

Dosimetric Evaluation of Advanced Radiotherapy Techniques in Treating Patients with Prostatic Cancer

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Background: Different radiotherapy techniques were developed to deliver optimal dose to prostate cancer while sparing nearby organs at risk (OARs).

Aim: To compare different dosimetric methods used to evaluate sparing of OARs and to select radiotherapy plan which provides the most OARs sparing during prostate cancer treatment.

Methods: We used computed tomography data sets of 10 patients. For each data set, six plans were calculated; two RapidArc, two intensity-modulated radiation therapy (IMRT), and two 3-dimensional conformal radiotherapy (3DCRT) plans. Isodose distribution and dose volume histograms (DVHs) were used for plan analysis and evaluation. The dose to OAR was compared by calculating the DVH for each OAR in different plans. The dose (D) delivered to certain percentage (n) of an organ (Dn) was then determined. In addition, the Critical Organ Scoring Index (COSI) and the modified COSI (mCOSI) were calculated.

Results: 3DCRT with 5 fields produced the lowest rectal dose, RapidArc with bladder avoidance sector (RapidArc-Bladder) produced the lowest bladder dose and IMRT with 9 beams produced the lowest dose to the femoral heads. The COSI and MCOSI values of the two IMRT plans were significantly lower than those of 3DCRT and RapidArc (<0.0001). The calculation of mCOSI produced similar results to that obtained with COSI (<0.0001).

Conclusion: The results of this study showed that COSI and MCOSI are better dosimetric methods in selecting the plan with more sparing of OARs than Dn. Meanwhile among advanced radiotherapy techniques, RapidArc and 3DCRT are more sparing of OARs than IMRT.

Keywords: Radiotherapy planning, Organ at risk, Dosimetric evaluation, Critical Organ Scoring Index (COSI)

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INTRODUCTION

Prostate cancer incidence is growing all over the world due to the rise in the median age of population and the increasing prostate-specific antigen screening. Prostate cancer is the 6th most common type of cancer worldwide and the 2nd most predominant in men, accounting for about 10% of all cancer cases¹.

The optimum treatment of localized prostate cancer stays debatable. There are three main options of treatment; surgery, radiotherapy (external beam radiotherapy or brachytherapy) and hormonal therapy². Radiation therapy is one of the main lines of treatment in early, locally advanced and even metastatic prostate cancer. In the new era of advanced radiotherapy techniques such as intensity-modulated radiation therapy (IMRT), several trials have documented its excellent results especially in the treatment of prostate cancer. IMRT permits dose escalation with high conformity and high dose to the prostate and while sparing normal tissues such as the bladder and rectum²⁻⁴. Moreover, IMRT results were much better as regards toxicity in comparison to three-dimensional conformal radiotherapy (3DCRT) technique plans⁵⁻⁷. Therefore, IMRT is being increasingly used in the treatment of prostate cancer.

Various modalities of IMRT delivery systems have been developed, such as linear accelerator based-IMRT systems, the Tomotherapy® system (Hi-Art system, Accuray Inc., Madison, WI, USA), the RapidArc system (Varian Medical System Inc., Palo Alto, CA, USA), the volumetric modulated arc therapy (VMAT) system (Elekta Instrument AB Stockholm), and the CyberKnife system (Accuray Inc., Sunnyvale, CA, USA), and proton systems.

Dosimetric studies have compared treatment plans using different IMRT modalities in patients with prostate cancer⁸⁻¹². The dosimetric outcome differed when comparing plans using RapidArc and the VMAT in comparison to IMRT in the treatment of prostate cancer¹³⁻²⁴. Many studies observed better normal tissue sparing with VMAT over IMRT when including simple target volume (prostate with or without seminal vesicles) though shortened treatment time did not differ between both modalities^{12, 14, 16, 17, 19-21, 23}. However, very few studies have focused on more complex pelvic target volumes, containing the prostate, seminal vesicles and pelvic lymph nodes^{15, 18, 22, 24}. Some of these studies found largely equivalent sparing of organs at risk (OARs) between VMAT and IMRT^{8, 14}. In contrast, other studies have reported contradictory results,

showing IMRT technique to give superior OARs sparing in comparison to VMAT¹⁵. Myrehaug et al found VMAT to have no consistent dosimetric advantage over IMRT²². Thus, those studies have produced diverse results.

