



Optimized Hybrid Arc for Improved Sparing of Organs at Risk: Balanced Combination of IMRT and VMAT in Prostate Cancer

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Abstract

Objective: In order to seek a lower toxicity risk prediction in patients with prostate cancer, we have evaluated whether prescribing a potential hybrid radiotherapy of intensity-modulated radiotherapy (IMRT) & volumetric modulated arc therapy (VMAT) optimization might increase sparing of organs at risk (OAR) and target dose conformity.

Methods: The cohort for this dosimetric planning study included ten consecutive prostate cancer patients previously treated with double arc VMAT to 78 Gy. New optimized hybrid arc plans for a combination of IMRT (8 step-and-shoot fix fields: 225°, 260°, 295°, 330°, 30°, 65°, 90°, 135°) and VMAT (182°-178° clockwise) besides new IMRT (8 step-and-shoot fix fields: 225°, 260°, 295°, 330°, 30°, 65°, 90°, 135°) plans were generated per patient. Dose volume histogram parameters were compared between treated VMAT, new IMRT and new optimized hybrid arc plans for OAR doses.

Results: The optimized hybrid arc technique revealed significantly lower rectum ($p=0.005$) and bladder ($p=0.005$) doses compared to stand alone VMAT and IMRT.

Conclusion: The optimized hybrid arc technique appears to combine the advantages of IMRT and VMAT to provide a more conformal and homogeneous plan with better OAR sparing in comparison to standalone VMAT or IMRT plans.

Keywords: VMAT, IMRT, hybrid arc, prostate cancer

INTRODUCTION

Prostate cancer is one of the most prevalent malignant diseases among men, where definitive radiotherapy (RT) plays an indispensable role in their current treatment algorithm (1,2). The triumphant introduction of intensity-modulated RT (IMRT) and its arc-based variant volumetric modulated arc therapy (VMAT) afforded more conformal dose distributions in the target volume(s) as opposed to the historic 3-dimensional conformal RT (3D-CRT) (3,4). The vast majority of the accessible treatment planning studies comparing VMAT and IMRT have reported

comparable target volume coverage results, to be specific the planning target volume (PTV) (5-7). Nevertheless, the reported outcomes for the PTV dose homogeneity, the conformality of the dose coverage, and particularly the organs at risk (OAR) doses or sparing capacities are contradictory, with certain insightful reports advocating improved conformality as well as homogeneity with VMAT while others fancying the fixed-field IMRT over the VMAT (4-7).

As of late, a further advance forward, the hybrid arc (HA) technique attained soaring research curiosity given its noteworthy potential



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to improve dose conformity with enhanced planner control and OAR sparing capabilities relative to the VMAT and fixed-field IMRT techniques (8,9). In this respect, Robar and Thomas (10) have convincingly demonstrated that dose homogeneity and OAR sparing was altogether more likely with the novel hybrid combination of the dynamic conformal arc technique and five-field IMRT in RT of the prostate cancer patients, which has been later affirmed by Matuszak et al. (8) by generating fusion treatment with the conformal arc and IMRT fields. The newer hybrid RT approach that typically combines the double arc VMAT and IMRT techniques with differing field numbers has exhibited promising dosimetric results in nasopharyngeal and non-small-cell lung cancer investigations (11,12). We have previously documented that optimized HA technique via combining two half-articulated VMAT technique and static IMRT fields in non-small-cell-lung cancer patients (13) reduced the lung V_{5Gy} and V_{10Gy} dose bath percentages of standalone VMAT and was superior to VMAT in terms of total lung low dose volumes, while delivering faster, more conformal, more homogeneous treatment than standalone IMRT. Hence, in the absence of comparable studies, we have evaluated whether prescribing an optimized hybrid RT of IMRT & VMAT might increase sparing of OAR and target dose conformity in patients with prostate cancer in order to seek a lower risk of toxicity prediction.

