



The Effects of Radiotherapy on the Quality of Life in Localized Prostate Cancer Patients

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OBJECTIVE

The present study aims to investigate the radiation-related toxicity and its effects on the quality of life in patients with prostate cancer who received definitive or adjuvant radiotherapy (RT).

METHODS

Eighty-seven localized prostate cancer patients who underwent RT between January 2011 and June 2016 were enrolled. Each patient filled the EORTC QLQC30 and QLQ-PR25 at four different times (starting and ending at RT, one and six months after RT). EORTC QLQ-C30 questionnaire consists of global health status, five functional (physical, role, cognitive, emotional, social) and nine symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). EORTC QLQ-PR25 consists of two functional (sexual activity and sexual functioning) and four symptom scales (urinary, bowel, hormonal treatment-related, incontinence aid).

RESULTS

According to the EORTC QLQ-C30 questionnaire, global health status score ($p=0.007$), emotional score ($p=0.016$), fatigue ($p=0.004$) and diarrhea score ($p=0.003$); according to EORTC QLQPR25 questionnaire, urinary score ($p=0.024$) were significantly poorer at the end of RT. When patients' quality of life questionnaires were compared concerning treatment type (definitive vs. adjuvant RT), RT technique (3D CRT vs. IMRT) and RT field (prostate/prostate+seminal vesicle vs. prostate+seminal vesicle+pelvic lymph node); EORTC QLQ C-30 and EORTC QLQ PR-25 functional and symptom scales were not different between groups.

CONCLUSION

The RT approach in prostate cancer produced temporary impairment in some scores of QLQ, but all these scores showed improvement from the first month after RT.

Keywords: Prostate cancer; quality of life; radiotherapy.

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Introduction

Prostate cancer is a quite common type of cancer in men and 1.6 million new cases are reported each year. [1] Prostate cancer is one of the tumors that can be

cured, especially when diagnosed at an early stage. Different treatments may be preferred depending on the cancer growth rate, spreading status, overall health status of the patient and the efficacy of the treatment to be performed, as well as possible side effects in the

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treatment of prostate cancer. While active monitoring is also an option of treatment in patients with low-risk prostate cancer, in moderate or high-risk groups, surgery or radiotherapy (RT) with or without hormone therapy constitutes radical treatment. The superiority of surgery or radiotherapy for survival has not been shown in local treatment.[2-4]

There are many studies showing that increased radiation doses significantly improved the rates of progression-free survival.[5-7] However, higher radiation doses increase acute and late adverse effects. Recently, the use of Intensity Modulated Radiotherapy (IMRT) somewhat reduced adverse effects compared to conventional radiotherapy.[8,9] However, organs at risk, such as bladder, rectum which are in the irradiation area, cannot be entirely protected from radiation. Thus, the quality of life of patients may alter due to the occurrence of radiation-related adverse effects.[9,10]

After the diagnosis, patients should deal with many problems, including the disease itself and the adverse effects related to the treatments. For diseases with alternative treatment options, the effects of therapies on quality of life (QoL) are important in choosing the treatment type. For this aim, the European Organization for Research and Treatment of Cancer (EORTC) has developed general and disease-specific QoL questionnaires to be used for cancer patients. EORTC QLQ-C30 is a questionnaire developed by EORTC that generally assesses the health-related QoL for cancer patients.[11] However, this questionnaire does not include issues specific to prostate cancer. Therefore, to specifically evaluate QoL of prostate cancer patients, EORTC has evolved a complementary module, QLQ-PR25.[12] Both questionnaires are reliable and commonly used in research all over the world.[13]

The present study aims to investigate the impacts of RT-related toxicity and its effects on the quality of life, using EORTC QLQ-C30 and QLQ-PR25 questionnaires in patients who received definitive or adjuvant RT for prostate cancer.

Materials and Methods

The Departmental Ethics Committee of Cumhuriyet University's Faculty of Medicine on non-invasive clinical research approved this trial in accordance with the Declaration of Helsinki with the decision no 2017-11/21, on 8 November 2017. Eighty-seven localized prostate cancer patients who underwent RT in our department between January 2011 and June 2016 were enrolled. A consent form was obtained from all pa-

tients who participated in this study. Prostate cancer patients who received curative or adjuvant RT were considered eligible.

