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Research Article

Comparison of standard optimization method and multicriteria optimization (MCO) method using intensity-modulated radiotherapy (IMRT) technique for patients with localized prostate cancer

Ayşe Gülbin Kavak[1*], Hatice Coşkun[2], Abdullah Tuncay Demiryürek[3]

[1*]Department of Radiation Oncology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey,(ORCID: 0000-0003-1995-1642), gulbinkavak@yahoo.com
[2]Department of Radiation Oncology, Adana City Training and Research Hospital, Adana, Turkey, (ORCID: 0000-0003-0146-8185),drhaticecoskun@hotmail.com
[3]Department of Medical Pharmacology, Faculty of Medicine, and Vocational School of Health Services, Gaziantep University, Gaziantep, Turkey, (ORCID:0000-0002-9994-8541), demiryurek@gaziantep.edu.tr

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Abstract

This study aimed to evaluate the implementation of intensity-modulated radiation therapy (IMRT) using multicriteria optimization (MCO) in the RayStation treatment planning system for patients with prostate cancer. A total of 10 consecutive prostate cancer patients previously treated by IMRT were included in this study and re-planned using the MCO modality. The plan quality was analyzed and compared using the conformity index (CI) and homogeneity index (HI) of the dose sparing of organs at risk (OAR) and planning target volume (PTV). Dose–escalation with PTV-based IMRT planning was closely connected with elevated OAR doses, particularly in high-dose areas. Although HI and CI were similar for both modalities, we detected a marked decrease in mean monitor units for MCO when compared to IMRT ($P < 0.05$). The MCO-plan showed markedly better bladder and femoral heads sparing effects ($P<0.05$). It has been found that the MCO method shortens the total planning time compared to the IMRT method ($P < 0.01$). Our findings showed that MCO improved plan quality and was the superior modality for prostate cancer in terms of PTV coverage and OAR sparing.

Keywords: Intensity-modulated radiation therapy, Multicriteria optimization, Plan quality, Prostate cancer.

Lokalize prostat kanserli hastalarda yoğunluk ayarlı radyoterapi (IMRT) tekniği kullanılarak standart optimizasyon yöntemi ile çok kriterli optimizasyon (MCO) yönteminin karşılaştırılması

Öz

Bu çalışmada, prostat kanserli hastalar için RayStation tedavi planlama sisteminde çok kriterli optimizasyon (MCO) yöntemi kullanılarak yoğunluk ayarlı radyasyon tedavisi (IMRT) uygulamasını değerlendirmek amaçlandı. Çalışmaya daha önce IMRT ile tedavi edilen toplam 10 ardışık prostat kanseri hastası dahil edildi ve MCO modalitesi kullanılarak yeniden planlandı. Plan kalitesi, risk altındaki organlar (OAR) ve planlama hedef hacminin (PTV) uygunluk indeksi (CI) ve homojenlik indeksi (HI) kullanılarak analiz edildi ve karşılaştırıldı. PTV tabanlı IMRT planlaması ile doz yükseltme, özellikle yüksek doz alanlarında, yüksek OAR dozları ile yakından bağlantılıydı. HI ve CI her iki modalite için benzer olmasına rağmen, IMRT ile karşılaştırıldığında MCO için ortalama monitör birimlerinde belirgin bir düşüş saptandı ($P < 0.05$). MCO planı, belirgin şekilde mesane ve femur başı için daha iyi koruyucu etkiler gösterdi ($P < 0.05$). MCO yönteminin IMRT yöntemine göre toplam planlama süresini kısalttığı görülmüştür ($P < 0.01$). Bulgularımız, MCO'nun plan kalitesini iyileştirdiğini ve PTV kapsamı ve OAR koruması açısından prostat kanseri için üstün bir modalite olduğunu göstermiştir.

Anahtar Kelimeler: Yoğunluk ayarlı radyasyon tedavisi, Çok kriterli optimizasyon, Plan kalitesi, Prostat kanseri.

[*]Corresponding Author:gulbinkavak@yahoo.com

1. Introduction

Prostate cancer represents the second most frequently diagnosed cancer (after lung cancer) in men worldwide and the fifth most common cancer-related mortality in men (Ferlay et al. 2019). Prostate cancer mortality and incidence rates are highly correlated to age with the highest incidence being seen in men who are 65 or older (Rawla 2019). The age-adjusted prostate cancer incidence rate was reported to be 35 cases per 100,000 in Turkey (Zorlu et al. 2014). Increased incidence rates for prostate cancer have been observed worldwide, particularly in Northern and Western Europe and Asia (Teoh et al. 2019).

