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Dosimetric comparison of IMRT, VMAT and HYBRID treatment methods in radical radiation therapy of prostate cancer

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ABSTRACT

***Background*:** Modern treatment techniques such as Intensity-Modulated Radiotherapy(IMRT)or Volumetric-Modulated Arc Therapy(VMAT) are standard in practice; it is possible to obtain much better dose distributions using HYBRID plans generated applying these techniques together. Thus patient's quality of life improves. ***Material and Methods*:** In this study, treatment plan is generated for 10 prostate patients who underwent primary prostate radiotherapy with 7-field IMRT, double arc VMAT and HYBRID techniques. The prescribed treatment dose (78 Gray(Gy)) is defined as the isodose covering 95% of PTV. ***Results*:** The study results revealed better Planning Target Volume (PTV) dose coverage in the HYBRID plan than the other plans. At the same time, HYBRID plans were found to be significant in terms of heterogeneity index. It was observed that there was no statistically significant difference in terms of fit index. Bladder and rectum V_{50} doses were lower in HYBRID plans than IMRT plans. The mean doses of the right and left femoral heads and the penile bulb V_{90} in HYBRID plans were statistically significant compared to the IMRT and VMAT plans. VMAT plans had a lower rate of Monitor Unit (MU) in the MU assessment than IMRT plans; however, the MU rate obtained in the HYBRID plan was lowest compared to IMRT and VMAT plans. ***Conclusion*:** It was concluded that the HYBRID method is suitable for routine clinical use together with IMRT and VMAT plans since more optimum results were obtained in HYBRID plans, especially in critical organ doses.

INTRODUCTION

Since the results of the first cancer cases treated with radiation (X-rays) were published in 1934, radiation is a widely used treatment method to treat cancer patients (1). Recently, with the development of computer technologies automation of radiotherapy treatment planning has become possible. This brought about improvements in radiotherapy treatment techniques and allowed safer protection of surrounding healthy tissues while giving higher doses to the treatment volume (2, 3). Studies have shown increased tumor control with high doses in prostate cancer treatment. Unfortunately, despite better tumor control, the higher the dose, the higher the treatment toxicity. Intensity-Modulated Radiotherapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT) are advanced forms of radiotherapy techniques (4-6). Utilizing these techniques, the targeted dose is distributed more homogeneously compared to Three Dimensional (3D) Conformal Radiotherapy, while the organs at risk receive lower doses, thus protecting normal tissues (OAR) (7-10).

One of the first pioneering publications, Zelefsky *et al.* (11), reported that it is possible to reduce rectal and bladder doses compared to IMRT plan with 3D conformal therapy in the IMRT plan, while Luxton *et al.* (12) proved that critical organs and normal tissues can be well preserved in IMRT plans. Also, Bednarz *et al.* (13) using Monte Carlo-based patient modeling confirms that the risk of developing secondary cancer in normal tissues outside the area after IMRT plans is below the predicted risk line. Similarly, Pesce *et al.* (14) used only VMAT plans in their study, and VMAT plans were reported to meet the desired clinical criteria. Mellon *et al.* (15) compared VMAT plans with step-and-shoot intensity modulated radiation therapy plans, and mentioned that VMAT plans reduce the irradiation time and a more homogeneous dose distribution is obtained with VMAT plans. In a retrospective study of 3D conformal, IMRT and VMAT techniques by Scott B. Crowe *et al.*, quality differences were found to be dosimetrically significant. In the same study, it was reported that IMRT and VMAT plans gave in terms of organ doses compared to traditional plans (16).

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The bladder and rectum, which are the closest to Planning Target Volume (PTV) in prostate cancer, are the most critical organs at risk. Wenting Ren *et al.*, in their study [17] in which they combined multicenter results on the dosimetric comparison of IMRT and VMAT techniques in patients with prostate cancer, stated that the VMAT technique reduces the rectum dose. In particular, Sale C and Moloney P [18] mentioned their study and stated that the rectal dose decreased at doses among 40 Gy, 50 Gy, 60 Gy and 70 Gy in VMAT plans. In addition, Elith *et al.* [19], mentioned that there was no significant reduction in VMAT plans at doses of 40-50 Gy, contrary to the view. The study stated that this difference might be caused by small sampling size, planning differences, and optimization algorithm differences. The bladder is another vital organ that must be protected in the treatment of prostate cancer. The same study noted that there was no significant difference between the two techniques (VMAT and IMRT) regarding bladder doses. Similarly, Pengpeng Zhang *et al.* compared the VMAT technique with the IMRT technique and reported that they "obtained better dosimetric results with VMAT plans, especially in terms of rectum doses (1,5%) and irradiation time (55%)" [20]. Ghadjar *et al.* [21] mentioned that at high treatment doses empty rectum doses are lower when rectum full and therefore rectum empty irradiation is performed.

