional conformal radiotherapy to a dose of 50 Gy delivered in 25 fractions in 5 weeks, followed by seven-field IMRT boost, to a dose of 24 Gy delivered in 12 fractions in 2.5 weeks, along with hormonal therapy. Acute and late toxicities were analyzed using Radiation Therapy Oncology Group toxicity criteria. Student's *t*-test was used for correlating doses received by normal tissues with toxicity grade. Five-year disease-free survival (DFS) and biochemical relapse-free survival (RFS) were evaluated using Kaplan–Meier analysis.

Results: Median follow-up of patients was 65 months. Of 25 patients, two developed acute Grade 2 rectal toxicity. Only 1 patient developed acute Grade 2 bladder toxicity. Late Grade 2 and 3 rectal toxicity was seen in 2 and 1 patient, respectively. Late Grade 2 and 3 bladder toxicity was seen in 1 patient each. Grade 2 or more acute rectal toxicity correlated significantly with rectal volume receiving >70 Gy ($P = 0.04$). The 5-year DFS and biochemical RFS was 70.2% and 79.2%, respectively. One patient failed locally and seven failed at distant sites.

Conclusion: Sequential IMRT with a dose of 74 Gy and maximum androgen blockade is well tolerated in high-risk patients in Indian setup with adequate control rates.

Key words: Correlation, dosimetry, high risk, intensity modulated radiotherapy, prostate cancer, three-dimensional conformal radiotherapy, toxicities

INTRODUCTION

In localized carcinoma prostate, radiation to prostate and pelvic lymph nodes (LNs) can be delivered by various techniques. Commonly used techniques are three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), simultaneous integrated boost IMRT, and sequential IMRT (3DCRT followed by IMRT or IMRT followed by IMRT).[1,2] The two-phase strategy commonly followed is 3DCRT for the initial pelvic phase followed by IMRT for later boost phase. This strategy has an advantage that the field sizes are reduced in stages to limit the dose to microscopic and subclinical disease, and to protect the critical structures.

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However, the limitation is that it requires the creation of different treatment plans for each phase of treatment and might take 5–7 weeks to complete. Still it is the commonly followed strategy in developing countries where the patient load is high, and IMRT cannot be planned for every patient. Furthermore, it is a time-tested technique.[3-5]

Increased radiation dose levels for patients with clinically localized prostate cancer have now become an established standard of practice. Four randomized trials have demonstrated improved prostate-specific antigen (PSA) relapse-free survival (RFS) outcomes for patients who received increased radiation dose levels.[6-9] Long-term results of single institution trials using escalated radiation doses up to 86.4 Gy have shown that higher doses are associated with improved tumor control outcomes and a concomitant reduction in the risk of distant metastases.[10,11]

However, the potential for increased risk of normal tissue toxicities has always been a concern with dose-escalation treatment programs. Several retrospective studies confirmed the increased risk of acute and late treatment-related complications when higher radiation doses are delivered using conventional external beam techniques.[12,13] The emergence of 3DCRT and IMRT have made it possible to reduce reliably the volume of rectum and bladder exposed to higher radiation doses and provide a mechanism for radiation oncologists to deliver higher doses in a safer fashion, without increasing normal tissue toxicities.

The aim of this study is to analyze dosimetrically sequential IMRT plan in terms of doses delivered to target volume and critical normal tissues. We also assess acute and late normal tissue toxicity and 5-year disease-free and biochemical RFS in high-risk prostate cancer patients treated with this plan.

MATERIALS AND METHODS

25 patients of carcinoma prostate were registered in Radiotherapy Department of our institute from July 2008 to December 2010. Twenty-five histologically proven cases of high-risk carcinoma prostate (classified as high risk according to D'Amicos classification,[14] i.e., with PSA >20 ng/mL and/or Gleason score [GS] 8–10 and/or stage ≥T2c) were enrolled in this study designed as a single arm prospective trial. All non-metastatic patients were excluded.

All patients were planned to undergo treatment with one cycle of neoadjuvant hormonal therapy, with luteinizing hormone-releasing hormone agonist (Goserelin 10.8 mg), followed by conformal radiation to a dose of 74 Gy, and adjuvant three monthly hormonal therapy which was continued up to 2 years, as per department treatment protocol.