Radiation therapy uses high-energy photons to eradicate prostate cancer while minimizing damage to critical organs. Intensity-modulated radiation therapy (IMRT) is generally accepted as a standard of care for dose-escalated radiotherapy of prostate cancer (Bauman et al. 2012; Yu et al. 2016; Thorwarth et al. 2017). The goal of IMRT is to deliver a radiation dose to the tumor volume while protecting pivotal organs and sparing healthy tissues (Troeller et al. 2015).

Multicriteria optimization (MCO) is an advanced feature of the optimization method and it has proven to be an efficient treatment planning modality, both in terms of dosimetric quality and planning time (Craft et al. 2012, Wala et al. 2013). It is based upon the approximation of the Pareto surface-based technique that refers to a state where one parameter cannot be improved without negatively affecting another (Haas et al. 1998, Cotrutz et al. 2001, Craft et al. 2005, Craft et al. 2006). MCO is a new generation method to see all plans in one optimization derived Pareto plans. MCO plans eliminate the time-consuming trial-and-error process of selecting appropriate weighting factors in conventional IMRT planning and calculate these dosimetric trade-offs (Thieke et al. 2007, Breedveld et al. 2009, Bodensteiner 2018). The purpose of this study was to compare the standard optimization method and MCO method using the IMRT technique for patients with localized prostate cancer.

2. Material and Method

2.1. Patients

In this retrospective study, a total of 10 consecutive patients (average age: 70.8±1.7 years) with localized prostate cancer who had received radiotherapy with the IMRT technique at the Gaziantep University Oncology Hospital were enrolled. This study was reviewed and approved by the Institutional Clinic Ethics Committee.

Inclusion criteria comprised histopathologically confirmed prostate adenocarcinoma, age ≥ 18 years old, localized disease (pelvic/abdominal CT, bone scan), high risk according to D'Amico classification (D'Amico et al. 1998), and no history of prior surgery to the prostate. All of the patients received hormonal treatment (neoadjuvant therapy) before Radiation Therapy.

Exclusion criteria included prior pelvic radiotherapy, prior prostatectomy, prior transurethral resection, brachytherapy, distant metastases, other concurrent severe diseases or malignancies (e.g., blood coagulation restrictions, chronic inflammatory bowel disease, decompensated heart insufficiency), and serious medical or psychiatric illness preventing safe administration of RT.

2.2. Treatment planning

All of these patients had high-risk prostate cancer and undergone 3-mm slice thickness-computed tomography (CT) (Philips Brilliance 64 Slice CT, Philips Medical Systems, Netherlands) performed with empty rectum, comfortably full bladder, with patients in the supine position. All patients received 1 liter of water before CT as recommended by the protocol (Esen & Demir Apaydın 2020). All patients received step-and-shoot IMRT to a total dose of 76 Gy in 38 fractions with 6MV photons linear accelerator (Elekta Synergy Platform Linear Accelerator, Elekta Inc., Stockholm, Sweden). The planning CT scan, beam angles, and structure definitions were imported into RayStation (version 6, RaySearch Laboratories, Stockholm, Sweden) for planning.

The clinical target volume (CTV) covered the entire seminal vesicles and the prostate. The planning target volume (PTV) was determined as CTV with a margin of 5 mm posterior and 7 mm in other directions. The rectum, penile bulb, femoral heads, and bladder were contoured as the organs at risk (OARs). PTV and OARs were shaped by an experienced radiation oncologist. The PTV depended on the Radiation Therapy Oncology Group atlas (Gay et al. 2012).

Treatment plans for the patients with prostate cancer were arranged using 7 coplanar fields with angle intervals of 51^0. Each plan was dependent on the principle of enhancing the dose coverage of the targets and minimizing the radiation of the normal tissues and OAR. The prescription was determined as follows: A 76 Gy total radiation dose was determined for PTV. At least 98% of the PTV received 98% of the prescribed dose. The maximum dose in the PTV had to be less than 107% of the prescribed dose. The rectum dose provides that D50% (dose at 50% volume) should not receive more than 50 Gy, D35% should not receive more than 65 Gy and D20% should not receive more than 70 Gy. The bladder dose provides that D35% should not receive more than 65 Gy. D5% of femoral heads should be less than 50 Gy. The maximum dose of the penile bulb should be less than 50 Gy. All plans were made by the same person who is a radiotherapy physicist experienced in IMRT treatment planning for more than 10 years to eliminate uncertainties due to the planner, and approved by a physician for clinical delivery. In order to experience the automatic planning feature while making treatment plans, templates were applied for each plan which was created for optimization objectives to provide the same conditions. Treatment plans were calculated and optimized on a single computer using collapsed cone algorithm (v3.2). The views of the treatment plan for both methods are shown in Figure 1.