Radiotherapy-induced side effects were assessed according to the Radiotherapy Oncology Group (RTOG) criteria.[14]

Quality of Life Scale

Each patient filled the EORTC QLQ-C30 and QLQ-PR25 at four different times: the start of RT (T1); the end of RT (T2); one month after completion of RT (T3); six months after completion of RT (T4).

Quality of life was judged using the EORTC QLQ-C30 version 3.0, a 30-item questionnaire. EORTC QLQ-C30 questionnaire consists of global health status, five functional (physical, role, cognitive, emotional, social) and nine symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties).[11] Cancer-specific QoL was evaluated utilising the EORTC QLQ-PR25 version 3.0, a 25-item questionnaire. EORTC QLQ-PR25 consists of two functional (sexual activity and sexual functioning) and four symptom scales (urinary, bowel, hormonal treatment-related, incontinence aid).[13] Patients' responses were assessed using the EORTC QLQ-C30 and QLQ-PR25 scoring manual. Scores as the symptom constituents were linearly turned into a scale of 0 to 100. A high score as a functional scale indicated a comparatively high level of functioning, while a high score as a symptom scale demonstrated severe symptoms or financial influences.[15]

Radiotherapy was conducted utilising a linear accelerator device (Varian Clinac DHX, Varian Medical Systems, Inc., Palo Alto, CA, USA) and TomoTherapy (Accuray). Three-dimensional conformal RT planning was carried out using ECLIPS (Varian Medical Systems, Inc., Palo Alto, CA, USA). IMRT planning was done using Tomotherapy Planning Workstation (TomoTherapy Inc., Madison, WI). Of the 87 patients, sixty-two patients (71%) were treated on the linear accelerator device, and twenty-five patients (29%) were treated on the TomoTherapy. Doses of RT ranged from 66 to 80 Gy.

Statistical Analysis

SPSS version 23 was employed in the calculation of statistical data. Medians and frequencies were computed for patient demographics. Questionnaire scores were matched across the four times using the repeated-measures analysis of variance (ANOVA) and Friedman test

(when distribution was not normal). A $p \leq 0.05$ was regarded as statistically significant.

Results

Eighty-seven patients who underwent definitive and adjuvant RT were included in this study. Their median age was 67 years (range 49-78 years). There were comorbid diseases in 55 of the patients (63%), 31 of these patients (56%) had hypertension, 26 (47%) had heart disease, and 18 (33%) had diabetes mellitus. Secondary primary malignancy was also present in four (5%) patients.

When the risk of disease was examined, 12 patients (14%) had low-risk disease, 18 patients (21%) had a moderate-risk disease and 57 patients (65%) had high-risk disease.

Sixty-three patients (72%) were treated with definitive RT and 24 patients (28%) received adjuvant RT. Sixty of the patients (69%) also received hormone therapy treatment (GnRH analogue as leuprolide acetate 11.25 mg, and goserelin acetate 10.8 mg was used for three months in moderate-risk patients, and two years

in high-risk patients). There was a surgical margin positivity in 18 patients (75%) who received adjuvant radiotherapy. In addition, 17 patients (71%) with adjuvant RT had extracapsular invasion and 11 patients (46%) had seminal vesicle invasion. Median radiation dose was 66 Gy (range 66-72 Gy) in patients treated with adjuvant RT, whereas the median radiation dose was 76 Gy (range 66-80 Gy) in patients who underwent definitive RT. Radiotherapy fields were prostate in 12 patients (14%), prostate+seminal vesicle in 57 patients (65%), and prostate+seminal vesicle+pelvic lymph nodes in 18 patients (21%). Patient characteristics and treatment details were given in Table 1.

When radiation-induced acute and late toxicities were examined, grade 3-4 lower gastrointestinal acute toxicity was observed in only one patient (1%), grade 3-4 genitourinary acute toxicity was observed in two patients (2%). Grade 3-4 late adverse effects were not observed. Radiotherapy-induced acute and late toxicities of scored according to RTOG were shown in Table 2. In addition, 56 of the patients (64%) had erectile dys-

Characteristic	No of patients	%
Comorbidity	55	63
Diabetes mellitus	18	21
Hypertension	31	36
Heart disease	26	30
Risk classification		
Low	12	14
Moderate	18	21
High	57	65
Treatment	No of patients	%
Treatment		
Definitive RT	63	72
Adjuvant RT	24	28
Hormonotherapy	60	69
RT dose (median)		
Definitive RT	76 (66-80) Gy	
Adjuvant RT	66 (66-72) Gy	
RT technique		
3D CRT*	62	71
IMRT*	25	29
RT field		
Prostate	12	14
Prostate+seminal vesicle	57	65
Prostate+seminal vesicle+pelvic LN*	18	21

