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Assessment of the Second Cancer Risk after Prostate Cancer Treatment: Comparison of 3D Conformal Radiotherapy and Intensity Modulated Radiotherapy

Ibrahim M. Hassana[1*], Ehab M. Attalla [2] , Mohamed I. El-Gohary [3]

1. Physics Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo 11884, Egypt.
2. Radiotherapy Department, National Cancer Institute, Cairo University, Giza, Egypt.
3. Physics Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo 11884, Egypt.

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ABSTRACT

Introduction: Radiation-induced secondary primary cancer is one of the significant late side effects and an undesired outcome of radiotherapy that can be observed in long-term cancer survivors**.** The present study aimed to estimate the risk of second cancer risk after Three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) for early stage prostate cancer patient.

Material and Methods: In this study, 10 patients with early stage prostate cancer have been chosen. Three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) plans were designed. The organ equivalent dose (OED) was calculated based on linear, linear-exponential, and plateau dose-response models. The Second cancer risks (SCR) were estimated by Excess absolute risk (EAR).

Results: The target dose coverage parameters were significantly improved in IMRT compared to 3DCRT. The rectum and bladder mean dose D_{Mean}, V50Gy% and V40Gy % were significantly decreased with IMRT. The maximum dose (D_{Max}), D_{Mean}, V30Gy % and V20Gy % for head of femurs significantly decreased with IMRT plans. However, the colon D_{Mean} significantly increased with in IMRT compared with 3DCRT. The IMRT plans were decreased SCR for the rectum by 10%, 26.6% and 19.5% for linear, plateau and linear-exponential dose- response models respectively. The bladder second cancer risk was decreased by 14% with linear dose-response model in comparison to 3DCRT plans. However, the second cancer risk for colon was significantly increased in average by 91.2% with IMRT plans.

Conclusion: IMRT technique demonstrated a clear advantage in dose coverage, conformity, and homogeneity over 3DCRT and was superior in terms of OAR-sparing. The Second cancer risk for in field organs (rectum and bladder) was decreased with IMRT compared 3DCRT plan.

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Introduction

Prostate cancer is the second most common diagnosis of cancer in men and the world's fifth leading cause of death [1].The worldwide incidence of prostate cancer corresponds to 1,414,259 new cases yearly, and 375,000 death according to the GLOBOCAN 2020, with a greater prevalence in developed countries [2]. Curative therapies for prostate cancer include radical prostatectomy and radiotherapy in the form of external beam radiotherapy (EBRT), brachytherapy, or a combination of radiotherapy and brachytherapy[3]. Prostatectomy carries a high risk of major early adverse effects, for instance, incontinence and impotence[4]. Radiotherapy is an alternate therapy option that is seen to be the best choice for elderly patients who are at risk of problems from surgery and also for individuals with a lower chance of organ-confined disease. EBRT can be delivered by three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), and Volumetric modulated arc therapy (VMAT) and proton beam therapy. The 3DCRT, IMRT, and advanced radiotherapy dose delivery techniques have been designed to permit high dose escalation and lower normal tissues toxicity[5]. Previous dosimetric studies demonstrated that IMRT is superior to 3DCRT in terms of target dose coverage, conformity, and sparing of normal tissues [6,7]. The improved conformality with IMRT allow for dose escalation to the prostate while decreasing dose to the rectum and bladder. Also, previous studies have demonstrated that the IMRT reduced toxicity to the rectum and bladder [8,9]. However, concern about its carcinogenic potential has been raised. Therefore, be expected to have a higher second cancer risk to normal tissues than 3DCRT[10]. Compared to 3DCRT there are several reasons why IMRT may increase second cancer risk (SCR). First, a move from 3DCRT to IMRT

*Corresponding Author: Tel: +201007373357; Email: ibrahim.omara@azhar.edu.eg

associates many fields, and therefore a larger volume of normal tissue is exposed to low doses. Second, IMRT requires larger number of beam monitor units (MU) a longer radiation beam-on time needed [11].Third collimator scatter and head leakage of linear accelerator (LINAC) during IMRT beams modulations may increase patient and normal tissues dose[12].

Radiation-induced secondary primary cancer is one of the significant late side effects and an undesired outcome of radiotherapy that can be observed in long-term cancer survivors. The data available about second cancer risk after radiotherapy have reviewed in the published reports of international organizations such as the International Commission on Radiological Protection (ICRP) [13], the National Academy of Sciences (BEIR VII)[14], the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)[15], and the National Council on Radiation Protection and Measurement (NCRP)[16], as well as epidemiological studies. The published reports and models of these international organizations, such as the BEIR VII model, also was used for radiation protection purposes to estimate the cancer risks from radiation exposure due to hypothetical accident of VVER-1000 nuclear power plant and accidental exposure inside neutron Laboratories [17,18].

With the availability of advanced radiotherapy techniques nowadays from brachytherapy, 3DCRT, IMRT, proton therapy, and heavy ion therapy, cancer cure rates have improved. This will increase the cancer long-term survivors which at risk of the late radiotherapy effects, including second cancers. So, comparing different radiotherapy modalities and techniques or plans to avoid the incidence of second cancer in normal organs will be needed in the future[19]. Recent review studies on second cancer after prostate cancer radiotherapy have suggested increased secondary cancer risk in the range of 1 in 220 to 1 in 290 [20,21]. The in-field organs such as the rectum and bladder and near the field organs such as the colon were the most affected organs with second cancers[22]. The second cancers induced by prostate cancer radiotherapy in some organs such as bladder are usually aggressive and sometimes lethal[23].