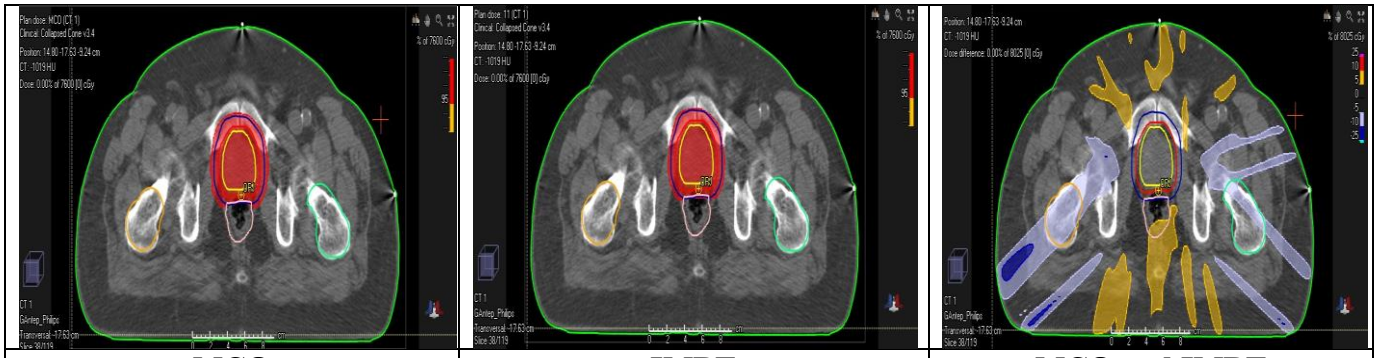

Figure 1. The views show 95% of the prescription dose for multicriteria optimization (MCO) and intensity-modulated radiotherapy (IMRT) optimization method for a typical patient. "MCO and IMRT" represents the dose difference region for a typical patient.

Şekil 1. Görünümler, tipik bir hasta için çok kriterli optimizasyon (MCO) ve yoğunluk ayarlı radyoterapi (IMRT) optimizasyon yöntemi için tanımlanan dozunun %95'ini göstermektedir. "MCO ve IMRT" tipik bir hasta için doz farkı bölgesini temsil eder.

2.3. Evaluation of the plan quality

The plan quality was determined using the OAR and PTV dose-volume histogram (DVH) values. Mean doses to the femoral heads, bladder, rectum, and penile bulb were recorded, as well as the number of monitor units (MUs) for both algorithms. The homogeneity index (HI) and conformity index (CI) for all plans were calculated using the Radiation Therapy Oncology Group (RTOG) definitions (Feuvret et al. 2006) as follows:

$$CI = VPI/TV$$

where VP1 is the volume of the prescribed isodose, and TV represents the planning target volume included by the prescribed isodose.

$$HI = D5/D95$$

D5 describes the minimum dose that covers 5% of the PTV, and D95 indicates the minimum dose that covers 95% of the PTV. For a perfectly homogeneous and conformal dose distribution, HI and CI should be equal to 1. CI > 1 describes undesired irradiation of healthy tissue with high doses and HI > 1 indicates inhomogeneous dose distributions in the target.

2.4. Quality Assurance (QA) analysis

2D ionization chamber array I'mRT MatriXX (IBA, Schwarzenbruck, Germany) was utilized to assess Quality Assurance (QA) passing rates on the basis of the gamma index (γ) analysis to compare the measured and calculated doses in terms of the distance to agreement (3%, 3 mm) and dose difference (Low et al. 1998).

2.5. Statistics

All results are expressed as mean ± standard error of the mean (SEM). Qualitative data are presented as ratios with percentages. The normal distribution of variables was firstly identified with the Kolmogorov–Smirnov test. Paired Student's t test was utilized to compare two groups of normally distributed data. Pearson analysis was applied to identify the correlations. Statistical analysis was performed using GraphPad Instat (version 3.05, GraphPad Software Inc., San Diego, CA, USA). Differences were considered to be statistically significant when $P < 0.05$.

