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Evaluation of Modern Radiotherapy Techniques in Treatment of Cancer Prostate

Dr. Amin El-Sayed Amin
Professor, Department of Medical Physics, Radiation Oncology and Nuclear Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Somaia Metwally El-Sayed
Senior Medical Physicist, Radiation Oncology and Nuclear Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Dr. El-Sayed Mahmoud El-Sayed
Professor, Department of Biophysics & Physics, Faculty of Science, Ain Shams University, Cairo, Egypt
Dr. Abdelsattar Mohamed Sallam
Professor, Department of Biophysics & Physics, Faculty of Science, Ain Shams University, Cairo, Egypt
Dr. Mona Salah El-Din Talaat
Professor, Department of Biophysics & Physics, Faculty of Science, Ain Shams University, Cairo, Egypt

Abstract:
Purpose: The aim of this study is to establish a procedure to allow evaluating physically and biologically a 3DCRT, IMRT and RapidArc treatment plans in radiotherapy of cancer prostate.
Material and Methods: In an attempt to launch a model to evaluate treatment plans in advanced radiotherapy, we have studied some common evaluation indices. In physical evaluation, we studied dose homogeneity indices (MHI and HI), target coverage and conformity indices (PITV, TCI, CI, and CN), dose gradient (GI and GM) and an index for overall plan quality factor (QF). In Biological evaluation we studied TCP and NTCP for tumor and critical structures, and P+ for free complication tumor control. Evaluation has been performed for six plans, four RapidArc plans, one IMRT and one 3DCRT plan.
Results: In physical evaluation, HI and MHI values indicated that 3DCRT has the best dose homogeneity. Calculated values of PITV, TCI, CI, and CN showed that both IMRT and RapidArc produce better dose conformity than 3DCRT. GM and GI values displayed that, RapidArc gives better dose gradient than IMRT and 3DCRT. So, none of these physical evaluation indices allowed ranking the plans. Calculating QF index allowed ranking the plans. The QF value of RapidArc plans gave the highest values. In Biological evaluation, in spite of the clear difference in NTCP values of OARs, the TCP values were almost equal. So P+ was calculated to integrate both of TCP and NTCP in one index. RapidArc plans with avoidance of both bladder and rectum had the highest P+ values.
Conclusion: Physical evaluation of treatment plan can't be achieved by calculating dose homogeneity, dose conformity, or dose gradient alone. This issue can be solved by calculating treatment plan quality factor. In biological evaluation of treatment plan, outcome can be estimated by calculating P+ rather than calculating TCP and NTCP alone.

Keywords: *Radiotherapy, Prostate, IMRT, RapidArc, 3DCRT, Physical Evaluation, Biological Evaluation.*

1. Introduction

Localized prostate cancer is one of the most common tumor sites treated with external beam therapy. The total radiation dose to the prostate has been shown to be important for disease control, but dose escalation was restricted because of the normal tissue toxicity.[1,2,3]Intensity Modulated Radiotherapy (IMRT) uses multiple fixed fields (from 5 to 11) with highly irregular intensity pattern to deliver remarkably conformal dose distribution. Since its introduction in the 1990s, IMRT has rapidly become the technique of choice for prostate cancer in modern radiotherapy centers.[4]IMRT has the ability to escalate the total dose to the target while minimizing the radiation exposure to the surrounding organs. This ability has developed the radiotherapy technology in the treatment of prostate cancer[5,6,7].

Despite the obvious benefits of IMRT, there are some disadvantages, first the relatively long time of treatment delivery which leads to: patient discomfort; the higher dose delivery uncertainty because of interfractional organ motion. Second the large number of monitor units (MUs) which mean increasing of total integral dose this raises the concern about secondary malignancies after curative treatment due to the exposure to more leakage radiation[8].

Technological fusion of IMRT and Arc modalities resulted in the RapidArc® (Varian Medical Systems) technique which provides comparable or sometimes even better dosimetric parameters of dose distribution than IMRT alone. Beam intensity is modulated continuously during gantry rotation around the patient's body. In IMRT and RapidArc, treatment plans are reported to provide highly conformal dose distribution with good sparing of normal tissues[9,10]. However, the duration of the therapeutic session in RapidArc is reported to be even 8 times shorter in comparison to therapeutic time of the other dynamic techniques, which benefits the quality of treatment delivery. Therefore, RapidArc is presented by some authors as a fast and simple treatment modality, with precision that matches or exceeds dose conformity of the IMRT technique[9,10,11,12,13].However, unambiguous analysis should be done to point whether Rapid Arcplans are superior to the IMRT in respect to dosimetric parameters for a specific patient plan.

Recently several studies have compared RapidArc with IMRT as the most advanced radiotherapy techniques for cancer prostate treatment[14-29]. The most common finding reported was the shortened treatment time, but there are inconsistencies in the dosimetric outcome. Many studies considering relatively simple target volumes that included prostate only or prostate with seminal vesicles found that VMAT achieved equal or better normal tissue sparing over IMRT[14,19,20,22,23, 25-27].However, very few studies have focused on more complex pelvic target volumes, including the prostate, seminal vesicles and pelvic lymph nodes[21,24,28,29]. Some of these studies found largely equivalent sparing of organs at risk (OARs) between RapidArc and IMRT[24,29]. However, other planning studies have reported contradictory results. Yoo et al[21] noted superior OARs sparing with IMRT to rapidarc. Myrehaug et al[28] found Rapidarc have no consistent dosimetric advantage over IMRT. Thus, those studies have yielded mixed results.

1.1. Aim of the Work

The aim of this study is to establish a procedure to allow physical and biological evaluation of 3DCRT, IMRT and RapidArc treatment plans in radiotherapy of cancer prostate.

2. Material and Methods

2.1. Cases and Plans

In this study we used de-identified CT data sets from 18 patients that had been previously treated at Oncology Department, Ain Shams University Hospitals with 3DCRT to the prostate only.

Dose distributions were generated retrospectively for each data set using six plans; four RapidArc beam arrangements, IMRT, and one 3DCRT plan (all plans are detailed below). All planning was done on v13.5 of Varian Medical Systems Eclipse planning software.

2.2. Techniques

Four different techniques of RapidArc were designed and compared with IMRT and 3D conformal plans. The used RapidArc plans are;

One 300^{o} arc from 210^{o} to 150^{o} with anterior 40^{o} avoidance sector, (1FRA) (figure1A)

- One full rotation single arc (SA) (figure 1B)
- Two 130^{o} lateral arcs (from 210^{o} to 340^{o} and from 20^{o} to 150^{o}) (2HA) (figure 1C)
- Double Arcs with one full rotation (360^{o}) arc and one (260^{o}) Arc: from 230^{o} to 130^{o} (DA) (figure 1D).

In IMRT the number of fields was optimized using Eclipse IMRT optimizer. The optimum number of fields was seven fields. The fields angles were optimized using Eclipse angle optimization facility (figure 1E). In 3D conformal techniques, five fields have been used (figure 1F).

2.3. Dose Prescription

A conventional schedule with a daily dose of 2 Gy for a total dose of 76 Gy in 38 fractions over treatment time of 52 days has been used. Dose distribution was normalized and prescribed on mean dose.