While IMRT benefits from intensity modulation at appropriate static beam angles, VMAT also takes advantage of the extra degrees of freedom provided by multiple angular fields. These limitations make it difficult to choose the appropriate technique in different treatment situations. Although modern treatment techniques such as IMRT or VMAT are standard in prostate irradiation, more optimal dose distributions with acceptable protection at critical organ doses may be achieved using HYBRID techniques, which improves patients' quality of life [2,3].

Although IMRT and VMAT treatment techniques are frequently used in the treatment of prostate cancer, they are insufficient in some cases. In such insufficient situations, HYBRID techniques can give good results especially in terms of critical organ doses[22-23].IMRT and VMAT plans pros and cons, in this study we aimed to explore if we can achieve better plan quality by combining VMAT and IMRT.

MATERIAL AND METHODS

Patient selection

In this study, 10 patients are selected with a diagnosis of 2 patients T1b, 2 patients with T1c and 6 patients with stage T2a between November 2020 and April 2021 and they are included at low-risk prostate cancer who received primary prostate radiotherapy and were of Caucasian origin (median age 55-79 years = 68 years). The study was approved by the institutional ethics committee (Aydın Adnan Menderes University, Medical School, Non-interventional Clinical Research Ethics Committee, Registration number = 2021-143 and date :26.08.2021).

Before the simulation, the patients were asked to emty their bowel and drink enough water until they felt the sensation of full bladder's swelling [24]. The patients were immobilized under lower extremities with angular wedge supports in the supine position. Computed Tomography Simulation (CTSIM) was performed with the Toshiba Aquillion Lightning (Toshiba Medical Systems Corporation, JAPAN) 64 CT (Computed Tomography) Simulator. Adhering to our clinical protocol (at least 5 cm added from the irradiation volume to the upper and lower limits) 3 mm thick sections were taken with the bladder full and the empty rectum.

Volume definitions

"Male Pelvis Normal Tissue RTOG Consensus Contouring Guidelines" is referred for contouring the structures in all patient plans [25].

According to our clinical protocol, the Planning Target Volume (PTV) was given an automatic margin of 3 mm after defining the PTV and critical organs adjacent to the PTV were identified. Using the criteria in table 1 to access Organs at Risk (OAR), the treatment dose (39 fractions from 2 Gy per day Total 78 Gy) was defined to the isodose line covering 95% of the PTV. Since V_{50} values for bladder and rectum and V_{90} values for penile bulb were more decisive in terms of complication rates, they are chosen as OAR criterion.

Table 1. Critical organ doses.

PTV (Total Dose 78 Gy)	REFERENCE ISODOSE 95 %
Bladder	All < 50Gy V_{65} < 25% V_{50} < 50% (post op <60%) V_{40} < 50% Doz_{max}< 80Gy
Rectum	$V_{65} \leq 17\%$ $V_{40} \leq 35\%$ $V_{50} \leq$ 60-50% 90% isodose should not exceed the diameter of the rectum
Femoral heads (right/left)	< 45 Gy $V_{50} \leq 5\%$
Penile bulb	Mean Dose ≤ 52,5Gy
Normal tissue	Minimum Dose

IMRT plans

Treatment plans were generated by Monaco (Version 5.10) Treatment Planning System (Elekta, Business Area Software Systems, United Kingdom) using the parameters of the 6 MV Elekta Agility Linear Accelerator (Elekta LIMITED, United Kingdom) devices (leaf thickness 0.5 cm) with 6MV photon energy. IMRT plans in 7 field were calculated

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using the dynamic IMRT treatment technique and Monte Carlo Algorithm at 0°, 50°, 100°, 140°, 220°, 260°, 310°. Collimator defined as 2° to prevent leaf leakage.