3. Results

Dosimetric comparisons of PTV and OARs for the IMRT and MCO planning methods in patients with prostate cancer are shown in Figure 2. Dose-escalation to 76 Gy was determined to be feasible in all patients. The 99.38% and 99.63% of the target volume for IMRT and MCO methods were covered by 74.4 Gy. The average value of D95 for PTV was found 75.90 Gy and 75.88 Gy, and the average value of D1 for PTV was found at 79.60 Gy and 79.45 Gy for IMRT and MCO methods, respectively. Significant reductions in PTV D1 and D2 values were evident in MCO plans than in IMRT plans.

Table 1 shows the comparison of the IMRT and MCO plans. Lower D1 and higher D50 values were observed with MCO plans in the rectum. The mean V65 for bladder was received at 14.7% and 15.2% for IMRT and MCO plans. Both D1 and D2 values were markedly low in the bladder with MCO plans ($P<0.05$). Penile bulb doses were obtained in the limit of 50 Gy except for two patients. Penile bulb doses can be obtained below 50 Gy for all cases if PTV dose coverage is sacrificed in treatment planning. There were no significant changes in penile bulb values between IMRT and MCO methods. The mean D1 dose value decreased from 39.25 Gy to 36.08 Gy for the femoral head right and 38.72 Gy to 34.28 Gy for the femoral head left in the IMRT plan to MCO plan. D1 dose values for femoral heads did not exceed 45 Gy for both methods. However, the MCO plans showed the greatest sparing of right and left femoral heads in all dose levels. Moreover, dose-volume histogram (DVH) for IMRT and MCO methods are created by entering the PTV's, CTV's and OAR's (rectum, bladder, femoral heads and penile bulbs) dose values of the patients separately for each structure. They were illustrated in Figure 3 for IMRT.

The monitor units per fraction, conformity index (CI), and homogeneity index (HI) for the IMRT and MCO planning methods in patients with prostate cancer are presented in Table 1. The mean monitor unit was significantly low in MCO (640.41 ± 27.87 monitor units per fraction) when compared to IMRT (685.66 ± 36.52 monitor units per fraction, $P = 0.0356$). Neither conformity index (CI) nor homogeneity index (HI) was markedly changed.