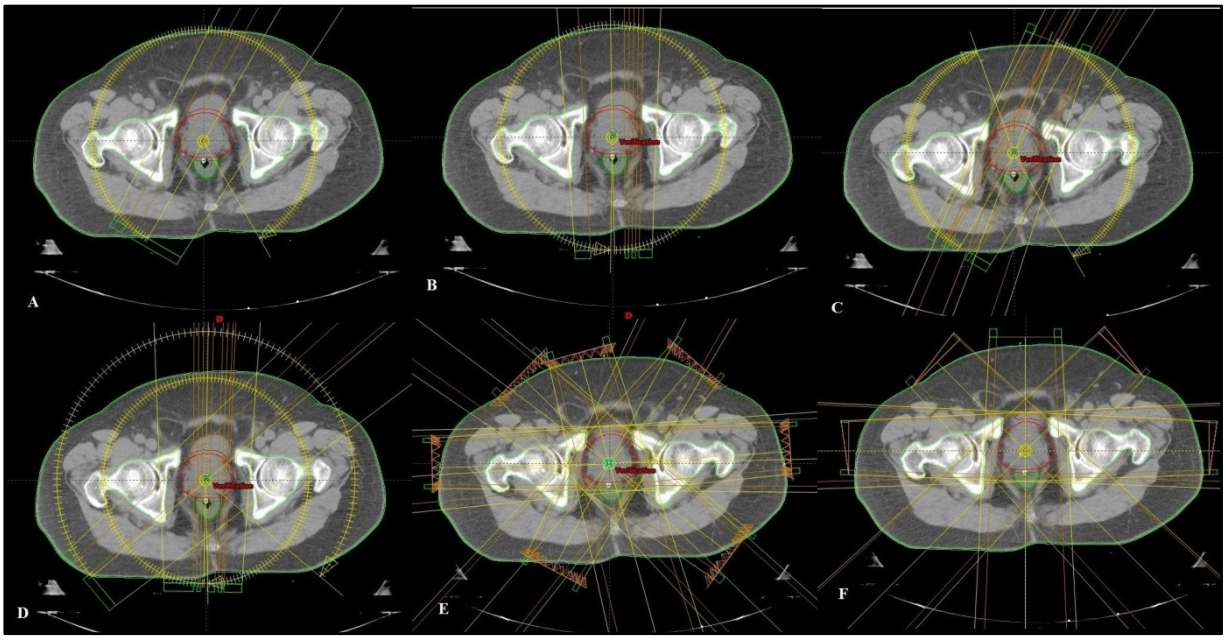

Figure 1: Beam arrangements in different techniques. A: One 300^o arc from 210^o to 150^o with anterior 40^o avoidance sector, (1FRA). B: One full rotation single arc (SA). C: Two 130^o lateral arcs (from 210^o to 340^o and from 20^o to 150^o) (2HA). D: Double Arcs with one full rotation (360^o) arc and one (260^o) Arc: from 230^o to 130^o (DA). E: IMRT technique with 7 fields (IMRT7). F: 3D Conformal technique using 5 fields (3DCRT).

3. Data Analysis

3.1. Physical Evaluation

Both of isodose distribution and Dose volume histograms (DVH's) are used for plan analysis and evaluation. Dose volume histograms (DVH's) were calculated and generated based on 3D reconstructed images for PTV and all OARs in treatment plans. Isodose distribution and DVH analysis were insufficient to distinguish which plan was superior. As a result, there are several indices that may represent target conformity and dose homogeneity[30-34].

A dose distribution was considered acceptable for treatment if able to meet the prescribed prostate planning constrains outlined in table (1). The target coverage was quantitatively assessed by using dosimetrical indices like prescription isodose to target volume (PITV) ratio, homogeneity index (HI), conformity index (CI), target coverage index (TCI), modified dose homogeneity index (MHI), conformity number (CN), gradient index (GI), gradient measure (GM), and planning quality factor (QF).

Volume/organ at risk (OAR)	Dose constraint
Planning target volume (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

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

3.2. PTV Dose Statistics

The PTV DVH's of the different used techniques were used to generate the statistical parameters of PTV dose. The generated parameters are; the maximum and minimum doses and mean, modal and median doses as well as the standard deviation (STD) of the PTV dose distribution.

3.3. Homogeneity Index (HI)

The concept of HI was developed as an extension of section-by-section dosimetric proposed guidelines for routine evaluation of stereotactic radiotherapy (SRT) plans based on several parameters and HI was described as,

$$HI = \frac{D_{Max}}{D_p} \quad (1)$$

Where D_{Max} is PTV maximum dose and D_p is the prescribed dose[35].

An HI of 1 represents the ideal uniform dose within a target. Higher HI values indicate greater dose heterogeneity in the PTV[36]. According to ARTOG, if the HI was ≤2, treatment was considered to comply with the protocol, if this index was between 2 to 2.5, it was considered as minor violation, but if the index exceeded 2.5, the violation of the protocol was considered to be major, but might nevertheless considered acceptable[36,37].

3.4. Modified Homogeneity Index (MHI)

MHI is similar to HI, and is expressed as[35]:

$$MHI = \frac{D_{Max}}{D_{Min}} \quad (2)$$

Where, D_{Max} and $D_{Min}$are PTV maximum and minimum doses respectively.

In most of the publications D_{max} and $D_{min}$are expressed in terms of D_{95} and D_5 respectively or either D_{98} and D_2 or D_{99} and D_1. The reason for choosing those doses rather than the actual maximum and minimum doses, is that the calculation of true minimum or maximum dose is sensitive to the dose-calculation parameters, such as grid size and grid placement, and the high dose gradient is common in Intensity Modulated Radio-Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). Therefore, the true minimum or maximum dose is typically not reliable[38]. This is the reason for choosing the maximum or minimum dose in a volume (D_1, D_2, or D_5 and D_{99}, D_{98}, or D_{95}) rather than at a point. Thus, in all definitions, MHI basically indicates the ratio between the maximum and minimum dose in the target volume and the lower value indicates a more homogenous dose distribution within this volume.In this study we expressed D_{max} and D_{min} in terms of D_{99} and D_1 i.e. in this study MHI is calculated as;

$$MHI = \frac{D_{99}}{D_1} \quad (3)$$

We used equation (3) in that form to calculate MHI because it is very sensitive to any variation in dose distribution more than that calculated in terms of D_{98} and D_2 or D_{95} and D_5

3.5. Target Coverage Index (TCI)

TCI accounts for the exact coverage of PTV in a treatment plan at a given prescription dose. The target coverage Index (TCI) is defined as the ratio of the target volume receiving at least the prescription dose, V_T, to the total target volume, V_t. Typically; the coverage index should be at least 95%. TCI is expressed as[39];

$$TCI = \frac{V_{tP}}{V_t} \quad (4)$$

3.6. Prescription isodose to Target Volume (PITV) Ratio

The prescription isodose to target volume PITV ratio, obtained by dividing surface volume surrounded by prescription isodose level (inside and outside the PTV), V_p divided by target volume V_t, i.e. PITV is expressed as;

$$PITV = \frac{V_P}{V_t} \quad (5)$$

The PITV ratio is a conformity measure, and a value of 1.0 indicates that the volume of the prescription isodose surface equals that of the PTV. A PITV ratio of 1.0 does not necessarily imply that both volumes are similar. To ensure adequate PTV coverage, this measure should always be used in conjunction with a PTV-DVH[36].

3.7. Conformity Index (CI)

The conformity index (CI) is defined as the ratio of the total volume receiving at least the prescription dose, Vp, to the target volume receiving at least the prescription dose, Vtp[40], i.e.

$$CI = \frac{V_p}{V_{tp}} \quad (6)$$

The value of CI is always greater than unity. A value that is closer to unity represents a better target conformity of radiation dose in the treatment plan.

CI is generally used to indicate the portion of a prescription dose that is delivered inside the PTV. CI of 1 indicates that 100% of a prescription dose is delivered to the PTV, and no dose is delivered to any adjacent tissue[41]. The CI is less than 1 for most clinical cases. Higher CI values indicate poorer dose conformity to the PTV.

3.8. Conformity Number (CN)

Dose conformity evaluates the dose fit of the PTV relative to the volume covered by the prescription dose[21]. Ideally the prescribed dose should fit tightly to the target volume, therefore, reducing the side effects occurred by treating surrounding tissues and organs. The CN simultaneously takes into account irradiation of the target volume and irradiation of healthy tissues[42]. The CN is defined as;

$$CN = TCI\ X\ CI = \frac{V_{tP}}{V_p}\ X\ \frac{V_{tp}}{V_t} \quad (7)$$

where V_p is the total volume receiving the prescription, V_t is the target volume, and V_{tp} is the target volume covered by the prescription[43]. A CN value closer to 1 indicates that the dose distribution fits more tightly to the target volume preserving healthy tissue.

3.9. Gradient Index

The gradient index (GI) is defined as the ratio of the volume covered by at least a given percentage of the prescription dose (V_G) to the volume covered by the full prescription dose (V_P)[44]. In most of dosimetric studies, the given percentage is set at 50% of the prescription dose and that is what we used in this study. Mathematically, GI is expressed as:

$$GI = \frac{V_G}{V_p} = \frac{V_{50}}{V_{100}} \quad (8)$$

The value of GI is greater than unity. A value that is closer to unity represents a faster dose fall-off in normal

3.10. Gradient Measure (GM)

Gradient Measure is a quantity calculated by Eclipse treatment planning software to express the dose gradient value in centimeters. Gradient measure is given by the difference between the equivalent sphere radius of the prescription and half prescription isodoses). In this study GM is given by the difference between the equivalent sphere radius of 100% and 50% isodoses.