The secondary cancer incidence after radiotherapy has been estimated in many previous studies based on the average organ dose[24–26]. The average organ dose can be used with a linear dose-response model for evaluation of secondary cancer incidence rates when the dose is lower than 2Gy and homogeneously distributed in the organ. However, for dose > 2Gy and inhomogeneously distributed dose (e.g., in radiotherapy patients), the relationship between dose and the second cancer incidence is no longer linear. This is due to the cell sterilization effects at doses higher than 2–4 Gy. So, the second cancer risk estimation based on an average organ dose is no longer appropriate. The organ equivalent dose (OED) was proposed by Schneider et al. for estimation of second cancer risks to take account of the inhomogeneous distribution in modern radiotherapy techniques[27]. To our knowledge, a few studies estimated the secondary cancer risks based on OED with dose-response models[28,29]. These studies evaluated the secondary cancer risks from 3DCRT, IMRT, and VMAT for a small number of patients (3-5), which affects the statistical significance. Also, their studies were focused on the second cancer risk estimation only and did not compare the different techniques with respect to the dose coverage to the target and the doses to OARs. In this study, our aim is to conduct a comparative study between two used techniques in modern radiotherapy which is the 3DCRT and IMRT for ten prostate cancer patients with respect to the dose coverage to the target, the dose to OARs and with respect to the estimated secondary cancer risk for the normal tissues based on the excess absolute risk (EAR) calculated from OED with linear, linear-exponential, and plateau dose-response models.

Materials and Methods

Patients and Contouring of Treatment Planning Volumes

For this study ten early-stage prostate cancer patients were selected. The selected patients' characteristics, including age, tumor staging, prostate-specific antigen (PSA) levels, and patients' weight are shown in Table 1. Patients were advised to maintain empty rectum and a full bladder prior to CT simulation and each treatment session. The full bladder and empty rectum advised to minimizes dose to critical structures (bladder, small bowel, rectum and colon). A CT simulator Somatom definition AS 20 (Siemens Healthcare) was used to acquire CT images for radiotherapy planning. A knee and ankle support were used for patient immobilization in supine position and computed tomography (CT) slices in pelvis region with 3mm slice thickness for each patient were acquired according to treatment protocol. A CT images for each patient was exported to Elekta Monaco SIM (Version 5.11.02) for target and organs at risk (OARs) contouring as show in Figure 1. The prostate treatment structures and OAR contouring was based on RTOG protocol 0415 [30]. The gross tumor volume GTV was delineated to include the prostate gland. The clinical target volume (CTV) was defined by adding 5mm to GTV to contain the microscopic disease. The Planning Target Volume (PTV) was contoured by add 10mm margin around CTV in to compensate for the variability of treatment set up and internal organ motion. Also, OARs were contoured, including the rectum, bladder, femoral heads, and colon.

Table 1. Patients characteristics **(**Age, Tumor Staging, prostate-specific antigen (PSA) level, and patients' weight (kg))

Patient Number	Patient age in year	Tumor Staging	PSA (ng/ml)	Patient weight (kg)
1	50	T2BN0M0	5.62	97
2	52	T2AN0M0	6.76	81
3	60	T2CN0M0	4	104
4	63	T2BN0M0	7.3	99
5	66	T2BN0M0	8.54	85
6	51	T1CN0M0	5.4	77
7	48	T2BN0M0	3.41	92
8	53	T2AN0M0	6.52	95
9	49	T1CN0M0	3.71	103
10	55	T1CN0M0	8.61	86

PSA: prostate-specific antigen

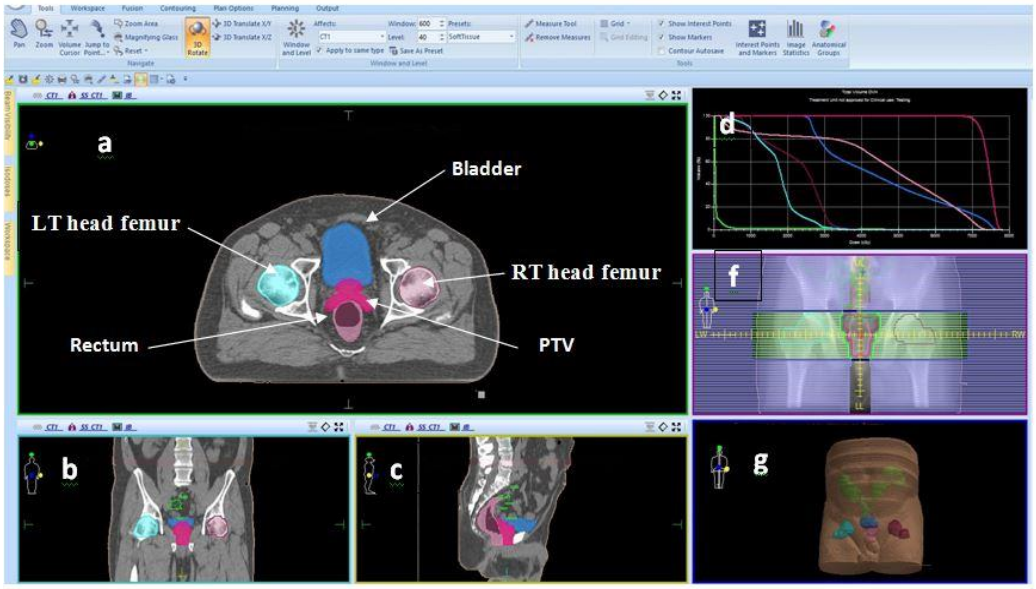

Figure 1. The patient contours of the planning target volume (PTV) and organs at risk (OARs) on computed tomography CT slices. (A) Patient contours on CT axial view, (b) patient contours on CT coronal view, (c) patient contours on CT sagittal view, (d) The dose-volume histograms (DVH), (f) the beam eye view BEV, (g) the patient 3D model