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 before CT scan. Oral contrast was given by dissolving 20 ml urograffin in 1 L 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 omnipaque dye was used. Patient was then made to lie in a supine position on the couch in CT simulator machine GE Light Speed VFX in our Radiotherapy Department. 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, and small bowel) was done for each patient on individual axial CT slices on Eclipse TPS, according to Radiation Therapy Oncology Group (RTOG) guidelines. The whole prostate was contoured as gross tumor volume. Two separate clinical target volumes (CTVs) were defined: One for prostate and seminal vesicle (CTV [P + SV]); another accounting for microscopic disease in pelvic LNs (CTV [LN]). Contouring of pelvic LNs was done according to RTOG guidelines.[13] To account for organ motion and setup uncertainty, planning target volume (PTV) (P + SV) 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) was created by expanding CTV LN uniformly by 1 cm. The bladder was contoured according to the extent seen. Rectum was contoured and delineated from anal margin to rectosigmoid junction.

Treatment plan was then made for sequential-IMRT plan using Eclipse TPS as follows: In this two phase strategy, the initial phase was planned with 3DCRT which was created 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; to which dose of 50 Gy delivered in 25 fractions in 5 weeks was prescribed. Further, 24 Gy boost dose in 12 fractions in 2.5 weeks was planned to deliver with IMRT, prescribed to PTV (P + SV) only by seven equally spaced 6 MV coplanar fields.

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.[15] 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%).

A plan sum was made for a sequential-IMRT plan which gave the total dose received by P + SV, LNs, critical structures (bladder, rectum, and small intestine) by the whole sequential-IMRT plan. The plan was then analyzed in terms of target volume coverage and doses received by normal organs by evaluating dose – volume histograms (DVHs), i.e., target volumes: (PTV-P + SV) and (PTV LN): 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) of normal structures, the volume of rectum and bladder receiving 70 Gy (V70).

Follow-up was done 3 monthly for first 2 years, and then 4 monthly for next 3 years, with clinical examination and digital rectal examination. Contrast enhanced CT pelvis and PSA were done 6 monthly for first 2 years and then yearly. Median follow-up time was 65 months (range: 10–93 months). Acute and late toxicities were scored using RTOG morbidity grading scales.[16] Student's *t*-test was used for correlating doses received by normal tissues with grade of acute toxicity. Kaplan–Meiyer survival analysis was used to evaluate 5-year disease free survival (DFS) and biochemical RFS, using SPSS v 20 Statistical Package for the Social Sciences (IBM, Armonk, NY, United States of America).

RESULTS

Patient characteristics

The mean age of the patients was 66 years (range: 51–76 years). All patients belonged to high-risk category. Of 25 patients, 7 (28%) had Stage T2, 12 (48%) had Stage T3b and 6 (24%) were had node positive disease. Five (20%) patients had GS ≤6, 6 (24%) had GS of 7, and 14 (56%) had GS more than 7. PSA was <10 in 1 (4%) patient, 4 (16%) had PSA between 11 and 20, and 20 (80%) had PSA more than 20.

Dosimetric details

PTV coverage [Table 1] – the average volume of PTV P + SV and PTV LN receiving 95% of prescribed dose (V95) is 100% and 99%, respectively, indicating adequate coverage with sequential IMRT plans.

Dose to critical structures [Table 1] – the rectal V > 70 Gy was 22.8% and the bladder V >70 Gy was 34.8% using sequential-IMRT plans. Mean doses to rectum and bladder also indicate adequate sparing of these structures using sequential IMRT plans.

Acute rectal and bladder toxicity [Table 2] – two patients (8%) developed acute rectal symptoms (Grade ≥2) during radiotherapy. Acute urinary symptoms were less common than rectal symptoms. Only 1 patient (4%) experienced Grade ≥2 acute urinary symptoms, which were often ameliorated with α-blockers or anti-inflammatory medications.

