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Original Article

Studying the efficacy of escalated dose conformal radiation therapy in prostate carcinoma − Pakistan experience

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Abstract

Background: Our objective in this study was to evaluate the role and benefits in terms of local toxicity and biochemical disease-free survival (bDFS) following escalated-dose conformal radiation therapy in prostate adenocarcinoma.
Methods: The study population was composed of 53 patients with histologically proven T1b-T4, NO, MO prostate adenocarcinoma, having any Gleason score with prostate-specific antigen (PSA) of less than 50 ng/mL at diagnosis, given escalated dose EBRT (74 Gy) during the period between January 2011 and December 2013, retrospectively and evaluated for a period of 2 years post-radiation. Patients were followed up for a period of 2 years, beginning after completion of escalated dose external beam radiotherapy (EBRT) for biochemical failure as defined in ASTRO consensus committee guidelines 1996 and investigated for gastrointestinal, genitourinary skin toxicity.
Results: Out of 53 patients, 35 showed no biochemical failure at the end of 2 years following the completion of definitive escalated dose conformal radiotherapy while 18 were observed to have biochemical relapse. Acute gastrointestinal grade 1 toxicity was found in 26 patients, grade 2 in 24, and grade 3 only in 3 patients. Late gastrointestinal grade 0 toxicity was found in 16 patients, grade 1 in 28, grade 2 in 7 and grade 3 only in 2 patients. Grade 1 acute genitourinary toxicity was the highest in frequency observed in 28 of the total population followed by grade 2 in 21, grade 0 and grade 3 each, only in 2 patients. Late genitourinary Grade 0 toxicity was observed in 32 patients, grade 1 in 19, grade 2 and 3 only in 1 patient of the total population, respectively.
Conclusion: Our data were comparable to international studies of dose escalation using 3D and beneficial as compared to conventional radiation therapy delivered by 2D in terms of biochemical failure rate and treatment related toxicity.

Keywords: Biochemical failure; Conformal radiotherapy; Prostate cancer; Prostate-specific antigen; Toxicity

1. Introduction

Radiation therapy plays a vital role in the management of prostate cancer. Radical prostatectomy with pelvic lymph node dissection is only a standard option for T1 or T2 lesions if nodes are clinically negative, PSA is less than or equal to 20 ng/mL and Gleason score is less than or equal to 7. Even in these cases, carefully planned external beam radiotherapy (EBRT) leads to equivalent oncologic outcomes as compared with radical prostatectomy. In all other cases, EBRT with or without hormone therapy for localized prostate cancer is standard of care.[1] However, total dose of EBRT plays a critical role in treatment response, as does the fractionation protocol. Modality-specific toxicity profile and logistics should be

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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incorporated into the decision-making process of the individual patient.[2−6]

Conventional radiotherapy (RT) of 66 Gy in 2-Gy fractions was practiced up till 2010 in our set up and is still used in most radiotherapy institutes in our country. In leading radiotherapy institutes in the world, practice has long been changed to prescribing escalated doses of radiation by means of IMRT.[7−11]

We have studied escalated-dose conformal radiotherapy of 74 Gy in 2-Gy per fraction with the aim of observing the biochemical progression-free survival and treatment-related gastrointestinal and urinary tract toxicities of escalated dose-conformal radiation of 74 Gy, which is currently being practiced in our setup. The efficacy data for escalated-dose treatment are weighed against the increase in acute and late toxicities associated with the escalated dose and emphasize the importance of using appropriate modern radiotherapy methods to reduce side-effects and provide maximum dose to cure the disease.

Objective

To evaluate escalated-dose conformal radiotherapy in localized prostate cancer in terms of biochemical failure as well as escalated EBRT-related acute toxicities.

Operational definitions

Treatment-related side effects were characterized as acute and late bowel and urinary side effects using the RTOG/EORTC Acute and Late Radiation Morbidity Scoring Schema. Biochemical failure was defined using the American Society for Therapeutic Radiology and Oncology (ASTRO) published Consensus Panel Guidelines 1996, for testing prostate-specific antigen (PSA) levels following radiation therapy. These guidelines define biochemical failure as three rises in PSA value over three consecutive readings following radiotherapy or any rise great enough to provoke initiation of treatment ($\geq$2 ng/mL rise in our study) with the date of failure being the midpoint between the PSA nadir and the first PSA rise. Later ASTRO consensus guidelines were not used in our study as for them to be applicable, the patient population is not supposed to receive ADT, which is impractical when treating locally advanced disease. Conventional fractionation is delivery of external beam radiotherapy to a total dose of 66 Gy in 2 Gy per fraction. Dose escalation in our study is defined as dose delivery of 74 Gy at 2 Gy per fraction.