The aim of this study was to examine a dosimetric evaluation method to evaluate sparing of OARs in advanced radiotherapy techniques. Then, we apply the evaluation method to select radiotherapy plan which provides most OARs sparing in prostate cancer.

METHODS

Cases and Plans

In this study, we used computed tomography data sets from 10 patients who had been previously treated with 3DCRT for prostate cancer at the Clinical Oncology Department, Ain Shams University Hospitals.

For designing treatment plans and calculating dose distributions for all applied radiotherapy techniques, Eclipse treatment planning system V13.5 (Varian

Medical System Inc., Palo Alto, CA, USA) with AAA algorithm have been used.

For each data set, six plans have been calculated; two RapidArc, two IMRT, and two 3DCRT plans. The planning target volume (PTV) was contoured by expanding the prostate contour with a 10 mm margin in all directions except in the posterior direction where only 8 mm margin was applied to spare additional rectal tissue from receiving radiation dose. The prescribed dose was 76Gy in 38 fractions over 52 days. The dose was prescribed and normalized at the isocenter point in all techniques.

Figure 1 shows the different plans studied in this work. The studied plans were as follows:

- 3DCRT: Two different plans with different number and arrangements of fields:
 - 3DCRT with five fields (3DCRT-5): the beam angles of this plan were 0°, 50°, 90°, 270° and 310° (Figure 1.A).
 - 3DCRT with seven fields (3DCRT-7): the beam angles of this plan were 0°, 50°, 90°, 130°, 220°, 270° and 310° (Figure 1.B).