METHODS

Patients

Our cohort comprised 10 patients with unfavorable intermediate & high-risk prostate adenocarcinoma, staged as stage $T_{2-3}N_0M_0$ with baseline characteristics given in Table 1. All study patients were treated with a double full arc VMAT technique between January 2016 and January 2018, and were selected for this retrospective dosimetric study. All patients were imaged in the

supine position using 3-mm scanner computerized tomography (Philips Brilliance Big Bore 16 slice CT; Philips Medical Systems Inc, Cleveland, OH) slice thickness from the umbilicus to the middle of the femoral bone with full bladder in the A-bar and knee-foot stopper immobilization (CIVCO, Kalona, Iowa). Reproducibility in bladder filling at simulation CT and fractions per day was based on our simulation routine of requesting the patient to empty bladder first, drinking 1 L water in an hour (4-6 cups, 1 cup/10 minutes), informing therapists with the first sign of bladder fullness to measure the filling with a bladderscan (Bladder Scan BVI 6400 bladder volume instrument, Verathon Healthcare, USA) to ensure ≥ 250 mL, finally verifying the volume measured with bladderscan on the simulation CT; similar procedure per daily fractions were performed accompanied by volumetric cone beam CT for reproducibility.

Treatment Planning

All previously treated plans and study IMRT and optimized plans were generated on the Philips Pinnacle treatment planning system (9.0, Philips Medical Systems Inc. Cleveland, OH) which implements the Collapsed Cone Convolution algorithm. The same dose objectives and weightings of the initial VMAT plans were used for all study plans generated.

The study design was approved by the institutional review board before collection of any patient data, and written informed consent was provided by each participant either themselves or legally authorized representatives.

Conventional Planning

All patients had previously treated VMAT plans, to a total dose of 78 Gy in 39 daily fractions, utilized by two full arcs with the same isocenter rotating clockwise and counter-clockwise starting from 182° and 178° with different collimator angles, respectively.

Table 1. Patient's characteristics

Patient	Age	T-stage	PSA (ng/mL)	Gleason score	PTV volume (cc)
1	68	T3b	15	7 (4+3)	132.73
2	84	T2	4.07	7 (4+3)	108.75
3	78	T2b	15.08	7 (4+3)	102.55
4	77	T2c	7.21	7 (4+3)	90
5	71	T2c	0.5	8 (4+4)	121.22
6	68	T3a	3.93	8 (4+4)	103.25
7	73	T2	8.04	7 (3+4)	93.75
8	80	T2c	3.09	9 (4+5)	142.50
9	79	T3b	6.70	7 (3+4)	112.40
10	71	T2b	22.1	9 (4+5)	100.30

T: Tumor stage, PSA: Prostate-specific antigen, PTV: Planning target volume, cc: cm³

For each study patient, a static gantry step and shoot IMRT plan was created with 8 coplanar fields of 225°, 260°, 295°, 330°, 30°, 65°, 100°, 135° gantry angles and a total of 160 segments (14).

Optimized Hybrid Arc [(oHA): Optimization of IMRT and VMAT Combination]

oHA technique was created by optimizing an 8-field IMRT (225°, 260°, 295°, 330°, 30°, 65°, 100°, 135° gantry angles) and one full arc VMAT combination, as the optimization strategy is shown in Figure 1. Our strategy was based on three steps: First step to generate one full arc VMAT and 8-field IMRT, where dose weight of 50% for VMAT and IMRT was defined as a starter optimization; second step to start optimization with direct machine parameter optimization for IMRT and the Smart Arc optimization for VMAT separately with same normalization volume chosen to achieve the same coverage for both techniques; third step to allow unlimited field weight ratio for Pinnacle treatment planning system to optimize based on our constraints. The final optimized plan was manually decided based on initial goals of target coverage and OAR sparing. Isodose distribution and DVH graphic for each technique on the sample case are shown in Figures 2 and 3.