VMAT plans

VMAT plans were generated using dynamic VMAT and Monte Carlo Algorithm using full IMRT contours, central axis and isocenter in clockwise and counterclockwise double arc (angles of approximately 330^{O}-340^{O}). The collimator was defined as 2° to prevent leaf leakage. Precise dose targets and criteria were used for both IMRT and VMAT plans.

HYBRID plans

HYBRID plans are a 50% combination of pre-calculated IMRT and VMAT plans (IMRT 50%/ VMAT 50% weight). In the IMRT treatment technique, while irradiating is performed at fixed gantry angles by modulating the multi-leaf collimator (MLC) according to the doses defined in the VMAT treatment technique (PTV, OAR), MLCs irradiate in a modulated manner depending on the gantry rate and dose rate.

For all plans (IMRT, VMAT, HYBRID), 95% of the dose, average conformity index (CI) is expressed according to the equation 1.

$$\text{Conformity Index (CI)}=\frac{(V_{Rx})^2}{(TV \ x V_{RI})} \quad (1)$$

According to the planning system's definition of the CI, "where TV is the structure volume , V_{RX} is the structure volume covered by the Dose of İnterest and V_{RI} is the total volume of the Dose of İnterest . The Conformity Index describes the degree to which the prescribed isodose volume conforms to the shape and size of the target volume. This value is reported for Monaco Planning System ".

This formulation (equation 1) helps for Bladder, rectum, right and left femoral heads, penile bulb doses, and MU/cGy (MU: Monitor Unit, cGy: centi Gy) ratio is examined as organs at risk [23]. This ideal value of CI's was expected for a "correct" plan when CI was expected to be close to "1" [26, 27].

Bladder, rectum, right and left femoral heads, penile bulb doses, and MU/cGy ratio were examined as organs at risk [23]. The ideal value of CI was expected for a "correct" plan. Since the heterogeneity is defined in the algorithm of the planning system, the Heterogeneity Index formula definition is given as equation 2.

$$Heterojenity\ Indeks\ (HI) = \frac{(D5\%)}{(D95\%)} \quad (2)$$

According to the planning system's definition of the HI, "The heterogeneity index defines the dose of uniformity in a target volume and is calculated directly from the dose-volume histogram (DVH) statistics. Although both D_5 % and D_{95} % values are defined by default, both values can be edited from the statistics tables. Here D_5 % is the dose given to the warmest 5% of the tissue. D_{95} % is the minimum dose absorbed by 95% of the tissue and these values are defined for the Monaco Planning System".

Statistical analysis

Statistical Package for the Social Sciences (SPSS Statistics 25.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The data analyzed in this study are the values obtained by calculating the means of the values of all patients (10 patients), and their standard deviations were calculated using these averages and the results were evaluated accordingly. The Kolmogorov-Smirnov test is used to check the normality of all raw data sets and the differences between data sets. In evaluating the study data and descriptive statistical methods (mean, standard deviation, frequency), paired comparisons of normally distributed parameters were made with Paired Sample *t-test*. A ***"p"***-value <0.05 indicated the differences were statistically significant.

RESULTS

Considering the reference dose values in table 1, the dose values obtained by giving 78 Gy to the 95% reference dose of IMRT, VMAT, HIBRT plans planned in the Monaco Treatment Planning System for each patient are shown in table 2. There is no statistically significant difference among the plans in terms of the dose covering PTV. When the ***"p"*** values of the pairwise comparisons were examined, it was seen that the HYBRID plans were better than all the other plans, even though they did not reach a statistically significant level ($p<0.059$). When the heterogeneity index, which is another index, was compared, it was seen that the HYBRID plans were statistically significant compared to the VMAT plans ($p<0.006$). No statistically significant difference was found in the comparison made between the plans in terms of HI. When the statistical values were examined the p value was lower than the VMAT plans, although the HYBRID plans were not statistically significant ($p<0.392$). When the V_{50} value of the bladder was evaluated, it was determined that IMRT plans were significantly better compared to the VMAT plans ($p<0.000$), and HYBRID plans were also significant compared to both IMRT and VMAT ($p<0.000$). When the bladder V_{50} doses correlations were examined, it was seen that the HYBRID plans were much stronger than the values between the second (HYBRID&IMRT=0.972) and third pairs (HYBRID&VMAT=0.974).