*3D CRT: 3-dimensional radiotherapy, *IMRT: Intensity-modulated radiotherapy, *LN: Lymph nodes

Early toxicities	No of patients	%
Lower GIS* tract		
Grade 0	46	53
Grade 1-2	40	46
Grade 3-4	1	1
Genitourinary tract		
Grade 0	15	17
Grade 1-2	70	81
Grade 3-4	2	2
Hematologic		
WBC* grade 1-2	3	3
Platelet grade 1-2	2	2
Neutrophil grade 1-2	1	1
Hemoglobin grade 1-2	3	4
Hematocrit grade 1-2	2	2
Late toxicities	No of patients	%
Bowel		
Grade 0	80	92
Grade 1-2	7	8
Bladder		
Grade 0	57	65
Grade 1-2	30	35
Erectile dysfunction	56	64
Loss of libido	54	62
Urinary incontinence	21	24

*GIS: Gastrointestinal; *WBC: White Blood Cell

function, 54 of patients (62%) had a loss of libido, and 21 of patients (24%) had urinary incontinence.

Table 3 shows the results of the mean and standard deviation of EORTC QLQ-C30 measurements at the four-time points. EORTC QLQ-C30 questionnaire response ratios were 100 % (n=87) at T1, 100% (n=87) at T2, 72% (n=63) at T3, and 68% (n=59) at T4. According to the EORTC QLQ-C30 questionnaire, the results of global health status score, emotional score in functional scale, fatigue and diarrhea score in symptoms scale were statistically significant.

Table 4 summarizes the EORTC QLQ-PR25 QOL results at the four-time points. EORTC QLQ-PR25

questionnaire response rates were 44% (n=38) at T1, 38% (n=33) at T2, 28% (n=24) at T3, and 16% (n=14) at T4. According to the EORTC QLQ-PR25 questionnaire, the result of the only urinary score in symptoms scale was statistically significant.

Figure 1 shows the graphics of the statistical significance results in the EORTC QLQ-C30 and QLQ-PR25 questionnaires.

When patients' QLQ were compared concerning treatment type (definitive RT vs. adjuvant RT), RT technique (3D conformal radiotherapy vs. IMRT) and RT field (prostate/prostate+seminal vesicle vs. prostate+seminal vesicle+pelvic lymph node); EORTC