2. Methods

2.1. Sample selection

Radically treated cases of prostate cancer randomly selected from January 2011 to December 2013.

Inclusion criteria:

- Histologically proven prostate adenocarcinoma either on transrectal ultrasound (TRUS) guided biopsy or on transurethral resection of prostate chips (TURP).
- Radiologically staged T1b-T4, N0, M0 disease with the help of MRI of pelvis with contrast, along with CT abdomen with contrast and MDP-Tc^{99m} Bone scan.
- No previous pelvic radiotherapy.
- Any age
- Performance status ECOG 0−1

Exclusion criteria

- PSA >50 ng/dL due to high probability of occult distant metastases
- Moderate to severe ischemic heart disease
- Renal insufficiency
- Uncontrolled diabetes Mellitus (DM)
- Uncontrolled hypertension

2.2. Study design

The study was carried out retrospectively to evaluate the role of escalated-dose conformal radiation therapy in patients who fulfilled the above-mentioned criteria. Neo-adjuvant, adjuvant or concurrent ADT was not part of the exclusion criteria. Since 96.2% of patients fell into either the intermediate or high risk group of patients, all such patients were offered hormone therapy for three months in neoadjuvant setting before definitive RT. Furthermore, patients in the intermediate risk group were planned for hormone therapy for an additional 3 months during and post RT, while those in the high-risk group were planned for hormone therapy for an additional 21 months during and post RT. The hormone therapy offered in each case was a subcutaneous depot injection of Leuprolide (22.5 mg) administered once every 3 months in the anterior abdominal wall.

No formal stopping rules were specified.

2.3. Data collection

Data were collected at Institute of Nuclear Medicine and Oncology (INMOL) Hospital, Lahore which serves as catchment cancer care centre for Punjab in particular and all of Pakistan, in general. Sampling was carried out from amongst patients registered for treatment from January 2011 to December 2013 in order to ensure a minimum follow-up record of 2 years post EBRT completion. All data were collected with informed consent from all participating adult subjects and from parents or legal guardians for minors or incapacitated adults, together with the manner in which informed consent was obtained (e.g., oral or written). Data regarding the variables of interest were collected through the patient's medical record. Risk grouping was done on the basis of T stage, PSA levels and Gleason scoring.

2.4. Data analysis

For data entry and analysis, (version 16, SPSS, Inc., Chicago, IL) software was used.

3. Results

In our study, we selected patients retrospectively who had received 74 Gy of radiation doses via external-beam radiation therapy with or without androgen deprivation therapy (ADT) in neo-adjuvant, concurrent and/or adjuvant setting. Response to therapy and various toxicities were measured for higher doses, e.g., 74 Gy in our population.

3.1. Sample characteristics

3.1.1. Age distribution

Prostate cancer incidence is the highest in the 6th and 7th decade of life worldwide. In our study, the highest incidence rate of prostate adenocarcinoma was found in the age group of 70 years and above (n = 19, 35.8%). This was followed by younger age groups, e.g., (n = 14, 26.4%) in age group between 66 and 70 years, (n = 8, 15.1%) in the age group between 61 and 65 years and (n = 9, 17.0%) in age group between 56 and 60 years (Table 1).

3.1.2. T-stage distribution

In our study population, most patients presented with locally advanced disease stage, e.g., 24 cases (45.3%) out of the total population were classified as T4, (n = 15, 28.3%) as T3, (n = 6, 11.3%) as T2c and (n = 8, 15.1%) as T2b. None of the total 53 patients in study population had T1-T2a disease at presentation (Table 1).

3.1.3. PSA at diagnosis

Serum PSA is an important factor in the disease stratification of prostate adenocarcinoma. In our study population (n = 36, 67.9%) patients had PSA levels greater than 20 ng/mL at the time of diagnosis, whereas (n = 13, 24.5%) of the total study population lay in the range of 10−20 ng/mL and in (n = 4, 7.5%) patients, PSA levels were measured to be less the 10 ng/mL (Table 1).

3.1.4. Gleason score

Gleason score is also an important factor of the risk stratification of prostate adenocarcinoma. In our study population, (n = 35, 66.0%) of the total 53 patients fell into the higher Gleason score of 8−10 on pathology, (n = 15, 28.3%) were in the Gleason score of 7 and (n = 3, 5.7%) patients had Gleason score of less than or equal to 6 (Table 1).