3.11. Dose to Organs at risk

The dose to the organs at risk (OAR) was compared by calculating the dose volume histograms (DVH) for each OAR in different plans. Then, determining the percentage volume (V) of an organ receiving n dose (Vn). For rectum and bladder V15, V25, V35 and V50 were determined. For the two heads on femur, the V25and V40 were determined.

3.12. Number of Mus

The total number of MUs needed to deliver each treatment plan was summed and recorded.

3.13. Quality Factor (QF)

Quality Factor (QF) is a dosimetrical index that can evaluate the quality of the entire plan. The quality factor (QF), was introduced by Pyakuryal, (2010)[39]. The QF of a plan can be analytically expressed as:

$$QF = [2.718 \exp(-\sum_i^n W_i X_i)] \quad (9)$$

In the above equation, X_i represents all of the PTV indices used for evaluating a plan. The values of the weighting factor (W_i) can be adjusted between 0 and 1 for all relatively weighted indices for a user-defined number of indices (N). In this study the indices that used in calculating QF are HI, MHI, TCI, PITV, CI, CN, GI and GM. The weighting factor (W_i) that applied in equation (9) for calculating QF is 1/8 for the eight indicies.

3.14. Biological Evaluation of Treatment Plans

Biological evaluation has been performed using the Eclipse TPS system. This software can produce tumor control probability (TCP), Normal tissue complication probability (NTCP) and Complication-free tumor control probability (P+) based on radiobiological models using a combination of biological and physical criteria. The TCP and NTCP Poisson-LQ could be obtained either based on the Linear Quadratic (LQ) cell survival model or equivalently the linear dose-response model with the Equivalent dose in 2-Gy fractions(EQD2).

3.15. Tumor Control Probability (TCP)

The Poisson TCP model is based on Poisson statistics and describes the probability of no surviving clonogens[45]. If we assume there are total *N* clonogenic cells and the survival fraction (*SF*) of clonogenic cells of a given dose *D* is SF_D, the Poisson TCP is

$$TCP = \exp(-N\ .\ SF_D) \quad (10)$$

Now let us apply the LQ model to include fractionation sensitivity. Recall that

$$SF_D = exp(-\alpha D - \beta D d) \quad (11)$$

The Poisson TCP based on the LQ model becomes

$$TCP = exp\left(-N\ exp(-\alpha D - \beta D d)\right) \quad (12)$$

A common parameter in using the Poisson TCP model is SF_2which is the surviving fraction after a single 2Gy dose. If we convert physical dose to dose in 2Gy fractions (i.e. EQD_2), the Poisson TCP model can be express in $SF_2$and EQD_2or $gEUD_2$:

$$TCP = \exp\left(-N\ .SF_2^{EQD_2/2}\right) \quad (13)$$

Where EQD_2 is given by;

$$EQD_2 = D\ \frac{\left(\frac{\alpha}{\beta}+\frac{D}{N}\right)}{\left(\frac{\alpha}{\beta}+2\right)} \quad (14)$$

3.16. Normal Tissue Complication Probability (NTCP)

The relative seriality model proposed by Kallman et al[46]. was used for NTCP Poisson-LQ. A high value of seriality would be used for serial organs that were sensitive to high local doses even though the mean doses were low, while a lower value of seriality would be

used for parallel organs that were less sensitive to local high doses, but still affected by high and low doses[46].The relative seriality NTCP modelis derived based on the architecture of tissues (parallel, serial, and/or cross-linked functional subunits). The NTCP is given by:

$$NTCP = \left[\prod_{i=1}^{n}(1 - P\,(D_i)^s)^{1/n}\right]^{\frac{1}{s}} \quad (15)$$

And

$$P(D_i) = \left[1 + \left(\frac{D_{50}}{gEUD_{2,i}}\right)^{4\gamma}\right]^{-1} \quad (16)$$

where $D_{50}$is the dose that would cause 50% complication; γ is the slope of dose response curve at D_{50}; s is the fitted relative seriality parameter of the tissue; n is the total number of voxels.

In equation (16) $gEUD_2$ is the generalized Equivalent Uniform Dose. $gEUD_2$ is calculated by the following equation;

$$gEUD = (\frac{1}{N}\sum_{i=1}^{N} d_i^a)^{1/a} \quad (17)$$

Where, $d_i$is the dose in voxel i; N is the total number of voxels; a is the volume parameter which indicates the relevance of the non-uniformity of dose distributions[47,48].

The Eclipse system allows the users to adjust the parameters of the TCP and NTCP functions in the biological evaluation template such as the D_{50}, γ and α/β. The values of D_{50}, γ and α/β which used in this study are shown in table (2).

Tissue	End Point	D50 (Gy)	γ	α/β (Gy)	s	Reference
PTV	Stage B TCP	52.7	4.2	10	_	Perez (1986)[49]
	Stage C TCP	63.3	5	10	_	Perez (1986)[49]
Bladder	Contruction	80	3	3	3	Ågren Cronqvist (1995)[50]
Rectum	Necrosis/Stenosis	80	2.2	3	1	Ågren Cronqvist (1995)[50]
Femoral Head	Necrosis	65	2.7	3	1	Ågren Cronqvist (1995)[50]

Table 2: Parameters of TCP and NTCP functions that applied in this study for different tissues.

3.17. Complication-free Tumor Control Probability (P+)

Complication-free tumor control probability or tumor control without normal tissue complications (P+) is another term that combines TCP and NTCP and is commonly used to predict treatment outcomes. It gives a single value that takes into account the predicted tumor control and predicted normal tissue complications for a treatment plan. In general,

$$P^+ = TCP(1 - NTCP)$$
$$= TCP - NTCP + \delta\,.(1 - TCP)\,.NTCP \quad (18)$$

where δ specifies the fraction of patients with statistically independent TCP and NTCP. The approximate value of δ is 0.2[46,51].

3.18. Statistical Analysis

Statistical analysis was conducted using Graphpad Prism version 7 for windows (www.graphpad.com).The 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.,$P < 0.05$).

4. Results

4.1. Physical Evaluation

All treatment plans of the three different techniques were able to satisfy all dose-volume constrains prescribed in table (1) for all cases.

4.2. Dose Distribution

Figure (2)shows the typical isodose distributions of 6 plans applied in this study and described above. The dose distribution of 3DCRT technique is shown in figure (2A), IMRT technique is shown in figure (2B) and the four RapidArc plans are shown in figures 2C, 2D,…,2F.

Dose volume histograms (DVHs) for the PTV, rectum, bladder, and heads of femurs, for each of the six plans are presented in Figure (3)

4.3. PTV Dose Statistics

As shown in table (3) and Figure (4) the Mean, Mode and medial doses of the six plans are almost equal this means that the dose distribution in the PTV has a normal statistical distribution and this lead to conclude that the dose distribution in the PTV is highly homogeneous in all plans. In figure (5) we notice that the IMRT plan has the lowest value of the STD of the PTV dose distribution. In Figure 6 it is obvious that the Maximum Dose (Dmax) in RapidArc is higher that of both 3DCRT and IMRT, but the difference was not statistically significant. It is also clear in figure 6 that the IMRT plan has the highest minimum dose (Dmin). The difference between Dmin in IMRT and RapidArc is statistically significant.

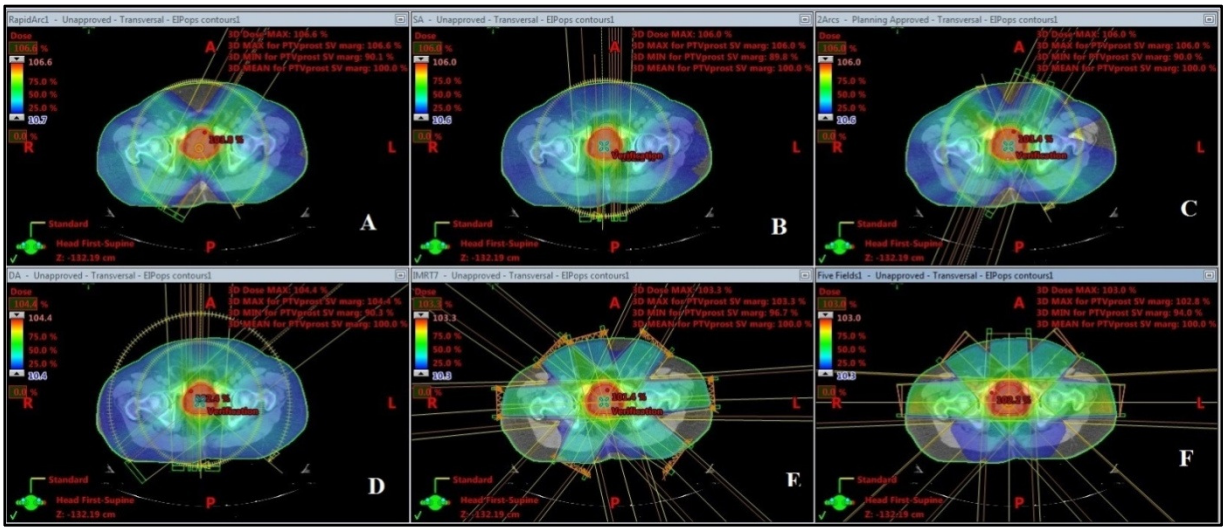

Figure 2: Dose Distribution of all plans. A: 1FRA, B: SA, C: 2HA. D: DA, E: IMRT7, F: 3DCRT.