Table 3 The EORTC QLQ-C30 QOL results at the four-time points

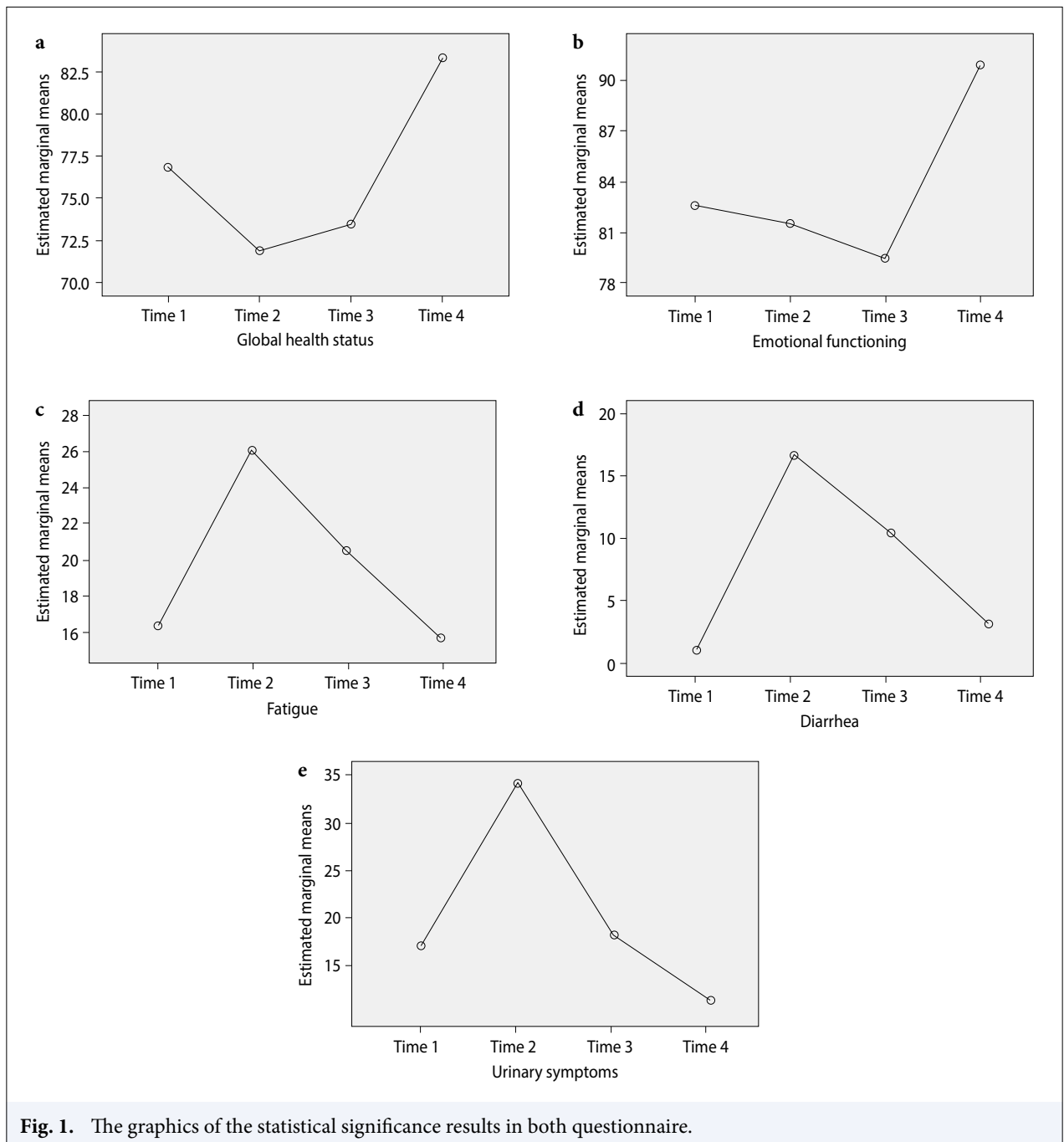
EORTC QLQ-C30 Component	Item No./s	T ₁ (n=87)	T ₂ (n=87)	T ₃ (n=63)	T ₄ (n=59)	p
Global health status	29-30	77±13	72±26	73±25	83±25	0.007
Functional scale						
Physical	1-5	79±18	79±24	80±24	85±27	0.135
Role	6,7	80±24	77±27	79±28	86±29	0.057
Emotional	21-24	83±21	82±20	79±23	91±16	0.016
Cognitive	20,25	83±14	86±17	86±17	85±16	0.082
Social	26,27	85±25	86±17	90±18	88±19	0.833
Symptoms scale						
Fatigue	10,12,18	16±15	26±23	20±21	16±23	0.004
Nausea/vomiting	14,15	2±7	6±17	5±11	2±2	0.226
Pain	9,19	8±9	19±22	13±22	12±25	0.069
Dyspnea	8	11±21	18±29	14±24	14±20	0.438
Insomnia	11	8±17	20±31	21±28	13±26	0.068
Appetite loss	13	6±18	14±22	11±22	8±19	0.142
Constipation	16	7±18	15±24	10±23	4±11	0.153
Diarrhea	17	1±6	17±30	10±23	3±10	0.003
Financial difficulties	28	10±20	13±18	9±19	14±25	0.644

T₁: Start of radiotherapy; T₂: End of radiotherapy; T₃: 1 month after completion of radiotherapy; T₄: 6 months after completion of radiotherapy

Table 4 The EORTC QLQ-PR25 QOL results at the four-time points

EORTC QLQ-PR25 Functional scale	Item No./s	T1 (n=38)	T2 (n=33)	T3 (n=24)	T4 (n=14)	p
Sexual activity	20,21	77±37	93±15	83±29	80±30	0.801
Sexual functioning*	22-25	-	-	-	-	-
Symptoms scale	No./s	(n=54)	(n=54)	(n=32)	(n=24)	p
Urinary	1-7,9	17±12	34±20	19±13	11±12	0.024
Bowel	10-13	0.7±3	6±11	2±3	0.7±3	0.216
Hormonal treatment-related	14-19	15±8	12±11	12±10	10±10	0.270
Incontinence aid	8	6±20	9±20	30±11	0±0	0.488

T₁: Start of radiotherapy; T₂: End of radiotherapy; T₃: 1 month after completion of radiotherapy; T₄: 6 months after completion of radiotherapy; *: The number of cases responding to this question was insufficient



QLQ C-30 and EORTC QLQ PR-25 functional and symptom scales were not different between groups ($p > 0.05$).