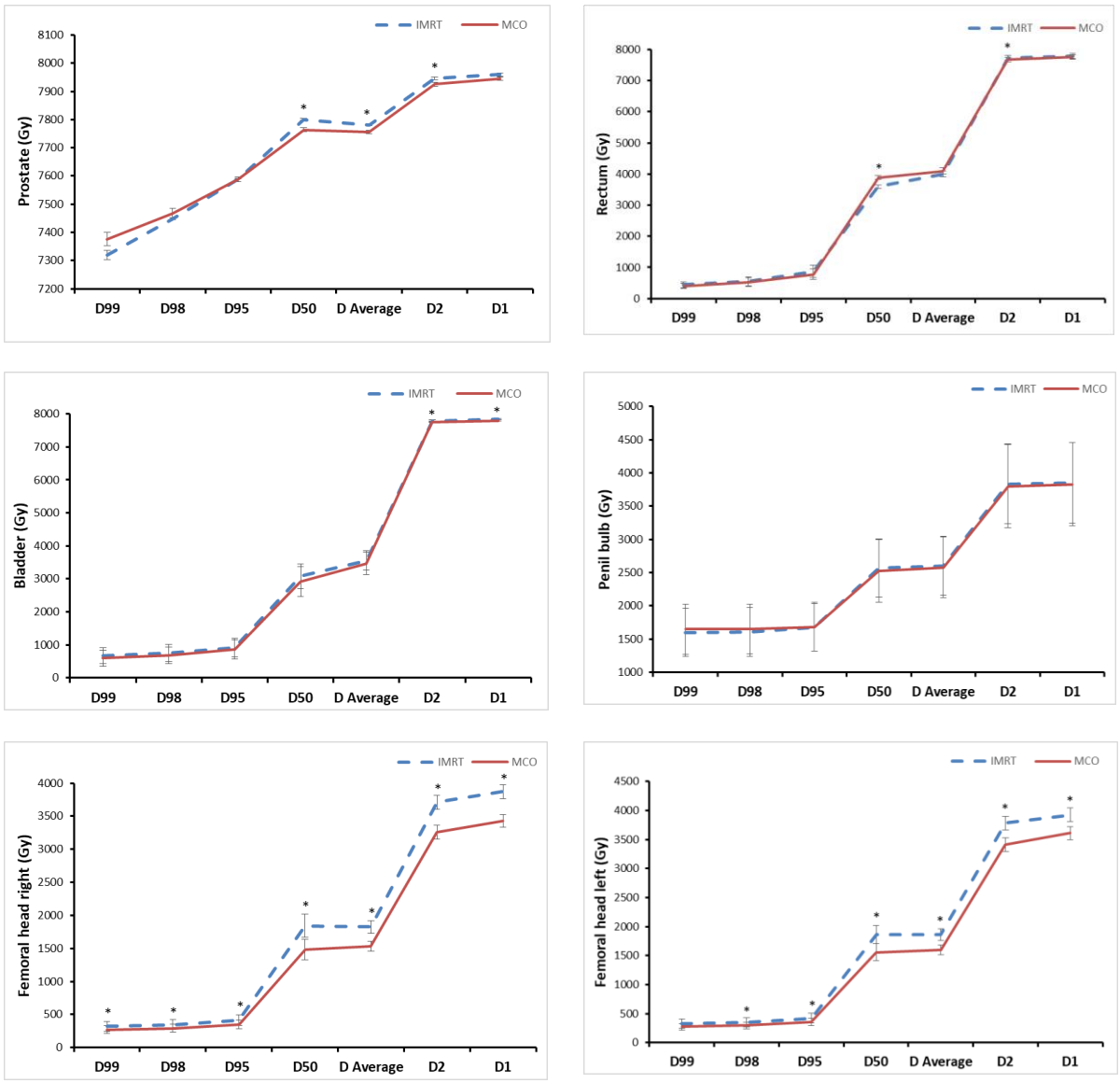

*Figure 2. Dosimetric comparisons of the clinical planning target volume (PTV) and organs at risks (OARs) for the IMRT and MCO planning methods in patients with prostate cancer. All values were reported as mean ± SEM. D99: Dose 99%, D98: Dose 98%, D95: Dose 95%, D50: Dose 50%, D Average: Average Dose, D2: Dose 2%, D1: Dose 1%. *P<0.05*

*Şekil 2. Prostat kanserli hastalarda IMRT ve MCO planlama yöntemleri için klinik planlama hedef hacminin (PTV) ve risk altındaki organların (OAR'lar) dozimetrik karşılaştırmaları. Tüm değerler ortalama ± SEM olarak rapor edildi. D99: Doz %99, D98: Doz %98, D95: Doz %95, D50: Doz %50, D Ortalama: Ortalama Doz, D2: Doz %2, D1: Doz %1. *P<0.05*