In terms of rectum doses, IMRT plans for rectum V_{50} values were found to be significant compared to the VMAT plan ($p <0.018$), while HYBRID plans were

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found to be significant according to both IMRT and VMAT (p <0.001).

HYBRID plans were found to be statistically significant compared to IMRT and VMAT plans in terms of right and left femoral head doses (HYBRID right, left femoral head & IMRT comparison p<0.001, HYBRID right femoral head & VMAT value p<0.001, and left femoral head value <0.002).

In terms of V_{90} penile bulb values, another parameter we examined, IMRT plans were more significant than VMAT (p<0.002). In terms of HYBRID plans, the values are statistically more significant than IMRT, and VMAT plans (p<0.000). In the MU evaluation, it was found that the VMAT plans were statistically less significant than IMRT plans (p<0.014), and MU values of HYBRID plans were statistically more significant than both IMRT plans (p<0.002) and VMAT plans (p<0.000).

Table 2. Statistical summary of CI, HI, OAR and MU values obtained from IMRT, VMAT and HYBRID (IMRT 50% - VMAT 50%) plans using Elekta Agility Linear Accelerator device and Monaco (Version 5.10) planning system.

		IMRT&VMAT				HYBRID & IMRT				HYBRID&VMAT				IMRT & VMAT	HYBRID & IMRT	HYBRID & VMAT
	N	**Mean**	**Std, Deviation**	**Std, Error Mean**	**Correlation**	**Mean**	**Std, Deviation**	**Std, Error Mean**	**Correlation**	**Mean**	**Std, Deviation**	**Std, Error Mean**	**Correlation**	**Sign (p)**	**Sign (p)**	**Sign (p)**
PTV	10	-5,26000	106,91295	33,80884	-0,305	37,22000	70,5252	22,30203	0,295	31,96000	46,96917	14,85295	0,614	0,391	0,408	0,059
HI	10	-0,01100	0,00994	0,00314	-0,055	-0,00300	0,00675	0,00213	0,345	-0,01400	0,00516	0,00163	0,791	0,881	0,329	**0,006**
CI	10	-0,00900	0,07978	0,02523	0,000	8,27700	25,97404	8,21371	0,023	8,26800	25,99116	8,21913	-0,305	1,000	0,950	0,392
Blader V_{50}	10	111,45000	608,72547	192,49590	0,893	-50,24700	317,69841	100,46506	0,972	61,20300	291,35025	92,13304	0,974	**0,000**	**0,000**	**0,000**
Rectum V_{50}	10	-177,76000	392,57932	124,14448	0,722	47,13000	236,09112	74,65857	0,873	-130,63000	259,40565	82,03127	0,889	**0,018**	**0,001**	**0,001**
R femoral head V_{50}	10	-198,75000	382,74574	121,03483	0,571	85,65000	202,87882	64,15591	0,888	-113,10000	192,54362	60,88764	0,871	0,085	**0,001**	**0,001**
L femoral head V_{50}	10	-212,97000	320,5117	101,35470	0,626	91,54800	191,88269	60,67864	0,870	-121,42200	215,24550	68,06660	0,839	0,053	**0,001**	**0,002**
Penil bulp V_{90}	10	-202,52000	426,76934	134,95631	0,856	132,50000	227,39860	71,90975	0,947	-70,02000	207,00314	65,46014	0,974	**0,002**	**0,000**	**0,000**
MU	10	-26,40000	170,45768	53,90345	0,741	22,20000	100,21399	31,69045	0,840	-4,20000	78,65508	24,87292	0,978	**0,014**	**0,002**	**0,000**

HI, CI, MU and critical organ dose values obtained by giving 72 Gy to the 95% reference dose covered PTV. HI: heterogeneity index, CI: quality index, MU:Monitor Unit, N:number of samples, IMRT: Intensity-Modulated Radiotherapy ,VMAT: Volumetric-Modulated Arc Therapy . Std: Standard, Vn: The percentage volume (V) of an organ receiving **n** dose. Sing: Significance. Data distributions were calculated by Kolmogorov Smirnov test, statistical methods Paired Sample T test. p <0.05 and less were considered significant.