Discussion

Prostate cancer constitutes a patient group with longer life expectancy compared to other cancer types. The effects of treatments on the quality of life are very essen-

tial, especially for patients with early-stage, slow-growing tumors that are expected to live longer. In patients without metastatic disease, radical prostatectomy and RT constitute local treatments. In the present study, we investigated the effects of RT-related toxicity and its effects on the quality of life in patients with prostate cancer received definitive or adjuvant RT. Acute, grade 3-4 lower gastrointestinal toxicity was observed in only one patient (1%), acute grade 3-4 genitourinary toxic-

ity was observed in two patients (2%). Fifty-six of the patients (64%) had erectile dysfunction, 54 of patients (62%) had a loss of libido and 21 of patients (24%) had urinary incontinence. In the EORTC QLQ-C30 questionnaire, global health status, emotional score in functioning scale, fatigue and diarrhea scores in symptoms scale were negatively affected during RT. However, all these scores showed improvement from the first month after RT. In the EORTC QLQ-PR25 questionnaire, only the urinary score was negatively affected by RT, which also improved as the others.

Marchand et al.[16] examined radiotherapy-induced toxicity and its effect on QoL of 55 patients receiving RT for localized prostate cancer. External RT was applied with IMRT technique in doses of 76 Gy. EORTC QLQ C30 and QLQ PR25 questionnaires, which were used to assess QoL, were administered on patients before RT (baseline) and 2, 6 and 18 months after RT. The results of the study showed acute grade 1 and grade 2 urinary toxicity was 56.4% and 38.2%, respectively, while acute grade 1 and grade 2 bowel toxicity were 36.4% and 12.7%, respectively. Significant improvements were reported in the bowel and urinary toxicity six months after RT. Urethral stenosis was observed in a patient as an acute grade 3 genitourinary adverse effect. In addition, grade 1 and grade 2 sexual impotence were reported in 33% and 12% of patients, respectively, in the 18th month after RT.[16] In another similar study, Goineau et al.[17] studied the effects of high dose (76 Gy) RT on acute and late toxicity and on QoL in 38 patients with localized prostate cancer. They utilised the Common Terminology Criteria for Adverse Events questionnaire (version 3.0) to assess toxicity and EORTC QLQ-C30 and QLQ-PR25 questionnaires to assess QoL. Questionnaires were applied before and 2, 6, 18 and 54 months after RT. Acute urinary and gastrointestinal grade 1 toxicities were 36.8% and 23.7%, grade 2 toxicities were 5.3% and 5.3%, and grade 3 toxicities were 2.6% and 0%, respectively.[17] In the same study, grade 1 urinary and gastrointestinal toxicities in 18th month were 23.7% and 10.3%, grade 2 were 26.3% and 13.2% and grade 3 were 0% and 2.6%, respectively, while in the 54th-month grade 1 toxicities were 34.2% and 23.7%, grade 2 were 5.3% and 5.8% and grade 3 were 5.3% and 0%, respectively. In the present study, relatively higher side effects due to radiotherapy were observed compared to those two studies.[16,17] However, the patients undergoing both conformal RT and IMRT were included in our study. Acute grade 1-2 gastrointestinal toxicity was observed in 46% of patients and grade 3-4 toxicity in 1% of pa-

tients, while acute grade 1-2 urinary toxicity was observed in 81% and grade 3-4 toxicity in 2% of patients in the present study. As late toxicity, urinary and gastrointestinal grade 1-2 toxicities were seen in 8% and 35% of patients, respectively, whereas none of the patients had grade 3-4 toxicities.

In the present study, other adverse effects, observed in late periods, were erectile dysfunction (64%), loss of libido (62%) and urinary incontinence (24%). In our patients, the rate of sexual impotence was also high with the addition of hormone therapy (69%) and adjuvant RT (28%), which cause loss of libido. In addition, urinary continence was the most commonly encountered adverse effect in patients receiving adjuvant RT. In their studies examining the side effects of RT after 2-3 years, Little et al.[18] determined that 83% of patients had an erectile function before RT, they showed that this rate decreased to 49% two years after RT and to 41% after three years. A urinary incontinence rate of 36% was also reported in the same study.