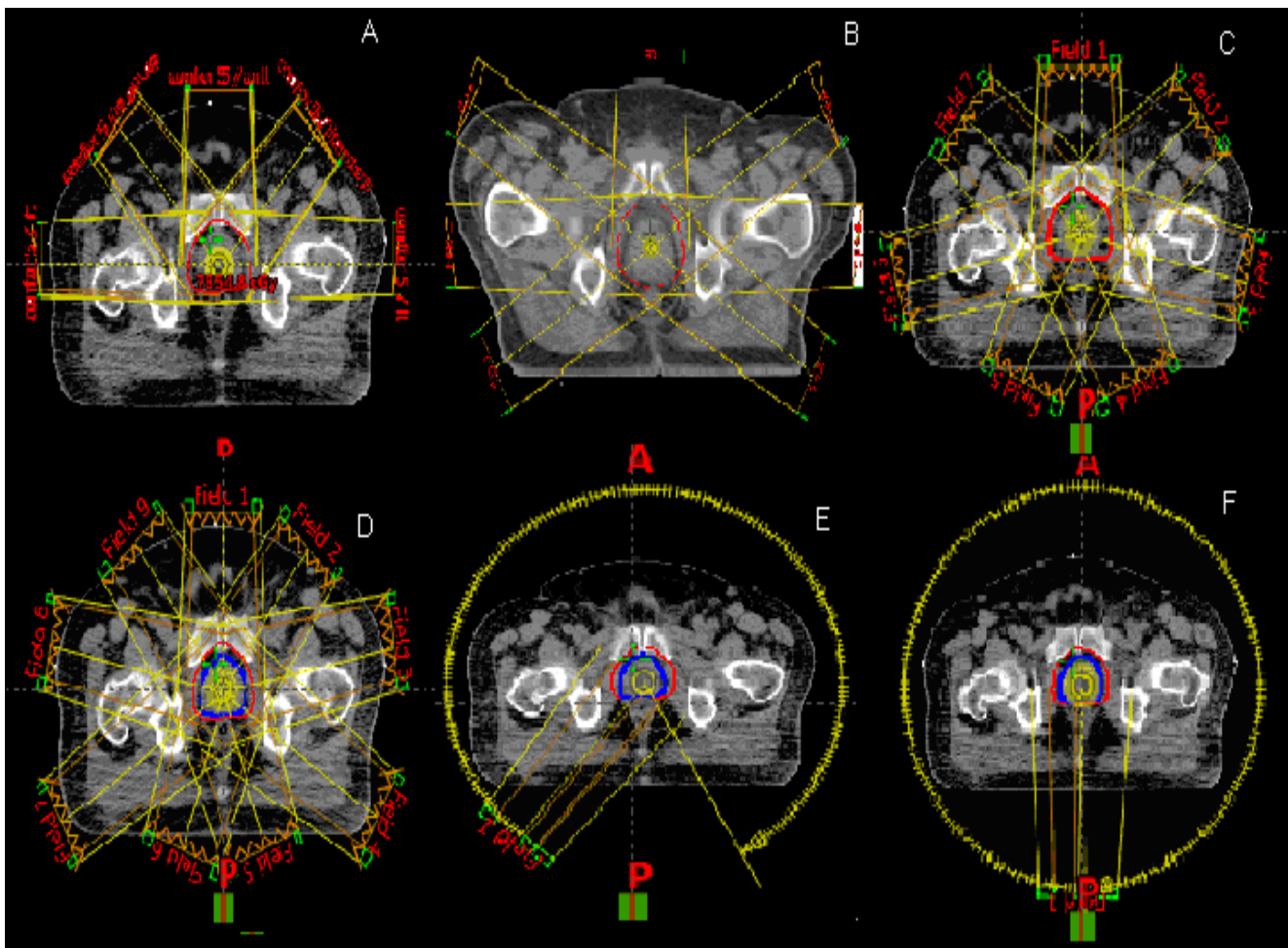


Figure 1: Beam arrangement for six plans. **A:** 3DCRT with five fields (3DCRT-5); **B:** 3DCRT with seven fields (3DCRT-7); **C:** IMRT with seven fields (IMRT-7); **D:** IMRT with nine fields (IMRT-9); **E:** Single arc with 300° arc angle (RapidArc-rectum); **F:** A single full arc (RapidArc-bladder).

- IMRT: Two different plans with different number and arrangements of fields:
 - IMRT with seven fields (IMRT-7): The beams were arranged with equal angle separation of 51 degrees between each two beams. IMRT-7 had gantry angles of 0°, 51°, 102°, 153°, 204°, 255° and 306° (Figure 1.C).
 - IMRT with nine fields (IMRT-9): The beams were arranged with equal angle separation of 40 degrees between each two beams. IMRT-9 had gantry angle of 0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320° (Figure 1.D).
- RapidArc: Two different plans with different arc shapes:
 - RapidArc-Rectum: A single arc with 300° arc that started with a gantry angle of 150° and rotated in a counter clockwise to gantry angle 210°. The arc deliberately avoided treating through the rectum from the posterior direction (Figure 1E).
 - RapidArc-Bladder: A single full arc utilized an arc that started with the gantry at 179° and rotated in a counter clockwise to gantry angle 181°, for a total 360° arc. An anterior 60° avoidance sector was applied to avoid the bladder anteriorly. The avoidance sector started at 330° to 30°. In the RapidArc plans, the collimator was set at 30° to minimize the multileaf collimator tongue and groove effect (figure 1F).

Data analysis

Both of isodose distribution and dose volume histograms (DVHs) were used for plan analysis and evaluation. DVHs were calculated and generated based on 3D reconstructed images for PTV and all OARs in treatment plans. A dose distribution was considered acceptable for treatment if it is able to meet the prescribed prostate planning dose-volume constrains outlined in table 1. The target coverage was quantitatively assessed by using dosimetrical indexes like prescription isodose to target volume ratio, homogeneity index, conformity index (CI), target coverage index (TCI), conformity number (CN) and dose gradient.