Treatment planning system

For every patient two plans 3DCRT and IMRT were designed using Elekta Monaco Treatment Planning System TPS (version 5.11.02 Elekta, CMS software, St. Louis, USA). Monaco TPS combines the accuracy of the dose calculation of the Monte Carlo algorithm with various tools to simulate the actual delivered dose to the patient while ensuring the consistent and effective creation of high-quality treatment plans. The Monaco TPS supports most of the modern radiotherapy techniques and modalities (e.g., 3DCRT forward and field in-field (FiF) planning; dynamic and step-and-shoot (IMRT); arc therapy techniques, including VMAT and dynamic conformal arc therapy (DCAT)). Dose calculation algorithms included in Monaco TPS are X-ray voxelized Monte Carlo (XVMC), collapsed cone, and pencil beam algorithm for photon beam. Also, Voxelized Monte Carlo++ (VMC++) algorithm was included for electron dose calculation. Monaco provides various biological and physical cost functions for IMRT and VMAT plan optimization. The biological cost functions have been developed to model the biological response of tumors and normal tissues to radiation doses. There are three biological cost functions (Target equivalent uniform dose (Target EUD), parallel, and serial cost functions) and another seven physical cost functions (Target Penalty, Quadratic Overdose, Quadratic Underdose, Conformality, Maximum Dose, Overdose DVH, and Underdose DVH) available in Monaco TPS for inverse plan optimization.

3DCRT treatment planning

For 3DCRT technique, 7-beams at gantry angles 0°, 50°, 105°, 155°, 205°, 255° and 305° with a collimator angle of 0° was used as shown in Figure 2. All beams isocenter were located at the center of the PTV and 1cm margin was applied around the PTV. The beam energy of 10MV delivered on Elekta Synergy linear accelerator with agility head 160-leaf multileaf collimator (MLC) was utilized, and a collapsed con algorithm was applied for dose calculation. All beams were set to have equal weights. The prescribed dose for 3DCRT and IMR plans was 74 Gy given with 2Gy per fraction and normalized to 100% at the plan isocenter. The plan objectives were

at least 95% of the prostate PTV covered with the prescribed dose and no more than two-percent of its volume to receive a 107% of dose.

IMRT treatment planning

For the IMRT plans, 7-beams at the same gantry, collimator angles, and beam isocenter of the 3DCRT plan was used as shown in Figure 2. Also, 10MV beam energy was used on Elekta Synergy linear accelerator with agility head 160-leaf MLC. The inverse-planning IMRT using a Monte Carlo dose calculation algorithm with dynamic MLC (DMLC) dose delivery technique was applied**.** The calculation properties for a Mote Carlo algorithm were 0.2cm a grid spacing, 2% for statistical uncertainty per calculation to decrease a plan calculation time and calculate dose to medium was selected**.** The same prescribed dose of 3DCRT plan was applied (74Gy delivered in 2Gy per fraction) and the plan objectives were at least 95% of the PTV covered with the prescribed dose and no more than two-percent of its volume to receive a 107% of dose. The OAR_S dose–volume constrains were used in present study are listed in Table 2.

Table 2. The organs at risk (OARs) dose constraints

Organ	Dose constraint
Rectum	$V_{70} \leq 20\%$
	$V_{50} \leq 50\%$
Bladder	$V_{70} \leq 30\%$
	$V_{50} \leq 50\%$
Femoral heads	$V_{50} \leq 5\%$

For IMRT plan optimization a biological and physical cost functions were used together. The Target EUD cost function was used for PTV dose coverage. However, the Target EUD does not penalize high doses; the Quadratic Overdose cost function was used to control the maximum dose and hot spot in the PTV. A serial cost function was used to decrease the rectum and bladder dose because these organs are considered serial structures. To keep the dose to a minimum and avoid any hot spots in the patient contour (unspecified tissue), the Quadratic Overdose, Conformality, and Maximum Dose cost functions were used.

Plan evaluation dosemitric parameters and statistics

The PTV dose coverage was evaluated based on dosemitric parameters, the maximum D_{max}(Gy), the means dose D_{Mean}(Gy), and the minimum dose D_{Mim} Gy. Also, the percentage of PTV volume that receive 95% of prescription dose V_{95} (%) was used for plans evaluation. The conformity of dose in the target was evaluated by the conformation number (CN), which defined as following equation [31].

$$CN = \left(\frac{TV_{RI}}{TV}\right) \times \left(\frac{TV_{RI}}{V_{RI}}\right) \quad (1)$$

Where TV_{RI} is the volume of the PTV covered by the reference isodose, TV is PTV volume, and V_{RI} is the reference isodose volume. The reference isodose used in this study was 95% of the prescription dose. Homogeneity of dose in the PTV has been evaluated by using homogeneity index (HI) as defined with equation (2) as follow.

$$HI = \frac{D_{5\%}}{D_{95\%}} \quad (2)$$

Where D5% and D95% represent the dose to 5% and 95% of the PTV volume respectively. When HI equal one that indicate high dose homogeneity in the PTV[32]. Moreover, the beam monitor unit (MU) per treatment fraction was evaluated. The dosimetric parameters from the (DVH) for the rectum and bladder (V50 %, V40Gy %, and V20Gy %), which is the percentage of the volume of these organs receiving 50Gy,40Gy, and 20Gy, were compared between 3DCRT and IMRT plans. Also, the D_{max}(Gy) and D_{Mean}(Gy) in the rectum, bladder, and both head of femurs (Right and Left head of femur) were evaluated for 3DCRT and IMRT plans. The V30Gy % and V20Gy% for both head of femurs and D_{Mean}(Gy) for colon were compared for 3DCRT and IMRT plans.