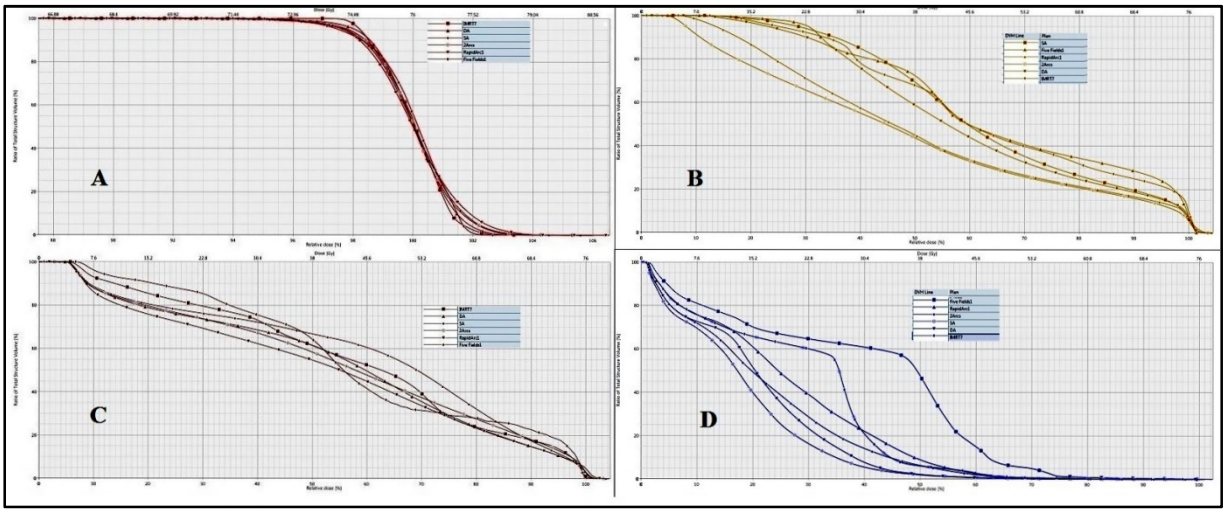

Figure 3: DVH's of all plan. A: DVH's of PTV, B: DVH's of Bladder, C: DVH's of Rectum, D: DVH's of Femoral Heads.

4.4. Homogeneity Indices

Figure 7 shows both HI and MHI of all plans. We can see that both HI and MHI can lead to the same conclusion regarding PTV dose homogeneity. It is obvious that IMRT and 3DCRT have homogeneity indices closer to 1 more than RapidArc i.e. the best dose homogeneity. This harmonizes with the results shown in figures 5 and 6 that IMRT and 3DCRT has lowest STD and the highest minimum doses.

4.5. Target Coverage Index (TCI) and PITV

Figure (8) displays the calculated TCI and PITV for all plans. It is apparent that, TCI values of all plans are almost equal with no significant difference and the PITV values of IMRT and RapidArc have very close values. On the other hand the highest value of PITV is obtained in 3DCRT.

4.6. Dose Conformity

Figure 9 shows the CI and CN values of different plans. It is clear that, the values of both CI and CN in all RapidArc plans are almost equal. The IMRT have a slightly higher value of CI but with no significant difference and an almost similar value of CN. The 3DCRT produced a higher and significantly different value of CI and a lower value of CN but with no significant difference.

4.7. Dose Gradient

Figure 10 shows the values of GI of different plans. We can notice that the GI values of all RapidArc plans are very close. While IMRT and 3DCRT have lower GI values. This means that in RapidArc the dose drop outside the PTV is very quick in comparison with IMRT and 3DCRT.

Figure 11 shows the Gradient measure values of the six plans. The GM represents the distance of dose drop between PTV and OARs. This means that the higher the GM value is the longer of the distance of dose drop. The RapidArc plans and IMRT have almost equal

GM values but 3DCRT has a higher and significantly different GM value. So this means that in 3DCRT the dose drop outside PTV occurs in a larger volume.

Index	3DCRT	IMRT	RApidArc			
			2HA	DA	1FRA	SA
Max Dose	102.8±1.6	103.3±1.42	106±1.52	104.4±1.45	106.6±1.38	106±1.44
Min Dose	94±2.24	96.7±2.12	90±2.31	90.3±2.41	90.1±2.38	89.8±1.98
Mean Dose (Gy)	100	100	100	100	100	100
Mode Dose (Gy)	100.2±0.12	100.1±0.11	99.9±0.09	100.2±0.11	100±0.1	100±0.11
Median Dose (Gy)	100.2±0.08	100.1±0.09	100±0.07	100±0.08	100±0.07	100.1±0.09
STD	1.3±0.12	1.1±0.1	1.3±0.12	1.2±0.11	1.5±0.14	1.4±0.13
HI	1.028±0.015	1.033±0.014	1.06±0.012	1.044±0.013	1.066±0.013	1.06±0.014
MHI	1.061±0.012	1.046±0.011	1.07±0.012	1.062±0.011	1.079±0.013	1.073±0.012
CI	1.332±0.14	1.099±0.13	1.014±0.11	1.053±0.11	1.037±0.12	1.058±0.12
CN	0.405±0.041	0.482±0.049	0.521±0.048	0.484±0.043	0.484±0.051	0.483±0.05
TCI	0.539±0.019	0.53±0.017	0.528±0.016	0.509±0.014	0.502±0.012	0.51±0.015
PITV	0.719±0.081	0.582±0.077	0.536±0.073	0.536±0.072	0.521±0.071	0.54±0.075
GI	1.853±0.049	1.887±0.051	1.9±0.053	1.964±0.054	1.99±0.057	1.96±0.055
GM	4.41±0.91	3.02±0.73	2.79±0.71	2.42±0.65	2.66±0.68	2.57±0.66
MU	406±62	692±89	617±91	542±75	579±82	532±72
QF	0.711±0.076	0.864±0.081	0.889±0.085	0.931±0.088	0.901±0.085	0.912±0.087

Table 3: Physical evaluation indices averaged over 18 patients for different techniques.

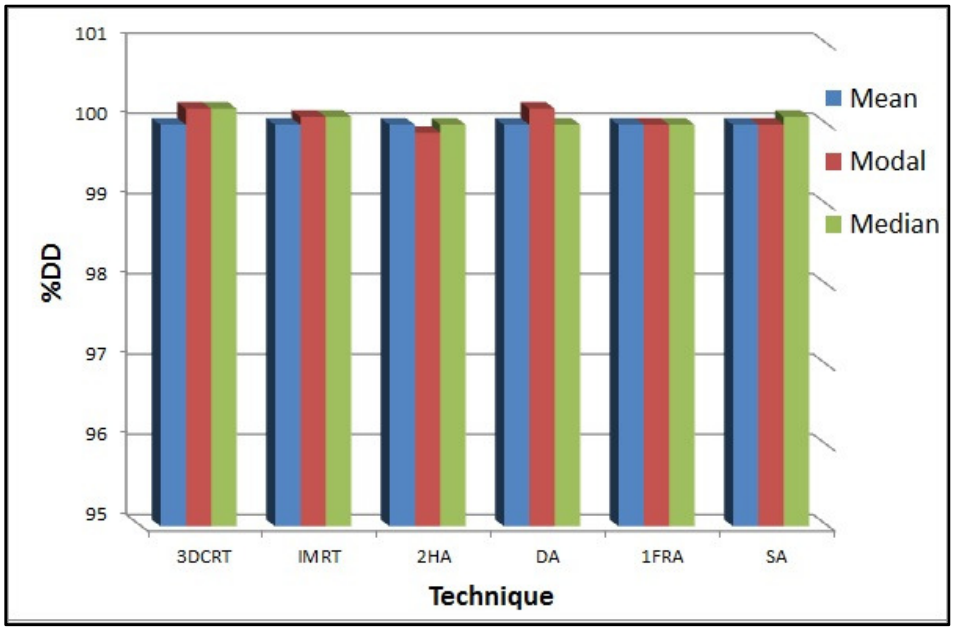

Figure 4: Dose Statistics of PTV indicating mean dose, modal dose, and median dose.

