TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Results and Adverse Effect Evaluations in Localized Prostate Cancer Patients Undergoing Intensity Modulated Radiotherapy with Tomotherapy

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Abstract

Background: The aim of this study is assess the dosimetric results and early and late adverse effects of radiotherapy with tomotherapy in localized prostate cancer patients.

Material and Methods: Treatment results and early and late adverse effects in 60 patients who had undergone curative radiotherapy due to prostate cancer and who had been followed up for at least 6 months in the post-treatment process were assessed retrospectively. 28 of the patients were in the low-intermediate risk group, whereas 32 were in the high-risk group. 74 Gy radiotherapy was delivered to the prostate with simultaneous integrated boost strategy, 60 Gy to seminal vesicles, and 52 Gy to pelvic lymph nodes of the cases. Patients with at least 6 months of post-treatment follow-up were assessed in terms of early and late adverse effects.

Results: Twenty patients had grade 1, and two patients had grade 2 acute genitourinary toxicity, whereas 15 patients had grade 1, and 4 patients had grade 2 acute gastrointestinal toxicity. Twelve patients had grade 1, and 3 patients had grade 2 late genitourinary toxicity, 6 patients had grade 1, and two other patients had grade 2, and grade 3 late gastrointestinal toxicity. Biochemical recurrence developed in four patients. One of the patients with recurrence died in the 14th month of recurrence due to organ metastasis.

Conclusions: Image-guided dose-escalated radiotherapy with IMRT technique is a reliable method in prostate cancer treatment. Increased toxicity was not observed in the cases with lymph node irradiation despite the increased radiotherapy field.

Turk J Int Med 2021;3(2):73-79
DOI: 10.46310/tjim.871471

Keywords: *Prostate cancer, Intensity modulated radiotherapy, Acute-late toxicity.*

Received: February 01, 2021; Accepted: February 28, 2021; Published Online: April 29, 2021

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Introduction

Prostate cancer is the second most frequent malignancy in males following lung cancer.[1] Radiotherapy (RT) is one of the main treatment methods of localized prostate cancer and developments in RT techniques in recent years have enabled safe application of higher doses of RT.[2] RT can be used alone for early-stage prostate cancer, whereas it is used with hormonotherapy with locally advanced tumors.[3,4]

The main purpose in RT is to reduce the radiation dose to normal tissues while increasing the dose to tumor tissue.[5] Dose escalation in prostate RT can lead to interruption of RT by increasing normal tissue toxicity and especially causing rectal and urinary adverse effects.[6] Long lasting studies on localized prostate cancer have demonstrated that there is an increasing dose-response relationship in RT.[7,8] In many studies it has been shown that better biochemical control is achieved with doses between 74-80 Gy compared to conventional doses under 70 Gy.[9-11] Toxicity, which is the most important restraint of high dose RT delivery, is controlled with developments in RT techniques. It has become possible to significantly reduce the irradiated normal tissue volume with engagement of intensity-modulated radiation therapy (IMRT) following three-dimensional conformal radiotherapy (3D-CRT).[12-14] In some studies comparing 3D-CRT and IMRT it has been observed that acute gastrointestinal (GI) and genitourinary (GU) toxicity are significantly decreased with the IMRT technique with reduction of high dose receiving volumes of bladder and rectum.[15-17]

Some recent studies have also shown that dose fractionation schemes used in RT significantly affect prostate specific antigen (PSA) control.[8,18] There are randomized trials showing that radiation therapy with increased fraction (fx) dose and reduced fx quantity (>75 Gy biologically equivalent dose) improves prostate cancer control and it has become the standard treatment for prostate cancer.[19-21] Therefore, currently high dose IMRT is the recommended standard treatment in early and locally advanced prostate cancer. It is of great importance to predict organ movements in the treatment field and to pay attention to bladder and bowel filling rates and regulation of eating habits during RT in order to increase IMRT success and reduce adverse effects.

In this study we evaluated the efficacy and early and late toxicity outcomes of localized prostate cancer patients who had undergone IMRT with a tomotherapy device using image-guided simultaneous integrated boost.