Table 1: Dose coverage of the planning target volume and dose to critical structures

Dose volume parameters	Sequential IMRT
V100% (%)	
PTV P + SV	99.55 (97-100)
PTV LN	99.74 (98.49-100)
V95% (%)	
PTV P + SV	100±0.0
PTV LN	99.50±0.0
Mean dose (Gy)	
PTV P + SV	76.20±0.94
PTV LN	52.20±1.15
Rectum	
D max (Gy)	79.46±1.29
D mean (Gy)	64.40±1.74
V70 Gy (%)	26.82±11.88
Bladder	
D max (Gy)	79.98±1.22
D mean (Gy)	68.39±3.85
V70 Gy (%)	45.89±14.86
Intestine	
D max (Gy)	69.82±8.98
D mean (Gy)	36.60±14.09

V100% and V95% refer to volume of PTV receiving 100% and 95% of the prescribed dose respectively, PTV P + SV=PTV covering prostate and seminal vesicles, PTV LN=PTV covering lymph nodes, D max and D mean refers to the maximum and mean doses respectively received by critical structures, V70 Gy refers to volume of the critical structure in percentage receiving dose of 70 Gy. PTV=Planning target volume, IMRT=Intensity modulated radiotherapy

Table 2: Acute and late rectal and bladder toxicity

Grade	Acute rectal toxicity (%)	Acute bladder toxicity (%)	Late rectal toxicity (%)	Late bladder toxicity (%)
No toxicity	18 (72)	20 (80)	21 (84)	21 (84)
Grade 1	5 (20)	3 (12)	1 (4)	2 (8)
Grade 2	2 (8)	1 (4)	2 (8)	1 (4)
Grade 3	-	-	1 (4)	1 (4)
Grade 4	-	-	-	-

Late rectal and bladder toxicity [Table 2] – three (12%) developed Grade ≥2 late rectal toxicities, out of which one developed Grade 3 toxicity. The 2-year actuarial likelihood of Grade ≥2 late rectal toxicity is 10%. One patient who developed Grade 3 proctitis was treated with laser coagulation and required a blood transfusion for hematologic support. Of the patients who developed gastrointestinal (GI) toxicity, most common manifestation was rectal bleeding and mucous discharge/leakage. Late Grade 2 bladder toxicity was seen in 2 patients (8%). None developed Grade 3 or 4 toxicity. The 2-year actuarial likelihood of ≥ late Grade 2 bladder toxicity is 7%. Of the patients who developed Grade 2 urinary toxicity, the most common presentation was chronic frequency and urgency.

Dosimetric comparison with acute toxicity [Table 3] – a comparison of acute bladder and rectum dosimetry was done for patients experiencing Grade ≥2 toxicity, with those patients who experienced only (Grade 1) or no toxicity. The results suggest that Grade ≥2 acute rectal toxicity correlates significantly with rectal volume receiving >70 Gy (P = 0.04). However neither mean bladder doses nor V70 bladder correlated with acute bladder toxicity.

Dosimetric comparison with late toxicity [Table 3] – a similar comparison of late bladder and rectum dosimetry was done for patients experiencing Grade ≥2 versus those patients who experienced only (Grade 1) or no toxicity. Neither mean rectal or bladder doses nor V70 rectum or bladder correlated with late rectal or bladder toxicity respectively.

Survival outcome: 5-year DFS [Figure 1] and biochemical RFS [Figure 2] was 70.2% and 79.2% respectively. One patient developed local failure. Seven patients failed distally, 3 each at bone and lung, and 1 patient failed with disseminated metastasis.

Table 3: Dosimetric correlation with acute and late toxicity (using Student's *t*-test)

Dose volume parameters	Grade ≥2	Grade ≤1	*P**	Grade ≥2	Grade ≤1	*P**
Rectum						
Mean dose (Gy)	64.40	63.89	0.66	64.36	63.45	0.98
V70 Gy (%)	29.5	24.06	0.04	25.6	23.06	0.23
Bladder						
Mean dose (Gy)	68.45	68.22	0.86	69.35	67.66	0.83
V70 Gy (%)	45.9	42.3	0.74	44.9	41.3	0.42

*V70 Gy refers to volume of the critical structure in percentage receiving dose of 70 Gy