Dosimetric comparison: For each case, the competing VMAT, IMRT, and HA plans were compared on the basis of several criteria as specified below. For the rectum, DVH points of $D_{15\%}$ (Gy), $D_{25\%}$ (Gy), $D_{35\%}$ (Gy), and $D_{50\%}$ (Gy), as well as the $V_{75\text{ Gy}}$ (%), $V_{70\text{ Gy}}$ (%), $V_{65\text{ Gy}}$ (%), and $V_{60\text{ Gy}}$ (%), were examined. For the bladder, DVH points of $D_{15\%}$ (Gy), $D_{25\%}$ (Gy), $D_{35\%}$ (Gy), and $D_{50\%}$ (Gy), as well as $V_{80\text{ Gy}}$ (%), $V_{75\text{ Gy}}$ (%), $V_{70\text{ Gy}}$ (%), and $V_{65\text{ Gy}}$ (%), were examined. For total bilateral femur heads and penile bulb, the maximum (D_{max}) and mean (D_{mean}) dose values were compared. For target coverage

(PTV), maximum dose (D_{max}), mean dose (D_{mean}), conformity index (CI) as recommended by RTOG and homogeneity index (HI) as recommended by ICRU 83 were compared. Low dose to the body, the body $V_{5\text{ Gy}}$ (%) and $V_{10\text{ Gy}}$ (%) was used as a point of comparison. In addition, a monitor unit [(MU): one fraction] comparison was made between each techniques.

Statistical Analysis

The three different techniques were compared using two-tailed pairwise Wilcoxon signed-ranked tests. A value of $p < 0.05$ was considered to indicate statistically significant differences (please provide the open form of each abbreviation where it is used, such as, RTOG, ICRU, V_{60} , $D_{\%35}$, additionally, is it $D_{\%35}$ or $D_{35\%}$, please correct if not right). We have included 10 random cases as the arbitrary minimum number to demonstrate the statistical difference.

RESULTS

Plan Quality

The IMRT, VMAT, and HA treatment plans were generated for each of 10 prostate cancer patients separately. All plans were clinically acceptable with at least 95% of PTV being covered with %95 of the prescribed dose. The typical isodose distributions for each planning strategy and matching DVH findings were as pictured in Figure 3, while the results of the PTV coverage were as tabulated in Table 2. The PTV mean doses (D_{mean}) of the three techniques were statistically almost indistinguishable, whereas both the CI and the HI of the HA plans were significantly superior to both the IMRT and VMAT plans. “The conformity index CI95 was calculated as the ratio of the volume enclosed by the 95% isodose volume to the part of the target volume receiving more

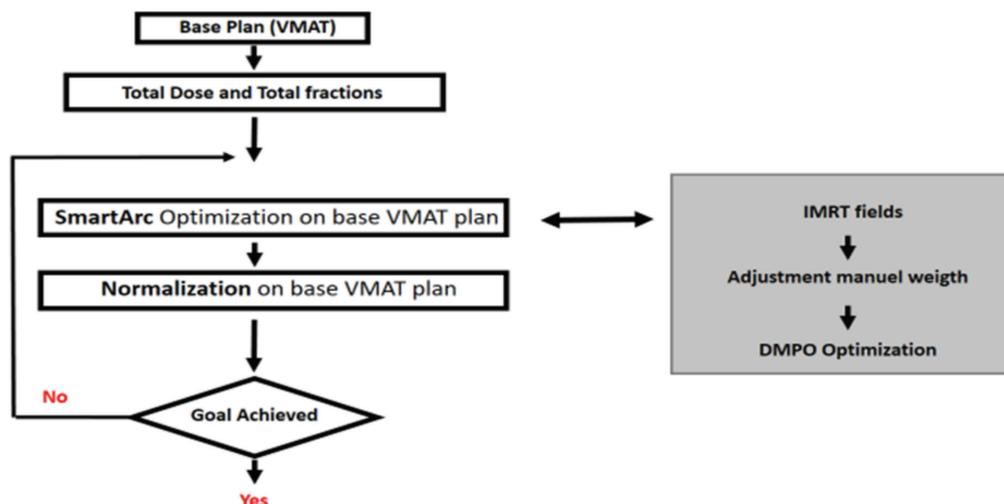


Figure 1. The research strategy for HA optimization

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, DMPO: Direct machine parameter optimization, HA: Hybrid arc