Material and Methods

60 patients who had undergone curative RT due to T1-3N0M0 stage prostate cancer diagnosis between the years 2012-2019 and who had been followed-up for at least 6 months in the post-treatment period were included in this study. All of the patients were histologically diagnosed with prostate cancer. Patients were classified in three risk groups before treatment according to D'Amico risk classification by assessing PSA value, Gleason score and T stage; low risk (T1-T2a, Gleason ≤6, PSA ≤10 ng/mL), intermediate risk (patients who are not in low or high-risk groups) and high risk (≥T2c or Gleason >7 or PSA >20 ng/mL) groups. Patients in intermediate and high-risk groups were assigned androgen deprivation therapy (ADT) comprised of LHRH and anti-androgen, 2-3 months prior to RT. Anti-androgen therapy was interrupted at the end of RT. ADT was applied for 6 months in the intermediate risk group and for 2-3 years in the high-risk group. ADT was not delivered to patients in the low-risk group.

All cases were recommended a diet therapy to avoid flatulent foods and prevent constipation and increase water consumption and physical activity. Patients' planning tomographies were scanned prior to the RT in a computed tomography (CT) simulator in supine position by fixing the patient with knee and feet supports, with a full bladder and empty rectum, covering the whole pelvis with 3 mm intervals. CT data were transferred to the treatment planning system and then clinical target volume (CTV), planned target volume (PTV) and adjacent organs at risk were identified. Three separate target volumes were created. CTV consisted of prostate and proximal seminal vesicles in the low-risk group, prostate and all seminal vesicles in the intermediate risk group and prostate and all seminal vesicles and lymph nodes in the high-risk group. Bladder, rectum and femur heads were determined as organs at risk.

Small bowel was added to organs at risk in the high-risk group to be irradiated with pelvic lymph nodes. During PTV establishment, 7 mm margins were given to CTV for each direction, whereas a 5 mm margin was given posterior. During pelvic lymph node PTV establishment, 5 mm margins were given to each direction to external, internal iliac and obturator lymph nodes referring to the iliac vessels. It was assured that the patients underwent the treatment with the same bladder and rectum volume every day.

All patients underwent IMRT with a Tomotherapy Hi art device with simultaneous integrated boost technique. Three separate target volumes were established in total. The prostate was irradiated with 74 Gy (2.24 Gy/fx), prostate + seminal vesicles were irradiated with 60 Gy (1.81 Gy/fx) and lymph nodes were irradiated with 52 Gy (1.57 Gy/fx) doses. In the planning, it was provided that 95% of PTV delivered 100% of the target dose. The whole treatment was completed at 33 fx.

Patients were called for weekly outpatient clinic control during the treatment. In the post-treatment period, the patients were evaluated with complete blood count, total PSA, biochemistry and yearly pelvic tomography in the 1st month, every 3 months within the following first 2 years, and then every 6 months. GI and GU adverse effects were graded according to Radiation Therapy Oncology Group (RTOG) toxicity scoring.

Statistical Analysis

Statistical analysis was performed with SPSS 20.0 (SPSS Inc. Chicago, IL, USA) software. Descriptive statistics of all variables in the study were calculated. Normality of the data distribution was evaluated with Shapiro-wilk test, and its homogeneity was assessed with Levene's test. Continuous variables are expressed as mean±standard deviation. For inter-group comparisons of numerical data, Kruskal-Wallis test was used for non-parametric data and student-t test was used for parametric data. Paired comparisons in case of significancy were done with Mann-Whitney U test. Categorical variables were compared with chi-square test, Pearson chi-square and Fisher's exact chi-square test. Survival analysis was performed with Kaplan-Meier survival analysis. $P<0.05$ was considered significant.

Results

Mean age of all patients was calculated as 69.19 (49-80) years. Pre-treatments mean PSA level was 31.19 (4.2-201) ng/mL and Gleason score were 7 (4-10). Clinical features of the cases by risk groups were shown in Table 1.

Mean follow-up time of the cases was 36.36 (6-96) months. It had been observed that in the dose volume histogram, at least 95% of the PTV volume of all cases received 100% of the target dose, whereas in the adjacent organ doses, an excess of less than 15% was detected in 3 patients

Table 1. Patient characteristics by risk groups

	Low-Intermediate risk	High risk
Age (mean-years)	68.07 (52-80)	70.28 (49-79)
Clinical T1-T2b (n)	24	4
T2c-T3	0	32
Mean Gleason score	5.89 (4-7)	7.66 (5-10)
Mean PSA (ng/mL)	11	48.86
Androgen suppression treatment (n)	23 (6 months)	32 (2-3 years)
Disease free survival (months)	35.66	37.48
Overall survival (months)	39.64	43.55

in the low-intermediate risk group and in 7 patients in the high-risk group in V40 criteria for the bladder. Mean V40 value for the bladder was 41.3 (17-57) and mean V65 value was 13.6 (3-21). V40 value for the rectum exceeded less than 20% in 4 patients in the low-intermediate risk group and 7 patients in the high-risk group. Mean V40 and V65 values for the rectum were respectively 44.6 (33-59.6) and 12.4 (4-27). Femur head mean doses were 23.08 Gy for the right femur head and 23.24 Gy for the left femur head.