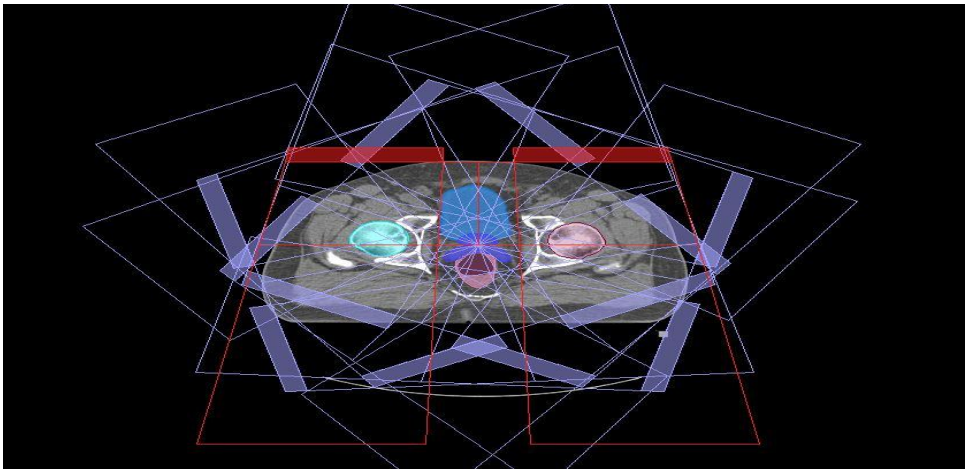

Figure 2. A computed tomography CT transverse plane with 7-beams arrangements for 3DCRT and IMRT plans

Calculation of second cancer risk (SCR) for normal tissues

The second cancer risk (SCR) in normal tissues following radiotherapy is often measured by excess absolute risk (EAR) per 10,000 persons per year. The EAR is the difference in cancer incidence rates between persons who are exposed to a dose of radiation and those not exposed above the natural exposure radiation [33]. The equation (3) was used to calculate the EAR as follows[34].

$$EAR = EAR_0 \times OED \quad (3)$$

EAR_0 is the dose-response curve's initial slope in case of a low dose exposure and incorporated population-related parameters, such as sex, age at exposure (agex), and attained age (agea). The normal tissues EAR depends on agex and agea was calculated with equation (4) as follows.

$$EAR = OED\ \beta' exp[\gamma_e(agex - 30) + \gamma_a ln(agea/70)] \quad (4)$$

Where β′ was the initial slope for the dose-response relationship of second cancer induction, γ_e and γ_a were the age-modifying parameters. All parameters for EAR calculation are listed in Table 3**.** The OEDs in equation (4) were calculated from differential DVH bases up on the linear, linear-exponential and plateau dose–response models for OARs (rectum, bladder and colon)[35]. In this study the patiens's age at exposure were from 48-66 years as shown in Table 1 and attained age was 80 year. The linear model assuming that the dose-response or cancer risk in normal tissue directly proportional to organ absorbed dose. The linear $OED_{T,linear}$,for an organ T, was calculated according to equation (5) as follows.

$$OED_{T,linear} = \frac{1}{V_T}\sum_i\{DVH(D_i).D_i\} \quad (5)$$

For the linear-exponential model**,** which considering the possibility of cell killing effect increased exponentially with organ absorbed dose which would reduce the induction of cancer because the death of mutated cells. The linear-exponential model $OED_{linear-exp}$ for an organ by equation (6) as follows.

$$OED_{T,linear-exp} = \frac{1}{V_T}\sum_i\{DVH(D_i).D_i.e^{-\alpha D_i}\} \quad (6)$$

$$\alpha = 0.044Gy^{-1}$$

In a plateau model which basd on the fact that the dose-response initially increases linearly with dose until a threshold dose at which the dose-response and cancer risk reach to a plateu due to sterilization of cell at higher doses and full repair of normal tissues in a fractionated scheme. The plateau model $OED_{plateau}$ for an organ calculated as follows:

$$OED_{T,plateau} = \frac{1}{V_T}\sum_i\{DVH(D_i).(1 - e^{-\delta D_i})/\delta\}; \quad (7)$$

$$\delta = 0.139Gy^{-1}$$

Where V_T, and $DVH(D_i)$, represented the total volume of organ T and the volume of organ T receiving dose D_i, respectively. For OED estimation using linear, linear-exponential, and plateau dose-response models, the summation runs over all voxels of the organ(T). The parameters α and δ for a linear-exponential and a plateau model were obtained from Hodgkin, and the Japanese A-bomb cohorts combined fit [35]. The statistical analyses were achieved utilizing the paired student's t-test to see if the means of the two plans were statistically significant. If the P-value was less than 0.05, the dosimetric parameter was declared statistically significant between the two plans.

Table 3. The Excess absolute risk (EAR) calculation parameters from Sechnider et al. [33].

organ	β_{init}	γ_e	γ_a
Rectum	0.73	-0.024	2.38
Bladder	3.8	-0.024	2.38
Colon	7.4	-0.056	6.9

Results

Figure 3. Shows the DVH's for both 3DCRT and IMRT treatment plans for one of the present study prostate cases. The PTV dosimetric parameters for 3DCRT and IMRT plans are indicated in (Table 4). The results have shown that the maximum dose D_{Max} in the PTV significantly increased (P-value =0.042) with IMRT plans but not more than 107% of the prescription dose. Most of the dose indices for the PTV are better for the IMRT plans than for the 3DCRT plans and it were statistically significant at mean dose (D_{Man}) (P-value=0.0023) and V_{95}% (P-value=0.02). In comparison to 3DCRT the IMRT plans have higher values for CN (0.71 ± 0.02) vs (0.51 ± 0.01). So, the IMRT improve dose conformity around PTV in comparison to 3DCRT. Also, the homogeneity index (IH) among IMRT plan was slightly better than 3DCRT. The beam monitor units (MUs) were increased significantly (P=0.0013**)** in IMRT plans (715 ± 67) relative to 3DCRT plans (497 ± 80).