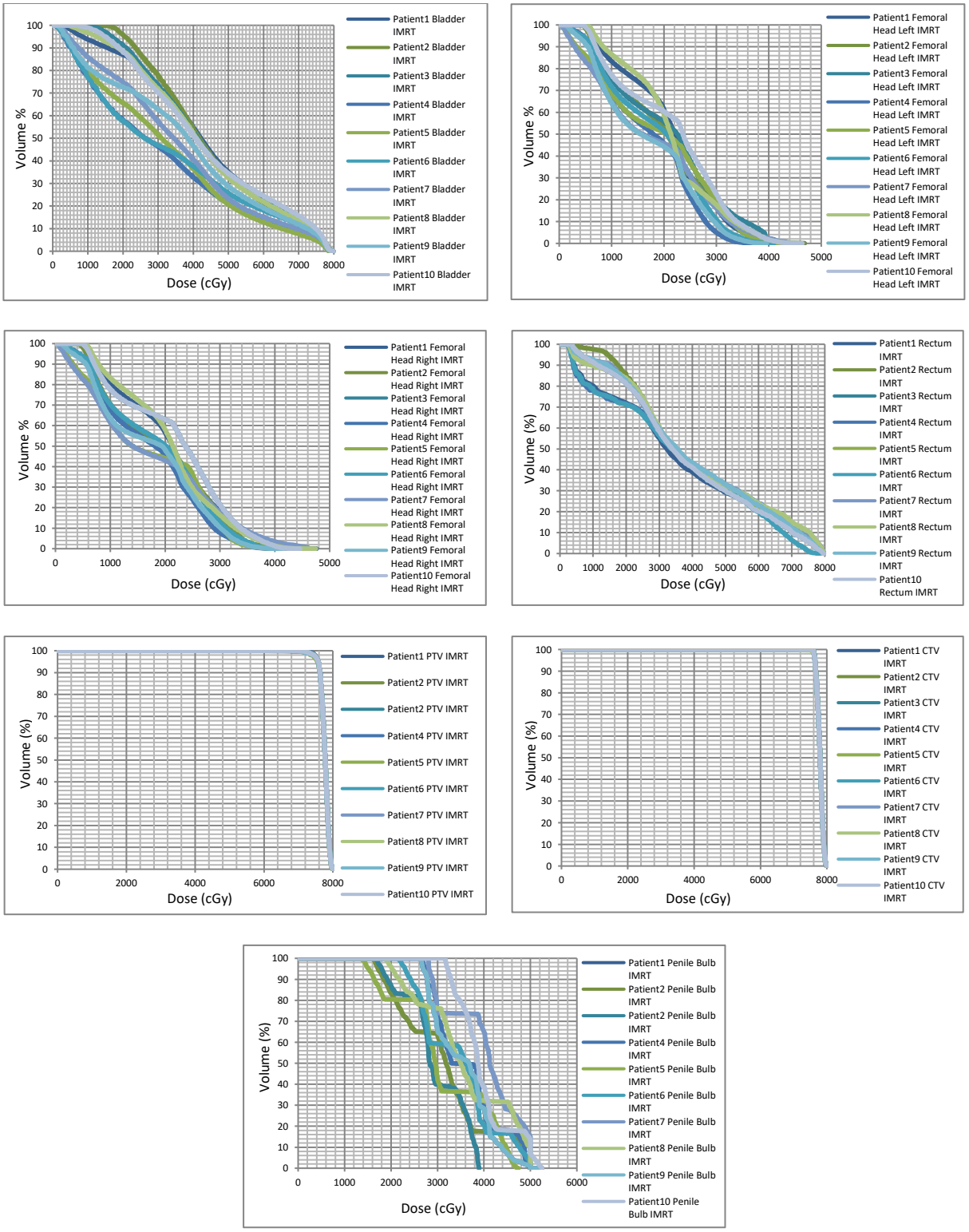

Figure 3. The values of Dose Volume Histogram (DVH) for PTV and OAR's for IMRT methods.

Şekil 3. IMRT yönteminde PTV ve OAR'ler için Doz Hacim Histogramı (DVH) değerleri.

Table 1. Comparision of the IMRT and MCO plans.

Tablo 1. IMRT ve MCO planlarının karşılaştırılması.

Index	IMRT	MCO	P
PLANNING TARGET VOLUME (PTV)			
V95 (%)	99.38 ± 0.08	99.63 ± 0.08	0.0400
D95 (Gy)	75.90 ± 0.02	75.88 ± 0.08	0,0900
D1 (Gy)	79.60 ± 0.06	79.45 ± 0.06	0.0600
Conformity index (CI)	0.995 ± 0.001	0.997 ± 0.001	0.0957
Homogeneity index (HI)	1.044 ± 0.001	1.040 ± 0.002	0.0670
Monitor units (MU)	685.66 ± 36.52	640.41 ± 27.87	0.0356
RECTUM			
V50 (%)	32.35 ± 0.72	34.31 ± 1.12	0.1600
V65 (%)	17.03 ± 1.08	17.58 ± 1.69	0.6100
V70 (%)	11.82 ± 1.19	12.37 ± 1.61	0.5100
V75 (%)	6.46 ± 1.00	6.60 ± 1.33	0.8100
Dmean (Gy)	40.03 ± 0.92	40.96 ± 1.07	0.0960
D50 (Gy)	35.99 ± 0.52	38.82 ± 0.61	0.0019
D2 (Gy)	77.36 ± 0.82	76.73 ± 0.76	0.0175
D1 (Gy)	77.96 ± 0.79	77.63 ± 0.71	0.1070
BLADDER			
V50 (%)	26.28 ± 2.44	27.27 ± 3.42	0.6200
V65 (%)	14.70 ± 1.32	15.25 ± 1.78	0.5870
V70 (%)	11.32 ± 1.03	11.74 ± 1.34	0.5970
V75 (%)	7.04 ± 0.69	7.14 ± 0.84	0.8300
Dmean (Gy)	35.62 ± 2.85	34.67 ± 3.37	0.4031
D2 (Gy)	77.91 ± 0.20	77.57 ± 0.20	0.0097
D1 (Gy)	78.38 ± 0.16	77.99 ± 0.18	0.0070
FEMORAL HEAD LEFT			
Dmean (Gy)	18.61 ± 0.97	15.98 ± 0.81	0.0006
D1 (Gy)	39.25 ± 1.19	36.08 ± 1.16	0.0520
FEMORAL HEAD RIGHT			
Dmean (Gy)	18.24 ± 0.93	15.31 ± 0.76	0.0002
D1 (Gy)	38.72 ± 1.07	34.28 ± 0.96	0.0010
PENILE BULB			
Dmean (Gy)	26.00 ± 4.39	25.77 ± 4.60	0.8500
D1 (Gy)	38.51 ± 6.05	38.29 ± 6.28	0.8300