In general, the treatment was well tolerated. As acute adverse effects, 5 patients in the low-intermediate risk group (17.8%) experienced grade 1 and 1 patient (3.5%) grade 2 GI toxicity; 10 patients in the high-risk group (31.2%) experienced grade 1 and 3 patients (9.3%) grade 2 GI toxicity. The most frequent GI toxicity was proctitis. An increase in preexisting hemorrhoidal complaints was observed in 2 patients. As acute GU adverse effect, grade 1 toxicity was observed in 8 patients in the low-intermediate risk group (28.5%), grade 1 toxicity in 12 patients in the high-risk group (37.5%) and grade 2 toxicity in 2 patients (6.2%) in the same group. The most frequent GU toxicities were pollakiuria, nocturia and dysuria. Symptoms regressed by using alpha blockers, anti-inflammatory medications and spasmolytic agents in the treatment. Grade 3 and higher acute toxicity were not detected. Statistically no significant difference was detected in terms of toxicity in any of the groups. Hematologic toxicity was not observed in any patient. Acute adverse effect rates by risk groups are shown in Table 2.

In late adverse effect evaluation, grade 1 GI toxicity was observed in 2 patients (7.1%) and grade 3 GI toxicity was observed in 1 patient (3.5%) in the low-intermediate risk group, whereas in the high-risk group, grade 1 GI toxicity developed in 4 patients (12.5%) and grade 2 GI toxicity was seen in 1 patient (3.1%). Grade 3 toxicity was not observed. As GU adverse effects, grade 1 toxicity developed in 5 patients (17.8%) and grade 2 toxicity was observed in 3 patients (10.7%) in the low-intermediate risk group, whereas in the high-risk group 7 patients (21.8%) experienced grade 1 toxicity, however grade 2 and greater toxicity was not observed in this group. In the whole group, grade 1 toxicity was observed in 12 patients (20%) and grade 2 in 3 patients (5%). Late adverse effects by risk groups are shown in Table 3.

During the follow-up period of the patients, PSA recurrence developed in a total of 4 patients by the 31st month on average. All patients with recurrence were in the high-risk group. Follow-up of one patient with recurrence continued at an external center. This patient was declared excitus in the post-recurrence 14th month due to organ

Table 2. Acute Adverse Effect Rates by Risk Groups

	Acute Gastrointestinal			Acute Genitourinary		
Grade	1	2	3	1	2	3
Low-Intermediate risk	5 (17.8%)	1 (3.5%)	0	8 (28.5%)	0	0
High risk	10 (31.2%)	3 (9.3%)	0	12 (37.5%)	2 (6.2%)	0
Total	15 (25%)	4 (6.6%)	0	20 (33.3%)	2 (3.3%)	0

Table 3. Late Adverse Effect Rates by Risk Groups

	Late Gastrointestinal			Late Genitourinary		
Grade	1	2	3	1	2	3
Low-Intermediate risk	2 (7.1%)	0	1 (3.5%)	5 (17.8%)	3 (10.7%)	0
High risk	4 (12.5%)	1 (3.1%)	0	7 (21.8%)	0	0
Total	6 (10%)	1 (1.6%)	1 (1.6%)	12 (20%)	3 (5%)	0

metastasis. There was no organ metastasis in the other 3 patients during recurrence and androgen deprivation treatment was started. One of these patients received chemotherapy for hormone refractory prostate cancer during the follow-ups. Follow-up of the other two patients still continues with ADT.