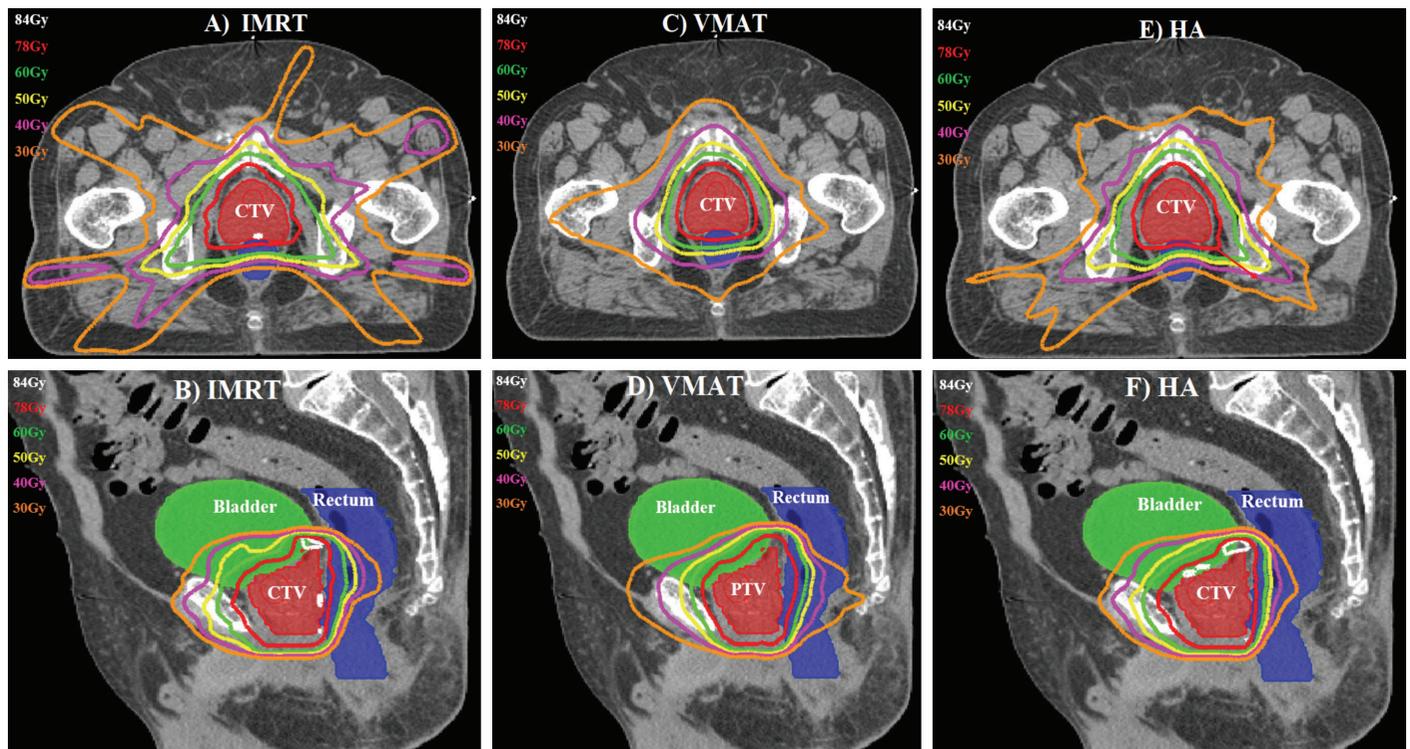


Figure 2. The isodose distribution of A) axial and B) sagittal view of IMRT, C) axial and D) sagittal view of VMAT, E) axial and F) sagittal view of HA
 VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, CTV: Clinical target volume