3.1.5. Risk stratification distribution

Risk stratification is a very important step in initiating the management of patients with prostate adenocarcinoma. According to NCCN guidelines, risk stratification is based on T-stage, PSA levels at diagnosis and Gleason score on histopathology. In our study, (n = 46, 86.8%) patients of the total study population fell in the high-risk category and (n = 5, 9.4%) were in the intermediate-risk, whereas (n = 2, 3.8%) in the low risk group (Table 1).

3.2. PSA levels post definitive RT

3.2.1. PSA levels at first follow-up visit

Following completion of escalated dose radiotherapy, all patients were monitored on a 3 monthly follow-up basis. Post-treatment measurements of PSA levels were carried out on each visit. The data showed that at 3-month follow-up after completion of escalated-dose EBRT, (n = 25, 47.2%) of the total patients had PSA levels between 1 and 10 ng/mL, (n = 5, 9.4%) in the range of 10−20 ng/mL and (n = 23, 41.1%) patients had PSA value of greater than 20 ng/mL (Table 2).

3.2.2. PSA levels at last follow-up visit

The last follow-up visit record was evaluated for the study population. The visit date was different for each patient depending upon date when treatment was started. However, each patient was followed up for the same period of time, which is 2 years. The data indicate that (n = 40, 75.5%) patients of the total study population had a PSA of less than 10 ng/mL, (n = 1, 1.9%) patient had PSA in the range of 10−20 ng/mL and (n = 12, 22.6%) had PSA greater than 20 ng/mL (Table 2).

Table 1
Study population characteristics.

Characteristic		Frequency	Percentage (%)
Age at diagnosis (years)	45−50	1	1.9
	51−55	2	3.8
	56−60	9	17.0
	61−65	8	15.1
	66−70	14	26.4
	70+	19	35.8
Pretreatment 'T' stage	T_2b	8	15.1
	T_2c	6	11.3
	T_3a	4	7.5
	T_3b	11	20.8
	T_4	24	45.3
PSA levels at diagnosis (ng/mL)	<10	4	7.5
	10−20	13	24.5
	20−50	36	67.9
Gleason score at diagnosis	≤6	3	5.7
	7	15	28.3
	8−10	35	66.0
NCCN risk category	Low risk	2	3.8
	Intermediate risk	5	9.4
	High risk	46	86.8

Table 2
Post-RT PSA levels.

	PSA range (ng/mL)					
	<10		10−20		>20	
	Patient number	Percentage	Patient number	Percentage	Patient number	Percentage
At first follow-up visit	25	47.2	5	9.4	23	41.1
At last follow-up visit	40	75.5	1	1.88	12	22.6

3.3. Frequency of biochemical failure

A patient was labeled as having "biochemical failure" following definitive RT if:

1. An increase in serum PSA levels was detected on three consecutive readings.
2. An increase in serum PSA levels of more than or equal to 2 ng/mL above nadir value was seen on any single reading.

Patients were observed for biochemical failure by comparing their serum PSA levels on each 3 monthly visit up to completion of 2 years of follow-up. Out of 53 patients included in the study, (n = 18, 34%) developed biochemical failure within a 2 year follow-up period, while (n = 35, 66%) remained free of biochemical disease progression till the end of the 2-year follow-up (Table 3).

3.4. Frequency of biochemical failure and PSA value at 3 months post RT

While correlating PSA level after 3 months following completion of radiotherapy to the incidence of biochemical failure over a 2 years follow-up period, it was seen that in the group of patients who had post-radiation PSA of <20 ng/mL, the average biochemical relapse rate was 6 out of 30 e.g., 20%, while in the group with post-radiation PSA ≥20 ng/mL, 12 out of 23 patients developed biochemical recurrence; e.g., the rate of biochemical failure was 52.2%, over a 2-year follow-up (Fig. 1). The relative risk of biochemical recurrence for the two groups of patients, e.g., those with PSA levels ≥20 ng/mL and those with PSA levels <20 ng/mL, was calculated and found to be 1.56 (95% CI = 0.73–3.35).

Table 3
Frequency of biochemical failure.