Isodose distribution and DVH analysis were insufficient to distinguish which plan was superior in terms of higher sparing of OARs. As a result, more dosimetric calculations have been performed for each OAR. The dose to the OAR was compared by calculating the DVH for each OAR in different plans. Then, determining the dose delivered to certain percentage of an organ (Dn). For the rectum and the bladder; D15, D25, D35 and D50 were determined. For the head of femur; D0 (Dmax), D25 and D40 were determined. In addition to that, two more indexes were calculated to account for the irradiation of all OARs regarding their tolerance. One of these indexes is the Critical Organ Scoring Index (COSI) which takes into account both the target coverage and the critical organ

irradiation^{25, 26}. The main advantage of this index is its ability to account of the irradiation of all OARs simultaneously in one index. The COSI can be expressed as:

$$COSI = 1 - \sum_1^n w_i \frac{V_i(OAR)_{>tol}}{TC}$$

Where "V(OAR)_{>tol}" is the fraction of the volume of OAR that receives more than a predefined tolerance dose, and TC is the volumetric target coverage, which is defined as the fractional volume of the PTV covered by the prescribed isodose. The target coverage (TC) is defined as the ratio of the target volume receiving at least the prescription dose (V_{T,PI}) to the total target volume (V_T). Typically; the coverage index should be at least 95%. TC is expressed as: TC = V_{T,PI} / V_T²⁵.

COSI may also be expressed as:

$$COSI = 1 - \frac{V(OAR)_{>tol}}{TC_V}$$

In this study we used the first equation for calculating COSI. The reason of using the first equation is accounting for the irradiation of the four OARs simultaneously.

The other index that was calculated in this study is the modified COSI (mCOSI) which is expressed as:

$$mCOSI = \sum_{i=1}^n Wi \left[\frac{COSI_{10} + COSI_{20} + \dots + COSI_{80}}{8} \right]$$

Although the COSI focuses only on OARs receiving high dose region volumes, the mCOSI considers both high dose and low dose regions.

Table 1: Planning objectives for intensity modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (RapidArc) treatments of the prostate

Volume/ OAR	Dose constraint
PTV	99% of the volume to get ≥95% of the prescription
	Minimum dose > 90% of the prescription
	Maximum dose <107% of the prescription
	The maximum dose must be within the PTV
Rectum	<50% of the volume to receive 60 Gy
	<35% of the volume to receive 65 Gy
	<25% of the volume to receive 70 Gy
	<15% of the volume to receive 75 Gy
Bladder	<50% of the volume to receive 65 Gy
	<35% of the volume to receive 70 Gy
	<25% of the volume to receive 75 Gy
	<15% of the volume to receive 80 Gy
Head of femur	<45% of the volume to receive 40 Gy
	<25% of the volume to receive 45 Gy
	0% of the volume to receive 50 Gy

OAR: Organ at risk; PTV: Planning target volume

Statistical analysis was conducted using Graphpad Prism version 7 for windows (www.graphpad.com). Statistical comparison between the evaluation factors of different plans was done using the one way ANOVA test. To be statistically different, the values were needed to be significant at the 95% level (i.e. $p < 0.05$).

RESULTS

Doses delivered to OARs are presented in table 2. 3DCRT-5 produced the lowest rectal dose. The rectal doses in the other five plans were very close. However, the differences of the four dosimetric doses of the rectum between all plans were not statistically significant. The RapidArc-bladder produced the lowest bladder dose which was statistically significant when compared to the other techniques. The bladder doses in the other five plans were very close. The differences in the four dosimetric doses of the bladder in all other plans were not statistically significant. IMRT-9 produced statistically significant lower doses to the left and right femoral heads.

The COSI and mCOSI values of all applied plans are shown in table 2. The COSI values of the 3DCRT and RapidArc plans were very close with no significant

difference. The COSI values of the two IMRT plans were lower than that of 3DCRT and RapidArc and the difference between them was statistically significant. This means that 3DCRT and RapidArc may spare all OARs simultaneously more than IMRT.

Calculation of the mCOSI produced similar results to that obtained with COSI. The mCOSI values of both 3DCRT and RapidArc were very close with no significant difference. The mCOSI values for the IMRT plans were significantly lower than those of 3DCRT and RapidArc plans. This confirms that 3DCRT and RapidArc may spare all OARs simultaneously more than IMRT.