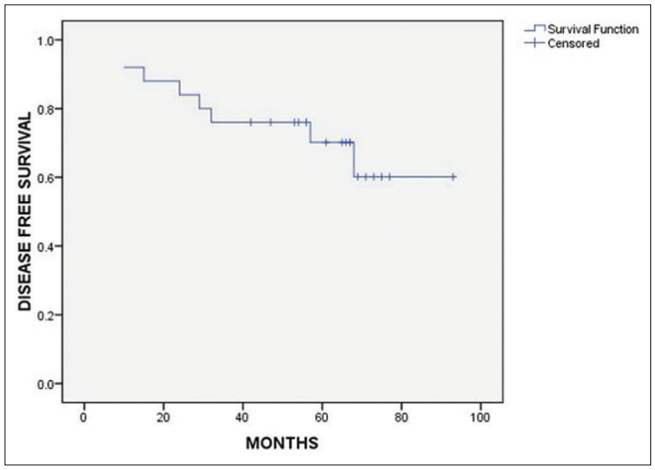

Figure 1: Disease free survival

DISCUSSION

Higher radiation doses for patients with clinically localized prostate cancer are now considered standard of care; therefore it has become ever more important to understand the potential for long-term treatment-related toxicities after conformal external beam radiotherapy. Our results demonstrate several important aspects concerning the dosimetric correlation with acute and late rectal and bladder toxicity. In our study, despite the use of higher radiation doses, the incidence of Grade ≥3 toxicities was relatively low.

Heemsbergen *et al*. reported on late rectal toxicity outcomes from a Dutch randomized dose-escalation trial (68 Gy vs. 78 Gy).[17] Toxicity was scored according to RTOG criteria. In that report, 28% developed late rectal toxicity. Severe rectal bleeding was noted in 6% of patients, and incontinence pads were required for mucous discharge or fecal soilage in 9%. In our patients, however, the overall toxicity outcome despite the delivery of even higher radiation doses seemed to be lower than that reported by the Dutch group, and that may be attributed to the use of IMRT in the boost phase.

Skwarchuk *et al*. treated 743 prostate cancer patients with 3DCRT with prescribed doses of 64.8–81.0 Gy.[18] A dose response for ≥ Grade 2 late rectal toxicity was observed. In addition to this, acute rectal toxicity was also significantly correlated (P = 0.05) with late rectal bleeding.

Fellin *et al*. in a multicentric study treated 1132 prostate cancer patients and evaluated late rectal toxicity by a self-reported questionnaire.[19] Results concerning bleeding and fecal incontinence of 718/1132 patients with a complete follow-up at 36 months were analyzed. 52 (7.2%) and 57 (7.9%) patients were scored as moderate/severe bleeders

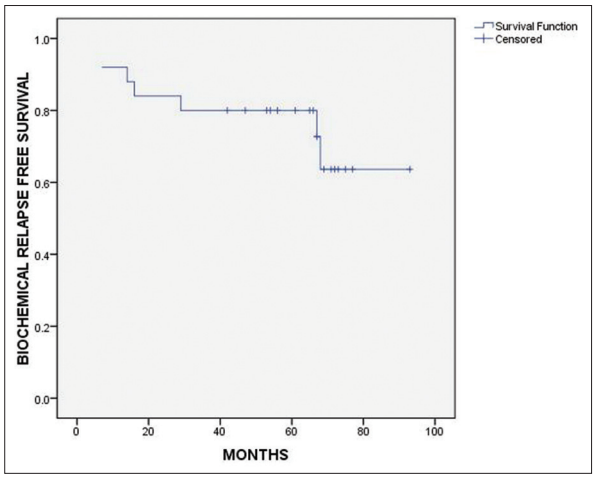

Figure 2: Biochemical relapse free survival

and fecal incontinents, respectively. The study concluded that the application of rectal dose–volume constraints can limit the incidence of rectal bleeding. The risk of bleeding may be further reduced by limiting V75 Gy <5% and in the case of patients previously submitted to abdominal/pelvic surgery, V70 Gy <15–20%. Fecal incontinence seems to be mainly a consequential effect after acute toxicity.