Marchand et al.[16] reported significant impairments in some scores of QoL questionnaires after RT applied to patients with localized prostate cancer at 76 Gy doses. In the second month after RT, deteriorations in QoL were seen in fatigue and dyspnea scores of symptoms scale, in emotional, social, cognitive, physical scores of the functional scale of EORTC QLQ C-30 questionnaire, and in urinary symptom scores of EORTC QLQ PR-25 questionnaire. In the sixth month after RT, there were improvements in emotional, social, cognitive, physical, fatigue scores, and in 18th month, only treatment-related symptoms score was higher compared to baseline. [16] In the present study, global health status, emotional scores of functional scale, fatigue and diarrhea scores of symptom scale in the EORTC QLQ C-30 questionnaire were negatively affected at the end of RT. These scores, which had been impaired as a result of early adverse effects of RT, returned completely to baseline levels in the first and sixth months after RT. In the EORTC QLQ PR-25 questionnaire, only urinary score was negatively affected, which returned to normal in the first and sixth months after RT, similar to other scores. Since enough number of patients did not answer the questions related to sexual function in the questionnaire, the sexual functioning score was not assessed. Although some studies reported permanent impairments in QoL associated with sexual activity after RT,[18-22] there was no change in sexual activity score compared to before RT in the present study.

Lips et al.[23] compared 88 patients with localized prostate cancer who received 70 Gy doses via 3D-

Conformal radiotherapy technique and 92 patients who received 76 Gy doses using the IMRT technique concerning their quality of life. RAND-36, EORTC QLQ C-30 and QLQ PR25 questionnaires were used to evaluate QoL of patients before RT (baseline), one and six months after RT. No grade 3-4 bowel and urinary toxicities were reported in both treatment groups. Only one patient had grade 3 urinary infection in the high dose treatment group. Based on the EORTC questionnaire, the patients who had 70 Gy RT had a temporary deterioration in pain and urinary symptom scores of symptoms scale. In higher doses, i.e. in the group of IMRT, QoL did not alter significantly compared to conformal RT. Despite higher dose application to patients receiving IMRT, impairment of QoL due to bowel functioning was reported to be lower compared to patients receiving conformal RT.[23] In another similar study from Japan, 110 patients with prostate cancer who underwent conformal RT (median 70 Gy) and 30 patients who underwent IMRT (median 76 Gy) were compared in terms of their quality of life. [19] As a difference, the authors assessed QoL using the Medical Outcomes Study 36-Item Short Form (SF-36) and prostate-specific QoL using the University of California, Los Angeles, Prostate Cancer Index (UCLA PCI). There was no difference between the two groups for urinary symptoms, but the Japanese study demonstrated that bowel functions and sexual activity of the patients were significantly impaired in the third and sixth months after RT in the conformal radiation group.[19] In the present study, RT was applied to 71% of patients with 3D-conformal RT technique. Similar to the above-mentioned studies,[19,23] there were no differences in the scores of the QoL questionnaires between the groups of patients receiving conformal radiotherapy and IMRT. Also, no significant difference was found between patients who had undergone definitive and adjuvant RT concerning QoL.

Some researchers have shown that pelvic lymph node irradiation in high-risk patient groups negatively affects symptom-related QoL, especially diarrhea because more intestine enters the RT field.[24,25] Majewski et al.[24] studied the effects of RT on QoL of 180 prostate cancer patients using EORTC questionnaires. A total of 76 Gy was implemented to 85% of the patients using the IMRT technique and the remaining 15% to the patients using the conformal technique. Pelvic lymph node irradiation (44 Gy) was performed for a high-risk patient group (41%). Especially, in patient group receiving pelvic lymph node irradiation, significant deteriorations in symptom-related QoL (urinary

symptoms and diarrhea) were observed.[24] Unlike the above-mentioned studies, no significant difference was found in any of the QoL questionnaire scores of patients who were irradiated to the pelvic lymph nodes compared to patients without pelvic lymph node irradiation in our study.

Conclusion

The RT approach in prostate cancer caused temporary impairment in some scores of QLQ, but all these scores showed improvement from the first month after RT.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest.

Ethics Committee Approval: The Departmental Ethics Committee of Cumhuriyet University's Faculty of Medicine on non-invasive clinical research approved this trial in accordance with the Declaration of Helsinki with the decision no 2017-11/21, on 8 November 2017.

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