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A Comparison of Intensity Modulated and 3- Dimensional Conformal Radiotherapy for Prostate Cancer Using 6-MV and 15-MV Photon Energies

Jamal M. AL-Shareef [1,2] , Ehab M.Attalla [3], Magdy M. Khalil [2] , Ahmed M Abdelaal [4], M. S. El- Nagdy [2]

(1) Physics Department, Sana'a University, Sana'a, Yemen

(2) Physics Department, Faculty of Science, Helwan University, Cairo, Egypt

(3) Department of Radiotherapy and Nuclear Medicine, National Cancer Institute, Cairo University, Cairo, Egypt

(4) Radiotherapy Department, Nasser Institute, Cairo, Egypt

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Prostate cancer is one of the most common cancers in men. The purpose of this work is to compare between intensity-modulated radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3D-CRT) planning in patients with prostate cancer using 6-MV and 15-MV photon energies. Twenty patients with localized prostate cancer were planned on Xio treatment planning system. Four treatment plans were generated for each patient. IMRT whether 6 or 15 MV beam was slightly better in terms of target coverage, but not significant (p>0.05) in comparison to 3D-CRT in both beam energies. IMRT was better than 3D-CRT in terms of organs at risk (OARs) sparing and conformity index (CI) in both 6 and 15-MV whereas 3D-CRT in both 6 and 15-MV yielded better homogeneity index (HI) compared to IMRT 6 and 15-MV. The number of monitor units (MU) increased in IMRT compared to 3D-CRT. Also, MU increased in low energy compared to high energy whether in 3D-CRT or IMRT (p<0.05). When IMRT 6-MV and IMRT 15-MV were compared, no significant difference was found in terms of target coverage and OARs except the rectum which was better in IMRT 6-MV compared to IMRT 15-MV. IMRT 6-MV technique should be prioritized when user has options for treatment and then 3D-CRT as a second line when the former is not available. The choice of the energies (6 and 15MV) used with 3D-CRT depends largely on patient's body geometry, while the use of a high energy IMRT 15-MV is not recommended.

Keywords: *Intensity modulated radiotherapy/ 3D-conformal radiotherapy/ high energy/prostate cancer*

Introduction

Prostate cancer is the most common cancer in men and is the second most common cause of cancer related death in men [1]. It is potentially curable if detected and treated in the early stages. So, there are several treatment options available. External beam radiation therapy (EBRT) is considered to be one of the curative treatment options for localized prostate cancer [2, 3] 3D-CRT and IMRT have been used for curative treatments of prostate cancer.

Radiotherapy aims to give the prescribed dose to the tumor and to protect, as much as possible, the organs at risk (OARs) and surrounded healthy tissue [4]. 3D-CRT is defined as forward planning, multiple fields from different gantry angles around the patient is used to concentrate the radiation dose on the tumor and spare the surrounding normal tissue. The multileaf collimator (MLC) is used to define the shape of each treatment field to fit the projection of the tumor. 3D-CRT treatment planning is manually optimized. This means that the treatment planner chooses all beams parameters, such as the number of beams, beam directions, shapes, wedge, weights etc., and the computer calculates the resulting dose distribution [5- 7].

Corresponding author: jamal777207713@gmail.com
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IMRT is an advanced inverse planning treatment modality where each field is divided into many "beamlets" carrying different intensities of radiation. This is achieved by superimposing many MLC shapes that are often smaller than the target to deliver various beam intensities. One variant of IMRT is step-and-shoot, where the radiation beam is off during gantry rotation and when the MLC is moving to shape the field. The beam is turned on once the field shaping is complete [8]. IMRT is a modern radiation technique with a higher precision in the delivery of radiation dose. It can reduce the dose to surrounding critical organs and deliver the dose to targets with the nominal risk of side effects [9,10].

High-energy photons have dosimetric advantages in some situations thanks to their greater depth of penetration for deep seated tumors in the pelvic region; such energies are commonly used in 3D conformal radiotherapy. With IMRT, however, high-energy photons may present more disadvantages than advantages [11,12].

This study was undertaken to compare between IMRT versus 3D-CRT planning in patients with prostate cancer using 6-MV and 15-MV photon energies.

Materials and Methods

Patients and data acquisition

Patients were immobilized in supine position. The target volumes and organs at risk were delineated by the radiation oncologist.

Computer tomography was acquired for all patients (Toshiba, Asteion model, Japan) providing 4 multi-slices with 65 cm bore and a carbon fiber flat table to simulate radiotherapy machine. Patients are scanned with a full bladder and an empty rectum before the scanning and treatment. All patient scout scans were obtained from the upper border of iliac bone down to mid-thigh. Skin reference tattoos were placed on position of lead wires marks on the patient's skin. These cuts of patient were transferred to another workstation to delineate target and OARs by the radiation oncologist then sent to the XIO treatment planning system (version 4.6.2, Elekta, CMS, and England). It employs convolution, Clarkson and superposition algorithms in dose calculation for photon mode therapy. Treatment was performed using a Siemens ONCOR linear accelerator with 6 MV photon energy operating up to 500 MU/min and a multi-leaf collimator delivery system replaces the lower movable jaws inside the linear accelerator head. The OPTIFOCUS MLC for the ONCOR linear accelerator has 41 pairs of inner leaves of a 1.0 cm width that is projected at isocenter and two pairs outer leaves of a 0.5 cm width.