DISCUSSION

Treatment techniques based on technological developments can be used in a treatment center to the extent that current systems allow. Techniques recommended according to the system should be investigated, and their place in clinical practice and routine use should be evaluated. Increasing the dose of Prostate Carcinoma (Ca) radiation therapy provides better tumor control; however, delivering critical organ doses within limits becomes a challenge. While frequently preferred IMRT and VMAT plans meet the criteria for safe irradiation, they may present difficulties in managing critical organ doses and optimum planning [28].

HYBRID plans can provide solutions to go beyond the standard plans as needed to provide patient-based improvement.

Wiggenraad *et al.* [29] IMRT and double arc plans were generated for 25 patients diagnosed with glioma or meningioma. Plans were evaluated using CI and HI. The results revealed no statistically significant difference in terms of CI. It has also been reported that dynamic conformal arc plans were more significant in HI in small PTVs and this difference disappears as the volume increases. Results of HYBRID arc plans in a randomized study by Robar and Thomas [30] in ten cranial (8 benign meningioma's and 2 glomus tumors) and ten prostate patients to compare the optimized dynamic arc and IMRT plans, both plans CI and HI were similar. In the same study, comparison of the HYBRID arc and IMRT plans revealed that HYBRID plans had significantly lower dose maximum values at both rectum and bladder maximal doses. Information that can be drawn from the previous studies confirms that HYBRID plans provide adequate protection over IMRT and VMAT [31, 32], resulting in reduction in mean doses for the bladder and rectum [6]. In addition, Bedford *et al.* [31] suggested that the reduction in irradiated rectum volume seen in HYBRID plans would also reduce the likelihood of second-degree rectal toxicity. In other toxicity studies, it is stated that IMRT plans [33, 34] cause less toxicity than conformal plans.

Amaloo *et al.* [32], focusing on the doses of organs at risk stated that" the left femoral head dose was lower in the HYBRID plan than in the VMAT (15.41 difference 1.90), while the right femoral head was lower in the VMAT plan in terms of mean femoral head doses". Several studies have reported that improvement in PTV homogeneity due to the HYBRID can result in correct dose distribution, with a small and statistically insignificant increase in the mean dose for the penile bulb [32].

Matuszak *et al.* [22] reported in Monitor Unit's context, VMAT plans are reported to be 12.2%-18.5% lower in MU compared to IMRT.

Longer treatment times are likely to degrade the quality of the plan [35, 36]. The prolonged periods also affects the quality of treatment depending on organ movements. Alexis *et al.* [37] shows that "intrafraction movement is quite common on a 5-7minutes time

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scale, with 66% of fractions outside the 2 mm range and 28% outside the 3 mm range. Ghilezan *et al.* [38] obtained that the duration of treatment time was 20 minutes. Depending on the time, the effects of the possibility of intrafraction internal movement is still unclear [25]. In the study of Mahdavi SRM *et al.* in which they compared IMRT prostate plans that received 5 and 7, they reported that there was no significant difference except for MUs [39].

The duration of the patient's treatment is also a factor that varies from one treatment center to another. The IMRT and VMAT plan calculations, MLC sequences and critical values around the target volume are used. The difference between organs is the difference between MLC sequences. MLC sequences. Optimizing critical organ doses will require more MU to deliver the targeted dose to the patient as dose blockade increases PTV [40].

CONCLUSION

When the data on IMRT, VMAT, HYBRID plans were evaluated dosimetrically, it was found that PTV dose coverage in the HYBRID plans was better than the VMAT plans. In terms of critical organ doses, lower doses were encountered in HYBRID plans compared to IMRT and VMAT. Also, studies in the literature [41] show that HYBRID plans improve plan quality compared to VMAT. Critical organ doses in our study were found to be compatible with the literature. In the light of our findings, it can be concluded that this method is suitable for routine clinical use on a patient basis since it is known that more optimum results can be achieved with the HYBRID plan in case of necessity.

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Conflicts of interest: Nothing to declare.

Ethical considerations: Ethical standards: This study is a retrospective analysis of radiotherapy plans. For this article, no work with human participants or animals were performed by any of the authors. The study was approved by the institutional ethics committee (Aydin Adnan Menderes University, Medical School, Non-interventional Clinical Research Ethics Committee, Registration number = 2021-143 and date: 26.08.2021) and was conducted in accordance with the Helsinki declaration.

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