Storey *et al.* compared early and late side effects in 189 prostate cancer patients with stage T1b–T3 disease randomized to receive 70 Gy or 78 Gy, with a minimum follow-up of 2 years.[20] All patients were initially treated with a 4-field box to an isocenter dose of 46 Gy at 2 Gy/fraction. Side effects were graded on a 1–4 scale, adapted from RTOG criteria. No significant differences in acute rectal or bladder toxicity were seen between the two treatment techniques ($P > 0.6$ for all comparisons). Grade 2 or higher late bladder toxicity were 20% and 9% for 70-Gy and 78-Gy groups, respectively ($P = 0.8$). The 5-year risks of Grade 2 or higher late rectal toxicity were 14% and 21% for 70 Gy and 78 Gy, respectively ($P = 0.4$). DVHs analysis of the 78-Gy patients showed a significant correlation between the percentage of rectum irradiated to 70 Gy or greater and the likelihood of developing late rectal complications. Patients with more than 25% of the rectum receiving 70 Gy or greater had a 5-year risk of Grade 2 or higher complications of 37% compared to 13% for patients with 25% or less ($P = 0.05$). All three Grade 3 complications occurred when >30% of the rectum received 70 Gy or more. The study concluded that the overall rate of complications was similar in both treatment arms. However, there is evidence for a significant increase in late rectal complications when more than 25% of the rectum received 70 Gy or greater.

Ballare *et al.* treated 104 patients with stage T1b–T3b with 3DCRT to a total dose of 74 Gy at 2 Gy per fraction.[21] No Grade 3 toxicity was observed. Acute and late Grade 2 toxicity rates were 5.8% and 9.0% for rectum and 12.5% and 2.0% for bladder, respectively. Rectal V70 influenced the occurrence of late Grade 2 toxicity. A relationship between acute and late urinary toxicity was also found. After a median follow-up of 30 months, the actuarial overall and biochemical RFS rates were 84% and 77%, respectively, with a significant difference between low-intermediate and high-risk patients. The study concluded that rectal V70 proved to be a reliable prognosticator of late toxicity.

Drodge *et al.* treated 40 high-risk prostate cancer patients using hypofractionated IMRT to 75 Gy in 25 fractions.[22] Acute genitourinary and GI toxicity were Grade 2 in 6 of 36 evaluated patients (16.6%) and in 4 of 31 evaluated patients (12.9%) respectively. Dose-volume parameters were not found to be correlating with toxicity.

In our study, the rate of Grade 2 and above toxicities appears to be lesser than reported in the literature.[17-22] Higher toxicities in the studies done in past could be attributed to the fact that whole of the dose to the target volume was planned with 3DCRT technique only. However, in our study the doses to rectum and bladder could be decreased significantly, by effectively utilizing IMRT plans in the second phase. Furthermore, the majority of the patients in our study had Grade 1 toxicities.

With higher radiation doses more frequently being used in the treatment of localized prostate cancer, it is incumbent on clinicians to exercise more caution in the management of patients with treatment-related complications. Proctitis should be managed conservatively with increased dietary fiber intake, steroid suppositories, and only if required selective laser cauterization. Aggressive deep biopsies are not only unnecessary but can significantly impair the healing of radiation-induced ulceration and lead to fistula formation. Aggressive transurethral resection of the prostate after high-dose radiation can lead to higher rates of urinary incontinence and needs to be performed with a great deal of caution only when clinically indicated.

The 5 years DFS and biochemical RFS in our study was 70.2% and 79.2%, respectively. Johnson *et al.* treated high-risk prostate patients with pelvic radiotherapy followed by high-dose-rate brachytherapy boost and found 5- and 10-year biochemical-free survival to be as higher as 90% and 73% respectively and very low rates of severe (Grade ≥3) toxicity.[23] Wang *et al.* reported outcome in 1091 patients of localized high-risk prostate cancer, and concluded that patients in the radiotherapy + androgen therapy cohort were less likely to have biochemical failure compared with the radical prostatectomy + radiotherapy group ($P < 0.001$), with no significant difference in the development of distant metastasis or cause-specific mortality.[24]

The strength of this study is the long-term follow-up of the patients which resulted in the better assessment of late toxicities several years after radiation completion. However, the limitation of the study is that the significance of the impact of Grade 2 toxicities on the general function and overall quality of life for the individual patient was not taken into consideration.

CONCLUSION

Our results show that sequential IMRT with a dose of 74 Gy and maximum androgen blockade is well tolerated in Indian setup giving a 5 years DFS of 70.2%, with acceptable toxicity profile.

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Conflicts of interest
There are no conflicts of interest.

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