Planning techniques (3D-CRT vs. IMRT)

Four treatment plans were developed for each patient in the study population (n=20), namely 3D-CRT and IMRT. For every patient, two plans with 3D-CRT were generated for both 6 MV and 15 MV and similarly two plans with IMRT for both 6 MV and 15 MV photon beams using step- and-shoot technique were generated as shown in Figure (1). Each plan was prescribed with a total dose of 76Gy. In 3D-CRT five fields with 0^o, 45^o, 90^o, 270^o and 315^o gantry angles were used employing virtual wedges 60^o at both of 90^o, 270^o gantry angles to modify the dose in the treatment plan and to perform dose homogeneity in PTV while in IMRT, all plans consisted of seven coplanar fields, with 0°, 51°, 101°, 152°, 203°, 254° and 305° gantry angles.

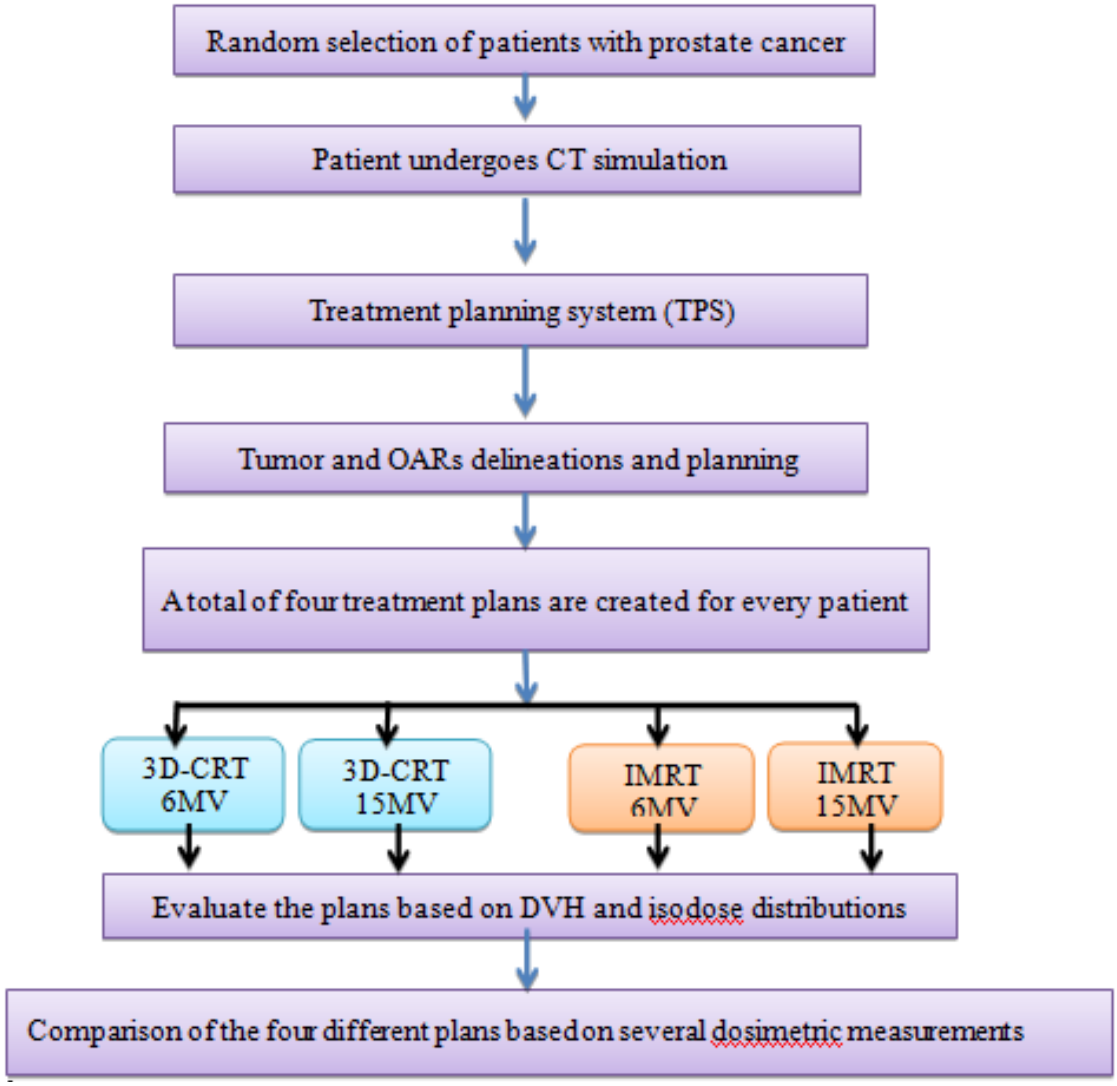


Fig. (1): Schematic chart of the present work, for both 3D-CRT and IMRT with 6MV and 15MV

Treatment planning evaluation parameters

Treatment Planning systems have many tools for qualitative and quantitative evaluation of the treatment plans. The qualitative evaluation is important to identify the locations of the hot and cold areas in the treatment plans and to display a complete review for treatment plans using isodose line. The quantitative evaluation is carried out with the use of DVH. It was generated to evaluate the dose to the PTV coverage and the dose reaching OARs that included rectum, bladder and femoral heads for each of plans.

PTV was planned in the constraints of 95-107% and doses for 3D-CRT and IMRT plans were 95% of the PTV receives at least 95% of the prescription dose and the following critical tolerance dose criteria were used; V50 (the volume receiving 50Gy) of rectum ≤50% of all volume, V70 (the volume receiving 70Gy) of bladder ≤35% of all volume and the mean dose to the femoral heads and used total number of MU. In addition to this ,other parameters such as HI and CI were used to compare the dose homogeneity and dose distribution in the PTV.