To generate the average time Pareto plans for MCO modality took 1.34 minutes for the number of Pareto plans is 20. We increased the number of Pareto plans from 20 to 40, the calculation time was 5.57 minutes. When the number of Pareto plans incremented to 60, this period took more than 20 minutes on average. Average optimization times for IMRT and MCO plans were found 1.50 and 1.45 minutes, respectively (Figure 4). While the mean of the total planning time was 16.47 ± 0.32 min for the IMRT method, it was 10.5 ± 0.26 min (P=0.0001) for the MCO method.

We performed a correlation analysis between prostate-specific antigen and testosterone levels with MU, CI, and HI. These analyses revealed that there was only significant negative correlation between MU for MCO planning and pre-treatment testosterone levels ($r = -0.7288$, $r^2 = 0.5312$, $P = 0.0168$). Other comparisons demonstrated no marked correlations.

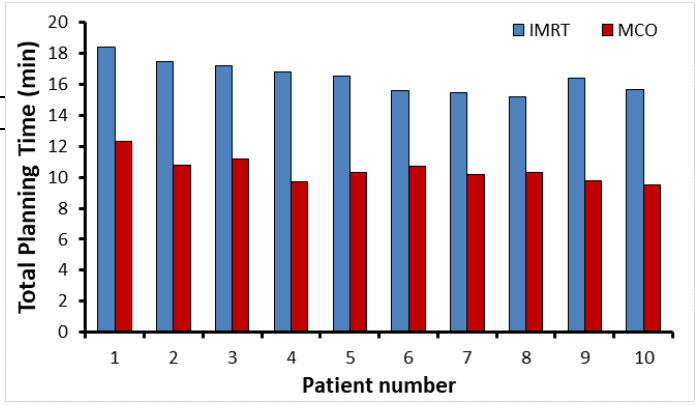

Figure 4. Total Planning Time per patient for IMRT and MCO methods with prostate cancer.

Şekil 4. Prostat kanserli IMRT ve MCO yöntemleri için hasta başına Toplam Planlama Süresi.

QA analyses were evaluated by OmniPro IMRT Software (Scanditronix Wellhofer, Germany). The average gamma that QA passing rate was determined as the percentage of points with $\gamma > 1$ were attained 0.69 and 0.35 for IMRT and MCO plans, respectively. The screen view of QA analysis for a patient planned with the MCO method showed in Figure 5.

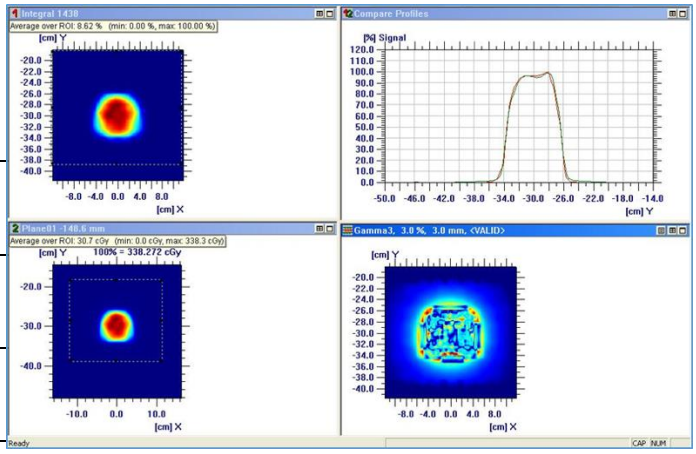

Figure 5. The screen view of Quality Assurance (QA) analysis for a typical patient.

Şekil 5. Tipik bir hasta için Kalite Kontrol (QA) analizinin ekran görüntüsü.