Table 5. shows the dose–volume parameters for OARs from 3DCRT and IMRT plans. The rectum mean dose (D_{Mean} (Gy)), the percentage of volumes that received 50, 40, and 20 Gy (V50Gy (%), V40Gy (%), and V20Gy (%)) have smaller values in IMRT plans compared with 3DCRT plans**.** The IMRT plans were shown significant decrease (P<0.05) in the bladder mean dose D_{Mean}**,** the percentage of volume that received 50, 40, and 20 Gy (V50Gy (%), V40Gy (%), and V20Gy (%)). Although the mean values of D_{Max}**,** $D_{Mean,}$ V30 Gy(%) and V20Gy (%) for both head of femurs (right and left head of femur) have been decreased in IMRT plans with significant difference (P<0.05) compared with 3DCRT plans. However, the IMRT plans were shown significant increase in the mean dose of colon versus 3DCRT plans.

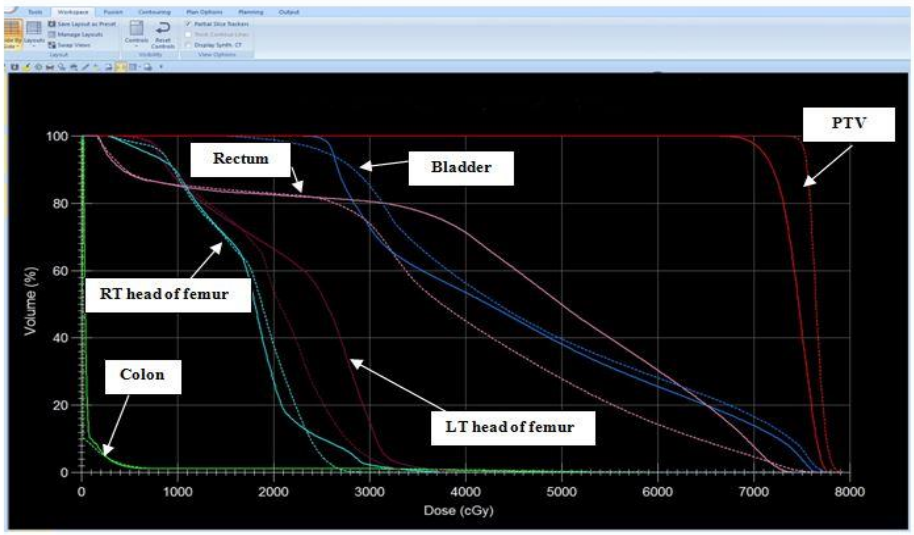

Figure 3. The cumulative DVHs of the representative patient for PTV, Rectum, Bladder, RT head of femur, LT head of femur and Colon for 3DCRT plan (Solid line) and IMRT plan (Dashed line)

Table 4. The PTV mean values of dose-volume parameters comparison in 3DCRT and IMRT Plans

DVH parameters	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
D_{Max}(Gy)	74.78 ± 0.2	78.14 ± 0.12	0.042
D_{Mean}(Gy)	73.36 ± 0.4	74.16 ± 0.31	0.0023
D_{Mim}(Gy)	66.77 ± 0.23	69.92 ± 0.71	0.2455
V_{95}(%)	96.87 ± 0.65	99.2 ± 0.12	0.02
CN	0.51 ± 0.01	0.71 ± 0.02	0.0036
HI	1.05 ± 0.001	1.02 ± 0.003	0.022
MU per fraction	497 ± 80	715 ± 67	0.0013

Table 5. The dose–volume parameters and mean doses comparison in OARs for 3DCRT and IMRT Plans

OARs	DVH parameters	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
Rectum	D_{Max}(Gy)	73.82 ± 0.51	76.31± 0.33	0.0032
	D_{Mean}(Gy)	43.7 ± 4.4	40.971 ± 2.1	0.0013
	V50Gy(%)	49.84 ± 1.4	22.33± 3.2	0.004
	V40Gy(%)	84.58± 3.4	43.94± 2.7	0.02
	V20Gy (%)	99.14± 2.6	99.23± 3.3	0.1
Bladder	D_{Max}(Gy)	74.25± 0.4	78.36± 0.7	0.0021
	D_{Mean}(Gy)	40.07 ± 4.6	34.39 ± 8.2	0.0043
	V50Gy(%)	26.05± 5.1	23.94± 3.2	0.0331
	V40Gy(%)	41.2± 2.1	37.07± 1.7	0.041
	V20Gy(%)	79.6± 1.9	75.78± 2.2	0.052
RT head of femur	D_{Max}(Gy)	37.16± 0.81	32.42± 0.54	0.001
	D_{Mean}(Gy)	25.18± 2.8	20.33± 3.3	0.045
	V30Gy(%)	12 ± 2.2	1.46± 0.1	0.0021
	V20Gy(%)	92.98± 4.1	45.91± 3.5	0.0001
LT head of femur	D_{Max}(Gy)	33.04± 0.53	31.23± 0.81	0.04
	D_{Mean}(Gy)	22.56± 1.4	20.96± 2.1	0.002
	V30Gy(%)	3.27± 4.4	1.51± 0.2	0.0031
	V20Gy (%)	84.89± 4.4	64.27± 3.2	0.0001
Colon	D_{Mean}(Gy)	0.188 ± 0.12	0.457±0.24	0.0035

The OED for rectum, bladder and colon estimated by linear, plateau, linear-exponential dose – response models are shown in Table 6. The results data of the OED shows in Table 6 were averaged over all patients. The rectum mean OED for all three dose– response models for 3DCRT plans and IMRT plans were 19.9 Gy and 18.7 Gy respectively.