Homogeneity and conformity index

Dose homogeneity and dose conformity are independent specifications of the quality of the absorbed dose distribution. HI characterizes the uniformity of the absorbed-dose distribution within the target volume. It is defined as the ratio of the difference between the maximum and minimum dose to the median dose of PTV and smaller HI

indicates a better plan, where HI = Zero is an ideal value.

$$\mathbf{HI} = \frac{\mathbf{D2\% - D98\%}}{\mathbf{D50\%}}$$

Where D2, D98, D50 indicated to the maximum, minimum and median dose, these values represented the doses received by 2, 98 and 50% volumes of PTV respectively.

Dose conformity characterizes the degree to which the high-dose region conforms to the target volume, usually the PTV. CI is defined as the ratio of the tumor volume enclosed by the 95% isodose line to the total PTV volume and CI = 1 is an ideal dose conformity **[13,14].**

$$\mathbf{CI} = \frac{\mathbf{Volume\ of\ PTV\ covered\ by\ 95\%\ of\ prescribed\ dose}}{\mathbf{Total\ PTV\ volume}}$$

Statistical analyses

Data collection and analyses were performed using SPSS program (version 21). Paired sample t-test was carried out to compare data in 3D-CRT versus IMRT plans. Probability (p-value) equal or less than 0.05 is considered statistically significant. Data are presented as average ± standard deviation (SD).

Results

In the present work, patients with localized prostate cancer were randomly selected. Four treatment plans were generated for each patient as shown in Figure (1) and the comparison was performed as follows:

- **3D-CRT 6-MV vs. IMRT 6-MV**
- **3D-CRT 15-MV vs. IMRT 15-MV**
- **3D-CRT 6-MV vs. 3D-CRT 15-MV**
- **IMRT 6-MV vs. IMRT 15-MV**

All plans were evaluated quantitatively including target coverage (D95%), (D2%), (D98%) and (D50%). In addition, the HI of PTV, CI and dose to OARs were also recorded. Treatment efficiency was assessed using the number of MU delivered. Data obtained were derived from DVH.

3D-CRT 6-MV versus IMRT 6-MV

Both techniques 3D-CRT 6-MV and IMRT 6-MV provided acceptable results and IMRT was slightly better in terms of target coverage. CI was better in IMRT ($p<0.05$) whereas HI was better in 3D-CRT ($p<0.05$) (Table 1). As demonstrated in Figures (2) and (3), it can be seen that both techniques achieved organs sparing according to QUANTIC guide constrain. The DVHs analysis for rectum, bladder and both femoral heads showed that IMRT 6-MV was better than 3D-CRT 6-MV in all OARs and the differences were statistically significant ($p<0.05$). The number of MU increased in IMRT 6-MV compared to 3D-CRT 6-MV and the difference was statistically significant ($p= 0.014$) as shown in Figure (4).

3D-CRT 15-MV versus IMRT 15-MV

Both techniques 3D-CRT 15-MV and IMRT 15-MV were comparable in terms of target coverage while there was a better performance of the later when measuring the conformity index ($p<0.05$), but the opposite was true in case of homogeneity index ($p<0.05$). Both techniques achieved organs sparing according to QUANTIC guide constrain. The DVHs analysis for bladder and both femoral heads showed that IMRT 15-MV was better than 3D-CRT 15-MV and the differences were statistically significant ($p<0.05$) whereas in rectum measurements, the former outperformed the later, but without statistical significance ($p>0.05$)(Figures 2 and 3). The number of MU was reduced in 3D-CRT 15-MV compared to IMRT 15-MV by approximately 38.74 % and the difference was statistically significant ($p<0.05$) as displayed in Figure (4).

3D-CRT 6-MV versus 3D-CRT 15-MV

As shown in Table (1), 3D-CRT in both low energy (6-MV) and high energy (15-MV) revealed good results and 3D-CRT 15-MV showed slightly better results in terms of PTV coverage. HI and CI were slightly better in 3D-CRT 15-MV compared to 3D-CRT 6-MV. As shown in Figures (2) and (3) both techniques achieved organ sparing according to QUANTIC guide constrain. The DVHs analysis for rectum, bladder and both femoral heads showed that 3D-CRT 15-MV was better than 3D-CRT 6-MV in bladder and both femoral heads and the differences were statistically significant ($p< 0.05$). On the other hand, 3D-CRT 6-MV was slightly lower in rectum; however, the difference was statistically not significant ($p> 0.05$). The number of MUs increased in 3D-CRT 6-MV compared to 3D-CRT 15-MV with statistical significant ($p= <0.05$) Figure (4).

3.4. IMRT 6-MV versus IMRT 15-MV

As shown in Table (1), data analysis showed that both photon beams of IMRT had comparable results in terms of target coverage (D95%), D2%, D50%, D98%, homogeneity index and conformity index with no statistical significance (p>0.05). As shown in Figures (2) and (3), IMRT in both 6 and 15-MV achieved organs sparing according to QUANTIC guide constrain. The DVHs analysis for bladder and femoral heads showed that both energies had nearly the same outcomes without significance whereas in case of rectum the difference was statistically better with 6 MV than 15MV. IMRT 15-MV has reduced MU by approximately 18% compared to IMRT 6-MV with statistical significance (p= <0.05) Figure (4).