Discussion

Several studies have demonstrated that treatment applied in prostate cancer RT with IMRT is superior to 3-dimensional conformal RT in terms of local, biochemical control and adverse effect aspects, and high dose IMRT application in prostate cancer RT has become a standard treatment method.[22-24] Therefore, accurate evaluation of treatment-related toxicities is essential for clinicians.[25]

Zelefsky et al.[26] have reported acute grade 2 and grade 3 GU toxicity rates of 28% and 0.1%, and acute grade 2 GI toxicity rate of 4.5% in 772 prostate cancer cases who received high doses with IMRT (81 Gy-86.4 Gy). Grade 2 and greater rectal toxicity have not been reported in this study. In the randomized trial performed by Pollack et al.[27] comparing IMRT applying 76 Gy and hypo-fractionated 70.2 Gy, in multivariate analysis the combined rectal DVH parameter of V65 Gy/V50 Gy for GI toxicity and bladder volume for GU toxicity was significant.

In the study of Ozdemir et al.[28] consisting of 101 patients in which they delivered a median of 76 Gy with IMRT/VMAT, grade 1 GU adverse effects developed in fifty-seven (56.4%) patients and grade 2 GU adverse effects developed in three (3%) patients. In this study, grade 1 GI adverse effects were observed in 15 (15%) patients. Grade 2 and greater GI early adverse effects were not reported in any of the cases.[28]

In this study, we evaluated the results of localized prostate cancer patients who underwent image guided IMRT with tomotherapy. Our fraction dose was higher than conventional fractionation (2.24 Gy/fx) and our total length of treatment period was 6.5 weeks. Acute grade 1 and grade 2 GU toxicity was 33.3% and 3.3%, respectively. Grade 3 and greater acute toxicity were not detected.

According to the randomized dose escalation trial (68 Gy-78 Gy) of Heemsbergen et al.[29] conducted in the Netherlands, 28% late rectal toxicity was reported. Massive rectal bleeding occurred in 6% of these patients. In the study of Al-Mamgani[30], grade 2 and greater early GI toxicity after 78 Gy in prostate cancer cases was reported as 20%. In this study, conformal RT and IMRT therapies have been compared and bladder dose reduction has been provided by IMRT. However, similar adverse effect rates have been reported in both groups. This situation was associated with similar urethra doses with both techniques.[30]

In some studies, it has been demonstrated that bladder, rectum and small bowel doses can be significantly reduced with IMRT in cases with pelvic lymph node irradiation.[31,32] In a study evaluating 230 high risk prostate cancer patients, significantly less grade 2 GI and grade 3 GU adverse effects were observed in the group treated with IMRT with respect to four-field delivery. In multivariate analysis, bladder fullness was found as the dominant factor determining acute GI adverse effect.[34]

In another randomized trial, hypo-fractionated dose-escalated intensity-modulated radiation therapy (HIMRT) and conventional fractionated intensity-modulated radiotherapy (CIMRT) were compared. Patients were randomly assigned to 75.6 Gy with 1.8 Gy/fx delivered over 8.4 weeks (CIMRT) or 72 Gy with 2.4 Gy/fx fractions delivered over 6 weeks (HIMRT). In this trial, 10.7% recurrence was observed in HIMRT and 15.4% recurrence was observed in CIMRT. In terms of toxicity, GU toxicity rates were similar with both techniques, whereas there was a non-significant increase in late grade 2 and 3 GI toxicity with HIMRT. A lower rectal toxicity was reported when the rectal volume receiving 65 Gy of HIMRT was ≤15.[34]

In our study, statistically no significant difference was detected in terms of adverse effects between the high risk group irradiated in pelvic lymph nodes and the low-intermediate risk group, which was not irradiated ($p>0.05$). This situation is related to the possibility to reduce normal tissue doses provided by IMRT despite larger field of irradiation in patients assigned to pelvic nodal irradiation. This advantageous

situation in IMRT planning requires a sensitive accuracy of daily fractions. Otherwise, planned target volume doses may decrease or adjacent organ doses may increase.

Conclusion

We observed that image-guided dose-escalated IMRT with tomotherapy is well tolerated in prostate cancer treatment. In terms of early and late adverse effects, our results are within acceptable limits compatible with the literature. Moreover, an increase in adverse effects has not been observed in pelvic lymph node irradiation patients despite enlargement of the RT field. Therefore, dose-escalated RT can be safely applied in localized prostate cancer treatment. Long-term studies are needed in terms of late adverse effects.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: GAO, MO; Study Design: GAO, MO; Supervision: GAO, MO; Funding: GAO; Materials: GAO; Data Collection and/or Processing: GAO, MO; Statistical Analysis and/or Data Interpretation: GAO, MO; Literature Review: GAO, MO; Manuscript Preparation: GAO, MO; and Critical Review: GAO, MO.

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