The IMRT plans significantly reduced (P-value<0.05) the rectum OED with linear, plateau and linear –exponential dose response models (Figure. 4). The bladder average OED values calculated based on the three models was 17.8 Gy and 16.2 Gy with 3DCRT plans and IMRT plans respectively (Figure.5). Compared with 3DCRT the bladder OED decreased significantly with IMRT plan based on linear dose-response models. While the colon OED shows in average 0.38 Gy with IMRT plans and 0.19Gy with 3DCRT plans based on linear, plateau, and linear-exponential model (Figure.6).

Table 6. The organ equivalent dose OED (Gy) (mean ± standard deviation (SD)) with 3DCRT and IMRT plans for the organs of interest

OARs	Model	3DCRT	IMRT	P-Value
Rectum	Linear	43.7 ± 9.4	40.9 ± 9.5	0. 004
	Plateau	7.9 ± 1.19	7.6 ± 1.3	0.002
	Linear - exponential	8.3 ± 1.2	7.8 ± 1.4	0.032
Bladder	Linear	40.07 ± 4.6	34.4 ± 8.2	0.0043
	Plateau	7 ± 0.18	7.18 ± 0.5	0.19
	Linear - exponential	6.5 ± 0.3	6.9 ± 0.8	0.032
Colon	Linear	0.18 ± 0.1	0.45 ± 0.25	0.006
	Plateau	0.188 ± 0.08	0.34 ± 0.13	0.0049
	Linear - exponential	0.195 ± 0.88	0.36 ± 0.14	0.0046

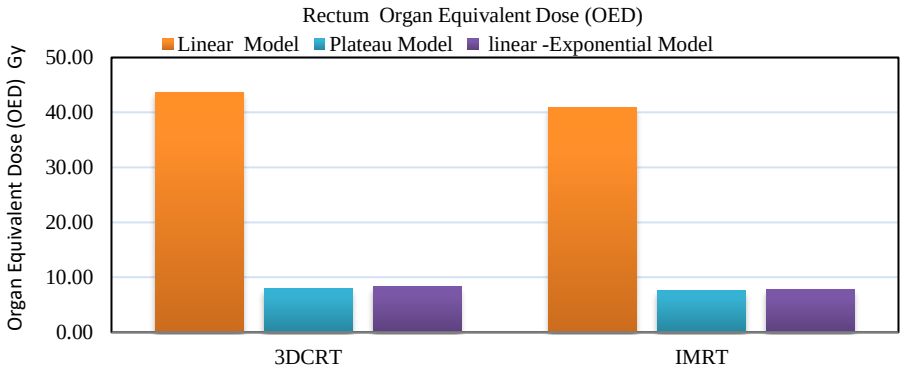

Figure.4. The rectum organ equivalent dose OED with linear (blue), plateau (red) and linear –Exponential (green) dose-response models for 3DCRT and IMRT.

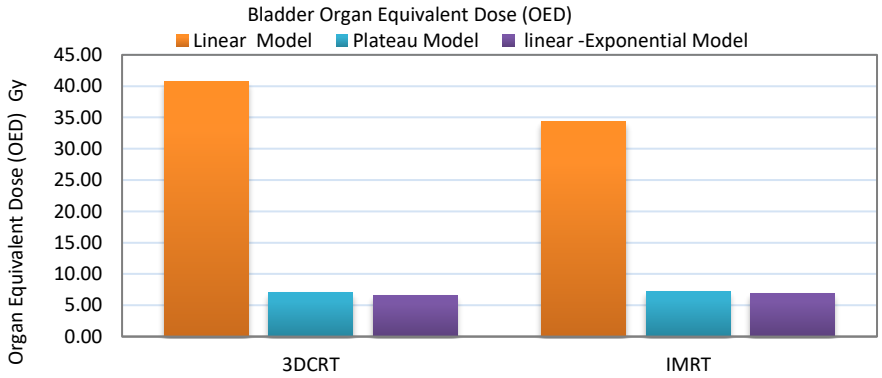

Figure.5. The bladder organ equivalent dose OED with linear (blue), plateau (red) and linear –Exponential (green) dose-response models for 3DCRT and IMRT.

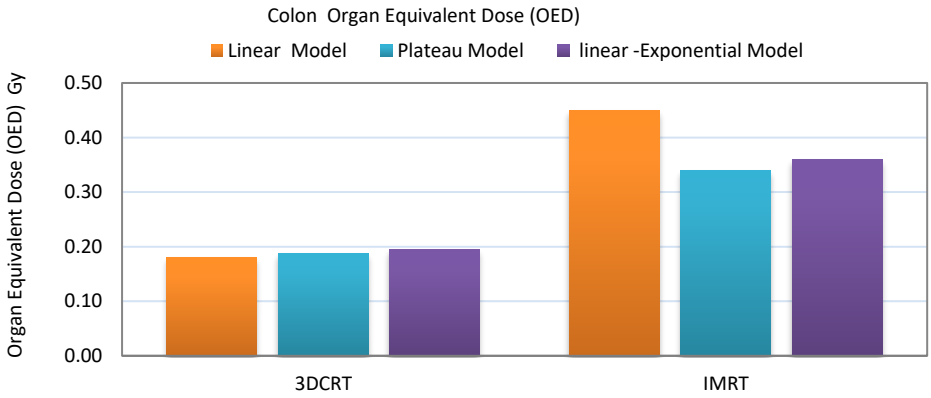

Figure.6. The colon organ equivalent dose OED with linear (blue), plateau (red) and linear –exponential (green) dose-response models for 3DCRT and IMRT.