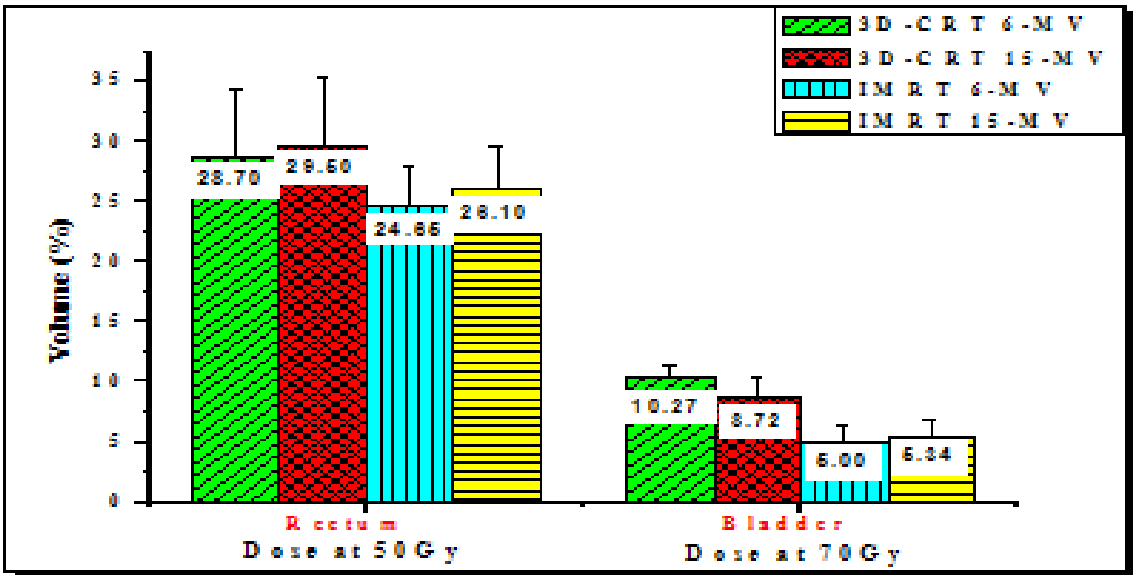


Fig. (2): Average mean volume (%) for rectum at V50 Gy and bladder at V70 Gy for both 3D-CRT and IMRT with 6-MV and 15-MV

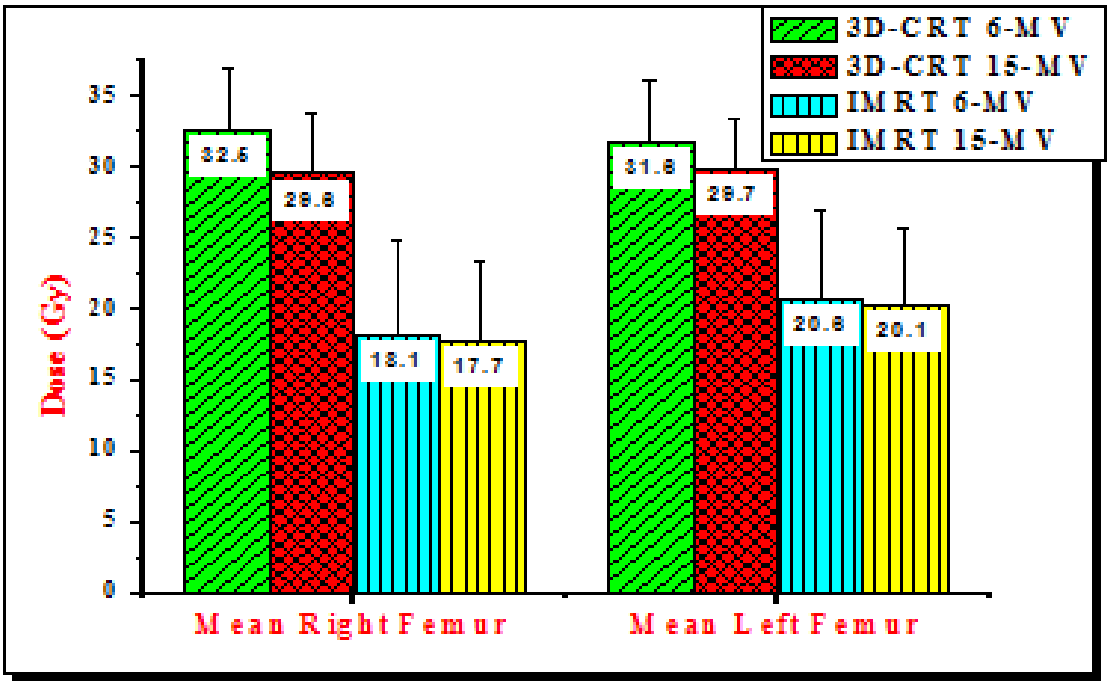


Fig. (3): Average mean dose for both right and left femoral head for both 3D-CRT and IMRT with 6-MV and 15-MV