DISCUSSION

Radiation treatment planning analyses usually depend on DVH as the most widely used dosimetric tool to physically evaluate different plans. The results of this study indicated that the selection of a plan depending on dose volume objectives only may spare one OAR but not the others. Accordingly, we examined two other methods, the COSI and the mCOSI to evaluate dose-sparing of all OARs simultaneously in different treatment plans for prostate cancer.

Table 2: Doses to organs at risk using the six radiotherapy techniques

OAR	Radiotherapy technique						F	p-value
	3DCRT-5	3DCRT-7	IMRT-7	IMRT-9	RapidArc - rectum	RapidArc - bladder		
Mean \pm SD								
Rectum								
D50%	38 \pm 7.76	35 \pm 7.41	43 \pm 8.78	42 \pm 8.34	37 \pm 7.62	34 \pm 6.27	2.1897	0.0687
D35%	47 \pm 9.93	49 \pm 8.43	56 \pm 9.90	55 \pm 9.59	48 \pm 8.68	51 \pm 8.13	1.6764	0.1561
D25%	51.6 \pm 8.96	55 \pm 8.88	62 \pm 9.13	61 \pm 9.33	54 \pm 8.15	60 \pm 9.24	2.2869	0.06
D15%	59 \pm 8.83	65 \pm 8.27	70 \pm 10.1	69 \pm 9.87	62 \pm 8.67	67 \pm 9.50	2.0970	0.0798
Bladder								
D50%	27 \pm 4.5	26 \pm 4.1	31 \pm 5.8	30 \pm 3.9	27 \pm 4.3	17 \pm 2.1	13.6017	<0.0001
D35%	34 \pm 4.5	32 \pm 4.8	37 \pm 5.1	35 \pm 5.4	33 \pm 4.2	24 \pm 2.3	10.0338	<0.0001
D25%	41 \pm 5.8	40 \pm 6.1	45 \pm 5.6	46 \pm 4.9	43 \pm 5.2	32 \pm 3.1	9.3449	<0.0001
D15%	51 \pm 5.9	49 \pm 5.1	53 \pm 5.6	52 \pm 5.3	50 \pm 4.8	42 \pm 4.1	5.808	<0.0001
Lt. Femur								
D max%	50 \pm 9.3	39 \pm 7.2	42 \pm 7.6	29 \pm 2.8	48 \pm 7.2	47 \pm 6.9	11.3455	<0.001
D 25%	29 \pm 4.3	31 \pm 3.3	27 \pm 2.3	22 \pm 2.3	28 \pm 3.3	30 \pm 3.5	9.6672	<0.001
D 40%	30 \pm 5.1	31 \pm 5.3	26 \pm 2.1	20 \pm 1.3	27 \pm 3.3	28 \pm 4.2	10.2784	<0.001
Rt. Femur								
Dmax%	42 \pm 6.7	39 \pm 4.6	40 \pm 4.8	29 \pm 5.3	41 \pm 4.5	40 \pm 5.4	8.1758	<0.0001
D25%	31 \pm 4.9	30 \pm 5.2	32 \pm 4.3	22 \pm 1.6	34 \pm 3.5	33 \pm 3.8	11.3372	<0.0001
D40%	33 \pm 6.1	32 \pm 5.6	28 \pm 3.5	21 \pm 2.1	31 \pm 3.3	30 \pm 4.8	9.5502	<0.0001
COSI	0.828 \pm 0.10	0.817 \pm 0.11	0.615 \pm 0.041	0.610 \pm 0.062	0.835 \pm 0.12	0.843 \pm 0.15	11.8815	<0.0001
mCOSI	0.126 \pm 0.021	0.116 \pm 0.021	0.075 \pm 0.010	0.056 \pm 0.011	0.114 \pm 0.031	0.109 \pm 0.032	14.6399	<0.0001

OAR: Organ at risk; **3DCRT:** three-dimensional conformal radiotherapy; **IMRT:** intensity-modulated radiation therapy; **COSI:** Critical Organ Scoring Index; **mCOSI:** modified Critical Organ Scoring Index

Another advantage of COSI and mCOSI is the evaluation of TC as well as evaluating the sparing of OARs. Our results showed that using a certain technique may spare one OAR but not the other which may be spared by another technique. On the other hand, COSI and mCOSI may specify the technique with the most dose-sparing of all OARs.