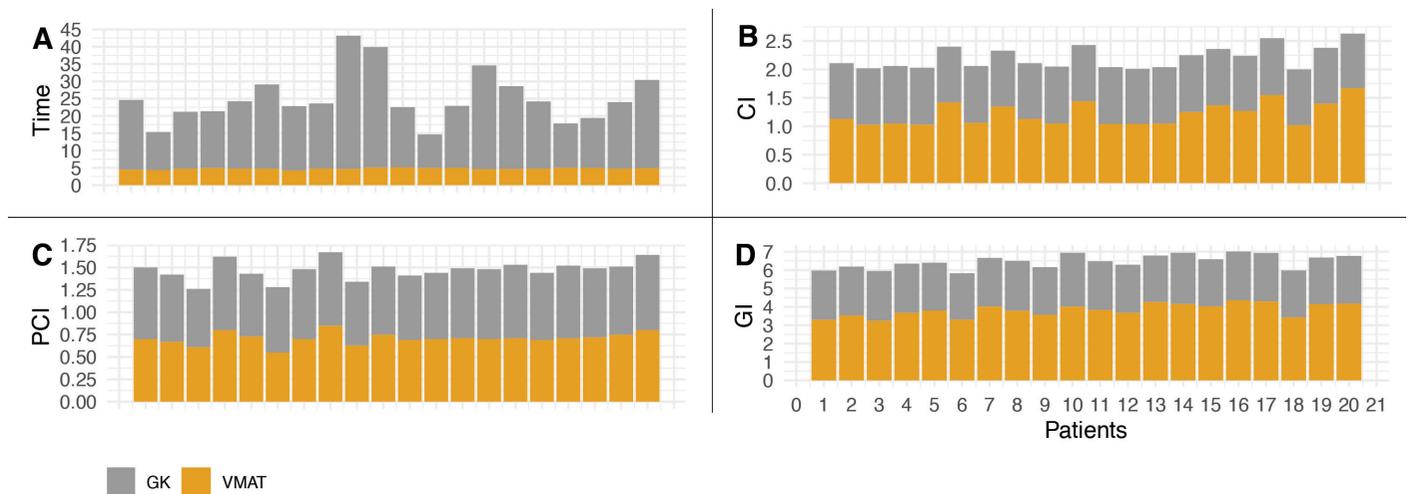


Figure 3. The bar plot of treatment time and index according to GK and VMAT. (a) The treatment times were higher in GK plans (19.00 minutes, range: 9.70-38.50 minutes) compared to VMAT plan (4.80 minutes, range: 4.23-5.15 minutes; $p < 0.01$). (b) CI were similar in both treatment plans. (c) and (d) plot showed that PCI and GI indexes for each patient which revealed, GK is higher than VMAT
 VMAT: Volumetric modulated arc therapy

than 95% (i.e., CI 95= V95%/TV95%). The 95% isodose was chosen (the ICRU-62 report) to provide 95% target volume coverage. HI was also calculated as $HI = D2\%-D98\%/D 50\%$, according to the ICRU-83 report.

As presented in Table 2, the MU of VMAT technique was lower than the MUs of IMRT technique (678.7 vs. 814; $p=0.028$), while, although the MU of the HA was slightly higher than that of the VMAT technique (776.9 vs. 678.7; $p=0.037$) as expected, yet it was statistically comparable with the calculated MU of the IMRT (776.9 vs. 814; $p=>0.05$).

Figure 2 exhibits the dose distributions of the three RT techniques in sagittal and axial views. Considering the doses received by the body, either of $V_{5\text{ Gy}}$ and $V_{10\text{ Gy}}$ were lower with the HA technique as opposed to the VMAT (for $V_{5\text{ Gy}}$ 18.8 vs. 22; $p=0.008$ and for $V_{10\text{ Gy}}$ 14.3 vs. 17.3; $p=0.007$) and IMRT (for $V_{5\text{ Gy}}$ 19.75 vs. 22; $p=0.007$ and for $V_{10\text{ Gy}}$ 15.4 vs. 17.3; $p=0.014$) techniques, respectively. Likewise, the IMRT was found to lead to lower body doses than the VMAT technique.