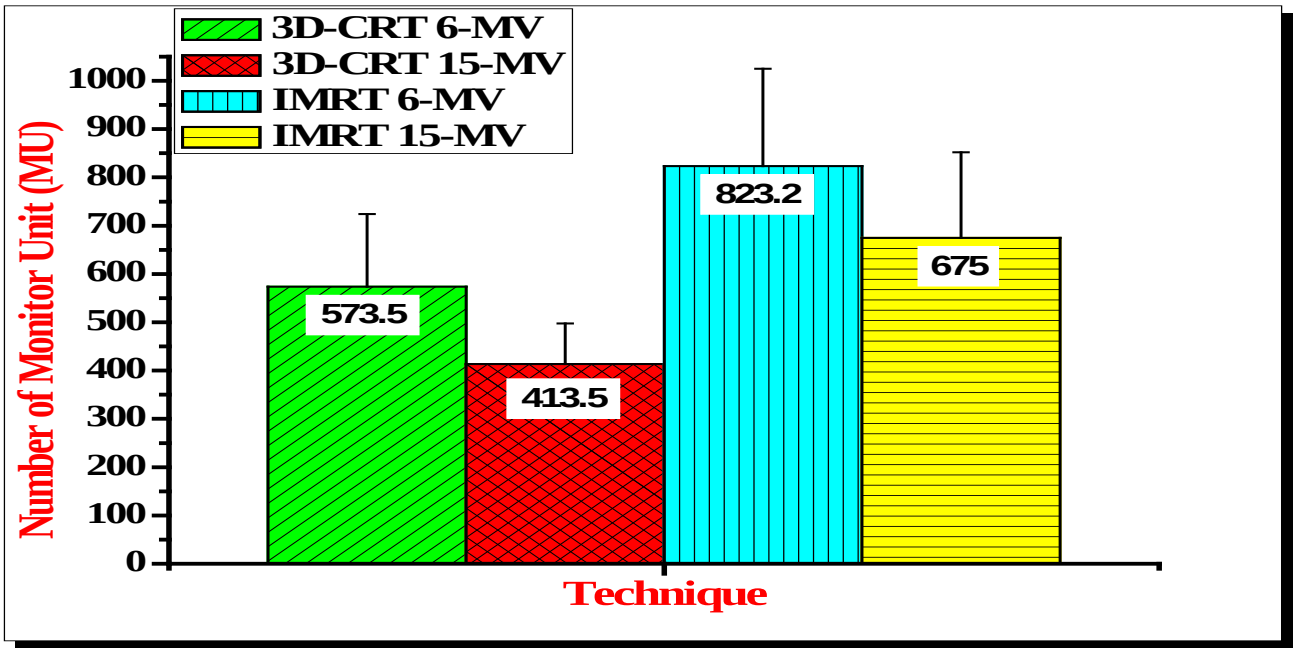


Fig. (4): Performance of 3D-CRT and IMRT in both 6-MV and 15-MV in MU measurements

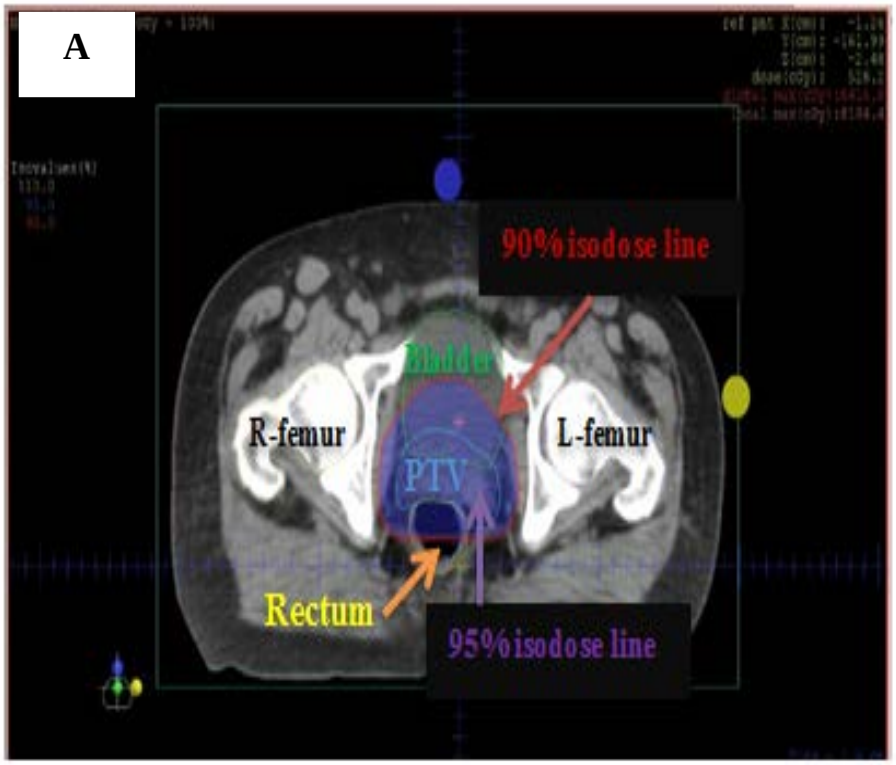
Table (1): Summarizes the dosimetric parameters for both 3D-CRT and IMRT with 6-MV and 15-MV