Consecutive PSA levels monitoring outcome	Frequency	Percentage (%)
Stable PSA or decrease in PSA up till last follow-up	32	60.38
Increase in PSA over time but not fulfilling ASTRO criteria up till last follow-up	3	5.66
Increase in PSA over time fulfilling ASTRO criteria to label biochemical failure	18	33.96

3.5. Frequency of biochemical failure and initial T stage of tumor

T-Stage of the disease was statistically analyzed and co-related with biochemical disease-free survival. The data indicate that as the disease becomes locally advanced, the frequency of cases recorded in biochemical relapse also increases and vice versa, e.g., (n = 11, 45.8%) patients bearing stage T4 tumors were found to have developed biochemical relapse compared to (n = 1, 12.5%) of stage T2b, (n = 2, 33.3%) of stage T2c, (n = 1, 25%) of stage T3a and (n = 3, 27.3%) of stage T3b, respectively (Fig. 2). The patients in the sample were divided into two groups: one with organ-confined disease (up to T2) and the second with locally advanced disease breaching the prostate capsule (T3 and T4). The relative risk of biochemical recurrence between the two groups was calculated and found to be 1.79 (95% CI = 0.61–5.28).

3.6. Acute gastrointestinal side effects distribution

Side effects were monitored using the RTOG-Acute Radiation Toxicity Schema. Grade 1 toxicity was observed in (n = 26, 49.1%), Grade 2 in (n = 24, 45.3%) and Grade 3 in (n = 3, 5.7%) of the total patient population (n = 53). Data are shown in Table 4.

3.7. Late gastrointestinal toxicity distribution

In our study, the population was followed for late gastrointestinal toxicity after completion of EBRT was monitored. The data indicate that Grade 0 toxicity was observed in (n = 16, 30.2%), Grade 1 in (n = 28, 52.8%), Grade 2 in (n = 7, 13.2%) and Grade 3 in (n = 2, 3.8%) of the total patient population (n = 53). Data are shown in Table 4.

3.8. Acute genitourinary toxicity distribution

Similarly, acute genitourinary radiation toxicity was measured on the basis of the RTOG-Acute Radiation Toxicity

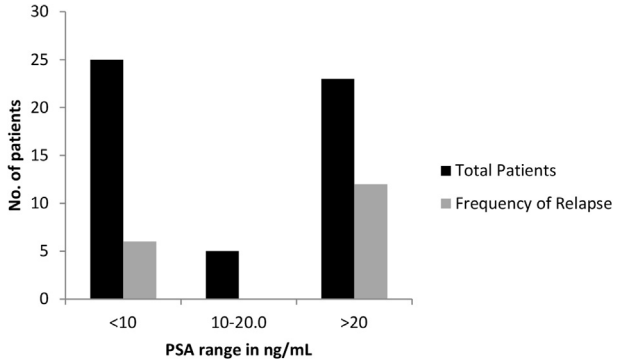

Fig. 1. Association of post RT PSA at 3 months with biochemical relapse.

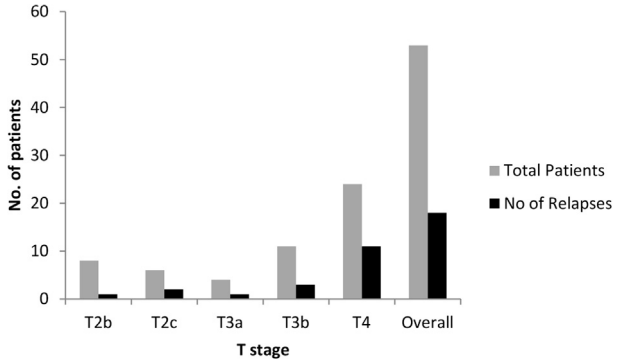

Fig. 2. Association of T-stage with biochemical relapses.

Table 4
Acute and late toxicity: frequency and percent distribution of the study population after receiving EBRT.

Grade	Acute gastrointestinal toxicity distribution N (%)	Late gastrointestinal toxicity distribution N (%)	Acute genitourinary toxicity distribution N (%)	Late genitourinary toxicity distribution N (%)	Acute skin toxicity distribution N (%)	Late skin toxicity distribution N (%)
Grade 0	−	16 (30.2)	2 (3.8)	32 (60.4)	5 (9.4)	11 (20.8)
Grade 1	26 (49.1)	28 (52.8)	28 (52.8)	19 (35.8)	35 (66.0)	34 (64.2)
Grade 2	24 (45.3)	7 (13.2)	21 (39.6)	1 (1.9)	12 (22.6)	8 (15.1)
Grade 3	3 (5.7)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)	−

Schema. Highest incidence of toxicity was observed in Grade 1 (n = 28, 52.8%), then Grade 2 (n = 21, 39.6%), followed by Grade 0 and Grade 3 with patient populations (n = 2, 3.8%), respectively, out of the total patient population (n = 53). Data are shown in Table 4.