4.8. Number of MUs

The highest number of MUs was resulted in IMRT technique while the lowest number was resulted in 3DCRT. In different RapidArc plans the number of MUs had mid values between IMRT and 3DCRT (figure 12). The largest number of monitor units (MUs) in IMRT technique means that it has the highest total integral dose and accordingly the highest probability of secondary cancer after curative treatment.

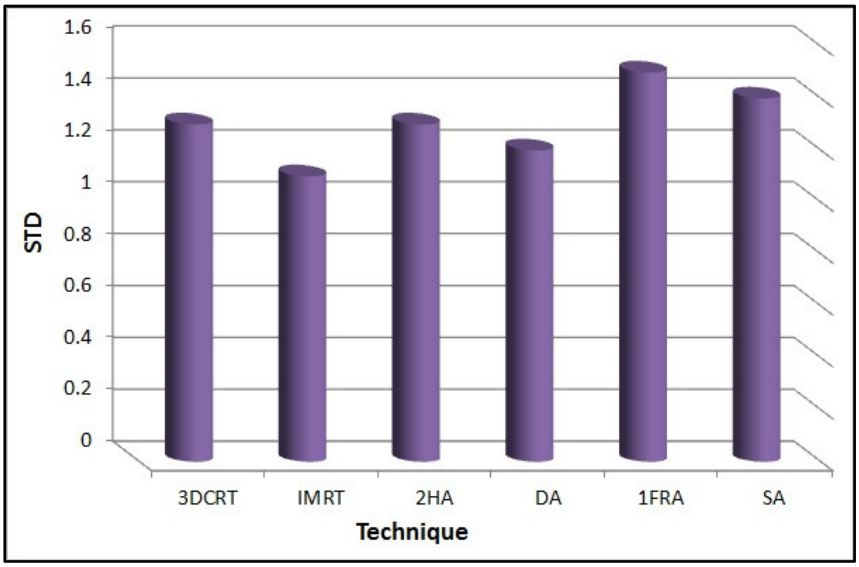

Figure 5: The STD values of the six plans.

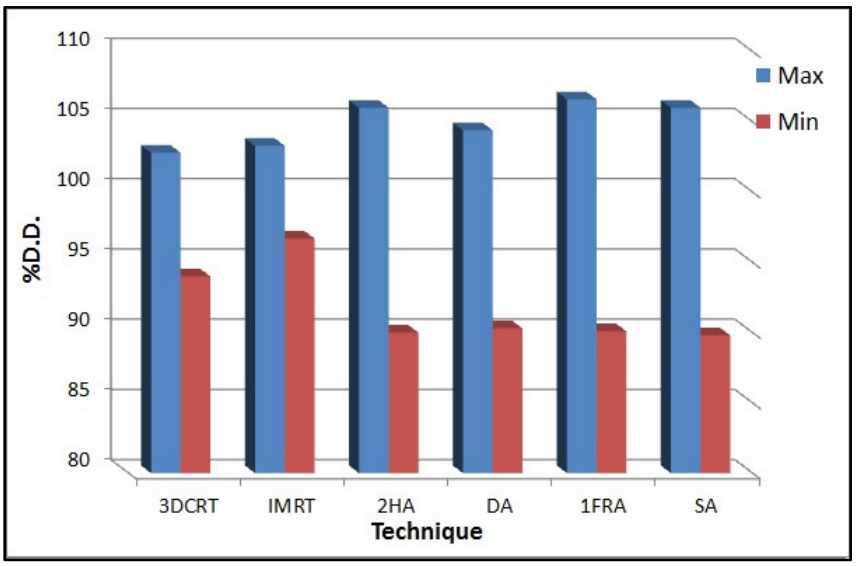

Figure 6: Maximum and minimum PTV doses of the six plans.

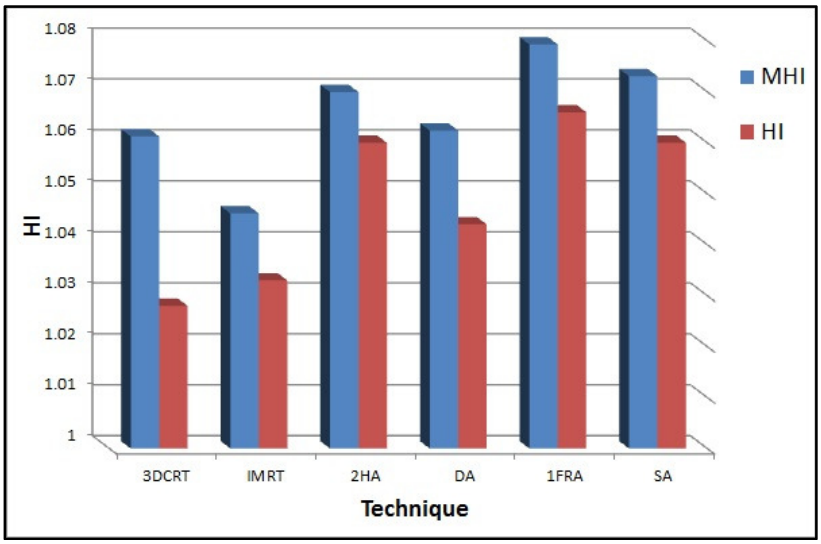

Figure 7: Dose Homogeneity Index (HI) in comparison with Modified Homogeneity Index (MHI) for different techniques.

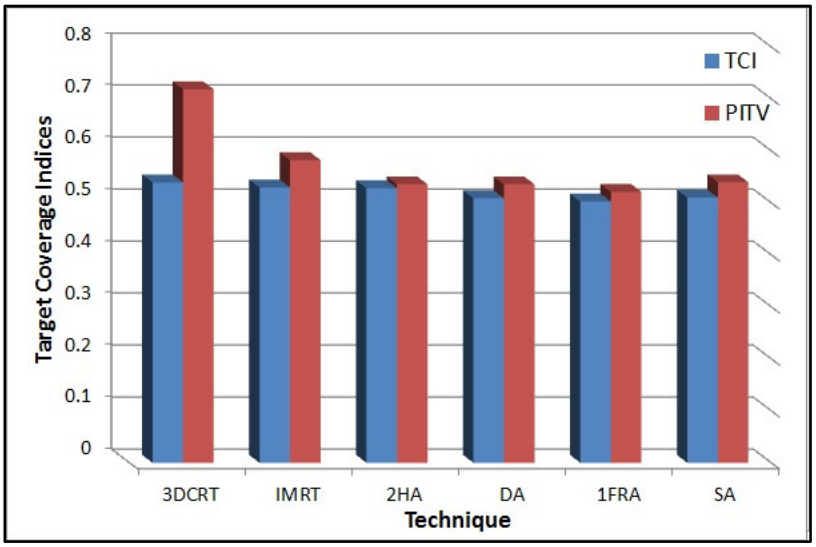

Figure 8: Target Coverage expressed in terms of TCI in comparison with PITV for all plans.