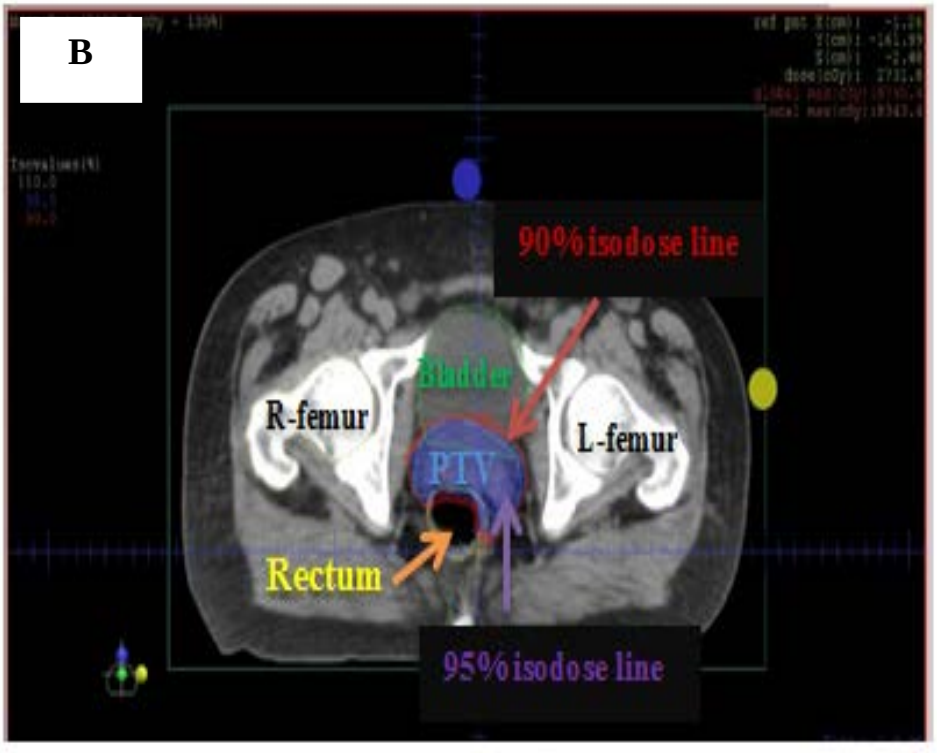
Parameters	3D-CRT 6-MV	3D-CRT 15-MV	IMRT 6-MV	IMRT 15-MV	Paired sample t-test (P-value)			
					3D-CRT 6-MV Vs. IMRT 6-MV	3D-CRT 15-MV Vs. IMRT 15-MV	3D-CRT 6-MV Vs. 3D-CRT 15-MV	IMRT 6-MV Vs. IMRT 15-MV
PTV D2% (Gy)	79.77±1.55	77.90±1.06	80.53±2.07	80.40±1.93	0.41	0.01*	0.001*	0.79
PTV D50% (Gy)	76.22±1.10	75.95±1.29	76.67±1.02	76.89±1.81	0.25	0.18	0.060	0.49
PTV D98% (Gy)	72.44±1.44	71.57±1.01	69.85±1.66	70.00±1.28	0.001*	0.002*	0.008*	0.54
PTV D95%	95.05±0.74	96.08±1.14	96.07±1.60	96.14±1.24	0.12	0.92	0.061	0.92
HI	0.095±0.01	0.08±0.01	0.14±0.02	0.13±0.02	0.003*	0.00*	0.016*	0.55
CI	0.93±0.043	0.95±0.02	0.97±0.02	0.97±0.01	0.006*	0.034*	0.120	0.66

* indicates significant difference; P-value < 0.05 is considered statistically significant.
3D-CRT = 3- dimensional conformal radiation therapy; IMRT = Intensity modulated radiotherapy
Dx%: Dose delivered to x % volume of the PTV; D2, D98 and D50 indicate the maximum, minimum and median dose respectively; CI = conformity index; HI = homogeneity index

Plan evaluation

Both techniques (3D-CRT and IMRT) were evaluated qualitatively by comparing the isodose lines distributions to know the location of the hot and cold areas in the treatment plans presented as isodose colors superimposed on transverse CT sectionni nwohs saFigure (5 A-D).