3.9. Late genitourinary toxicity distribution

Late genitourinary radiation toxicity side effects were also observed using the RTOG-Late Radiation Toxicity Schema. The data indicate that Grade 0 toxicity was observed in (n = 32, 60.4%), Grade 1 in (n = 19, 35.8%), Grade 2 in (n = 1, 1.9%) and Grade 3 again in (n = 1, 1.9%), respectively, of the total patient population (n = 53). Data are shown in Table 4.

3.10. Acute skin toxicity distribution

Acute skin toxicity was observed in the selected patient population by using the RTOG-Acute Radiation Toxicity Schema, with Grade 1 toxicity found in (n = 35, 66.0%), Grade 2 toxicity in (n = 12, 22.6%)and Grade 0 toxicity in (n = 5, 9.4%), whereas Grade 3 toxicity was found in (n = 1, 1.9%) of the total patient population (n = 53). Data are shown in Table 4.

3.11. Late skin toxicity distribution

Late skin toxicity was also measured using the RTOG-Late Radiation Toxicity Schema. The data indicate that Grade 0 toxicity was observed in (n = 11, 20.8%), Grade 1 toxicity in (n = 34, 64.2%), and Grade 2 toxicity was found in (n = 8, 15.1%), respectively, of the total patient population (n = 53). Data are shown in Table 4.

4. Discussion

In men with localized prostate cancer, escalated radiotherapy can deliver higher doses of radiation than does standard-dose conventional radical external-beam radiotherapy, and can improve long-term efficacy, potentially at the cost of increased toxicity. In our study, out of 53 patients included, 35 (66%) were biochemically event-free at the end of the defined event-free point that was the PSA level monitored at the completion of the definitive escalated-dose conformal radiotherapy treatment and subsequent PSA levels over a 2-year follow-up period. Eighteen patients (34%) of the total population developed biochemical failure within a 2-year follow-up period. When these data were compared with the Medical Research Council (MRC) RT01 randomized controlled trial (UK) − (1998−2002) to either a standard dose of 64 Gy or an escalated dose of 74 Gy, a 60% versus 71% (p = 0.1) biochemical-progression-free survival (bPFS), respectively, was noted in 5 years, which is comparable to our study population which showed 66% bPFS.[12] It is widely agreed that PSA at time of diagnosis has predictive value with regards to treatment outcome in prostate cancer patients. Our study results demonstrate that first PSA following completion of EBRT at a 3-month follow-up may also be used to predict disease outcome in terms of likelihood of biochemical failure.

Findings from several randomized phase 3 trials (GETUG 06, DUTCH Multicenter Trial, M.D. Anderson Dose Escalation Randomized Control Trial, MRC RT01) and the long-term results of single-institution studies demonstrate a significant improvement in treatment outcome with higher radiation doses in patients with clinically localized disease.[13−15] These studies have generally demonstrated a 10%−20% improvement in 5- to 10-year PSA survival outcome when higher doses of 78 Gy−80 Gy are applied, compared with dose levels of 70 Gy, and such benefits have been observed for low-, intermediate-, and high-risk cohorts. Although overall survival benefits have not been demonstrated with dose escalation, improvement in distant metastasis-free survival is emerging with longer follow-up, suggesting that survival benefits will be seen as these studies mature. In one report, a significant reduction in mortality due to prostate cancer was observed at 10 years for intermediate- and high-risk patients treated with doses of 78 Gy, compared with those treated with 70 Gy.[16]

In this study, side effects were monitored using the RTOG-Acute Radiation Toxicity Schema. Out of 53 total patients studied, grade 1 acute gastrointestinal toxicity was observed in (n = 26, 49.1%) and grade 2 toxicity in (n = 24, 45.3%), whereas grade 3 toxicity was seen only in (n = 3, 5.7%) patients. Similarly, grade 0 late gastrointestinal toxicity was observed in (n = 16, 30.2%), grade 1 toxicity in (n = 28, 52.8%), and grade 2 toxicity in (n = 7, 13.2%), whereas grade 3 toxicity was found only in (n = 2, 3.8%) out of total 53 patients. Our results were compared with results from the MRC RT01 trial (Dearnaley DP, *Radiother Oncol.* 2007 Mar 26) grade 2 standard vs. escalated: bladder 38% vs. 39%, bowel 30% vs. 33%, respectively.