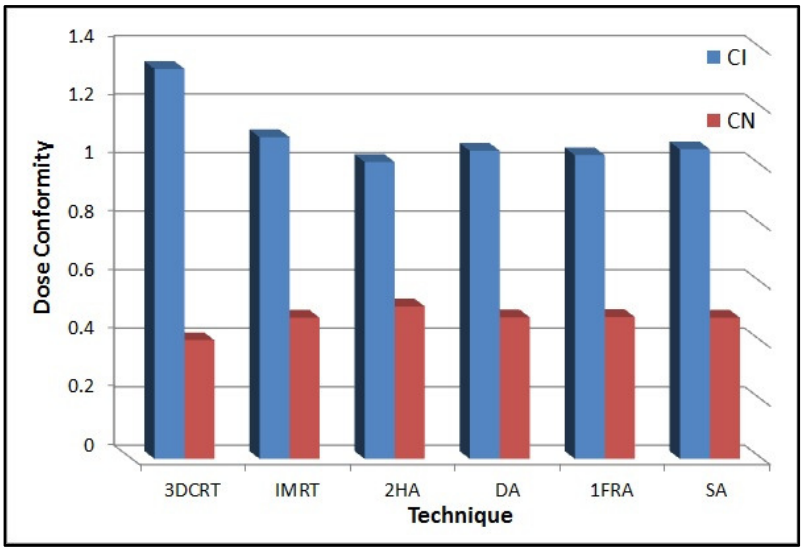

Figure 9: Dose conformity expressed in terms of conformity index (CI) in comparison with conformity number (CN) for all techniques

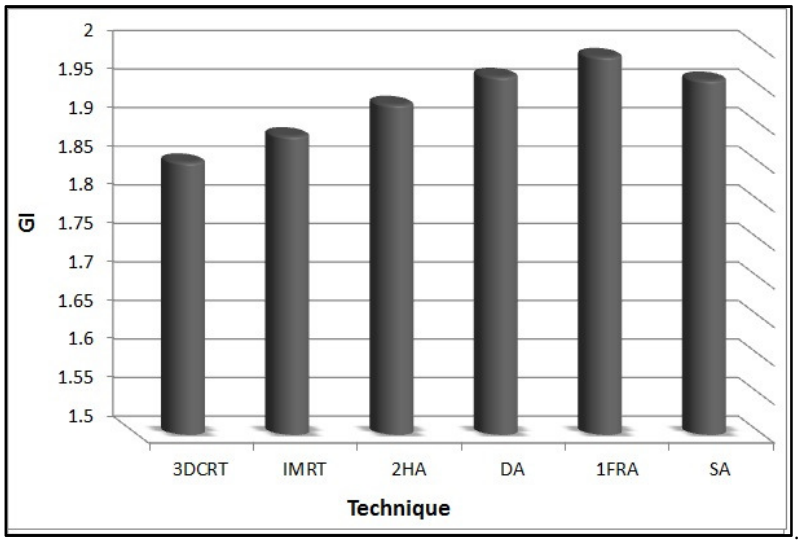

Figure 10: Dose gradient index (GI) for different treatment plans.

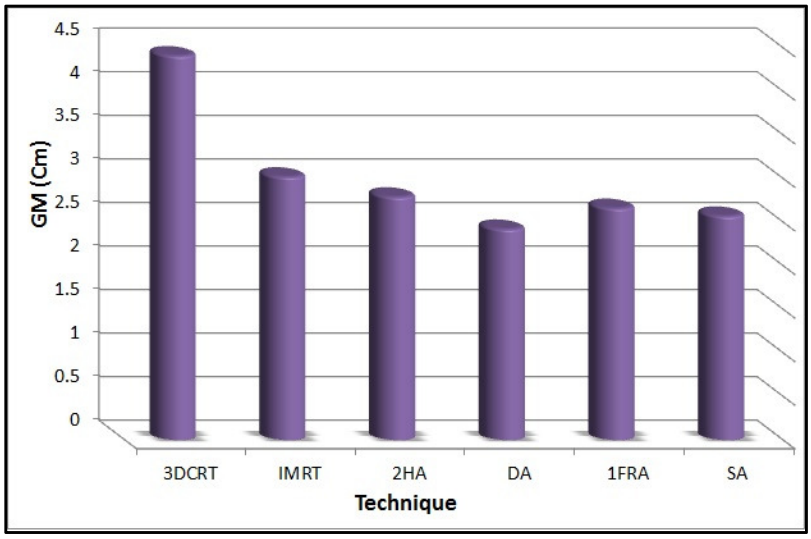

Figure 11: Gradient measure of different plans.

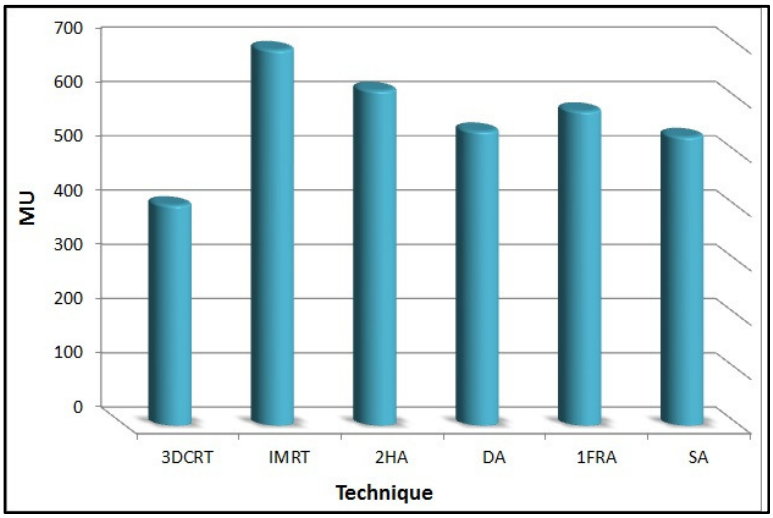

Figure 12: The number of Mus in different treatment plans.

4.9. Quality Factor (QF)

In spite of the higher dose homogeneity of 3DCRT, we can point out in figure 13 that the lowest QF value was obtained in 3DCRT with a statistically significant difference between it and the QF values obtained in the other plans of the recent techniques IMRT and RapidArc. On the other hand the higher values of QF were obtained in the four RapdArc plans and IMRT plan. While the heights QF values were obtained in RapidArc technique with no statically significant difference with IMRT.

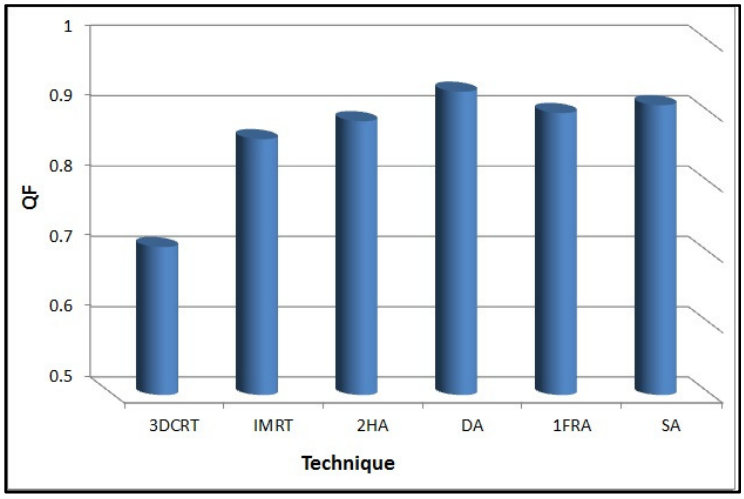

Figure: 13: Treatment plan quality factor (QF) for different plans.

4.10. Dose to Organs at Risk

Dose delivered to OARs are presented in table 4 and figures 14, 15 and 16. RapidArc is demonstrated to deliver the lowest doses to the bladder, rectum and heads of femur. Both RapidArc and IMRT have a lower dose to bladder, rectum and heads of femur. Difference in bladder and rectal doses are not significantly different while the difference of dose to the heads of femur is significantly different.

Dose To OARs		3DCRT	IMRT	Rapid Arc			
				2HA	DA	1FRA	SA
Bladder	D15	75.08±2.01	74.45±1.81	69.59±1.66	72.67±1.74	70.8±1.69	72.95±1.78
	D25	71.59±5.25	68.31±5.12	54.25±4.68	60.36±4.85	72.75±5.21	62.15±4.92
	D35	59.96±5.03	58.12±4.98	43.79±4.03	51.23±4.65	58.5±5.08	53.36±4.9
	D50	45.27±4.57	45.34±4.61	33.93±3.81	42.36±3.98	45.89±4.53	45.2±4.51
Rectum	D15	73.44±1.81	71.47±1.64	70.81±1.61	68.3±1.53	68.19±1.49	69.98±1.59
	D25	66.08±2.78	59.57±2.48	62.81±2.75	60.34±2.45	59.49±2.42	64.2±2.77
	D35	48.94±2.45	54.51±2.81	55±2.91	53.5±2.84	52.26±2.71	59.48±3.11
	D50	42.33±2.95	47.59±3.45	44.03±3.15	45.39±3.24	41.9±2.88	52.59±4.11
Femoral Head	D25	42.12±8.52	29.51±6.94	24.29±5.62	22.18±4.19	28.82±6.82	19.09±3.95
	D40	39.31±10.11	27.79±7.63	18.49±4.97	17.74±4.89	22.35±5.33	15.15±4.56
	Dmax	77.8±1.21	76.1±1.11	74.5±1.01	76.9±1.1	76.7±1.12	74.1±0.98

Table 4: Doses to OAR's averaged over 18 patients for different techniques.