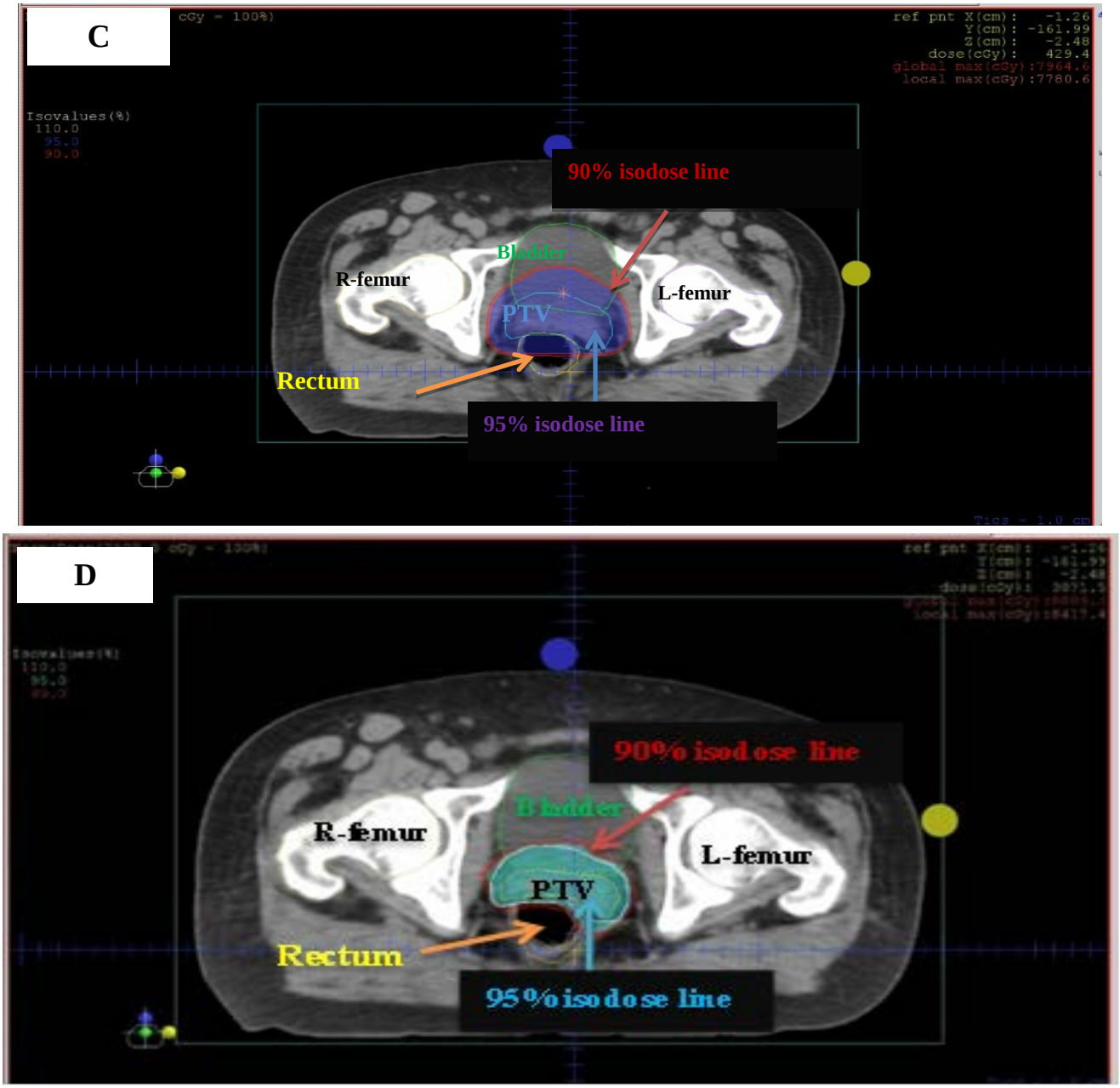


Fig. (5): The isodose distribution in the transverse CT section for (A) 3D-CRT 6-MV (B) IMRT 6-MV (C) 3D-CRT 15-MV and (D) IMRT 15-MV

Discussion

Target coverage, conformity and homogeneity index

Both t 3D-CRT and IMRT techniques, using 6 and 15-MV photon energies, resulted in similar outcomes in measurements of PTV. There was no significant difference between the two treatment modalities using the two beam energies in terms of the target coverage. However, IMRT whether 6 or 15 MV beam, was slightly better but not significant ($p>0.05$) in comparison to 3D-CRT in both beam energies.

The ICRU recommends that the absorbed dose in the PTV be confined from 95% to 107% of the prescribed absorbed dose. The results of the present study are in good agreement with those recommendations and consistent with previous reports which concluded that the PTV coverage was matching for both 3D-CRT and IMRT [15]. The median dose (D50%) was has nearly approached from prescribed dose in both techniques (3D-CRT and IMRT) plan with 6 and 15-MV and this is consistent with ICRU and other reports [16].

IMRT in both 6 and 15-MV had higher CI when compared to 3D-CRT 6 and 15-MV respectively, and it is able to conform the dose distribution to the concavity target volume and achieved an improvement in delivering higher doses to PTV with better sparing of critical and normal surrounding structures. This result was consistent with the study reported by Kinhikar et al. [3].

CI in the current study showed that high energy in comparison to low energy, especially 3D-CRT 15-MV was a bit better when compared to 3D-CRT 6-MV; however, the difference was not significant. The reason was due to the power of penetration in high energy especially in the pelvis. It has the ability to achieve better coverage to the required depth without large margin around the target, but with the energy 6-MV, a large margin around the target is needed to cover the tumor. Thus, it causes poor matching between volume of 95% and PTV volume.

This is identical to the study by Reft et al. and Welsh et al. [11, 12] where they concluded that the high-energy photons greater than 10 MV had dosimetric advantages in some situations thanks to their greater depth of penetration for deep seated tumors in the pelvic region. Higher photon energies are increasingly being employed with skin sparing potential; such energies are commonly used in 3D-CRT. In IMRT, high-energy photons may present more disadvantages than advantages, these disadvantage are causing increased secondary radiation to tissues outside the treated area from leakage and scatter, as well as a possible increase in the neutron dose from photon interactions in the machine head.

The results of the present study for HI showed that 3D-CRT in both 6 and 15-MV was better in comparison to IMRT 6 and 15-MV. The present results were in concordance to the studies reported by Shirani et al. [17] and contrast to the results achieved by Zheng et al. [18]. The reason was due to the fact that the difference between D2% and D98% revealed by IMRT was higher than those measured for 3D-CRT in both beam energies as a result of small variation in dose and absence of segment field in 3D-CRT.

When comparing 3D-CRT 6-MV to 3D-CRT 15-MV, HI was better with high energy (3D-CRT 15-MV) due to high penetration power of the later. On the contrary, low energy needs maximum dose and increases in monitor unit to deliver an adequate dose at the required depth. Thus, when the target has the maximum dose, the distribution is no longer sufficiently homogeneous.

Ezzell et al. [19] have reported that IMRT plans need to be evaluated carefully and somewhat differently than 3D-CRT. Inspecting and comparing DVH is useful, but not sufficient, since DVH has no spatial information. IMRT may create hot spots or cold spots in unexpected locations. For example, in 3D-CRT treatments in which beams are defined using beam's eye views, the user typically knows that the PTV is well surrounded with MLC within every field and so a low-dose tail on a DVH for the PTV reflects penumbra at the periphery. With IMRT, there is a high dose gradient inside and outside PTV according to the site of OARs relative to the PTV. Planners need to inspect (review) the isodose lines on each image slice included PTV and OARs.

According to the ICRU 83, 2010 [14] guidelines about the accredit amount of HI and CI the obtained values were acceptable. As mentioned above, the goal of HI and CI is to approach HI= 0 and CI=1 as ideal values.

The benefits of 10-MV as compared with 6-MV photons was more pronounced for thicker patients (anterior–posterior separation > 21 cm) for most

parameters, with statistically significant differences in bladder, integral dose (ID), and MU. There was no difference in PTV coverage, CI and possibly at the expense of higher rectum with high energy [20].

Organs at risk sparing

Both 3D-CRT and IMRT techniques with 6 and 15-MV had achieved QUANTEC constraint as described by Marks et al. [21] that recommended the relative volume receiving 70 Gy (V70%) for bladder must be less than 35% of total bladder volumes and 50Gy (V50%) for the rectum must be less than 50% of total rectum volumes.