OAR Doses

The outcomes of OAR doses unveiled from the DVHs of each planning technique are shown in Table 3. Accordingly, the HA technique revealed significantly lower mean OAR values for each organ than the VMAT technique. Likewise, the HA plans were found to provide significantly lower values with the exceptions of the rectal $D_{50\%}$ (Gy) and $V_{65\text{ Gy}}$ (%) as opposed to IMRT plans. The IMRT plans emerged to render meaningfully more acceptable OAR doses in almost all dosimetric parameters, but the rectal $D_{15\%}$ (Gy) and $D_{25\%}$ (Gy) values. Comparably, the HA plans were found to reveal significantly lower OAR doses than the VMAT in all OAR parameters except for the bladder $V_{80\text{ Gy}}$ (%) with a difference of only 0.18%. Moreover, the HA technique was significantly superior over IMRT in provision of lower OAR doses, but bladder except $V_{80\text{ Gy}}$ (%) value. Considering the D_{max} and D_{mean} doses of total femoral heads (left + right) and the penile bulb

were significantly lower with the HA planning strategy compared to the VMAT and IMRT strategies.

DISCUSSION

We have demonstrated that our novel oHA plans theoretically revealed significantly lower organ at risk doses for rectum ($p=0.005$) and bladder ($p=0.005$) compared to previously treated VMAT and generated IMRT plans.

After almost reaching the technical plateau with either of the IMRT and VMAT, researchers tried to further force the limits by consolidating various advanced RT planning techniques to enable extra technical gains, which may translate to better PTV dose conformality and OAR sparing. Acknowledging these facts, the relatively novel HA technique seems to represent a superior approach in accomplishing preferred treatment designs over the IMRT and VMAT counterparts (8,12,15). Paralleling with the recent hybrid RT literature (11-13), we examined the clinically viable and actually costless blend of VMAT and IMRT to see whether this new technique could meaningfully improve the dose conformity, OAR avoidance, and reduction of the integral dose. Providentially, our results uncovered that the overall plan quality was positively enhanced with the combination of 8-field IMRT and single-arc VMAT techniques, as will be discussed in detail below. Of note, the critical distinction between our current research and the previously published hybrid RT studies is our HA optimization strategy (13), where we consolidated 8-field IMRT and single-arc VMAT techniques explicitly for prostate cancer RT planning.

The VMAT and IMRT techniques have been comparatively studied by various researchers before in terms of dosimetric outcomes of prostate cancer RT planning, however, the results of such studies have for the most part been conflicting (4,5,14,16-20). Some studies have shown that VMAT were all significantly superior to IMRT in most of the relevant values evaluated of target

Table 2. Dosimetric comparison of PTV for IMRT, VMAT and HA plans, including MU, CI HI and body values

Parameter	VMAT	IMRT	HA	p value (VMAT vs. IMRT)	p value (HA vs. VMAT)	p value (HA vs. IMRT)
PTV D_{max} (Gy)	82.77	83.23	82.84	0.005	NS	0.005
PTV D_{mean} (Gy)	79.95	80.27	80.02	0.007	0.047	0.012
MU	678.7	814	776.9	0.028	0.037	NS
CI	1.016	1.009	1.005	0.018	NS	0.014
HI	0.196	0.266	0.208	0.005	NS	0.005
Body $V_{5\text{ Gy}}$ (%)	22	19.75	18.8	0.007	0.008	NS
Body $V_{10\text{ Gy}}$ (%)	17.3	15.40	14.3	0.014	0.007	NS

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, PTV: Planning target volume, MU: Monitor unit, CI: Conformity index, HI: Homogeneity index, D_{max} : Maximum dose, D_{mean} : Mean dose, D_{xx} (Gy): Dose on %X, V_{XGy} (%): Volume on XGy, NS: Not significant

coverage, OARs and normal tissue sparing (4,14,17); on the other hand some studies demonstrate that IMRT is a better technique to spare OARs and has comparable dosimetric parameters of two techniques for plan quality (5,19). Additionally, in a study from MD Anderson Cancer Center, Quan et al. (15) reported that the VMAT was more efficient than the IMRT with regard to the treatment delivery efficiency (14). Nevertheless, whether the VMAT technique may also generate more qualified treatment plan quality than IMRT in the setting of the RT planning of the prostate cancers remains to be clarified. The plan qualities of VMAT and IMRT are for the most part reliant on the notable differences between the number of beam angles and the level of modulation from each angle used (17-21). Results of the joint studies have revealed that larger beam angle numbers with fewer modulations (control points) were significantly more capable of accomplishing superior plan qualities than the philosophy which lean towards many modulations with smaller