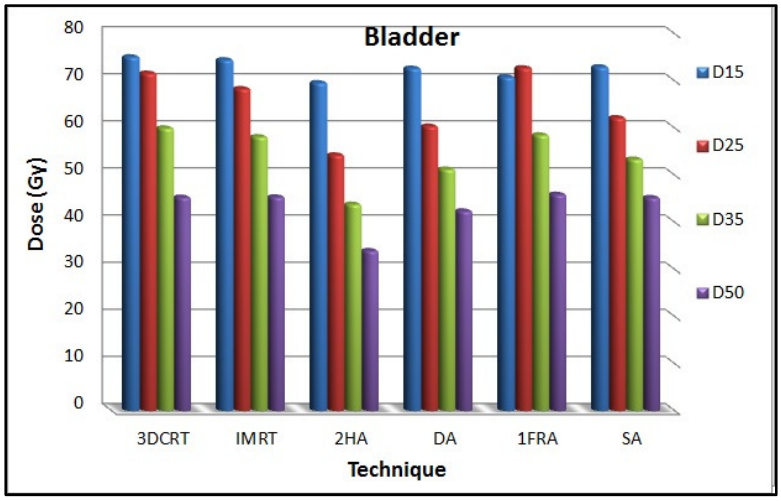

Figure 14: D15, D25, D35, and D50 of Bladder in different plans.

5. Biological Evaluation of Treatment Plans

5.1. Tumor Control Probability and Normal Tissue Complication Probability

The TCP values are illustrated in both figure 17 and table 5. It is obvious that TCP values for all plans are close with no significant difference. The reason of this likeness in the TCP values is the similarity in prescribed dose and dose normalization in all plans.

The difference in NTCP values for bladder between 3DCRT and the other techniques is quite clear as shown in figure 18. IMRT technique has a lower NTCP for bladder than 3DCRT.ON the other hand, all RapidArc plans have the lowest values of NTCP for bladder (Figure 18).

The NTCP Values for both of the rectum and heads of femur are higher in 3DCRT than all the other plans, as shown in figures 19 and 20.

The values of P+ for 3DCRT are much less than that of IMRT and also less than that of some RapidArc plans (1FRA and 2HA). In the two RapidArc plans in which we have used full arc rotation (SA and DA), the P+ is lower than that of the two plans in which we have used avoidance sectors (1FRA and 2HA).

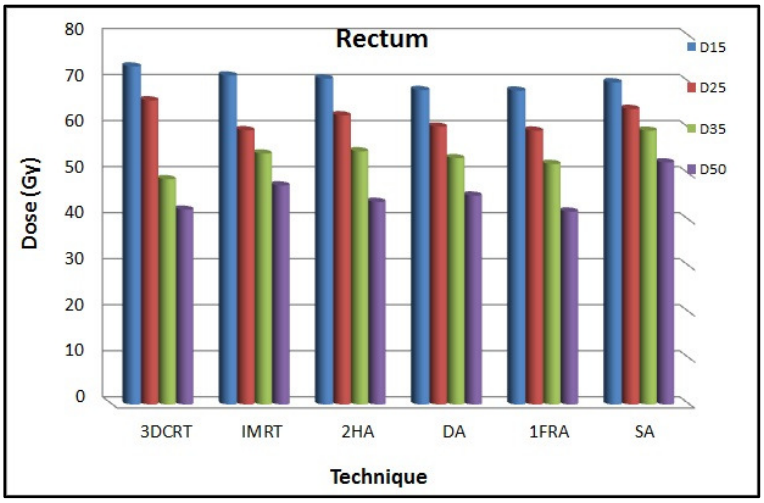

Figure 15: D15, D25, D35, and D50 of rectum in different plans.

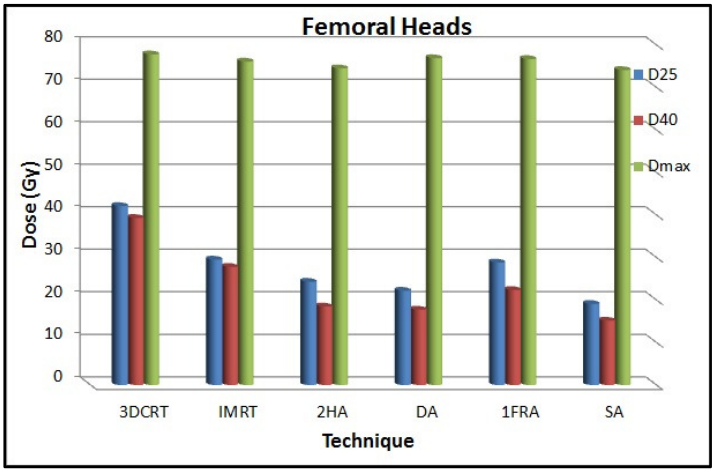

Figure 16: D25, D40, Dmax of heads of femur in different plans.

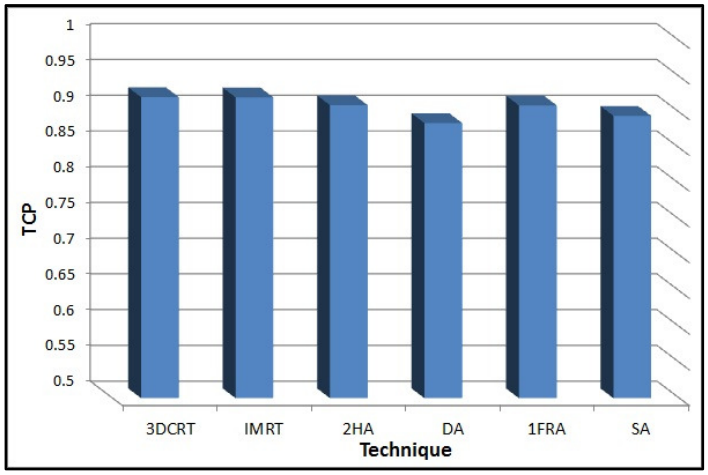

Figure 17: TCP Values of different treatment plans.

5.2. Dissection

In this study, we intended to evaluate the differences between different treatment techniques of cancer prostate. To perform physical evaluation of the different plans, dose distributions and DVH's for PTV and all OAR's were generated. All techniques were able to generate a dose distribution that was adequate for treatment. The overall qualities of the plans produced were very close; however, statistically significant differences were noted among the three techniques. The similarity in the overall qualities of the plans was also obtained in the evaluation of the DVH's of different targets. All DVH's satisfied the dose-volume constrains. This means that dose distribution and DVH's alone are not capable to rank the treatment plans. In spite of that, in radiation treatment planning analysis, dose volume histograms were the most widely used quantitative results.

Probability	3DCRT	IMRT7	RapidArc			
			2HA	DA	1FRA	SA
TCP	0.921±0.012	0.921±0.013	0.91±0.012	0.885±0.010	0.91±0.011	0.895±0.011
Bladder NTCP	0.0049±0.005	0.0035±0.003	0.0021±0.002	0.001±0.001	0.0005±0.001	0.0011±0.001
Rectum NTCP	0.085±0.01	0.068±.007	0.073±0.007	0.06±0.006	0.063±0.006	0.07±0.007
Femoral heads NTCP	0.0085±0.008	0.0015±0.002	0.0012±0.001	0.0005±0.001	0.0008±0.001	0.0004±0.001
PPlus	0.831±0.008	0.853±0.009	0.84±0.009	0.83±0.008	0.851±0.011	0.831±0.009

Table 5: TCP, NTC of different OAR's, and PPlus averaged over 18 patients for different techniques.