Table 7. The excess absolute risk EAR per 10,000 persons per year per Gy (mean ± standard deviation) with 3DCRT and IMRT

OARs	Model	3DCRT (Mean ±SD)	IMRT (Mean ±SD)	P-Value
Rectum	Linear	24.7 ± 6.9	22.2 ± 6.7	0.033
	Plateau	4.5 ± 1	3.3 ± 0.9	0.052
	Linear - exponential	4.6 ± 1.04	3.7 ± 1	0.021
Bladder	Linear	116.5 ± 19.1	100.3 ± 27.9	0.0043
	Plateau	20.5 ± 2.9	21 ± 3.6	0.180
	Linear - exponential	19 ± 3.3	20.2 ± 4.1	0.1808
Colon	Linear	0.99 ± 0.08	2.2 ± 1.5	0.009
	Plateau	0.98 ± 0.06	1.7 ± 0.9	0.0061
	Linear - exponential	1.01 ± 0.61	1.8 ± 0.9	0.0058

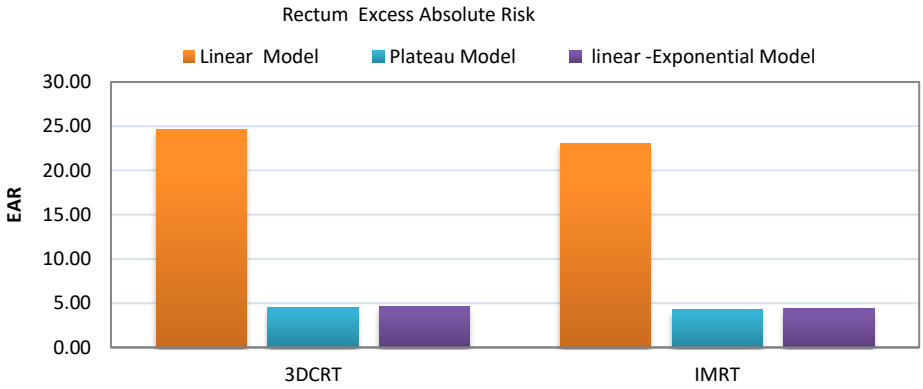

Figure.7. The rectum excess absolute risk EAR with linear (blue), plateau (red) and linear –exponential (green) dose-response models for 3DCRT and IMRT.

The excess absolute risk EAR per 10,000 persons per year per Gy for rectum, bladder, and colon are shown in Table 7. Compared to 3DCRT plans, the rectum EAR with IMRT plans decreased significantly by 10%, 26.6% and 19.5% for linear, plateau and linear-exponential dose-response models respectively (Figure.7). On average, the IMRT plans reduced SCR of the rectum by 13.6% relative to 3DCRT plans for the dose-response models used. Also, the bladder EAR with IMRT plans was decreased significantly (p-value<0.05) by 14% for linear dose-response model in comparison to 3DCRT plans (Figure.8). But for plateau and linear –exponential models, the EAR for the bladder has a small difference between 3DCRT and IMRT plans. In comparison to 3DCRT, the SCR in average was decreased by 9.3% with IMRT plans. However, the colon EAR was increased significantly in IMRT plans by 122.2%, 73.4%, and 78.2% with linear, plateau and linear-exponential dose–response models respectively (Figure.9). The IMRT plans were increased the SCR in the colon with 91.2% compared with 3DCRT plans.

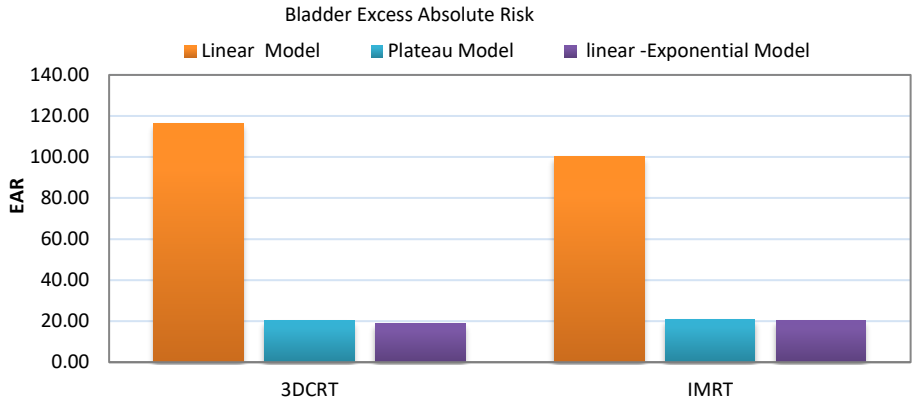

Figure.8. The bladder excess absolute risk EAR with linear (blue), plateau (red) and linear –exponential (green) dose-response models for 3DCRT and IMRT.