beam angle numbers (14,15). Comparing VMAT to IMRT plans which ranged from 12 to 24 for the set of patients VMAT plan quality resulted in approximately 30% more monitor units than the 8-beam IMRT plans, as well as similar dose distributions as the number of angle increases (15). On the other hand, particular to the IMRT procedure, larger modulation numbers from many beam angles may still compensate for the insufficient number of beams in the generation of highly qualified treatment plans (14). To minimize unknown certainties, target definitions, pre-set dose constraints, planning strategies, optimization algorithms, and beam angles, all plans were performed and defined by a single physician (US) and physicist (YS). Framing a sound ground for our present 8-field IMRT plan, it has likewise been contended that IMRT with >8 beams was clinically impractical considering its lower conveyance productivity (14).

The overall treatment durations with VMAT plans have been established to be significantly shorter than the IMRT plans

Table 3. Average dosimetric results for OARs sparing for VMAT, IMRT and HA

Parameter	VMAT	IMRT	HA	p value VMAT vs. IMRT	p value HA vs. VMAT	p value HA vs. IMRT
Rectum						
D _{15%} (Gy)	63.33	61.27	51.95	NS	0.005	0.005
D _{25%} (Gy)	49.66	47.30	37.56	NS	0.005	0.005
D _{35%} (Gy)	37.05	33.26	26.63	0.013	0.005	0.005
D _{50%} (Gy)	22.63	17.28	16.87	0.005	0.005	NS
V _{75 Gy} (%)	7.09	4.65	3.48	0.007	0.007	0.019
V _{70 Gy} (%)	11.5	7.42	6.16	0.008	0.008	0.018
V _{65 Gy} (%)	14.65	8.99	8.85	0.005	0.008	NS
V _{60 Gy} (%)	17.76	12.16	11.39	0.005	0.005	0.047
Bladder						
D _{15%} (Gy)	54.14	48.47	47.37	0.005	0.005	0.021
D _{25%} (Gy)	35.76	29.78	28.97	0.007	0.005	0.013
D _{35%} (Gy)	24.65	20.11	18.92	0.005	0.005	0.047
D _{50%} (Gy)	15.34	12.40	11.37	0.005	0.005	0.005
V _{80 Gy} (%)	1.89	2.11	2.07	NS	NS	NS
V _{75 Gy} (%)	7.89	6.82	6.07	0.005	0.005	0.012
V _{70 Gy} (%)	10.13	9.16	7.94	0.032	0.005	0.007
V _{65 Gy} (%)	11.92	10.69	9.6	0.005	0.005	0.005
Femoral heads						
D _{max} (Gy)	50.19	49.35	45.54	NS	0.028	0.005
D _{mean} (Gy)	22.76	22.10	19.37	NS	NS	0.005
Penile bulb						
D _{max} (Gy)	51.7	53.31	44.71	NS	0.005	0.005
D _{mean} (Gy)	24.58	25.67	22.18	NS	NS	0.037

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiation therapy, HA: Hybrid arc, PTV: Planning target volume, D_{max}: Maximum dose, D_{mean}: Mean dose, D_{xx} (Gy): Dose on %X, V_{XGy} (%): Volume on XGy, NS: Not significant

although the total monitor units were comparable (18). Therefore, as can be assumed, treatment durations with HA-IMRT will unavoidably be longer than the VMAT procedures regardless of the primary tumor sites being dealt with. Confirming this reasonable assumption, formerly Zhao et al. (11,12) demonstrated that the hybrid IMRT/VMAT technique was linked with longer treatment durations and higher MUs compared to the VMAT but shorter treatment durations and lower MUs compared to the IMRT. Thusly, our present discoveries concerning the treatment durations and the calculated MUs for HA-IMRT were in accordance with Zhao's findings, albeit neither of the contrasts between HA-IMRT versus VMAT or HA-IMRT versus IMRT could accomplish factual importance. In addition, Quan et al. (15) revealed that hybrid technique having IMRT segment with a different rate between 0% and 100% improved plan quality definitely by the use with 100% IMRT segments (9).