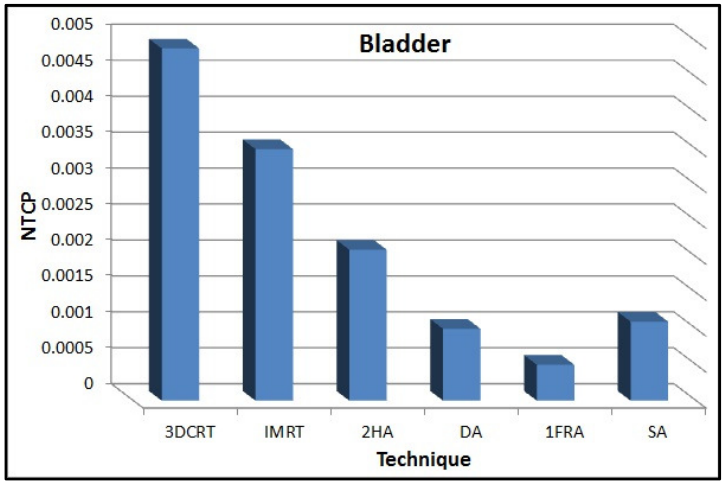

Figure 18: NTCP of the bladder in different plans.

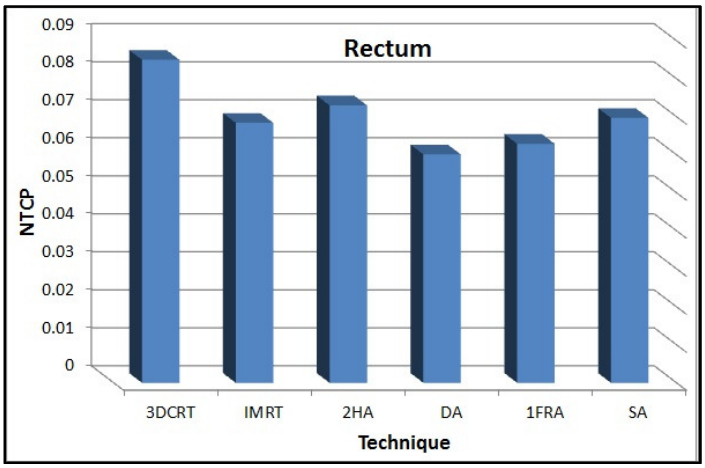

Figure 19: NTCP of the rectum in different plans.

To comprehensively evaluate a certain DVH, we used several dosimetrical and biological models. For dosimetrical models, there were mean, mode, median dose, maximum, minimum dose and standard deviation for PTV dose statistics, PITV, TCI, CI, and CN for target coverage index, and MHI, HI for homogeneity index, GI and GM for dose gradient and QF, for overall index. For radiobiological models, there were TCP and NTCP for tumor or critical structures, and P+ for free complication tumor control. There were still another factor like overall monitor unites irradiated in patients could be helpful for making more reasonable decision.

The PTV dose statistical analysis indicates the homogeneity of dose distribution in all plans. The similarity of the statistical quantities of the different plans didn't allow us to show the priority of one plan over the others.

HI is a good indicator of pattern of dose distribution in a target volume. In literatures few forms of HI have been suggested. It is still unclear that what are the factors influencing this index and what is the most appropriate form of this index to express the PTV dose homogeneity. Therefore, we have applied two forms in calculation of this index. In comparison of dose homogeneity of different plans we have used HI and MHI. The trend in the priority of different plans over the others observed by using HI doesn't differ than that observed by MHI. The two indices showed that IMRT and 3DCRT have better dose homogeneity than RapidArc

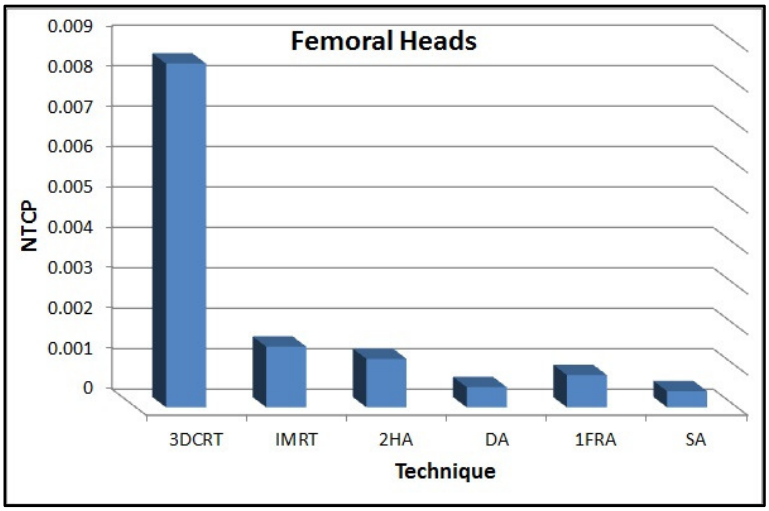

Figure 20: NTCP of the femoral heads in different plans.

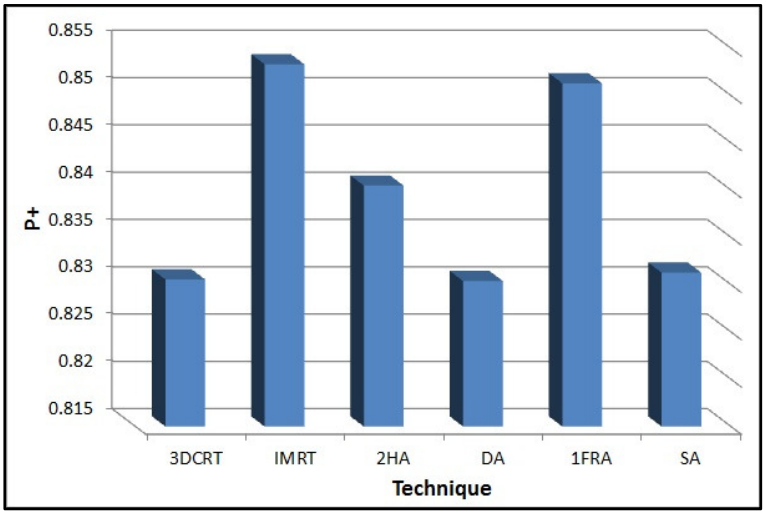

Figure 21: P+ of different treatment plans.

The conformity index constitutes an attractive tool, because it could facilitate decisions during analysis of various treatment plans. Its advantages are its simplicity and the integration of multiple parameters. In literatures PITV, TCI, CI, and CN indices have been used for target coverage and conformity. These indices are too diverse to achieve the desired objective, i.e., to quantify the quality of a treatment with 100% sensitivity and specificity. All of these indices displayed good PTV coverage and dose conformity in all plans with no significant difference. In spite of that none of these indices allowed us to rank the plans.The future of conformity indices in everyday practice therefore remains unclear.

Although GI and GM are good indicators of both PTV dose conformity and OAR's doses, they are not commonly used in clinic. In this study we have used the two indices to predict the dose gradient. We noticed that GM is more sensitive than GI. GM has an advantage of its availability in Eclipse treatment planning system. Better dose gradient was obtained in RapidArc and IMRT.

Plan comparison studies still remain controversial. The main reason for this is because plan parameters, optimization methods, and OAR constraints are difficult to clearly define. Many researchers have focused on the influence of planning parameters on the results of treatmentplans[54-56]. Another bias of plan comparison studies is that the quality of a planner's abilities and planning techniques may vary. Other major issues among plan comparison studies are the method of plan analysis and evaluation. Many studies have focused on developing a simple index that represents the overall quality of plans[35,37,43,52,53]. However, none of these indices are easily used in a clinic. Therefore all the physical evaluation indices have been integrated in one index. This index is the planning quality factor (QF). When we used QF in the physical evaluation, it was sensitive to the variation in dose homogeneity, conformity and gradient. The difference in plan quantitative quality was very clear and statistically significant between different plans.

In biological evaluation of different treatment plans we have used TCP, NTCP and P+. TCP values did not give any indication of plan priority over another. NTCP values estimated in 3DCRT were higher than that of RapdArc and IMRT. But the difference between NTCP values for IMRT and different RapidArc plans were very close, so we needed for another biological index to clarify the difference biological outcome the different plans. So P+ has been estimated to get an evidence of the priority of one plan over another. We noticed that the highest P+ value was achieved in IMRT and RapidArc with avoidance sectors (1FRA and 2HA) while the lowest values of P+ were obtained in 3DCRT and RapidArc plans with no avoidance sectors(SA and DA).

6. Conclusion

Physical evaluation of treatment plan can't be achieved by calculating dose homogeneity, dose conformity, or dose gradient alone. This issue can be solved by calculating treatment plan quality factor (QF). In biological evaluation of treatment plan outcome can be estimated by calculating P+ rather than calculating TCP and NTCP alone.

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