Acute genitourinary radiation toxicity was also measured on the basis of the RTOG-Acute Radiation Toxicity Schema. The highest incidence observed was of grade 1 toxicity in (n = 28, 52.8%) of the total population, followed by grade 2 toxicity, with frequency of (n = 21, 39.6%). Grade 0 and grade 3 toxicities were found in only (n = 2, 3.8%) patients each. Late genitourinary side effects were also observed using the RTOG-late radiation toxicity schema. Grade 0 toxicity was observed in (n = 32, 60.4%) and grade 1 in (n = 19, 35.8%), whereas grade 2 and grade 3 toxicities were observed in (n = 1, 1.9%) patients each, among the total population, respectively.

Skin toxicities were also observed in the selected population using the RTOG-acute radiation toxicity schema. The acute skin toxicity distribution pattern showed grade 1 toxicity in (n = 35, 66.0%), grade 2 toxicity in (n = 12, 22.6%) and grade 0 toxicity in (n = 5, 9.4%), whereas grade 3 toxicity was seen in only (n = 1, 1.9%) of the total 53 patients. Similarly, late skin toxicity distribution was also measured using the RTOG-Late Toxicity Criteria. Accordingly, the grade 1 toxicity was observed having the highest frequency in (n = 34, 64.2%) patients, followed by grade 0 in (n = 11, 20.8%) and grade 2 in (n = 8, 15.1%) of the total patient population.

Most complications attributed to radiation therapy are observed within the first 3−4 years after treatment, and the likelihood of developing complications after 5 years is low. The risks of developing complications increase with radiation dose exceeding 72 Gy. Several factors have been found to be associated with increased bowel or rectal toxicity after EBRT.[17] These include the volume of the rectum exposed to higher doses of radiation, increasing age of the patient, concomitant use of androgen-deprivation therapy, and the presence of diabetes and inflammatory bowel disease. Even patients with a prior history of inflammatory bowel disease currently in remission may have significant increase of rectal toxicity, and alternative treatments should be considered for these patients. Michalskietal[18,19] reported the toxicity outcome of various risk groups enrolled in RTOG 9406, a phase I dose-escalation study. The dose levels evaluated in this report included patients treated to the initial two dose levels of the study, 68.4 and 73.8 Gy. The median follow-up times in these subgroups ranged from 2.2 to 3.4 years. The acute grade 2 bowel/rectal toxicity rates ranged from 16% to 25%. The crude incidence of late bowel/rectal toxicities ranged from 2% to 8%. With a median follow-up of 2.5 years, the crude late grade 2 and 3 gastrointestinal toxicities for those patients treated to 78 Gy (2-Gy fractions) were 22% and 2%, respectively.

Storey et al.[19] reported late rectal toxicity among patients treated in the phase III trial from the M.D. Anderson Hospital. The 5-year actuarial risks of late grade 2 rectal toxicity for the 70- and 78-Gy dose level arms were 14% and 21%, respectively. In that report, the dose-volume histogram analyses of the patients treated to 78 Gy were analyzed to ascertain whether there were any predictive patterns for late rectal toxicity. These investigators reported a significant correlation for the percentage of the rectum treated to 70 Gy or higher and the likelihood of late rectal toxicity. Patients with >25% of the rectal wall treated to 70 Gy or higher had a 37% risk of grade 2 rectal toxicity, compared with 13% among patients who had <25% of the rectal wall exposed to these doses (p = 0.05). In an update of that experience, Kuban et al.[16] noted that the volume of rectum exposed to higher radiation dose was associated with the risk of rectal toxicity after external-beam radiotherapy. The incidence of grade 2 rectal toxicity was 46% when >26% of the rectal volume was exposed to >70 Gy of the prescription dose. In contrast, among patients who had lower volume of rectum exposed to these dose levels, the incidence of grade 2 toxicity was significantly lower (14%).

In conclusion, our study included 53 patients who fulfilled the inclusion criteria for receiving higher doses of 74 Gy. Acute and late toxicity of gastrointestinal and genitourinary tract determined by using RTOG-Acute and Late Radiation Toxicity Schema Grading and DFS in terms of biochemical relapse was observed and compared with international studies. Results were comparable to already published data regarding dose escalation using 3D and beneficial as compared to conventional radiation therapy delivered by 2D.

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