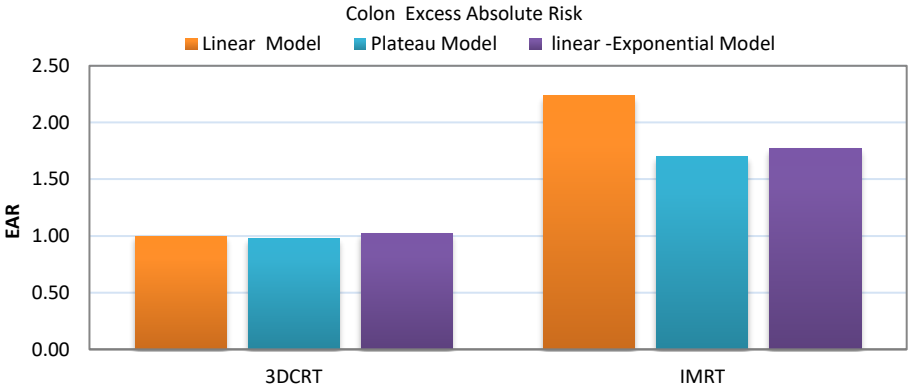

Figure.9. The colon excess absolute risk EAR with linear (blue), plateau (red) and linear –exponential (green) dose-response models for 3DCRT and IMRT.

Discussion

In the current study, the 3DCRT and IMRT radiotherapy techniques for treating localized prostate cancer were compared based on different dosimetric parameters for the prostate and organs at risk. In addition, the risk of developing second cancer was estimated in healthy tissues such as the bladder, rectum, and colon based on OED calculated with linear, plateau, and linear- exponential dose-response models. In the present study, the IMRT techniques showed a systematic and a significant improvement over 3DCRT in terms of PTV dose coverage and conformality. In term of normal tissues sparing the IMRT was significantly better than 3DCRT for rectum and bladder. Our results was consistent with previous studies [6,36 – 38]. In our study the IMRT plan significantly decreases (P-value <0.05) D_{Max}, D_{Mean}, V30Gy and V20Gy for femur heads in comparison to 3DCRT plan. Previous investigations has concluded that most second cancers occur in normal organs adjacent to or close to the target volume [39,40]. This explains the reason that in our study IMRT achieved a reduction in the SCR to organs adjacent to the target volume (bladder and rectum) compared to 3DCRT because of the improved dose conformality with this technique [41]. SCR for rectum and bladder in our study were decreased by 13.6% and 9.3% relative to 3DCRT this in agreement with the results of Murray et al. [28]. It's also worth mentioning that the reduction of dose and dose-volume parameters with IMRT for rectum and bladder can significantly decrease the incident of 2–4 grade acute and late gastrointestinal (GI) toxicity, late rectal bleeding, and achieves better prostate-specific antigen (PSA) relapse free survival compared 3DCRT as has been reported by Yu et al. [42].

On the other hand, the out of field organ as the colon in our study has a significant increase in the mean dose with IMRT technique and consequently the SCR is also increased. This is due to higher numbers of MUs, radiation scattered from treatment head of the linear accelerator during the beam modulation and higher volumes of normal tissues exposed to low doses[43,44].

It should be mentioned that with IMRT, the radiation beams MU in our study was increased by 43.8% (1.4-fold) compared to 3DCRT. Kry et al. [11] has shown that the increase in the MU translates into an increase in the risk of second cancer induction in distant organs. The lower the beam energy, the higher the MUs needed for the patient treatment. Thus, this could add another advantage to using the 10MV instead of using 6MV owing to its consequence in having an increased risk of secondary cancer. Also, Stathakis et al.[45] demonstrated that the 10MVphoton beam energy is

preferable, if available because 6MV has insufficient penetrating power when larger patients were treated and beams with energy higher than 10MV will introduce neutrons.

Our results for the rectum EAR ranged from 3.3 to 3.7 per 10 000 persons per year for a plateau and a linear-exponential model respectively with IMRT which is lower in comparison with the results of Haciislamoglu et al. [29] as their results was in the order of 6.36 to 7.94 using the same models. While our results for the bladder was in the order of 20.2 to 21 which was much higher than their results which was in the order of 1.47 to 5.82 using the same models. However, it's important to point out that direct comparison of our study results with the results from other groups cannot be considered a straight forward comparison because of the difference in irradiation volumes and in the number of patients used in their studies [28,29]. The radiotherapy planning different software and hardware combinations, as well as the prescribed dose and dose per fraction, may all contribute to variation in second cancer risk calculations [46]. Thus, in our study plans for IMRT and 3DCRT were done using the same TPS and by delivering all plans on the same treatment machine. Monte Carlo dose calculation algorithm and Collapsed Cone algorithm were used for the dose calculation of the radiotherapy treatment plans of our prostate cases. Both algorithms has been reported to be effective and accurate dose calculation algorithms [47,48].

It should be also pointed out that more research work is needed to address some of the problems with the current models used to estimate the secondary cancer risk as there is significant uncertainty due to the unknown shape of the dose–response relationship. Schneider et al.[49] demonstrated that the dose–response curve for cancer induction is expected to be between the linear and linear–exponential models. In another study the calculated second cancer risk results were fitted best with observed risks when the linear–exponential model was used rather than the use of a plateau dose-response model [50]. In another study by Filippi et al. [51] suggested a linear dose-response model for second cancer risk. In our study the SCR in healthy tissues such as the bladder, rectum, and colon was estimated based on OED concept calculated with linear, plateau, and linear- exponential dose-response models to have all cancer risk possibilities. Our study did not consider the dose from patient imaging that are usually done during image guided radiotherapy as this was already reported in other studied to be very small in comparison to the primary treatment beam[52,53].

Conclusion

Three-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) afforded accepted dose coverage to PTV. However, IMRT technique demonstrated clear advantage in PTV dose coverage, conformity, and homogeneity over 3DCRT technique. The IMRT was superior to 3DCRT in terms of OARs-sparing of rectum, bladder and both head of femur (right and left head of femur). However, the beam MU was increased by 1.4-fold with IMRT compared to 3DCRT, and this was one of the reasons for the increase in second cancer risk in out-of-field organs such as the colon in this study with IMRT technique. The second cancer risks for in field organs rectum and bladder were decreased with IMRT plan in comparison to 3DCRT plan.

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