In this current dosimetric research, we mainly attempted to lessen the inevitable disadvantage of the VMAT, mainly the spread out low doses over a large volume of healthy tissue around the PTV by consolidating the VMAT with IMRT: HA-IMRT. We witnessed that the HA-IMRT plans were superior to both of the VMAT and IMRT alone plans concerning more desirable or if nothing else comparative OAR sparing and PTV dose conformity acquired with the HA-IMRT. Moreover, better dose modulation and dose fall-off around the PTV seemed, by all accounts, to be more favorable with HA than the VMAT technique. Our outcomes which recommended lower OAR dosages with HA than both VMAT and IMRT are in acceptable agreement and land further support on the published results of previous research proposing lower OAR doses with hybrid RT technique which incorporated volumetric/conformal arc and IMRT (9,11,12,22). As depicted in Table 2, being in line with the previous hybrid technique studies, the PTV dose homogeneity was also notably improved with the HA technique. In addition, Amaloo et al. (23) have been shown that Hybrid technique included combine of two dynamic IMRT fields with VMAT has a lower dose of integral dose and whole body. However, our HA optimization strategy trying to optimize different treatment techniques together has reduction value in V5 -V10 of the whole body on average compared to VMAT and IMRT. As well as our study improved OAR sparing and target homogeneity, on the other hand, lower receiving 5 Gy and 10 Gy overall. Despite statistical significant results, the differences were small and clinical relevance could be minimal, but in a challenging case, we can propose hybrid planning as a promising technique for OAR preservation.

Our dosimetric study sustains some specific confinements. First, the present research was impeded by its limited sample size as

we typically intended to assess our hypothesis in a dosimetric pilot study. Second, we distributed the dose equally (50% for each technique) among the two constituents of our novel technique to carefully adjust the possible advantages and entanglements of the individual procedure. Therefore, various other dose combinations may prompt better PTV and OAR results, particularly for patients presenting with differently sized and shaped prostate glands and overall distinct anatomical variances of the OARs. Third, although HA plans generated here implement an optimal treatment technique for radiation oncology clinics readily treating prostate cancer with IMRT or VMAT techniques without further specific requirements for additional equipment, yet, placing the conduction of further large-scale clinical studies with adequate follow-up times, no clinically pertinent erudition can be got as a result of the examination's dosimetric nature.

CONCLUSION

The results of the present dosimetric study firmly proposed that the novel HA technique described herein was able to consolidate the unique advantages of the IMRT and VMAT techniques in terms of providing more conformal and homogenous dose distributions in the intended targets and lowering the inadvertent dosages got by the OARs, compared with the traditional VMAT technique. The HA technique essentially reduced all bladder and rectum doses except for the $V_{80\text{Gy}}$ (%) of the bladder. Thus, despite recognizing the exact necessity for further studies with sufficient follow-up durations to reliably interpret the likely consequences of such remarkable discoveries on the patients' clinical results, we believe that our current study could be perceived as the first endeavor on a novel but potentially more effective and secure treatment approach for the RT of prostate cancer patients: So-called HA technique, which combines 8-field IMRT and VMAT.

Ethics

Ethics Committee Approval: 2017-111-IRB2.032 approval was obtained from Koç University Faculty of Medicine.

Informed Consent: Written informed consent was provided by each participant either themselves or legally authorized representatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.S., Y.B., U.S., Concept: Y.S., Design: Y.S., A.B., Data Collection or Processing: Y.S., Y.B., U.S., Analysis or Interpretation: Y.S., Y.B., A.B., U.S., Literature Search: Y.S., Y.B., A.B., U.S., Writing: Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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