The COSI was described by Menhel et al in 2006 as a new index to compare between radiotherapy plans ²⁵. They tested the new index on the planning of the following sites: head and neck, cavernous sinus and pancreas. They compared treatment plans of conformal noncoplanar 3D and IMRT techniques. For all three sites the usage of COSI index was so helpful in comparing between the treatment plans and facilitated the choice of the optimal one. Analysis of individual DVHs and isodose lines were done and the results were compared to the widely used conformation number. They confirmed the efficiency of COSI in assessing different treatment plans through evaluating the different dosimetric parameters and choosing the optimal plan. The COSI tool was found to be objective, quick and accurate tool in choosing the best plan. Similar to our results, Menhel et al found that a non-coplanar 3D plan was superior to the IMRT plan ²⁵.

Levin et al in their retrospective study on ten patients with maxillary sinus tumors compared treatment plans of 9-field IMRT, directionally optimized IMRT, and 3D noncoplanar planning in terms of critical organ sparing and TC ²⁷. They used the COSI in the analysis of different treatment plans and compared it to other widely used conformation numbers. In cases where the choice of best treatment plan was difficult, the 2D COSI-CI index gave an accurate evaluation of TC and OAR overdoses, even in the situation where other conformity indices failed. Both IMRT techniques gave comparable results. They delivered lower doses to ipsilateral structures while 3D plans delivered lower doses to contralateral structures with more homogeneous dose distribution.

In this study, we compared the quality of RapidArc technique with that of IMRT and 3DCRT in the treatment of prostate cancer patients with prophylactic pelvic radiotherapy and simultaneous dose escalation to the prostate. All the three techniques were able to meet all of our plan acceptance criteria. The results showed that RapidArc and 3DCRT resulted in slightly superior conformity of prostate PTV as they have higher COSI and mCOSI than IMRT. The COSI and mCOSI values indicated also that RapidArc was more sparing of OARs (bladder, rectum and heads of femur) than IMRT. These results are in compliance with RapidArc demonstrating better conformity to the PTV than IMRT. Similar results were observed by Elith et al in their study on twenty prostate cancer cases ²⁸. They assessed the plan quality of both VMAT and IMRT and concluded that IMRT plans had the advantages of more homogeneous dose distribution and less time in calculation, while the VMAT plans gave better conformity to the target volume with more sparing of OAR.

Lee et al performed a planning study on ten patients with prostate cancer ²⁹. Different modalities of IMRT

were used, like the linac step and shoot, RapidArc and proton systems. Analysis and comparison between different treatment plans were carried out using variable dosimetric indexes such as COSI, homogeneity index, quality factor, and conformation number. Superior conformity index, homogeneity index, and CN values in addition to higher COSI were recorded with RapidArc plan denoting better coverage of PTV. In terms of more sparing of OAR especially in high dose volumes, the tomotherapy and RapidArc plans were much better than other techniques.

Our observation is different from that reported by Yoo et al ¹⁵. They reported that IMRT plans in cases with large PTVs (including the prostate, seminal vesicles and lymph nodes) were more sparing to the bladder, rectum, and small when compared to the RapidArc technique. Meanwhile for small PTVs (including the prostate and seminal vesicles) both conventional IMRT and RapidArc technique with two arcs were comparable as regards OAR sparing. The differences in their results could be explained as they increased the number of beams for IMRT, which shows better results with more beams in general. The differences in the volume and shape may be also contributing. Another factor is the dose-volume constraints for OARs and their weightings as they tightened the dose-volume constraints during the optimization process. Also the treatment planning using RapidArc was still in its early stages, whereas treatment planning using IMRT has actively progressed over 10 years.

Conclusion

The results of the current study shows that COSI and mCOSI are better in selecting the plan with more sparing of OARs than Dn. When comparing the advanced radiation therapy modalities, RapidArc and 3DCRT were found to be more sparing of OARs than IMRT in the treatment of patients with prostate cancer.

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