When comparing (3D-CRT 6-MV vs. IMRT 6-MV) and (3D-CRT 15-MV vs. IMRT 15-MV) in terms of OAR, the results of IMRT in both 6 and 15-MV were better sparing in OARs while those of the 3D-CRT 6 and 15-MV were within accepted tolerance. The present results reported a lower dose to OARs than that reported by Sale and Moloney, 2011 [22] as they found that 50 Gy reached 53.78% vs. 35% in 3D-CRT and IMRT respectively of rectum volumes and V70 of bladder was 44.50% vs. 33.63% in 3D-CRT and IMRT respectively.

IMRT with 6 and 15-MV had better protection for both femoral heads compared to that for 3D-CRT in both 6 and 15-MV photons. The present study is consistent with an article by Uysal et al. **[23]** who concluded that the mean dose to right head of femur was 31.95 Gy in 3D-CRT and 17.98 Gy in IMRT and the mean dose to left head of femur was 31.5 Gy 18.79 Gy in 3D-CRT vs. IMRT respectively and consistent with other studies by Reddy et al. [24].

When comparing low energy (3D-CRT 6-MV) vs. high energy (3D-CRT 15-MV) in terms of OARs, 3D-CRT 15-MV was slightly superior in sparing bladder and both femoral heads compared to 3D-CRT 6-MV and the differences were statistically significant. The reason was due to the large margin around target volume in 3D-CRT 6-MV plan used to improve the coverage that increases the dose exactly from side of femoral heads, while in high energy with 3D-CRT 15-MV does not need a large margin because the coverage is already better due to the power of penetration**.**

When comparing low energy (IMRT 6-MV) vs. high energy (IMRT 15-MV), there was no significant difference in terms of target coverage and OARs. This is in accordance with the findings by Weiss et al. who analyzed the benefits of 6-MV over 18-MV photon energy plans for IMRT of lung cancer and they concluded that on average differences between 6 and 18-MV both for the PTV and normal tissues were not statistically significant [25]. In a similar fashion, the rectum sparing was superior in low energy IMRT 6-MV compared to high energy IMRT 15-MV and the difference was statistically significant.

Also 3D-CRT 6-MV was slightly better for rectum when compared to 3D-CRT 15-MV and the difference was not significant. The rectum is exposed to a higher dose from high energy 15-MV compared with less energy 6-MV whether from 3D-CRT 15-MV or IMRT 15-MV. This may be because of a higher percentage depth dose (PDD %) and exit dose with 15-MV photons. This is in accordance with the findings by Bhardwaj et al. who found that IMRT techniques have superiority in sparing surrounding critical organs compared to 3D-CRT and no significant difference was observed between IMRT 6-MV and IMR 15-MV techniques [26].

Number of Monitor Units (MU)

3D-CRT in both 6 and 15-MV has reduced MU due to absence of segment field in 3D-CRT in comparison to IMRT 6 and 15-MV. This is one of the advantages of 3D-CRT in shortening the treatment time compared to IMRT. This result was consistent with Kinhikar, Pawar et al., Cristofaro et al. and Mansouri et al. [3,27,28], regarding increase of MU in low energy compared to high energy due to the fact that the penetration power in low energy is lesser than ոihigh energy and hence more MU to deliver the same dose at the required depth. This is in accordance with the findings by De Boer et al. that reported that IMRT with 18 MV photons required 18% less MU than similar plans with 6 MV [29] .

Prolongation of the treatment time has been identified as one of the major drawbacks of IMRT and it has several negative consequences:

- Increased machine time required for quality assurance (QA) of complex IMRT plans for each patient and limitation of the number of patients who can be treated by treatment unit and increasing the patient waiting list. This is in addition to increased treatment cost in IMRT

compared to 3D-CRT and cost related to time and to administrative and technical staff [1].

- Patient discomfort with increased risk of movement during treatment is also a limiting factor [30].

-The higher number of MU in IMRT had effect in increasing the risk of a secondary malignancy due to an increase in amount of radiation transmitted, leakage and scattering through MLC [31,32].

-From the radiobiological point of view, some authors have suggested that increasing the treatment time allow tumor cells to repair radio-induced DNA damages and then pursue their proliferation [33,34].

Conclusions

The dosimetric comparison between 3D-CRT and IMRT in both 6 and 15-MV provided reasonable and very comparable results regarding PTV coverage. IMRT was better than 3D-CRT in OARs sparing and CI in both 6 and 15-MV whereas 3D-CRT in both 6 and 15-MV yielded better HI compared to IMRT 6 and 15-MV. The number of MU increased in IMRT compared to 3D-CRT. Also, MU increased in low energy compared to high energy whether in 3D-CRT or IMRT. The results also indicated that IMRT 6-MV technique should be prioritized over 3D-CRT 6-MV when the user has both options. Almost the 3D-CRT 15-MV technique was found to be superior than 3D-CRT 6-MV due to the huge separation of the bony pelvis in most patients diagnosed with prostate cancer. On the other hand, when IMRT 6-MV and IMRT 15-MV techniques were compared, no significant difference was found in terms of target coverage and OARs except the rectum, which was better in IMRT 6-MV compared to high energy IMRT 15-MV, perhaps of higher PDD% as well as exit dose. Therefore, IMRT 6-MV technique should be preferred over IMRT 15 MV technique.

This study recommends the use of IMRT 6-MV in treatment of prostate cancer and then 3D-CRT as a second line of treatment when the former is not available. The choice of the energies (6 and 15MV) used with 3D-CRT depends largely on patient's body geometry, while the use of high energy IMRT 15-MV is not recommended.

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