4. Discussion

We applied IMRT and MCO planning modalities to demonstrate the feasibility and to compare the optimization algorithm in patients with prostate cancer. When we compared 95% of the prescription dose for both plans, PTV coverage was slightly better than the mean of MCO plans and the mean of IMRT plans. While the mean rectum doses were found slightly less in the IMRT method in our study, McGarry et al. (2014) showed that the mean rectum doses were lower in the MCO method. We demonstrated that the mean bladder dose values were obtained lower in the IMRT method compared to the MCO method. This result is in agreement with the data presented by McGarry et al. (2014). Although the contours of shell or similar structures were not used for any of the treatment plans in RayPlan Software,

similar OAR's results were obtained in our study and in the research published by McGarry et al. (2014). Moreover, our results of gamma analyses were also compatible with that study. In the present study, both femoral head dose values for MCO plans were found superior to IMRT plans. If femoral head doses were sacrificed, better rectum and bladder dose values would have been obtained with MCO plans than IMRT plans. Meanwhile, all dose values for OAR's were obtained below RTOG 0415 dose constraints (Lee et al. 2016). Collectively, we showed that MCO planning produced marked dose reductions and sparing of bladder and right and left femoral heads in prostate cancer patients. MCO provided an efficient planning modality by enabling to view of trade-offs in real-time for prostate cancer treatment.

IMRT is currently the standard treatment technique for prostate cancer, allowing for the delivery of highly conformal dose distributions. Therefore, IMRT has been extensively used as a method to diminish unwanted effects of treatment or as a tool for dose escalation to augment cure rates and local control. IMRT usually utilizes multiple beam angles, each of which is subdivided into multiple beamlets of varying intensity, permitting for an infinite number of treatment plans. Although IMRT provides greater flexibility in treatment planning, in reality, the standard IMRT treatment planning can reduce the flexibility for the physicians to change radiation plans as a result of process inefficiency. So, the current IMRT treatment planning process does not encourage physician participation and takes too long. To avoid drawbacks offered by IMRT, a new approach to MCO is gaining prominence. Our results also suggest that Pareto surface-based MCO approach is effective, faster, and yields better plans. Several studies have reported that the amount of time spent on optimization can be reduced, and the performance of the treatment plan can be improved by using MCO (Craft et al. 2007, Craft et al. 2012, Hong et al. 2008). Additionally, toxicity and cure rates of prostate IMRT can both be influenced by inappropriate PTV margins. Thus, compared with the traditional planning strategy, the MCO planning strategy reduced significantly the dose on the bladder and femoral heads. These results are in line with the data provided by Wala et al. (2013) who reported that MCO planning decreased high-dose of the bladder and femoral heads effectively. So, MCO provided acceptable planning target volume coverage with high conformity to the primary tumor and achieved better sparing effect on OAR. Another important advantage that was noted in our study was the much fewer monitor units in MCO than in IMRT. Collectively, these data showed that the MCO planning modality has proven to be an effective approach, both in terms of planning efficiency and dosimetric quality.

The total mean planning time in the MCO method was found shorter than in the IMRT method. Generated Pareto plans for different probability provided easiness to choose the optimal plan. In our study, the mean total treatment planning time was found to be shorter than the study of Wala et al. (2013) who showed that the total planning time in the RayStation treatment planning system was about 60 minutes per case. Since all treatment plans were made using the same treatment planning software, it was more meaningful in terms of evaluating to total planning time for the Pareto-based MCO method in our study.

As a result, the planning process time is shortened. Nevertheless, it is not recommended that the number of Pareto plans produced in the MCO method should be preferred bigger than 40 because of extending process time. However, it is necessary to run the optimization process over and over again until the optimal solution is found in the IMRT method. Therefore, this calculation process can take more than the mean of planning time for IMRT plans. The planning time per patient for MCO was markedly low. Previous studies have demonstrated that plan quality relying on minimizing a weighted sum of the objectives (i.e., RayArc) depends on the time spent optimizing a plan and the planner's experience (Bohsung et al. 2005, Batumalai et al. 2013).

The main limitation of this study is that the number of study subjects is relatively small, therefore, the results of the present study should be interpreted with caution.

5. Conclusions and Recommendations

In summary, this work demonstrates MCO can improve planning efficiency. MCO plans substantially diminished the dose of OARs and active planning time without sacrificing the target coverage. Our findings also show that MCO-based treatment planning is an effective method for generating high-quality IMRT plans for localized prostate cancer treatment. Further investigations could provide some insight into human vs. automated planning methods which is of interest in this era where artificial intelligence is being used in more and more situations.

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